Persistent Musculoskeletal Pain in Individuals with Inflammatory Bowel Diseases

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Abstract

Background: Pain affects over 70% of individuals with inflammatory bowel disease (IBD), with abdominal and musculoskeletal (MSK) pain representing the most common complaints identified by patients. To date most studies in IBD have concentrated on inflammatory arthropathies. However, recent guidelines and investigations suggest that the majority of MSK pain in IBD is likely to be non-inflammatory in nature, although the scope and nature of MSK pain in IBD remains unclear with limited understanding of underlying mechanisms and factors moderating pain experiences. Consequently, further investigation and expanded theoretical frameworks are required in order to develop effective assessment and treatment pathways to improve patient outcomes in this population.

Aim: The aim of the present thesis was to explore persistent MSK pain in individuals with IBD, in order to identify shared mechanisms and factors which influence MSK pain experiences in this population.

Methods: Two narrative reviews of current literature were conducted to identify fundamental concepts and models in IBD and pain pathways, in order to develop a new framework for persistent MSK pain, primary thesis domains, and thesis methodologies. Two primary thesis studies were used to investigate MSK pain within this framework, including 1) a population-based survey characterizing MSK pain in New Zealand adults through subgrouping and mediation analyses, and 2) a clinic-based investigation investigating measures of central sensitization in American adults with IBD.

Results: Subgrouping analysis of Study 1 demonstrated three distinct profiles of MSK pain in individuals with IBD. These profiles indicated that individuals with worse pain experiences presented with greater symptoms related to central sensitization, increased

probability of presenting with multiple pain qualities, and active IBD. Sub-analysis of Study 1 further indicated that IBD activity was a significant predictor of worse MSK pain experiences, where symptoms of central sensitization demonstrated significant mediation of this relationship.

Study 2 of the present thesis indicated that assessments of somatosensory functioning did not differ between three study groups (i.e. IBD patients with MSK pain, IBD patients without MSK pain, and healthy controls). However, the burden of symptoms related to central sensitization was found to be significantly different between all study groups. Furthermore, Study 2 demonstrated association of measures of central sensitization and a range of participant features (i.e. IBD, psychological, and lifestyle factors).

Conclusion: The current thesis presents a new framework to consider and explore persistent MSK pain in IBD patients. Findings from the two primary thesis studies indicated that a sub-population of IBD patients with and without MSK pain presented with features suggesting the presence central sensitization. Individuals with MSK pain and symptoms of central sensitization presented with worse IBD, HRQOL, and pain experiences. MSK pain in IBD presented as distinct profiles, suggesting influences from worse IBD severity to pain presentations and the presence of central sensitization. Measures of central sensitization in IBD were associated with a range of patient features (i.e. IBD, pain, psychological, lifestyle, and comorbidity), highlighting potential risk factors for the development of central sensitization leading to worse pain experiences in IBD patients.

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Falling, C. L., Stebbings, S., Baxter, G. D., Gearry, R. B., & Mani, R. (2018) Central sensitization inventory mediates the relationship between inflammatory bowel disease activity and musculoskeletal pain experiences. *NZ Society of Gastroenterology: Annual Scientific Meeting*, held at: Dunedin, New Zealand.

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List of Abbreviations and Terms

CNS:	Central nervous system
CPM:	Conditioned pain modulation
CSS:	Central sensitivity syndrome
CSI:	Central sensitization inventory
EIM:	Extra-intestinal manifestation
GBA:	Gut-brain axis
HADS:	Hospital Anxiety and Depression Scale
HBI:	Harvey Bradshaw Index
HRQOL:	Health-related quality of life
IBD:	Inflammatory bowel disease
IBS:	Irritable bowel syndrome
LCA:	Latent class analysis
MSK:	Musculoskeletal
NRS:	Numeric rating scale
PANAS:	Positive and Negative Affective Schedule
PCS:	Pain Catastrophizing Scale
PPT:	Pressure pain threshold

PROMIS: Patient-Reported Outcomes Measurement Information System

PSS: 10-item Perceived Stress Scale

QST: Quantitative sensory testing

SCCAI: Simple Clinical Colitis Activity

SIBDQ: Index Short Inflammatory Bowel Disease Questionnaire

TS: Temporal summation

1 Introduction

1.1 Background

Inflammatory bowel disease (IBD) comprises a group of conditions, the most prevalent of which are Crohn's disease and ulcerative colitis. These chronic inflammatory diseases are characterized by relapsing-remitting courses of gastrointestinal tract inflammation, as a result of dysregulated immune responses (Böhmig, 2019; Burisch & Munkholm, 2015; M'Koma, 2013). Although the epidemiology of IBD varies considerably both within and between geographic regions, global trends show an increasing prevalence worldwide, especially in regions where the incidence was once low (Burisch & Munkholm, 2015; Molodecky et al., 2012). The prevalence of IBD is reported to be highest in the Western world, affecting up to 0.5% of the general population, with an incidence ranging from 10 to 30 per 100,000 (Molodecky et al., 2012). A recent systematic review indicated that Southern Australia and New Zealand represent some of the highest global incidence rates for IBD (Molodecky et al., 2012).

The variation in incidence rates of IBD around the world has led to theories for the evolution of this disease coinciding with industrialization of societies, north-south geographic gradients, and patient demographics (e.g. ethnicity, age, and gender) (Karlinger, Györke, Makö, Mester, & Tarján, 2000; Molodecky et al., 2012). However, influences of westernization (e.g. diets, food additives, and medications) alongside and/or independently to that of industrialization have more recently received consideration (Kaplan, 2015; Molodecky et al., 2012). As a whole, current literature clearly indicates a global rise in the presence of IBD with disease onset occurring at a significantly younger ages than previously noted (Burisch & Munkholm, 2015;

Molodecky et al., 2012). As a result, the direct and indirect health-care burden of managing IBD in the western world has become substantial (Kaplan, 2015).

In addition to characteristic gut symptoms, pain is a commonly reported symptom which affects over 70% of IBD patients, with abdominal and musculoskeletal (MSK) pain representing the most common pain complaints (Brakenhoff, van der Heijde, & Hommes, 2011; Palm, Bernklev, Moum, & Gran, 2005; van der Have et al., 2015; S. J. van Erp et al., 2016; Zeitz et al., 2016). MSK pain in IBD is typically considered within the framework of extra-intestinal manifestations (EIMs), a group of comorbidities with known associations to IBD. Although EIMs encompass a broad range of conditions affecting nearly every organ system, MSK manifestations are reported to be the most common EIM in IBD (Marcus Harbord et al., 2016; Levine & Burakoff, 2011; Trikudanathan, Venkatesh, & Navaneethan, 2012).

While reports from the literature describe several MSK-related EIMs, such as arthropathies (inflammatory and non-inflammatory), osteoporosis, and tendinopathies (M. Harbord et al., 2016; Levine & Burakoff, 2011; Trikudanathan et al., 2012), to date inflammatory arthropathies are by far the most studied MSK-related EIM in IBD. Interest in investigating inflammatory arthropathies may reflect ongoing efforts to understand underlying inflammatory pathways which are common to joint conditions and IBD (Levine & Burakoff, 2011). As a result, the clinical assessment and treatment of inflammatory arthritis in the context of active IBD shares a common approach (Fornaciari et al., 2001; Levine & Burakoff, 2011; Zeitz et al., 2016).

Although inflammatory arthropathies are predominantly considered in IBD literature, an investigation of back/joint pain in IBD demonstrated that 87.7% of study participants did not satisfy inflammatory diagnostic criteria, suggesting that the

majority of joint pain in IBD is potentially non-inflammatory in nature (S. J. van Erp et al., 2016). Furthermore, numerous reports and guidelines regarding MSK-related EIMs state that non-inflammatory joint pain, or arthralgia, is more common in IBD than primary inflammatory arthritis (M. Harbord et al., 2016; T. Sheth, Pitchumoni, & Das, 2015; S. J. van Erp et al., 2016). Unfortunately, studies investigating joint pain in IBD typically exclude non-inflammatory pain or mention it without further investigation (Brakenhoff et al., 2011). Consequently, the scope and nature of MSK pain in IBD remains unclear with a limited understanding of underlying mechanisms and influencing factors (Brakenhoff et al., 2011). This narrow focus when considering MSK pain has led to potentially incomplete management pathways, leaving many patients without treatment strategies for their pain. As a result, further investigation and an expanded theoretical framework for the presence of MSK pain are required in this population and proposed in the present thesis.

1.2 Framework for Persistent Musculoskeletal Pain in IBD

The present thesis proposes a new framework to consider and explore persistent MSK pain in IBD (Figure 1.1). This framework integrates current IBD, chronic inflammatory, and chronic MSK pain literature to describe the potential for shared mechanisms in the generation and maintenance of persistent pain.

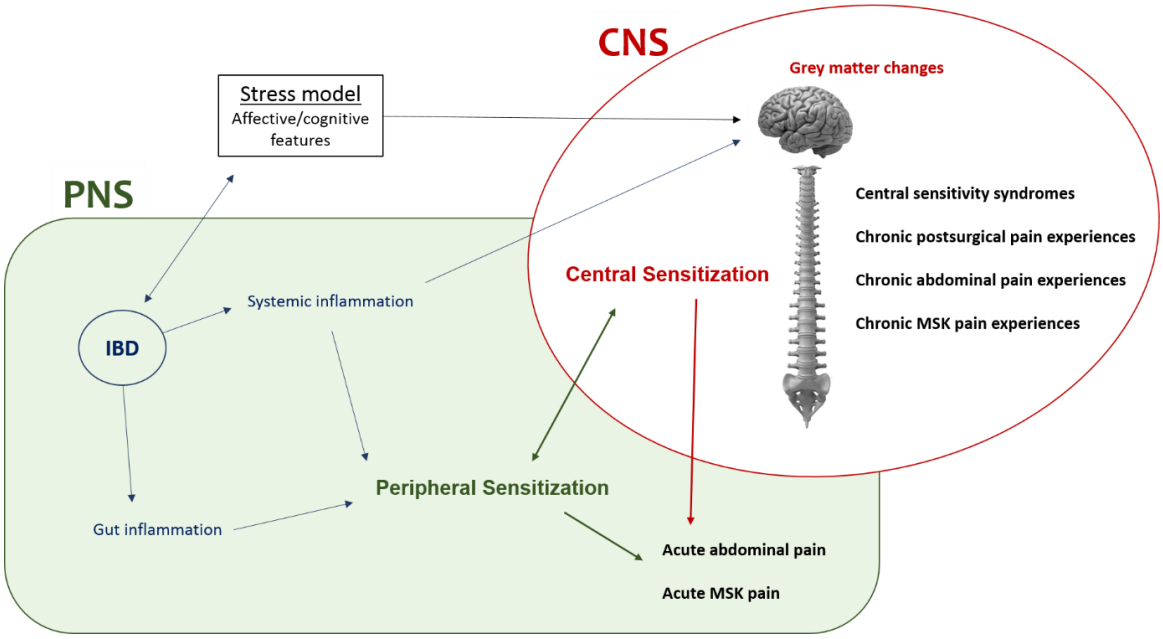

Figure 1.1. Framework for MSK-related pain in IBD. Inflammatory processes sensitize visceral afferent neurons, leading to increased central input and neural sensitization. Affective responses and coexisting emotional problems (stress model) influence arousal and cognitive processing in higher brain centres, thereby potentially further enhancing sensory input. Resultant neuroplastic changes in the CNS potentially contribute to multiple chronic pain states and central sensitivity syndromes.

1.2.1 Chronic MSK pain models

The literature presents complex pain models involving dynamic relationships between the nervous system, primary disease features, and concomitant pain states. The mechanisms involved in the generation and maintenance of chronic pain are postulated to include altered peripheral and central nervous system (CNS) activity. Peripheral injuries and/or inflammatory processes are believed to trigger changes in the nervous systems which may lead to the neuroplastic changes within the CNS seen in persistent pain states, including central sensitization, altered pain modulation, and structural brain changes (Curatolo & Arendt-Nielsen, 2015; Vardeh, Mannion, & Woolf, 2016).

In addition to altered nervous system activity, psychological factors, such as mood disorders and psychological distress, have been identified as important determinants of pain experiences in both acute and chronic conditions (Boersma & Linton, 2005; Roth, Tripp, Harrison, Sullivan, & Carson, 2007; Michael JL Sullivan et al., 2001; Villemure & Bushnell, 2002). As a result, evaluation of cognitive and affective features are commonly used to explore the modulation of pain perceptions (Villemure & Bushnell, 2002). Mechanisms by which psychological factors modulate pain experiences are complex. However, psychological factors have demonstrated an independent association with pain severity, disability, as well as neural hypersensitivity in multiple chronic pain (Finan, Quartana, & Smith, 2013; Sterling, Hodkinson, Pettiford, Souvlis, & Curatolo, 2008; Villemure & Bushnell, 2002) and healthy populations (Hven, Frost, & Bonde, 2017; Villemure & Bushnell, 2002).

1.2.1.1 Central sensitivity syndromes

The term 'central sensitivity syndromes' (CSSs) has been proposed to describe a group of interrelated disorders where the common aetiology is thought to be central sensitization, such as irritable bowel syndrome (IBS), temporomandibular joint disorder, and fibromyalgia (Arendt- Nielsen et al., 2018; Yunus, 2008). CSSs typically present with overlapping features, such as: psychological distress, sleep disturbances, fatigue, pain, allodynia, and hyperalgesia (Arendt- Nielsen et al., 2018; Verne, Robinson, & Price, 2001; Yunus, 2008). Although IBS is well-understood to be distinct from IBD, with separate aetiology and pathophsyiology (Schoepfer, Trummler, Seeholzer, Seibold-Schmid, & Seibold, 2008), reports of patients in long-standing remission have indicated that IBD patients are two to three times more likely to have comorbid IBS than the general population (Simrén et al., 2002). Similarly, although reports for the prevalence of fibromyalgia in IBD have been conflicting (Buskila, Odes,

Neumann, & Odes, 1999; Palm, Moum, Jahnsen, & Gran, 2001), a recent longitudinal investigation of 3,465 newly diagnosed IBD patients indicated a 2-fold increased risk of being diagnosed with fibromyalgia compared to patients without IBD (Larrosa Pardo, Bondesson, Schelin, & Jöud, 2019).

Although these findings highlight potential contributions of central sensitization to comorbid clinical presentations in some IBD patients, current literature has not investigated the presence of central sensitization related to features of IBD, including persistent MSK pain experiences. A large (N = 6309) epidemiology study in IBD indicated that only 20% of patients reported a coexisting IBS diagnosis (Abdalla et al., 2017). With pain reports in over 70% of IBD patients (Brakenhoff et al., 2011; Palm et al., 2005; van der Have et al., 2015; S. J. van Erp et al., 2016; Zeitz et al., 2016), these results suggest that mechanisms of central sensitization related to comorbid IBS are insufficient to explain ongoing pain presentations across the whole of IBD patients. As such, there is a need to explore potential pain mechanisms, including the presence of central sensitization, in the broader population of IBD patients in order to better understand the potential for shared mechanisms in persistent MSK pain experiences.

1.2.2 IBD Pain models

Although theoretical models regarding persistent MSK pain in IBD are lacking, over the past decade models for chronic abdominal pain in IBD have been described. Abdominal pain in IBD is well-understood to be a consequence of active inflammatory processes. However, current literature also reports abdominal pain experienced in periods beyond active inflammation (Bielefeldt, Davis, & Binion, 2009; Kristen E Farrell, Keely, Graham, Callister, & Callister, 2014). Consequently, abdominal pain in IBD is understood to often trigger pain in other body regions, such as the back and legs (Bielefeldt et al., 2009; Kristen E Farrell et al., 2014). This referred pain is thought to

be the result of central sensitization causing an overlap in activity between visceral and somatosensory neurons within the spinal cord (Bielefeldt et al., 2009; Kristen E Farrell et al., 2014). Additionally, contributions from altered affective and cognitive processing have been proposed in IBD abdominal pain models (Bielefeldt et al., 2009) and have demonstrated an independent association with IBD activity (Alessandro Agostini et al., 2014; Charles N Bernstein et al., 2010; Targownik et al., 2015). It is therefore unsurprising that models for chronic abdominal pain in IBD propose influences from central mechanisms, such as central sensitization, as well as changes to higher brain centres as a consequence of multiple pathways in IBD patients (Bielefeldt et al., 2009; Kristen E Farrell et al., 2014).

Similarly, investigations of chronic postsurgical pain indicate that IBD patients are two to three times more likely to develop chronic pain following gastrointestinal surgery than non-IBD populations (Bruce & Krukowski, 2006; Joris et al., 2015). Central sensitization has been found to play a major role in the pathophysiology of chronic postsurgical pain, with potentiation from prior disease inflammation thought to explain the increased prevalence of chronic pain in IBD patients (Bruce & Krukowski, 2006; Joris et al., 2015). It has been suggested that central sensitization in conditions such as IBD, reflect nervous systems primed with the potential to generate amplified and/or persistent pain states from subsequent injury and/or systemic inflammation (Hains et al., 2010).

1.2.3 Shared pain mechanisms

Previous studies of chronic inflammatory and MSK pain conditions in non-IBD populations have described influences from psychological and disease features (Arendt-Nielsen, Skou, Nielsen, & Petersen, 2015; Atzeni et al., 2015; Catalano et al., 2017; Kiltz, Baraliakos, Regel, Bühring, & Braun, 2017). These investigations highlight the

potential for multiple pain mechanisms which overlap in their presentation (Arendt-Nielsen et al., 2015; Atzeni et al., 2015; Catalano et al., 2017; Kiltz et al., 2017). For instance, in conditions such as ankylosing spondylitis and rheumatoid arthritis, it is not uncommon for patients to demonstrate both neuropathic and chronic widespread pain states, as a consequence of active inflammation and central mechanisms (Coutaux, Adam, Willer, & Le Bars, 2005; Koop, Peter, Vonkeman, Steunebrink, & van de Laar, 2015; Y. C. Lee, 2013; Wu, Inman, & Davis, 2013). Persistent MSK pain conditions, such as osteoporosis and chronic joint pain, have similarly demonstrated multiple pain mechanisms with concurrent nociceptive and central mechanisms in observed patients (Catalano et al., 2017).

Results from these investigations suggest that traditional frameworks for considering MSK pain in IBD, which tend to focused on isolated inflammatory mechanisms, may represent an over-simplification of the pathophysiology leading to persistent MSK pain in IBD. As such, there is a pressing need to reconsider how MSK pain is contextualized in IBD, in order to develop appropriate and effective assessment and treatment strategies in the future. The present thesis endeavoured to address this notable gap in current research and clinical practice through a series of investigations exploring a broader framework of self-reported MSK pain in IBD.

Although there are numerous approaches which could be employed to explore persistent MSK pain experiences in IBD, including both qualitative and quantitative methodologies, reports from current literature suggest quantitative designs may represent the best approach for objectively identifying the presence of shared mechanisms in this population (Arendt-Nielsen, Graven-Nielsen, & Petrini, 2012; Arendt- Nielsen et al., 2018; Catalano et al., 2017; Koop et al., 2015; S. M. Smith et

al., 2017; Wu et al., 2013). Therefore, the present thesis utilizes quantitative methodologies to explore the following research question and aims.

1.3 Research Question

Do persistent MSK pain experiences in patients with IBD represent shared mechanisms?

1.4 Research aims

- To review and synthesize IBD and chronic pain literature in order to develop a theoretical framework and identify primary thesis domains for exploring persistent MSK pain in IBD patients.
- To explore whether self-reported MSK pain presents in clinically meaningful patterns describing contribution from primary pain mechanisms and potential relationships between IBD, pain, and psychological features.
- To investigate potential predictive and causal relationships between IBD, central sensitization, and pain experiences.
- To investigate the presence of central sensitization, through symptomatic and bedside assessments, in patients with IBD and whether these measures of central sensitization differ in IBD patients with MSK pain.
- To investigate whether individual patient features are associated with measures of central sensitization in patients with IBD.

1.5 Research Pathway

The research pathway of this thesis is illustrated in Figure 1.2. As previously stated, consideration of central sensitization in patients with IBD has primarily been

reported in theoretical models of chronic abominal pain, without ojective investigation of related mechanisms and/or contributing factors in IBD patients. Furthermore, frameworks for considering persistent MSK pain in IBD, to include mechanisms of central sensitization, are lacking in current literature. Therefore, although a systematic review of constructs related to central sensitization in other populations may have highlighted general domains of interest to persistent pain exerpeiences across a spectrum of conditions, it is uncertain whether these findings would have been generalizable to IBD patients. Alternatively, a narrative review of the broader research themes identified in IBD and pain literature used to highlight shared constructs was considered useful for describing a new theoretical framework for exploring MSK pain experiences in IBD (Chapter 2). Constructs identified in this initial narrative literature review were further explored as the primary thesis domains in a second review of the literature, including a review of study methodologies relevant to the present thesis (Chapter 3). Results from the second literature review contributed to the methodological framework for two primary thesis studies, including Study 1: Profiles of self-reported MSK pain in IBD patients (Chapter 4) and Study 2: Assessment of central sensitization in IBD patients with and without MSK pain and healthy controls (Chapter 7). Study 1 examined self-reported pain and disease features in New Zealand adults with IBD. These self-report measures were used to identify profiles of MSK pain through subgroup-based analysis (Chapter 5). Predominant pain and IBD features identified during subgrouping were further explored in a sub-analysis examining the predictive relationship between these features (Chapter 6). Study 2 investigated differences in assessments of central sensitization across three study groups: 1) IBD patients with MSK pain, 2) IBD patients without MSK pain, and 3) health controls (Chapter 8). Additionally, Study 2 explored associations of psychological, IBD,

demographic, comorbidity, and lifestyle features to measures of central sensitization in IBD patients (Chapter 9). Finally, the present thesis concludes with a general discussion of overall thesis findings, strengths, limitations, and recommendations for future research (Chapter 10).

1.6 Significance of the Research

This research contributes to a broader understanding of the mechanisms involved in MSK pain experiences in patients with IBD. The proposed theoretical framework for considering MSK pain experiences (Figure 1.1) provides a new context to guide current and future research efforts and clinical practice. Specifically, this research explores the presence of central sensitization and the relationships between measures of central sensitization, psychological factors, IBD features, and painful MSK experiences. Results provide not only a deeper understanding of mechanisms of persistent MSK pain in IBD but also highlights the need for new targeted management pathways in this population.

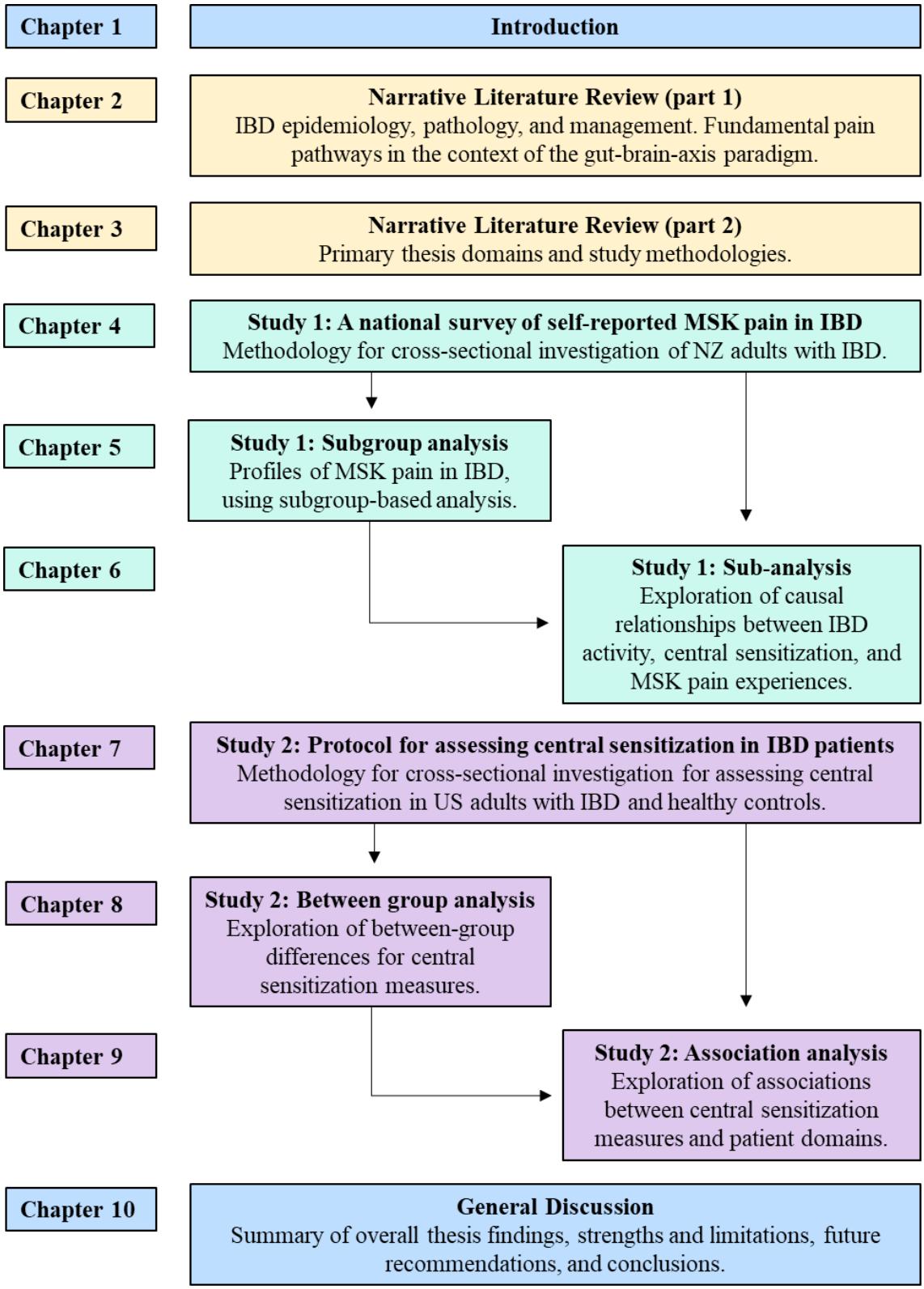

Figure 1.2. Thesis outline.

2 Inflammatory Bowel Disease, Fundamental Pain Pathways, and the Gut-Brain-Axis: Review of the Literature

2.1 Chapter overview

The current chapter first presents an overview of the literature regarding IBD processes and management frameworks, as well as fundamental pathways leading to chronic MSK pain experiences. These pathways are contextualised within the 'gut-brain-axis' (GBA) paradigm in order to illustrate constructs common to both gastrointestinal and pain literature (Figure 2.1).

2.2 Inflammatory Bowel Disease

The gastrointestinal tract is primarily protected by a mechanical barrier and the intestinal immune system (Figure 2.1) (Tortora & Derrickson, 2008). The inner mucus layer of the tract allows small molecules to pass through while preventing large particles from contacting the epithelial layer (Böhmig, 2019; Tortora & Derrickson, 2008). The structure of the epithelial layer includes a single layer of tightly joined cell junctions which selectively allows particles to pass from the intestinal lumen (Böhmig, 2019; Tortora & Derrickson, 2008). The epithelial layer also provides additional protection by secreting chemical mediators which further prevent microorganisms from coming into contact with epithelial cells (Böhmig, 2019; Tortora & Derrickson, 2008).

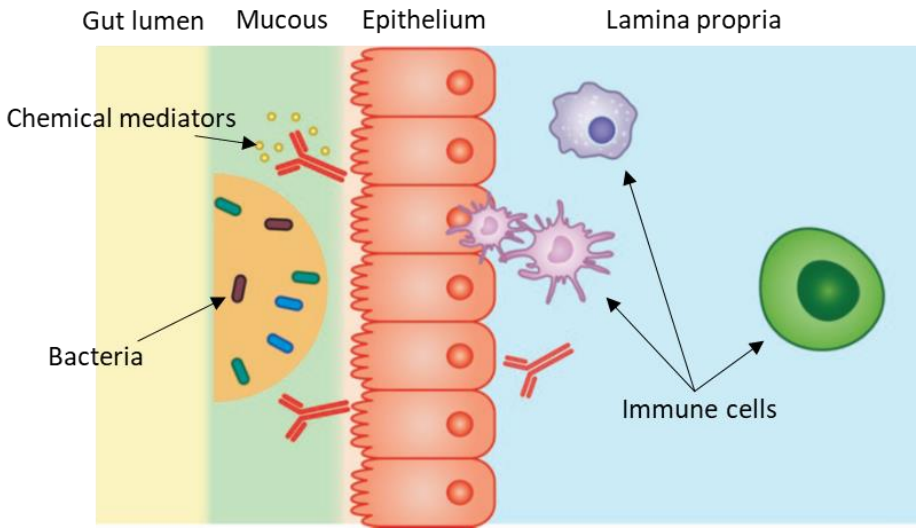

Figure 2.1. Intestinal barrier and local immune system, adapted from: (Böhmig, 2019).

The gastrointestinal tract, particularly the terminal ileum and the colon, are colonised by over 1014 commensal bacteria (Böhmig, 2019; Tortora & Derrickson, 2008). In fact, there are more bacteria living in the human gut than cells in the body. This complex ecosystem is collectively termed the human gut microbiome and is essential to nutrition, metabolism, and development of the immune system (Böhmig, 2019; Tortora & Derrickson, 2008). Homeostasis between an adequate tolerance to "healthy" bacteria and appropriate responsiveness to pathogenic bacteria is carried out by balanced immune responses (Böhmig, 2019). Evidence is emerging that disruption of this balance, termed dysbiosis, may trigger and maintain active IBD; furthermore, IBD in itself may promote microbiome dysbiosis (Gevers et al., 2014; Halfvarson et al., 2017).

IBD is associated with increased permeability of the intestinal epithelial layer, which causes continuous stimulation of the immune system (Hanauer, 2006). IBD is understood to be a consequence of inappropriate activation of immune cells as a result

of both genetic and environmental factors (Bernstein, 2017; Hanauer, 2006). Characterized by relapsing and remitting episodes of inflammation, IBD presents with periods of active inflammation (i.e. "flares"), followed by periods of no activity (i.e. "remission"). Crohn's disease and ulcerative colitis both have distinct as well as overlapping pathologic and clinical characteristics. For instance, inflammation in ulcerative colitis is limited to the mucosal layer and is confined to the colon, whereas Crohn's disease can present with transmural inflammation which may affect any part of the gastrointestinal tract from mouth to anus (Böhmig, 2019). The most important prognostic factor for ulcerative colitis is reported to be the extent of bowel involvement (Conrad, Roggenbuck, & Laass, 2014). In Crohn's disease an unfavourable prognosis is commonly associated with young age at initial diagnosis, location of disease in both the small bowel and colon, perianal disease, and/or the necessity of steroids on first flare (Peyrin-Biroulet et al., 2016).

2.2.1 Management framework

Management paradigms for both Crohn's disease and ulcerative colitis aim at inducing and maintaining clinical remission (M. D. Regueiro, Greer, & Hanauer, 2016). Algorithms for treating the different IBD subtypes reflect the differences between these conditions, and in recent years have changed from an emphasis on symptom management towards control of inflammation and normalization of biologic processes (M. D. Regueiro et al., 2016). The foundation for management of both IBD subtypes is based on evaluating disease extent and severity, through endoscopic, histologic, radiographic, and biomarker investigations (Neurath & Travis, 2012; Walsh, Bryant, & Travis, 2016). However, additional factors are reported to significantly influence clinical decision making, including response or loss of response to medications, number of hospitalizations, risk of surgery, risk of developing colorectal cancer, impact on

health-related quality of life (HRQOL), as well as the presence of extra-intestinal manifestations (EIMs) (M. D. Regueiro et al., 2016). As noted earlier, EIMs are defined as a group of comorbidities with known associations to IBD, which may be diagnosed before, concurrently, or after IBD diagnosis (M. Harbord et al., 2016; Levine & Burakoff, 2011; Trikudanathan et al., 2012).

2.2.1.1 Musculoskeletal manifestations

Although EIMs are understood to encompass a broad range of conditions affecting nearly every organ system (Table 2.1), MSK manifestations are the most commonly reported EIMs in IBD (M. Harbord et al., 2016; Levine & Burakoff, 2011; Trikudanathan et al., 2012). Of the MSK EIMs reported in current literature, previous studies have primarily focused on inflammatory arthropathies with little consideration of other painful conditions (Trikudanathan et al., 2012; Vavricka et al., 2015). The aetiopathogenesis of inflammatory arthropathies in IBD patients is not well understood. Inflammatory arthropathies in IBD include peripheral arthritis (Type 1 & 2), as well as axial arthropathies including the spine and sacroiliac joints (Brakenhoff et al., 2011; Levine & Burakoff, 2011; Tejas Sheth, Pitchumoni, & Das, 2014; Zeitz et al., 2016).

Unlike other types of inflammatory arthropathies, such as psoriatic arthritis, peripheral arthropathies associated with IBD are generally non-erosive (M. Harbord et al., 2016). The clinical classification of peripheral arthropathies in IBD is based on a large study of IBD patients, where two empirical types of arthritis were identified (Table 2.2) (Orchard, Wordsworth, & Jewell, 1998). Type 1 arthritis is defined as joint pain with evidence of swelling or effusion affecting fewer than five joints, typically the large weight-bearing joints of the lower limb (M. Harbord et al., 2016). The symptoms related to Type 1 arthritis correlate with IBD flares and are usually acute (less than 10 weeks) without permanent damage to the affected joints. Type 2 arthritis affects more

than five joints with symmetrical distribution and predominantly affects the upper limbs. Symptoms associated with Type 2 arthritis are independent of IBD activity and can persist for months or years.

Table 2.1

Extra-intestinal Manifestations of Inflammatory Bowel Disease

<table>
<tr><th>Musculoskeletal</th><th>Neurologic</th><th>Hematologic</th></tr>
<tr><td rowspan="4">Peripheral arthritis
Ankylosing spondylitis
Psoriatic arthritis
Relapsing polychondritis
Granulomatous arthritis
Sacroiliitis
Clubbing
Rhabdomyolysis
Arthralgia
Tendinopathy</td><td rowspan="2">Peripheral neuropathy
Vestibular dysfunction
Meningitis
Pseudo cerebri</td><td>Anaemia
Hyposplenism</td></tr>
<tr><td>Ocular</td></tr>
<tr><td>Cardiac</td><td rowspan="2">Episcleritis
Scleritis
Uveitis
Conjunctivitis
Retrobulbar neuritis
Crohn's keratopathy</td></tr>
<tr><td>Pleuropericarditis
Endocarditis
Cardiomyopathy
Myocarditis</td></tr>
<tr><th>Hepato-pancreato-biliary</th><th>Respiratory</th><th>Skin/mucous membrane</th></tr>
<tr><td>Primary sclerosing cholangitis
Cholelithiasis
Primary biliary cirrhosis
Ampullary Crohn's disease
Cholangiocarcinoma
Hepatitis
Pancreatitis
Granulomatous pancreatitis</td><td>Chronic bronchitis
Granulomatous bronchiolitis
Bronchiectasis
Fibrosing alveolitis
Pulmonary vasculitis
Interstitial lung disease
Sarcoidosis
Tracheal obstruction</td><td rowspan="3">Erythema nodosum
Pyoderma gangrenosum
Sweet's syndrome
Pyostomatitis vegetans
Psoriasis
Polyarteritis nodosa
Oral aphthous ulcers
Cheilitis</td></tr>
<tr><th>Renal & genitourinary</th><th>Endocrine & metabolic</th></tr>
<tr><td>Nephrolithiasis
Renal amyloidosis
Retroperitoneal fibrosis
Glomerulonephritis
Nephrotoxicity</td><td>Osteoporosis, osteomalacia
Thyroiditis
Epidermolysis bullosa acquisitia
Cutaneous vasculitis</td></tr>
</table>

Note. (Levine & Burakoff, 2011).

Table 2.2

Inflammatory Arthritis in Inflammatory Bowel Disease

Type 1 arthritis	Type 2 arthritis
Less than five joints affected	Five or more joints affected
Asymmetric involvement	Symmetric or asymmetric
Lower limb more affected	Affects both large and small joints
Self-limited episodes that last < 10 weeks	Persistent inflammation for months/years
Usually concomitant IBD flares	Independent of IBD activity
High frequency of other EIMs	May be erosive

Note. Inflammatory bowel disease (IBD), and extra-intestinal manifestations (EIMs) (M. Harbord et al., 2016).

Despite acknowledgement that non-inflammatory MSK pain is more common in IBD (M. Harbord et al., 2016; T. Sheth et al., 2015; S. J. van Erp et al., 2016), previous MSK-related studies typically exclude non-inflammatory pain or mention it without further investigation (Brakenhoff et al., 2011). Consequently, while inflammatory arthropathies continue to remain the most investigated MSK condition in IBD, the scope and nature of other MSK conditions are still widely unknown. Furthermore, this bias in current research suggests the potential for a significant underestimation of the overall prevalence and burden of MSK pain in IBD.

2.3 Pain

The following section provides an overview of the literature regarding the pathway leading to MSK pain experiences, followed by an overview of the GBA framework relevant to IBD. Integration of these shared pathways is illustrated in Figure 2.2

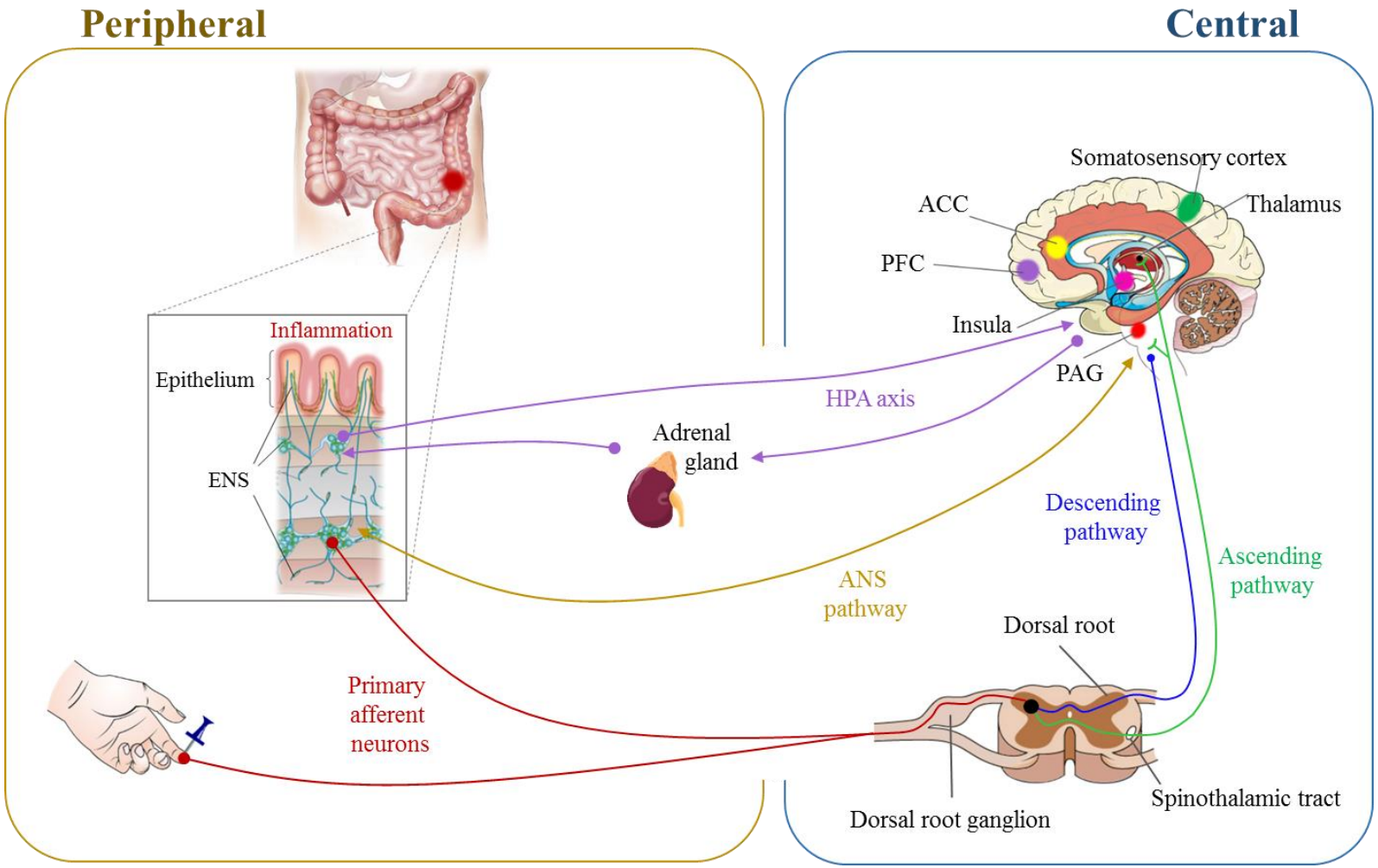

Figure 2.2. Shared peripheral and central pathways of inflammatory bowel disease and musculoskeletal pain experiences within the context of the gut-brain axis.

2.3.1 Pain pathway

An overview of the fundamental nociceptive pathways integral to pain experiences, including processes of transduction, transmission, modulation, and perception are described below and organised by peripheral versus central components to this framework.

2.3.1.1 Peripheral components

Nociceptive transduction is the process by which noxious thermal, mechanical, or chemical stimuli are detected and transformed into a perceivable signal by a group of peripheral sensory neurons, termed nociceptors (Basbaum, Bautista, Scherrer, & Julius, 2009; McEntire et al., 2016; C. J. Woolf, 2004). There are two major classes of nociceptors (Aδ and C fibres) that spread between epidermal cells and somatosensory organs in the periphery (Basbaum et al., 2009; DeLeo, 2006; McEntire et al., 2016). Both classes of nociceptors are functionally and molecularly heterogeneous, with subpopulations that respond to different types of stimuli (e.g. thermal vs mechanical). In general, medium-diameter myelinated (Aδ) afferents transmit acute, well-localized "first" or fast pain responses, whereas small-diameter unmyelinated "C" fibres convey poorly localized, "second" or slow pain responses (DeLeo, 2006; Meyer, 2008; C. J. Woolf, 2004). The peripheral terminal of the nociceptor will respond to environmental stimuli (e.g. thermal and mechanical), while both the peripheral and central terminals of the nociceptor will respond to a host of endogenous molecules (i.e. lipids and neurotransmitters) that regulate its sensitivity (Basbaum et al., 2009; DeLeo, 2006; McEntire et al., 2016).

With the exception of the face, all cell bodies of nociceptors are located in the dorsal root ganglia, with a peripheral axon that innervates their peripheral target organ and a central axon that terminates in the dorsal horn of the spinal cord (Basbaum et al.,

2009; Meyer, 2008). Consequently, once the noxious signal is transduced by the peripheral organ, a variety of voltage-gated ion channels are activated along the axon, transmitting signals to the dorsal horn of the spinal cord (DeLeo, 2006). These voltage-gated ion channels are critical for the generation of action potentials that deliver nociceptive signals (Cummins, Sheets, & Waxman, 2007; DeLeo, 2006).

2.3.1.1.1 Peripheral sensitization

One of the most important characteristics of both nociceptor subtypes is their ability to sensitize, thereby lowering their threshold for activation (Basbaum et al., 2009; DeLeo, 2006; McEntire et al., 2016). Similarly, axon voltage-gated ion channels also have this ability to sensitize and modify nociceptive signals *en route* to the dorsal horn (Cummins et al., 2007). These adaptive changes in sensitivity allow stimuli that would not normally cause pain to now do so (C. J. Woolf, 2004). Although important during acute pain states, maladaptive changes in peripheral nociceptors may lead to spontaneous firing, as well as changes in conduction and/or neurotransmitter properties. This process has been implicated in persistent pain associated with injury or diseases (i.e. diabetes, arthritis, or cancer) (Basbaum et al., 2009; DeLeo, 2006).

Hyperexcitability of the peripheral nervous system (i.e. peripheral sensitization) is thought to be associated with inflammatory changes in the chemical environment surrounding neurons (Basbaum et al., 2009; DeLeo, 2006). For instance, injury and subsequent tissue damage is often accompanied by the accumulation of endogenous factors released from activated nociceptors and/or immune cells that either reside within or infiltrate into the injured area, such as: mast cells, platelets, macrophages, neutrophils, endothelial cells, and fibroblasts (Basbaum et al., 2009). These endogenous factors increase the excitability of nociceptors, thereby increasing its sensitivity to, for instance, thermal and touch stimuli (Basbaum et al., 2009). Consequently, an increase

in nociceptor excitability results in greater nociceptive input into the spinal cord (Basbaum et al., 2009; DeLeo, 2006).

2.3.1.2 Central components

Primary afferent neurons terminate in the dorsal horn of the spinal cord in a highly organized fashion, innervating both dorsal horn interneurons and second-order projection neurons (Costigan & Woolf, 2000). Within the dorsal horn, afferent impulses are subjected to considerable local and descending pathway modulation, a process fundamental to the generation of pain and pain hypersensitivity (Costigan & Woolf, 2000). This complex network of synaptic transmission is mediated by neurotransmitters released within the dorsal horn (DeLeo, 2006). For instance, in the case of persistent injury, C fiber nociceptors fire repetitively thereby increasing the response of dorsal horn neurons. This phenomenon, referred to as 'wind-up', is dependent on the release of neurotransmitters (e.g. glutamate) as a consequence of repeated nociceptive input (Costigan & Woolf, 2000; DeLeo, 2006). Conversely, other neurotransmitters, such as serotonin, are released into the dorsal horn by descending inhibitory neurons from the brainstem, for instance during 'fight-or-flight' responses (Tracey & Mantyh, 2007).

The net sum of synaptic transmission between primary afferent and dorsal horn neurons results in the facilitation or inhibition of secondary afferent projection neurons (Basbaum et al., 2009; DeLeo, 2006). Secondary afferents then cross the midline of the spinal cord and transmit through ascending pathways (e.g. spinothalamic and spinoreticular tracts) to the thalamus and brainstem (Basbaum et al., 2009; Costigan & Woolf, 2000; DeLeo, 2006). Spinal projections to the brainstem are particularly important for integrating nociceptive activity with arousal and autonomic processes, as well as indirectly conveying nociceptive information to the forebrain after brainstem processing (Tracey & Mantyh, 2007). Secondary afferents projected to the brainstem

can directly influence both spinal (i.e. descending inhibitory projections) and forebrain activity, suggesting that these pathways mediate changes in pain perception (Tracey & Mantyh, 2007).

The thalamus is thought to have a prominent role in nociceptive processing and is the main relay for nociceptive signals to supra-spinal regions of the brain (Tracey & Mantyh, 2007). Literature suggests that no single region of the brain is essential nor solely responsible for painful experiences (Apkarian, Bushnell, Treede, & Zubieta, 2005). Rather, pain results from parallel activation of multiple supra-spinal structures, including the somatosensory, prefrontal, cingulate, and insular cortices (Apkarian et al., 2005). These regions have been implicated in the modulation of pain experiences through components related to sensory-discriminative features (somatosensory cortex and insula), as well as cognitive and affective features (prefrontal, cingulate, and insular cortices) of pain perception (Basbaum et al., 2009). It is important to note that these supra-spinal regions are not exclusively activated by nociception nor restricted solely to pain perception. These regions serve many neurological processes involved in cognition, emotion, motivation, and sensation (Apkarian et al., 2005; Basbaum et al., 2009). However, interaction among these sites provides a pathway whereby emotional and cognitive triggers can alter pain experiences and perceptions through interactions with descending modulatory systems.

2.3.1.2.1 Central sensitization

Peripherally sensitized neurons exhibit an increased discharge rate with each peripheral stimulus. This barrage of activity within the dorsal horn can have a number of consequences, including changes in ionic currents, altered receptor properties, modified gene expression, and loss of inhibition neurons (Costigan & Woolf, 2000). These alterations are believed to underlie the mechanisms leading to increased

responsiveness of nociceptive neurons within the CNS, termed central sensitization. In the present thesis central sensitization is defined according to the International Association for the Study of Pain (2017) definition: "*increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input*".

Central sensitization is a broad concept that includes multiple complex pathophysiological mechanisms, including changes to nociceptive facilitation, inhibition, and sensory processing (Clifford J Woolf, 2011, 2014). Common mechanisms are described as (Clifford J Woolf, 2011):

- Windup from individual neurons (temporal summation)
- Persistent increase in neural synaptic strength (long-term potentiation)
- Changes in the strength of synaptic connections (heterosynaptic potentiation)
- Dysfunctional descending inhibition and facilitatory pathways
- Neural receptive field expansion

These mechanisms are commonly reported to result in hyperalgesia (i.e. increased sensitivity to painful stimulus), allodynia (i.e. painful perception of non-painful stimuli), and increased temporal summation (i.e. increased pain perception in response to repetitive noxious stimuli over time) (den Boer et al., 2019; Clifford J Woolf, 2011).

2.3.1.2.2 Descending modulation

Modulation, including facilitation and inhibition, of nociceptive inputs by brainstem regions at the level of the spinal cord is a well-documented phenomenon (Basbaum et al., 2009; Porreca, Ossipov, & Gebhart, 2002). Descending modulation in this manner utilizes neurons of the rostral ventromedial medulla and periaqueductal

grey of the brainstem in order to influence the excitation of primary afferent terminals and/or dorsal horn interneuron excitability (Behbehani & Fields, 1979; Fields & Basbaum, 1978; Porreca et al., 2002).

Descending modulation of pain experiences is likely to be the result of multiple cognitive, attentional, and affective processes (Basbaum et al., 2009; Porreca et al., 2002). For example, acute stress and anticipation of pain relief (i.e. placebo effect) have shown to produce analgesic effects (i.e. inhibition) (Butler & Finn, 2009; Wager & Atlas, 2015), whereas chronic stress and anxiety have demonstrated facilitation of nociceptive pathways (Jennings, Okine, Roche, & Finn, 2014; Quartana, Campbell, & Edwards, 2009). Although classically, descending inhibitory processes have received significant attention in pain research, it has been suggested that descending facilitation may contribute to the development and maintenance of hyperalgesia seen in chronic pain states (Fields, 1992; Porreca et al., 2002).

2.3.1.2.3 Cortical grey matter

Changes to cortical grey matter have been described in multiple clinical pain populations, such as fibromyalgia (Kuchinad et al., 2007), low back pain (Apkarian et al., 2004), and ankylosing spondylitis (Wu et al., 2013). Investigations utilizing voxel-based morphometry have demonstrated changes in regions associated, for instance, with pain processing (e.g. cingulate, insulate, and prefrontal cortices) which have been linked to functional abnormalities in descending modulation of pain, as well as cognitive and emotional functioning (A Agostini et al., 2017; Kuchinad et al., 2007; Wu et al., 2013). Proposed mechanisms underlying grey matter changes in these populations include possible reduction in cell size, atrophy, and apoptosis from excitotoxicity and/or inflammatory mediators (A Agostini et al., 2013; Apkarian et al., 2004; Kuchinad et al., 2007; May, 2008). In chronic pain populations, for instance, the

often excessive and ongoing nociceptive inputs, as a consequence of nervous system sensitization, are thought to cause excitotoxicity resulting in neural loss (A Agostini et al., 2013; Apkarian et al., 2004; Kuchinad et al., 2007; May, 2008).

A study investigating Crohn's disease demonstrated a strong overlap in grey matter abnormalities compared with those seen in chronic pain conditions, suggesting a common basis (A Agostini et al., 2013). These authors suggest that the structural brain changes observed in Crohn's disease may account for persistent abdominal pain in patients demonstrating clinical disease remission. Similar to studies investigating chronic pain, Agostini et al. (2013) postulated that grey matter loss in IBD patients may also be related to excitotoxicity from excessive nociceptive afferents. However, these authors suggested that neuronal loss in IBD may be the consequences of recurrent intestinal inflammation, as well as the overproduction of inflammatory mediators. Circulating inflammatory cytokines are thought to directly induce neural apoptosis and decreased neurogenesis through signals which may be projected to several cortical and subcortical regions of the brain (A Agostini et al., 2013; Miller, Maletic, & Raison, 2009).

2.4 Gut-brain axis

Current literature describes multiple direct and indirect pathways that maintain an extensive bidirectional communication network between the gastrointestinal tract and the CNS, involving neuroendocrine and neuroimmune pathways (Carabotti, Scirocco, Maselli, & Severi, 2015; Grenham, Clarke, Cryan, & Dinan, 2011; Tillisch & Labus, 2014). Exploration of this communication network has led to the term GBA to describe the complex interactions of these systems. The GBA is thought to monitor and

integrate gut function with systemic processes, by linking higher brain centres with the gut through mechanisms such as immune activation, intestinal permeability, enteric reflexes, and neuroendocrine signalling (Carabotti et al., 2015).

2.4.1 Gut-brain-axis interactions

The GBA is comprised of multiple feedback loops with downstream effects aimed at maintaining homeostasis, involving the CNS, enteric nervous system (ENS), autonomic nervous system (ANS), and the hypothalamic-pituitary-adrenal (HPA) axis (Carabotti et al., 2015). The most consistent supra-spinal regions involved in GBA interactions include the limbic system (e.g. hypothalamus, amygdala, anterior cingulate cortex, prefrontal cortex, and hippocampus), and sensorimotor and integration centres (e.g. somatosensory cortices, insula, and thalamus) (Jones, Dilley, Drossman, & Crowell, 2006). The limbic system mediates emotional responses and is likely to be the primary driver for CNS interactions in the GBA (Jones et al., 2006).

Residing as two plexuses within the intestinal walls, the ENS is responsible for the intrinsic innervation of the gastrointestinal tract, primarily controlling motility, absorption, secretion, and visceral sensitivity (Mukhtar, Nawaz, & Abid, 2019). The ENS contains multiple terminals from efferent and afferent spinal pathways, as well as ANS pathways (e.g. vagal and sympathetic transmission). Within the brain, the ANS is primarily controlled by the hypothalamus, which acts to influence gut motility and secretion by modulating ENS activity (Taché & Bonaz, 2007). Factors such as stress, emotion, and cognition, modulated by supra-spinal regions, can independently trigger and/or influence ANS interactions with the gut (Mukhtar et al., 2019; Taché & Bonaz, 2007).

It has been understood for several decades that stress, whether inflammatory, traumatic, or psychological, triggers activation of the HPA axis (Tsigos & Chrousos, 2002). As the primary neuroendocrine driver of the body's stress response, HPA activation results in multiple protective processes, regulating immune activity to protect the individual from excessive inflammation (Toljan & Vrooman, 2017; Tsigos & Chrousos, 2002). During acute stress events, glucocorticoids (e.g. cortisol) are released from the adrenal glands as a consequence of HPA activation and act as the primary mediators of the stress response. In terms of the GBA, glucocorticoids are understood to affect local (gut) and systemic immune cell activity, thereby affecting gut permeability and gut microbiome composition (Toljan & Vrooman, 2017). In addition to immune regulating effects, glucocorticoids also act to downregulate the HPA axis itself through a negative feedback loop.

The GBA paradigm has previously been considered largely in the context of functional gastrointestinal disorders (e.g. irritable bowel syndrome (IBS) and gastroesophageal reflux disease) (Mukhtar et al., 2019). However, the role of the GBA in IBD has more recently received attention, primarily focusing on models exploring psychological features in patients with IBD, such as depression, anxiety, and stress (Bonaz & Bernstein, 2013; Borren, van der Woude, & Ananthakrishnan, 2018; Taché & Bonaz, 2007). Interestingly, it is well-understood that IBS is commonly reported in IBD, with patients in long-standing remission reported to be two to three times more likely to have IBS than the general population (Halpin & Ford, 2012; Simrén et al., 2002).

IBS is characterized by abdominal pain and altered bowel habits, where the diagnosis is based solely on clinical features and exclusion of other organic conditions, such as IBD (Canavan, West, & Card, 2014). IBS belongs to a group of conditions

termed ‘central sensitivity syndromes’ (CSS), also including interstitial cystitis, temporomandibular joint disorder, and fibromyalgia (Yunus, 2008). The underlying pathophysiology of CSSs is thought to be related to changes in higher brain centres, resulting in common symptomologies, such as psychological distress, sleep disturbances, fatigue, pain, allodynia, and hyperalgesia (Verne et al., 2001; Yunus, 2008). Specifically, systematic reviews reporting investigation of mechanisms related to central sensitization have been reported in individuals with IBS (Albusoda et al., 2018; Chakiath et al., 2015; Marcuzzi et al., 2019). Therefore, in addition to the notable overlap in neural pathways described in chronic pain and GBA literature, the high prevalence of IBS in IBD patients further suggests the potential for shared mechanisms mediating disease and pain processes in IBD.

2.5 Chapter Summary

Review of current IBD and chronic pain literature suggests an overlap in constructs seen in patient populations. Consideration of these constructs within the paradigm of the GBA illustrates shared mechanisms and the potential for common pathways in the maintenance of persistent MSK pain in IBD populations. In consideration of these shared constructs, the multifactorial nature of persistent MSK pain in patients with IBD is not well characterized nor fully captured through previous investigations. Therefore, Chapter 3 further explores these constructs as the primary thesis domains used to explore and re-contextualize MSK pain in this population.

3 Primary Thesis Domains and Study Methodologies: Review of the Literature

3.1 Chapter overview

The previous chapter highlighted the potential for shared mechanisms and constructs between pain responses and features of IBD, including nervous system pathways (peripheral, autonomic, enteric, and central) and psychological features. The following chapter presents a review of the literature exploring these shared constructs, including IBD, pain, central sensitization, and psychological features. This chapter also presents a review of the methodologies used to test study hypotheses in the current thesis.

3.2 Primary Domains

3.2.1 IBD features

Current literature describes ongoing challenges of characterizing features of IBD within broader clinical and research constructs, such as IBD activity and severity of the disease. Disease activity and severity are distinct yet overlapping concepts in IBD, both of which are used to evaluate the effectiveness of treatment (Peyrin-Biroulet et al., 2016; Siegel et al., 2016; Walsh et al., 2016). IBD activity is conceptualized as a cross-sectional assessment of inflammatory activity, whereas disease severity includes additional longitudinal and historical factors which are thought to provide a more complete clinical picture (Peyrin-Biroulet et al., 2016; Siegel et al., 2016; Walsh et al., 2016). Current literature suggests that some or all of the following factors may indicate the progression to severe IBD, including persisting disabling symptoms, impaired

health-related quality of life (HRQOL), repeated flares, development of irreversible penetrating and/or stricturing lesions, need for repeated courses of steroids, and need for surgery (Gomollón et al., 2016; Peyrin-Biroulet et al., 2016; Satsangi, Silverberg, Vermeire, & Colombel, 2006). Therefore, features of IBD explored in the present thesis are presented below under the sub-headings: IBD activity, disease course, and impact of the disease.

3.2.1.1 IBD activity

Following IBD diagnosis, the construct monitored by gastroenterologists is IBD activity in efforts to classify and treat the relapsing/remitting nature of this disease. From a theoretical and methodological point of view, diagnostic criteria and classification of a disease are understood to be distinct (Vitali & Del Papa, 2017). The differential diagnosis of IBD was not identified as an aim of the current research, therefore this thesis included investigation of individuals with previously established IBD diagnoses. As such, criteria for the differential diagnosis of IBD is not presented in the thesis. Conversely, IBD activity as a classification of relapsing or remitting IBD status, reflects a cross-sectional assessment of biological inflammatory activity using standardised tools with the intended purpose of guiding ongoing IBD management (C. N. Bernstein et al., 2010; Best, 2006; Siegel et al., 2016). Therefore, IBD activity in the present thesis is explored as separate construct from differential IBD diagnosis, and is presented below.

The current recommendation for assessing IBD activity include assessment of endoscopic, histologic, radiographic, biomarker, and symptomatic domains (Neurath & Travis, 2012; Walsh et al., 2016). Defining active IBD versus remission status generally involves a combination of these domains. However, characterizing IBD activity is challenging due to the heterogeneous nature of IBD, as well as the lack of

validated definitions of targets within some domains and consequently the disparity between findings in assessment domains (Walsh et al., 2016). For instance, mucosal healing (i.e. absence of ulcerations and erosions) is identified as a surrogate marker for effective disease control, and therefore the remission target of endoscopic assessments (Neurath & Travis, 2012; Walsh et al., 2016). The value in identifying endoscopic remission lies in its correlation with symptom relief, decreased surgical and hospital encounters, and overall improved HRQOL. However, current literature reflects a lack of defined and validated thresholds for mucosal healing (Khanna et al., 2016; Neurath & Travis, 2012; Sandborn et al., 2002; Vashist et al., 2018). Furthermore, poor correlation between measures within symptomatic and endoscopic domains are well-described (Neurath & Travis, 2012; Walsh et al., 2016).

Measures of symptomatic IBD activity, such as the Simple Clinical Colitis Activity Index, have previously demonstrated good to excellent psychometrics (Higgins et al., 2007) with sufficient validity to discriminate IBD activity (area under the receiver operating characteristic curve > 0.90) and strong test-retest reliability (ICC, 0.94; 95% CI, 0.86 – 0.97) (Turner et al., 2009). However, they have often been criticised for their poor correlation with the objective clinical features, such as endoscopic and biomarker assessments (Gracie et al., 2016; Sipponen et al., 2008). Functional gastrointestinal disorders (e.g. IBS) present with similar symptoms as active IBD, but without intestinal inflammation (Burgmann et al., 2006). The presence of overlapping IBS has been proposed as an explanation for the inconsistent correlation of symptomatic IBD assessments with other measures of disease activity (Burgmann et al., 2006). However, when considering the collective versus individual indications of IBD activity, symptomatic assessments have demonstrated adequate ability to discriminate between remission and active IBD status (Turner et al., 2009). Assessing IBD activity

using more invasive endoscopic and radiologic investigations is costly, limiting the ability for regular and/or repeated testing in some patients. Thus, symptomatic assessments, such as the Harvey-Bradshaw Index and Simple Clinical Colitis Activity Index, have become popular as screening tools to indicate the need for further clinical assessment of IBD activity (Turner et al., 2009).

3.2.1.2 Disease course

Current opinion in IBD literature suggests that assessment of disease course in IBD should include consideration of IBD subtype, previous surgical interventions, medication use, presence of EIMs, age at diagnosis, and disease extent (Peyrin-Biroulet et al., 2016; Siegel et al., 2016). Disease extent in Crohn's disease and ulcerative colitis is most frequently assessed using the Montreal classification system, which is currently considered the gold standard for describing phenotypes of IBD and takes into account the location and behaviour of active disease (Gomollón et al., 2016). Using this criteria Crohn's disease is classified by age at diagnosis and disease extent (location and behaviour), and ulcerative colitis is classified by disease extent. Disease location in Crohn's disease is classified as terminal ileum, colonic, and ileocolonic, as well as with or without upper gastrointestinal tract location (Satsangi et al., 2006). Disease extent in ulcerative colitis is described as: (1) disease limited to the rectum (i.e. distal to the rectosigmoid junction), termed ulcerative proctitis, (2) disease distal to the splenic flexure, termed left-sided or distal ulcerative colitis, and (3) disease extending proximal to the splenic flexure, termed extensive ulcerative colitis or pancolitis (Satsangi et al., 2006). Although the classification of ulcerative colitis by disease behaviour has received significantly less attention, identification of stricturing and penetrating disease, as well as perianal involvement, are understood to be important indicators of disease severity in Crohn's disease (Satsangi et al., 2006).

3.2.1.3 Impact of the disease

Review of the current literature suggests widespread agreement that a primary outcome of IBD management is improved HRQOL (Gomollón et al., 2016; Peyrin-Biroulet et al., 2016; Satsangi et al., 2006). A number of clinical, psychological, and demographic factors have been found to be predictors of HRQOL in IBD. Current literature demonstrates differences in predictors of Gender, clinical symptoms, severity of disease, surgical interventions, flares per year, comorbidity, and perceived stress have consistently demonstrated association with HRQOL (Francesc Casellas, López-Vivancos, Badia, Vilaseca, & Malagelada, 2000; F Casellas, Lopez-Vivancos, Vergara, & Malagelada, 1999; Hjortswang et al., 2003; Moradkhani, Beckman, & Tabibian, 2013). However, factors such as age, type of IBD, socioeconomic status, and marital status have less consistently been found to influence HRQOL (E. J. Irvine, 1997; Moradkhani, Kerwin, Dudley-Brown, & Tabibian, 2011; Oxelmark, Magnusson, Löfberg, & Hillerås, 2006).

Interestingly, although the different phenotypes of IBD have not been identified as a predictor of HRQOL, a recent study (Perera et al., 2018) suggests the IBD phenotypes may demonstrate a unique profile of predictors. For instance, factors such as current age, age at diagnosis, and disease duration have not shown to be predictors of with phenotype (Gurková & Soósová, 2018; Perera et al., 2018), psychological stress and disease extent were shown to have a negative impact on patients with CD only (Perera et al., 2018). These results suggest that although disease features, such as activity, have been identified as important determinants of HRQOL in IBD, the assumption that IBD phenotypes represent similar determinants and that achieving clinical remission results in improved HRQOL is less supported. Consequently, current

literature would signify the need to specifically evaluate HRQOL across the different types of IBD in order to indicate the presence of additional risk factors.

3.2.2 Pain features

The use of a mechanistic approach to evaluate features of chronic MSK pain has been actively promoted over the past few decades in reflection of the growing knowledge related to underlying pathophysiological processes (Smart, Blake, Staines, & Doody, 2011; Vardeh et al., 2016; C. J. Woolf, 2004; Clifford J Woolf et al., 1998). It has been suggested that exploration of pain features with mechanism-based considerations could improve management pathways by facilitating targeted treatment strategies, thereby optimizing patient outcomes (Nijs et al., 2014; Smart et al., 2011; Clifford J Woolf et al., 1998). As such, mechanism-based classification, whereby pain is classified according to the dominant pathophysiological mechanisms responsible for its generation and/or maintenance, has been proposed (Smart et al., 2011). Distinct categories within this classification system commonly include nociceptive, peripheral neuropathic, and central sensitization pain types (Smart, Blake, Staines, Thacker, & Doody, 2012a, 2012b, 2012c).

The ongoing challenge of mechanism-based classification lies in the absence of gold standards for directly assessing pathophysiological pain mechanisms. However, it has been suggested that the different categories of pain mechanisms (i.e. nociceptive, peripheral neuropathic, and central sensitization pain) may be clinically identifiable and distinguishable, through clinical and self-reported measures, based on the pattern of signs and symptoms of each category (Cruz-Almeida & Fillingim, 2014; Nijs et al., 2015; Smart et al., 2011). As such, exploration of MSK pain in the present thesis

includes evaluation of typical pain features, including severity, location, quality, and interference.

3.2.2.1 Severity

Pain severity is widely accepted as one of the most fundamental dimensions of pain experiences regardless of the disease. The level of pain severity at initial assessment was found to be a significant predictor of complex pain management in some patients (Hjermstad et al., 2011). Pain severity is thought to be a primary factor that determines the impact of pain on the patient and is the most common feature explored within the "sensory/discriminative" dimension of pain experiences (Melzack & Casey, 1968). Current literature describes a vast array of pain severity assessment tools, of which the self-report unidimensional scales (i.e. numeric rating scale (NRS), visual analogue scale, or verbal rating scale) are recommended by expert consensus (Hjermstad et al., 2011; Williamson & Hoggart, 2005) and by far the most widely employed measures.

3.2.2.2 Location

Assessment and interpretation of MSK pain distribution is a fundamental consideration in the identification of predominant neuropathic, nociceptive, or central sensitization pain mechanisms (Nijs et al., 2015; Smart et al., 2011). For instance, the strongest indicator of predominately nociceptive pain was found to be pain localized to the area of injury or dysfunction (with or without some somatic referral) (Smart et al., 2011). In patients with low back pain, those presenting with localized pain were over 69 times more likely to be classified with a dominance of nociceptive pain compared to other pain types (Smart et al., 2011). Conversely, patients with low back pain distributed in a dermatomal or cutaneous referral pattern were over 24 times more likely to be classified with a dominance of neuropathic pain (Smart et al., 2011).

Finally, patients presenting with an unpredictable pattern in addition to other features, such as disproportionate pain severity and multiple/nonspecific aggravating/easing factors, were over 30 times more likely to be classified with a dominance of central sensitization pain (Smart et al., 2011). Specifically, distribution patterns indicative of central sensitization pain are thought to include diffused pain, such as bilateral pain, pain varying in anatomical locations, non-segmental distribution, and generalized pain (Nijs et al., 2014). As such, current literature supports distinguishing MSK pain locations as regional versus generalized in an effort to suggest dominant pain types described above.

3.2.2.3 Quality

Evaluating descriptors of pain may be useful in identifying pain types (Edwards et al., 2016; Jensen, 2006; Nijs et al., 2014; Victor et al., 2008; Clifford J Woolf, 2011). It has been well-described, for instance, that pain arising from nociception has a clear and proportionate mechanical/anatomical nature(Smart et al., 2011). Nociceptive pain may be described as 'sharp', intermittent pain occurring with movement and a more constant dull ache or throb described at rest (Smart et al., 2011). Conversely, neuropathic pain is commonly described as burning, shooting, or electrical in nature, with pain commonly referred to in dermatomal or cutaneous distributions (Smart et al., 2011).

Individuals who present with chronic pain often describe characteristics common to multiple pain types (Finnerup et al., 2016; Hochman, Davis, Elkayam, Gagliese, & Hawker, 2013; Spahr et al., 2017). For example, studies of patients with chronic low back pain report description of both neuropathic and central components, without meeting the diagnostic criteria for neuropathic lesions (Spahr et al., 2017). Similarly, changes to supra-spinal regions have been reported in nociceptive as well as

non-nociceptive pain types (Apkarian et al., 2004). Therefore, current literature suggests that consideration of pain quality within broader clinical algorithms may be more useful in differentiating pain types than using quality descriptors alone (Nijs et al., 2015; Smart et al., 2011).

3.2.2.4 Interference

Exploration of the extent to which pain hinders engagement with social, cognitive, and emotional activities, termed pain interference (Jensen et al., 2017), has been identified as an important construct of pain investigations. Previous pain models describe interference with daily activities resulting from ongoing painful experiences, with the assumption that relief from pain correlates with an improvement in function (Dworkin et al., 2005). However, exploration of interference constructs indicates that although severity, interference, and function are related, they are understood to be distinct domains, each requiring consideration (Amtmann et al., 2010; Karayannis, Sturgeon, Chih-Kao, Cooley, & Mackey, 2017).

The complexity of interference constructs is further highlighted by investigations of age-related influences on pain interference, specifically directional influences. A large study investigating pain interference in IBD patients demonstrated slightly improved scores in older adults (> 60 years) compared to younger individuals (Kappelman et al., 2014). However, indication of worse interference in older adults has been reported within the general population (Thomas, Mottram, Peat, Wilkie, & Croft, 2007). Here, poor social networks were found to be strongly linked with reports of worse pain interference (Thomas et al., 2007). Conversely, chronic pain populations have demonstrated greater interference in younger individuals, where results were strongly associated with greater social dissatisfaction (Blyth et al., 2001). As such,

current literature suggests influences to pain interference from common features of pain (i.e. severity and disability), as well as psychosocial factors.

3.2.3 Central sensitization

Risk factors associated with the development of central sensitization pain have been identified as greater pain severity, female gender, history of abuse, greater pain interference, sleep disturbances, stress, and multiple painful comorbidities (Kindler, Jones, Perrin, & Bennett, 2010; Nijs et al., 2017). However, in the absence of a gold standard to directly identify mechanisms related to central sensitization, a variety of diagnostic surrogate markers are commonly used to explore various clinical and experimental characteristics (Clifford J Woolf, 2011). Clinical algorithms have been proposed to identify central sensitization pain through symptom identification (Nijs et al., 2015). In addition exploration of somatosensory functioning through assessments, such as quantitative sensory testing (QST), have been proposed (Cruz-Almeida & Fillingim, 2014). Therefore, investigation of central sensitization in the present thesis is through assessment of symptoms related to central sensitization and assessment of somatosensory functioning.

3.2.3.1 Central sensitization symptomology

Current literature suggests that central sensitization represents the pathophysiological mechanisms responsible for the overlapping clinical features of central sensitivity syndromes (CSSs), such as fibromyalgia, chronic fatigue, IBS, and temporomandibular joint disorder (Mayer et al., 2012; Yunus, 2008). It has been proposed that the symptoms of these conditions can be considered not as belonging to individual disorders, but as different manifestations of a common aetiology (i.e. central sensitization) (Mayer et al., 2012). This viewpoint led to the development of the central sensitization inventory (CSI) as a screening tool which broadly assesses overlapping

dimensions of CSSs and quantifies the degree of related symptomatology (Mayer et al., 2012).

CSI has been validated to investigate an array of symptoms and risk factors associated with the development of central sensitization and CSSs, within the domains of physical, emotional distress, headache/jaw, and urological features (Mayer et al., 2012). The presence of these symptoms is understood to be related to sensitivity of the somatosensory system, where increased sensitivity implicates changes to sensory processing within the CNS (Mayer et al., 2012). A CSI score of ≥ 40 was originally validated as the benchmark to identify patients with positive symptomology correlating with the presence of CSSs (Neblett et al., 2013).

Psychometric evaluations of the CSI across languages have demonstrated good test-retest reliability (intraclass correlation coefficients ranging from 0.88 to 0.97) and internal consistency (Cronbach's a ranging from 0.88 to 0.91) (Cuesta-Vargas, Roldan-Jimenez, Neblett, & Gatchel, 2016; Kregel et al., 2017; Mayer et al., 2012; Pitance et al., 2016). Evidence of convergent and discriminant validity has also been found in a number of studies. Total CSI scores have shown strong correlations with other validated self-report measures of pain severity, depressive and anxiety symptoms, as well as sleep disturbance, all of which have been associated with central sensitization/CSSs (Neblett et al., 2013; Neblett, Hartzell, Mayer, Cohen, & Gatchel, 2017). When compared to healthy controls, higher CSI scores have demonstrated association with the presence of one or more CSSs in chronic pain patients (Neblett et al., 2013; Neblett, Hartzell, Mayer, et al., 2017). Total CSI scores have shown to discriminated between individuals with chronic musculoskeletal pain and pain-free controls (Kregel et al., 2017), individuals with fibromyalgia from both acute ankle sprain and pain-free controls (Pitance et al., 2016), and between individuals with

fibromyalgia/chronic widespread pain, regional chronic low back pain, and health controls. Higher CSI scores have demonstrated association with a wider body area distribution of self-reported pain in a group of osteoarthritis patients scheduled to undergo primary total knee arthroplasty (Lluch Girbés et al., 2016) and increased widespread pain sensitivity in shoulder patients undergoing QST testing (Coronado & George, 2018).

Recently, the use of five CSI severity levels has been proposed to offer better clinical utility in assessing a patient's symptom presentation, making initial treatment decisions, and identifying meaningful clinical changes in response to treatment (Neblett, Hartzell, Mayer, et al., 2017; Scerbo et al., 2018). The mean CSI scores in each different CSI severity categories have been shown to correlate with female gender, the number of CSS diagnoses, as well as the presence of psychological features. Although female gender is a known risk factor for CSS diagnoses (Arnold et al., 2006; Kurland, Coyle, Winkler, & Zable, 2006), the highest CSI severity group demonstrated the strongest association with female gender (Neblett, Hartzell, Mayer, et al., 2017). Higher CSI scores were also found to correlate with individuals presenting with more CSS diagnoses. Individuals presenting with one CSS diagnosis demonstrated mean CSI scores within the moderate severity range, while those with four or more diagnoses fell within the extreme severity range (Neblett, Hartzell, Mayer, et al., 2017). The lowest CSI severity group reported the least amount of depressive symptoms, pain intensity, and perceived disability, whereas the highest CSI severity group reported the greatest amount of these symptoms. Although the use of CSI severity levels described in this emerging literature has not been validated, it provides a useful way of interpreting this central sensitization screening tool in clinical practice (Scerbo et al., 2018).

3.2.3.2 Somatosensory

Over the last two decades, assessments such as QST and conditioned pain modulation (CPM) have been developed as bedside assessments of somatosensory functioning (Arendt-Nielsen & Yarnitsky, 2009; Fillingim, Loeser, Baron, & Edwards, 2016; Rolke et al., 2006). QST is a group of assessments (e.g. pressure pain threshold (PPT) and temporal summation (TS)) which evaluate the perceptual responses to systematically applied sensory stimuli, in an effort to characterize function or dysfunction within nociceptive pathways (Arendt-Nielsen & Yarnitsky, 2009; Fillingim et al., 2016; Rolke et al., 2006). Similarly, CPM is believed to reflect the perceptual manifestation of descending inhibition projection neurons from the brainstem to the dorsal horn (Arendt- Nielsen et al., 2018).

Although somatosensory assessments, such as QST, are understood to assess the functionality of the entire neural circuit from peripheral receptor to higher brain centres, they cannot identify the exact source of somatosensory dysfunction (Arendt- Nielsen et al., 2018; Cruz-Almeida & Fillingim, 2014). However, QST and CPM assessments are useful, non-invasive methods for assessing the loss and gain of sensory function, which may contribute to our understanding of participating pathophysiological pain mechanisms (Arendt- Nielsen et al., 2018; Cruz-Almeida & Fillingim, 2014). Therefore, exploration of somatosensory functioning in the present thesis is presented below and include assessments of PPT, TS, and CPM.

3.2.3.2.1 Pressure pain threshold

PPT is a static QST assessment, defined as the minimum force applied which induces pain (Arendt- Nielsen et al., 2018). Decreased thresholds are related to facilitated gains within pain pathways, and are used clinically to identify localised or widespread hyperalgesia (Arendt- Nielsen et al., 2018; Fillingim et al., 2016). PPT

performed at painful regions, such as the low back, may detect local hypersensitivity related to processes of peripheral sensitization, or alternatively detect regional hypersensitivity related to processes of central sensitization (Neziri et al., 2012). As such, PPT in isolation is unable to determine whether assessments at the painful region reflect peripheral sensitization, central sensitization, or both.

A recent systematic review indicated PPT to be both reliable and valid in the assessment of somatosensory functioning in low back pain patients (Alqarni, 2018). The reliability and discriminative validity of PPT were found to be a strong diagnostic predictor for ruling in/out chronic low back pain (Neziri et al., 2012; Vuilleumier et al., 2015). Additionally, after adjusting for confounders, such as age, gender, and psychological factors, PPT was identified as the most sensitive QST assessment to discriminate chronic low back pain patients from healthy controls (Neziri et al., 2012; Neziril et al., 2011). Interestingly, adjustments for these confounders demonstrated little effect on associations with PPT, suggesting PPT was confounded only to a small extent by these covariates (Neziri et al., 2012).

Results from an investigation exploring age and gender effects of PPT in healthy individuals, demonstrated a significant increase in PPT sensitivity in individuals aged 63 years and older at the distal phalanges; however no gender effects were found (Lautenbacher, Kunz, Strate, Nielsen, & Arendt-Nielsen, 2005). Conversely, PPT investigation of the face, hands, and feet in healthy controls identified gender effects in PPT, but only as a function of age (i.e. only patients $\leq$ 50 years old) (Magerl et al., 2010). As such, current literature suggests age effects on PPT may differ regionally, as well as mediate gender effects in a non-linear fashion.

3.2.3.2.2 Temporal summation

TS describes the wind-up process leading to a progressive increase in neuronal output within the dorsal horn from a barrage of identical afferent nociceptive stimuli (Arendt- Nielsen et al., 2018; Staud, Vierck, Cannon, Mauderli, & Price, 2001). In the presence of central sensitization, this increase in neuronal output translates into an integration of signalling causing greater pain experiences which last after the end of the repeated stimuli (Arendt- Nielsen et al., 2018). In experimental TS, it has been demonstrated that a painful stimulus repeated up to 3 times per second for 5 to 10 seconds will integrate, causing increased pain at the end of the stimulus series (Arendt- Nielsen et al., 2018). The increase in excitability of spinal cord neurons from TS is commonly quantified by a wind-up ratio and considered a measure of increased central gain of nociception or pain facilitation (Rolke et al., 2006).

Similar to PPT, after adjusting for confounders, TS was found to discriminate between chronic low back pain patients and healthy controls, where confounders ultimately demonstrated a little effect on associations (Neziri et al., 2012). However, unlike PPT, TS was found to be a strong predictor for ruling in chronic low back pain, while demonstrating a poor ability for ruling out chronic low back pain (Neziri et al., 2012). An investigation of TS performed at the volar forearm (Lautenbacher et al., 2005), as well as the face, hands, and feet (Magerl et al., 2010), in healthy controls found no age or gender effects on TS assessments.

3.2.3.2.3 Conditioned pain modulation

CPM is a dynamic sensory test believed to assess the descending inhibitory pathways in pain modulation (Arendt- Nielsen et al., 2018). CPM explores the change in pain reported from one stimulus (the test stimulus) before and after the application of a second pain stimulus at a remote body site (the conditioning stimulus). The

magnitude of the CPM effect is defined as the absolute difference of the test stimulus after minus before the conditioning stimulus. A positive CPM effect indicates successful modulation and the individual is said to be a CPM responder. This "pain-inhibits-pain" phenomenon is thought to trigger activation of a cortically regulated spinal-bulbo-spinal loop that involves the activation of descending inhibition processes (David Yarnitsky et al., 2010).

A recent systematic review identified CPM as a valid and reliable assessment of somatosensory functioning in low back pain patients (Alqarni, 2018). Decreased CPM responses have also been reported in patients with a variety of pain disorders (Lewis, Rice, & McNair, 2012; van Wijk & Veldhuijzen, 2010) compared with healthy individuals. Additionally, CPM responses were found to predict outcomes suggesting the development of chronic pain (David Yarnitsky et al., 2008), as well as predict pain treatment outcomes (David Yarnitsky, Granot, Nahman-Averbuch, Khamaisi, & Granovsky, 2012). Interestingly, a recent meta-analysis indicated that IBS patients are almost 5 times more likely to demonstrate decreased CPM responses compared to healthy controls (Albusoda et al., 2018).

A systematic review with meta-analysis indicated age to be the strongest moderator of CPM effects, with a decreased response in older adults (Lewis et al., 2012). Similarly, gender effects have been reported, with men demonstrating greater CPM responses compared to women (Popescu, LeResche, Truelove, & Drangsholt, 2010). Although psychological factors (i.e. depression, anxiety, and pain catastrophizing) have demonstrated association with CPM responses, influences of psychological features are reported to be specific to the CPM test modalities (i.e. electrical, heat, or pressure) (Nahman-Averbuch, Nir, Sprecher, & Yarnitsky, 2016).

3.2.4 Psychological features

Psychological factors, such as mood disorders, stress, and coping, have been identified as important influences not only to IBD HRQOL and frequency of flares, but also to acute and chronic pain experiences (Boersma & Linton, 2005; Roth et al., 2007; Michael JL Sullivan et al., 2001; Sweeney et al., 2018; Villemure & Bushnell, 2002). Evaluation of cognitive and affective features are commonly used to explore the modulation of pain perceptions and nociceptive transmission (Villemure & Bushnell, 2002). Mechanisms by which psychological factors modulate pain experiences are complex and include multiple supra-spinal regions. Psychological factors have demonstrated an independent association with pain severity, disability, as well as neural hypersensitivity in multiple chronic pain (Finan, Quartana, et al., 2013; Sterling et al., 2008; Villemure & Bushnell, 2002) and healthy populations (Hven et al., 2017; Villemure & Bushnell, 2002). Interstingly, psychological variables were found to more frequently change in parallel with fluctuations in CSS, specifically temporomandibar disorders, when compared to QST measures (Fillingim et al., 2018). Psychological factors explored in the present thesis are introduced below, including mood disorders, perceived stress, affective style, and pain catastrophizing.

3.2.4.1 Mood disorders

The presence of mood disorders is well-recognised in patients with IBD (Andrews, Barczak, & Allan, 1987; Farrokhyar, Marshall, Easterbrook, & Irvine, 2006; Guthrie et al., 2002; Simrén et al., 2002; Sweeney et al., 2018). Mood disorders in IBD have been shown to be associated with decreased HRQOL, increased bowel symptoms, and led to speculations for an aetiological role in IBD (Farrokhyar et al., 2006; Guthrie et al., 2002; Simrén et al., 2002). Furthermore, a large US survey indicated individuals

with chronic pain were over four times more likely than individuals with non-chronic pain to experience anxiety, and over twice as likely to experience depressive disorders (McWilliams, Cox, & Enns, 2003). Similarly, a meta-analysis looking at studies of psychological functioning in chronic pain indicated that individuals with chronic pain were consistently more depressed than healthy individuals and were comparatively more anxious, both generally and in response to pain (Burke, Mathias, & Denson, 2015). Much like in IBD, temporal effects of mood disorders in chronic pain patients are difficult to measure. In both conditions, it is unknown the degree to which the presence of mood disorders is a risk factor for the development of these chronic conditions, or whether mood disorders are a consequence of these troublesome conditions (Kurina, Goldacre, Yeates, & Gill, 2001).

3.2.4.2 Perceived stress

The psychological paradigm addressing how an individual appraises situations in their life as stressful is described as an individual's 'perceived stress' (Cohen, Kamarck, & Mermelstein, 1983). An important distinction between perceived and objective stress lies in the argument that the development of stress is the cognitively mediated emotional response to the objective event, not the objective event itself (Cohen et al., 1983). This paradigm conceptualises the stress response not as an inherent quality of the event (e.g. intensity), but rather as dependent on personal and contextual factors (e.g. coping resources) (Cohen et al., 1983). Therefore, the assessment of perceived stress is thought to evaluate an individual's appraisal of events and may be useful in understanding the role of cognitive/affective features in an individual's disease process and HRQOL.

A significant association between perceived stress, high job strain, and altered PPT was reported in a large investigation of asymptomatic workers (N=3123) (Hven et

al., 2017). These results suggest that perceived stress may modulate somatosensory functioning in otherwise healthy individuals. Investigation of stress influences on MSK pain experiences includes a diversity of stress domains, such as recovery-stress (Heidari et al., 2018), work-stress (Joksimovic, Starke, vd Knesebeck, & Siegrist, 2002), early-life stress (Kopec & Sayre, 2005), and perceived stress (Buscemi, Chang, Liston, McAuley, & Schabrun, 2019). A recent systematic review indicated that perceived stress and life stressors may have an etiologic role on the development of certain MSK pain types (i.e. arthritis and spinal pain) (Buscemi et al., 2019). Unfortunately, studies specifically investigating the influences from perceived stress to MSK pain experiences are limited and present with high levels of heterogeneity (Buscemi et al., 2019). Thus the difficulty in comparing known studies highlights the need for higher quality investigations to clarify and validate the roll of perceived stress in MSK pain experiences (Buscemi et al., 2019).

Measures of perceived stress have demonstrated a significant association with an increase in IBD flares (Charles N Bernstein et al., 2010) and reduced HRQOL in IBD patients (Moradkhani et al., 2013). A multivariate logistic regression model exploring common IBD risk factors (i.e. medication, infection, smoking, negative affect, perceived stress, etc.), indicated that high perceived stress was the only variable found to be associated with symptomatic IBD flares in the final model (Charles N Bernstein et al., 2010). Within the gut-brain axis (GBA) paradigm, the physiological response to stress is understood to involve a cascade of reactions along the hypothalamus pituitary adrenal axis and the autonomic nervous system that affects both immune and inflammatory functions. The consequence of these events is thought to contribute to intestinal inflammation (S. M. Collins, 2001).

3.2.4.3 Affective style

The two-dominant dimensions of emotional (i.e. affect) styles are referred to as positive and negative affect. Positive affect describes the extent to which a person feels enthusiastic, active, and alert (Watson, Clark, & Tellegen, 1988). A state of high positive affect reflects high energy, full concentration, and pleasurable engagement, whereas low positive affect is characterized by sadness and lethargy (Watson et al., 1988). Conversely, negative affect is characterized by distress, anger, contempt, disgust, guilt, fear, and nervousness (Watson et al., 1988). States of low negative affect reflect calmness and serenity. Positive and negative affect styles have been shown to independently associated with immune function (Cohen, Alper, Doyle, Treanor, & Turner, 2006), somatosensory function in chronic pain (Finan, Quartana, et al., 2013), CSI scores and widespread pain distribution (Coronado & George, 2018), as well as symptomatic flares in IBD (Charles N Bernstein et al., 2010).

Affective styles have demonstrated psychometric independence (Watson et al., 1988), where the absence of one does not necessarily reflect the presence of the other. Furthermore, an investigation in patients with osteoarthritis showed distinct differences in dispositional affect (i.e. trait) compared to situational affect (i.e. state) in response to clinical and experimental pain (Finan, Quartana, et al., 2013). Additionally, investigations in chronic pain populations have challenged the common preoccupation in research and clinical practice for assessing and treating negative affect style over positive effect (Strand et al., 2007; Zautra, Johnson, & Davis, 2005). These investigations demonstrated a strong association between positive affect and pain resilience in pain populations (Strand et al., 2007; Zautra et al., 2005). Therefore, it would appear that not only are positive and negative affect styles distinct dimensions

within this construct, their temporal behaviour and effect outcomes are also understood to be distinct requiring independent consideration.

3.2.4.4 Pain catastrophizing

Catastrophizing has been described as negative cognitive and affective responses to pain that includes elements of magnification, helplessness, pessimism, and focused attention on pain (Michael JL Sullivan et al., 2001). The literature indicates that the tendency to "catastrophize" during painful experiences is related to worse pain perceptions and increased emotional distress (Michael JL Sullivan et al., 2001). Similarly, significantly greater pain catastrophizing, alongside increased sensitivity in QST testing, has been demonstrated in individuals with chronic low back pain compared to healthy controls (Meints et al., 2019). Interestingly, a high degree of pain catastrophizing in chronic pain individuals demonstrated an association to increased serum inflammatory markers in response to experimental pain, when compared to health controls (Lazaridou et al., 2018). This general effect suggests that inflammatory responses to acute pain in persistent pain patients may be selective to those with greater catastrophizing thoughts.

The relationship between catastrophizing and pain experiences has shown remarkable consistency across a wide range of pain populations (Quartana et al., 2009; Michael JL Sullivan et al., 2001), including mixed chronic pain (Michael J Sullivan & D'Eon, 1990), low back pain (Flor, Behle, & Birbaumer, 1993), and rheumatoid arthritis (Keefe, Brown, Wallston, & Caldwell, 1989). Robust associations have been described between high level catastrophizing and worse pain-related measures, such as severity, interference, disability, and depression (Quartana et al., 2009). Longitudinal investigations found that higher baseline pain catastrophizing was associated with an increased risk of worse pain reports at 12 months in patients with osteoarthritis

(Edwards, Haythornthwaite, Smith, Klick, & Katz, 2009) and rheumatoid arthritis (Covic, Adamson, Spencer, & Howe, 2003). A prospective study in rheumatoid arthritis found that initial levels of catastrophizing predicted perceived disability scores in patients at 6 months, even after controlling for age, gender, illness duration, and initial perceived disability (Keefe et al., 1989).

Research exploring catastrophizing and pain is largely based on the premise that catastrophizing is causally linked to worse pain experiences, or at least precedes painful experiences (Michael JL Sullivan et al., 2001). As such, less consideration has been given to the influences that pain experiences may have on the initial development of catastrophic thinking (Quartana et al., 2009; Michael JL Sullivan et al., 2001). Additionally, the literature describes ongoing controversy around whether catastrophizing is a dispositional (trait) or a situational (state) psychological feature (Quartana et al., 2009; Michael JL Sullivan et al., 2001). Earlier perceptions regarding catastrophizing viewed it as a highly modifiable and situationally-specific cognition, whereas more contemporary perspectives suggest this modifiability does not negate catastrophizing as a trait, but rather that it is moderated by additional factors and may demonstrate a treatment response (Quartana et al., 2009; Spanos, Stam, & Brazil, 1981; Michael JL Sullivan et al., 2001; Vallis, 1984).

3.2.5 Study Methodologies

As previously stated, there are numerous methodologies which could have been used to investigation the current research question and stated reseach aims, to included both qualitative and quantitative methodologies. However, current literature suggests that quantitative designs may represent the best approach for the objective assessment

of the research domains identified above (Arendt-Nielsen et al., 2012; Arendt- Nielsen et al., 2018; Catalano et al., 2017; Koop et al., 2015; S. M. Smith et al., 2017; Wu et al., 2013). Therefore, exploration of persistent MSK pain in the current thesis includes two primary studies, which utilized quantitative methodologies, including: subgrouping-based analysis (Study 1, Chapter 5), mediation analysis (Study 1, Chapter 6), and classic regression-based modelling (Study 2, Chapters 8 and 9) to perform hypothesis testing. Of these methodologies, subgrouping and mediation analyses present with greater complexity and controversy regarding their application and interpretation. As such, an overview of these two models with recommendations from statistical literature is presented below.

3.2.5.1 Subgroup-based model

Bergman and Magnusson (Bergman & Magnusson, 1997) have described an important distinction in statistical methods used to explore human processes and development. Authors describe two fundamental paradigms as *variable-oriented* approaches or *person-oriented* approaches. Variable-oriented approaches aim to identify relationships between observed variables, with the assumption that these relationships apply to all individuals in a population (Bergman & Magnusson, 1997). The difficulty of variable-oriented research lies in translating findings into statements about individuals, not simply the variables (Bergman & Magnusson, 1997). This has led to an interest in person-oriented approaches, where the focus is the individual as a whole. As Bergman and Magnusson (Bergman & Magnusson, 1997) noted: *"Operationally, this focus often involves studying individuals on the basis of their patterns of observed characteristics that are relevant for the problem under consideration"*. However, these authors acknowledge that the goal is not simply to study individuals but to evaluate variable presentation within individuals in order to

draw broad conclusions and identify important constructs within a population (Bergman & Magnusson, 1997). Person-oriented approaches that have gained in popularity are subgrouping-based statistical models, such as k-means cluster and latent class analyses (LCA) (Bergman & Magnusson, 1997; L. M. Collins & Lanza, 2013).

A strength of subgroup-based models relates to the understanding that human processes, whether social, behavioural, or biological in nature, evolve over time (Nagin & NAGIN, 2005). Efforts to understand the developmental pathway of these processes have long been the focus of research efforts in the health sciences: for instance, to evaluate the impact of treatments on the progression of diseases (Nagin & NAGIN, 2005). However, a common challenge is that human processes often have multiple yet distinct developmental pathways, which are not identifiable based on individual characteristics, such as age or gender (L. M. Collins & Lanza, 2013; Nagin & NAGIN, 2005). Consequently, the aims of many research endeavours have focused on identifying distinct subgroups within a condition, by exploring what factors account for their distinctiveness (L. M. Collins & Lanza, 2013; Nagin & NAGIN, 2005).

Common subgrouping approaches used in health research include finite mixture modelling (e.g. LCA and latent transition analysis) or cluster analyses (e.g. hierarchical and k-means). Although several unique complexities exist within and between these two categories of subgroup-based analyses, a few key differences are described here. One of the main differences between finite mixture modelling and other clustering algorithms relates to how subgroups are identified. In models, such as LCA, subgroups are derived using a probabilistic model that describes the distribution of the data (L. M. Collins & Lanza, 2013). This allows the researcher to assess the probability of a patient belonging to a particular subgroup (L. M. Collins & Lanza, 2013). A strength of probabilistic approaches, such as LCA, means that patients are not fully assigned to a

subgroup, but rather allow for the uncertainty of some individuals to present with overlapping traits characteristic of more than one subgroup.

Conversely, cluster analyses involve algorithms which identify subgroups by partitioning variables that statistically exist in relatively close proximity to each other (Eshghi, Haughton, Legrand, Skaletsky, & Woolford, 2011). Unlike LCA, subgroups identified by cluster analyses are based on a predetermined, yet arbitrary, statistical distance between observed variables. This type of subgrouping often creates clear and compact subgroups by assigning individuals to one subgroup, regardless whether they demonstrate traits characteristic of differing subgroups. Additionally, clustering algorithms typically benefit from an assumed number of subgroups, whereas LCA can be used to explore data where a strong *a priori* hypothesis regarding the number or nature of subgroups does not exist (Hoijtink, 2001). In such cases, LCA allows several proposed models to be fit to the data, in order to later compare and determine which model best corresponds to the observed population (Finch & Bronk, 2011).

The different subgroup-based approaches require assumptions to be made about the distribution of the observed variables in the population (Nagin & NAGIN, 2005). Cluster analyses assume that the observed variables are continuously distributed throughout a population, according to the multivariate normal distribution (Nagin & NAGIN, 2005). Conversely, LCA utilizes categorical variables, where strict normality distributional assumptions are unnecessary (L. M. Collins & Lanza, 2013). This is particularly useful when individuals in a population present with different scoring patterns of observed variables where, for instance, some individuals may score high on one variable and low on another, while others may have the opposite scoring patterns (Kongsted & Nielsen, 2017).

Since the 1960s the conceptual and mathematical composition of LCA has evolved, including the development of reliable methods for obtaining model parameters (L. M. Collins & Lanza, 2013). Conceptually, LCA identifies a construct, or latent variable, by which subgroups are derived (L. M. Collins & Lanza, 2013). Here the construct itself is not directly measured as an independent variable, but is conceptualized through the assessment of observed variables, commonly referred to as *indicators* of the construct (L. M. Collins & Lanza, 2013). It is important to note that in LCA, the causal flow is understood to be from the construct to the indicator variables, not the other way around (L. M. Collins & Lanza, 2013). As such, the observed indicator variables measure the construct, but the observed indicator variables do not cause the construct (L. M. Collins & Lanza, 2013).

Within many pain conditions, such as fibromyalgia, osteoarthritis, chronic pelvic pain, and rheumatoid arthritis, multiple clinical features and patient characteristics are active to varying degrees in different individuals (Davis, Binik, Amsel, & Carrier, 2013; de Luca, Parkinson, Downie, Blyth, & Byles, 2016; Draper et al., 2012; Dworkin et al., 2005; Edwards et al., 2016; Rehm et al., 2010; Verra et al., 2009). Efforts to contextualize pain in these chronic conditions has led to investigations utilizing subgrouping-based analyses to explore complex interactions of such features in order to identify distinct patient profiles (de Luca et al., 2016; Y. C. Lee et al., 2014; Loevinger, Shirtcliff, Muller, Alonso, & Coe, 2012; Rehm et al., 2010). The ability to describe unique subgroups in this manner not only allows for a deeper understanding and context of potential pain mechanisms in patient populations, it also subsequently aids in the identification of targeted treatment strategies (de Luca et al., 2016; Edwards et al., 2016). However, unlike other chronic conditions, to date, there have been no investigations utilizing subgroup-based modelling to explore the scope of MSK-related

pain experiences in IBD. Therefore, as current IBD literature is unable to suggest the number and/or nature of MSK pain subgroups, the use of cluster analyses may be less useful. As such, the exploratory nature of present thesis investigations is most suited for finite mixture modelling, such as LCA.

3.2.5.2 Mediation analysis

Investigation of the process or mechanism by which an independent variable affects another dependent variable is a common method of hypothesis testing reported in current literature (Baron & Kenny, 1986; Hayes, 2009; MacKinnon, Fairchild, & Fritz, 2007). Although there are multiple methods of performing such hypothesis testing, the cornerstone of this analysis typically includes exploration of how a third variable affects the relationship between two such variables (Baron & Kenny, 1986; Hayes, 2009; MacKinnon et al., 2007). The third variable in these analyses are typically identified as having a moderator or mediator effect on the dependent variable. A moderating variable is one that affects the direction and/or strength of the relation between the independent and dependent variable (Baron & Kenny, 1986). Conversely, mediators are identified as: *"behavioral, biological, psychological, or social constructs that transmit the effect of one variable to another variable"* (MacKinnon et al., 2007).

Generally speaking, mediation analysis can be used to explore both experimental and observational data (Imai, King, & Stuart, 2008). Although somewhat overlapping in application, the purpose and interpretation in these two designs are distinct (Imai et al., 2008). Experimental studies typically aim to understand the treatment effects of the mediator as an intervention on the outcome (MacKinnon et al., 2007). Conversely, observational studies aim to explore theories as to how an independent variable affects a dependent variable by providing empirical evidence of mediating causal pathways (Imai et al., 2008; MacKinnon et al., 2007).

Of the mediation models reported, the *causal steps approach* made popular by Baron and Kenny (Baron & Kenny, 1986) has traditionally been the most widely-used model in research (Hayes, 2009; MacKinnon & Fairchild, 2009). However, this method of performing mediation analysis has received significant criticism, namely for its notable underperformance in simulation studies to detect mediating effects (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). Further, unlike the Baron and Kenny model which relies on examining multiple model pathways to infer the possibility of a mediating effect (Baron & Kenny, 1986), other methods, such as the Sobel test and bootstrapping, directly examine mediating pathways (Hayes, 2009). Of these two methods, bootstrapping, which uses resampling processes to generate an empirical representation of the mediating effect, has grown in popularity (Hayes, 2009).

Current literature indicates that the spectrum of mediation models continue to be utilized in causal hypothesis testing. The classic *causal steps approach* is still considered popular in current literature, including recent IBD investigations (Chouliaras et al., 2018). However, modernized statistical methods, such as the Sobel test (Freitas et al., 2015) and bootstrapping (Reed-Knight, Lee, Greenley, Lewis, & Blount, 2016; Sanne JH van Erp et al., 2017), have also been used to detect mediation in several cross-sectional IBD investigations. A systematic review with meta-analysis reporting on mediation studies in back and neck pain, indicated that the majority (7 out of 12) of included studies utilized a combination of Baron and Kenny's causal steps approach and Sobel's test of significance, with only 2 studies using bootstrapping analysis (H. Lee et al., 2015).

Despite the broad application of mediation analysis throughout current literature, simulation studies have demonstrated that bootstrapping is one of the more valid and powerful methods for directly testing mediating effects (MacKinnon,

Lockwood, & Williams, 2004). Therefore, mediation analyses included in the current thesis utilize the Baron and Kenny (Baron & Kenny, 1986) *causal steps approach* to illustrate associations of individual pathways within the model, while using bootstrapping to determine overall significance of the model through direct examination of mediating pathways (Hayes, 2009).

3.3 Chapter Summary

The current chapter presented an overview of primary domains used to explore persistent MSK pain in the present thesis. Additionally, this chapter reviewed methodologies of interest with implications for use in Study 1 (Chapters 4-6). The following chapter presents the protocol for Study 1: Profiles of Self-reported MSK Pain in IBD Patients.

4 Study One: A National Survey of Self-reported MSK Pain in Individuals with IBD – Study Protocol

4.1 Chapter overview

Review of the literature highlights the potential for multiple pain mechanisms, notably central sensitization, in the maintenance of persistent MSK pain in patients with IBD. However, previous investigations exploring MSK pain in IBD have not included an exploration of mechanisms beyond traditional inflammatory nociceptive models. As such, Study 1 of the present thesis aimed to investigate self-reported MSK pain in IBD in order to better characterize the nature, influences, and mechanisms contributing to persistent painful experiences. Study 1 of the present thesis includes a primary study aim to explore mechanism-based profiles of MSK pain in IBD (Chapter 5), and a sub-analysis aimed to investigate predictive and causal relationships between predominate features identified during the primary study analysis (Chapter 6).

The following chapter presents the full protocol for Study 1: A national survey assessing the multidimensional experience of self-reported MSK pain in adults with IBD living in New Zealand. Statistical analysis, results, and discussion of the primary and sub-analysis aims of Study 1 are presented in Chapters 5 and 6, respectively.

4.2 Background

Although potential for shared pathways have been proposed in the maintenance of MSK pain in IBD (Chapter 2), the multifactorial nature of these painful conditions is not well understood nor fully captured through standard investigations (Bielefeldt et al., 2009; Conigliaro et al., 2016; Zeitz et al., 2016). Population-based surveys have

described significant diversity in MSK pain in IBD, with reports of fluctuating and varying patterns of presentation (van der Have et al., 2015; S. Van Erp et al., 2015; Zeitz et al., 2016). While MSK pain in IBD is reported to be influenced by multiple clinical features of pain and disease (S. Van Erp et al., 2015; Vavricka et al., 2015), the scope and contribution of these features to pain experiences has not been investigated in this population.

The use of mechanism-based classification to explore the differing and potentially overlapping contributions of diverse pathophysiological mechanisms to MSK pain experiences has been presented (Chapter 3). However, studies investigating MSK pain in IBD rarely assess features, such as pain quality (de Luca et al., 2016; Schirbel et al., 2010), which has been previously been useful in identifying pain mechanism in clinical populations (Edwards et al., 2016; Jensen, 2006; Victor et al., 2008). As such, the use of mechanism-based assessments of MSK pain in IBD is indicated, where pain is characterized according to the dominant pain mechanism, including nociceptive pain, peripheral neuropathic pain, and 'central sensitization' pain (Nijs et al., 2014; Smart, Blake, et al., 2012a; Clifford J Woolf, 2011).

Current literature suggests that exploring profiles of MSK pain through subgroup-based analysis, such as latent class analysis (LCA) (Chapter 3), may provide a deeper understanding of pain experiences through consideration of identified pain mechanisms in relation to patient features (i.e. IBD, demographic, comorbidity, and pain) (de Luca et al., 2016; Edwards et al., 2016; Jensen, 2006; Clifford J Woolf, 2011). Additionally, the ability to describe unique patient profiles in this manner would not only provide empirical evidence for pain mechanisms active in this population, but also inform the development of targeted treatment strategies, leading to improved patient outcomes (de Luca et al., 2016; Edwards et al., 2016).

As previously described (Chapter 2), the predictive relationship between active IBD and the presence of certain MSK conditions is well documented in current literature (Brakenhoff et al., 2011; Vavricka et al., 2015). However, whether IBD activity influences MSK pain experiences (e.g. severity and interference) has received little attention. Similarly, although the presence of central sensitization has been proposed in theoretical models for chronic abdominal and post-surgical pain in IBD patients, the role of central sensitization leading to worse MSK pain experiences has not been considered. As presented in Chapter 3, exploration for how variables such as these are potentially linked, while assessing the significance of these links, is a common goal of mediation analysis.

4.3 Study Aims

4.3.1 Primary aims

- To investigate profiles, or subgroups, of self-reported MSK pain in individuals with IBD through LCA, exploring features of pain (location, intensity, quality, and interference), IBD (abdominal pain, IBD activity, and health-related quality of life (HRQOL)), and central sensitization symptomology (i.e. central sensitization inventory (CSI)).
- To investigate differences between subgroups with respect to patient characteristics, including demographics, comorbidity, and IBD (subtype and IBD course).

4.3.2 Sub-analysis aims

- To investigate the predictive relationship between IBD activity and MSK pain experiences (severity and interference).

- To investigate the mediating effects of CSI scores between IBD activity and MSK pain experiences.

4.4 Study Hypotheses

4.4.1 Primary hypothesis

It was hypothesized that the exploration of multiple patient features through LCA will demonstrate distinct subgroups related to MSK pain, IBD, and central sensitization symptomology. It is further hypothesized that patient characteristics (i.e. demographics, comorbidity, and IBD features) will differ between subgroups.

4.4.2 Sub-analysis hypothesis

It was hypothesized that active IBD is predictive of worse MSK pain experiences, mediated by greater symptoms of central sensitization (i.e. higher CSI scores).

4.5 Methods

4.5.1 Research Design

Alongside Māori consultation, the present cross-sectional survey was granted ethical approval by the University of Otago Human Ethics Committee (Health) (approval number - H17/095), in accordance with the Declaration of Helsinki (Appendix A and B).

4.5.2 Participants

Individuals with self-reported previous IBD diagnosis aged 18 years and older were invited to participate in an online survey. Investigation of self-reported medical history demonstrated that IBD patients are able to accurately report ($\kappa = 0.96–0.97$)

their medical history regarding type of disease through online investigations (Kelstrup, Juillerat, & Korzenik, 2014; Randell et al., 2014). Invitation to participate in the current study was through the email database of Crohn's and Colitis New Zealand Charitable Trust, and additional social media outlets associated with: IBD research groups, New Zealand health forums, patient support groups, and practitioner resource groups (Appendix C). Crohn's and Colitis New Zealand is a national organisation that provides support, advice, and information to individuals suffering from IBD.

All participants were provided with detailed information related to the study and signed an online consent form to participate (Appendix D and E). Participants were excluded if they reported any of the following: pregnancy, nerve injuries, neurological conditions (e.g. stroke, multiple sclerosis, peripheral neuropathy, and Parkinson's disease), and surgery within the last 3 months.

4.5.3 'New Zealand IBD Aches & Pains' Survey

4.5.3.1 Survey development

The present online survey (Appendix F) included validated questionnaires identified in current literature used in the assessment of IBD, pain, and similar chronic inflammatory conditions. The survey included three sections: 1) demographics and comorbidity, 2) IBD status, and 3) pain status. To improve comprehension of the overall survey, the order of administration for included questionnaires was standardized; however, skip patterns were utilized within the survey to direct participants toward relevant questionnaires corresponding to individually reported IBD and pain features. Details regarding constructs assessed in each of the survey sections are presented in Chapter 3. Measures used to assess these constructs are listed in Table 4.1 and described below.

Table 4.1

Measures used to Evaluate Disease and Pain Features in the New Zealand IBD Aches & Pains Survey

Domain	Outcome/Measure
Section 1: Demographics and comorbidity	
Demographics	Age
	Gender
	Ethnicity
Comorbidity	Self-Administered Comorbidity Questionnaire
	Extra-intestinal manifestation checklist
	Central Sensitization Inventory
Section 2: IBD status	
IBD subtype	Crohn's disease
	Ulcerative colitis / indeterminate colitis
IBD activity	Patient Harvey Bradshaw Index
	Patient Simple Clinical Colitis Activity Index
HRQOL	Short Inflammatory Bowel Disease Questionnaire
IBD features	Presence of abdominal pain
	Number of hospitalizations
	Number of surgeries
	Current medications
Section 3: Pain status	
Musculoskeletal	
Location	Body map
Severity	Numeric rating scale
Interference	PROMIS Pain Interference 4a
Quality	PainDETECT
	PROMIS Nociceptive Pain Quality 5a
Abdominal	
Severity	Numeric rating scale
Interference	Numeric rating scale

Notes. Inflammatory bowel disease (IBD), health-related quality of life (HRQOL), and Patient-Reported Outcomes Measurement Information System (PROMIS).

4.5.3.2 Expert consensus

Expert consensus for face and content validity of the present survey was conducted by four experienced clinicians/researchers in the fields of gastroenterology and chronic pain. Experts were asked to provide feedback on respective constructs used to evaluate stated IBD and pain domains. Experts (1, 2) in the field of gastroenterology

demonstrated 100% agreement for all consensus questions, with the exception of one recommendation (Expert 2) regarding the inclusion of an additional variable evaluating the severity of IBD course. Experts (3, 4) in the field of chronic pain similarly demonstrated 100% agreement for all consensus questions, with exception of one recommendation (Expert 3) regarding evaluation of an additional dimension of pain in the present survey.

4.5.3.3 Pilot testing

Pilot testing was performed on individuals with IBD, with a sample of convenience (n = 6). Pilot testing evaluated the feasibility of the present survey, including 1) time to complete, 2) overall clarity, and 3) ease of survey completion. Time to complete was calculated from 4 pilot testers, as 2 reported computer interruptions during testing. Average time to complete was 12:46 (min:sec), ranging from 8:23-15:13 (min:sec). Mean survey clarity was 8.40 (0 = unclear, 10 = very clear), and mean ease of completion was 9 (0 = difficult, 10 = very easy).

Participants identified through social media outlets were directed to the present study's primary webpage, with an associated information sheet, informed consent details, and hyperlink to the survey (Appendix E). Participants identified through Crohn's and Colitis New Zealand's email database were sent reminder emails at three and seven weeks following the initial invitation email, with a total of 12 weeks for data collection (Hoddinott & Bass, 1986).

4.5.4 Survey Section 1: Demographics and comorbidity

Participant demographics included: age, gender, and ethnicity. Comorbidities assessed in the present study included health conditions identified on the Self-Administered Comorbidity Questionnaire (Sangha, Stucki, Liang, Fossel, & Katz,

2003), extra-intestinal manifestation (EIM) checklist (described under IBD section), and conditions identified on part B of the CSI.

Use of CSI as an indirect measure of central sensitization has been validated (AUC= 0.86, Sensitivity = 81%, Specificity = 75%) in a large population study in patients with central sensitivity syndromes (Mayer et al., 2012; Neblett et al., 2013). CSI (part A) evaluates 25 features across an array of somatic and emotional symptoms, with each item scored on a scale of 0 to 4, and overall scoring ranging from 0 to 100 (Neblett, Hartzell, Mayer, et al., 2017). Higher CSI scores indicate increased symptomology related to central sensitization, with scores ≥ 40 indicating the likely presence of central sensitivity syndromes (Mayer et al., 2012; Neblett et al., 2013).

4.5.5 Survey Section 2: IBD status

Indicators of IBD status included in the present study were: IBD subtype, IBD activity, health-related quality of life (HRQOL), and clinical features (number of hospitalizations and surgeries, current medications, and EIM status).

4.5.5.1 IBD activity

IBD activity in the present survey was evaluated by the patient Harvey Bradshaw Index (P-HBI) for Crohn's disease and patient Simple Clinical Colitis Activity Index (P-SCCAI) for ulcerative colitis. P-HBI assesses five variables (general well-being, the severity of abdominal pain, number of liquid stools, presence of abdominal mass, and presence of complications) where scoring is based on symptoms from the previous day (Evertsz, Hoeks, et al., 2013; Walsh et al., 2016). The P-HBI is reported to highly correlate with the clinician administered HBI, with moderate to large agreement between clinicians and patients, and significant positive predictive value (96%) for identifying disease remission (Evertsz, Hoeks, et al., 2013).

The widely used clinician administered SCCAI demonstrated good to excellent psychometric and performance validity for detecting disease activity in ulcerative colitis (Higgins et al., 2007). The patient administered SCCAI (P-SCCAI) demonstrated substantial agreement (87%, κ=0.66) with the clinician administered SCCAI (Evertsz, Nieuwkerk, et al., 2013). P-SCCAI assesses six variables (daytime bowel frequency, night-time bowel frequency, blood in stool, general well-being, the urgency of defecation, and extra-colonic features) where scoring is based on symptoms from the previous week (Evertsz, Nieuwkerk, et al., 2013). Both P-SCCAI and P-HBI identify disease remission as scores of ≤ 4 (Evertsz, Nieuwkerk, et al., 2013; Walsh et al., 2016).

4.5.5.2 Severity of disease course

Based on recommendations reported in the literature, the best practice to indicate disease severity includes evaluation of HRQOL and aspects of IBD course (Peyrin-Biroulet et al., 2016; Walsh et al., 2016). In the present survey, HRQOL was assessed through the validated Short IBD Questionnaire (SIBDQ) (E. Irvine, Zhou, & Thompson, 1996; Peyrin-Biroulet et al., 2016). SIBDQ demonstrated significant retest reliability (ICC = 0.65, Cronbach's α = 0.78) with ability to detect clinically meaningful changes in HRQOL through the assessment of five heath dimensions (bowel symptoms, systemic symptoms, functional impairment, social impairment, and emotional function) (E. Irvine et al., 1996). SIBDQ scoring is interpreted as poor (10-29), moderate (30-49), and optimal (50-70) (E. Irvine et al., 1996; Peyrin-Biroulet et al., 2016).

Assessment of disease course in the present study includes self-reports for: hospitalizations, surgical interventions, medications, and EIM status (Peyrin-Biroulet et al., 2016; Siegel et al., 2016). Medications were recorded under the following categories: immunosuppressant, biologic, gut-specific anti-inflammatory, and steroids.

EIM status was evaluated through a 20-item checklist developed from multiple EIM investigations, to include the European Crohn's and Colitis Organisation Guidelines developed from expert consensus (Marcus Harbord et al., 2016; Huang, Mishra, Thanabalan, & Nguyen, 2013; Levine & Burakoff, 2011; Trikudanathan et al., 2012).

4.5.6 Survey Section 3: Pain status

MSK Pain dimensions evaluated in the present study included: location, severity, interference, and quality (nociceptive and neuropathic pain qualities). A body diagram demarcating 47 different body regions was used in the present study to record regional pain location and distribution, which previously demonstrated significant test-retest reliability (r=0.85) in chronic pain patients (Margolis, Chibnall, & Tait, 1988; S. Van Erp et al., 2015; Zeitz et al., 2016). This diagram was developed from recommendations regarding MSK conditions in IBD (S. J. van Erp et al., 2016; Zeitz et al., 2016) and investigations reporting the use pain drawing instruments (Margolis et al., 1988). Generalized pain was distinguished from regional pain using the modified widespread pain criterion which requires an individual to report pain in 4 out of 5 pain regions (4 quadrants plus axial pain) (Wolfe et al., 2016).

In the event that multiple painful regions were identified, participants were asked to nominate their 'main area of pain'. Pain severity was then evaluated as "the strongest pain during the past 4 weeks", solely for the regions identified as the 'main area of pain', using a numerical rating scale (NRS), with positive findings as mild (1-4), moderate (5-6), or severe (7-10) (Williamson & Hoggart, 2005). Evaluation of pain interference and nociceptive pain quality in the present survey were evaluated through Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference 4a and Nociceptive Pain Quality 5a short forms (Gershon, Rothrock, Hanrahan, Bass, & Cella, 2010). PROMIS short forms, developed by the National

Institutes of Health, have undergone extensive qualitative expert and patient review, as well as quantitative analysis of data collected on general populations and clinical samples (Gershon et al., 2010). Scoring of PROMIS short forms identify findings as: mild (50-59), moderate (60-69), or severe (≥70).

The presence of neuropathic pain quality was evaluated through PainDETECT, which has previously demonstrated significant sensitivity (85%), specificity (80%), and a positive predictive value (83%) for differentiating nociceptive from neuropathic pain, as well as identifying the contribution of neuropathic pain to overall pain experiences (Freynhagen, Baron, Gockel, & Tölle, 2006). PainDETECT identifies neuropathic pain through evaluation of three pain dimensions including: gradation of pain, pain course pattern, and radiating pain with possible scores ranging from 0 to 38 (Freynhagen et al., 2006). Interpretation of PainDETECT scores identify neuropathic components as likely (≥ 19), unlikely (≤ 12), and unclear (13-18) (Freynhagen et al., 2006).

Secondary evaluation of abdominal pain was also included in the present study. Abdominal pain was characterized through dimensions of intensity and interference, measured by NRS for both items. Positive findings for abdominal pain intensity and interference are identified as mild (1-4), moderate (5-6), or severe (≥7) (Williamson & Hoggart, 2005).

4.5.7 Sample Size Estimation

Sample size estimation for Study 1 was determined based on recommendations from current literature regarding LCAs (Chapter 5) and mediation-based analyses (Chapter 6). Current literature regarding subgrouping-based analyses offers no straightforward guidelines about the minimum nor maximum sample size necessary for

LCAs (Wurpts & Geiser, 2014). However, supporting evidence exists for a minimum sample size of $N = 200$ with respect to the number of present indicator variables and use of a medium to strong covariate (Finch & Bronk, 2011; Gudicha, Tekle, & Vermunt, 2016). Similarly, current literature recommends a sample size of $N = 150$ to 200 required to detect mediating effects in the absence of type-II errors (Fritz & MacKinnon, 2007). Therefore, minimum sample size estimate for both the primary aims and sub-analysis of Study 1 was 200 participants.

4.6 Chapter summary

This chapter presented the full protocol for Study 1 of the present thesis, aimed at exploring self-reported MSK pain in IBD. Results and discussion for the primary aim and sub-analysis of Study 1 are present in Chapters 5 and 6, respectively.

5 Study One: Profiles of Musculoskeletal Pain in Individuals with IBD

5.1 Chapter overview

Chapter 4 presented the full protocol for Study 1 aimed at exploring self-reported MSK pain in individuals with IBD. The following chapter presents the statistical analysis, results, and discussion related to the primary aims of Study 1.

5.2 Primary Study Aims

- To investigate profiles, or subgroups, of self-reported MSK pain in individuals with IBD through latent class analysis (LCA), exploring features of pain (location, intensity, quality, and interference), IBD (abdominal pain, IBD activity, and health-related quality of life (HRQOL)), and central sensitization symptomology (i.e. central sensitization inventory (CSI)).
- To investigate differences between subgroup with respect to patient characteristics, including demographics, comorbidity, and IBD (subtype and IBD course).

5.3 Hypothesis

It was hypothesized that the exploration of multiple patient features through LCA will demonstrate distinct subgroups related to MSK pain, IBD, and central sensitization symptomology. It was further hypothesized that patient characteristics (i.e. demographics, comorbidity, and IBD features) will differ between subgroups.

5.4 Data Reduction

Data collected during the present study was used to quantify variables used in LCA, including latent class indicators, potential latent class covariates, and external variables. As stated in Chapter 4, essential datasets for the present study required completion of all components related to the internal latent class variables. This includes all components necessary to calculate individual questionnaire scoring (e.g. PainDETECT and CSI) as well as composite scores (e.g. generalised pain). As such, LCA variables were characterized directly from raw data, scores from individual measures, or criteria identified from composite data. Measures used to characterize LCA variables is presented in Table 4.1, with parameters for each categorical variable defined in their respective subheadings in Chapter 4.

Categorical indicator variables utilized in the present study included: strongest pain severity, average pain severity, pain interference, generalized pain, neuropathic quality, nociceptive quality, CSI, IBD activity, and presence of abdominal pain. The use of categorical indicators reflects the clinical utility of variables, such as IBD activity, whereby assessment scores are typically interpreted as active versus not active, as opposed to continuous values. Variables considered for covariate analysis included: IBD subtype and HRQOL (i.e. short inflammatory bowel disease questionnaire (SIBDQ)). The variable(s) not utilized as a covariate was included in the list of external variables used to explore differences between subgroups. External variables included: gender, age, number of extra-intestinal manifestations (EIMs), total comorbidity score, hospitalizations, surgeries, and current medications.

To clarify: n=54 participants were excluded for incomplete survey responses, which was defined (page 71) in the thesis as: “Essential datasets for the present study were identified as completion of all components related to internal latent class variables

identified above." As presented in the methodology (Section 5.4), these variables included composite scores of individual questionnaires (e.g. CSI and PainDETECT). Therefore, participants had to complete all of questions pertaining to the individual questionnaires in order for the composite to be calculated and defined for each variable (Data reduction for latent class indicator variables is outlined in Section 5.4). As such, individuals that did not complete these questionnaires thereby negating the ability to calculate overall composite scores were exclude.

5.5 Statistical Analysis

Descriptive statistics (frequencies, means, and standard deviations (SD)) were used to characterize demographic, comorbidity, IBD, and pain characteristics of study participants. LCA was performed in two stages using R statistical software. Initial LCA was used to identify models with 1 to 6 subgroups (or classes) across the sample using indicator variables quantified during data reduction. Model fit was assessed using model fit statistics (Akaike information criterion (AIC) and Bayesian information criterion (BIC)), the goodness of fit G^2 which follows a chi-squared distribution, and model entropy (L. M. Collins & Lanza, 2013). Lower values for information criteria and higher values for G^2 and entropy between models suggest models with optimal balance between fit and parsimony (L. M. Collins & Lanza, 2013). Interpretability was also considered along with fit statistics when selecting the final model. Further assessment of the final model included average posterior probabilities and classification error. Average posterior probabilities ≥ 0.70 (L. M. Collins & Lanza, 2013) and classification error ≤ 0.10 were considered acceptable. Participants were assigned class membership based on their highest posterior probability. Chi-squared tests were used to identify a covariate with significant association ($p \leq 0.05$) with the final model. A subsequent LCA was then performed using the final model and the identified covariate

to predict indicator class membership. Conditional item probabilities of indicator variables reaching ≥ 0.500 were used to characterise each latent class (L. M. Collins & Lanza, 2013).

Subgroup profiling of the identified latent classes was performed to further describe the association of internal variables (indicators and covariate) unique to each class. Additionally, investigation of between class differences for external variables was performed. Chi-squared tests of association (dichotomous variables) and one-way analyses of variance (ANOVAs)/Kruskal-Wallis ANOVAs (continuous variables) were used to investigate between class differences for both internal latent class variables, as well as external demographic and comorbidity variables. Univariate logistic regression analysis was used to explore the association of individual comorbidities (independent variable) with latent class membership (dependent variable). Where Peduzzi's criteria for sample size allowed, variables demonstrating significance ($p \leq 0.05$) were adjusted for the confounding effects of age, gender, and IBD subtype (Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996). A confounder is understood to be a variable which may falsely accentuate the relationship between two factors of interest (MacKinnon, Krull, & Lockwood, 2000). As such, adjustment for potential confounders aims to provide an undistorted estimate of the relationship between the independent and dependent variables (MacKinnon et al., 2000). Assumptions for ANOVA and regression models were assessed where appropriate to ensure model fit, including: normality of scoring distribution (Shapiro-Wilk tests, significance ≤ 0.05)), collinearity diagnostics (variance inflation factor < 10 with tolerance > 0.2), and homoscedasticity (scatterplot of residuals).

5.6 Results

Results of this study are presented in two sections. The first section presents descriptive statistics for participant characteristics (demographics, IBD, and pain). The second section presents the results of the LCA and comparative analysis of the subgroup profiles.

5.6.1 Participant characteristics

5.6.1.1 Demographics

A total of 370 individuals with IBD volunteered to participate in the online survey. Eleven respondents were excluded due to minimum age requirements. An additional 54 respondents were excluded due to incomplete survey response. Essential datasets for the present study were identified as completion of all components related to internal latent class variables identified above. The remaining 305 respondents were included as study participants. Demographics for the excluded participants are presented in Table G.1 (Appendix G). Demographics (age and gender), IBD subtype, comorbidity, and CSI scores of study participants are presented in Table 5.1. Of the 305 participants, 201 (66%) individuals reported IBD subtype as Crohn's disease, 94 (31%) reported ulcerative colitis, and 10 (3%) reported indeterminate colitis. Participants in the study represented the following ethnic groups: New Zealand European (n=274), Maori (n=18), Indian (n=4), English (n=5), Australian (n=5), North American (n=4), Fijian (n=3), Dutch (n=2), Scottish (n=1), German (n=1), South African (n=2), Croatian (n=1), and other European (n=1).

Table 5.1

Demographic and Comorbidity Data

Characteristic	IBD (*N* = 305)	CD (*N* = 201)	UC/IC (*N*= 104)
Gender			
Male, *n* (%)	61 (20.1)	36	25
Female, *n* (%)	241 (79.3)	165	76
Gender diverse, *n* (%)	2 (0.7)	0	2
Age			
Range (years)	18-88	18-88	24-79
Mean (SD)	43.86 (14.76)	42.23 (14.65)	47.01 (14.52)
Comorbidity			
Total comorbidity			
Range (*n*)	0-8	0-8	0-5
Mean (SD)	1.85 (1.52)	1.92 (1.51)	1.70 (1.53)
CSI			
Range	3-82	9-82	3-76
Mean (SD)	43.79 (14.74)	44.91 (14.50)	41.40 (14.87)

Note. Inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), indeterminate colitis (IC), standard deviation (SD), and central sensitization inventory (CSI).

5.6.1.2 IBD status

Results from questionnaires assessing aspects of IBD status in this study are presented in Table 5.2. Of the participants who reported Crohn's disease (n=201), 4 indicated the presence of an ileostomy and therefore were unable to utilize the patient Harvey Bradshaw Index (P-HBI), which requires evaluation of bowel habits not assessable in patients with intestinal stomas. Consequently, the results of the P-HBI to indicate disease activity are reported for the remaining 197 participants with Crohn's disease.

Table 5.2

Summary of IBD characteristics

Questionnaire	*N* (%)
IBD activity	
P-HBI	
Active	105 (53)
Inactive	92 (47)
P-SCCAI	
Active	68 (65)
Inactive	36 (35)
SIBDQ	
Optimum	127 (42)
Moderate	165 (54)
Poor	13 (4)
Current medication use	
Biologics	85 (28)
Immunosuppressants	144 (47)
Gut specific anti-inflammatories	132 (43)
Steroids	49 (16)
Previous steroid courses [a]	229 (75)
None	43 (14)
Number of hospitalizations	
None	110 (68)
1-5	132 (81)
6-10	22 (14)
10+	40 (24)
Extra-intestinal manifestations (mean (SD))	0.98 (1.07)
Number of surgeries (mean (SD))	1.40 (2.78)

Note. Inflammatory bowel disease (IBD), patient Harvey Bradshaw Index (P-HBI), patient Simple Clinical Colitis Activity Index (P-SCCAI), Short Inflammatory Bowel Disease Questionnaire (SIBDQ), and standard deviation (SD).

[a] Steroid courses are indicated by use of 2 or more prescribed courses since IBD diagnosis

5.6.1.3 Pain status

Results from questionnaires assessing aspects of abdominal and MSK pain in this study are presented in Table 5.3 and 5.4, respectively. Of the included participants, 80% (n = 244) reported the presence of abdominal and/or MSK pain. Of these

participants, 15% (*n* = 36) reported the presence of only abdominal pain, 33% (*n* = 82) reported the presence of only MSK pain, and 52% (*n* = 126) reported the presence of both abdominal and MSK pain. Of the MSK regions identified as painful by study participants, the low back was overall the most frequently reported region (*n* = 124, 60%), while also identified most frequently as the 'main area of pain' (*n* = 41, 20%). A summary of all painful regions reported by participants is presented in Tables G.2 and G.3 (Appendix G).

Table 5.3

Summary of Abdominal Pain Characteristics of Study Participants (n = 162)

Pain severity (NRS)	
None	10 (6)
Mild	75 (46)
Moderate	63 (39)
Severe	14 (9)
Pain interference (NRS)	
None	24 (15)
Mild	84 (52)
Moderate	41 (25)
Severe	13 (8)

Note. Numeric rating scale (NRS).

Table 5.4

Summary of Musculoskeletal Pain Characteristics of Study Participants (n = 208)

Questionnaire	*N* (%)
Pain location	
Regional	101 (49)
Generalized	105 (51)
Strongest pain severity (NRS)	
Mild	24 (12)
Moderate	100 (48)
Severe	84 (40)
Average pain severity (NRS)	
None	2 (1)
Mild	93 (45)
Moderate	98 (47)
Severe	15 (7)
Pain interference (PROMIS Pain Interference 4a)	
None	27 (13)
Mild	99 (48)
Moderate	73 (35)
Severe	9 (4)
Neuropathic pain quality (PainDETECT)	
Unlikely	160 (77)
Likely	20 (77)
Unclear	28 (13)
Nociceptive pain quality (PROMIS Pain Interference 4a)	
None	133 (64)
Mild	45 (22)
Moderate	24 (12)
Severe	6 (3)

Note. Numeric rating scale (NRS), and Patient-Reported Outcomes Measurement Information System (PROMIS).

5.6.2 Subgrouping

5.6.2.1 Latent class analysis

Fit statistics for initial latent class models (1 to 6) are reported in Table 5.5. As indicated by the lowest BIC results, a 2-class model was most parsimonious, where AIC supported a 4-class model. Consideration of fit statistics along with interpretability of the models suggested that a 3-class model was optimal. Classification error of the 3-class model was acceptable at 0.087. Average posterior probabilities (SD) of the 3-class model were 0.920 (0.13), 0.851 (0.14), and 0.892 (0.15), respectively.

Table 5.5

Fit Statistics for Six Latent Class Models

Number of latent classes	Log-likelihood	*df*	BIC	AIC	G^2	Entropy
1	-1478.92	186	3053.56	2993.84	964.46	-
2	-1343.77	167	2884.32	2761.55	694.17	0.802
3	-1312.52	148	2922.85	2737.04	631.66	0.754
4	-1290.79	129	2980.44	2731.58	588.20	0.749
5	-1274.81	110	3049.52	2737.62	556.25	0.809
6	-1262.73	91	3126.41	2751.46	532.09	0.791

Note. Degrees of freedom (df), Bayesian information criterion (BIC), Akaike information criterion (AIC), and goodness of fit (G^2).

Class 1 included 30.8% of study participants and was characterized as “mixed mechanism”. Class 1 represents a high probability for presenting with positive CSI scores, active IBD, abdominal pain, severe MSK pain, and moderate MSK pain interference. Additionally, Class 1 demonstrated increased probability of presenting with nociceptive and/or neuropathic pain qualities when compared to Class 2 and 3.

Class 2 was characterized as “central mechanism” and represented the largest group (42.1%). Class 2 represented a high probability for presenting with positive CSI scores, active IBD, mild MSK pain interference, and no additional pain qualities (nociceptive or neuropathic). Class 2 also presented with moderate probability for presenting with abdominal pain and moderate MSK pain severity. The third, and smallest (26.9%) latent class was characterized as “regional & remission”. Class 3 represented a low probability for demonstrating positive CSI scores, active IBD, abdominal pain, or additional pain qualities (nociceptive or neuropathic). Additionally, Class 3 demonstrated a high probability of presenting with mild to no MSK pain interference, and a moderate probability of presenting with regional MSK pain and moderate MSK pain severity. Conditional item responses of indicator variables for each class are reported in Table 5.6.

Table 5.6

Conditional Item Response Probabilities of Three Latent Classes

Indicator variable	Probability of categorical presentation				
	Yes	No	Mild	Moderate	Severe
Class 1 "Mixed mechanism" (*n*=63, 30.8%)					
Strongest pain severity		0.000	0.000	0.093	**0.907**
Average pain severity		0.000	0.024	**0.764**	0.213
Pain interference		0.016	0.070	**0.784**	0.130
Generalized pain	**0.625**	0.375			
Neuropathic	0.229	**0.532**	0.240		
Nociception		0.239	0.409	0.255	0.097
Abdominal pain	**0.881**	0.119			
Central Sensitization Inventory	**0.903**	0.097			
IBD activity	**0.804**	0.196			
Class 2 "Central mechanism" (*n*=86, 42.1%)					
Strongest pain severity		0.000	0.053	**0.688**	0.259
Average pain severity		0.000	**0.536**	0.454	0.009
Pain interference		0.000	**0.764**	0.236	0.000
Generalized pain	**0.535**	0.465			
Neuropathic	0.070	**0.798**	0.133		
Nociception		**0.746**	0.168	0.086	0.000
Abdominal pain	**0.581**	0.419			
Central Sensitization Inventory	**0.916**	0.084			
IBD activity	**0.782**	0.219			
Class 3 "Regional & remission" (n=55, 26.9%)					
Strongest pain severity		0.017	0.303	**0.608**	0.072
Average pain severity		0.035	**0.748**	0.199	0.019
Pain interference		0.449	0.487	0.047	0.017
Generalized pain	0.334	**0.666**			
Neuropathic	0.000	**1.000**	0.000		
Nociception		**0.905**	0.095	0.000	0.000
Abdominal pain	0.390	**0.610**			
Central Sensitization Inventory	0.396	**0.604**			
IBD activity	0.404	**0.596**			

Note. Bold font indicates variables that characterize each class (> 0.500).

5.6.2.2 Subgroup profiles

Descriptive statistics with between class differences for external variables (demographics, total comorbidity, EIMs, and clinical IBD features) and internal latent class variables (indicator and covariate) are shown in Tables 5.7 to 5.9. Additionally, descriptive statistics with between class differences for individually assessed comorbidities are presented in Appendix H. No significant differences between latent classes were found for gender, age, EIMs, IBD subtype, hospitalizations, surgeries, or medications. All internal latent class variables (indicator and covariate) demonstrated significant between class differences ($p \leq 0$ .05) (Table 5.8), while total comorbidity score was the sole external variable demonstrating significance ($p = 0$ .005) (Table 5.7). Univariate logistic regression analysis for individual comorbidities, to include EIMs, identified statistically significant differences ($p \leq 0.05$) between latent classes for: osteoarthritis ($p = 0.027$), osteoporosis ($p = .045$), depression ($p = 0$ .001), anxiety ($p = 0.025$), and chronic fatigue syndrome ($p = 0.020$). Peduzzi's criteria for sample size was solely met by depression and anxiety variables (Peduzzi et al., 1996). As such, subsequent logistic regression analysis adjusting for age, gender, and IBD subtype indicated gender as a confounder for both depression and anxiety, and age as a confounder for anxiety (Table 5.9).

Table 5.7

Demographic and Comorbidity Data of Three Latent Classes

Variable	Class 1	Class 2	Class 3	*P*	Association
Age, mean (SD)	46.60 (13.71)	43.19 (13.19)	43.40 (13.77)	0.224	2.99 [a]
Female gender, *n* (%)	52 (83)	74 (86)	42 (76)	0.471	0.13 [b]
Comorbidity, mean (SD)	3.17 (1.91)	0.80 (0.87)	2.12 (1.66)	0.005*	10.44 [a]
EIMs, mean (SD)	2.03 (1.47)	1.71 (1.27)	1.60 (1.44)	0.184	3.38 [a]

Note. Standard deviation (SD), extra-intestinal manifestation (EIM), inflammatory bowel disease (IBD), ulcerative colitis (UC), and indeterminate colitis (IC).
[a] Kruskal-Wallis one-way analysis of variance, [b] chi-squared test.
* $p \leq .05$.

Table 5.8

Categorical Latent Class Variable Frequencies of Three Latent Classes

Variable	Class 1 *n* (%)	Class 2 *n* (%)	Class 3 *n* (%)	*P*	Phi
Strongest MSK pain severity (NRS)				<0.001*	0.844 [a]
None	0(0)	0(0)	1 (2)		
Mild	0(0)	2 (2)	20 (36)		
Moderate	5 (8)	64 (74)	30 (55)		
Severe	58 (92)	20 (23)	4 (7)		
Average MSK pain severity (NRS)				<0.001*	0.674 [a]
None	0(0)	0(0)	2 (4)		
Mild	1 (2)	46 (54)	43 (78)		
Moderate	49 (78)	39 (45)	9 (16)		
Severe	13 (21)	1 (1)	1 (2)		
PROMIS Pain Interference				<0.001*	0.943 [a]
None	1 (2)	0(0)	26 (47)		
Mild	3 (5)	68 (79)	26 (47)		
Moderate	51 (81)	18 (21)	2 (4)		
Severe	8 (13)	0(0)	1 (2)		
PROMIS Nociceptive Pain Quality				<0.001*	0.614 [a]
None	14 (22)	65 (76)	51 (93)		
Mild	27 (43)	14 (16)	4 (7)		
Moderate	16 (25)	7 (8)	0(0)		
Severe	6 (10)	0(0)	0(0)		
PainDETECT				<0.001*	0.419 [a]
Unlikely neuropathic	35 (56)	68 (79)	55 (100)		
Likely neuropathic	13 (21)	7 (8)	0(0)		
Uncertain	15 (24)	11 (13)	0(0)		
Generalized MSK pain	40 (64)	45 (52)	18 (33)	0.003*	0.236 [a]
CSI	55 (87)	82 (95)	19 (35)	<0.001*	0.606 [b]
IBD activity	50 (79)	66 (77)	23 (42)	<0.001*	0.344 [b]
Abdominal pain	55 (87)	50 (58)	21 (38)	<0.001*	0.389 [a]
SIBDQ [c]				<0.001*	0.528 [a]
Optimal	7 (11)	23 (27)	37 (67)		
Moderate	47 (75)	62 (72)	18 (33)		
Poor	9 (14)	1 (1)	0(0)		

Note. Musculoskeletal (MSK), numeric rating scale (NRS), Patient-Reported Outcomes Measurement Information System (PROMIS), Short Inflammatory Bowel Disease Questionnaire (SIBDQ), central sensitization inventory (CSI), and inflammatory bowel disease (IBD).

[a] large effect size, [b] moderate effect size, [c] latent class covariate.

* $p \leq 0.05$.

Table 5.9

Associations of Depression and Anxiety with Latent Class Membership Adjusted for Age, Gender, and IBD Subtype

Variable	Unadjusted		Adjusted (age)		Adjusted (gender)		Adjusted (IBD subtype)	
	Exp (β) (95% CI)	*P*	Exp (β) (95% CI)	*P*	Exp (β) (95% CI)	*P*	Exp (β) (95% CI)	*P*
Depression		0.001*		0.001*		0.007*		0.001*
Class 2	0.43 (0.22, 0.85)	0.014*	0.41 (0.21, 0.82)	0.011*	0.47 (0.16, 1.37)	0.166	0.43 (0.22, 0.85)	0.015*
Class 3	0.21 (0.09, 0.49)	<0.001*	0.20 (0.09, 0.47)	<0.001*	0.07 (0.12, 0.36)	0.002*	0.21 (0.09, 0.48)	<0.001*
Anxiety		0.054*		0.025*		0.078		0.054*
Class 2	0.52 (0.24, 1.12)	0.097	0.61 (0.29, 1.27)	0.187	0.51 (0.16, 1.61)	0.251	0.61 (0.29, 1.27)	0.187
Class 3	0.26 (0.10, 0.71)	0.008*	0.31 (0.12, 0.81)	0.017*	0.09 (0.01, 0.78)	0.029*	0.31 (0.12, 0.82)	0.017*

Note. Class 1 – reference class. Confidence interval (CI), inflammatory bowel disease (IBD).

* $p \leq 0.05$.

5.7 Discussion

Primary aims of this cross-sectional study were to explore MSK-related pain in individuals with IBD, in order to describe distinct patient subgroups and identify differences between the subgroups based on profiles of external variables. Current study results describe three distinct and clinically relevant subgroups characterized as "mixed mechanism" for Class 1, "central mechanism" for Class 2, and "regional & remission" for Class 3. Both Classes 1 and 2 demonstrated high probabilities of presenting with positive CSI scores (≥ 40) and active IBD states. However, Class 1 was the only class to demonstrate an increased probability of presenting with neuropathic and/or nociceptive pain qualities. Class 1 also presented with the highest MSK pain severity and pain interference scores, as well as the highest probability for presenting with abdominal pain. Class 3 was the only class to demonstrate increased probability for IBD remission and regional MSK pain, while also demonstrating low probability for positive CSI scores and abdominal pain.

In the current study, positive CSI scores were a dominant feature in Classes 1 and 2, thereby identifying significant symptomology commonly seen in patients presenting with underlying mechanisms of central sensitization. Additionally, Classes 1 and 2 also presented with increased MSK pain severity and interference profiles compared to Class 3 presenting with a low probability of positive CSI scores. As described by Woolf (Clifford J Woolf, 2011, 2014), the increased responsiveness of neurons within the central nervous system as a result of central sensitization leads to pain hypersensitivity. Previous studies of persistent pain in other populations, such as osteoarthritis, have shown an increase in pain severity in individuals demonstrating central sensitization (Akinci et al., 2016; Arendt- Nielsen et al., 2018; Lluch, Torres, Nijs, & Van Oosterwijck, 2014). Central sensitization is a broad concept that includes

numerous and complex pathophysiological mechanisms, including changes to pain facilitation, inhibition, and sensory processing (Clifford J Woolf, 2011, 2014).

Of the two classes presenting with central sensitization symptomology, Class 1 demonstrated a 91% probability of presenting with severe MSK pain, whereas Class 2 demonstrated a 69% probability of presenting with moderate pain. The presence of central sensitization has been described as different degrees over a continuum (Lluch et al., 2014), as opposed to simply present or not. The question then becomes: to what extent is central sensitization contributing to the clinical picture (Lluch et al., 2014)? Differences in pain profiles described here may be the result of greater contribution from mechanisms of central sensitization and/or additional factors (i.e. psychological and behavioural features) to the overall clinical picture of Class 1, leading to worse pain experiences. Previous investigation of chronic spinal pain found that higher CSI scores correlated with depressive symptoms, perceived disability, sleep disturbance, and increased pain severity (Neblett, Hartzell, Williams, et al., 2017). Similarly, current results demonstrated that higher CSI scores corresponded with the presence of depression and anxiety, as well as higher pain severity across subgroups.

In addition to higher CSI scores and greater pain severity, individuals in Class 1 were also more likely to present with multiple pain mechanisms, greater total comorbidity, as well as a higher prevalence of abdominal pain, osteoarthritis, and osteoporosis. Incidentally, the presence of central sensitization is thought to be an important contributor to increased painful comorbidities in chronic pain populations, as hypersensitivity due to central sensitization may result in pain from minimal nociceptive input of other structures (e.g. arthritic joints) (Arendt- Nielsen et al., 2018). As such, the presence of multiple comorbidities and/or overlapping peripheral

mechanisms in the presence of central sensitization, may have a cumulative effect leading to worse pain experiences in Class 1.

The current study demonstrated a notable pattern between CSI and IBD activity scores, suggestive of a directional relationship between these measures. Results indicated that a high probability of demonstrating positive CSI also represented a high probability of active IBD (Class 1 and 2), with the opposite being true in Class 3. IBD literature has previously described animal models of central sensitization and IBD activity, specifically with regards to the development and maintenance of chronic abdominal pain (Bielefeldt et al., 2009; K. E. Farrell, Callister, & Keely, 2014). These models describe modulation of neural activity as a consequence of pro-inflammatory mediators present in active IBD states leading to sensitized nervous systems (Bielefeldt et al., 2009; K. E. Farrell et al., 2014). Results from the present study suggest that contributions of central sensitization to pain in IBD may extend beyond models of abdominal pain to include MSK-related pain as well.

Subgroup profiling in the present study indicated no between-class differences for observed demographics, EIMs, IBD subtype, and clinical IBD features. In fact, of the variables assessing IBD in this study, IBD activity and HRQOL were the only ones to demonstrate a significant association. Determination of IBD severity is reported to consider the presence of mucosal lesions, as well as the accumulation of: IBD-related hospitalizations and surgeries, multiple EIMs, use of disease-modifying medications, and multiple steroid courses following IBD diagnosis (Peyrin-Biroulet et al., 2016; Siegel et al., 2016). Therefore, although the present study indicated that the majority of the observed IBD features in isolation did not predict subgroup membership, current literature would suggest that the combined consideration of these features to describe overall disease severity may be more useful. The relationship of active IBD and

HRQOL demonstrated during subgroup profiling would highlight the potential for influences from overall disease severity to MSK pain presentations. Therefore, future research should explore the construct of IBD severity as an independent risk factor for MSK pain experiences in this population.

Total comorbidity scores were the sole external variable to demonstrate an association with class membership, with increased prevalence in Class 1. Although comorbidities have shown to be independent predictors of several outcomes, such as mortality and disability, relatively little is known about the effect of disease combinations on outcomes (de Groot, Beckerman, Lankhorst, & Bouter, 2003). Investigation of individual disease combinations on disability indicated that the effects of some combinations were additive, while other effects were synergistic, leading to increased disability (de Groot et al., 2003). Results from the present study indicate that an increase in total comorbidity (e.g. disease count) is predictive of membership to the subgroup demonstrating worse MSK pain profiles (Class 1). However, it is unknown whether specific disease combinations would demonstrate differing effects on subgroup membership.

Analysis of individual comorbidities identified significant between class differences for osteoarthritis, osteoporosis, chronic fatigue syndrome, depression, and anxiety. Distribution of these comorbidities followed the total comorbidity distribution, with increased prevalence in Class 1. Similar to previous IBD investigations (Geng et al., 2018), the present study identified gender as a confounder for both depression and anxiety. Rates of mood disorders have been shown to be higher in IBD compared to other diseases and the general population (M. Regueiro, Greer, & Szigethy, 2017). Pooled incidence rates for anxiety and depression in IBD patients were reported to be 19% and 21%, respectively, was almost double those of healthy individuals (Mikocka-

Walus, Knowles, Keefer, & Graff, 2016). The presence of depression and anxiety, along with poor HRQOL, has shown significant correlation with increased number of relapses (Kendall's Tau = -0.40, p <0.001), suggesting mood disorders may be a risk factor in IBD (Mittermaier et al., 2004; M. Regueiro et al., 2017). However, it is unclear whether the temporal presentation and fluctuation of mood disorders in relation to the relapsing-remitting nature of IBD are significant beyond chance (Mikocka-Walus et al., 2007).

The current sample population is similar to current New Zealand epidemiological IBD data where approximately 97% of IBD patients identified as New Zealand Eurpeans, with significantly reduced representation of Māori (Su, Gupta, Day, & Gearry, 2016). This is the first study to characterize self-reported MSK pain through subgrouping analysis of multiple IBD and pain features. The present study included numerous standalone questionnaires, validated to assess respective pain and disease features. Face and content validity of survey questionnaires was provided by experts in the field of gastroenterology and chronic pain. Subgroups in the present study represent categorical interpretation of included questionnaires to reflect the clinical utility of these measures. However, subgrouping analysis performed on continuous indicator variables may lead to different subgrouping results.

A common limitation of online surveys relates to the assessment of IBD activity through self-reported measures. Standard clinical practice for estimating IBD activity typically includes clinical investigations, such as colonoscopies and serum biomarkers, alongside measures used in the present study (Peyrin-Biroulet et al., 2016; Siegel et al., 2016; Walsh et al., 2016). Therefore, estimation of IBD activity in the present study may not fully reflect findings from more invasive clinical assessments. Although the present study recorded all MSK pain regions reported by each participant, exploration

of pain features were solely recorded for regions identified as the participant's 'main area of pain'. Therefore, results may not characterize features specific to all painful regions reported in the present study. Similarly, as it was not possible to externally confirm the presence of IBD diagnosis through medical records, the current study utilized self-reports for previous IBD diagnosis. However, recruitment for the current sutyd was primarily through Crohn's and Colitis New Zealand to increase access to the target population.

However, as the primary source for recruitment of study participants was through Crohn's and Colitis New Zealand, study results may overly represent individuals who have previously or are currently seeking support in managing their IBD (Šimundić, 2013). Further, the present study represents individuals who have digital and online access, and may not be generalizable to the broader IBD population.

Future research should explore the presence and implications of central sensitization in IBD patients with and without persistent MSK pain, in order to provide further insight into the complex relationship between central sensitization, persistent MSK pain, and IBD. For instance, investigations exploring somatosensory functioning as a measure of central sensitization, as well as influences from psychological, comorbidity, and IBD features may reveal mechanisms as well as risk factors for ongoing painful experiences in patients. Future research of this nature would further develop and support the new model for MSK pain proposed in the present thesis, leading to targeted assessment and treatment pathways for MSK pain in IBD.

5.8 Chapter Summary

Exploration of self-reported MSK pain experiences through subgrouping in the current chapter provides evidence for the possibility of multiple mechanisms contributing pain experiences in IBD, including nociceptive, neuropathic, and central mechanisms. Study results describe three clinically relevant subgroups where individuals with worse MSK pain experiences also presented with active IBD and increased CSI scores, suggesting the potential modulation of pain experiences by shared mechanisms of central sensitization. Results from the sub-analysis aim of Study 1, exploring causal relationships between these variables are presented in Chapter 6.

6 Study One: IBD Activity, Central Sensitization Inventory, and Worse Musculoskeletal Pain Experiences

6.1 Chapter overview

The positive predictive relationship between active IBD and the presence of certain MSK conditions is well-documented in IBD literature (Brakenhoff et al., 2011; Vavricka et al., 2015). Additionally, literature exploring the gut-brain-axis paradigm (Chapter 2) suggests that intestinal inflammation results in changes to visceral afferent pathways, triggering a cascade of central nervous system, endocrine, and immune responses. However, IBD literature is unable to suggest whether IBD activity influences MSK pain experiences (e.g. severity and interference). Results from the previous chapter indicated that patients with active IBD and higher central sensitization inventory (CSI) scores, also demonstrated an increased probability of presenting with worse MSK pain experiences. However, subgrouping results are unable to determine whether these variables are co-dependant or simply co-exist in patients. Therefore, the following chapter presents the statistical analysis, results, and discussion of a causal model exploring the relationship between active IBD, increased CSI scores, and worse MSK pain experiences (Study 1 – sub-analysis).

6.2 Sub-analysis Study Aims

- To investigate the predictive relationship between IBD activity and MSK pain experiences (severity and interference).
- To investigate the mediating effects of CSI scores between IBD activity and MSK pain experiences.

6.3 Hypothesis

It was hypothesized that active IBD is associated with worse MSK pain experiences and this relationship is mediated by greater symptoms of central sensitization (i.e. higher CSI scores).

6.4 Statistical Analysis

Descriptive statistics (frequencies, means, and standard deviations (SD)) were used to characterize demographic, IBD, and pain characteristics of study participants. Univariate linear regression analyses (IBM SPSS Statistics 25) were used to explore the relationship between: independent variables (IBD activity scores) and dependent variables (pain severity scores and pain interference scores). Assumptions for linear regression models were assessed to ensure model fit, including: normality of scoring distribution (Shapiro-Wilk tests, significance ≤ 0.05)), collinearity diagnostics (variance inflation factor < 10 with tolerance > 0.2), and homoscedasticity (scatterplot of residuals).

Mediation analysis (PROCESS version 3) in the present study included: 1) simple mediation analysis (PROCESS - model 4) to assess the relationship between independent variable (IBD activity scores), dependent variable (pain severity scores), and mediator (CSI scores); and 2) serial mediation analysis (PROCESS - model 6) to assess the relationship between independent variable (IBD activity scores), dependent variable (pain interference scores), and mediators (CSI and pain severity scores). Both mediation models were adjusted for *a priori* confounders, including age, gender, and self-reported anxiety and depression, with significant confounding identified as >10% change in the regression coefficient from the unadjusted model. All three potential confounders have previously been shown to influence CSI scores and/or MSK pain experiences (Bair, Wu, Damush, Sutherland, & Kroenke, 2008; Fillingim, King,

Ribeiro-Dasilva, Rahim-Williams, & Riley III, 2009; Mayer et al., 2012). Heteroscedasticity-consistent standard errors were used and the statistical significance of mediation (i.e. indirect effects) was identified through bootstrapping of 5,000 samples (95% confidence intervals).

6.5 Results

A total of 305 individuals with IBD provided informed consent to participate in the online survey. Out of the survey respondents, 208 individuals reported the presence of MSK pain and were included as study participants. A summary of demographic data (age and gender) and IBD subtype are presented in Table 6.1. Of the 208 participants, 143 individuals reported IBD subtype as Crohn's disease, 59 reported ulcerative colitis, and six reported indeterminate colitis.

Table 6.1

Demographics and IBD Subtype of Survey Participants (N=208)

Characteristic	*n* (%)
Gender *	
Male	33 (16.9)
Female	172 (82.7)
Gender diverse	2 (0.01)
Age	
Range (years)	18 – 88
Mean (SD)	44.26 (13.89)
IBD subtype	
Crohn's disease	143 (68.8)
Ulcerative colitis	59 (28.4)
Indeterminate colitis	6 (0.03)

Note. *Gender was identified by *n* = 207 participants.

6.5.1 Survey measures

Results from questionnaires assessing IBD activity, MSK pain severity and interference, and CSI scores are presented in Table 6.2. Of the participants who reported Crohn's disease (*n* = 143), 4 indicated the presence of an ileostomy and therefore did not meet the criteria for completing the patient Harvey Bradshaw Index (P-HBI), which requires evaluation of bowel habits not assessable in patients with intestinal stomas. Consequently, results of the P-HBI are reported for the remaining 139 participants with Crohn's disease. Active IBD as indicated by scores > 4 for both the P-HBI and the patient Simple Clinical Colitis Activity Index (P-SCCAI), were found in 69% of survey participants (64% of Crohn's disease participants and 78% of ulcerative/indeterminate colitis participants).

Of the MSK regions identified as painful by study participants, the low back was the most frequently reported region (*n* = 124), and most frequently identified as the 'main area of pain' (*n* = 41). Pain severity scores ranged from 0 to 10 (numeric rating scale (NRS)), with only one participant reporting an NRS score of 0. PROMIS Pain Interference scores ranged from 41.6 to 75.6, with 93% of study participants demonstrating positive pain interference as scores > 50. CSI scores in the present study ranged from 12 to 82, with 75% of study participants demonstrating CSI scores ≥ 40.

Table 6.2

Self-reported Clinical Features of Survey Participants (N=208)

Questionnaire	Range	Mean (SD)
IBD activity		
P-HBI (*n*=139)	0-24	6.41 (4.08)
P-SCCAI (*n*=65)	1-16	6.98 (3.47)
Musculoskeletal		
Body map, painful regions (*n*)	1-21	7.51 (3.89)
Pain severity (NRS)	0-10	6.89 (2.06)
PROMIS Pain Interference	41.6-75.6	58.48 (6.97)
Central Sensitization Inventory	12 - 82	47.87 (13.70)

Note. Standard deviation (SD), Patient Harvey Bradshaw Index (P-HBI), Patient Simple Clinical Colitis Activity Index (P-SCCAI), numeric rating scale (NRS), and Patient-Reported Outcomes Measurement Information System (PROMIS).

6.5.2 IBD and musculoskeletal pain experiences

Unadjusted univariate linear regression analysis indicated that IBD activity was a significant predictor of both increased MSK pain severity ($R^2 = 0.039$, $F(1,202) = 8.235$, $p < 0.005$) and increased MSK pain interference ($R^2 = 0.067$, $F(1,202) = 14.542$, $p < 0.001$).

6.5.3 Mediation models

6.5.3.1 IBD activity and musculoskeletal pain severity

Simple mediation analysis indicated that IBD activity was a significant predictor of increased CSI scores ($\beta = 7.456$, $SE = 1.930$, $p < 0.001$) and CSI scores were a significant predictor of increased MSK pain severity ($\beta = 0.047$, $SE = 0.012$, $p < 0.001$). Furthermore, IBD activity was no longer a significant predictor of MSK pain severity after controlling for CSI scores ($\beta = 0.481$, $SE = 0.314$, $p = 0.127$). The greater

participation of females compared to males in the present study precluded the ability to control for gender confounding; however, neither age nor self-reported anxiety or depression demonstrated confounding effects on the mediation model. Approximately 14% of the variance in MSK pain severity was accounted for by IBD activity mediated by CSI scores ($R^2 = 0.145$). Results indicated the indirect effect was significant ($\beta = 0.352$, SE = 0.139, CI [0.127, 0.664]). Summary of mediation results is described in Table 6.3 and Figure 6.1.

Table 6.3

Simple Mediation Model for Active IBD and Musculoskeletal Pain Severity (N=208)

	β	*SE*	*t*	*P*	*CI*
Mediation model summary: $R^2 = 0.145$, $F(5,197) = 4.875$, $p < 0.001$*					
Effect: IBD activity on CSI	7.456	1.930	3.864	<0.001*	
Effect: CSI on pain severity	0.047	0.012	3.861	<0.001*	
Total effect	0.833	0.316	2.638	0.009*	
Direct effect	0.481	0.314	1.535	0.127	
Indirect effect	0.352	0.139			[0.127, 0.664]

Notes. Inflammatory bowel disease (IBD), central sensitization inventory (CSI), standard error (SE), confidence interval (CI).
* $p \leq 0.05$.

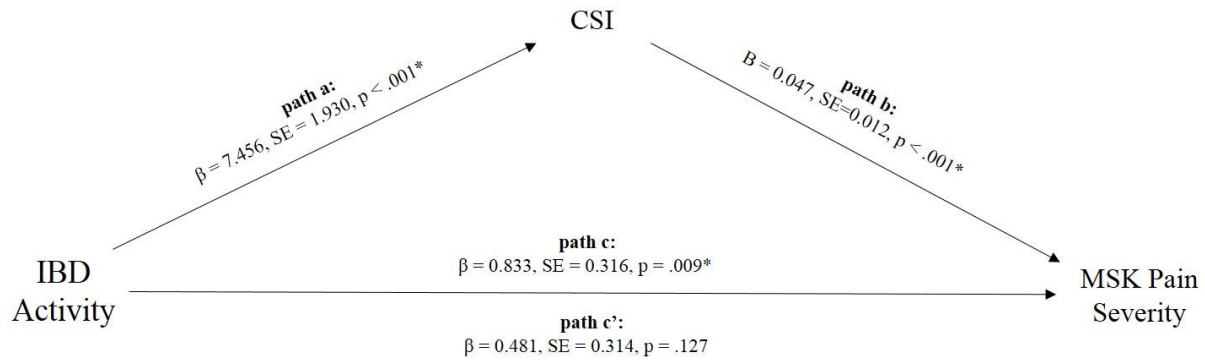

Figure 6.1. Simple Mediation Model for Active IBD and Musculoskeletal Pain Severity

6.5.3.2 IBD activity and musculoskeletal pain interference.

Serial mediation analysis indicated that IBD activity was a significant predictor of increased CSI scores ($\beta = 7.456$, SE = 1.930, $p < 0.001$) and CSI scores independently ($\beta = 0.143$, SE = 0.032, $p < 0.001$), as well as in series with MSK pain severity ($\beta = 1.846$, SE = 0.173, $p < 0.001$), were significant predictors of MSK pain interference. Furthermore, IBD activity was no longer a significant predictor of MSK pain interference after controlling for CSI and MSK pain severity scores ($\beta = 1.337$, SE = 0.826, $p = 0.107$). Similar to the simple mediation model, the greater participation of females compared to males in the present study precluded the ability to control for gender confounding. However, neither anxiety nor depression was found to have no effect, whereas age demonstrated a significant effect (regression coefficient change = 14%) on the serial mediation model ($\beta = 0.078$, SE = 0.023, $p < 0.001$). Approximately 54% of the variance in MSK pain interference was accounted for by IBD activity mediated in series by CSI and pain severity scores ($R^2 = 0.537$). Results indicated the indirect effect was significant ($\beta = 2.606$, SE = 0.755, CI [1.201, 4.164]). Summary of serial mediation results is describes in Table 6.4 and Figure 6.2.

Table 6.4

Serial Mediation Model for Active IBD and Musculoskeletal Pain Interference (N=208)

	β	*SE*	*t*	*P*	*CI*
Mediation model summary: R^2 = 0.537, F(6,196) = 46.151, p < 0.001*					
Effect: IBD activity on CSI	7.456	1.930	3.864	<0.001*	
Effect: IBD activity on pain severity	0.481	0.314	1.532	0.127	
Effect: CSI on pain severity	0.049	0.012	4.054	<0.001*	
Effect: CSI on pain interference	0.143	0.032	4.421	<0.001*	
Effect: pain severity on interference	1.846	0.173	10.675	<0.001*	
Total effect	3.943	1.030	3.828	<0.001*	
Direct effect	1.339	0.826	1.619	0.107	
Indirect effect	2.606	0.755			[1.201, 4.164]

Note. Inflammatory bowel disease (IBD), central sensitization inventory (CSI), standard error (SE), confidence interval (CI).
* $p \leq 0.05$.

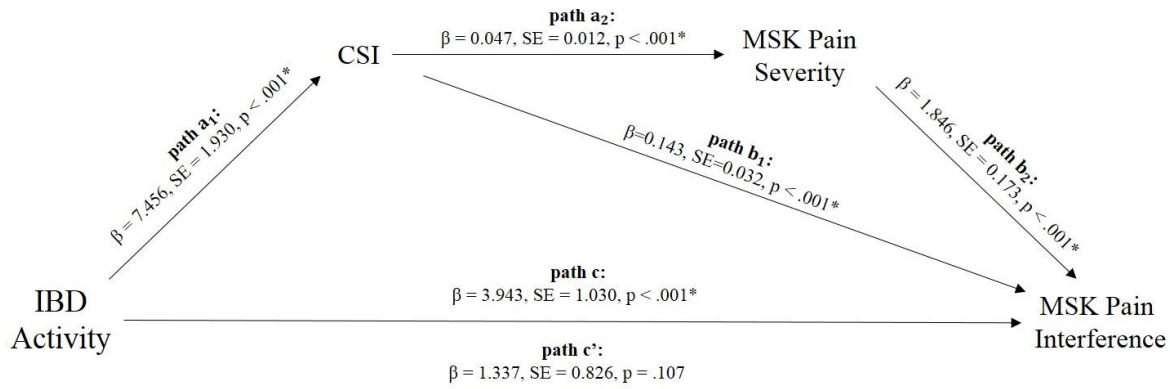

Figure 6.2. Serial Mediation Model for Active IBD and Musculoskeletal Pain Interference

6.6 Discussion

The first aim of the sub-analysis for Study 1 was to explore the predictive relationship between IBD activity and MSK pain experiences (severity and interference). Results demonstrated a significant positive predictive relationship between active IBD and worse MSK pain severity and interference, thereby confirming the primary sub-analysis hypothesis. Unsurprisingly, the univariate analysis suggests the possibility for additional influences on MSK pain experiences in IBD patients, as active IBD explained less than 10% of the variance in pain measures used in the present study. The second aim of the sub-analysis was to explore mediating effects of CSI scores in the relationship between IBD activity and MSK pain experiences, to include serial mediation by CSI and pain severity to MSK pain interference. The study results support the secondary hypothesis as CSI scores demonstrated significant mediation in the relationship between active IBD and MSK pain severity. Similarly, the analysis showed that CSI scores, both independently and in series with MSK pain severity, demonstrated significant mediation of the relationship between active IBD and MSK pain interference.

Exploration of how, for instance, a third variable affects the relationship between two other variables is the cornerstone of mediation analysis (MacKinnon et al., 2007). Although the consideration of a third variable may appear simple, the interactions in a three-variable system can be very complicated (MacKinnon et al., 2007). However, in exploratory investigations, such as the present sub-analysis, mediation-based analysis offers valuable insight into potential intervening variables when attempting to understand theoretical and causal pathways in relationships. Results in the present study suggest that the link between active IBD and worse MSK pain

experiences is significantly explained by symptoms related to central sensitization (i.e. CSI scores).

CSI has been validated to assess an array of symptoms and risk factors associated with the development of central sensitization (Mayer et al., 2012). This screening tool is unable to identify which central mechanisms are participating in an individual's clinical picture, but rather indicates that consideration of central sensitization may guide practitioners to appropriate diagnostic testing (Mayer et al., 2012). Although Study 1 of the present thesis is the first study to describe the potential for central mechanisms in MSK pain in this population, influences of central sensitization have been proposed in IBD-related postsurgical and abdominal pain (Bielefeldt et al., 2009; Bruce & Krukowski, 2006; Kristen E Farrell et al., 2014; Joris et al., 2015). Investigations of chronic postsurgical pain indicate that IBD patients are two to three times more likely to develop chronic pain following gastrointestinal surgery than non-IBD populations (Bruce & Krukowski, 2006; Joris et al., 2015). Central sensitization has been found to play a major role in the pathophysiology of chronic postsurgical pain, with its potentiation from prior disease inflammation thought to explain the increased prevalence of chronic pain in IBD patients (Bruce & Krukowski, 2006; Joris et al., 2015).

Investigations of abdominal pain in IBD have described pain experiences persisting beyond active inflammation seen in IBD flares, as well as pain experienced in other body regions, such as the back and legs (Bielefeldt et al., 2009; Kristen E Farrell et al., 2014). This referred pain is thought to be the result of central sensitization causing an overlap in activity between visceral and somatosensory neurons within the spinal cord (Bielefeldt et al., 2009; Kristen E Farrell et al., 2014). In addition to these changes in neural activity, chronic abdominal pain models describe the modulation of

descending inhibitory mechanisms as a result of affective and cognitive features in IBD (Bielefeldt et al., 2009). Increased stress, anxiety, and hypervigilance have been suggested as factors which may exacerbate not only clinical features of IBD but visceral pain states as well (Bielefeldt et al., 2009). Consequently, current sub-analysis results, as well as previous reports of chronic pain models in IBD, suggest that exploration of central mechanisms is worthy of further investigation, to include altered somatosensory function and affective/cognitive features in IBD patients with MSK pain.

Current sub-analysis results indicate that worse pain interference in active IBD is mediated in series by increased CSI and pain severity scores, thereby confirming the second study hypothesis. Additionally, increased CSI scores also demonstrated direct mediation of pain interference independent of pain severity scores. Similar to reports in the literature, pain interference in the present sub-analysis describes multiple and complex pathways by which pain may hinder one's engagement in physical, emotional, and social activities, also commonly described as one's function. Previous pain models describe interference with daily activities resulting from ongoing painful experiences, with the assumption that relief from pain correlates with an improvement in function (Dworkin et al., 2005). However, exploration of interference constructs indicates that although severity, interference, and function are related to each other, they are distinct domains each requiring consideration (Amtmann et al., 2010; Karayannis et al., 2017). Although current sub-analysis measures (i.e. CSI, severity, and interference) are understood to assess distinct constructs, the closely related nature of these constructs creates the potential for some inter-item overlap between measures. However, as mediation analysis does not require complete local independence as a statistical assumption, the small amount of variance potentially created by this overlap likely has

nominal effects. As such, the multiple pathways mediating pain interference in the present sub-analysis further suggests the unique complexity and likely independent nature for each of these constructs.

Of the potential confounders explored in the present sub-analysis, age demonstrated relationship to pain experiences. Specifically, increased age was identified as a significant confounder in the relationships with worse pain interference. A large investigation utilizing a PROMIS assessment of pain interference in IBD patients demonstrated slightly improved scores in older adults (> 60 years) compared to younger individuals (Kappelman et al., 2014). However, the authors did not identify which PROMIS Pain Interference assessment was used, nor whether results were statistically significant. Reports from the literature regarding the directional influence of age on pain interference in other populations are conflicting, with some reports of worse interference in older adults within the general population (Thomas et al., 2007), whereas chronic pain populations demonstrated greater interference in younger individuals (Blyth et al., 2001). These studies further highlight the complexity of interference constructs. Further investigation is needed in order to better understand the components for how increasing age influences pain interference in active IBD and MSK pain experiences.

In the present sub-analysis, increased CSI scores accounted for 14% of the variance in the relationship between active IBD and pain severity. Furthermore, CSI scores and pain severity accounted for 54% of the variance in the relationship between active IBD and pain interference. These results suggest that traditional inflammatory models, which exclude central mechanisms, in the context of MSK pain may be insufficient to explain the prevalence of pain in this population. This has implications for the management of MSK pain in IBD patients, where common pharmaceutical

approaches aimed at reducing inflammation may not be a successful strategy for a significant proportion of patients (Fornaciari et al., 2001; Levine & Burakoff, 2011; Zeitz et al., 2016). Furthermore, in a large study exploring pain in IBD, where over 50% of patients reported pain duration of more than five years, results indicated that one in four patients did not receive any pain management (Zeitz et al., 2016). Given this large symptom burden and evidence for inadequate pain management, further research into the participation of central mechanisms in ongoing MSK pain experiences is warranted to develop new assessment and treatment frameworks in IBD.

Standard clinical practice for assessing IBD activity typically includes clinical investigations, such as colonoscopies and serum biomarkers, alongside measures used in the present study (Peyrin-Biroulet et al., 2016; Siegel et al., 2016; Walsh et al., 2016). Therefore, IBD activity in the present sub-analysis may not reflect findings from clinical assessments. Similarly, as self-reported measures used in the present study are unable to differentiate between primary inflammatory versus non-inflammatory MSK conditions, the presence of inflammatory arthropathies in the present study was solely based on self-reports of previous diagnoses. The present sub-analysis explored pain severity and interference solely for regions identified as the participant's 'main area of pain'. Therefore, results may not be generalizable to all painful regions reported in the present study.

Although Crohn's and Colitis New Zealand and the social media groups targeted for recruitment in the present study are large, they are not restricted to IBD patients and include additional persons such as IBD providers, support networks, and family. Therefore, it is difficult to speculate the overall size of the source population. Current literature indicates significant gender effects with regards to measures of central sensitization and additional psychosocial factors, such as mood disorders. The

increased participation of females to males in the present sub-analysis did not allow for exploration nor controlling for gender effects of these measures. However, as this is the first study to explore the scope of MSK in IBD, it is unknown whether the increased female representation in the present sub-analysis represents true gender distribution in IBD, or is the result of sampling bias. However, current literature acknowledges an overall increased response rate of females over males typically seen in online survey based investigations (G. Smith, 2008). Therefore, determination of whether or not gender distribution in Study 1 represents true MSK pain demographics in IBD, or are simply due to response/sampling bias is uncertain.

As the present sub-analysis is cross-sectional by design, temporal causality between mediators and variables cannot be explored. However, the significant associations demonstrated in the present study highlight potentially important relationships between these variables. As such, future investigations utilizing longitudinal designs should explore the directional and temporal nature of these relationships in order to better understand the stated associations.

Future research should explore objective measures of central sensitization in IBD patients, as well as possible gender effects and modulating factors, such as psychosocial features. Additionally, investigation of clinical IBD activity (e.g. serum biomarkers and colonoscopies), as well as the severity of IBD alongside assessments of central sensitization would provide further insight and context into the nature of central pain mechanisms in this population. Such investigations may allow for individualised and targeted treatment pathways to improve MSK pain experiences in IBD.

6.7 Chapter Summary

The sub-analysis in the current chapter builds on results from the primary aims of Study 1 (Chapter 5) by demonstrating that subgrouping variables (i.e. active IBD, CSI scores, and MSK pain experiences) do not simply co-exist in the identified subgroups, but rather demonstrated significant predictive relationships. The mediation of MSK pain experiences by CSI scores in patients with active IBD further implicates the presence and participation of shared mechanisms of central sensitization in IBD patients.

Study 2 of the present thesis investigates assessments of central sensitization (i.e. symptomology and somatosensory functioning) in patients with IBD. Chapter 7 presents the full protocol for Study 2, with the results and discussion for primary and secondary aims presented in Chapters 8 and 9, respectively.

7 Study Two: Assessment of Central Sensitization in Patients with IBD and Healthy Controls – Study Protocol

7.1 Chapter overview

Study 1 in the present thesis characterized the multidimensional nature of self-reported MSK pain in IBD through the identification of distinct mechanistic profiles (Chapter 5), where features of active IBD and greater symptoms of central sensitization demonstrated positive predictive relationships to worse pain severity and interference (Chapter 6). Symptoms of central sensitization in Study 1 demonstrated a significant association with multiple patient features, including IBD, worse MSK pain experiences, and multiple pain types. An additional sub-analysis from Study 1 (Appendix H) indicated that CSI scores were significantly different in participants based on the presence of different pain states, such as solely abdominal pain versus abdominal and MSK pain. This suggests that additional measures of central sensitization in this population may be influenced simply based on the presence of IBD and/or the presence of MSK pain. Furthermore, the pattern of CSI scoring in relation to the variables characterizing the MSK pain profiles of Study 1, such as the presence of anxiety/depression, total comorbidity, active IBD, and IBD health-related quality of life (HRQOL), suggests that measures of central sensitization in this population may be influenced by these diverse features. Therefore, Study 2 of the present thesis explores assessments of central sensitization in IBD patients with and without MSK pain and healthy controls, in order to investigate: whether the presence of IBD and MSK pain influences assessments of central sensitization (Chapter 8), and whether individual patient characteristics influence assessments of central sensitization (Chapter 9).

The current chapter presents the protocol for Study 2: Assessment of central sensitization in patients with IBD and healthy controls. This was conducted at the IBD Center of Dartmouth-Hitchcock Medical Center in New Hampshire, USA. Results and subsequent discussions for the primary and secondary aims of Study 2 are presented in Chapters 8 and 9, respectively.

7.2 Background

As previously described, assessments of central sensitization commonly examine various clinical and experimental characteristics related to symptomology, somatosensory functioning, and factors influencing pain perceptions (Clifford J Woolf, 2011). Somatosensory functioning is widely used to evaluate the excitability of different nociceptive pathways within the central nervous system (CNS) through static sensory tests, such as pressure pain threshold (PPT), and dynamic sensory tests, such as temporal summation (TS) and conditioned pain modulation (CPM) (Arendt-Nielsen & Yarnitsky, 2009; Arendt- Nielsen et al., 2018). Along with the investigation of common symptomology, these assessments may act as surrogate markers suggesting the presence of central sensitization mechanisms (Arendt-Nielsen & Yarnitsky, 2009; Arendt- Nielsen et al., 2018).

In addition to these measures of central sensitization, cognitive and affective features are commonly explored as modulators of pain perceptions and nociceptive transmission in chronic pain (Villemure & Bushnell, 2002). Results from Study 1 indicated that the presence mood disorders (i.e. anxiety and depression), as well as features of IBD (i.e. activity and HRQOL) were strongly correlated with MSK pain profiles in IBD (Chapter 5). Interestingly, the presence of psychological features have

long been reported in IBD patients (Andrews et al., 1987; Charles N Bernstein et al., 2010; Farrokhyar et al., 2006; Guthrie et al., 2002; Simrén et al., 2002), with consequences ranging from decreased HRQOL, symptomatic flares, to speculations for an aetiological role in IBD (Chapter 3). Similarly, influences from lifestyle factors, such as substance use (i.e. smoking and alcohol) and sleep quality, have been described as predictors of worse IBD severity (Ali & Orr, 2014; Siegel et al., 2016) and modulators of central sensitization assessments (Finan, Goodin, & Smith, 2013; Gierthmühlen et al., 2015; Nijs et al., 2017). Consequently, results from Study 1 along with reports from pain and IBD literature suggests that exploration of influences from psychological, IBD, lifestyle, and comorbidity features may provide a deeper understanding to measures of central sensitization in this population.

7.3 Study Aims

7.3.1 Primary aims

- To investigate differences in measures of central sensitization (i.e. central sensitization inventory (CSI), PPT, CPM, and TS) across three groups: 1) IBD patients with MSK pain, 2) IBD patients without MSK pain, and 3) healthy controls.
- To investigate whether between-group differences demonstrated above are confounded by psychological factors (perceived stress, affect style, anxiety, depression, and pain catastrophizing).

7.3.2 Secondary aim

- To investigate the association between measures of central sensitization (i.e. CSI, PPT, TS, and CPM) and IBD features, as well as psychological, demographic, comorbidity, and lifestyle features in patients with IBD.

7.4 Study Hypotheses

7.4.1 Primary hypothesis

It was hypothesized that IBD patients with MSK pain will demonstrate greater symptomology related to central sensitization (i.e. CSI scores) and altered somatosensory functioning (i.e. PPT, CPS, and TS) compared to IBD patients without pain, and to healthy controls. It was further hypothesized that psychological factors will demonstrate a degree of confounding in the measures of central sensitization found to be statistically significantly different between the study groups described above.

7.4.2 Secondary hypothesis

It was hypothesized that IBD features will demonstrate a positive association with measures of central sensitization. It was further hypothesized that models predicting measures of central sensation will represent influences from multiple patient features, including worse IBD, psychological, lifestyle, and comorbidity status.

7.5 Methods

7.5.1 Research Design

The present cross-sectional study was granted ethical approval by the Institutional Review Board for Dartmouth College, Committee for the Protection of Human Subjects (STUDY00031471) (Appendix J).

7.5.1.1 Participants

Individuals aged 18 years or older presenting to Dartmouth-Hitchcock Medical Center (USA) were invited to participate across three study groups: (1) IBD with MSK pain, (2) IBD without MSK pain, and (3) healthy controls (Appendix K). Patients with a previously establish IBD diagnosis by a gastroenterologist were identified through the Dartmouth-Hitchcock's electronic medical records with written approval obtained by each treating physician prior to all recruitment efforts. Healthy controls were recruited through email invitations to staff members of Dartmouth-Hitchcock Medical Center, as well as friends/family members of Dartmouth-Hitchcock patients.

7.5.1.2 Exclusion criteria

IBD patients (with and without MSK pain) were excluded if they reported any of the following: pregnancy, current history of drug or alcohol abuse, any condition resulting in altered sensation such as: nerve injuries, neurological conditions (e.g. stroke, multiple sclerosis, and Parkinson's disease), or surgery within the last 3 months. Healthy controls were excluded if they reported any of the following: pregnancy, history of drug or alcohol abuse, a history of pain experiences lasting longer than 24 hours in the past 3 months, and/or a diagnosis of acute or chronic health conditions (e.g. neurological, cardiovascular, gastrointestinal, hepatobiliary, urogenital, psychological, and cancer) (Gierthmühlen et al., 2015).

7.5.1.3 Data collection

Participants meeting inclusion/exclusion criteria were invited to attend one examination session at Dartmouth-Hitchcock Medical Center. Participants were provided with detailed information related to the study and signed a consent form to participate (Appendix J). Examination included somatosensory testing, followed by completion of digitized questionnaires (Appendix M). The order of somatosensory

testing was standardized, whereas the order of questionnaires was randomized to reduce test order effects, with skip patterns to direct participants toward relevant questionnaires where applicable. Outcome measures used during the examination session are presented in Table 7.1. Following the examination sessions, data extraction from the patients' medical records was performed to further characterize IBD features (Table 7.2). Details of the constructs related to features included in the present study are presented in Chapter 3, with assessment scoring and psychometrics presented below.

7.5.2 Demographic, lifestyle, and comorbidity features

Participant demographics included: age, gender, and ethnicity. Lifestyle factors assessed included: smoking, alcohol consumption, cannabis use, and sleep quality. Sleep quality was assessed using a single item of the Pittsburgh Sleep Quality Index (Carpenter & Andrykowski, 1998). Participants were asked to respond to the question: During the past month, how would you rate your sleep quality overall? (Very good, fairly good, fairly bad, and very bad). Total comorbidity scores were calculated as disease counts using health conditions identified on the Self-Administered Comorbidity Questionnaire (Sangha et al., 2003), a 20-item extra-intestinal manifestation (EIM) checklist developed from multiple EIM investigations (Marcus Harbord et al., 2016; Huang et al., 2013; Levine & Burakoff, 2011; Trikudanathan et al., 2012), and conditions identified on the CSI (part B). HRQOL was assessed using the EuroQoL five-dimensional (EQ-5D) questionnaire (Buchholz, Janssen, Kohlmann, & Feng, 2018). The EQ-5D questionnaire descriptive system comprises five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each one with five possible levels: no problems (level 1), slight problems (level 2), moderate problems (level 3), severe problems (level 4), and extreme problems (level 5), as well as a visual analogue scale ranging from 0 to 100.

Table 7.1

Outcome Measures used to Evaluate Central Sensitization, IBD, and Pain Features

Domain	Outcome measure
Primary Outcomes	
Somatosensory function	Pressure pain threshold
	Conditioned pain modulation
	Temporal summation
Central sensitization symptoms	Central Sensitization Inventory (part A)
Secondary Outcomes	
Psychological factors	Hospital Anxiety and Depression Scale
	Perceived Stress Scale (10-item)
	Positive and Negative Affective Schedule
	Pain Catastrophizing Scale
Health-related quality of life	Short Inflammatory Bowel Disease Questionnaire
	EuroQoL five-dimensional questionnaire
Abdominal pain	PROMIS Pain Interference 4a
	Numeric rating scale (severity)
Musculoskeletal pain	Regional location (body diagram)
	PROMIS Pain Interference 4a
	Numeric rating scale (severity)
Sleep quality	Pittsburgh Sleep Quality Index (single item)
Total comorbidity score	Self-Administered Comorbidity Questionnaire
	Extra-intestinal manifestation checklist
	Central Sensitization Inventory (part B)

Note. Inflammatory bowel disease (IBD), and Patient-Reported Outcomes Measurement Information System (PROMIS).

7.5.3 Psychological features

Psychological features examined included: anxiety/depression, perceived stress, positive and negative emotional styles, and pain catastrophizing. Details of these psychological constructs are presented in Chapter 3, with assessment scoring and psychometrics presented below.

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS). Correlation between subscales (anxiety and depression) of HADS, and the internal consistency of the subscales were found to be strong with Cronbach's α values of 0.83 and 0.82, respectively (Bjelland, Dahl, Haug, & Neckelmann, 2002). Scores for each subscale range from 0 to 21, with a score of ≥ 8 representing clinically meaningful levels of anxiety or depression (Bjelland et al., 2002). Scores for the entire scale (emotional distress) range from 0 to 42, with higher scores indicating more distress.

Perceived stress in the present study was explored through the 10-item Perceived Stress Scale (PSS-10). The PSS-10 evaluates the degree to which individuals believe their life has been unpredictable, uncontrollable, and overloaded during the previous month, using a Likert scale (0-4) for each item (Cohen et al., 1983). A review of the psychometric evidence for the PSS-10 indicated good internal consistency and test-retest reliability with coefficients reaching > 0.70 in all cases (E.-H. Lee, 2012). PSS-10 scores can range from 0 to 40 with higher scores indicating higher perceived stress (Cohen et al., 1983). Categorical interpretation of PSS-10 scoring, includes: low stress (0-13), moderate stress (14-26), and high stress (27-40).

Emotional styles were explored through the Positive and Negative Affective Schedule (PANAS). This scale includes words describing 10 positive and 10 negative emotions, and requires participants to indicate on a Likert scale (1-5) the extent to which they felt each emotion during the previous week. Items included in PANAS were designed to allow independent positive and negative scoring, in acknowledgement that having, for instance, a low negative affect does not equate to having a high positive affect (Watson et al., 1988). PANAS subscales demonstrated very high correlation (α=.89 to .95) with their corresponding regression-based factor analysis scores, whereas

the discriminant correlations (α= -.02 to -.18) were quite low (Watson et al., 1988). Similarly, reliability of the positive (α=.86) and negative (α=.87) subscales were found to be high, while correlation between the scales (α= -.09) remained low.

Catastrophizing relative to pain experiences in the present study was explored through the Pain Catastrophizing Scale (PCS). This measure assesses three different domains of pain catastrophizing, including rumination, magnification, and helplessness (Michael JL Sullivan, Bishop, & Pivik, 1995). Participants are asked to indicate the degree to which they experience various thoughts and feelings when they are in pain using Likert scales ranging from (0) 'not at all' to (4), with total possible scores ranging from 0 to 52 (Michael JL Sullivan et al., 1995). Clinically relevant levels of pain catastrophizing are identified as PCS scores > 30. The Cronbach alpha values reported for the total PCS (α=.87) and factor scales (rumination, α= .87; magnification, α=.60; helplessness, α=.79) were found to be satisfactory and acceptable (Michael JL Sullivan et al., 1995). Subsequent investigations found that the PCS showed strong temporal stability and validity. Evidence for convergent validity was demonstrated with the moderate correlation of the PCS to scores on self-report measures of anxiety (r=.32; p<.001) and negative affect (r=.32; p<001). Test–retest reliability estimates for six weeks (r=.75) and 10 weeks (r=.70) in college undergraduates (Michael JL Sullivan et al., 1995), as well as in clinical adult populations (Osman et al., 2000), showed strong evidence for the stability of responses on the PCS.

7.5.4 IBD characteristics

The following IBD features were characterised in the present study: IBD subtype (Crohn's disease, ulcerative colitis, or indeterminate colitis), duration, medication use, abdominal pain, and disease severity.

Table 7.2

IBD Features Characterized through Data Extraction of Patient Medical Records

Feature	Description
IBD subtype	Crohn's disease, ulcerative colitis, indeterminate colitis
IBD duration	Months/years
Montreal classification	Age at diagnosis (≤ 16 years, 17-40 years, > 40 years)
	Disease behaviour (penetrating, stricturing, perianal)
Surgical input	Surgical history (resection and/or perianal)
	Stoma or j-pouch history
Medication use	Steroids, biologics, and immunosuppressants

Medication use in IBD participants included consideration of previous and current use of steroids, biologics, and immunosuppressants. Abdominal pain was evaluated in terms of interference and severity. Abdominal pain interference was evaluated through Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference 4a short form, developed by the National Institutes of Health. PROMIS short forms have undergone extensive qualitative expert and patient review, as well as quantitative analysis of data collected on general populations and clinical samples (Gershon et al., 2010). Positive findings for abdominal pain interference include: mild (50-59), moderate (60-69), or severe (≥70). Abdominal pain severity was evaluated using numeric rating scales recorded for worst, average, and current pain levels, with positive findings as mild (1-4), moderate (5-6), or severe (7-10) (Williamson & Hoggart, 2005).

Disease severity was assessed including: previous surgery, history of a stoma, age at diagnosis, disease behaviour, disease extent, and HRQOL. The Montreal classification system was used to describe phenotypes of IBD (Gomollón et al., 2016), to include: age at diagnosis (≤ 16 years old, 17-40 years old, and > 40 years old),

disease behaviour (penetrating, stricturing, and/or perianal disease), and disease extent. Disease extent for Crohn's disease was defined as limited disease (<40 cm ileal involvement or absence of pancolitis) or extensive disease (ileal involvement of at least 40 cm or presence of pancolitis) (Siegel et al., 2016). Disease extent for ulcerative colitis was defined as limited disease (distal to the splenic flexure) or extensive disease (beyond the splenic flexure) (Satsangi et al., 2006; Siegel et al., 2016).

HRQOL was assessed using the validated Short IBD Questionnaire (SIBDQ) (E. Irvine et al., 1996; Peyrin-Biroulet et al., 2016). SIBDQ demonstrated significant retest reliability (ICC = 0.65, Cronbach's $\alpha = 0.78$) with ability to detect clinically meaningful changes in HRQOL through the assessment of five health dimensions (bowel symptoms, systemic symptoms, functional impairment, social impairment, and emotional function) (E. Irvine et al., 1996). SIBDQ score ranges from 10 (poor HRQOL) to 70 (optimum HRQOL), with scoring interpreted as poor (10-29), moderate (30-49), and optimal (50-70).

7.5.5 MSK Pain characteristics

Characteristics of MSK pain evaluated included: location, duration, interference, and severity. Pain location was recorded regionally (n=47) using a body diagram, which previously demonstrated significant test-retest reliability (r=0.85) in chronic pain patients (Margolis et al., 1988; S. Van Erp et al., 2015; Zeitz et al., 2016). Individuals with multiple pain regions were instructed to identify their "main" area of pain. Assessments of MSK pain interference and severity related to an individual's "main" area of pain, using PROMIS Pain Interference 4a and numeric rating scales, respectively. Positive findings for the PROMIS Pain Interference 4a, include: mild (50-59), moderate (60-69), or severe (≥70). Numeric rating scales for pain severity were

recorded for worst, average, and current pain levels, with positive findings as mild (1-4), moderate (5-6), or severe (7-10) (Williamson & Hoggart, 2005).

7.5.6 Measures of central sensitization

Surrogate markers of central sensitization utilized in the present study included investigation of symptomology (i.e. CSI) and somatosensory functioning (i.e. PPT, CPM, and TS). Assessment of constructs related to central sensitization is presented in Chapter 3, with assessment scoring and psychometrics presented below.

7.5.6.1 Symptoms of central sensitization

The use of CSI as an indirect measure of central sensitization has been validated previously (AUC= 0.86, Sensitivity = 81%, Specificity = 75%) in a large population with central sensitivity syndromes (Mayer et al., 2012; Neblett et al., 2013). CSI (part A) evaluates 25 features across an array of somatic and emotional symptoms, with each item scored on a scale of 0 to 4, and overall scoring ranging from 0 to 100 (Neblett, Hartzell, Mayer, et al., 2017). Higher CSI scores indicate increased symptomology related to central sensitization, with scores ≥ 40 indicating the likely presence of central sensitivity syndromes (Mayer et al., 2012; Neblett et al., 2013).

7.5.6.2 Somatosensory functioning

7.5.6.2.1 Sensory testing conditions

All three study groups underwent the same standardized examination protocol (Appendices M & N), performed by a single investigator (CF). This investigator received training by a senior investigator (RM) for all testing procedures, and performed repeat pilot testing of all procedures on $n = 5$ healthy individuals prior to all data collection. Testing was performed in a quiet room, with participants positioned in comfortable prone lying for PPT and in supine for screening assessments, TS, and

CPM. All participants were provided a trial of each assessment to familiarize themselves with the procedure at remote body locations before data collection was initiated.

7.5.6.2.2 Screening assessments

Screening assessments used to detect the presence of peripheral neuropathies in the present study included Semmes-Weinstein monofilament examination (SWME) (Feng, Schlösser, & Sumpio, 2009; Olaleye, Perkins, & Bril, 2001) and vibration detection threshold (VDT) (Whitton, Johnson, & Lovell, 2005). The SWME demonstrated high sensitivity (93.1%) and specificity (100%) for identifying decreased sensation confirmed by gold standard nerve conduction tests (Feng et al., 2009). SWME of the upper limb was performed using a 4.56 (4 g) monofilament at six locations divided over the palm and fingers, bilaterally (Schreuders, Selles, van Ginneken, Janssen, & Stam, 2008). SWME of the lower limb was performed using a 5.07 (10 g) monofilament at the pulp of the great toe, as well as the first, third, and fifth metatarsal heads, bilaterally (Feng et al., 2009). VDT was assessed using a Rydel–Seiffer graded tuning fork (64 Hz, 8/8 scale) placed over bony prominences (styloid process of the ulna and medial malleolus), bilaterally. Participants were instructed to verbally indicate the moment they could no longer feel the sensation of vibration, and this value was recorded. VDT of each site was described as the mean of three trials (Rolke et al., 2006).

7.5.6.2.3 Pressure pain threshold

PPT was assessed at two locations for all groups: 1) low back (local) – at the middle of a horizontal line drawn between the upper border of the iliac crest and the corresponding spinous process, divided randomly between the left/right sides of the

body; and 2) contralateral Tibialis anterior (5 cm distal to the Tibial tuberosity) (Neziri et al., 2013).

Previous reports of chronic abdominal pain have hypothesized the presence of central sensitization as a consequence of relapsing/remitting courses of peripheral inflammation (Bielefeldt et al., 2009). Periods of active inflammation typically result in acute abdominal pain, which often refers to the low back region as a result of neural sensitivity between visceral and somatosensory neurons within the spinal cord (Bielefeldt et al., 2009; Kristen E Farrell et al., 2014). Reports of abdominal pain experienced in periods beyond active inflammation is thought to demonstrate enduring mechanisms of central sensitization along these same neural pathways (Bielefeldt et al., 2009; Kristen E Farrell et al., 2014). Therefore, the low back may represent the MSK region most likely to demonstrate changes in neural sensitivity (i.e. peripheral and central sensitization) in this population. Conversely, sensitivity demonstrated at a remote region (e.g. Tibialis anterior) may be suggestive of widespread versus regional sensitivity, characteristic of mechanisms related to central sensitization (den Boer et al., 2019; Clifford J Woolf, 2011).

PPT was assessed using an electronic handheld algometer (Wagner Force One™ FDIX), by a series of three ascending stimulus intensities with a 60 second interval between trials. Each stimulus was given as a slowly increasing ramp (approximately 50 kPa/s) from 0 to a maximum pressure of 1000 kPa (Neziri et al., 2013; Rolke et al., 2006). If the participant did not indicate pain at 1000 kPa, this value was considered as the PPT. Participants were instructed to verbally stop the test when the sensation of pressure alone changed to one of pressure and pain, with the corresponding pressure recorded for each trial. PPT for each region was described as the mean of three trials. Lower scores indicate greater pain sensitivity.

Assessment of PPT in the low back region previously demonstrated positive test–retest reliability and agreement using electronic algometers (Vuilleumier et al., 2015). Specifically, PPT assessments demonstrated excellent intra-examiner reliability at the Tibialis anterior muscle (ICC=0.91; 95 % CI 0.31–0.95) and lumbar muscles (ICC=0.82; 95 % CI 0.65–0.97) (Corrêa, Costa, de Oliveira, Sluka, & Liebano, 2015). PPT similarly demonstrated strong discriminative validity between chronic pain patients and healthy controls (OR=0.10; 95% CI 0.04-0.24), p<.001) (Neziri et al., 2012).

7.5.6.2.4 Conditioned pain modulation

Assessment of CPM was performed immediately following the assessment of PPT described above. PPT of Tibialis anterior was used as the test stimulus and a standardized ice bath to the contralateral hand as the conditioning stimulus. The magnitude of the CPM effect in the present study was defined as the percent change score between PPT after compared to before the conditioning stimulus. A higher CPM change score suggested greater pain modulation and the participant is said to be a CPM responder. CPM has previously demonstrated positive evidence of test–retest reliability and agreement using PPT and an ice bath as test and conditioning stimulus, respectively (Vuilleumier et al., 2015).

Pressure stimulation

PPT on Tibialis anterior was performed as described above, prior to and immediately following the conditioning stimulus.

Conditioning stimulus

Participants were asked to submerge their hand contralateral to the test site (Tibialis anterior), wide open and up to the wrist, in a container of circulating ice water,

for a maximum of 2 minutes. The temperature of the ice water was maintained below 3°C, monitored by a thermometer with a digital display (Mlekusch et al., 2016; Neziri et al., 2013; D Yarnitsky et al., 2015). Participants were instructed to withdraw their hand when the pain perceived became intolerable or when the 2 minute maximum was reached. Participants were asked to give a numeric pain rating (0-10) at the time of hand removal. Total immersion time and pain rating of the conditioning stimulus were recorded.

7.5.6.2.5 Mechanical temporal summation

Mechanical TS was assessed on the volar aspect of the non-dominant arm using a Semmes-Weinstein monofilament (no. 6.65) (LeResche, Turner, Saunders, Shortreed, & Von Korff, 2013). The perceived intensity of a single stimulus was compared with that of a series of 10 repetitive stimuli of the same physical intensity (1/s applied within an area of 1 cm^2) (Rolke et al., 2006). Participants were asked to give a pain rating for the single stimulus and a pain rating for the series of 10 stimuli as a whole, using a '0–10' numerical rating scale. This procedure was repeated for three trials, with 1 minute between trials, and performed at different areas of the volar forearm for each trial. Mechanical TS in the present study was defined as the percent change score between the mean pain rating of 10 series and the mean pain rating of the single stimuli. Higher percent change scores indicated greater TS, indicating an increased gain or facilitation into the CNS. Assessments of TS have previously demonstrated positive evidence of test–retest reliability and agreement (Vuilleumier et al., 2015), with strong discriminative validity between chronic pain patients and healthy controls (OR=0.30; 95% CI 0.17-0.54), p<.001) (Neziri et al., 2012).

7.5.7 Sample size

A priori sample size estimation for the between-group comparison in the present study (Chapter 8) was calculated using G*Power based on the mean and standard deviation (SD) of PPTs previously reported for the low back region in chronic low back pain, chronic widespread pain, central sensitivity syndromes, and health populations (Gerhardt et al., 2016; Marcuzzi, Wrigley, Dean, Adams, & Hush, 2017; Meeus, Roussel, Truijen, & Nijs, 2010; Vuilleumier et al., 2015). Given the available data, total sample size of N=120 was estimated as able to demonstrate between group differences at 80% power and 5% level of significance.

7.6 Chapter summary

This chapter presents the full protocol for Study 2 of the present thesis, aimed at exploring measures of central sensitization across three groups, as well as associations of IBD, psychological, demographic, comorbidity, and lifestyle factors to measures of central sensitization. The results and discussion related to the primary and secondary aims of this study are presented in Chapters 8 and 9, respectively.

8 Study Two: Between-group Comparisons for Measures of Central Sensitization

8.1 Chapter overview

The following chapter presents the statistical analysis, results, and discussion related to the primary aim of Study 2 to assessing central sensitization in IBD patients with MSK pain.

8.2 Study Aims

1. To investigate differences in measures of central sensitization (i.e. CSI, PPT, CPM, and TS) across three groups: 1) IBD patients presenting with MSK pain, 2) IBD patients without MSK pain and 3) healthy controls.
2. To investigate whether between-group differences demonstrated above are confounded by psychological factors (PSS, PANAS (positive), PANAS (negative), HADS (anxiety), HADS (depression), and PCS).

8.3 Hypotheses

1. IBD patients presenting with MSK pain will demonstrate greater symptomology related to central sensitization (i.e. CSI scores) and altered somatosensory functioning (i.e. PPT, CPS, and TS) when compared to IBD patients without MSK pain and to healthy controls. Similarly, IBD patients without MSK pain will demonstrate greater symptomology related to central sensitization (i.e. CSI scores) and altered somatosensory functioning (i.e. PPT, CPS, and TS) when compared to health controls.

2. Psychological factors will demonstrate a degree of confounding in the measures of central sensitization demonstrating between-group differences described above.

8.4 Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics (version 26). Descriptive statistics were used to characterize IBD, pain, psychological, demographic, comorbidity, lifestyle, and measures of central sensitization evaluated in the present study. Where appropriate, Chi-square/Fisher's exact tests (categorical variables) and independent t-tests (continuous variables) were used to characterize differences between the two IBD groups with regards to IBD features. Similarly, where appropriate, Chi-square/Fisher's exact tests (categorical variables) and one-way analyses of variance (ANOVAs)/Kruskal-Wallis ANOVAs (continuous variables) were used to characterize differences between the three groups for psychological, demographic, lifestyle, and comorbidity features. Significance was identified at $P \leq .05$.

ANOVAs/Kruskal-Wallis ANOVAs were used to investigate between-group differences for measures of central sensitization as the primary aim of the current study. Assumptions for all ANOVA models were assessed to ensure model fit, including: normality of scoring distribution (Shapiro-Wilk tests) and homoscedasticity (scatterplot of residuals). Bonferroni and Mann Whitney's tests were used to explore post hoc comparisons for measure of central sensitization, with significance identified at $P \leq .05$.

One-way Analyses of covariance (ANCOVAs) were used to investigate potential confounding by psychological features for measures of central sensitization demonstrating significant between-group differences ($P \leq .05$). Adjustment for potential confounders aims to provide an undistorted estimate of the relationship

between the independent and dependent variables (MacKinnon et al., 2000). Additional assumptions for ANCOVAs were explored, including tests of normality listed above and Levene's test for homogeneity.

8.5 Results

A total of 77 individuals (53 IBD patients and 24 healthy controls) volunteered to participate in Study 2 of the present thesis. Of the patients with IBD, 24 reported no history of MSK pain and 29 reported the presence of MSK pain lasting longer than 3 months within the past year. None of the IBD patients nor the healthy controls were indicated as having features of peripheral neuropathy during screening assessments (i.e. SWME and VDT). However, two IBD patients were later diagnosed with neurological conditions and were therefore excluded from the present analysis. Similarly, 2 healthy controls were excluded due to a diagnosis of diabetes mellitus. With the exception of one participant representing an 8 year age gap, the remaining participants were age (± 5 years) and gender matched across the following three study groups: IBD patients with MSK pain (n=22), IBD patients without MSK pain (n=22), and healthy controls (n=22).

Results of Study 2 (primary aims) are presented below under the subheadings: 1) demographics, comorbidity, and lifestyle factors (descriptive statistics), 2) IBD features (descriptive statistics), 3) MSK pain features (descriptive statistics), Psychological features (descriptive), and 4) measures of central sensitization (descriptive and between-group comparisons).

8.5.1 Demographics, comorbidity, and lifestyle factors

Demographic, lifestyle, and comorbidity status of the study participants are presented in Table 8.1. Participants represented the following ethnic groups, with one

participant identifying with two groups: White (*n*=63), African American (*n*=1), and Asian American (*n*=3).

Table 8.1

Participant Characteristics across the Three Study Groups (N = 66)

Characteristic	IBD with MSK pain (*n* = 22)	IBD without MSK pain (*n* = 22)	Healthy controls (*n* = 22)	*P*
Gender				-
Male, *n* (%)	10 (45)	10 (45)	10 (45)	
Female, *n* (%)	12 (55)	12 (55)	12 (55)	
Age				-
Range (years)	18 - 68	21 - 67	19 - 59	
Mean (SD)	37.64 (11.50)	37.95 (12.97)	37.73 (11.12)	
Total comorbidity				
Range (*n*)	1 - 6	0 - 5	0	
Mean (SD)	3.14 (1.73)	1.68 (1.52)	0	
Smoking (yes, *n* (%))	1 (5)	1 (5)	0 (0)	
Alcohol consumption				0.019[a*]
Yes, occasionally	12 (55)	13 (59)	16 (73)	
Yes, regularly	2 (9)	5 (23)	6 (27)	
No	8 (36)	4 (18)	0 (0)	
Cannabis use (yes, *n* (%))	9 (41)	4 (18)	2 (9)	0.048[b*]
Poor sleep quality	10 (45)	4 (18)	0 (0)	0.012[a*]
EuroQol-5D-5L				
Total (mean (*SD*))	7.29 (1.62)	5.45 (0.74)	5.41 (0.80)	<0.001[c*]
VAS (mean (*SD*))	70.48 (20.55)	83.64 (11.40)	89.91 (8.33)	<0.001[c*]

Note. Inflammatory bowel disease (IBD), musculoskeletal (MSK), standard deviation (SD), health-related quality of life questionnaire (EuroQol-5D-5L), and visual analogue scale (VAS).

[a] Fisher's exact test.

[b] Chi-squared.

[c] Kruskal-Wallis analysis of variance.

* Significant at $p \leq 0.05$.

8.5.2 IBD features

A summary of IBD features observed in the current study are presented in Tables 8.2 to 8.4. No significant differences were found between the two IBD groups for any of the observed IBD features.

Table 8.2

IBD Features of Study participants across Two Study Groups (n = 44)

Assessment	IBD with MSK pain (*n* = 22)	IBD without MSK pain (*n* = 22)	*P*
IBD subtype			0.901 [a]
Crohn's disease (*n* (%))	11 (50)	13 (59)	
Ulcerative colitis (*n* (%))	9 (41)	7 (32)	
Indeterminate colitis (*n* (%))	2 (9)	2 (9)	
IBD duration, years (mean (*SD*))	13.77 (10.47)	14.45 (10.38)	0.985 [b]
Range	1-42	2-41	
Surgical history, yes (*n* (%))	10 (45)	8 (36)	0.540 [c]
SIBDQ	51.50 (6.47)	55.77 (9.38)	0.355 [b]
Abdominal pain (*n* (%))	13 (59)	7 (32)	0.069 [c]
Severity (NRS) (mean (*SD*))	4.23 (2.09)	2.57 (2.51)	
PROMIS Pain interference 4a (mean (*SD*))	57.30 (9.51)	53.26 (12.79)	

Note. Inflammatory bowel disease (IBD), musculoskeletal (MSK), standard deviation (SD), Short Inflammatory Bowel Disease Questionnaire (SIBDQ), numeric rating scale (NRS), and Patient-Reported Outcomes Measurement Information System (PROMIS).

[a] Fisher's exact test.

[b] Independent t-test.

[c] Chi-squared.

Table 8.3

Montreal Classification of Two Study Groups (n = 44)

Characteristic	IBD with MSK pain (*n* = 22)	IBD without MSK pain (*n* = 22)	*P*
Age at diagnosis (*n* (%))			0.056 [a]
≤ 16 years old	8 (36)	3 (14)	
17-40 years old	12 (55)	18 (82)	
> 40 years old	2 (9)	0 (0)	
Location (*n* (%))			-
Crohn's disease			
Terminal ilium	4 (31)	2 (13)	
Colon	4 (31)	3 (20)	
Ileocolon	5 (38)	9 (60)	
Ulcerative colitis			
Proctitis	1 (11)	1 (14)	
Left-sided	0 (0)	2 (29)	
Extensive	8 (89)	5 (71)	
Behaviour (*n* (%))			1.000 [a]
Stricturing	3 (14)	3 (14)	
Penetrating	4 (18)	5 (23)	
Both stricturing/penetrating	3 (14)	3 (14)	
Perianal	9 (41)	8 (36)	

Note. Inflammatory bowel disease (IBD) and musculoskeletal (MSK).
[a] Fisher's exact test.

* Significant at $p \leq 0.05$.

Table 8.4

IBD Medication Use of Study Participants (n = 44)

Characteristic	IBD with MSK pain (n = 22)	IBD without MSK pain (n = 22)	P
Steroids (n (%))			0.318 [a]
Never	3 (14)	8 (36)	
Previous	17 (77)	12 (55)	
Current use	2 (9)	2 (9)	
Biologic (n (%))			0.414 [a]
Never	1 (5)	4 (18)	
Previous	2 (9)	2 (9)	
Current	19 (86)	16 (73)	
Immunosuppressant (n (%))			0.602 [a]
Never	13 (59)	10 (45)	
Previous	7 (32)	8 36)	
Current	2 (9)	4 (18)	

Note. Significance identified at $p \leq 0.05$. Inflammatory bowel disease (IBD) and musculoskeletal (MSK).

[a] Chi-squared.

8.5.3 Musculoskeletal Pain features

MSK pain features of IBD patients are presented in Tables 8.5. Of the participants reporting the presence of MSK pain, 59% (n = 13) also reported the presence of abdominal pain. Of the MSK regions identified as painful by study participants, the low back (n = 11, 31%) and mid back (n = 11, 31%) were the most frequently reported regions, while the posterior neck (n = 4, 27%) was most frequently identified as the 'main area of pain'. A summary of all painful regions reported by participants is presented in Tables O.1 – O.3, located in Appendices O.

Table 8.5

Summary of Musculoskeletal Pain Characteristics of Study Participants

Characteristic	Range	Mean (*SD*)
Body map, painful regions (*n*)	2-17	8.32 (4.61)
Strongest pain severity (NRS)	0-9	4.86 (2.55)
Average pain severity (NRS)	0-7	3.14 (2.05)
PROMIS Pain Interference 4a	41.6 - 66.6	53.83 (7.54)

Note. Standard deviation (SD), numeric rating scale (NRS), and Patient-Reported Outcomes Measurement Information System (PROMIS).

8.5.4 Psychological features

8.5.4.1 Descriptive statistics

Psychological features of the study participants are presented in Table 8.6. The majority of participants in both IBD groups (*n* = 12, 55%) demonstrated moderate levels of perceived stress, while the majority of healthy controls (*n* = 14, 64%) demonstrated mild perceived stress. Only one IBD patient without MSK pain reached a clinically meaningful score (>30) of pain catastrophizing. HADS subscales indicated 45% (*n* = 10) of IBD patients with MSK pain demonstrated clinically meaningful scores for the presence of anxiety (≥ 8), whereas only 14% (*n* = 3) of these same patients demonstrated clinically meaningful scores for depression (≥ 8). Conversely, 23% (*n* = 4) of IBD patients without MSK pain and 23% (*n* = 4) of healthy controls demonstrated clinically meaningful scores for anxiety, with no IBD patients without MSK pain and 5% (*n* = 1) of the healthy controls demonstrating clinically meaningful scores for depression.

Table 8.6

Psychological Features across Three Study Groups (N = 66)

Assessment	IBD with MSK pain Mean (*SD*)	IBD without MSK pain Mean (*SD*)	Healthy controls Mean (*SD*)	*P*
HADS				
Anxiety	7.59 (3.97)	6.05 (3.08)	5.45 (3.58)	0.175[a]
Depression	4.05 (3.44)	2.73 (2.12)	2.50 (2.60)	0.226[a]
10-PSS	15.55 (7.58)	13.55 (7.35)	10.18 (5.88)	0.043[b*]
PANAS				
Positive affect	31.05 (6.19)	33.95 (7.38)	35.86 (5.70)	0.052[b]
Negative affect	19.18 (6.90)	16.27 (4.23)	16.18 (3.70)	0.270[a]
PCS	8.76 (7.53)	7.45 (9.26)	1.95 (2.98)	0.001[a*]

Note. Inflammatory bowel disease (IBD), musculoskeletal (MSK), standard deviation (SD), Hospital Anxiety and Depression Scale (HADS), 10-item Perceived Stress Scale (PSS), Positive and Negative Affective Schedule (PANAS), and Pain Catastrophizing Scale (PCS).

[a] Kruskal-Wallis analysis of variance

[b] One-way analysis of variance

* Significant at $p \leq 0.05$.

8.5.5 Measures of central sensitization

8.5.5.1 Descriptive statistics

A summary of participant scores for CSI, PPT, CPM, and TS are presented in Table 8.7. CSI scores were normally distributed (Shapiro-Wilk, $p \geq 0.05$), with an overall range of 3 to 56 in study participants. Within the three study groups, 45% (n = 10) of IBD patients with MSK pain demonstrated benchmarked CSI scores (≥40) representing patients with the likely presence of central sensitivity syndromes. Conversely, 18% (n = 4) of patients without MSK pain and no healthy controls demonstrated benchmarked CSI scores. PPT of the Tibialis anterior region was normally distributed (Shapiro-Wilk, $p \geq 0.05$), with an overall range of 118.01 to 754.13 kPa in study participants. PPT of the low back, CPM, and TS were not normally

distributed (Shapiro-Wilk, $p < 0.05$) within study groups. PPTs of the low back region ranged from 115.06 to 793.36 kPa, CPM scores ranged from - 43% to 185%, and TS scores ranged from 0% to 4% in study participants

8.5.5.2 Between group comparisons

Results for one-way ANOVAs to examine between-group differences for measures of central sensitization are summarised in Table 8.7. There was a statistically significant difference between groups for mean CSI scores ($F(2,63) = 19.835$, $p < 0.001$, $r = .62$), with an observed power of greater than 90%. A Bonferroni post hoc test revealed that mean CSI scores were significantly ($p \leq 0.05$) different between groups (mean difference ± standard error, [95% confidence intervals]), including IBD patients with MSK pain compared to without MSK pain (10.64 ± 3.15, [2.89, 18.38], $p = 0.004$), IBD patients with MSK pain compared to healthy controls (19.82 ± 3.15, [12.07, 27.56], $p <0.001$), and IBD patients without MSK pain compared to healthy controls (9.18 ± 3.15, [1.44, 16.93], $p = 0.015$). There were no statistically significant differences between group means for remaining measures of central sensitization, including: PPT of Tibialis anterior ($F(2,63) = 0.906$, p = 0.409), PPT of the low back ($H(2) = 1.620$, $p = 0.445$), CPM ($H(2) = 2.671$, $p = 0.263$), and TS ($H(2) = 3.129$, $p = 0.209$).

Table 8.7

Measures of Central Sensitization across Three Study Groups (N = 66)

Measure	IBD with MSK pain Mean (*SD*)	IBD without MSK pain Mean (*SD*)	Healthy controls Mean (*SD*)	One-way ANOVA/Kruskal-Wallis
CSI	36.86 (9.63)	26.23 (12.68)	17.05 (8.58)	$F(2,63)=19.84$, $p<0.001$*
PPT (LB) [a]	370.07 (168.14)	369.98 (215.77)	432.29 (182.12)	$H(2) = 1.62$, $p = 0.445$
PPT (TA) [a]	381.94 (178.77)	398.77 (174.17)	450.05 (171.50)	$F(2,63) = 0.91$, $p = 0.409$
TS [b]	100 [54 - 146]	133 [100 - 200]	100 [62 - 144]	$H(2) = 2.67$, $p = 0.263$
CPM [a b c]	20 [8 - 29]	29 [13 - 47]	24 [16 - 30]	$H(2) = 3.13$, $p = 0.209$

Note. Inflammatory bowel disease (IBD), musculoskeletal (MSK), standard deviation (SD), analysis of variance (ANOVA), central sensitization inventory (CSI), pressure pain threshold (PPT), low back (LB), Tibialis anterior (TA), temporal summation (TS), and conditioned pain modulation (CPM).

[a] Values represent raw scoring for measures.

[b] Values represent percent change for dynamic somatosensory measures.

[c] Median [interquartile range]

* Significant at $p \leq 0.05$.

Results for one-way ANCOVAs comparing CSI scores between study groups while controlling for individual psychological features are presented in Table 8.8. There was a significant difference in mean CSI scores between study groups when individually controlling for PSS ($F(2,62) = 15.445$, $p < 0.001$, $r = .75$), PANAS (positive) ($F(2,62) = 15.058$, $p < 0.001$, $r = .71$), PANAS (negative) ($F(2,62) = 15.058$, $p < 0.001$, $r = .75$), HADS (anxiety) ($F(2,62) = 18.173$, $p < 0.001$ $r = .73$), HADS (depression) ($F(2,62) = 18.978$, $p < 0.001$, $r = .76$), and PCS and $F(2,55) = 12.488$, $p < 0.001$, $r = .78$). Post hoc comparisons indicated that after controlling for psychological variables, CSI scores were still significantly different ($p \leq 0.05$) between IBD patients with and without MSK pain, as well as healthy controls. However, adjustment for PSS and PCS no longer demonstrated significant differences in CSI scores between IBD patients without MSK pain and healthy controls ($p = 0.063$ and $p = 0.593$, respectively).

Table 8.8

Mean differences for Central Sensitization Inventory Scores between Three Study Groups Adjusted for Psychological Features

CSI		IBD with MSK pain compared to IBD without MSK pain		IBD with MSK pain compared to healthy controls		IBD without MSK pain compared to healthy controls	
	Model summary	MD (SE), [95% CI]	*P*	MD (SE), [95% CI]	*P*	MD (SE), [95% CI]	*P*
Unadjusted	R=0.62, F(2,63)=19.84, p<.001*	10.64 (3.15), [2.89, 18.38]	.004*	19.82 (3.15), [12.07, 27.56]	<.001*	9.18 (3.15), [1.44, 16.93]	.015*
Adjusted							
PSS	R=0.75, F(2,62)=15.45, p<.001*	9.01 (2.68), [2.41, 15.62]	.004*	15.46 (2.80), [8.57,22.35]	<.001*	6.45 (2.72), [-0.243, 13.14]	.063
PANAS-positive	R=0.71, F(2,62)=15.06, p<.001*	8.60 (2.91), [1.44, 15.76]	.013*	16.44 (3.00), [9.07, 23.82]	<.001*	7.84 (2.88), [0.75, 14.94]	.025*
PANAS-negative	R=0.75, F(2,62)=18.17, p<.001*	7.45 (2.75), [0.69, 14.21]	.026*	16.53 (2.75), [9.76, 23.31]	<.001*	9.08 (2.68), [2.50, 15.66]	.004*
HADS-anxiety	R=0.73, F(2,62)=17.25, p<.001*	8.41 (2.81), [1.50, 15.33]	.012*	16.74 (2.85), [9.73, 23.76]	<.001*	8.33 (2.77), [1.51, 15.15]	.011*
HADS-depression	R=0.76, F(2,62)=18.98, p<.001*	7.82 (2.67), [1.26, 14.38]	.014*	16.52 (2.69), [9.91, 23.13]	<.001*	8.70 (2.62), [2.26, 15.14]	.004*
PCS	R=0.78, F(2,55)=12.49, p<.001*	10.56 (2.81), [3.63, 17.49]	.001*	14.17 (2.95), [6.88, 12.47]	<.001*	3.61 (2.77), [-3.23, 10.45]	.593

Note. Central sensitization inventory (CSI), inflammatory bowel disease (IBD), musculoskeletal (MSK), standard error (SE), perceived stress scale (PSS), positive and negative affect schedule (PANAS), hospital anxiety and depression scale (HADS), and pain catastrophizing scale (PCS).

* $p \leq 0.05$.

8.6 Discussion

The primary aim of Study 2 was to explore between-group differences for measures of central sensitization (i.e. CSI, PPT, CPM, and TS). Analysis indicated that CSI was the only measure of central sensitization to demonstrate a significant difference between study groups. Investigation of confounding factors for between-group differences demonstrated a significant influence on CSI scores from all of the psychological features explored in the present study. However, CSI scores remained significantly different between all study groups even after controlling for psychological confounding, with the exception of perceived stress and pain catastrophizing. Models controlling for PSS and PCS demonstrated that mean CSI scores were no longer significantly different between IBD patients without MSK pain and healthy controls. However, the modest sample size may have resulted in a type II error causing analysis for PSS and PCS to falsely not reach significance. Future research utilizing a larger sample size would help to confirm whether PSS and PCS influence differences in CSI scoring between IBD patients without MSK and healthy controls.

The present study did not demonstrate significant differences in somatosensory functioning (i.e. PPT, CPM, and TS) between the three study groups. These results may suggest that either altered somatosensory functioning is not contributing to persistent MSK pain in IBD patients, or that altered somatosensory functioning represents a more complex construct than is simply identified by the presence of IBD and/or MSK pain. Current literature suggests measures of somatosensory functioning may be influenced by additional features, such as specific pain presentations (Blumenstiel et al., 2011; Maier et al., 2010). Previous studies investigating a variety of discrete pain types, including neuropathic conditions, fibromyalgia, and chronic back pain, have indicated that different conditions present with different somatosensory profiles (Blumenstiel et

al., 2011; Maier et al., 2010). Similarly, different neurological conditions demonstrated a mixed profile of altered somatosensory functioning, suggesting that somatosensory assessments vary within as well as between pain types (Maier et al., 2010). Therefore, the diversity of MSK pain types represented in the present study may have contributed to variability in somatosensory assessments, resulting in a lack of statistical difference between the current study groups.

In addition to MSK pain types, influences from various lifestyle factors to somatosensory assessments have been documented for both pain and healthy populations (Gierthmühlen et al., 2015; Mani, Adhia, Leong, Vanneste, & De Ridder, 2019; Schuh-Hofer et al., 2013). An ongoing challenge of investigations utilizing current somatosensory assessments relates not only to identify, for instance, lifestyle factors which influence assessments but also in recruiting healthy participants across demographic spectrums which adhere to the strict exclusion of common factors stated in current guidelines, such as sleep disturbances, (Gierthmühlen et al., 2015). Although the present study attempted to closely follow these guidelines for healthy controls, strict adherence was not feasible. Therefore, results may reflect influences from factors, such as sleep disturbances, across all study groups, thus contributing to the variability in somatosensory assessments. Similarly, IBD patients in the present study did not differ significantly based on individual IBD factors. As such, results are unable to suggest whether certain IBD factors may have influenced measures of central sensitization in the present study, such as previous surgical history and/or abdominal pain experiences.

Although central sensitization has been proposed in the generation and maintenance of chronic abdominal and post-surgical pain in IBD patients, (Bielefeldt et al., 2009; Kristen E Farrell et al., 2014; Hains et al., 2010), there have been few investigations of somatosensory functioning in IBD (Huehne et al., 2009; Munster et

al., 2015). These investigations were limited in their scope, assessing the dorsum of bilateral hands in patients specifically with Crohn's disease. Similar to current study results, Munster, et al. (2015) reported no difference in PPT and TS between Crohn's disease patients and healthy controls. Conversely, the same authors reported a significant decrease in heat detection, vibration detection, and mechanical pain thresholds in Crohn's disease patients compared to healthy controls (Munster et al., 2015). However, authors did not report on factors known to influence somatosensory assessments, such as psychological and lifestyle factors, as well as the use of biologic therapies, which are recognized as a cause of peripheral neuropathy (i.e. altered somatosensory functioning) in IBD patients (Burger & Florin, 2009; Singh, Kumar, Loftus Jr, & Kane, 2012).

The between-group differences for CSI scoring seen in current results are similar to those in Study 1 of this thesis, where the presence of persistent MSK pain demonstrated greater symptoms of central sensitization (higher CSI scores). Previous studies report similar findings, with higher CSI scoring in chronic MSK pain patients when compared to healthy controls (Kregel et al., 2017; Mayer et al., 2012). In fact, a study exploring subpopulations of MSK pain (i.e. fibromyalgia, chronic widespread pain, and chronic regional low back pain) showed that all MSK pain types presented with greater symptoms of central sensitization compared to healthy controls (Mayer et al., 2012). However, in addition to MSK pain, the between-group differences for CSI scoring in the current study indicate that the presence of IBD independent of MSK pain was also associated with higher CSI scoring. These results highlight the need for further investigation to understand the relationship between IBD and central sensitization outside of MSK pain experiences.

The influences of psychological features on CSI scoring in the present study are similar to previous reports in the literature. Psychometric validation of CSI indicated that symptoms of emotional distress accounted for over 7% of the variance in CSI scoring and consequently have been identified as one of the four primary domains of this measure (Mayer et al., 2012). However, in the current study, it was interesting to note that CSI scores remained significantly different between all of the study groups after controlling for psychological features. This suggests that the relationship between greater symptoms of central sensitization and the presence of MSK pain and IBD is not explained by psychological functioning alone, therefore implicating participation from other CSI domains.

As previously described, the CSI questionnaire was developed with the intention of producing a screening assessment to identify patients whose presenting symptoms are related to an underlying presence of central sensitization (Mayer et al., 2012; Neblett et al., 2015). CSI explores features of psychological distress, sleep disturbances, fatigue, pain, and hyperalgesia/allodynia (i.e. visceral and somatic) in order to quantify the sensitivity of the somatosensory system (Kregel et al., 2017; Mayer et al., 2012; Verne et al., 2001; Yunus, 2008). Therefore, in addition to psychological features, interpretation of current study results within the domains of CSI would suggest that IBD patients with and without MSK pain may demonstrate a greater influence from features such as sleep quality, multiple pain sources (i.e. abdominal and MSK), as well as visceral hypersensitivity (i.e. functional bowel changes). Interestingly, sleep quality was found to be significantly different between the three study groups, where IBD patients with MSK pain demonstrated worse sleep quality (Table 8.1). Future research should explore the contributions of additional patient

features to overall CSI scores in order to better understand the nature of somatosensory sensitivity in IBD patients.

As previously described, the use of CSI has been promoted in chronic pain algorithms as a method of identifying the need for further mechanistic investigation (Nijs et al., 2015; Nijs et al., 2014). Therefore, although the present study did not identify differences in somatosensory functioning across the study groups, the fact that CSI scores were significantly higher in IBD patients, increasingly so in those with MSK pain presentations, supports continued investigation of central mechanisms in this population. However, future research should employ methodologies to account for the variability in measures described above, such as investigation of targeted MSK pain subtypes, as well as an exploration of influences from additional participant features, such as lifestyle and clinical IBD features.

Additionally, although the present study included age and gender matching across all of the groups, interpretation of study results should consider the modest sample size. The sample size estimate (N = 120) in the present thesis was based on the mean (SD) of PPTs previously reported for the low back region. However, due to restrictions during the data recruitment phase of this study, the resultant sample size (N = 66) suggests the current results are likely significantly underpowered. Post hoc analysis for CSI scores (>90%) suggest that the current sample may be sufficient to detect between-group differences for CSI, while remaining insufficient to detect differences in PPT, CPM, and TS assessments. The consequence of the resultant small sample size is primarily a reduced probability of detecting a difference between groups, where a difference exists for these assessments (type II error). Therefore, future IBD research should explore PPT, CPM, and TS assessments in adequately powered investigations to confirm current study findings. Similarly, the sample size in the

present study did not allow for a final ANCOVA to present a model of best fit, controlling for the combined psychological variables reaching significance.

Assessment of somatosensory functioning in the current study did not include the full battery of quantitative sensory testing. Therefore, interpretation of somatosensory functioning in the current study relates only to PPT, mechanical TS, and CPM, without indication of additional sensory modalities, such as thermal and pain tolerance thresholds. PPT investigated in the present thesis included assessments at the low back and Tibialis anterior regions only. While the low back region was overall the most frequently reported pain region among IBD patients, it was not the most frequently reported "main" region of pain. Therefore, between-group comparison for this measure does not reflect differences for the most painful region in most patients.

8.7 Chapter summary

The present study is the first to investigate differences in measures of central sensitization between three groups: IBD patients with and without MSK pain, and healthy controls. Study results indicate that IBD patients demonstrated significantly greater symptoms of central sensitization compared to healthy controls. Furthermore, results indicated that the additional presence of persistent MSK pain in IBD demonstrated the greatest magnitude of central sensitization symptoms compared to patients without MSK pain and healthy controls. Study results also suggest that somatosensory assessments may be influenced by additional patient features, such as IBD, psychological, pain, demographics, comorbidity, and lifestyle factors. Therefore Chapter 9 presents the statistical analysis, results, and discussion related to the secondary aims of Study 2, to investigate associations between measures of central sensitization and IBD, as well as features within additional patient domains (i.e. psychological, demographic, comorbidity, and lifestyle).

9 Study Two: Associations between Measures of Central Sensitization and Multiple IBD Patient Domains

9.1 Chapter overview

The current chapter presents the statistical analysis, results, and discussion related to the secondary aims of Study 2: to investigate associations between measures of central sensitization and IBD, as well as features within additional patient domains (i.e. psychological, demographic, comorbidity, and lifestyle). Therefore, the results presented below relate to data collected solely on IBD patients (n = 51) in Study 2, who are thus referred to as the "participants" in this chapter.

9.2 Secondary Study Aim

- To investigate the association between measures of central sensitization (i.e. CSI, PPT, TS, and CPM) and IBD features, as well as psychological, demographic, comorbidity, and lifestyle features in patients with IBD.

9.3 Hypothesis

It was hypothesized that IBD features will demonstrate a positive association with measures of central sensitization. It was further hypothesized that models predicting measures of central sensitization will demonstrate influences from multiple additional domains, including worse IBD, psychological, lifestyle, and comorbidity status.

9.4 Statistical Analysis

All statistical analysis was performed using IBM SPSS Statistics (version 26). Descriptive statistics were used to characterize IBD, pain, psychological, demographic, comorbidity, lifestyle, and central sensitization features evaluated in the present study.

A 2-step procedure was used to investigate the relationship between IBD features and measures of central sensitization. Step 1 included calculation of correlation coefficients (Pearson product-moment, Spearman rank-order, and point-biserial) to assess bivariate relationships between independent variables (IBD, psychological, demographics, comorbidity, and lifestyle features) and dependent variables (CSI, PPT, CPM, and TS). Significant correlations were identified as $p \leq 0.05$ and strength of correlation defined as: very strong (≥ 0.80), strong ($0.50 – 0.79$), moderate ($0.30 – 0.50$), weak ($0.20 – 0.30$), and very weak (< 0.19).

Step 2 involved multiple linear regression analyses for each dependent variable (CSI, PPT, CPM, and TS) and primary independent variables (IBD features), if they demonstrated significant correlation ($p \leq 0.05$). Secondary independent variables demonstrating significant correlations were individually assessed for their overall impact to step 2 modelling through stepwise entry into the model. Secondary variables resulting in a $\geq 10\%$ change in R^2 were included in the final backward regression model. Due to the modest sample size ($n = 51$), a maximum of 5 independent variables was added into the multiple regression models. Assumptions for correlation and linear models were assessed where appropriate, including: normality of scoring distribution (Shapiro-Wilk tests), collinearity diagnostics (variance inflation factor < 10 and tolerance > 0.2), and homoscedasticity (scatterplot of residuals).

9.5 Results

A total of 53 patients with IBD volunteered to participate in Study 2. Two IBD patients reported the presence of neurological conditions and were therefore excluded from the present analysis. Therefore, the final sample size included 51 IBD patients. Results of this secondary analysis are presented in three sections. The first section presents descriptive statistics for participant demographics, comorbidity, lifestyle, psychological, pain and IBD features, as well as measures of central sensitization (CSI, PPT, TS, and CPM). The second section presents correlation analyses of IBD, pain, psychological, demographic, comorbidity, and lifestyle features to measures of central sensitization. The third section presents multiple linear regression analyses between independent variables (IBD, psychological, demographic, comorbidity, and lifestyle features) and dependent variables (CSI, PPT, and CPM).

9.5.1 Section 1: Descriptors of participant characteristics

9.5.1.1 Demographics, comorbidity, and lifestyle factors

The demographic, lifestyle, and comorbidity status of study participants are presented in Table 9.1. Participants in the study self-identified as the following ethnic groups: White (*n*=50), African American (*n*=1), and Asian American (*n*=1).

Table 9.1

Participant Demographic, Lifestyle, and Comorbidity Characteristics (N = 51)

Characteristic	*N* (%)
Gender	
Male	21 (41)
Female	30 (59)
Age	
Range (years)	18-76
Mean (SD)	40.20 (14.28)
Smoking (yes)	8 (16)
Alcohol consumption	
Yes, occasionally	28 (55)
Yes, regularly	9 (18)
No	14 (27)
Cannabis use	16 (31)
Poor sleep quality	18 (35)
Total comorbidity (mean (SD))	2.63 (1.93)
Range (*n*)	0 - 8

Note. Standard deviation (SD).

9.5.1.2 Psychological features

Psychological features assessed in study participants are presented in Table 9.2. In total, 57% (*n* = 29) of participants demonstrated moderate levels of perceived stress, although only 1 participant reached a clinically meaningful score (>30) of pain catastrophizing. HADS subscales indicated 37% (*n* = 19) of study participants demonstrated clinically meaningful scores for the presence of anxiety (≥8), whereas only 8% (*n* = 4) demonstrated clinically meaningful scores for the presence of depression (≥8).

Table 9.2

Psychological Features of Study participants (N = 51)

Measure	Mean (SD)
Perceived stress scale	15.02 (7.46)
PANAS (positive affect)	32.70 (7.12)
PANAS (negative affect)	17.94 (5.77)
HADS (anxiety)	6.98 (3.64)
HADS (depression)	3.49 (3.21)
Pain catastrophizing scale (median (IQR))	6.5 (7.75)

Note. Standard deviation (SD), Positive and Negative Affective Schedule (PANAS), Hospital Anxiety and Depression Scale (HADS), and interquartile range (IQR).

9.5.1.3 Pain features

Pain features identified in study participants are presented in Table 9.3. In total, 71% (*n* = 36) of participants reported the presence of MSK and/or abdominal pain. Of these participants, 26% (*n* = 13) reported the presence of only MSK pain, 16% (*n* = 8) reported the presence of only abdominal pain, and 29% (*n* = 15) reported the presences of both abdominal and MSK pain. Of the MSK regions identified as painful by study participants, the low back was overall the most frequently reported region (*n* = 15, 35%), while the right knee (*n* = 4, 24%) and posterior neck (*n* = 4, 24%) were most frequently identified as the 'main area of pain'. A summary of all painful regions reported by participants is presented in Tables P.1 – P.3, located in Appendix P.

Table 9.3

Pain Features of Study participants (N = 51)

Feature	Mean (SD)
Musculoskeletal pain (yes (*n* (%))	28 (55)
Duration (years, median (IQR))	5.04 (8.13)
Regions	8.79 (4.48)
Strongest severity (NRS)	5.14 (2.69)
Average severity (NRS)	3.32 (2.11)
PROMIS Pain interference 4a	53.94 (7.30)
Abdominal pain (yes, *n* (%))	23 (45)
Strongest severity (NRS)	4.04 (2.82)
Average severity (NRS)	2.35 (2.08)
PROMIS Pain interference 4a	56.07 (10.71)

Note. Standard deviation (SD), interquartile range (IQR), numeric rating scale (NRS), and Patient-Reported Outcomes Measurement Information System (PROMIS).

9.5.1.4 IBD features

IBD features of study participants are presented in Tables 9.4 and 9.5. The majority of study participants were diagnosed with Crohn's disease (59% (*n* = 30)), with a mean IBD duration of 13.77 years (SD = 10.47). Of the participants, 45% (*n* = 23) had previously received surgical management of their IBD, and 63% (*n* = 32) identified as having extensive disease. The majority (*n* = 39, 76%) of study participants were taking biologic medication at the time of data collection, whereas significantly fewer participants were taking immunosuppressant medication (*n* = 7, 14%) and steroids (*n* = 5, 10%).

Table 9.4

IBD Features of Study participants (N = 51)

Feature	*N* (%)
IBD subtype	
Crohn's disease	30 (59)
Ulcerative colitis	17 (33)
Indeterminate colitis	4 (8)
IBD duration (years, mean (SD))	13.77 (10.47)
Range	1 - 42
Age at diagnosis, (years, mean (SD))	25.41 (13.24)
Surgical input (yes)	23 (45)
Stoma (yes)	10 (20)
Disease behaviour	
Stricturing disease (yes)	13 (25)
Penetrating disease (yes)	19 (37)
Perianal disease (yes)	21 (41)
Disease extent (extensive)	32 (63)
SIBDQ (mean (SD))	53.10 (8.46)

Note. Inflammatory bowel disease (IBD), standard deviation (SD), and Short Inflammatory Bowel Disease Questionnaire (SIBDQ).

Table 9.5

Medication use of Study participants (N = 51)

Medication	*N* (%)
Steroids	
Never	13 (25)
Previous	33 (65)
Current use	5 (10)
Biologic	
Never	7 (14)
Previous	5 (10)
Current	39 (76)
Immunosuppressant	
Never	25 (49)
Previous	19 (37)
Current	7 (14)

9.5.1.5 Measures of central sensitization

Summary of participant scoring for CSI, PPT, CPM, and TS are presented in Table 9.6. CSI scores were normally distributed among study participants (Shapiro-Wilk, $p \leq 0.05$), with 31% ($n = 16$) of participants demonstrating CSI scoring (≥ 40) representative of patients with central sensitization syndromes. PPT of the low back and Tibialis anterior regions were normally distributed among study participants (Shapiro-Wilk, $p \leq 0.05$), whereas TS and CPM scores were not normally distributed (Shapiro-Wilk, $p > 0.05$), and therefore were logarithmically converted prior to multiple linear regression modelling.

Table 9.6

Mean Scores for Measures of Central Sensitization in Study Participants (N = 51)

Assessment	Mean (SD)	Range
Central sensitization inventory	32.55 (12.54)	8 - 62
Benchmark score ≥ 40 (*n* (%))	16 (31)	
Pressure pain threshold		
Low back	368.23 (189.82)	115.06 - 793.36
Tibialis anterior	383.25 (174.26)	118.33 - 754.13
Temporal summation [a]	1.00 (0.83)	0 - 5
Conditioned pain modulation [a]	24 (28)	-52 - 178

Note. Standard deviation (SD).

[a] Median (interquartile range) for percentage change scores.

9.5.2 Section 2: Correlation analysis

Results of the analysis examining the correlation between IBD, psychological, demographic, comorbidity, and lifestyle features to measures of central sensitization are presented in Tables 9.7 – 9.0.

9.5.2.1 IBD features

TS was the only measure of central sensitization which did not demonstrate a significant correlation with at least one IBD feature (Table 9.7). The presence of abdominal pain (r_{pb} = -0.332, p = 0.009) and worse HRQOL (SIBDQ, *rho* = -0.552, p < 0.001) was significantly correlated with greater symptoms of central sensitization (higher CSI scores). Conversely, better HRQOL (SIBDQ, *rho* = 0.441, p = 0.001) correlated with greater pain modulation (higher CPM scores). Previous surgical input (r_{pb} = 0.257, p = 0.034) was correlated with increased pressure sensitivity (lower PPT

of the low back), whereas the presence of a stoma was correlated with lower PPT in the low back (r_{pb} = 0.386, p = 0.003) and Tibialis anterior (r_{pb} = 0.289, p = 0.017).

Table 9.7

Spearman Rank-order Correlations of IBD Features to Measures of Central Sensitization in IBD Participants (N = 51)

Feature	CSI		PPT (LB)		PPT (TA)		CPM		TS	
	Rho	*P*	*Rho*	*P*	*Rho*	*P*	*Rho*	*P*	*Rho*	*P*
IBD subtype [a]	.085	.554	.151	.145	.095	.505	-.168	.135	.022	.443
IBD duration	.054	.353	-.224	.057	-.182	.101	.066	.334	-.012	.470
Age at diagnosis [b]	-.095	.253	.132	.177	.028	.423	-.012	.468	.117	.225
Disease extent [a]	-.028	.423	-.039	.417	-.014	.462	-.015	.460	-.082	.258
Surgical input [a]	.081	.570	**.257**	**.034**	.152	.286	-.097	.263	.017	.445
Stoma [a]	-.006	.483	**.386**	**.003**	**.298**	**.017**	-.087	.284	.094	.227
Stricturing [a]	.251	.076	.142	.160	.069	.629	.116	.224	.038	.380
Penetrating [a]	.132	.355	.161	.129	.024	.867	-.007	.481	.149	.167
Perianal [a]	.063	.662	.107	.228	-.020	.889	-.045	.384	.188	.111
SIBDQ	**-.557**	**<.001**	.111	.219	.034	.406	**.441**	**.001**	.002	.496
Abdominal pain [a]	**-.334**	**.007**	.158	.134	.180	.103	.196	.099	.128	.152

Note. Bold font indicates significant correlation ($p \leq .05$). Central sensitization inventory (CSI), pressure pain threshold (PPT), low back (LB), Tibialis anterior (TA), conditioned pain modulation (CPM), temporal summation (TS), inflammatory bowel disease (IBD), and Short Inflammatory Bowel Disease Questionnaire (SIBDQ).

[a] Point-biserial coefficient (r_{pb}).

[b] Montreal classification.

9.5.2.2 Psychological features

CSI was the sole measure of central sensitization to demonstrate significant association with all psychological factors, where worse psychological functioning correlated with greater symptoms of central sensitization (Table 9.8). Conversely, higher CPM scores demonstrated significant correlation with decreased stress (*rho* = -

0.303, $p = 0.022$), negative affect (PANAS) (*rho* = -0.253, $p = 0.047$), anxiety (HADS) (*rho* = -0.350, $p = 0.009$), and depression (*rho* = -0.332, $p = 0.013$).

Table 9.8

Spearman Rank-order Correlations of Psychological Features to Measures of Central Sensitization in IBD Participants (N = 51)

Feature	CSI		PPT (LB)		PPT (TA)		CPM		TS	
	Rho	*P*	*Rho*	*P*	*Rho*	*P*	*Rho*	*P*	*Rho*	*P*
PSS [a]	**.524**	**<.001**	.036	.400	.039	.394	**-.303**	**.022**	-.131	.147
PANAS (p) [a]	**-.389**	**.002**	.001	.498	.049	.367	.141	.178	.164	.094
PANAS (n)	**.485**	**<.001**	-.004	.490	.048	.369	**-.253**	**.047**	-.048	.352
HADS (a)	**.517**	**<.001**	-.090	.265	-.084	.278	**-.350**	**.009**	-.131	.148
HADS (d)	**.523**	**<.001**	.006	.484	-.013	.464	**-.332**	**.013**	-.081	.258
PCS	**.571**	**<.001**	-.210	.091	-.174	.136	-.198	.117	.176	.092

Note. Bold font indicates significant correlation ($p \leq .05$). Central sensitization inventory (CSI), pressure pain threshold (PPT), low back (LB), Tibialis anterior (TA), conditioned pain modulation (CPM), temporal summation (TS), perceived stress scale (PSS), positive and negative affect schedule (PANAS), hospital anxiety and depression scale (HADS), pain catastrophizing scale (PCS).

[a] Pearson's coefficient (*r*).

9.5.2.3 Demographic, lifestyle, and comorbidity features

Demographic, lifestyle, and comorbidity features most frequently demonstrated correlation with CSI scores, with 4 out of 7 characteristics reaching significance (Table 9.9). Poor sleep quality (*rho* = 0.379, $p = 0.003$), higher total comorbidity (*rho* = 0.429, $p = 0.001$), lack of current cannabis use ($r_{pb} = -0.399$, $p = 0.029$), and the presence of MSK pain ($r_{pb} = -0.427$, $p = 0.001$) were correlated with higher CSI scores. Male gender was significantly correlated with higher PPT scores for both the low back ($r_{pb} = -0.418$, $p = 0.001$) and Tibialis anterior ($r_{pb} = -0.563$, $p < 0.001$). Improved sleep quality

was significantly correlated with both higher CPM scores (*rho* = -0.314, *p* = 0.006) and higher PPT of Tibialis anterior (*rho* = -0.232, *p* = 0.050).

Table 9.9

Spearman Rank-order Correlations of Demographic, Lifestyle, and Comorbidity Features to Measures of Central Sensitization in IBD Participants (N = 51)

	CSI		PPT (LB)		PPT (TA)		CPM		TS	
Feature	*Rho*	*P*	*Rho*	*P*	*Rho*	*P*	*Rho*	*P*	*Rho*	*P*
Age [a]	-.002	.495	-.120	.201	-.218	.063	.070	.325	.060	.317
Gender [b]	.207	.079	**-.418**	**.001**	**-.576**	**<.001**	.172	.130	.040	.374
Smoking	-.161	.129	.055	.351	.055	.351	.174	.127	.028	.412
Alcohol	-.051	.361	.005	.485	-.040	.391	.136	.186	-.119	.170
Cannabis [b]	**-.399**	**.029**	.023	.436	-.083	.484	.068	.329	.133	.143
Sleep quality	**.379**	**.003**	-.088	.269	**-.232**	**.050**	**-.374**	**.006**	.061	.314
Comorbidity	**.456**	**<.001**	-.198	.082	-.198	.082	-.143	.175	-.001	.497
MSK Pain [b]	**-.427**	**.001**	.029	.419	.141	.162	.082	.296	.031	.402

Note. Bold font indicates significant correlation ($p \leq .05$). Central sensitization inventory (CSI), pressure pain threshold (PPT), low back (LB), Tibialis anterior (TA), conditioned pain modulation (CPM), temporal summation (TS), and musculoskeletal (MSK).

[a] Pearson's correlation (*r*).

[b] Point-biserial coefficient (r_{pb}).

9.5.3 Section 3: Multiple linear regression analysis

Results of the multiple linear regression analyses between independent variables (IBD, psychological, demographic, comorbidity, and lifestyle features) and dependent variables (CSI, PPT, and CPM) are presented in Table 9.10.

9.5.3.1 CSI

Individual stepwise multiple regression analysis for CSI scores (dependent variable) and SIBDQ (primary independent variable) indicated a ≥ 10% R^2 change

score for the following secondary independent variables: PSS, PANAS (positive), PANAS (negative), HADS (anxiety), HADS (depression), PCS, sleep quality, MSK pain, and total comorbidity. The final backward multiple regression model for CSI showed significant positive associations of poor HRQOL (SIBDQ), greater pain catastrophizing, the presence of MSK pain, poor sleep quality, and greater total comorbidity to greater symptoms of central sensitization (higher CSI scores) (Table 9.10).

Table 9.10

Associations between Participant Features and Measures of Central Sensitization

	β	*SE*	*t*	*P*
CSI model summary: R^2 = 0.74, F(4,36) = 20.16, p < 0.001*				
SIBDQ	-0.42	0.14	-3.01	0.005*
Pain catastrophizing	0.70	0.14	4.97	<0.001*
Musculoskeletal pain	-5.37	2.49	-2.15	0.038*
Sleep quality	4.33	1.36	3.19	0.003*
Total comorbidity	1.39	0.64	2.18	0.036*
PPT (low back) model summary: R^2 = 0.32, F(3,47) = 7.33, p < 0.001*				
Stoma	160.67	56.41	2.85	0.006*
Gender	-170.64	45.51	-3.75	0.000*
PPT (Tibialis anterior) model summary: R^2 = 0.43, F(2,48) = 18.26, p < 0.001*				
Stoma	126.43	47.27	2.68	0.010*
Gender	-205.47	38.14	-5.39	<0.001*
CPM model summary: R^2 = 0.27, F(2,44) = 7.88, p < 0.001*				
SIBDQ	0.02	0.01	2.19	0.034*
HADS (depression)	-0.04	0.02	-2.12	0.040*

Note. Standard error (SE), pressure pain threshold (PPT), conditioned pain modulation (CPM), Hospital Anxiety and Depression Scale (HADS), Short Inflammatory Bowel Disease Questionnaire (SIDBQ), and central sensitization inventory (CSI).

* $p \leq 0.05$.

9.5.3.2 PPT

The backward regression model for PPT of the low back and Tibialis anterior regions showed significant positive associations from female gender and history of a stoma to increased pressure sensitivity at both regions (Table 9.10).

9.5.3.3 CPM

Individual stepwise multiple regression analysis for CPM scores (dependent variable) and SIBDQ (primary independent variable) indicated a ≥ 10% R^2 change score for the following secondary independent variables: HADS (anxiety), HADS (depression), and sleep quality. The final backward multiple regression model for CPM showed significant positive associations of better HRQOL (SIBDQ) and lower depression scores to greater pain modulation (higher CPM scores) (Table 9.10).

9.6 Discussion

The secondary aim of Study 2 was to investigate the association between measures of central sensitization and IBD features, as well as features within additional patient domains (i.e. psychological, demographic, comorbidity, and lifestyle). TS was the only measure of central sensitization to not correlate with any of the participant features examined in the current study, whereas CSI demonstrated the greatest number of correlations and was the only measure to demonstrate significant relationships within each feature domain. The final regression models indicated that women with a history of a stoma demonstrated increased pressure sensitivity in both the low back and Tibialis anterior regions. This study also showed that less effective pain modulation was demonstrated in patients with poor HRQOL and greater depression scores. Patients

with poor HRQOL, greater pain catastrophizing, MSK pain, poor sleep quality, and greater total comorbidity were shown to have greater symptoms of central sensitization.

Along with female gender, the history of a stoma positively predicted lower PPT of both low back and Tibialis anterior regions. Although the surgical formation of stomas is generally considered a simple undertaking, the consequences can be complex and life- threatening, ranging from early (i.e. leakage, retraction, and necrosis) to late complications (i.e. herniation, prolapse, and stenosis) reported in 20-70% of patients (Shabbir & Britton, 2010). Furthermore, although stomas differ, for instance in type and duration, their presence is suggestive of overall worse disease severity (Siegel et al., 2016). Therefore, the relationship between a history of stoma formation and increased pressure pain sensitivity may reflect somatosensory changes as a consequence of worse IBD severity and/or complications directly related to the stoma itself. Interestingly, patients with a history of stomas in the present study demonstrated decreased PPT at two regions, where regions were always located in opposing body quadrants (e.g. left low back and right Tibialis anterior). Distribution of sensitivity in this manner is suggestive of widespread versus regional sensitivity, characteristic of mechanisms related to central sensitization (den Boer et al., 2019; Clifford J Woolf, 2011).

The pattern of association between patient features (i.e. worse psychological functioning, the presence of pain, greater overall comorbidity, etc.) and higher CSI scores found in the current study is similar to reports in the literature. CSI broadly assesses features across multiple dimensions (e.g. physical symptoms and emotional distress), in order to quantify the presence of central sensitization related symptomology (Mayer et al., 2012; Neblett, Hartzell, Williams, et al., 2017). Therefore, it is unsurprising that current features related to these dimensions were found to

correlate with higher CSI scores. However, higher CSI scores have also previously demonstrated association to additional factors not directly assessed in the measure, such as greater number of painful regions and greater comorbidity (Neblett, Hartzell, Williams, et al., 2017).

CSI and CPM were the only measures of central sensitization to correlate with IBD HRQOL (i.e. SIBDQ). Similarly, these measures demonstrated the most correlations to psychological features. The final models for both CSI and CPM retained the positive associations of both SIBDQ and a psychological feature. Current literature reports significant influences from primary psychological features to both CSI and CPM scoring in pain populations, as well as healthy controls (Mayer et al., 2012; Nahman-Averbuch et al., 2016). Similarly, reports of IBD HRQOL have indicated that worse psychological functioning is a significant determinant of poor HRQOL in patients (Guthrie et al., 2002; van der Eijk et al., 2004). As such, the relationship between IBD HRQOL and measures of central sensitization demonstrated in the present study, may represent complex mediating pathways from psychological factors within these domains.

Although sleep quality was the feature which most frequently correlated with measures of central sensitization, it was only retained in the model associated with CSI scores. Altered sleep behaviour has been well described in pain and immune populations (Finan, Goodin, et al., 2013; Y. C. Lee et al., 2013; M. T. Smith & Haythornthwaite, 2004). Consequently, research regarding influences of sleep disturbances has moved from simple associations towards mechanistic explorations, for instance examining changes in neurotransmitter signalling, mediating pathways through psychological features, and changes in CNS cell activation (Finan, Goodin, et al., 2013; Nijs et al., 2017).

Disturbed sleep is a well-described clinical observation in IBD patients, particularly during active IBD (Ali & Orr, 2014). A review of sleep disturbances in IBD described associations with gastrointestinal symptoms, suggesting that altered sleep quality increases immune activity, and in turn, worsening IBD severity (Ali & Orr, 2014). A large prospective study reporting on the association between active IBD and worse sleep quality also found a strong correlation between sleep quality, psychological functioning, and IBD HRQOL (Graff et al., 2010). These reports are similar to findings in the current study for patient features associated with CSI scores. Similarly, findings from Study 1 in the present thesis (Chapter 6) showed positive associations between active IBD and higher CSI scores. Therefore, CSI may represent a mediating pathway in the complex relationship between these patient features and active IBD.

Interpretation of current study results should consider the potential bias related to limitations of the statistical modelling from the modest sample size. Additionally, measures of central sensitization in the present study included a limited range of somatosensory assessments, and as such, not representative of the full battery of available quantitative sensory testing. Therefore, future research should include a more comprehensive exploration of quantitative sensory testing suggested in current literature to provide the best evidence for altered somatosensory functioning in this population.

An ongoing challenge in IBD research continues to be predicting how individual clinical IBD features contribute to overall patient outcomes (Siegel et al., 2016). Several of the IBD features explored in the present study were not found to be significantly correlated with measures of central sensitization. However, correlations with structural IBD features found in the present study, such as a history of stomas,

suggests that further investigation of structural changes in IBD patients (e.g. number and/or extent of bowel resections) may reveal additional relationships to measures of central sensitization. Additionally, the present study did not include IBD features characterized by common clinical assessments (i.e. biomarker, endoscopic, and histologic investigations). Therefore, future research should consider the exploration of these assessments of immune and structural characteritics, and their potential association to measures of central sensitization in IBD patients.

9.7 Chapter summary

The current chapter presents analysis, results, and discussion from the secondary aims of Study 2. Current study results are the first to describe correlations of multiple participant features across IBD, psychological, demographic, comorbidity, and lifestyle domains, to measures of central sensitization in IBD patients. Findings from this study highlight the need, not only for the ongoing investigation of central mechanisms in IBD (i.e. comprehensive quantitative sensory testing), but also into the complexity of how multiple features are related to these assessments in order to identify targeted assessment and treatment pathways.

10 General Discussion

10.1 Chapter overview

This thesis proposes a new framework to consider and explore persistent MSK pain in IBD (Chapter 1). This framework integrates models described in IBD and chronic pain literature, describing common constructs and the potential for shared mechanisms leading to worse pain experiences (Chapter 2). The present thesis explored MSK pain in individuals with IBD within this framework through two primary studies. The current chapter integrates results from these studies to present overall thesis findings situated within current literature, highlight the strengths while acknowledging the limitations of this thesis, and present recommendations for future research. Contributions to research and clinical practice are presented throughout the sections of this chapter together with concluding statements.

10.2 Summary of thesis findings

Overall, findings from the present thesis suggest that a sub-population of IBD patients with and without MSK pain present with features indicative of central sensitization. Thesis findings further suggest that central sensitization in IBD represents a spectrum of symptom severity levels, whereby worse severity is associated with worse morbidity. Additionally, results suggest that MSK pain experiences, together with the presence of central sensitization, are potentially associated with IBD severity. Key results from the two primary thesis studies are discussed below within the broader context of these main findings.

10.2.1 Central sensitization in IBD

This thesis is the first to describe the presence of symptoms and potential risk factors for central sensitization, assessed through CSI, in individuals with IBD. Results from an additional sub-analysis of Study 1 indicated that a proportion of patients with and without MSK and/or abdominal pain demonstrated CSI scores benchmarked (≥ 40) to suggest the dominant presence of central sensitization (Appendix I). There is uncertainty in the current literature as to why central sensitization presents in only sub-populations for certain conditions, such as rheumatoid arthritis and low back pain, while presenting as the predominate feature in other populations, such as fibromyalgia and irritable bowel syndrome (Nijs et al., 2014). However, reports of influences from biopsychosocial factors have been implicated in the sub-populations presenting with features of central sensitization (Nijs et al., 2014; Phillips & Clauw, 2011). Interestingly, the results presented in this thesis indicated that measures of central sensitization were most commonly associated with patient characteristics, including historic or the current presence of a stoma, psychological distress, greater comorbidity, and worse HRQOL (Chapter 9). Therefore, the sub-population of IBD patients demonstrating features of central sensitization may represent individuals with a unique profile of IBD-related risk factors for developing central sensitization.

10.2.2 Central sensitization symptom severity

Exploration of CSI scores in the present thesis suggests a scoring pattern similar to recent reports describing different CSI severity levels, where worse symptom severity correlated with worse pain severity, worse psychological functioning, and greater sleep disturbances in chronic pain populations (Neblett, Hartzell, Mayer, et al., 2017). Investigation of CSI in the present thesis indicated that IBD patients presenting with both MSK and abdominal pain demonstrated significantly greater symptom

severity (higher CSI scores) compared to those presenting with a single type of pain (abdominal or MSK) or no pain (Appendix I). Additionally, greater symptom severity demonstrated associations with active IBD, greater psychological distress, and greater comorbidity (Chapters 5, 6, 8, and 9). Previous chronic MSK pain investigations have consistently reported similar directional relationships across these features in patients demonstrating mechanisms of central sensitization (Nijs et al., 2014; Smart, Blake, Staines, & Doody, 2012). Therefore, findings from the present thesis suggests that the presence of central sensitization in IBD may represent a spectrum of severity levels which correlate with overall patient morbidity.

10.2.3 Links to IBD severity

Thesis findings suggests that MSK pain experiences and measures of central sensitization in IBD are potentially linked to IBD severity, characterized by features such as: HRQOL, persisting and disabling symptoms, surgical input, and repeated flares (Gomollón et al., 2016; Peyrin-Biroulet et al., 2016; Satsangi et al., 2006; Siegel et al., 2016). This was first conceptualized through the subgrouping analysis of Study 1, where the pattern of IBD features presented across the subgroups was suggestive of different levels of IBD severity (Chapter 5). This implies that IBD severity may be the construct which informed the nature of the MSK pain profiles generated through this subgrouping analysis (Chapter 5). For instance, Study 1 characterized a MSK pain subgroup which demonstrated active IBD, the presence of abdominal pain, greater comorbidity, higher CSI scores, poor IBD HRQOL, and worse MSK pain experiences (Chapter 5). Conversely, another subgroup was characterised by IBD remission, no abdominal pain, fewer comorbidities, and better HRQOL. Interpretation of subgrouping results in this manner suggests that consideration of the MSK pain profiles described in the present thesis alongside additional features of IBD (i.e. colonoscopy reports) may

offer a meaningful dimension for further evaluating disease severity in patients with IBD.

Findings from Study 2 indicated that somatosensory functioning in IBD patients is associated with other patient features such as a history of a stoma, the presence of abdominal pain, and poor HRQOL. As stated above, the presence of these features has been well-described in patients understood to have worse IBD severity (Gomollón et al., 2016; Peyrin-Biroulet et al., 2016; Satsangi et al., 2006). Similar to MSK pain profiles of Study 1, interpretation of these relationships suggests that somatosensory functioning, a surrogate marker of central sensitization, may also be influenced by the construct of IBD severity. Therefore, future investigation of somatosensory functioning based on different levels of disease severity may identify potential risk factors for developing central sensitization in IBD.

10.3 Clinical implications

The current research provides evidence for potential abnormal central nervous system functioning in patients with IBD. This could influence clinical practice by making clinicians more aware of potential mechanisms, such as central sensitization, leading to the development of targeted management pathways. As in many conditions, clinical decision-making regarding management of IBD patients is related to clinicians' perspectives regarding symptomology and results from clinical assessments. Identifying patients whose clinical presentation (i.e. history of a stoma) and/or current symptoms (i.e. poor sleep and decreased HRQOL) which are understood to be correlated to measures of central sensitization may impact management strategies. Similarly, results from Study 1 offers clinicians a guide for identifying the probability that patients may present with certain mechanistic profiles of MSK pain. Recognition of risk factors and MSK pain profiles may trigger the use of screening tools, such as CSI, and/or referral to

pain specialists for further evaluation and treatment. Although literature in other chronic pain populations has explored treatments, such as psychological interventions (Hoffman, Papas, Chatkoff, & Kerns, 2007), brain stimulation (Leo & Latif, 2007), and acupuncture (MacPherson et al., 2017), these concepts have not been investigation in the treatment of persistent MSK pain in patients with IBD. Future research should explore targeted treatment strategies in patients with IBD to identify appropriate and effective treatement pathways.

10.4 Strengths

10.4.1 Statistical analysis

Exploring complex disease and pain constructs through investigation of individual characteristics may not provide insight into developmental pathways for worse pain experiences (Bergman & Magnusson, 1997). In view of this, the present thesis utilized subgrouping-based analysis to characterize profiles of MSK pain in over 200 patients with IBD. The use of subgrouping analysis provides the opportunity to observe patterns of multiple IBD and pain characteristics across a sampling of patients, in order to draw broad conclusions and identify important constructs which influence pain presentations. Therefore, the use of subgrouping analysis in the present thesis not only provided evidence for distinct profiles of MSK pain, but it also identified both IBD and pain features which accounted for their distinctiveness. Characterising MSK pain profiles in this manner may, therefore, provide a useful clinical framework to identify patients with an increased probability of presenting with central sensitization. Individuals with active IBD, multisite pain, and severe MSK pain experiences can be seen as presenting with a high risk for central sensitization, thereby signifying the need for further investigation. The use of self-reported measures to characterize IBD and pain features within these MSK pain profiles increases the clinical utility beyond

gastroenterology, allowing clinicians such as physiotherapists, who typically do not have access to more invasive clinical investigations, to better determine appropriate pain management pathways. Furthermore, the relationships between IBD, central sensitization, and pain features also provide direction for future research to explore predictors for patient outcomes.

10.4.2 Study sampling and design

The present thesis explored persistent MSK pain in two populations, including a population-based investigation (New Zealand) and a clinic-based investigation (United States of America). These two study populations also recruited different patient profiles, in terms of the proportion of patients who were currently being treated at a gastroenterology clinic, compared to those not actively under care. Thus, although these studies each have limitations from sampling biases inherent to each study design, the homogeneity in findings across the studies suggest external validity of overall thesis findings.

10.4.3 Spectrum of MSK conditions

Previous investigations of MSK pain in IBD have primarily reported on inflammatory arthropathies, with less consideration of additional MSK pain conditions in this population. Although the present thesis did not investigate clinical diagnoses of inflammatory versus non-inflammatory pain types, thesis studies ultimately described a broader spectrum of persistent MSK conditions in IBD, ranging from regional to multisite pain, where less than 30% of participants reported previous inflammatory joint diagnoses (Appendix G). The present thesis is the first to explore measures of central sensitization related to MSK pain in IBD, including the use of CSI and somatosensory assessments. Findings from both primary studies contribute to the growing body of evidence for the relationship between CSI and multiple patient

domains, including pain, psychological, lifestyle, and comorbidity factors, in IBD-related MSK pain. Finally, the present thesis proposed a new framework for persistent MSK pain in IBD, where exploration of this framework indicated the participation of central sensitization in the modulation of painful experiences.

10.5 Limitations

Although specific limitations for each study have already been discussed in the previous chapters, this section highlights the limitations in the context of the whole thesis.

10.5.1 Study methods

The present thesis solely utilized quantitative methods for exploring and charactizing persistent MSK pain in individuals with IBD. Although this approach has been recommended for the objective assessment of the present research question (Arendt-Nielsen et al., 2012; Arendt- Nielsen et al., 2018; Catalano et al., 2017; Koop et al., 2015; Wu et al., 2013), the inclusion of a qualitative component may have provided a valuable context to thesis findings. Future research should consider utilizing mixed methodological approaches to allow for a deeper understanding of persistent MSK pain experiences in individuals with IBD. Similarly, the present thesis utilized narrative reviews of the literature to explore current research themes. Inclusion of systematic reviews of current literature may have further informed methodologies used in the present thesis.

10.5.2 Surrogate markers of central sensitization

Interpretation of study results should include consideration of measures used in the present thesis to assess central sensitization in patients with IBD. In the absence of a

gold standard to investigate mechanisms of central sensitization, current literature suggests the use of diagnostic surrogate markers to indicate the presence of central sensitization (Arendt- Nielsen et al., 2018; Clifford J Woolf, 2011). Therefore, assessment of central sensitization in the present thesis included investigation of symptomology (i.e. CSI) and somatosensory functioning (i.e. quantitative sensory testing (QST)). However, although CSI has been validated to evaluate an array of symptoms related to the sensitivity of the somatosensory system, thereby implicating changes to CNS processing, it does not assess individual mechanisms related to central sensitization. Therefore, CSI has been described as a screening tool to identify the need for further assessment of central sensitization mechanisms (Arendt- Nielsen et al., 2018; Mayer et al., 2012; Nijs et al., 2015).

Since instigating the work reported in the present thesis, the taxonomy used to describe pain mechanisms related to abnormal nociceptive neuronal activity in the CNS has evolved and now includes the term "nociplastic" pain (International Association for the Study of Pain (IASP) Taxonomy 2017). The term "central sensitization" is understood to specifically refer to an increase in nociceptive neuronal activity of the CNS, whereas "nociplastic" provides a broader understanding that abnormal changes can include an increase or decrease in nociceptive activity (IASP Taxonomy 2017). This distinction has important implications for future research investigating the complexity of chronic pain experiences described in this thesis and in current IBD literature (i.e. MSK, abdominal, and post-surgical pain). As such, future investigation of chronic pain in IBD should embrace this new taxonomy and the features which operationalize "nociplastic" as a pain mechanism (Aydede & Shriver, 2018).

10.5.3 Assessment of IBD

Assessment of IBD features in this thesis utilized self-reported measures (i.e. symptomatic IBD activity, HRQOL, psychological, and lifestyle factors), as well as features extracted from patients' charts (i.e. medication use, disease extent and behaviour, surgical history, subtype, and duration). Thesis investigations did not include clinical assessments of IBD activity (i.e. colonoscopy, histology, and biomarkers). Therefore, relationships between IBD features, MSK pain experiences, and measures of central sensitization described in the present thesis do not include these clinically important assessments of disease activity. Additionally, due to the differences in study design, characterization of IBD features differed somewhat between Study 1 and 2 of the thesis. For instance, Study 1 utilized a self-reported measure of IBD activity, and Study 2 characterized structural IBD changes (i.e. stricturing, penetrating, stomas, surgical input, etc.) through investigations extracted from patient charts

IBD literature and clinical practice reflects a longstanding interest in distinguishing IBD, representing an organic disease with strong genetic links, from irritable bowel syndome (IBS), which is a functional gastrointestinal disorder classified as a central sensitivity syndrome (Schoepfer et al., 2008). However, as previously stated, IBS is reported in 20% of IBD patients (Abdalla et al., 2017). Similarly, results from Study 1 in the present thesis indicated that approximately 30% of the participants had coexisting IBS (Table G.2, Appendix G). Future research should consider exploring constructs of central sensitization in IBD patients with and without IBS in order to understand the influence of comorbid central sensitivity syndromes to current thesis findings.

10.5.4 Validity of thesis findings

A significant challenge of investigating MSK pain in patients with IBD relates to the often overlapping presence of abdominal pain. As previously described (Chapters 1 and 2), abdominal pain is the most common pain complaint in this population, often signifying the presence of active disease. Therefore, stratifying patient groups, for instance, in Study 2 by the presence of MSK pain as well as the presence of abdominal pain would have been ideal to solely investigate influences of MSK pain to measures of central sensitization. However, stratifying patients in this manner is significantly less feasible and may unintentionally bias groups based on active versus non-active IBD. Participants in both thesis studies demonstrated that 60% of the participants with MSK pain also presented with overlapping abdominal pain, which may represent associations to active IBD. However, both thesis studies demonstrated that 30% of participants without MSK pain presented with abdominal pain. Therefore, the decision to only stratify patient groups based on the presence of MSK pain in Study 2 may have influenced the measures of central sensitization, particularly somatosensory assessments, causing an overall threat to the validity of present thesis findings.

As previously stated, investigations utilizing somatosensory assessments in IBD have been limited in scope with focus solely on peripheral neuropathies (Huehne et al., 2009; Munster et al., 2015). Additionally, although current literature exploring the psychometric properties of these assessments in other populations (i.e. low back pain) have demonstrated sufficient measurement properties (Vuilleumier et al., 2015), psychometric investigations specifically in IBD patients are lacking. Therefore, current literature is unable to suggest whether the somatosensory assessment procedures utilized in Study 2 demonstrate acceptable properties to explore somatosensory functioning in IBD patients. Future research should explore the psychometrics (e.g.

discriminative validity and test re-test reliability) of somatosensory assessments in IBD patients in order to make recommendations for their use in clinical and research practices.

10.6 Recommendations for future research

10.6.1 Risk factors for central sensitization

Findings from the present thesis, as well as reports from current literature, suggest that a sub-population of IBD patients, with and without pain, may present with central sensitization. Thus, it is important to identify the risk factors for developing central sensitization in IBD. Current literature proposes a complex range of risk factors for presenting with central sensitization, including early childhood trauma, immune activity, and psychological stress (Kindler et al., 2010; Nijs et al., 2017). Similarly, findings from the present thesis indicated that measures of central sensitization are associated with a range of patient features (i.e. IBD, pain, psychological, and lifestyle) which have previously been described as determinants of IBD severity (Gomollón et al., 2016; Peyrin-Biroulet et al., 2016; Satsangi et al., 2006; Siegel et al., 2016). However, the development of a novel tool to assess IBD severity, indicated different weighted contribution from patient features in the overall determination of disease severity (Siegel et al., 2016). Therefore, future research should utilize a prospective study design to examine IBD severity, as a potential risk factor for patients presenting with central sensitization through the use of a novel assessment, such as the IBD Disease Severity Index (Siegel et al., 2016).

10.6.2 Chronic postsurgical pain in IBD

Investigations of chronic postsurgical pain indicate that IBD patients are two to three times more likely to develop chronic pain following gastrointestinal surgery than non-IBD populations (Bruce & Krukowski, 2006; Joris et al., 2015). Although studies have postulated that chronic post-surgical pain may be the result of altered CNS processing in patients, this has yet to be investigated. The present thesis demonstrated an association between a history of stomas to increased somatosensory sensitivity (i.e. lower PPT scores) in IBD patients. Similarly, present investigations demonstrated higher CSI scoring (i.e. greater symptoms of central sensitization) in patients presenting with worse pain experiences. Previous investigations of post-surgical pain in other populations demonstrated that preoperative CSI scores predicted worse post-operative outcomes (i.e. worse pain severity, poor HRQOL, and longer hospital stays) (Bennett, Walsh, Thompson, & Krishnaney, 2017; M. S. Kim et al., 2019; S. H. Kim, Yoon, Yoon, Yoo, & Ahn, 2015). Therefore, future research utilizing prospective study designs should explore the predictive relationship between CSI and post-surgical outcomes as a tool to identify IBD patients at risk of greater pain (i.e. abdominal and MSK) and disability following bowel surgery.

10.6.3 Targeted assessment of MSK pain types

The results in Chapter 8 suggest that the observed somatosensory measures (i.e. PPT, CPM, and TS) applied at the specified body sites were not significantly different between this sampling of IBD patients with/without MSK pain and health controls. However, these results are unable to suggest whether the scope of somatosensory measures applied at different body sites would demonstrated similar findings. Additionally, in order to explore differences in somatosensory assessments in IBD patients, investigation for the discriminative validity of somatosensory assessments in

IBD is needed. Future research should consider the psychometric properties (i.e. discriminative validity and reliability) of the different assessment modalities and procedures in IBD patients in order to make recommendations for clinical and research practices. Additionally, the development of a composite score, comprised of the different assessment modalities meaningful to IBD, may offer a valuable way for considering central sensitization in future investigations.

Current literature provides a growing body of knowledge surrounding measures of central sensitization specific to pain regions, often providing normative data for future use in research and clinical practice. However, the primary thesis studies did not aim to characterize measures of central sensitization by each pain region. Therefore, future research exploring the regional assessment of central sensitization would provide a better understanding of whether somatosensory functioning in IBD patients differs by pain location.

The burden of inflammatory arthropathies has been well-described in IBD literature, where inflammation is the mechanism typically described in the generation of painful joint pain experiences. However, investigations of chronic pain in primary inflammatory arthritis conditions have implicated altered CNS processing in ongoing and worse pain experiences (Y. C. Lee, Nassikas, & Clauw, 2011). Results from the present thesis indicated that a profile of MSK pain in IBD suggested the participation of multiple pain mechanisms, such as nociceptive, neuropathic, and central mechanisms (Chapter 5). Incidentally, this particular profile presented with the worse MSK pain experiences when compared to the other profiles. Although MSK profiles did not demonstrate differences in the frequency of patients reporting previous inflammatory arthritis diagnoses, it is unknown whether arthritis patients presented with active arthritis at the time of investigation or not. Therefore, future research should explore the

role of central sensitization in IBD patients with inflammatory arthropathies to better understand the contributions of different mechanisms to pain experiences in this population.

10.7 Conclusion

Two primary thesis studies were conducted to explore the potential for shared mechanisms in individuals with IBD presenting with persistent MSK pain. A sub-population of IBD patients with and without MSK pain presented with features suggesting the presence of central sensitization. Individuals with MSK pain and symptoms of central sensitization presented with worse IBD, HRQOL, and pain experiences. MSK pain in IBD presented as distinct profiles, suggesting influences from worse IBD severity to pain presentations and the presence of central sensitization. Measures of central sensitization in IBD were associated with a range of patient features (i.e. IBD, pain, psychological, lifestyle, and comorbidity), highlighting potential risk factors for the development of central sensitization leading to worse pain experiences in IBD patients.

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Appendices

Appendix A – Study 1: University of Otago Ethical Approval

Academic Services
Manager, Academic Committees, Mr Gary Witte

H17/095

28 August 2017

Dr R Mani
School of Physiotherapy

Dear Dr Mani,

I am again writing to you concerning your proposal entitled **"Profile of persistent musculoskeletal pain among individuals with Inflammatory Bowel Disease - a national survey"**, Ethics Committee reference number **H17/095**.

Thank you to Carrie Falling, PhD student investigator on the above project, for her email of 24th August 2017 with response attached addressing the issues raised by the Committee.

On the basis of this response, I am pleased to confirm that the proposal now has full ethical approval to proceed.

The standard conditions of approval for all human research projects reviewed and approved by the Committee are the following:

Conduct the research project strictly in accordance with the research proposal submitted and granted ethics approval, including any amendments required to be made to the proposal by the Human Research Ethics Committee.

Inform the Human Research Ethics Committee immediately of anything which may warrant review of ethics approval of the research project, including: serious or unexpected adverse effects on participants; unforeseen events that might affect continued ethical acceptability of the project; and a written report about these matters must be submitted to the Academic Committees Office by no later than the next working day after recognition of an adverse occurrence/event. Please note that in cases of adverse events an incident report should also be made to the Health and Safety Office:

http://www.otago.ac.nz/healthandsafety/index.html

Advise the Committee in writing as soon as practicable if the research project is discontinued.

Make no change to the project as approved in its entirety by the Committee, including any wording in any document approved as part of the project, without prior written approval of the Committee for any change. If you are applying for an amendment to your approved research, please email your request to the Academic Committees Office:

Appendix B – Study 1: Māori Consultation

NGĀI TAHU RESEARCH CONSULTATION COMMITTEE
TE KOMITI RAKAHAU KI KĀI TAHU

Wednesday 13 September 2017

Dr Ramakrishnan Mani,
School of Physiotherapy,
DUNEDIN.

Tēnā koe Dr Ramakrishnan Mani,

Profile of persistent musculoskeletal pain among individuals with Inflammatory Bowel Disease – a national survey

The Ngāi Tahu Research Consultation Committee (the committee) met on Tuesday, 12 September 2017 to discuss your research proposition.

By way of introduction, this response from The Committee is provided as part of the Memorandum of Understanding between Te Rūnanga o Ngāi Tahu and the University. In the statement of principles of the memorandum it states "Ngāi Tahu acknowledges that the consultation process outline in this policy provides no power of veto by Ngāi Tahu to research undertaken at the University of Otago". As such, this response is not "approval" or "mandate" for the research, rather it is a mandated response from a Ngāi Tahu appointed committee. This process is part of a number of requirements for researchers to undertake and does not cover other issues relating to ethics, including methodology they are separate requirements with other committees, for example the Human Ethics Committee, etc.

Within the context of the Policy for Research Consultation with Māori, the Committee base consultation on that defined by Justice McGechan:

"Consultation does not mean negotiation or agreement. It means: setting out a proposal not fully decided upon; adequately informing a party about relevant information upon which the proposal is based; listening to what the others have to say with an open mind (in that there is room to be persuaded against the proposal); undertaking that task in a genuine and not cosmetic manner. Reaching a decision that may or may not alter the original proposal."

The Committee considers the research to be of importance to Māori health.

As this study involves human participants, the Committee strongly encourage that ethnicity data be collected as part of the research project as a right to express their self-identity. That is the questions on self-identified ethnicity and descent, these questions are contained in the latest census.

The Committee suggests dissemination of the research findings to relevant Māori health organisations regarding this study, including Taeora Tinana, Māori Physiotherapists within the New Zealand Society of Physiotherapists.

We wish you every success in your research and the committee also requests a copy of the research findings.

The Ngāi Tahu Research Consultation Committee has membership from:

Te Rūnanga o Otākou Incorporated
Kāti Huirapa Rūnaka ki Puketeraki
Te Rūnanga o Moeraki

NGĀI TAHU RESEARCH CONSULTATION COMMITTEE
TE KOMITI RAKAHAU KI KĀI TAHU

This letter of suggestion, recommendation and advice is current for an 18 month period from Tuesday, 12 September 2017 to 12 March 2019.

Nāhaku noa, nā

Mark Brunton
Kaiwhakahaere Rangahau Māori
Research Manager Māori
Research Division
Te Whare Wānanga o Otāgo
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The Ngāi Tahu Research Consultation Committee has membership from:

Te Rūnanga o Ōtākou Incorporated
Kāti Huirapa Rūnaka ki Puketeraki
Te Rūnanga o Moeraki

Appendix C – Study 1: Email, Social Media, and Webpage Invitations to Participate

As a member of Crohn's and Colitis NZ, you are invited to participate in an online survey about ongoing **pain in people with Inflammatory Bowel Disease**. This survey is part of a larger study at the University of Otago, aimed at investigating why individuals with IBD develop persistent pain in order to help find targeted treatments.

Attached to this email is an Information Sheet and Consent Form with details about this study, to include contact details if you have any additional questions.

The survey takes approximately **10-15 minutes** to complete. At the end of the survey you will be given the opportunity to enter in a **prize draw for a $50 Prezzy card**! There are 5 chances to win!

Thank you for your time and interest in this study. After reviewing the Information Sheet and Consent Form, you can begin the survey by **clicking the link below:**

NZ IBD Aches & Pains Survey

You are invited to participate in an online survey about ongoing **pain in people with Inflammatory Bowel Disease**. This survey is part of a larger study at the University of Otago, aimed at investigating why individuals with IBD develop persistent pain in order to help find targeted treatments.

The survey takes approximately **10-15 minutes** to complete. At the end of the survey you will be given the opportunity to enter in a **prize draw for a $50 Prezzy card** with 5 chances to win!

For more information regarding this study and to proceed to the survey - click the link below:

NZ IBD Aches & Pains Survey

New Zealand IBD Aches & Pains Survey

What is this study about?

The aim of this study is to investigate why individuals with IBD develop persistent pain in order to help find targeted treatments.

Am I eligible for the study?

You are eligible to participate if you are:

- Living in New Zealand
- Have been diagnosed with IBD (Crohn's disease, ulcerative colitis, or unspecified colitis)
- Not pregnant (to include less than 6 months post-partum)
- Do not have any neurological diseases (i.e., multiple sclerosis, Parkinson's disease, stroke)
- Have not had a nerve injury
- Have not had surgery in the last 3 months

What will I be asked to do?

You will be invited to complete and online survey that takes approximately 10-15 minutes to complete. Please read the attached Information Sheet and Informed Consent carefully before you decide to participate in this survey.

Upon completing the survey, you will be given the opportunity to enter in a prize draw for a $50 Prezzy card, with 5 chances to win.

To participate click on the link below:

NZ IBD Aches & Pains Survey

Thank you for your time in supporting this study. The study has ethical approval from the University of Otago (Reference: H17/095).

Contact details: PhD Candidate: Carrie Falling (carrie.falling@postgrad.otago.ac.nz)

Appendix D – Study 1: Information Sheet

New Zealand IBD "Aches & Pains" Survey

INFORMATION SHEET FOR PARTICIPANTS

Thank you for showing an interest in this project. Please read this information sheet carefully before deciding whether or not to participate. If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you and we thank you for considering our request.

What is the Aim of the Project?

We are trying to understand the nature of musculoskeletal pain in people with Inflammatory Bowel Disease (IBD). More specifically, we are interested how different aspects of pain, IBD, and general health contribute to an individual's overall pain experience. We will do this by asking a series of questions around these themes, and then identify how these themes relate to each other. The aim of this project is to better understand the mechanisms behind why people with IBD develop persistent pain, and also to identify targeted treatments.

What Type of Participants are being sought?

Adults that have been diagnosed with IBD (Crohn's disease, ulcerative colitis, or unspecified IBD) living in New Zealand who have ongoing pain.

Adults who have following conditions/situations will unfortunately not be able to take part in this study. This includes:

- Neurological diseases (i.e., multiple sclerosis, Parkinson's disease, stroke)
- Nerve injuries
- Surgery in the last 3 months
- Pregnancy (to include less than 6 months post-partum)

What will Participants be asked to do?

Should you agree to take part in this project, you will be asked to complete an online survey (approximately 10-15 minutes). Hyperlink to the survey is included in the body of the original invitation email. You will be able to stop the survey at any time to withdraw from this study. Alternatively, you may decide not to take part in the project without any disadvantage to yourself of any kind. If you choose to participate in this survey, you will be offered the chance to enter in a prize draw for a $50 Prezzy card as reimbursement for your participation, with 5 chances to win.

Is there any Risk of Discomfort or Harm from Participation?

This study consists of one online survey that requires approximately 10-15 minutes to complete. No risks of discomfort or harm have been identified for potential participants.

What Data or Information will be collected and What Use will be Made of it?
This online survey asks questions relating to three categories: 1) participant information (age, gender, and ethnicity) & general health, 2) IBD related questions (type of IBD, disease activity, and disease severity), and 3) pain related questions (location, intensity, duration, and quality of pain).

Identifying the relationship between pain and disease features will help indicate why individuals with IBD develop persistent pain and to identify possible treatment plans.

- Who will have access to the data or information?
  The collected data will be securely stored in such a way that only the primary investigator and PhD candidate will be able to gain access to it for analysis.

- How will data or information be securely managed, stored and destroyed?
  The data collected will be securely stored on a password protected computer located in the PhD candidate's locked office. Data obtained as a result of the research will be retained for **at least 10 years** in secure storage. Any personal information (such as: name and contact details) you provide will only relate to prize draws and requests for study information. Personal information will be collected separately from health data and therefore not linked at any time with collected health data. Any personal information collected will be destroyed once the study is completed. Reasonable precautions will be taken to protect data gathered and documented by electronic means during the study period through password protected computer.

- What data or information will be reflected in the completed research?
  Completed research will reflect only summary measures of the gathered data. Any personal information gathered during the survey will be collected separately and not at any time linked to health data. Every attempt will be made to preserve your confidentiality and anonymity. You will be given a computer generated identification code upon initiation of the survey, and data will be linked to that code only.

- Will the participants have the opportunity to correct or withdraw the data/information?
  You will have full rights to correct or change the information until the completion of your online survey session. Once the survey session is complete, the anonymous data will no longer be accessible to participants.

- Will participants be given the opportunity to view the data or information that relates to them either before or after the completion of the research? At what stage will this opportunity be given to them?
  You will have the opportunity to navigate through any portion of the survey until completion of your survey session. Once the survey session has ended, the anonymous data will no longer be accessible to participants.

- Will participants be provided with the results of the study?
  Yes. Results from this study will be provided on the study's website (www….).

Can Participants Change their Mind and Withdraw from the Project?
You may withdraw from participation in the project at any time during the online survey and without any disadvantage to yourself of any kind.

What if Participants have any Questions? If you have any questions about our project, either now or in the future, please feel free to contact either:

Ms Carrie Falling
PhD Candidate & Co-investigator
Centre for Health, Activity & Rehabilitation Research
School of Physiotherapy
University of Otago
325 Great King Street
Dunedin 9016
Email: carrie.falling@otago.ac.nz

Phone : 03 479 5422

Dr Ramakrishnan Mani
Primary Investigator & Lecturer
Centre for Health, Activity & Rehabilitation Research
School of Physiotherapy
University of Otago
325 Great King Street
Dunedin 9016
Email: ramakrishnan.mani@otago.ac.nz

Phone : 03 479 3485

This study has been approved by the University of Otago Human Ethics Committee. If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph. 03 479 8256 or email gary.witte@otago.ac.nz). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.

Appendix E – Study 1: Participant Consent Form

New Zealand IBD Aches & Pains Survey

Investigators:

Carrie Falling, PhD candidate, School of Physiotherapy (carrie.falling@otago.ac.nz)

Dr Ramakrishnan Mani, Principal Investigator, School of Physiotherapy (ramakrishnan.mani@otago.ac.nz)

CONSENT FORM

At the *start of the survey* you will be asked to provide your informed consent acknowledging the following:

1. I have read the Information Sheet concerning this study and understand the aims of this research project.
2. I have had sufficient time to talk with other people of my choice about participating in the study.
3. I confirm that I meet the criteria for participation which are explained in the Information Sheet.
4. All my questions about the project have been answered to my satisfaction, and I understand that I am free to request further information at any stage.
5. I know that my participation in the project is entirely voluntary, and that I am free to withdraw from the project at any time during my survey session without disadvantage.
6. I know that as a participant I will be asked to *complete one online survey that explores questions regarding aspects of pain, IBD and general health.*
7. I understand that I may decline to answer any question(s), and/or may withdraw from the project during the active survey session without disadvantage of any kind.
8. I understand the nature and size of the risks of discomfort or harm which are explained in the Information Sheet.
9. I know that when the project is completed all personal identifying information will be destroyed, and anonymous health data will be placed in secure storage and kept for at least ten years.
10. I understand that the results of the project may be published and be available in the University of Otago Library, but I understand that any personal identifying information will remain confidential between myself and the

researchers during the study, and will not appear in any spoken or written report of the study.

11. I know that I will be offered the opportunity to voluntarily be entered into a prize draw for a $50 Prezzy card as reimbursement for my participant.
12. I know that no commercial use will be made of data from this study.

Appendix F – Study 1: Survey

New Zealand IBD Aches & Pains Survey

Q1. I have read the study Information Sheet provide and consent to participate in: New Zealand IBD Aches & Pains National Survey

- ❍ Yes
- ❍ No

Condition: No Is Selected. Skip To: End of Survey.

The following are some questions about your IBD history and general health.

Q2. Which form of Inflammatory Bowel Disease (IBD) have you been diagnosed with?

- ❍ Crohn's Disease
- ❍ Ulcerative colitis
- ❍ IBD Unspecified

Q3. How long ago were you diagnosed with IBD?
Years: _____
Months: _____

Q4. How many times have you been admitted to hospital for IBD flares or complications of IBD (excluding surgeries)? _____

Q5. How many IBD related surgeries have you had in total? _____

Q6 Please indicate any of the following medication that you are currently taking:

- ❑ Gut specific anti-inflammatories, such as:
  Mesalazine (Asacol®, Pentasa®, Asamax 500®)
  Sulphasalazine (Salazopyrin®)
  Olsalazine
- ❑ Steroids, such as:
  Budesonide (Entocort®)
  Hydrocortisone acetate (Colifoam®)
  Prednisone Methylprednisone (Medrol®, Solu-Medrol®, Depo-Medrol®)
- ❑ Immunosuppressants, such as:
  Methotrexate (Methoblastin®, Trexate®, Hospira®)
  Azathioprine (Imuran®, Azamun®, Imuprine®)
  Ciclosporin
- ❑ Biologics (TNF inhibitors), such as:
  Infliximab (Remicade)
  Adalimumab (Humira)

Q7 Have you received 2 or more courses of steroids (eg. budesonide, hydrocortisone, prednisone, etc.) as treatment for your IBD since your initial diagnosis?

- ❍ Yes
- ❍ No

Q8. Have you ever been diagnosed with any of the following:

- ❑ Osteoporosis
- ❑ Colorectal cancer
- ❑ Sweet's Syndrome
- ❑ Psoriasis
- ❑ Episcleritis
- ❑ Scleritis
- ❑ Kidney stones (nephrolithiasis)
- ❑ Primary sclerosing cholangitis
- ❑ Rheumatoid arthritis
- ❑ Ankylosing spondylitis
- ❑ Sacroiliitis
- ❑ Inflammatory arthritis
- ❑ Osteoarthritis
- ❑ Arthralgia
- ❑ Uveitis
- ❑ Erythema Nodosum
- ❑ Mouth ulcers (Oral aphthous ulcers)
- ❑ Pyoderma Gangrenosum
- ❑ Anal fissure / fistula
- ❑ Abscess
- ❑ Heart Disease
- ❑ Vascular disease
- ❑ Respiratory disease
- ❑ Diabetes
- ❑ Kidney disease
- ❑ Liver disease
- ❑ Dementia
- ❑ Cancer
- ❑ AIDS/HIV

Display Q9-Q12:
If Crohn's Disease is selected for Q2 “Which form of Inflammatory Bowel Disease (IBD) have you been diagnosed with?”

The following are specific questions regarding your Crohn's disease: Please check one box per number.

Q9. General well-being (yesterday)
- ❍ Very well
- ❍ Slightly below par
- ❍ Poor
- ❍ Very poor
- ❍ Terrible

Q10 Abdominal pain (yesterday)
- ❍ None
- ❍ Mild
- ❍ Moderate
- ❍ Severe

Q11 Number of liquid or soft stools per day (yesterday) _____

Q12. Abdominal mass:
- ❍ None
- ❍ Dubious
- ❍ Definite
- ❍ Definite and tender

Display Q13-Q25:
If Crohn's Disease is ***not*** selected for Q2 “Which form of Inflammatory Bowel Disease (IBD) have you been diagnosed with?”

The following questions concern your Ulcerative colitis. These questions refer to your symptoms during the PREVIOUS WEEK.

Q13 On average per day (24 hours), how many times did you use the toilet for defecation during the previous week? Blood and slime discharge is also considered defecation.
- ❍ 0 to 3 times
- ❍ 4 to 6 times
- ❍ 7 to 9 times
- ❍ More than 9 times

Q14. On average per night, how many times did you get out of bed to use the toilet for defection during the previous week?
- ❍ Never
- ❍ 1 to 3 times
- ❍ More than 3 times

Q15. During the previous week, were you able to hold up your stool for 15 minutes or longer, when you felt the urge to use the toilet?
- ❍ Yes
- ❍ No
- ❍ I don't know

Q16. During the previous week, did you have to make adjustments to your activities, to ensure that there was a toilet nearby?
- ❍ Yes
- ❍ No
- ❍ I don't know

Q17. During the previous week, have you found stool in your underwear?
- ❍ Yes
- ❍ No
- ❍ I don't know

Q18. During the previous week, how many times did you see blood in your stool?
- ❍ Never
- ❍ Much less than half of the times
- ❍ A little less than half of the times
- ❍ More than half of the times

Q19. If you would have to rate your general well-being during the previous week by giving it a number, what number would you choose? (1 = very bad, 10 = perfect)

_____

Q20. During the previous week, did you have joint pain which was worse at rest than after activity?

- ❍ Yes
- ❍ No
- ❍ I don't know

Q21. During the previous week, were your joints red or swollen?

- ❍ Yes
- ❍ No
- ❍ I don't know

Q22. During the previous week, have you ever woken up from joint pain?

- ❍ Yes
- ❍ No
- ❍ I don't know

Q23. During the previous week, have you had a skin disorder that has been diagnosed as erythema nodosum by your treating specialist?

- ❍ Yes
- ❍ No
- ❍ I have a skin disorder but have not seen my specialist for it or do not know what the disorder is called.

Q24. During the previous week, have you had a skin disorder that has been diagnosed as pyoderma by your treating specialist?

- ❍ Yes
- ❍ No
- ❍ I have a skin disorder but have not seen my specialist for it or do not know what the disorder is called.

Q25. Do you momentarily have an eye infection, that you have seen an eye-specialist for and which your treating specialist diagnosed as uveïtis?

- ❍ Yes
- ❍ No
- ❍ I have an eye infection but have not seen an eye specialist for it or do not know what the infection is called.

The following are questions regarding the impact of IBD on your quality of life.

Q26. Please respond to each question or statement by marking one box per row.

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
How often has the feeling of fatigue or being tired and worn out been a problem for you during the past 2 weeks?	❍	❍	❍	❍	❍	❍	❍
How often during the last 2 weeks have you delayed or canceled a social engagement because of your bowel problem?	❍	❍	❍	❍	❍	❍	❍
How often during the past 2 weeks have you been troubled by pain in the abdomen?	❍	❍	❍	❍	❍	❍	❍
How often during the past 2 weeks have you felt depressed or discouraged?	❍	❍	❍	❍	❍	❍	❍
How often during the past 2 weeks have you felt relaxed and free of tension?	❍	❍	❍	❍	❍	❍	❍
How much of the time during the past 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty?	❍	❍	❍	❍	❍	❍	❍
How often during the past 2 weeks have you felt angry as a result of your bowel problem?	❍	❍	❍	❍	❍	❍	❍

Q27. Please respond to each question or statement by marking one box per row.

	A major problem	A big problem	A significant problem	Some problem	A little trouble	Hardly any trouble	No trouble
Overall, in the past 2 weeks, how much of a problem have you had with passing large amounts of gas?	❍	❍	❍	❍	❍	❍	❍
Overall, in the past 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be?	❍	❍	❍	❍	❍	❍	❍

Q28. As a result of your bowel problems, how much difficulty did you experience doing leisure or sports activities you would liked to have done during the past 2 weeks?

❍ A great deal of difficulty; activities made impossible
❍ A lot of difficulty
❍ A fair bit of difficulty
❍ Some difficulty
❍ A little difficulty
❍ Hardly any difficulty
❍ No difficulty; the bowel problem did not limit sports or leisure activities

Q29. Have you experienced abdominal pain that lasted longer than 1 week during the past year? (Please do not report pain from feverish illness, menstruation, or from surgery within the past year)

❍ Yes
❍ No

Display Q30-Q31:
If yes is selected for Q29 “Have you experienced abdominal pain that lasted longer than 1 week during the past year? (Please do not report pain from feverish illness, menstruation, or from surgery within the past year)”

Q30. In the past 7 days…

	None 0 1 2 3 4 5 6 7 8 9 10 Max
How would you rate your abdominal pain on average?	

Q31. In the past 7 days…

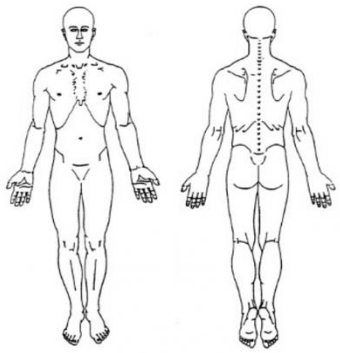
	None 0 1 2 3 4 5 6 7 8 9 10 Max
How much did abdominal pain interfere with your day to day activities?	

Q32. Have you experienced any bodily aches or pains OTHER THAN abdominal pain, headaches and/or chest pain, such as pain from muscles, joints, or bones that has lasted longer than 1 week in the past year? (Please do not report pain from feverish illness, menstruation, surgery within the past year, or acute injury within the past 3 months)

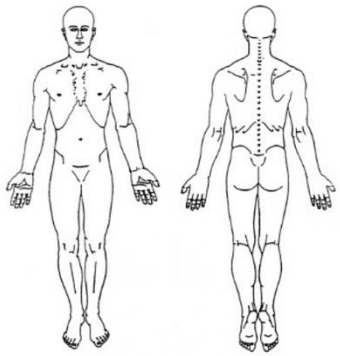
- ❍ Yes
- ❍ No

IF: No Is Selected. Skip To: Q45

Q33. Please mark all of the areas that you have had pain in the past 12 months that lasted longer than 1 week.(Please do not report pain from feverish illness, menstruation, surgery within the past year, or acute injury within the past 3 months)



Q34. Please mark your MAIN area of pain. (Please do not report pain from feverish illness, menstruation, surgery within the past year, or acute injury within the past 3 months)



Q35. Have you ever been diagnosed with peripheral or diabetic neuropathy?

- ❍ Yes
- ❍ Maybe
- ❍ No

Q36. Does your pain radiate to other regions of your body?

- ❍ Yes
- ❍ No

Q37. How long have you had pain in this area? (Please answer in years)

Years: _____

Months: _____

Q38. In the past 7 days…

	Not at all	A little bit	Somewhat	Quite a bit	Very
How much did pain interfere with your day to day activities?	❍	❍	❍	❍	❍
How much did pain interfere with work around the home?	❍	❍	❍	❍	❍
How much did pain interfere with your ability to participate in social activities?	❍	❍	❍	❍	❍
How much did pain interfere with your household chores? (4)	❍	❍	❍	❍	❍

Q39.

	None 0 1 2 3 4 5 6 7 8 9 10 Max
How would you assess your pain NOW, at this moment?	

Q40.

	None 0 1 2 3 4 5 6 7 8 9 10 Max
How strong was the STRONGEST pain during the past 4 weeks?	

Q41.

	None 0 1 2 3 4 5 6 7 8 9 10 Max

How strong was the pain during the past 4 weeks on AVERAGE?	

Q42. Mark the picture that best describes the course of your pain:

❍  Persistent pain with slight fluctuations

❍  Persistent pain with pain attacks

❍  Pain attacks without pain between them

❍  Pain attacks with pain between them

Q43. Please respond to each question or statement by marking one box per row.
In the past 7 days...

	Never	Hardly noticed	Slightly	Moderately	Strongly	Very strongly
Do you suffer from a burning sensation (e.g. stinging nettles) in the marked areas?	❍	❍	❍	❍	❍	❍
Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical)?	❍	❍	❍	❍	❍	❍
Is light touching (clothing, a blanket) in this area painful?	❍	❍	❍	❍	❍	❍
Do you have sudden pain attacks in the area of your pain, like electrical shocks?	❍	❍	❍	❍	❍	❍
Is cold or heat (bath water) in this area occasionally painful?	❍	❍	❍	❍	❍	❍
Do you suffer from a sensation of numbness in the areas that you marked?	❍	❍	❍	❍	❍	❍

Q44. Please respond to each question or statement by marking one box per row.
In the past 7 days...

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Did your pain feel sore?	❍	❍	❍	❍	❍
Did your pain feel tender?	❍	❍	❍	❍	❍
Did your pain feel achy?	❍	❍	❍	❍	❍
Did your pain feel deep?	❍	❍	❍	❍	❍
Did your pain feel steady?	❍	❍	❍	❍	❍

The following are questions about your general health and well-being:
Q45. Please choose the best response to the right of each statement.

	Never	Rarely	Sometimes	Often	Always
I feel tired and unrefreshed when I wake from sleeping.	❍	❍	❍	❍	❍
My muscles feel stiff and achy.	❍	❍	❍	❍	❍
I have anxiety attacks.	❍	❍	❍	❍	❍
I grind or clench my teeth.	❍	❍	❍	❍	❍
I have problems with diarrhea and/or constipation.	❍	❍	❍	❍	❍
I need help in performing my daily activities.	❍	❍	❍	❍	❍
I am sensitive to bright lights.	❍	❍	❍	❍	❍
I get tired very easily when I am physically active.	❍	❍	❍	❍	❍
I feel pain all over my body.	❍	❍	❍	❍	❍
I have headaches.	❍	❍	❍	❍	❍
I feel discomfort in my bladder and/or burning when I urinate.	❍	❍	❍	❍	❍
I do not sleep well.	❍	❍	❍	❍	❍
I have difficulty concentrating.	❍	❍	❍	❍	❍
I have skin problems such as dryness, itchiness, or rashes.	❍	❍	❍	❍	❍
Stress makes my physical symptoms get worse.	❍	❍	❍	❍	❍
I feel sad or depressed.	❍	❍	❍	❍	❍
I have low energy.	❍	❍	❍	❍	❍
I have muscle tension in my neck and shoulders.	❍	❍	❍	❍	❍
I have pain in my jaw.	❍	❍	❍	❍	❍

Certain smells, such as perfumes, make me feel dizzy and nauseated.	❍	❍	❍	❍	❍
I have to urinate frequently.	❍	❍	❍	❍	❍
My legs feel uncomfortable and restless when I am trying to go to sleep at night.	❍	❍	❍	❍	❍
I have difficulty remembering things.	❍	❍	❍	❍	❍
I suffered trauma as a child.	❍	❍	❍	❍	❍
I have pain in my pelvic area.	❍	❍	❍	❍	❍

Q46. Have you been diagnosed by a doctor with any of the following disorders?

- ❑ Restless Leg Syndrome
- ❑ Chronic Fatigue Syndrome
- ❑ Fibromyalgia
- ❑ Temporomandibular Joint Disorder (TMJ)
- ❑ Migraine or tension headaches
- ❑ Irritable Bowel Syndrome
- ❑ Multiple Chemical Sensitivities
- ❑ Neck Injury (including whiplash)
- ❑ Anxiety or Panic Attacks
- ❑ Depression

The following are a more few questions about you:

Q47. Select your gender

- ❍ Male
- ❍ Female
- ❍ Gender diverse (please specify) _____

Q48. What is your age in years? _____

Q49. Which ethnic group do you belong to? Mark the space or spaces that apply to you

- ❑ New Zealand European
- ❑ Māori
- ❑ Samoan
- ❑ Cook Island
- ❑ Tongan
- ❑ Niuean
- ❑ Chinese
- ❑ Indian
- ❑ Other (such as Dutch, Japanese, Tokelauan). Please state.

  _____

Appendix G – Study 1: Tables of Participant Characteristics (Chapter 5)

Table G.1

Study One: Included and Excluded Participant Characteristics

Characteristic	Included (*N* = 305)	Excluded (*N* = 54)
Gender [a]		
Male, *n* (%)	61 (20.1)	2 (9.09)
Female, *n* (%)	241 (79.3)	19 (86.36)
Gender diverse, *n* (%)	2 (0.7)	2 (5.00)
Age [a]		
Range (years)	18-88	22-77
Mean (SD)	43.86 (14.76)	448.55 (15.34)
Ethnicity [a]		
New Zealand European, *n* (%)	273 (89.51)	19 (86.36)
IBD type [b]		
CD, *n* (%)	201 (65.90)	30 (66.67)
UC, *n* (%)	94 (30.82)	13 (28.89)
IC, *n* (%)	10 (3.29)	1 (2.22)

Note. Inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), indeterminate colitis (IC), standard deviation (SD), and central sensitization inventory (CSI).

[a] Answered by *n* = 22 excluded participants

[b] Answered by *n* = 45 excluded participants

Table G.2

Comorbidity Characteristics of Three Latent Classes

Comorbidity	Class 1 (*n*=63) *n* (%)	Class 2 (*n*=86) *n* (%)	Class 3 (*n*=55) *n* (%)	*P*
Depression	31 (49)	32 (37)	14 (26)	0.001*
Anxiety	19 (30)	22 (26)	8 (15)	0.054
Heart Disease	3 (5)	2 (2)	2 (4)	0.726
Vascular disease	1 (2)	2 (2)	0(0)	0.952
Respiratory disease	3 (5)	4 (5)	3 (6)	0.975
Diabetes	6 (10)	3 (4)	4 (7)	0.337
Kidney disease	2 (3)	1 (1)	0(0)	0.709
Liver disease	2 (3)	4 (5)	2 (4)	0.894
Dementia	0(0)	0(0)	0(0)	-
Cancer	1 (2)	5 (6)	0(0)	0.480
AIDS/HIV	0(0)	0(0)	0(0)	-
Restless leg syndrome	6 (10)	3 (4)	3 (6)	0.322
Chronic fatigue syndrome	9 (14)	2 (2)	2 (4)	0.020*
Fibromyalgia	3 (5)	4 (5)	0(0)	0.999
TMJ	2 (3)	4 (5)	0(0)	0.904
Migraine	16 (25)	17 (20)	6 (11)	0.145
Irritable bowel syndrome	18 (29)	28 (33)	16 (29)	0.847
Multiple Chemical Sensitivities	1 (2)	4 (5)	0(0)	0.619
Neck Injury (including whiplash)	12 (19)	9 (11)	3 (6)	0.080

Note. * Significance identified as $p \leq 0.05$.

Table G.3

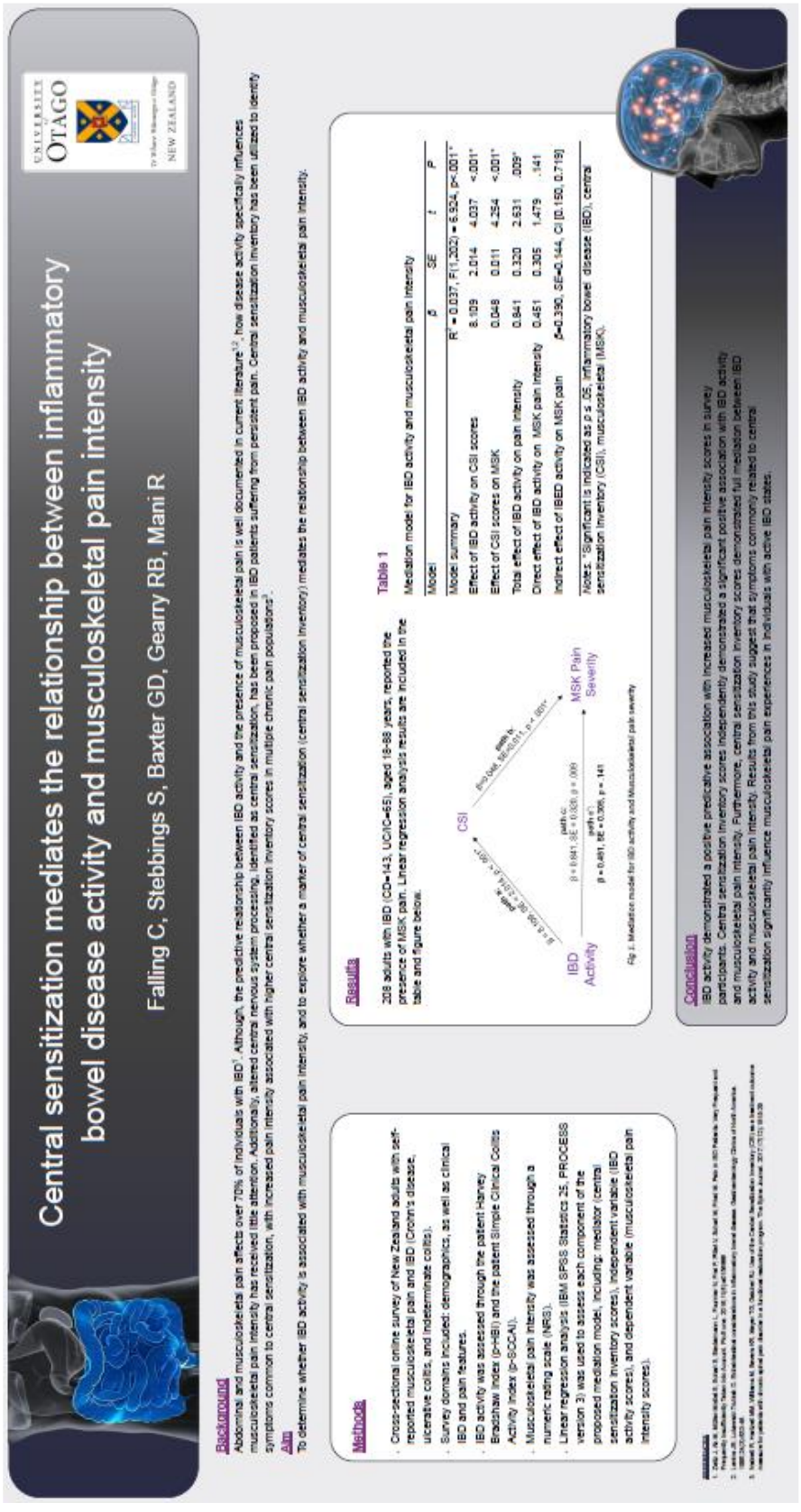
Extra-intestinal Manifestations of Three Latent Classes

Extra-intestinal manifestations	Class 1 (*n*=63) *n* (%)	Class 2 (*n*=86) *n* (%)	Class 3 (*n*=55) *n* (%)	*P*
Inflammatory Arthritis	21 (33)	22 (26)	15 (27)	0.572
Osteoarthritis	13 (21)	9 (11)	2 (4)	0.027*
Arthralgia	19 (30)	21 (24)	9 (16)	0.222
Osteoporosis	12 (19)	7 (8)	3 (6)	0.045*
Colorectal cancer	0(0)	0(0)	1 (2)	-
Sweet's Syndrome	0(0)	1 (1)	0(0)	-
Psoriasis	6 (10)	6 (7)	3 (6)	0.693
Episcleritis	0(0)	0(0)	1 (2)	-
Scleritis	0(0)	0(0)	0(0)	-
Nephrolithiasis	3 (5)	5 (6)	1 (2)	0.555
Primary sclerosing cholangitis	2 (3)	2 (2)	2 (4)	0.897
Uveitis	1 (2)	1 (1)	2 (4)	0.595
Erythema Nodosum	1 (2)	4 (5)	2 (4)	0.619
Oral aphthous ulcers	22 (35)	29 (34)	21 (38)	0.862
Pyoderma Gangrenosum	1 (2)	0(0)	1 (2)	0.995
Anal fissure or fistula	21 (33)	31 (36)	21 (38)	0.859
Intestinal abscess	6 (10)	9 (11)	4 (7)	0.816

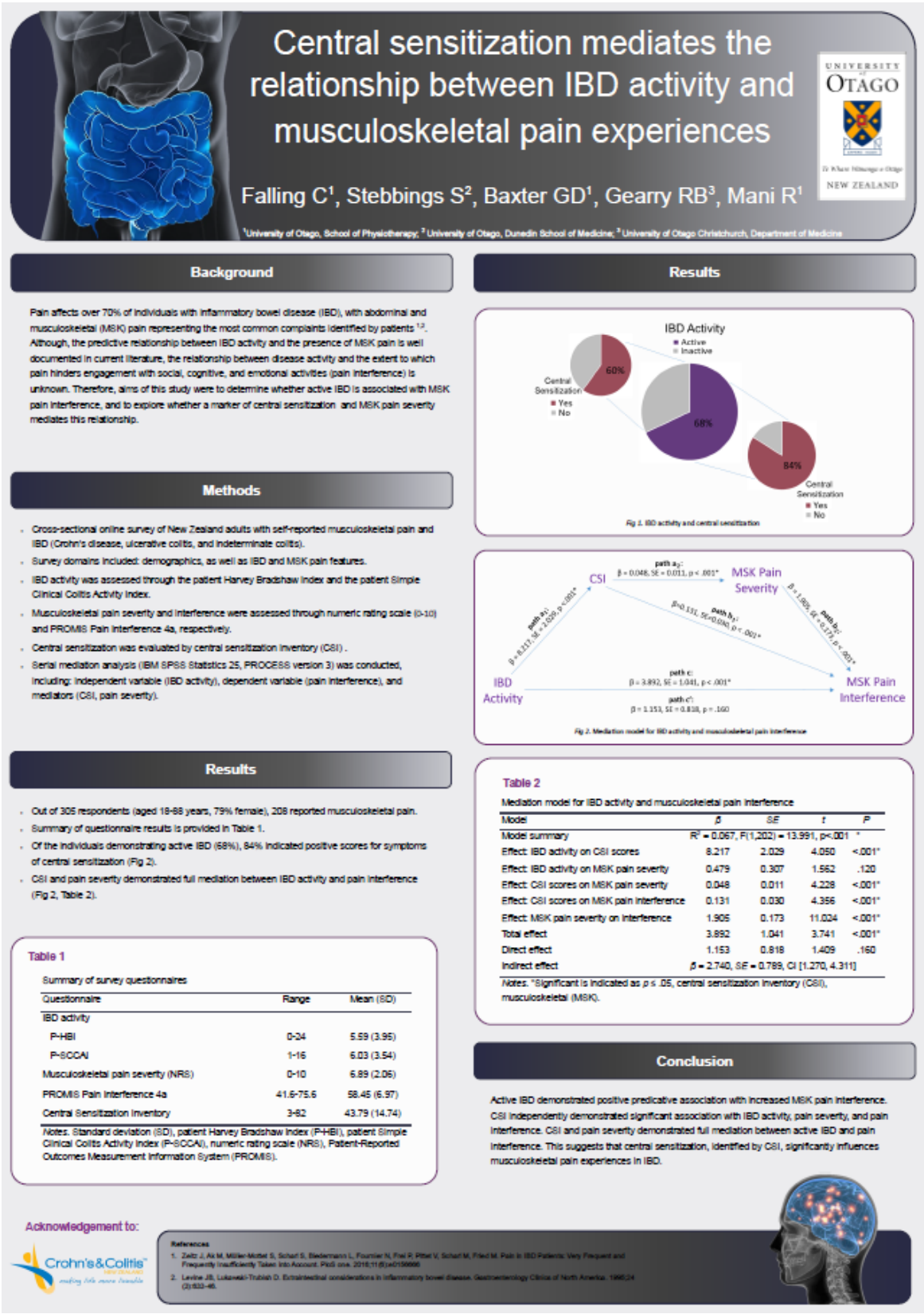
Note. * Significance identified as $p \leq .05$.

Appendix H – Study 1: Sub-analysis Poster Presentations

Falling, C., Stebbings, S., Mani, R., Baxter, D., & Gearry, R. (2018). (424) Central Sensitization Mediates the Relationship between Inflammatory Bowel Disease Activity and Musculoskeletal Pain Severity. *The International Association for the Study of Pain: 17th World Congress on Pain*, held at: Boston, Massachusetts, United States of America.



Falling, C. L., Stebbings, S., Baxter, G. D., Gearry, R. B., & Mani, R. (2018) Central sensitization inventory mediates the relationship between inflammatory bowel disease activity and musculoskeletal pain experiences. *NZ Society of Gastroenterology: Annual Scientific Meeting*, held at: Dunedin, New Zealand.



Central sensitization mediates the relationship between IBD activity and musculoskeletal pain experiences

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[1]University of Otago, School of Physiotherapy; [2] University of Otago, Dunedin School of Medicine; [3] University of Otago Christchurch, Department of Medicine

Background

Pain affects over 70% of individuals with inflammatory bowel disease (IBD), with abdominal and musculoskeletal (MSK) pain representing the most common complaints identified by patients [1,2]. Although, the predictive relationship between IBD activity and the presence of MSK pain is well documented in current literature, the relationship between disease activity and the extent to which pain hinders engagement with social, cognitive, and emotional activities (pain interference) is unknown. Therefore, aims of this study were to determine whether active IBD is associated with MSK pain interference, and to explore whether a marker of central sensitization and MSK pain severity mediates this relationship.

Methods

- Cross-sectional online survey of New Zealand adults with self-reported musculoskeletal pain and IBD (Crohn's disease, ulcerative colitis, and indeterminate colitis).
- Survey domains included: demographics, as well as IBD and MSK pain features.
- IBD activity was assessed through the patient Harvey Bradshaw Index and the patient Simple Clinical Colitis Activity Index.
- Musculoskeletal pain severity and interference were assessed through numeric rating scale (0-10) and PROMIS Pain Interference 4a, respectively.
- Central sensitization was evaluated by central sensitization inventory (CSI) .
- Serial mediation analysis (IBM SPSS Statistics 25, PROCESS version 3) was conducted, including: independent variable (IBD activity), dependent variable (pain interference), and mediators (CSI, pain severity).

Results

- Out of 305 respondents (aged 18-88 years, 79% female), 208 reported musculoskeletal pain.
- Summary of questionnaire results is provided in Table 1.
- Of the individuals demonstrating active IBD (68%), 84% indicated positive scores for symptoms of central sensitization (Fig 2).
- CSI and pain severity demonstrated full mediation between IBD activity and pain interference (Fig 2, Table 2).

Table 1

Summary of survey questionnaires

Questionnaire	Range	Mean (SD)
IBD activity		
P-HBI	0-24	5.59 (3.95)
P-SCCAI	1-16	6.03 (3.54)
Musculoskeletal pain severity (NRS)	0-10	6.89 (2.06)
PROMIS Pain Interference 4a	41.6-75.6	58.45 (6.97)
Central Sensitization Inventory	3-82	43.79 (14.74)

Notes. Standard deviation (SD), patient Harvey Bradshaw Index (P-HBI), patient Simple Clinical Colitis Activity Index (P-SCCAI), numeric rating scale (NRS), Patient-Reported Outcomes Measurement Information System (PROMIS).

Results

Fig 1. IBD activity and central sensitization

Fig 2. Mediation model for IBD activity and musculoskeletal pain interference

Table 2

Mediation model for IBD activity and musculoskeletal pain interference

Model	β	SE	t	P
Model summary	R^2 = 0.067, F(1,202) = 13.991, p<.001			*
Effect: IBD activity on CSI scores	8.217	2.029	4.050	<.001*
Effect: IBD activity on MSK pain severity	0.479	0.307	1.562	.120
Effect: CSI scores on MSK pain severity	0.048	0.011	4.228	<.001*
Effect: CSI scores on MSK pain interference	0.131	0.030	4.356	<.001*
Effect: MSK pain severity on interference	1.905	0.173	11.024	<.001*
Total effect	3.892	1.041	3.741	<.001*
Direct effect	1.153	0.818	1.409	.160
Indirect effect	β = 2.740, SE = 0.789, CI [1.270, 4.311]			

Notes. *Significant is indicated as $p \leq .05$, central sensitization inventory (CSI), musculoskeletal (MSK).

Conclusion

Active IBD demonstrated positive predicative association with increased MSK pain interference. CSI independently demonstrated significant association with IBD activity, pain severity, and pain interference. CSI and pain severity demonstrated full mediation between active IBD and pain interference. This suggests that central sensitization, identified by CSI, significantly influences musculoskeletal pain experiences in IBD.

Acknowledgement to:

Crohn's&Colitis NEW ZEALAND making life more liveable

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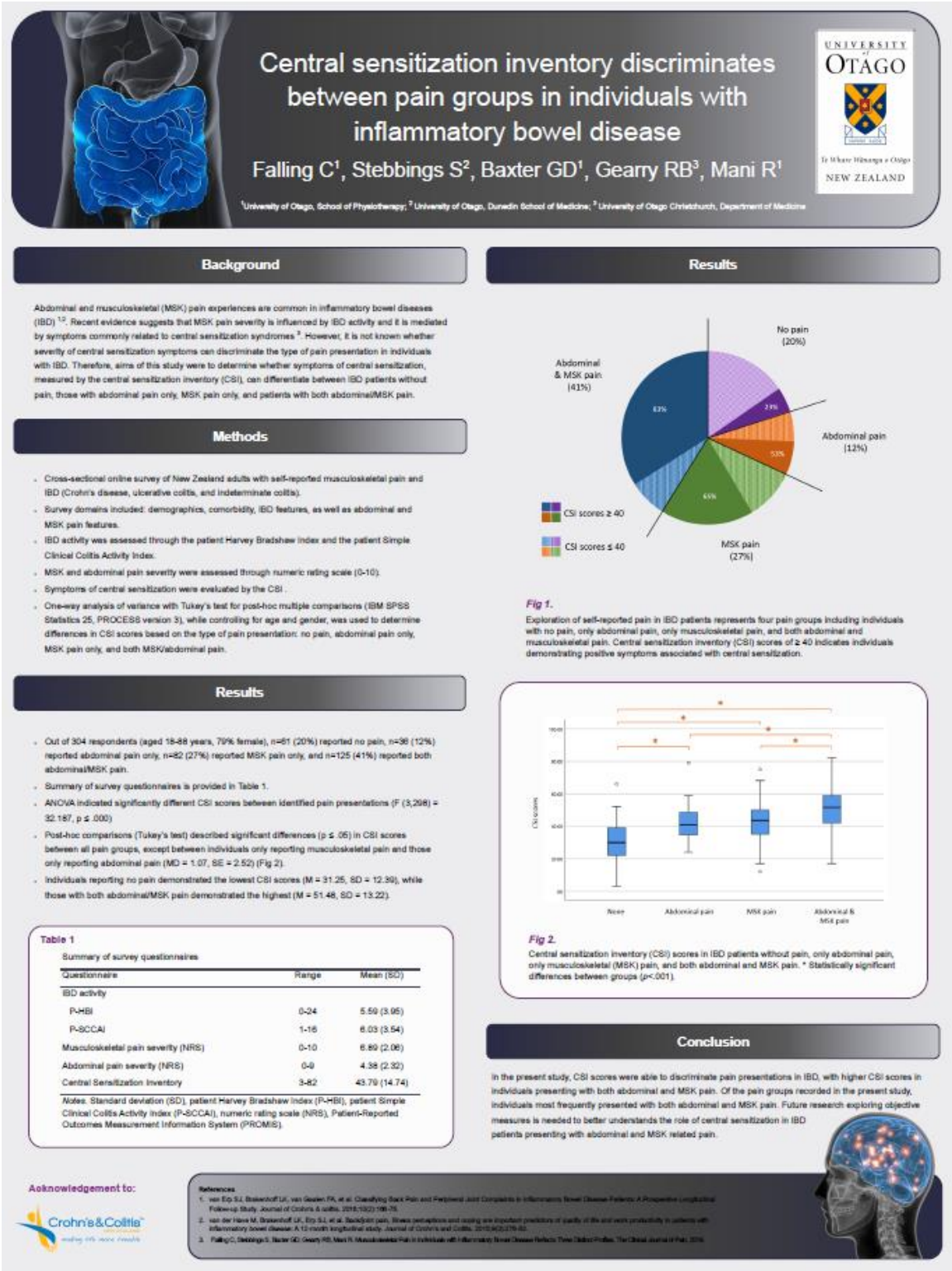
2. Levine JS, Lukewich-Trubiak D. Extraintestinal considerations in inflammatory bowel disease. Gastroenterology Clinics of North America. 1995;24(3):633-46.

Falling, C., Stebbings, S., Mani, R., Baxter, D., & Gearry, R. (2019). Central Sensitization Inventory Discriminates between Pain Groups in Individuals with Inflammatory Bowel Disease. *American Pain Society: Annual Scientific Meeting*, held at: Milwaukee, Wisconsin, United States of America.



Appendix I – Study 1: Accepted abstract for Secondary Sub-analysis

Falling, C., Stebbings, S., Mani, R., Baxter, D., & Gearry, R. (2019). (183) Central Sensitization Inventory Discriminates between Pain Groups in Individuals with Inflammatory Bowel Disease. The Journal of Pain, 20(4), S21.

Central sensitization inventory discriminates between pain groups in individuals with inflammatory bowel disease

Falling C, Stebbings S, Baxter GD, Gearry RB, Mani R

Abdominal and musculoskeletal (MSK) pain experiences are common in inflammatory bowel diseases (IBD). Recent evidence suggests that MSK pain severity is influenced by IBD activity and it is mediated by symptoms commonly related to central sensitization syndromes. However, it is not known whether severity of central sensitization symptoms can discriminate the type of pain presentation in individuals with IBD. A cross-sectional online survey among 305 New Zealand adults with IBD (aged 18-88 years) was conducted. Features of IBD, abdominal pain, and MSK pain were examined using multiple validated questionnaires. Presence and severity of symptoms commonly seen in central sensitivity syndromes were assessed using the central sensitization inventory (CSI). One-way analysis of variance with post-hoc multiple comparisons, while controlling for age and gender, was used to determine differences in CSI scores based on the type of pain presentation: no pain (n=61), only abdominal pain (n=36), only MSK pain (n=82), and both abdominal/MSK pain (n=125). Analysis indicated significantly different CSI scores between identified pain presentations (F (3,298) = 32.187, $p \leq 0.000$). Individuals reporting no pain demonstrated the lowest CSI scores (M = 31.25, SD = 12.39), while those with both abdominal/MSK pain demonstrated the highest (M = 51.48, SD = 13.22). Post-hoc

comparisons described significant differences ($p \leq 0.05$) in CSI scores between all pain groups, except between individuals only reporting musculoskeletal pain and those only reporting abdominal pain (*MD* = 1.07, *SE* = 2.52). In the present study, CSI scores were able to discriminate pain presentations in IBD, with higher CSI scores in individuals with both abdominal/MSK pain. Future research should explore the relationship between CSI scores in this population with clinical measures of central sensitization.

Appendix J – Study 2: Information Sheet, Consent Form, Ethical Approval

CONSENT TO TAKE PART IN RESEARCH

Dartmouth-Hitchcock Medical Center

Study title: IBD Aches & Pains Study
Principal Investigator: Dr. Corey Siegel

You are being asked to take part in a research study. Taking part in research is voluntary.

There will be no disadvantage to you whether or not you choose to take part in this study. Please ask questions if there is anything about this study that you do not understand.

What is the purpose of this study?

The purpose of the study is to better understand why individuals with inflammatory bowel disease (IBD) experience ongoing musculoskeletal pain. More specifically, we are interested in whether nervous system hypersensitivity is contributing to painful experiences in IBD. To do this, we will perform traditional sensory tests on individuals with and without IBD to explore nervous system sensitivity, as well as ask a series of questions around pain and disease experiences.

Will you benefit from taking part in this study?

There is little chance you will personally benefit from being in this research study. We hope to gather information that may help people in the future.

What does this study involve?

If you take part in this study, all of the following activities will be done only for research purposes:
Your participation in this study includes 1 online screening questionnaire (approx. 5-7 minutes), and 1 examination session with digital questionnaires and sensory testing at DHMC IBD Clinic (approx. 60 minutes). You will be able to stop the digital questionnaires and/or sensory testing at any time without any disadvantage to yourself of any kind. Alternatively, you may decide not to take part in the project prior to testing.

The examination session will include the following experimental sensory tests:

1. Pain pressure threshold – this includes receiving a touch stimulus, about the size and shape of a large pencil eraser, pressed against: your low back, the muscle on the front of your lower leg, and your main area of pain (for people with musculoskeletal pain only). You will be asked to state when the sensation of pressure alone changes to one of pressure and pain. This is not intended to test your pain tolerance, but only the point to which pressure just becomes painful.
2. Repeated mechanical testing – this includes receiving a touch stimulus by a tool made of flexible nylon hair and shaped similar to a thin tooth pick. You will be asked to rank any discomfort experienced after 1 stimulus, and then to rank any discomfort experienced after a series of 10 consecutive stimuli.

3. Cold pressor test – this includes submerging one hand in ice water until you can no longer tolerate it OR for a maximum of 2 minutes (whichever comes first).
4. Vibration threshold test – This includes placing a vibration sensation provided by a tuning fork on both wrists and ankles. You will be asked to report the moment you no long feel the sensation of vibration.

What are the risks involved with being enrolled in this study?

This study consists of digital questionnaires exploring aspects of your health and pain experiences (if applicable) and sensory testing. This testing is intended to only assess sensations within the limits of your pain tolerance without exceeding these limits. Therefore, discomfort from testing is expected to be moderate. However, if at any time you experience discomfort beyond your tolerance, testing will be stopped immediately. We do not expect you to experience actual harm or injury from participating in this study. You will be given a short training session prior to testing to familiarize yourself with the procedures. Sensory testing will be performed by a trained investigator who will be present throughout the entire testing session.

Other important items you should know:

• **Leaving the study:** You may choose to stop taking part in this study at any time without any disadvantage to yourself of any kind.
• **Number of people in this study:** We expect a total of 120 people to enroll in this study here.
• **Funding:** The University of Otago (New Zealand) is providing some funding for this research project.

How will your privacy be protected?

The information collected as data for this study includes:

- Results of sensory testing
- Results of questionnaires evaluating: stress, anxiety, depression, pain experiences, quality of life, and IBD history
- Personal health information, including: health conditions, medication use, etc.

We are careful to protect the identities of the people in this study. We also keep the information collected for this study secure and confidential. All data obtained as part of this study will be de-identified by using anonymous identification codes and stored in a locked filing cabinet or on a password protected hard drive. Research data will be transferred by the investigator to the University of Otago (New Zealand) for further analysis on a password protected hard drive. Anonymous data collected for this study will be maintained for at least 10 years.

Who may use or see your health information?

By signing this form, you allow the research team to use your health information and give it to others involved in the research. The research team includes the study director plus others

working on this study at Dartmouth-Hitchcock Medical Center and elsewhere. You also permit any health care provider holding health information needed for this study to give copies of your information to the research team.

The information collected for this study may be used by researchers or officials of the following institutions.

- Dartmouth College
- Dartmouth-Hitchcock Medical Center.
- University of Otago
- Committee for the Protection of Human Subjects (ethical review board)

In order to conduct this study, researchers need to use your health care information. This data is called Protected Health Information ("PHI"). PHI is protected by federal privacy laws (HIPAA). By signing this consent form, you give your permission to have your PHI collected, used and disclosed for purposes of this study. There is no intention to disclose your PHI to others outside of the study. There are protections in place to keep your PHI and research data confidential. However, HIPAA requires notification so you are aware *if your* PHI is disclosed to others, it may no longer be protected by federal privacy laws.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Identifiable data collected for this study will be used for research purposes which are determined to be reasonable and in line with expectations by a review committee.

Once data collected for this research study is no longer identifiable, the data may be used or disclosed for other purposes.

Your permission to use your health information for this study will not end until the study is completed. During this study, you and others who take part in the study may not have access to the study data. You may ask for study data once the study is over. You have a right to receive a copy of the information in your medical record at any time.

It is possible for a court or government official to order the release of study data including information about you.

What if you decide not to give permission to use and share your personal health information?

If you do not allow use of your health information for this study, you may not take part in this study. If you choose to stop taking part in this study, you may cancel permission for the use of your health information. You should let the researcher know if you want to cancel your permission. The study team will assist you in putting your wishes in writing. Information collected for the study before your permission is cancelled will continue to be used in the research.

Will you be paid to take part in this study?
Yes. You will be given one $20 amazon gift voucher as reimbursement for your time.

Whom should you call with questions about this study?
If you have questions about this study or concerns about a research related problem or injury, you can call the research director for this study: Dr. Corey Siegel at (603) 650-5261 during normal business hours.

If you are injured or become ill as a result of research procedures, you will be provided with medical treatment, but the following organizations do not plan to pay for this treatment.

- Mary Hitchcock Memorial Hospital
- Dartmouth-Hitchcock Clinic
- Dartmouth-Hitchcock Medical Center
- Trustees of Dartmouth College

If you have questions, concerns, complaints, or suggestions about human research at Dartmouth, you may call the Office of the Committee for the Protection of Human Subjects at Dartmouth College (603) 646-6482 during normal business hours.

If you agree to take part in this study and you sign this consent form, you are not giving up any of your legal rights.

CONSENT
I have read the above information about the IBD Aches & Pains Study and have been given time to ask questions. I agree to take part in this study and I will be given a copy of this signed consent form.

_____

Participant's Signature and Date PRINTED NAME

_____

Researcher or Designee Signature and Date PRINTED NAME

Appendix K – Study 2: Participant Invitation Letters

IBD Aches & Pains Study

As a patient of Dartmouth-Hitchcock Medical Center who has been diagnosed with inflammatory bowel disease (IBD), you are invited to participate in a study investigating **pain in people with IBD.** This study is part of a larger study from the University of Otago (New Zealand), aimed at investigating why individuals with IBD develop ongoing pain in order to help find targeted treatments.

In order to explore pain in IBD, we are looking for IBD patients **WITH musculoskeletal pain** (i.e. bones, joints, and/or muscles) as well as IBD patients **WITHOUT pain**.

If you are 18 years or older, and would like more information about this study, please contact: Carrie Falling (email: carrie.falling@postgrad.otago.ac.nz).

$20 amazon gift vouchers will be given to each eligible participant as reimbursement for your time.

Dartmouth-Hitchcock

University of Otago
Te Whare Wānanga o Otāgo
New Zealand

IBD Aches & Pains Study

As a patient of Dartmouth-Hitchcock Medical Center with a routine upcoming appointment, you are invited to participate as a **healthy individual** in a study investigating pain in patients with inflammatory bowel disease (IBD). This study is part of a larger study from the University of Otago (New Zealand), aimed at investigating why individuals with IBD develop ongoing pain in order to help find targeted treatments.

In order to do this, we must also evaluate healthy individuals to better understand pain in patients with IBD.

If you are 18 years or older, and would like more information about participating in this study as a **healthy individual**, please contact: Carrie Falling (email: carrie.falling@postgrad.otago.ac.nz).

$20 amazon gift vouchers will be given to each eligible participant as reimbursement for your time.

Dartmouth-Hitchcock

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

Appendix L – Study 2: Questionnaires

Q1-Q32: Questionnaires for all Participant groups

Q1. Participant ID code:

_____

(Q2: Situational Catastrophizing Questionnaire. To be completed immediately following Cold pressor assessment during sensory testing)

Q2. For the following questions, we are interested in the type of thoughts and feelings that you had while you were participating in these pain procedures. Listed below are several statements describing different thoughts and feelings that may be associated with pain. Please indicate the degree to which you had these thoughts and feelings during this pain testing session.

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
I worried about when it would end.	❍	❍	❍	❍	❍
I thought that the pain might overwhelm me.	❍	❍	❍	❍	❍
I felt that I couldn't stand it.	❍	❍	❍	❍	❍
I couldn't stop thinking about how much it hurt.	❍	❍	❍	❍	❍
I kept wishing that it would be over.	❍	❍	❍	❍	❍
I felt that the procedures were awful.	❍	❍	❍	❍	❍

(Q3: Central Sensitization Inventory)

Q3. The following are questions about your general health and well-being: Please choose the best response to the right of each statement.

	Never	Rarely	Sometimes	Often	Always
I feel tired and unrefreshed when I wake from sleeping.	❍	❍	❍	❍	❍
My muscles feel stiff and achy.	❍	❍	❍	❍	❍
I have anxiety attacks.	❍	❍	❍	❍	❍
I grind or clench my teeth.	❍	❍	❍	❍	❍
I have problems with diarrhea and/or constipation.	❍	❍	❍	❍	❍
I need help in performing my daily activities.	❍	❍	❍	❍	❍
I am sensitive to bright lights.	❍	❍	❍	❍	❍
I get tired very easily when I am physically active.	❍	❍	❍	❍	❍
I feel pain all over my body.	❍	❍	❍	❍	❍
I have headaches.	❍	❍	❍	❍	❍
I feel discomfort in my bladder and/or burning when I urinate.	❍	❍	❍	❍	❍
I do not sleep well.	❍	❍	❍	❍	❍
I have difficulty concentrating.	❍	❍	❍	❍	❍
I have skin problems such as dryness, itchiness, or rashes.	❍	❍	❍	❍	❍
Stress makes my physical symptoms get worse.	❍	❍	❍	❍	❍
I feel sad or depressed.	❍	❍	❍	❍	❍
I have low energy.	❍	❍	❍	❍	❍
I have muscle tension in my neck and shoulders.	❍	❍	❍	❍	❍
I have pain in my jaw.	❍	❍	❍	❍	❍

Certain smells, such as perfumes, make me feel dizzy and nauseated.	❍	❍	❍	❍	❍
I have to urinate frequently.	❍	❍	❍	❍	❍
My legs feel uncomfortable and restless when I am trying to go to sleep at night.	❍	❍	❍	❍	❍
I have difficulty remembering things.	❍	❍	❍	❍	❍
I suffered trauma as a child.	❍	❍	❍	❍	❍
I have pain in my pelvic area.	❍	❍	❍	❍	❍

(Q4: 10-item Perceived Stress Scale)

Q4. The questions in this scale ask you about your **feelings and thoughts during the last month**. In each case, you will be asked to indicate by circling **how often** you felt or thought a certain way:

	Never	Almost never	Sometimes	Fairly often	Very often
In the last month, how often have you been upset because of something that happened unexpectedly?	❍	❍	❍	❍	❍
In the last month, how often have you felt that you were unable to control the important things in your life?	❍	❍	❍	❍	❍
In the last month, how often have you felt nervous and "stressed"?	❍	❍	❍	❍	❍
In the last month, how often have you felt confident about your ability to handle your personal problems?	❍	❍	❍	❍	❍
In the last month, how often have you felt that things were going your way?	❍	❍	❍	❍	❍
In the last month, how often have you found that you could not cope with all the things that you had to do?	❍	❍	❍	❍	❍
In the last month, how often have you been able to control irritations in your life?	❍	❍	❍	❍	❍
In the last month, how often have you felt that you were on top of things?	❍	❍	❍	❍	❍
In the last month, how often have you been angered because of things that were outside of your control?	❍	❍	❍	❍	❍
In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	❍	❍	❍	❍	❍

(Q5: Positive and Negative Affective Schedule)

Q5. This scale consists of a number of words that describe different feelings and emotions. Read each item and then list the number from the scale below next to each word. Indicate the extent you have felt this way over **the past week:**

	Very slightly OR Not at all	A little	Moderately	Quite a Bit	Extremely
Interested	❍	❍	❍	❍	❍
Distressed	❍	❍	❍	❍	❍
Excited	❍	❍	❍	❍	❍
Upset	❍	❍	❍	❍	❍
Strong	❍	❍	❍	❍	❍
Guilty	❍	❍	❍	❍	❍
Scared	❍	❍	❍	❍	❍
Hostile	❍	❍	❍	❍	❍
Enthusiastic	❍	❍	❍	❍	❍
Proud	❍	❍	❍	❍	❍
Irritable	❍	❍	❍	❍	❍
Alert	❍	❍	❍	❍	❍
Ashamed	❍	❍	❍	❍	❍
Inspired	❍	❍	❍	❍	❍
Nervous	❍	❍	❍	❍	❍
Determined	❍	❍	❍	❍	❍
Attentive	❍	❍	❍	❍	❍
Jittery	❍	❍	❍	❍	❍
Active	❍	❍	❍	❍	❍
Afraid	❍	❍	❍	❍	❍

(Q6-Q11: EuroQoL 5D)

Under each heading, please tick the ONE box that best describes your health TODAY.

Q6. MOBILITY

- ❍ I have no problems walking around
- ❍ I have slight problems walking around
- ❍ I have moderate problems walking around
- ❍ I have severe problems walking around
- ❍ I am unable to walk around

Q7. SELF-CARE

- ❍ I have no problems washing or dressing myself
- ❍ I have slight problems washing or dressing myself
- ❍ I have moderate problems washing or dressing myself
- ❍ I have severe problems washing or dressing myself
- ❍ I am unable to wash or dress myself

Q8. USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- ❍ I have no problems doing my usual activities
- ❍ I have slight problems doing my usual activities
- ❍ I have moderate problems doing my usual activities
- ❍ I have severe problems doing my usual activities
- ❍ I am unable to do my usual activities

Q9. PAIN / DISCOMFORT

- ❍ I have no pain or discomfort
- ❍ I have slight pain or discomfort
- ❍ I have moderate pain or discomfort
- ❍ I have severe pain or discomfort
- ❍ I have extreme pain or discomfort

Q10. ANXIETY / DEPRESSION

- ❍ I am not anxious or depressed
- ❍ I am slightly anxious or depressed
- ❍ I am moderately anxious or depressed
- ❍ I am severely anxious or depressed
- ❍ I am extremely anxious or depressed

Q11. We would like to know how good or bad your health is TODAY

This scale is numbered from 0-100.

100 means the best health you can imagine

0 means the worst health you can imagine

Slide the bar to indicate how your health is TODAY

	0 10 20 30 40 50 60 70 80 90 100
Your health TODAY	

(Q13-26: Hospital Anxiety and Depression Scale)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over your replies: your immediate answer is best.

Q13. I feel tense or 'wound up':

- ❍ Most of the time
- ❍ A lot of the time
- ❍ From time to time, occasionally
- ❍ Not at all

Q14. I still enjoy the things I used to enjoy:

- ❍ Definitely as much
- ❍ Not quite so much
- ❍ Only a little
- ❍ Hardly at all

Q15. I get a sort of frightened feeling as if something awful is about to happen:

- ❍ Very definitely and quite badly
- ❍ Yes, but not too badly
- ❍ A little, but it doesn't worry me
- ❍ Not at all

Q16. I can laugh and see the funny side of things:

- ❍ As much as I always could
- ❍ Not quite so much now
- ❍ Definitely not so much now
- ❍ Not at all

Q17. Worrying thoughts go through my mind:

- ❍ A great deal of the time
- ❍ A lot of the time
- ❍ From time to time, but not too often
- ❍ Only occasionally

Q18. I feel cheerful:

- ❍ Not at all
- ❍ Not often
- ❍ Sometimes
- ❍ Most of the time

Q19. I can sit at ease and feel relaxed:

- ❍ Definitely
- ❍ Usually
- ❍ Not Often
- ❍ Not at all

Q20. I feel as if I am slowed down:

- ❍ Nearly all the time
- ❍ Very often
- ❍ Sometimes
- ❍ Not at all

Q21. I get a sort of frightened feeling like 'butterflies' in the stomach:

- ❍ Not at all
- ❍ Occasionally
- ❍ Quite Often
- ❍ Very Often

Q22. I have lost interest in my appearance:

- ❍ Definitely
- ❍ I don't take as much care as I should
- ❍ I may not take quite as much care
- ❍ I take just as much care as ever

Q23. I feel restless as I have to be on the move:

- ❍ Very much indeed
- ❍ Quite a lot
- ❍ Not very much
- ❍ Not at all

Q24. I look forward with enjoyment to things:

- ❍ As much as I ever did
- ❍ Rather less than I used to
- ❍ Definitely less than I used to
- ❍ Hardly at all

Q25. I get sudden feelings of panic:

- ❍ Very often indeed
- ❍ Quite often
- ❍ Not very often
- ❍ Not at all

Q26. I can enjoy a good book or radio or TV program:

- ❍ Often
- ❍ Sometimes
- ❍ Not often
- ❍ Very seldom

Q27. During the past month, how would you rate your sleep quality overall?

- ❍ Very good
- ❍ Fairly good
- ❍ Fairly bad
- ❍ Very bad

Q28. Do you smoke?

- ❍ Yes, **LESS** than 39 cigarettes per day
- ❍ Yes, **MORE** than 39 cigarettes per day
- ❍ No

Q29. How often do you drink alcohol?

- ❍ Never
- ❍ Occasionally, moderate amount
- ❍ Occasionally, alot
- ❍ Regularly, moderate amount
- ❍ Regularly, alot
- ❍ Often, beyond the proper amount

Q30. Select your gender

- ❍ Male
- ❍ Female

Q31. What is your age in years?

_____

Q32. Which ethnic/race designation best describes you? More than one choice is acceptable.

- ❑ Native American or Alaska Native
- ❑ Hispanic or Latino
- ❑ Asian
- ❑ Black or African American
- ❑ Native Hawaiian or Other Pacific Islander
- ❑ White
- ❑ Other (Please state) _____

Q33-Q34: Additional questions - Health Control Group only

Q33. Do you regularly take medication?

- ❍ No
- ❍ Yes, please list _____

Q34. Have you ever been told by a doctor that you have any of the following:

- ❑ Osteoporosis
- ❑ Colorectal cancer
- ❑ Sweet's Syndrome
- ❑ Psoriasis
- ❑ Episcleritis
- ❑ Scleritis
- ❑ Kidney stones (nephrolithiasis)
- ❑ Primary sclerosing cholangitis
- ❑ Rheumatoid arthritis
- ❑ Ankylosing spondylitis
- ❑ Sacroiliitis
- ❑ Inflammatory arthritis
- ❑ Osteoarthritis
- ❑ Unspecified joint pain (arthralgia)
- ❑ Uveitis
- ❑ Mouth ulcers (Oral aphthous ulcers)
- ❑ Pyoderma Gangrenosum
- ❑ Erythema Nodosum
- ❑ Anal fissure or fistula
- ❑ Intestinal abscess
- ❑ Heart Disease
- ❑ Vascular disease
- ❑ Respiratory disease
- ❑ Diabetes
- ❑ Kidney disease
- ❑ Liver disease
- ❑ Cancer
- ❑ AIDS/HIV
- ❑ Dementia
- ❑ Anxiety disorder or panic attacks
- ❑ Depression
- ❑ Neck injury (including whiplash)
- ❑ Multiple chemical sensitivities
- ❑ Irritable bowel syndrome
- ❑ Migraine or tension headaches
- ❑ Temporomandibular Joint Disorder
- ❑ Fibromyalgia
- ❑ Chronic Fatigue Syndrome
- ❑ Restless Leg Syndrome

Q35-Q47: Additional questions - IBD Groups only

Q35. Have you experienced **abdominal** pain that lasted **longer than 1 week during the past year**? (Please do not report pain from feverish illness, menstruation, or from surgery within the past year)

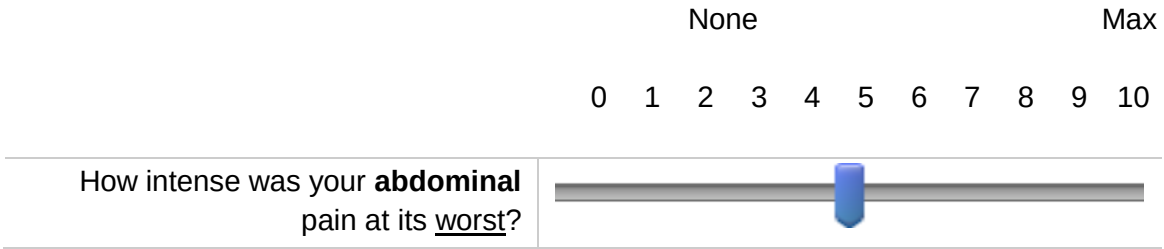
- ❍ Yes
- ❍ No

(Q36: PROMIS Pain Interference 4a – Abdominal pain)

Q36. In the past 7 days…

	Not at all	A little bit	Somewhat	Quite a bit	Very
How much did abdominal pain interfere with your day to day activities?	❍	❍	❍	❍	❍
How much did abdominal pain interfere with work around the home?	❍	❍	❍	❍	❍
How much did abdominal pain interfere with your ability to participate in social activities?	❍	❍	❍	❍	❍
How much did abdominal pain interfere with your household chores?	❍	❍	❍	❍	❍

Q37. In the past 7 days…



Q38. In the past 7 days…

	None 0 1 2 3 4 5 6 7 8 9 10 Max
How intense was your <u>average</u> **abdominal** pain?	

Q39. Today...

	None 0 1 2 3 4 5 6 7 8 9 10 Max
What is your level of **abdominal** pain <u>right now</u>?	

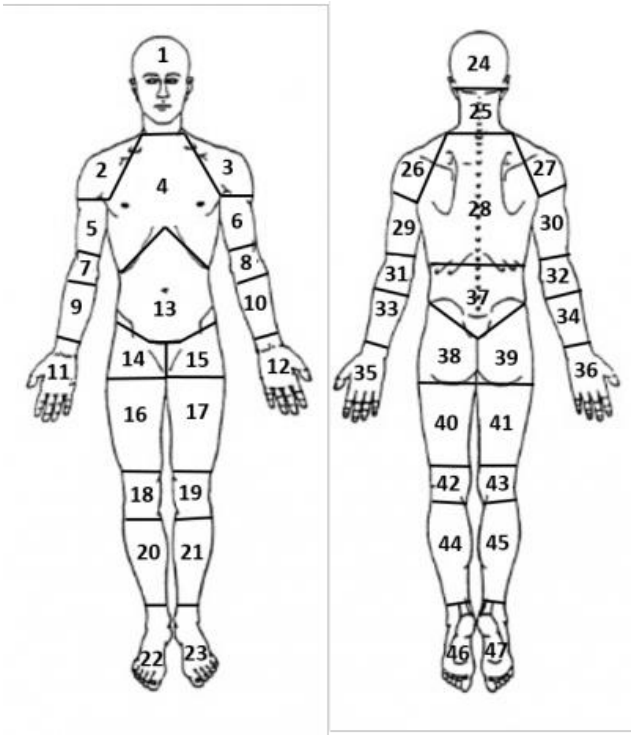
Q40. Have you experienced any bodily aches or pains **OTHER THAN** abdominal pain, headaches and/or chest pain, such as pain from **muscles, joints, or bones** that has lasted **longer than 1 week in the past year**? (Please do not report pain from feverish illness, menstruation, surgery within the past year, or acute injury within the past 3 months)

- ❍ Yes
- ❍ No

Q41. Please mark of the REGIONS that you have had pain in the past 12 months that lasted longer than 1 week

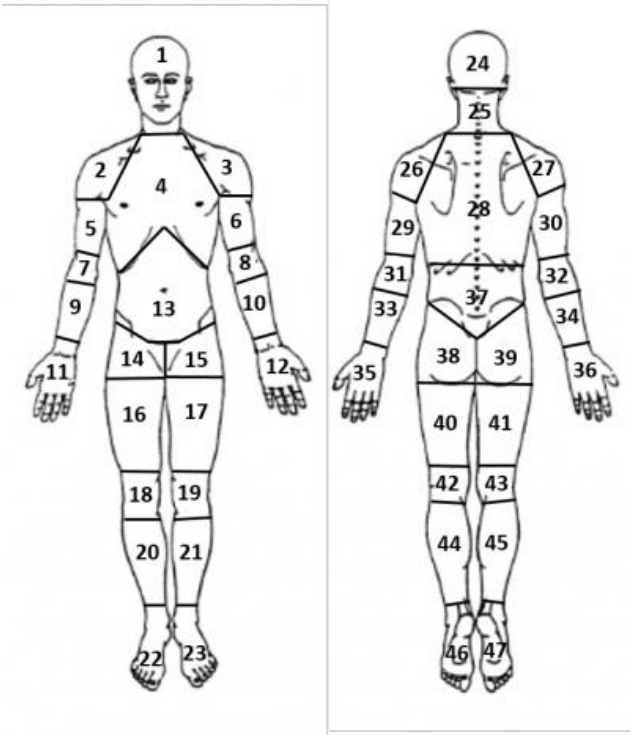
(Please do not report pain from feverish illness, menstruation, surgery within the past year, or acute injury within the past 3 months)

Maximum of 10 regions can be selected - additional charts will be displayed to select more regions.



Q42. Please mark **ONE** region that is your “MAIN" area of pain.

(Please do not report pain from feverish illness, menstruation, surgery within the past year, or acute injury within the past 3 months)



Q43. How long have you had pain in this area?

- ❍ Years _____
- ❍ Months _____

(Q44: PROMIS Pain Interference 4a – Musculoskeletal pain)

Q44. In the past 7 days…

	Not at all	A little bit	Somewhat	Quite a bit	Very
How much did your MAIN pain interfere with your day to day activities?	❍	❍	❍	❍	❍
How much did your MAIN pain interfere with work around the home?	❍	❍	❍	❍	❍
How much did your MAIN pain interfere with your ability to participate in social activities?	❍	❍	❍	❍	❍
How much did your MAIN pain interfere with your household chores?	❍	❍	❍	❍	❍

Q45. In the past 7 days…

	None 0 1 2 3 4 5 6 7 8 9 10 Max
How intense was your **MAIN** pain at its worst?	

Q46. In the past 7 days…

	None 0 1 2 3 4 5 6 7 8 9 10 Max
How intense was your average **MAIN** pain?	

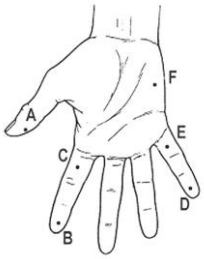
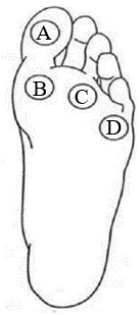
Q47. Today...

	None 0 1 2 3 4 5 6 7 8 9 10 Max
What is your level of **MAIN** pain right now?	

Appendix M– Study 2: Data Collection Sheet

Participant ID	Dominant Hand	Time	Date (dd/mm/yyyy)

VDT	Test site	Trial	Left	Right
	Ulna (styloid process)	1		
		2		
		3		
	Medial malleoli	1		
		2		
		3		

SWME	Left (y/n)	Right (y/n)		Left (y/n)	Right (y/n)
	A			A	
	B			B	
	C			C	
	D			D	
	E				
	F				

<table>
<tr><td rowspan="6">TS

Side: L / R</td><td>Trial</td><td colspan="2"></td><td>NRS (0-100)</td></tr>
<tr><td rowspan="2">1</td><td colspan="2">Single Stimulus</td><td></td></tr>
<tr><td colspan="2">Series (10)</td><td></td></tr>
<tr><td rowspan="2">2</td><td colspan="2">Single Stimulus</td><td></td></tr>
<tr><td colspan="2">Series (10)</td><td></td></tr>
<tr><td rowspan="2">3</td><td colspan="2">Single Stimulus</td><td></td></tr>
<tr><td colspan="2">Series (10)</td><td></td></tr>
<tr><td rowspan="12">PPT</td><td colspan="2">Test site</td><td>Trial</td><td>kPa</td></tr>
<tr><td colspan="2" rowspan="3">Low back

Side: L / R</td><td>1</td><td></td></tr>
<tr><td>2</td><td></td></tr>
<tr><td>3</td><td></td></tr>
<tr><td colspan="2" rowspan="3">Tibialis anterior

Side: L / R</td><td>1</td><td></td></tr>
<tr><td>2</td><td></td></tr>
<tr><td>3</td><td></td></tr>
<tr><td colspan="2" rowspan="3">‘Main pain’

Region: _____

Side: L / R</td><td>1</td><td></td></tr>
<tr><td>2</td><td></td></tr>
<tr><td>3</td><td></td></tr>
<tr><td colspan="4">RETEST (Ice bath)</td></tr>
<tr><td colspan="2" rowspan="3">Tibialis anterior

Side: L / R</td><td>1</td><td></td></tr>
<tr><td>2</td><td></td></tr>
<tr><td>3</td><td></td></tr>
<tr><td>Ice bath

Side: L / R</td><td colspan="2">Time of removal</td><td colspan="2">NRS (0-100)</td></tr>
<tr><td></td><td colspan="2"></td><td colspan="2"></td></tr>
</table>

Appendix N – Study 2: Verbal instructions for sensory testing

Vibration Detection Threshold

This is a test of your ability to detect vibration. Once I make it vibrate, I will place this tuning fork on bones of both of your wrists and the inside of your ankle. I will have you tell me when you feel the sensation of vibration, and then say 'NOW' when you no longer feel the vibration. I will have you close your eyes for the testing, and do this test 3 times at each location.

Semmes-Weinstein Monofilament Examination

This is a test of your ability to detect light touch on your hands and feet. Once again I will have you close your eyes, and then I will press this filament to 6 different places on both of your hands, and this different filament to 4 places on both of your feet. I will have you say 'YES' when you feel the filament touching you.

Temporal Summation

This is a test of repeated stimulus with a similar filament used in the last test. I will first apply a single touch, and ask you to give a number between 0-100 for the discomfort of the one touch, where '0' is no pain, and '100' is the most intense pain imaginable.

Then I will apply a series of 10 stimuli in a row with the same filament, and ask you to give a number between 0-100 for any discomfort of the series as a whole.

Pressure Pain Threshold

This is a test of your sensitivity to deeper pain. I will take this pressure meter and press it against one area on your low back and one area on your leg below your knee, and will gradually increase the pressure. I want you to say 'NOW' as soon as the pressure starts to be painful. I am not looking to see how much pain you can tolerate, just simply the moment when pressure starts becoming painful. I will do this test 3 times on your back, and 3 times on your leg.

Cold Pressor Test

This test includes 2 procedures that I will do one after another. I will measure your pressure pain threshold again (the test we just did) after you have your hand in cold water for 2 minutes. I will have you place your hand in this ice bath up to your wrist with your fingers spread apart until you can no longer tolerate it OR for a maximum of 2 minutes (digital timer). You can remove your hand whenever you wish or when the timer goes off. I will have you give me warning just before you take your hand out so I can record the time. And then I will ask you to give a number between 0-100 for the amount of discomfort at the time you pulled your hand out.

Appendix O – Study 2: MSK Pain Regions in IBD Patients (Chapter 8)

Table O.1

Summary of Self-reported Musculoskeletal Pain Regions of the Upper Body in IBD Patients (N=22)

Body region	Identified as painful	Identified as region of main pain
Right anterior (*n*)		
Wrist/hand	8	1
Forearm	0	0
Elbow	1	0
Upper arm	1	0
Shoulder	8	0
Left anterior (*n*)		
Wrist/hand	7	1
Forearm	0	0
Elbow	1	0
Upper arm	0	0
Shoulder	7	0
Right posterior (*n*)		
Wrist/hand	3	0
Forearm	0	0
Elbow	3	0
Upper arm	0	0
Shoulder	4	0
Left posterior (*n*)		
Wrist/hand	2	0
Forearm	0	0
Elbow	2	0
Upper arm	0	0
Shoulder	4	2

Table O.2

Summary of Self-reported Musculoskeletal Pain Regions of the Lower Body in IBD Patients (N=22)

Body region	Identified as painful (*n*)	Identified as region of main pain (*n*)
Right anterior		
Ankle/foot	5	0
Lower leg	4	1
Knee	9	2
Upper leg	3	0
Hip/groin	7	1
Left anterior		
Ankle/foot	4	0
Lower leg	5	0
Knee	6	1
Upper leg	2	0
Hip/groin	6	1
Right posterior		
Ankle/foot	0	0
Lower leg	0	0
Knee	0	0
Upper leg	1	0
Gluteus/hip	4	2
Left posterior		
Ankle/foot	0	0
Lower leg	2	0
Knee	0	0
Upper leg	3	0
Gluteus/hip	5	1

Table O.3

Summary of Self-reported Axial Musculoskeletal Pain Regions in IBD Patients (N=22)

Body region	Identified as painful	Identified as main region of pain
Post neck (*n*)	8	4
Mid back (*n*)	11	1
Low back (*n*)	11	3
Chest (*n*)	3	1

Appendix P – Study 2: MSK Pain Regions in IBD Patients (Chapter 9)

Table P.1

Summary of Self-reported Musculoskeletal Pain Regions of the Upper Body in IBD Patients (N=51)

Body region	Identified as painful	Identified as region of main pain
Right anterior (*n*)		
Wrist/hand	10	2
Forearm	1	0
Elbow	3	0
Upper arm	1	0
Shoulder	10	0
Left anterior (*n*)		
Wrist/hand	11	1
Forearm	1	0
Elbow	2	0
Upper arm	0	1
Shoulder	8	0
Right posterior (*n*)		
Wrist/hand	5	0
Forearm	0	0
Elbow	4	0
Upper arm	1	0
Shoulder	7	1
Left posterior (*n*)		
Wrist/hand	3	0
Forearm	0	0
Elbow	3	0
Upper arm	0	0
Shoulder	5	2

Table P.2

Summary of Self-reported Musculoskeletal Pain Regions of the Lower Body in IBD Patients (N=51)

Body region	Identified as painful (*n*)	Identified as region of main pain (*n*)
Right anterior		
Ankle/foot	7	0
Lower leg	4	1
Knee	11	4
Upper leg	3	0
Hip/groin	10	1
Left anterior		
Ankle/foot	6	0
Lower leg	5	0
Knee	9	0
Upper leg	3	0
Hip/groin	8	1
Right posterior		
Ankle/foot	2	0
Lower leg	1	0
Knee	0	0
Upper leg	3	0
Gluteus/hip	5	3
Left posterior		
Ankle/foot	2	0
Lower leg	4	0
Knee	1	0
Upper leg	2	0
Gluteus/hip	5	1

Table P.3

Summary of Self-reported Axial Musculoskeletal Pain Regions in IBD Patients (N=51)

Body region	Identified as painful	Identified as main region of pain
Post neck (*n*)	12	4
Mid back (*n*)	14	1
Low back (*n*)	15	3
Chest (*n*)	3	1

Appendix Q – Study 2: Correlations of Central Sensitization Measures (Chapter 9)

Table Q.1

Spearman Rank-order Correlations of Measures of Central Sensitization in IBD Participants

Feature	CSI a		PPT (LB)		PPT (TA)		CPM [a]		TS	
	Rho	*P*	*Rho*	*P*	*Rho*	*P*	*Rho*	*P*	*Rho*	*P*
CSI [a]	-	-	-.218	.063	**-.338**	**.008**	**-.285**	**.021**	.011	.471
PPT (LB)	-.218	.063	-	-	**.876**	**<.001**	**.390**	**.002**	**-.456**	**<.001**
PPT (TA)	**-.338**	**.008**	**.876**	**<.001**	-	-	**.433**	**.001**	**-.464**	**<.001**
CPM [a]	**-.285**	**.021**	**.390**	**.002**	**.433**	**.001**	-	-	-.184	.098
TS [b]	.011	.471	**-.456**	**<.001**	**-.464**	**<.001**	-.184	.098	-	-

Note. Bold font indicates significant correlation ($p \leq .05$). Central sensitization inventory (CSI), pressure pain threshold (PPT), low back (LB), Tibialis anterior (TA), conditioned pain modulation (CPM), temporal summation (TS).

[a] Pearson's coefficient (r).

[b] Calculated as absolute change score

Appendix R – Study 2: Correlations of Absolute Change Scores for Temporal Summation to Participant Features (Chapter 9)

Table 8

Spearman Rank-order Correlations of IBD Characteristics to Absolute Change Scores for Temporal Summation in Study Participants (N = 51)

Characteristic	Temporal summation	
	Rho	*P*
IBD subtype [a]	0.178	0.105
IBD duration	-0.127	0.188
Age at diagnosis [b]	0.233	0.050
Disease extent [a]	-0.150	0.147
Surgical input [a]	0.160	0.131
Stoma [a]	0.065	0.325
Stricturing [a]	0.183	0.100
Penetrating [a]	0.052	0.358
Perianal [a]	0.067	0.320
Short Inflammatory Bowel Disease Questionnaire	0.214	0.065
Abdominal pain [a]	0.081	0.286

Note. Inflammatory bowel disease (IBD.

[a] Point-biserial coefficient (r_{pb}).

[b] Montreal classification.

Table 9

Spearman Rank-order Correlations of Psychological Characteristics to Absolute Change Scores for Temporal Summation in Study Participants (N = 51)

Feature	Temporal summation	
	Rho	*P*
Perceived stress scale [a]	-0.035	0.404
Positive and negative affect schedule (positive) [a]	0.072	0.308
Positive and negative affect schedule (negative)	-0.065	0.324
Hospital anxiety and depression scale (anxiety)	-0.021	0.441
Hospital anxiety and depression scale (depression)	-0.195	0.085
Pain catastrophizing scale	0.238	0.064

[a] Pearson's coefficient (*r*).

Table 10

Spearman Rank-order Correlations of Demographic, Lifestyle, and Comorbidity Features to Absolute Change Scores for Temporal Summation in IBD Participants (N = 51)

Feature	TS	
	Rho	*P*
Age [a]	0.225	0.056
Gender [b]	0.119	0.202
Smoking	0.197	0.083
Alcohol	-0.048	0.370
Cannabis [b]	0.134	0.174
Sleep quality	0.123	0.194
Total comorbidity	-0.066	0.324
Musculoskeletal pain [b]	0.075	0.301

[a] Pearson's correlation (*r*).

[b] Point-biserial coefficient (r_{pb}).