VALIDITY OF THE CENTRAL SENSITIZATION INVENTORY IN PATIENTS WITH KNEE OSTEOARTHRITIS

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By

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Science in Rehabilitation Science

McMaster University

McMaster University, MASTER OF SCIENCE IN REHABILITATION SCIENCE

(2022) Hamilton, Ontario

TITLE: Validity of the Central Sensitization Inventory in patients with Knee Osteoarthritis

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NUMBER OF PAGES: 108

ABSTRACT:

Osteoarthritis is the 12th leading cause of years lived with disability globally and by 2040 more than 10 million Canadians will have knee osteoarthritis (KOA). Pain in persons with KOA is well-recognized, persistent and chronic with central sensitization (CS) being prevalent in ~30%. CS is measured by psychophysical testing and patient-reported methods such as the Central Sensitization Inventory (CSI). The CSI was developed using subgroups of people with chronic pain, but not those with KOA. Therefore, validity of the CSI in people with KOA is lacking. CS as indicated by psychophysical tests is associated with CSI scores lower than the recommended cut score. Therefore, we aimed to evaluate the validity of the CSI through Rasch analysis in persons with KOA. We then sought to determine the agreement of the Rasch calibrated (RC-CSI) version of the CSI with the original and to evaluate the validity of the RC-CSI with psychophysical tests in people with KOA. In the first study, the CSI was able to fit Rasch model. After iterative analysis, we found the CSI to be a singular construct with acceptable unidimensionality while retaining all 25 items. Only two items - frequent urination (item 21) and Skin problems (item 19) showed a pattern of uniform differential item functioning by age and sex respectively. Moreover, we generated a RC-CSI cut score of 31.37 that we used to compare with the original cut score of 40. In second study, the findings suggested a lack of agreement between the two versions of the CSI demonstrating small bias. When exploring sensitivity and specificity with psychophysical tests, the RC-CSI showed little clinical value over the original CSI. We therefore recommend that the original CSI should be used with individual clients as our preliminary findings suggest that there is no added benefit to using the RC-CSI.

ACKNOWLEDGEMENTS

My acknowledgements go to the Faculty and Staff of the school of Rehabilitation Science of McMaster University for doing everything in their power to help me throughout two academic years.

I am indebted to my Master's supervisor, Dr. Lisa Carlesso, for her guidance throughout the proposal to thesis writing process. This thesis work would not have been possible without her support. Her detailed and constructive feedback has substantially helped in improving the research skills, dissertation and presentation. Furthermore, I would also like to thank the other members of the supervisory committee: Dr. Tara Packham, Dr. Joy MacDermid for their guidance and feedback regarding the proposal and thesis. They have been generous enough to give their invaluable opinion, time and feedback to guide my research study.

Finally, A wholehearted thank you to my family members, who inspired me through their unconditional love and care. I am also grateful to all my friends for their cooperation during this journey of my master's degree.

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LIST OF ABBREVIATIONS

OA: OsteoArthritis

KOA: Knee Osteoarthritis

CS: Central Sensitization

CSI: Central Sensitization Inventory

RC-CSI: Rasch Calibrated Central Sensitization Inventory

WHO: World Health Organization

WSP: Widespread Pain

PPT FA: Pressure Pain Threshold at the ForeArm

PPT PAT: Pressure Pain Threshold at the PATella

TS FA: Temporal Summation at the ForeArm,

TS PAT: Temporal Summation at the PATella

PCS: Pain Catastrophic Scale

NPRS: Numeric Pain Rating Scale

CPM: Conditioned Pain Modulation

ROC: Receiver Operating Characteristic

AUC: Area Under the Curve

DIF: Differential Item Functioning

DECLARATION OF ACADEMIC ACHIEVEMENT:

The body of the thesis consists of two separate research studies, and both of them formatted according to the journal they are submitted. Naym Uddin Roby contributed to the study conception, research design, data analysis, drafting the thesis and made revisions. Lisa Carlesso supervised and provided constant support to the research projects from study conception, research design, data acquisition, analysis, and revisions. Tara Packham assisted in study conception, data analysis and critical revisions to the thesis. JC MacDermid provided constructive feedback on the study conception, data analysis and made critical revisions to the thesis.

CHAPTER 1 **: INTRODUCTION**

1.1 Epidemiology of Osteoarthritis

Osteoarthritis (OA) is the most common degenerative joint disease in adults and a prominent cause of disability worldwide (Bennell et al., 2012; Felson, 2004). Between 1990 and 2007, OA had a significant increase of 63.1% and represented 7.1% of the global burden of disease (James et al., 2018). In 2017, OA affected more than 303 million people globally (James et al., 2018).The prevalence will continue to increase due to aging and obesity (French et al., 2016; Plotnikoff et al., 2015). OA is a frequent cause of pain, loss of function and it is more common in women than men (Arden et al., 2006; Michael et al., 2010). A disease that progresses slowly over time, OA often affects the articular surfaces of a joint especially in the hands, hips, spine and knees, with the latter being the most prevalent (Felson, 2004). Long believed to be triggered by wear and tear, coupled with aging, research has shown that it is due to the body's failed attempt to repair joint tissues (Kraus et al., 2015). This process can occur due to abnormal joint loading, joint injury and obesity. Radiographic evidence suggests that the majority of people experience OA joint changes by 65 years of age (Arden et al., 2006). Multiple genetic factors have also been identified as robust determinants, though not all are known or understood (Spector et al., 2004).

The Public Health Agency of Canada reported, approximately 3.9 million (13.6%) Canadians over 20 years of age live with identified OA (Public Health Agency of Canada, 2020). In 2016–2017, over 219,000 cases were newly diagnosed (Public Health Agency of Canada, 2020) and the prevalence of OA is expected to increase from 13.8% to 18.6% from 2010 to 2031 (Sharif et al., 2015). Of the Canadians reporting OA in 2009, 29% reported

the knee joint being affected (MacDonald et al., 2014). It is predicted that OA prevalence and disability burden will increase with a growing age and population. Typically, OA does not result in death, however studies have shown a slight increase in mortality risk among those with diagnosed OA (Public Health Agency of Canada, 2020).In addition, OA can lead to other health conditions. For example, increasing age and obesity are often seen in those with OA and can lead to immobility/loss of function resulting in hypertension, depression, COPD, and diabetes (Marshall et al., 2019; Swain et al., 2020). The presence of these chronic conditions can further worsen the pain and decline in functional activities among individuals with OA (Swain et al., 2020). (Public Health Agency of Canada, 2020). Importantly, these wide-ranging effects on health status of individuals with OA also impacts their ability to work. 25% of Canadians and almost 30% of the labor force are expected to have OA by 2040 (Bombardier et al., 2011). There is a growing detection of the effects of OA on younger adults who are still participants in the workforce. Studies documented that OA is associated with substantial reductions in productivity among employed individuals (Gunnarsson et al., 2015; Kleinman et al., 2009; Ricci et al., 2005) and costs linked to work productivity are the leading cause of the economic burden of OA (Gupta et al., 2005). According to the Population Health Model, the productivity costs of work loss associated with OA in Canada are set to increase 2031 (Sharif et al., 2017). Moreover, the pain and physical disability due to OA also affect social functioning and mental health, further diminishing the patient's quality of life (Lee et al., 2020; Verges et al., 2019). As a result, OA is expected to impose a significant burden to the health economy and will increase healthcare costs in Canada (estimated $2.9 billion to $7.6 billion from

2010 to 2031) (Sharif et al., 2015). This increase may place a particular burden on primary care.

1.2 Definition of KOA

KOA is defined as a disease of the whole joint affecting multiple tissues including cartilage, synovium, and sub-chondral bone (Dieppe, 2011; Martel et al., 2008). Anatomically, the knee is a complex synovial joint in the human body, formed by the medial and lateral condyles of the femur, proximal part of tibia and patella, meniscus, hyaline cartilage and ligaments. This joint is filled with synovial fluid providing lubrication as well as nutrients to the associated cartilage (Mora et al., 2018). When KOA develops, it can result in joint failure (Vad et al., 2004). This process is the consequence of degenerative processes being greater than regenerative ones (Dieppe, 2011)and leads to cartilage destruction, thickening or alterations in the architecture of subchondral bone, and the formation of new bone (osteophytes) (Mora et al., 2018). At the early stage of the disease, the pain is mainly derived from changes to the non-cartilaginous components of the joint (e.g. joint capsule, synovium, subchondral bone, muscles and ligaments) (Dieppe, 2011; Martel et al., 2008). As the disease advances, joint tissue changes may include osteophyte formation, synovial hyperplasia, fibrosis, capsule thickening and sometimes lymphocytic infiltrate, meniscal erosions or tears, weakening of periarticular muscles and bone marrow abnormalities (Dulay et al., 2015; Vad et al., 2004).

1.3 Diagnosis and Symptoms of KOA

OA is identified clinically based on the patient's history, signs and symptoms or radiographic findings. The typical clinical symptoms of KOA may include pain over the

knee that worsens with activity, stiffness and swelling, resting pain and crepitus (Bennell et al., 2012; Katz et al., 2021). Clinical classification criteria for KOA have been provided by the National Institute for Health and Care Excellence (NICE), European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) diagnostic guidelines. According to NICE diagnostic criteria, the clinical diagnosis of KOA can be made without investigations if a person's age is 45 years old or more, has joint pain during activity, and has no morning joint stiffness or morning stiffness that lasts no longer than 30 minutes (National Institute for Health and Care Excellence (UK), 2014). Similarly, EULAR diagnostic criteria identify KOA if someone is over 40 years old with activity-related joint pain, short period of morning stiffness, functional limitation, and joint crepitus/ restricted joint movement/ bony enlargement (Zhang et al., 2010). Lastly, the American College of Rheumatology (ACR) identifies KOA with any of three following criteria- Age >50 years, morning stiffness <30 minutes, crepitus on active movements, tenderness of the bony margins of the joint, bony enlargement or no palpable warmth (Altman et al., 1986). A study comparing the three commonly applied criteria for KOA, reported that the NICE criteria identified most patients (89-90%) with or without self-reported radiographic KOA, suggesting that the NICE criteria would be most appropriate to identify individuals treated for KOA in primary care (Skou et al., 2020). Radiographic findings (e.g. x-ray, MRI) have traditionally been used to diagnose KOA which mostly includes joint space narrowing, subchondral sclerosis, and osteophyte formation (Altman et al., 2007). However, it is now commonly accepted that imaging is no longer required for a diagnosis of OA.

It is well known that KOA symptoms vary with disease stage. However, a qualitative study has identified that people with KOA generally experience three distinct types of pain patterns and these patterns were described in terms of disease progression (Hawker et al., 2008). The first type, intermittent pain, is intense and episodic that is often triggered by activity early on in the disease course. The second type is constant or persistent pain which appears as the disease progresses (Hawker et al., 2008). Lastly, at end stage disease, constant pain can be overlaid with unpredictable and severe intermittent pain described as constant plus intermittent pain or a mixed pattern (Hawker et al., 2008). Importantly, these pain patterns have been validated with disease duration, radiographic severity and pain intensity, highlighting the fact that the pain patterns are important for understanding the symptomatic progression of KOA (Carlesso et al., 2021).

1.4 Management of KOA

Treatment for KOA can be divided into non-surgical and surgical management. The primary treatment begins with non-surgical strategies and moves to surgical procedures once the non-surgical approaches are no longer helpful. Modern clinical management of KOA aims to reduce pain and sustain physical activity through the combination of pharmacologic and non-pharmacologic interventions (Hochberg et al., 2012). These interventions do not change the inherent disease process, but they may significantly reduce pain and disability. As disease-related pain and disability become more problematic, interprofessional management with physicians, (general practitioners, rheumatologists or orthopaedic surgeons), physiotherapists, dietitians, nurses, and pharmacists is recommended (Vad et al., 2004). Among the published guidelines for the management of

KOA, those from the Osteoarthritis Research Society International (OARSI) (Bannuru et al., 2019) and American College of Rheumatology (ACR) (Kolasinski et al., 2020) were updated in 2019 and will be summarized briefly. The OARSI guideline (Bannuru et al., 2019) suggests treatment on the basis of good clinical practice statements and recommendations by experts (e.g. Level 1A/1B: 75-100% in favor, Level 2: 60-74% in favor of expert) for people with KOA and four clinically relevant subgroups of co-morbidities – gastrointestinal, cardiovascular, frailty and widespread pain and/or depression. The recommendations formulated by GRADE methodology possess both directionality ("in favor" or "against") and strength ("strong" or "conditional") (Andrews et al., 2013). The core non-surgical treatment for most people with KOA includes education, and either structured land-based exercise programs or mind-body exercises (Tai Chi and Yoga), with or without dietary weight management. These may be used in isolation or in combination with other recommended interventions.

Table-1. OARSI Guidelines Recommended Treatments for KOA with High Consensus (Bannuru et al., 2019)

Recommendation level	**Strength**	**Treatment type**	**No comorbidities**	**Gastrointestinal**	**Cardiovascular**	**Frailty**	**Widespread pain/depression**
CORE	Strong	Arthritis Education; Structured Land-Based Exercise Programs (Type 1- strengthening and/or cardio and/or balance training/neuromuscular exercise OR Type 2- Mind-body Exercise including Tai Chi or Yoga) with or without Dietary Weight Management					

Level 1A **High Consensus** ≥75% "in favor	Strong	Pharmacologic Non-Pharmacologic	Topical NSAIDs refer to Level 1B	Topical NSAIDs refer to Level 1B		Topical NSAIDs refer to Level 1B	refer to Level 1B
Level 1B **High Consensus** ≥75% "in favor" & >50% "conditional" Recommendation	Conditional	Pharmacologic	*Non-selective NSAIDs *Non-selective NSAIDs + PPI *COX-2 Inhibitors *IACS	COX-2 Inhibitors IACS, IAHA	IACS, IAHA	IACS, IAHA	Non-selective NSAIDs Non-selective NSAID + PPI COX-2 Inhibitors
		Non-Pharmacologic	Aquatic Exercise, Gait Aids, Self-Management Programs	Aquatic Exercise, Gait Aids, Self-Management Programs		Aquatic Exercise, Gait Aids, Self-Management Programs	Aquatic Exercise, Cognitive Behavioral Therapy (with or without Exercise), Self-Management Programs, Gait Aids

Abbrebiation: IACS = Intra-articular corticosteroids (IACS), IAHA Intra-articular Hyaluronic Acid (IAHA), NSAIDS: Non-steroidal anti-inflammatory drugs, PPI= Proton pump inhibitor

Next at Level 1A are treatments that are strongly recommended and include pharmacologic treatment in the form of topical non-steroidal anti-inflammatory drugs (NSAIDs) as they have modest effects and mild adverse reactions. There are no strongly recommended treatments for those with cardiovascular comorbidities, widespread pain disorders

(fibromyalgia) and/or depression. At Level 1B, the recommendations are conditional and include both pharmacologic and non-pharmacologic treatment with the former varying according to comorbidities. The non-pharmacologic treatment recommends aquatic exercise, gait aids and self-management for all comorbidities except cardiovascular. For those with widespread pain or depression, cognitive behavioural therapy is also suggested (Bannuru et al., 2019).

The American College of Rheumatology (ACR) /Arthritis Foundation Guideline -2019 (Kolasinski et al., 2020) similarly recommends non-pharmacological and pharmacological strategies. The former include exercise, weight loss programs, self-efficacy and self-management programs, cane, tibiofemoral knee braces and tai chi with a strong recommendation. For pharmacological management, ACR strongly recommends topical and oral NSAIDS and intraarticular glucocorticoid injections. Both non-pharmacological and pharmacological strategies include conditional recommendations depending on patient condition and associated morbidities (Kolasinski et al., 2020).

Table 2. ACR Strong and Conditional Recommendations for the Management of KOA

Recommendation	**Non-pharmacologic**	**Pharmacologic**
Strongly recommended	Exercise, Weight loss, Self-efficacy and self-management programs, Tai chi, Cane, Tibiofemoral knee braces	Topical nonsteroidal anti-inflammatory drugs, Oral nonsteroidal anti-inflammatory drugs, Intraarticular glucocorticoid injection
Conditionally recommended	Balance training, Yoga, Cognitive behavioral therapy, Patellofemoral braces, Kinesiotaping, Acupuncture, Thermal interventions, Radiofrequency ablation	Topical capsaicin, Intraarticular glucocorticoid injection compared to other injections, Acetaminophen, Duloxetine, Tramadol

1.5 KOA structural changes and association with pain

The development of KOA is dependent on interactions between systemic and local factors. Previously it was believed that OA was primarily a degenerative disease of the cartilage, but studies in recent years have shown OA to be a multifactorial potentially involving trauma, mechanical forces, inflammation, biochemical and metabolic reactions (Dieppe, 2011). The main source of pain is thought to be due to non-cartilaginous components such as synovium and bone (Loeser et al., 2012). Pain resulting from mechanisms such as inflammation can adversely affect these joint structures, resulting in structural progression (Neogi et al., 2016; Wang et al., 2015). As the disease advances, changes in these structures

such as bone remodeling, osteophyte formation, weakening of periarticular muscles, laxity of ligaments, and synovial effusion can become more evident (Dulay et al., 2015).

Synovitis is a common finding of KOA and can occur in early stages of the disease, but is more prevalent towards the more advanced stages and can be related to the severity of pain (Baker et al., 2010; Robinson et al., 2016). Studies have reported that synovial inflammation (synovitis) score was strongly related to change in pain with an increase in score being associated with an increase in knee pain (Hill et al., 2007; Y. Zhang et al., 2011). Synovitis has also been associated with the presence and development of pain sensitization (Neogi et al., 2016b). Synovial fluid contains multiple mediators that contribute to synovial inflammation (Sellam et al., 2010). These catabolic and proinflammatory mediators (e.g. cytokines, and prostaglandins) are produced by the inflamed synovium, altering the balance of cartilage matrix degradation and repair, leading to excess production of the proteolytic enzymes responsible for (David T. Felson et al., 2003) cartilage breakdown (Richards et al., 2016; Robinson et al., 2016; Sellam et al., 2010).

Another structure associated with pain is subchondral bone marrow lesions (BMLs) which play a major role in the pathogenesis of OA (Felson et al., 2003). In a healthy joint, daily activities of repetitive loading cause acute subchondral damage which is balanced by consistent repair. When damage persistently exceeds repair, or bone is unable to heal after periods of unloading, chronic BML edema may develop. Ischemia of subchondral bone may be a mechanism whereby vascular pathology contributes to the development of BMLs (Doré et al., 2012). Longitudinal studies have shown that BMLs can regress and progress

over time (Foong et al., 2014) contributing not only to pain severity but to knee pain fluctuation (Zhang et al., 2011b).

Osteophytes are a common feature of KOA found on x-ray that have historically been used to define the presence of OA (Nagaosa et al., 2002). They are most commonly found at the margins of the joint, as outgrowths of cartilage which undergo ossification (Nagaosa et al., 2002). There is limited evidence for their association with pain, and in fact the discordance between pain and the presence of OA on x-ray is well known (Neogi, 2017). However, Sowers et al. found that large MRI-detected osteophytes were associated with increased odds of knee pain and reduced physical function (Sowers et al., 2011). Risk factors for the development of osteophytes include age, body mass index, physical activity, and other genetic and environmental factors (Wong et al., 2016). Importantly, changes in any of the aforementioned structures in the knee may affect joint biomechanics and significantly reduce the surface contact between the meniscus and articular cartilage which may lead to maldistribution of biomechanical loads (Łuczkiewicz et al., 2016).

1.6 Knee Biomechanics

The knee has complex movements that occur linearly (flexion-extension) and rotation (medial-lateral) while transmitting forces across joint surfaces during activities of daily life (Woo et al., 2006). The menisci play a critical role in the mechanical protection of knee cartilage by distributing stress, absorbing shock, enhancing joint congruity, and stabilizing the knee joint. Alteration of joint structures such as the meniscus, or cartilage can change the load distribution and mechanical axis which can lead to further joint damage and enhanced progression to KOA (Brouwer et al., 2007; S. Tanamas et al., 2009). Previous

studies have shown that malalignment (i.e. valgus or varus) may be an important risk factor for knee cartilage damage and incident radiographic changes and their progression (Brouwer et al., 2007; Felson et al., 2013). Static parameters such as femorotibial alignment may have less influence over medial KOA progression than dynamic factors such as varus thrust, which is a bowing-out of the knee during gait (Omori et al., 2016). Studies have found that varus thrust increases the risk of medial KOA progression and is associated with WOMAC pain and function scores (Chang et al., 2010; Omori et al., 2016). Mild to severe pain has been associated with gait speed and neuromuscular activation patterns in KOA patients (Astephen Wilson et al., 2011). There are many extrinsic and intrinsic factors that increase joint mechanical loading leading to greater intensity of knee pain (Silverwood et al., 2015). One that has received much attention is the external knee adduction moment (KAM) which is a measure of excessive knee loading during gait. Older adults with higher peak KAM have been shown to be more likely to develop chronic knee pain within 3–4 years (Amin et al., 2004). Moreover, the peak external knee flexion moment (KFM) another measure of joint loading, has been reported to trigger pain in participants with KOA (Asay et al., 2018).

1.7 Risk factors for KOA

The development of KOA is correlated with several risk factors including increasing age in the general population (Peat et al., 2001; Srikanth et al., 2005). Person-level risk factors include increasing age, female sex, race (e.g African American), obesity, genetic and dietary factors, low bone density and family history. Local or joint level factors include knee alignment, knee laxity, physical activity and occupational stress, periarticular muscle

weakness, or history of injury, all of which can affect the distribution of load across the knee joint (Allen et al., 2022). KOA Risk factors can also be categorized according to the etiology as primary and secondary (Mora et al., 2018). Primary KOA occurs due to joint failure without any other fundamental cause. It is thought that the main factors for this are due to age, sex and obesity (Michael et al., 2010; Vad et al., 2004). Women have a higher risk of KOA compared to men (Boyan et al., 2012). Reasons for this are not fully understood, however, it is hypothesized that there is a vital role of sex hormone levels changes on the development of OA mostly in post-menopausal women than men (Tanamas et al., 2011). It was found that like sex, racial differences impact developing KOA (Almeida et al., 2014a). For instance, African Americans have been reported to have higher chance to develop KOA compared to whites (Almeida et al., 2014b; Jordan et al., 2009). Moreover, people with high body mass index (BMI) have a greater risk of developing KOA (Raud et al., 2020) and reported to have greater joint space narrowing (Çimen et al., 2004), higher pain scores, and greater disability (Li et al., 2016; Raud et al., 2020). Weight loss for obese patients with KOA has been established as a strategy that is clinically beneficial to reduce pain and improve function (Raud et al., 2020). Obesity is associated with increased inflammation which in turn is associated with changes in metabolism (Ellulu et al., 2017). It has been shown that inflammatory factors like resistin, interleukin-8 have an association with KOA severity and symptoms (Ruan et al., 2019).

Secondary OA often results from post-traumatic injury or possibly surgery whereby disruption of joint tissues alters force across the joint and to the articular cartilage (Vad et al., 2004). This is particularly true for older adults whereby the development of OA is

accelerated (Davis et al., 2017). In young athletic individuals, knee injuries such as anterior cruciate ligament and meniscal tears, contributing to their higher likelihood of developing OA (Amoako et al., 2014; Losina et al., 2013). There are mixed results found regarding surgery as a risk factor for KOA. A recent study suggested that arthroscopic meniscectomy is a risk factor for incident radiographic KOA and OA progression in those who did not have a history of injury (Roemer et al., 2017). In contrast, another study found that adults with degenerative meniscal tears who received surgery (i.e., arthroscopic partial meniscectomy) did not have higher risk for developing radiographic OA compared to adults who received no surgery (i.e., exercise therapy only) (Berg et al., 2020).

1.8 Overview of Pain in People with KOA:

The International Association for the Study of Pain (IASP) describes pain as "an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage" (Raja et al., 2020). Pain can occur when sensory nerve endings (nociceptors) are stimulated by a noxious stimulus. This is true of acute pain, but does not necessarily apply to chronic pain. The resulting impulse (nociception) travels from the sensory nerve ending, enters the dorsal horn of the spinal cord, and travels to different parts of the brain. The brain processes the nociceptive signal in combination with multiple contextual factors including factors such as prior experience, or beliefs and knowledge about pain to make a determination as to whether protection is needed. If the answer is yes, resulting in pain, a motor response often accompanies this as a means to stop the action causing the pain (Trouvin et al., 2019). Chronic pain is a multidimensional construct including sensory, cognitive, and affective dimensions which typically remain for more

than three to six months (Treede et al., 2015). The chronic nature of OA pain may therefore be best identified using multidimensional pain assessment tools, including self-reported measures and psychophysical tests which attempt to quantify the sensitivity of the somatosensory system. Besides pain intensity and activity-related pain, other measures have been developed to describe pain qualities that relate to stages of KOA disease progression (Hawker et al., 2008a).

Pain in people with KOA tends to increase over time with worsening disease, however this does not happen to everyone with radiological evidence of KOA (Pan et al., 2018). There are three patterns of pain (e.g. intermittent, constant, or constant plus unpredictable intermittent) reflected during the different stages of KOA (Hawker et al., 2008). Intermittent pain is typically experienced early in the disease process and often is triggered by higher-intensity activities such as jumping and is described as being sharp and intense. Conversely, constant pain appears as the KOA progresses and is generally chronic in nature, described as dull and achy. Lastly, at the end stage of KOA, constant pain increases in severity and can be overlaid by unpredictable intermittent pain(Hawker et al., 2008b; Stewart, et al., 2008). These pain patterns have been shown to be related to increased sensitivity in the central nervous system, known as central sensitization (CS) (Carlesso et al., 2020). There is evidence that altered sensitivity of the nerves which supply the knee (peripheral sensitization) or from within the central nervous system (CNS) may explain more persistent pain in OA (O'Neill et al., 2018).

The term "Sensitization" refers to a neurophysiologic response in which the nociceptors and the transmission of nociception is altered by changes in nociceptor thresholds and

firing (Finnerup et al., 2021). Peripheral sensitization is known to occur locally at the knee, whereby nociceptive stimuli such as inflammation or pressure associated with joint loading (Carpenter et al., 2005; Schaible, 2012) lead to increased responsiveness or lowered thresholds of the nociceptors, causing them to fire more easily (Toth, 2011). Hyperalgesia has been seen at local and remote sites in persons with KOA and is thought to reflect the presence of peripheral and central sensitization (CS) respectively, however local hyperalgesia does not rule out that it is related to CS resulting from elsewhere in the body (Fingleton et al., 2015). Primary hyperalgesia is contributed to by changes in functioning of peripheral nerve endings known i.e. peripheral sensitization, whereas secondary hyperalgesia is due to changes in the spinal cord and higher brain areas (CS) (Vardeh et al., 2017). About 30% of people with KOA develop an increased sensitivity to pain, resulting from altered excitability of neurons in the central nervous system (Woolf, 2011). CS in OA may present with several clinical features which can overlap with those seen in neuropathic pain conditions (Hochman et al., 2010). While neuropathic pain has been increasingly recognized in KOA patients, it has mainly been evaluated through the use of questionnaires such as the modified painDETECT (Hochman et al., 2013). However, to our knowledge there has been no validation of these questionnaires with a clinical exam or diagnostic tests such as nerve conduction studies in people with KOA.

Sensitization can be measured using either psychophysical tests (i.e. quantitative sensory testing (QST) or patient-reported methods (Suokas et al., 2012). Common QST used in KOA studies include pressure pain thresholds (PPT) and temporal summation (TS) which have been found to be linked with KOA-related pain severity and pain descriptors

(intermittent, constant) (Carlesso et al., 2020), but with not radiographic KOA (Carlesso et al., 2020; Neogi et al., 2015). Conditioned pain modulation (CPM) is a test measuring the efficiency of an individual's endogenous pain modulatory pathway: it is calculated as the difference between 2 stimulus applications, a test stimulus and a conditioning stimulus (Kennedy et al., 2016). CPM has been studied in people with KOA, but to a lesser degree than PPTs or TS. Findings include adequate CPM being associated with a greater likelihood of having mixed pain (constant plus intermittent) versus only intermittent pain (Carlesso et al., 2020), as well as improved pain reduction after taking nonsteroidal anti-inflammatory medication (Edwards et al., 2016). Inadequate CPM has been associated with increased pressure sensitivity in response to exercise (Fingleton et al., 2017), and has been shown to be responsive to manual therapy interventions applied to the knee joint (Courtney et al., 2016). Unfortunately, QST is considered costly and difficult for clinicians to administer and interpret and therefore has not been widely adopted for clinical use (Lluch et al., 2013).

Furthermore, a gold standard for pain assessment in individuals with KOA has not been established, thereby necessitating the use of a combination of pain outcome measures (Dworkin et al., 2011). There are also many self-report pain measurement tools that exist, which span from standard pain intensity measures, to multidimensional measures. The most commonly used tools are those used to assess pain intensity i.e. the visual analogue scale (VAS) and the numerical pain rating scales (NPRS) (Frampton et al., 2011). Pain subscales from larger multidimensional measures include that of the Western Ontario and McMaster Universities OA index (WOMAC) which asks five questions about pain

intensity during low-level daily activities and at night in bed (Dworkin et al., 2011) and the Knee Injury and Orthopaedic Outcomes scale (KOOS) which asks about knee-related problems such as pain, symptoms and functions in daily living, sport and quality of life (Roos et al., 2003). Other pain-related constructs that are commonly evaluated in studies of people with KOA include the use of scales to measure anxiodepressive symptoms, pain catastrophizing and to a lesser extent fear avoidance. Widespread pain (WSP) has also been evaluated as a proxy measure for CS however recently there has been increasing use and interest in the Central Sensitization Inventory (CSI).

The CSI was developed to describe the phenomenon of CS in patients with Central Sensitivity Syndromes, a group of medically indistinct (or nonspecific) disorders such as fibromyalgia, irritable bowel syndrome, temporomandibular joint disorder, migraine and tension headache, myofascial pain syndrome, low back pain and some chronic pelvic pain disorders (Mayer et al., 2012). People with KOA were not included in the scale development and there has thus been interest in validating the scale in this population. Previous work in people with KOA has assessed the presence of CS by comparing the CSI to the costly and clinically challenging QST. Results indicated that the CSI is weakly correlated with QST, more strongly correlated with psychological constructs. Additionally, lower cut scores were recommended to indicate the presence of CS as identified by QST in patients with KOA (Gervais-Hupé et al., 2018).

Similarly, another study suggested a lower cut-score when comparing CSI scores with widespread pain and QST between people with chronic low back pain or KOA. The widespread pain score and QSTs did not correlate with the CSI score in either the CLBP

or KOA group. This study also observed a lower CSI cut score of 17 to identify CS syndrome in patients with KOA and a cut score of 28 for the chronic low back pain group. Patients with chronic low back pain showed a greater indication of CS symptoms and higher prevalence of CS syndromes compared to the patients with KOA (Mibu et al., 2019). In people with shoulder pain, a non-significant association between the CSI and QST scores was reported (Coronado et al., 2018). However, in a study of people with chronic musculoskeletal pain, a CSI cut-off score of >33.5 had significant associations with QST measures. Overall this evidence suggests that different populations may require distinct cut scores (Zafereo et al., 2021).

1.9 Thesis Objectives

Previous literature suggests that the CSI is effective in identifying central sensitization syndromes (CSS) in chronic pain patients with good sensitivity (81%) and specificity (79%), however people with KOA were not included as part of the sample used for the tool's development (Neblett et al., 2013). Therefore, further examination is necessary to determine the validity of the CSI in people with KOA. We hypothesized that Rasch analysis will generate insights into the metric properties of the CSI while incorporating important factors with a known direct relationship with CS in people with KOA, such as body mass index, pain intensity, negative pain beliefs, and quantitative sensory testing results. Thus we conducted a Rasch analysis of the CSI to examine for potential bias in the scale and explore opportunities to optimize a clinically feasible and robust surrogate measure of sensitization. Second, we assessed the agreement of the Rasch calibrated version of the CSI

with the original version in people with KOA and consider its validity with psychophysical tests, including their sensitivity and specificity.

Therefore, the objectives of this thesis were:

Study 1. To evaluate the validity of the CSI through Rasch analysis in persons with KOA. (Chapter-2)

Study 2. To determine the validity of the Rasch calibrated (RC-CSI) version of the CSI with psychophysical tests in people with KOA. (Chapter-3)

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CHAPTER 2 : STUDY ONE

Validity of the Central Sensitization Inventory (CSI) through Rasch Analysis in Patients with Knee Osteoarthritis

Title: Validity of the Central Sensitization Inventory (CSI) through Rasch Analysis in Patients with Knee Osteoarthritis.

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Published in Clinical Rheumatology and reproduced with permission from Springer Nature : Roby NU, Packham TL, MacDermid JC, Carlesso LC. Validity of the Central Sensitization Inventory (CSI) through Rasch analysis in patients with knee osteoarthritis. Clin Rheumatol. 2022 Jun 27. doi: 10.1007/s10067-022-06248-2. Epub ahead of print. PMID: 35754083.

Abstract

Introduction/objective: Central sensitization (CS) is a known contributor to chronic pain in people with knee osteoarthritis (KOA) and is commonly measured by psychophysical testing or patient reported methods such as the Central Sensitization Inventory (CSI). However previous studies have shown a weak association between the two. We therefore sought to evaluate the validity of the CSI through Rasch analysis in patients with KOA.

Method: We performed a secondary analysis of a multicenter cohort study with patients with KOA consulting orthopaedic surgeons. Rasch analysis was conducted considering person factors of age, sex, BMI, pain intensity, pain catastrophizing and quantitative sensory test findings using pressure pain thresholds and temporal summation to assess how the CSI fit to the Rasch Model (supporting validity). We used RUMM2030 software to model fit estimates, making adjustments as required to achieve model fit (P>0.05).

Results: Data from 293 patients were included (58.7% female, mean age 63.6 years, 49.1% obese) Initial evaluation with Rasch modelling indicated misfit. Eleven of 25 items on the CSI displayed disordered thresholds which were re-scored by collapsing response categories until the thresholds demonstrated sequential progression. Re-analysis demonstrated persistent model misfit so a subtest was developed to address local dependency of 6 items. Thereafter, model fit was achieved (P=0.071, indicating not differing from Rasch model) and acceptable unidimensionality (P=0.068 with 95%CI 0.043-0.093).

Conclusions: The CSI was able to be fit to the Rasch model after rescoring while retaining all 25 items. The unidimensionality validates CS as measured by the CSI as a singular construct.

Keywords: Central Sensitization Inventory, Knee Osteoarthritis, Knee Pain, Rasch Analysis.

2.1 Introduction:

The experience of pain in knee osteoarthritis (KOA) is well-recognized, often persistent and chronic in nature and may lead to physical disability (Neogi, 2013). It is acknowledged that pain perception in patients with KOA often depends on multiple variables including peripheral tissue damage, other coexisting conditions cognitive or emotional factors and central mechanisms of pain sensitization (Bedson et al., 2008; Finan et al., 2013; Georgiev, 2019). Central sensitization (CS) is one of the factors contributing to chronic pain, exemplifying the fundamental role of the central nervous system in the generation of pain hypersensitivity (Latremoliere et al., 2009). The International Association for the Study of Pain describes CS as a form of nociplastic pain presenting as increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent input (Raja et al., 2020). The clinical features of CS are recognized in people with KOA (Lluch et al., 2018) and evidence of CS demonstrated by the presence of hyperalgesia at local and remote sites (Fingleton et al., 2015).

CS is measured by psychophysical testing (Mayer et al., 2012; Neblett, 2018) and by patient-reported methods such as the Central Sensitization Inventory (CSI) (Mayer et al., 2012). The CSI was first developed to describe the phenomenon of CS in persons with Central Sensitivity Syndromes such as fibromyalgia, irritable bowel syndrome, and chronic low back pain (Yunus, 2007). However, in a sample of people with KOA, the CSI cut-point of 40 or more provided low to moderate sensitivity (30.8–58.3%), and higher specificity (75–79.2%) when compared to CS detected by quantitative sensory tests (Gervais-Hupé et al., 2018). Moreover, results illustrated moderate to large correlations

between CSI scores and widespread pain, pain catastrophizing, somatization, and anxiodepressive symptoms (Gervais-Hupé et al., 2018), demonstrating that in people with KOA, the CSI is more significantly associated with psychological factors than psychophysical tests. These results question the validity of the CSI to measure CS in people with KOA.

Rasch analysis uses an alternate framework to analyze responses to self-report questionnaires with the goal of improving measurement accuracy and reliability (Nishigami et al., 2018). Rasch modelling is a probability-based strategy within the domain of item response theory (IRT) used to estimate the difficulty parameters of both items and person abilities (Salkind, 2012). The key approaches to validation used in Rasch are model fit, unidimensionality, local dependency, person separation index (PSI), and differential item functioning (DIF) (Tennant et al., 2011). One of the primary benefits of Rasch analysis is providing a pathway to achieve interval level scaling by reconsidering the item pool and scoring metrics. This is particularly important when Rasch analysis was not used in development of the questionnaire. Rasch modelling can also be used to reduce items in questionnaires by removing linked items while ensuring good psychometric properties are maintained (Bilbao et al., 2011; Vergara et al., 2016). For example, a previous Rasch study of the CSI in people acute and chronic musculoskeletal pain disorders, reduced the number of items from 25 to 9 using the person factors of age, sex, pain duration, intensity and interference (Nishigami et al., 2018). The resulting shorter version (CSI-9) showed acceptable internal consistency, exhibited unidimensionality and no noticeable differential item functioning with this heterogenous sample of patients (Nishigami et al., 2018).

While the previous study demonstrated with a sample of mixed musculoskeletal pain, but the factors important to the KOA pain experience such as body mass index (BMI) (Torensma et al., 2016), negative cognitions and emotions, and quantitative sensory testing were not addressed. Given the limited information on the validity of the CSI for people with KOA, further examination is warranted. Rasch analysis may generate insights into the metric properties of the CSI while incorporating important factors with a known direct relationship with CS in people with KOA. This study examined for potential bias in the CSI and explored opportunities to optimize a clinically feasible and robust surrogate measure of sensitization. The main purpose of this study was to evaluate the validity of the CSI through Rasch analysis in persons with KOA.

2.2 Methods

Study design and participants

We performed a secondary analysis of data from a cross-sectional cohort study assessing pain phenotypes in people living with KOA (Gervais-Hupé et al., 2018). Total 293 study participants were recruited from three major university-affiliated hospitals in Montreal, Quebec, Canada. Inclusion criteria were patients at least 40 years old, having a first-time consultation with an orthopedic surgeon, who were diagnosed with KOA. Exclusion criteria included any patients presenting with a systemic inflammatory condition disorder, severe cardiac or vascular condition, having suffered significant trauma to the affected knee in the previous year, or could not provide informed consent or understand study questionnaires.

Informed consent was obtained prior to participation in the study. The study obtained ethical approval from the CIUSSS de l'Est-de-l'Île-de-Montréal Research Ethics Board (#MP-12-2017-829), Montreal, Canada, and was performed according to ethical standards following the 1964 Declaration of Helsinki and its later amendments.

Data Collection

After consenting, subjects received electronic or paper questionnaires. All participants completed demographic questionnaires based on items from the 1998 Québec Health Survey, including age, sex, self-reported weight and height to calculate BMI in kg/m2. A BMI of more than 30 was categorized as obese, 25.0 to 29.9 as overweight, while the normal range was 18.5 to 24.9 (Nuttall, 2015)

Questionnaires

The CSI is a patient-reported outcome measure designed to identify persons with symptoms typically associated with CS. It has 25 questions asking about the frequency of a range of symptoms such as widespread pain, abdominal pain, fatigue, poor sleep, headaches, anxiety, depression and poor memory or concentration. Items are scored from 0 (never) to 4 (always) with a total score of 100. Studies illustrate strong psychometric properties (test-retest reliability: ICC = 0.94; Cronbach's alpha = 0.96 to 0.97) of the CSI in cohorts of people with chronic pain syndromes (Cuesta-Vargas et al., 2018; Pitance et al., 2016).

The Numeric Pain Rating Scale (NPRS) is a self-reported outcome measure of pain intensity in adults. The NPRS is rated from '0' which represents no pain to '10' which represents the worst pain imaginable (Rodriguez, 2001). The NPRS has shown significant test–retest reliability when observed in rheumatoid arthritis patients (r = 0.95) and it is highly associated with the visual analog scale in patients with rheumatic and chronic pain disorders (correlations 0.86 to 0.95) (Ferraz et al., 1990).

The Pain Catastrophizing Scale (PCS) was used to measure cognitions associated with an individual's pain experience. (Quartana et al., 2009). The PCS has 13-items scored from 0 to 4, for a total score of 52. Higher scores indicate higher levels of pain catastrophizing in patients (Sullivan et al., 1995). Strong metrics have been reported for key psychometric properties, including high test-retest reliability and internal consistency (Cronbach's alpha = 0.87-0.95)(Osman et al., 2000; Augustine et al., 1997). A cut score of more than 30 has been demonstrated to be clinically relevant (Sullivan et al., 1995). In our study, it was operationalized by quartiles (0= 0-15, 1=16-30, 2=30-40 and 3=41-52) as a categorical variable.

Quantitative Sensory Tests

A trained research assistant following standardized protocols conducted testing at the index knee and the volar aspect of the contralateral forearm. Pressure pain thresholds (PPT) were measured by an electronic hand-held algometer (Wagner Instrument, CT) and a probe (1-cm^2). Measurements were taken at the patella, as an indicator of peripheral sensitization and central sensitization. Pressure was applied at a rate of 0.5 kg/s until respondents

verbally indicated they felt a painful sensation (Neogi et al., 2016). The mean value was calculated as the average of three trials. Tertiles were then created where the lowest tertile represented the least sensitivity and highest tertile the most sensitivity. Previous work demonstrates PPT measured at local and remote sites indicates involvement of CS in people with KOA (Neogi et al., 2015). PPT has good relative and absolute test-retest reliabilities in patients with KOA (Pratheep et al., 2018).

Temporal summation is a test of wind up or facilitation in the central nervous system and was measured at the forearm. A weighted Von Frey monofilament of 60g (Bioseb) was applied at the rate of 1 stimulus/second using a previously reported protocol (Neogi et al., 2016). An initial 4 taps were applied and the patient provided a pain rating out of 100. Next, a set of 30 consecutive stimuli were applied in the same manner after which a second pain rating was provided. TS was calculated by subtracting the first pain rating from the second. Positive values (≥ 1) indicate CS involvement and scores ≤ 0 were considered normal (Neogi et al., 2016). Studies show that the inter-rater reliability of TS is moderate to good (ICC range 0.69-0.91) for patients with musculoskeletal trauma (Middlebrook et al., 2020).

2.3 Analysis:

Descriptive characteristics were calculated through means and standard deviation for continuous variables and proportions for categorical variables. Analysis of variance was conducted to examine association between CSI scores and person variable groupings. CSI item score data was used to examine fit to the Rasch model. Rasch analysis includes testing multiple scale characteristics relative to the assumptions of the model. The appropriate

model is selected based on item characteristics (dichotomous or polytomous ratings) and analysis of the log-likelihood ratio (Tennant et al., 2011). Prior to analysis, the distribution of responses was examined to consider the range of possible responses and potential for floor or ceiling effects and biases (Pallant et al., 2007). No formal sample size calculation was performed. Previous literature suggests that 10 participants per item in the scale or n=200 is sufficient (Linacre, 1994).

Rasch analysis uses a sequence of individual item and person fit statistics to test the variance between observed responses and expected responses from the model. The overall fit of the data to the Rasch model is tested with a chi-square (χ^2) statistic which is a summary of the individual item χ^2 fit statistics. When the χ^2 statistics are non-significant ($p>0.05$), the overall and individual item fit are confirmed as not differing from the model (Gibbons et al., 2011). Items with disordered thresholds are rescored where measurement anomalies have been found, and sub testing using subscales to address multidimensionality or item bundling to address local dependency. The presence of item bias from DIF is also examined, as this also leads to item misfit (Van et al., 2009). It is discovered by analysis of variance for each item by comparing across levels of subject characteristics and levels of the latent trait, with Bonferroni correction for multiple analyses. (Van et al., 2009). We tested DIF for all person factors but were specifically interested in understanding any DIF regarding age and sex.

A person separation index is calculated by using an equation similar to Cronbach's alpha, except the logit scale estimates for each person are used instead of raw scores (Van et al.,

2009). We interpreted the calculated PSI using recommended values of 0.8 or greater as an acceptable indication of scale reliability (Prodinger et al., 2012).

The assumptions of local independence and unidimensionality highlight that the performance of items does not depend on traits other than the latent trait being tested. If local dependence was identified by a residual correlation of 0.2 or greater, then a subtest or 'testlet' was created which treated the items as a single unit to address the violation of the assumption of independence during fit calculations.

The test for unidimensionality is conducted with a principal component analysis (PCA) of the standardized residuals. First, factor analysis identifies how the items load onto the principal components. The subsequent t-testing compares the positively loading items against the negatively loading items. These groups will have a positive t-test at p= 0.05 if the scale is unidimensional (Prodinger et al., 2012; Van et al., 2009).The data were compiled into SPSS 24.0 for examination of demographics and imported to RUMM2030 version 5.1 (RUMM Laboratory Pty Ltd, Perth, Australia) for Rasch analysis.

2.4 Results:

Demographics:

A total of 293 participants with complete CSI data were used for the analysis. 58.7% of the patients were female with a mean age of 63.6 (±9.5). Moreover, almost half (49.1%) of the participants met the BMI-based standard for obesity (Nuttall, 2015). We also found the average CSI score (30.8 +/- 14.3) to be below the recommended cut score of 40/100 (Mayer et al., 2012).

Table: 1 - Demographics (including description and coding of person variable) (n=293)

Person Variable	Coding	Frequency n(%)
Age	40-49 years	19 (6.5)
	50-59 years	82(28.0)
	60-69 years	110(37.5)
	70-79	68(23.3)
	80 years plus	14(4.8)
Sex	Male	121(41.3)
	Female	172(58.7)
Body Mass Index (BMI)	Normal (18.5 – 24.9)	49(17.0)
	Overweight (25.0 – 29.9)	98(33.9)
	Obese (30 plus)	142(49.1)
		Mean (SD)
CSI		30.8 (±14.3)
NPRS		3.3 (±2.6)
PCS		17.7 (±12.8)
PPT (Patella)		4.5 (±2.6)
TS		12.6 (±14.3)

Analysis of variance demonstrated sample differences in CSI scores between the levels of person factors sex, PCS and PPT which are statistically significant ($p<0.001$). This means

female patients answered the CSI differently than male participants. Also, CSI scores were found to be different for the groups who have greater PCS or PPT scores. (Table:2)

Table:2 Analysis of Variance across person factors

	Sex	Age	BMI	PCS	PPT (Patella)	NPRS	TS
Total CSI (p-values)	<0.001*	0.403	0.145	<0.001*	<0.001*	0.292	0.703

Abbreviations: CSI- Central sensitization inventory, BMI- Body Mass index, NPRS- Numeric Pain Rating Scale, PCS- Pain Catastrophizing Scale, PPT- Pressure pain thresholds, TS- Temporal summation;

*Denotes statistical significance.

The log-likelihood ratio test was significant at $p<.001$, indicating the scaling differed across items therefore a partial credit model for polytomous responses was used.

Distribution of responses:

Not all levels within items were endorsed at least once. Moreover 9 categories fell below the suggested distribution target of at least 5 endorsements (Chachamovich et al., 2008a). For example, no or only one participant scored 4/4 on item 03 (anxiety), 16 (sad), or 25 (pelvic pain) (see Table 3). Given the low endorsements seen were concordant with the item difficulty, we did not feel that this precluded continuing with the data analysis. We elected to use a 5-class interval structure for our statistical modeling.

Thresholds:

On initial examination, 11 of the 25 items on the CSI displayed disordered thresholds by failing to follow predicted response pattern. These items were rescored by collapsing

response categories based on the category probability curves until the thresholds demonstrated sequential levels (Fig. 1 for rescored threshold map). This resulted in a decrease in the number of response categories for 11 items (see highlighted items Table 3).

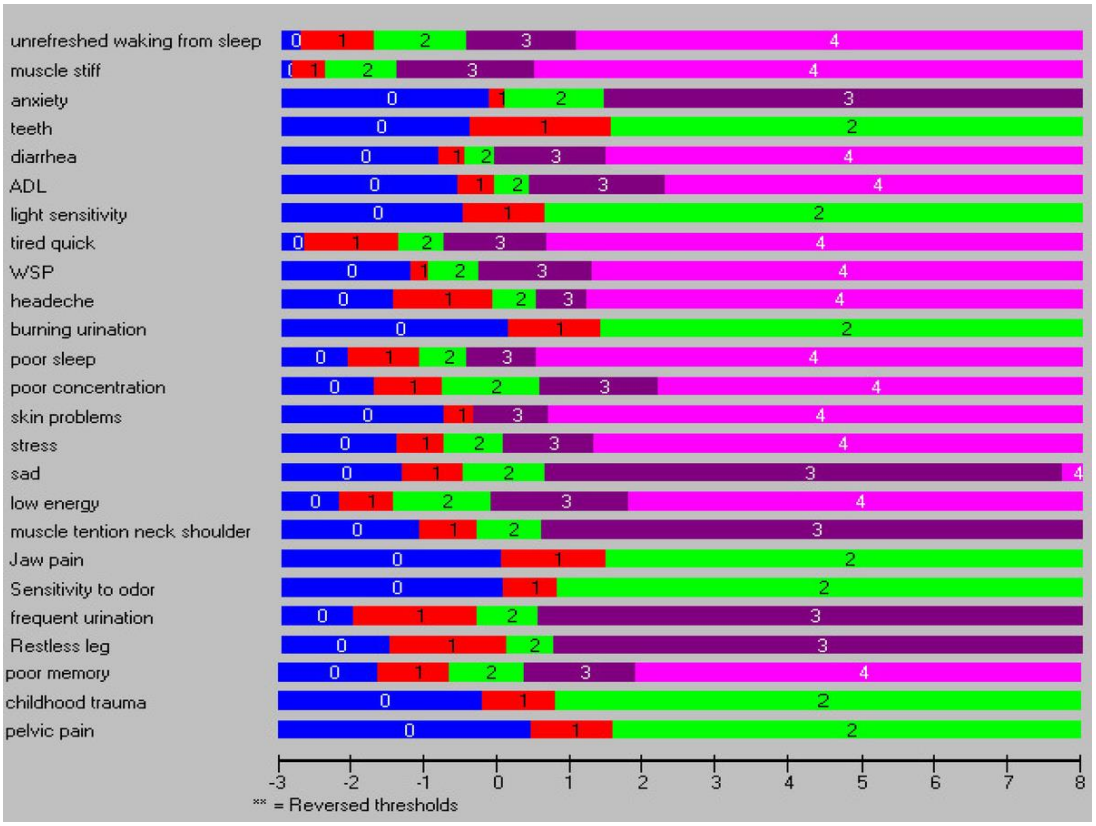
Table: 3 Frequency of item endorsement (category frequency of original data)

No.	Statement	0	1	2	3	4	Rescoring required = X
1	Unrefreshed waking from sleep	26	64	105	78	19	-
2	Muscle Stiff	11	32	83	124	42	-
3	Anxiety	175	71	39	6	1	X
4	Teeth	178	47	34	20	13	X
5	Bowels	114	78	58	36	6	-
6	ADL	142	83	45	20	2	-
7	Light sensitivity	164	52	46	22	8	X
8	Tire quickly	27	69	86	83	27	-
9	WSP	81	72	74	54	11	-
10	Headache	93	115	58	21	5	-
11	Burning Urination	208	50	22	10	2	X
12	Poor sleep	45	77	83	63	24	-
13	Poor concentration	76	92	89	32	3	-
14	Skin problems	115	75	51	38	13	-

15	Stress	84	81	76	42	9	-
16	Sad	95	96	75	26	0	-
17	Low energy	44	73	104	63	8	-
18	Muscle tension in neck and shoulder	59	52	94	63	24	X
19	Jaw pain	203	55	23	9	2	X
20	Sensitivity to odor	199	41	32	13	7	X
21	Frequent Urination	64	65	62	76	25	X
22	Restless legs	94	60	66	55	17	X
23	Poor memory	78	96	82	32	4	-
24	Childhood trauma	185	43	41	17	6	X
25	Pelvic pain	226	39	19	7	1	X

**Shaded boxes indicate the response categories that were merged to obtain ordered response category thresholds*

Figure 2: Rescored item threshold map



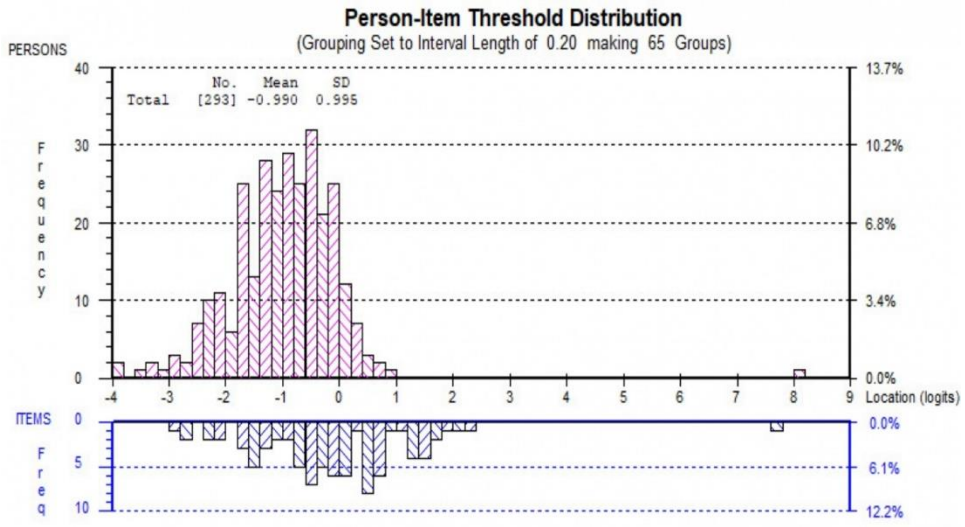
Initial fit to the Rasch model:

After the initial analysis of the CSI fit to the Rasch model, a highly significant chi-square value for item-trait interaction [$x^2(100) = 198.9$, $p < 0.001$ indicated lack of fit to the Rasch model. Once the disordered thresholds were rescored, the chi-square value for item-trait interaction [$x^2(100) = 146.5$, $p= 0.001$] remained significant, indicating persistent lack of fit. Consequently, we proceeded to comprehensively examine individual areas to identify where the misfit was coming from, and consider if this could be addressed by combining, splitting or deleting items within the CSI.

Person and item fit:

The person-item map displays the location of person abilities and item difficulties respectively along the same latent dimension. The person parameter is located on the scale from symptoms weakly aligned with CS features to symptoms strongly aligned with CS. The bar chart on the top depicts that our sample with KOA had low central sensitization scores, with the mean person location (-0.99 logits) falling almost a full standard deviation below the average item difficulty (which is set to zero logits). The item parameter on the bottom graph also illustrates that there are more items location above the average level of CS in the sample than below the average sample level of CS. (Figure 2)

Figure 2: Person item threshold distribution



After taking out the principal component correlations identified by factor analysis, person item residual correlations above 0.2 (Tennant et al., 2011) indicated local dependency between items 1(unrefreshed walking from sleep) and 12 (poor sleep); items 2(muscle stiff), 9 (wide spread pain) and 18 (Muscle tension in neck and shoulder); items 4(teeth

problem) and 19 (jaw pain); 8 (tire quickly) and 17 (low energy); items 11(burning urination), 21(frequent urination) and 25 (pelvic pain); items 14 (skin problems) and 15 (stress); and items 13 (poor concentration) and 23 (Poor memory).

Reliability of fit estimates and the total scale:

Cronbach's alpha was calculated on data sets without missing data, which for our sample was n = 293, at 0.89 with a PSI of 0.91 for the total scale after rescoring of the thresholds.

Differential item functioning:

Only two CSI items, 14- skin problems and 21- frequent urination showed a pattern of uniform DIF by sex and age which was statistically significant ($p<0.001$) after Bonferroni correction.

Reassessment of Rasch Model:

Following iterative creation of subtests to link locally dependent items, the chi-square value for item-trait interaction [$X^2(80) = 99.1$, $P = 0.071$] was found to be non-significant, indicating fit to Rasch model. After the subtest analysis, PSI values for reliability of the fit estimates ranged from 0.89 to 0.91. Cronbach's alpha for the CSI was 0.89 (including extremes).

Unidimensionality:

Initial analysis of the total CSI scale without adjustments for fit issues failed the test of unidimensionality (P=0.171). After the creation of subtests to address local dependency, the CSI demonstrated acceptable unidimensionality (P= 0.068, 95% CI: 0.043-0.093)

(Table 4). As the unidimensionality criteria was met for the full scale, we have provided a Rasch-corrected scoring key in Appendix A.

Table:4 Summary statistics for all Analysis

	Unidimensionality	Item Location	Person Location	Item fit residual	Person fit residual	Item-trait interaction	PSI
CSI unadjusted	P= 0.171* (95% CI:0.146-0.196)	logits = 0.00 SD=0.67	logits = -0.89 SD=0.91 Excluding extremes (n=292)	Z= 0.47 SD=1.62	Z= -0.13 SD=1.37	$X^2(100)$= 198.9 P= <0.001	0.91 incl. extremes 0.89 no extremes
CSI Rescored	P= 0.140* (95% CI:0.115-0.165)	logits = 0.00 SD= 0.70	logits = -0.99 SD=0.10 Including extremes (n=293)	Z= 0.16 SD=1.34	Z= -0.17 SD=1.31	$X^2(100)$= 146.5 P= 0.001	0. 19 incl. extremes 0.89 no extremes
CSI with Subtest	P= 0.068 (95% CI: 0.043-0.093)	logits = 0.00 SD=0.68	logits = -1.09 SD= 0.92 Including extremes (n=293)	Z= 0.07 SD=1.11	Z= -0.18 SD=1.18	$X^2(80)$ =99.1 P= 0.071	0.91 incl. extremes 0.89 no extremes

Abbreviations: CSI- Central sensitization inventory;

*Denotes results which demonstrate persistent misfit.

2.5 Discussion:

The purpose of this secondary analysis was to assess the validity of the CSI in patients with KOA using Rasch analysis to explore model fit, unidimensionality and influence of bias. Studies have used Rasch analysis on the CSI with samples including people with acute and chronic musculoskeletal pain which did not include those with KOA (Ohashi et al., 2020). To our knowledge, Rasch analysis of the CSI in people with KOA has not been previously performed. The findings of this study have the potential to add important psychometric evidence for the validity CSI in this population, who were not included in the development of the scale.

The CSI is a screening tool, which aims to identify those with and without CS. Central sensitization, while observed in this population, is not a primary feature and therefore we would anticipate the average score to be below the cut score published in previous literature (Gervais-Hupé et al., 2018). Similarly, a study of people with hip OA reported a mean score on the CSI of 19.5 ± 11.3 (Ohashi et al., 2020). The slight differences in our findings may be due to differences in sample sizes and populations. Additionally, the response distribution across the scoring options for all items indicated floor effects on at least 8 items where more than 50% of the participants scored 0. The person item threshold distribution recorded here depicts there are more items above the average sample level of CS in our sample than below the average sample level of CS. While this could be interpreted as a mismatch between the sample and the items, it supports the intended function of the CSI as a screening tool for this population.

We included all extreme scores in our fit estimates as the extreme scores are used when the scores (person location) are lower or higher than would be predicted based on the class interval. In a study with a sample of mixed musculoskeletal patients with chronic pain, a shorter version of the CSI was developed after initial Rasch analysis (Nishigami et al., 2018). While we did not reduce any items, we instead applied iterative corrections based on analysis until model fit was able to be demonstrated. For example, the earlier study deleted item 8 (quickly tired) and 17 (low energy) to reduce misfit in the shorter version (Nishigami et al., 2018) while we included those items in a subtest along with 4 other items to address local dependency. We found good reliability for the CSI after sub testing, with person separation index (PSI) values and a good Cronbach's alpha (internal consistency) for the entire scale including extremes which is supported by other studies (Mayer et al., 2012; Nishigami et al., 2018). The strong PSI values suggest the CSI is able to differentiate between at least 4 groups or levels of patients because of the robust reliability of the fit statistics (Chachamovich et al., 2008b). Our reliability findings are concordant with both what was reported by the original developers in a classical test paradigm, as well as by others using Rasch analysis (Mayer et al., 2012; Packham et al., 2013). Our study showed acceptable unidimensionality of the CSI in KOA patients: this is in contrast to another study showing multidimensionality in musculoskeletal problems (Nishigami et al., 2018). In that study, factor analysis suggested the full CSI contained five factor dimensions and the shorter (9 item) version contained two factor dimensions (Nishigami et al., 2018). We can hypothesize the difference in these findings may reflect that our study participants were more homogeneous, and we created subtests to address local dependence which helped to

obtain unidimensionality; it may also reflect variation in person factors used for modelling and the resultant class intervals. Item 21- frequent urination, showed a pattern of uniform differential item functioning by age was significant which means younger patients would answer differently on that item than the older patient with KOA. This is concordant with other studies which reported that frequent urination and urinary incontinence is common with older age due to reduction in bladder capacity, uninhibited contractions and uneven urinary flow rate (Batmani et al., 2021; Potts et al., 2018). Additionally, item 14-skin problems demonstrated DIF by sex, indicating males and females with similar amounts of central sensitization scored differently on this item: however, we are unaware of any studies exploring sex differences in perceptions of skin issues such as dryness, itchiness, or rashes. We can hypothesize that women may report skin concerns more frequently than men.

The analysis of variance in this sample demonstrates sex influenced how people scored the CSI. This is concordant with studies suggesting sex differences influence vulnerability to CS (Smith et al., 2019) and increased risk for chronic pain for females (Bartley & Fillingim, 2013; Racine et al., 2012) . Other studies have reported that age (Lautenbacher et al., 2017) and increased BMI (Tashani et al., 2017; Torensma et al., 2016) influence pain sensitivity and tolerance, but we did not find any statistically significant differences in CSI scores due to these person factors. We did find significant differences in CSI scores with the PCS and PPTs at the patella. However, there were no statistically significant differences in CSI scores based on the NPRS or TS. Interestingly, this would indicate that persons with peripheral sensitization (PPT patella) but not CS (TS) would score differently on the CSI

across different levels of the trait, suggesting that the measure is not necessarily sensitive to CS as measured by QST as previously reported (Cliton Bezerra et al., 2021; Gervais-Hupé et al., 2018).

Our study has limitations to consider. Our sample was relatively small, which may have contributed to less precise estimates: this was likely compounded by the lack of fit between person and items. The main strength of this study is that it is the first to our knowledge to perform a Rasch analysis of the CSI in people with KOA, modelling with pain related variables known to have associations with CS. Our results add to the building literature examining the validity of the CSI in this population. While our results suggest rescoring of the CSI for people with KOA, our results should be confirmed in an external cohort and replicated in larger samples prior to clinical use.

2.6 Conclusion:

In conclusion, our findings identified the CSI was able to be fit to the Rasch model after rescoring while retaining all 25 items. Rasch analysis has provided additional confidence in the measure while providing a scoring metric to provide interval level scaling. Floor effects were seen, potentially due to a lower prevalence of CS in this sample. We were able to maintain the original structure of CSI through item rescoring and subtesting, creating an alternate scoring key that can be easily implemented (see Appendix A). The unidimensionality validates CS as measured by the CSI as a singular construct. Prior to widespread clinical use future studies should include a larger sample for further validation of the CSI in people with KOA and could explore the use of cognitive debriefing interviews

to determine its content validity and consider calibration of Rasch-adjusted cut-scores indicating clinically important levels of central sensitization.

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Appendix A:

Rasch informed rescoring key

CSI questionnaires with complete answers, the following table can be used to convert raw scores to a more precise value.

Rasch transformed scores:

Raw Score	Location	Std Error	Rasch rescored	Transformed scores
1	-4.18	0.82	0.00	1.00
2	-3.67	0.64	4.14	5.14
3	-3.32	0.54	6.92	7.92
4	-3.06	0.48	9.01	10.01
5	-2.85	0.44	10.71	11.71
6	-2.67	0.40	12.15	13.15
7	-2.52	0.38	13.39	14.39
8	-2.38	0.36	14.50	15.50
9	-2.25	0.34	15.50	16.50
10	-2.14	0.33	16.41	17.41
11	-2.04	0.31	17.25	18.25
12	-1.94	0.30	18.02	19.02
13	-1.85	0.29	18.75	19.75
14	-1.76	0.28	19.43	20.43
15	-1.68	0.27	20.07	21.07
16	-1.61	0.27	20.68	21.68
17	-1.54	0.26	21.25	22.25
18	-1.47	0.25	21.81	22.81
19	-1.40	0.25	22.33	23.33
20	-1.34	0.24	22.84	23.84
21	-1.28	0.24	23.32	24.32
22	-1.22	0.24	23.79	24.79
23	-1.17	0.23	24.24	25.24
24	-1.11	0.23	24.68	25.68
25	-1.06	0.22	25.10	26.10
26	-1.01	0.22	25.51	26.51
27	-0.96	0.22	25.90	26.90
28	-0.91	0.21	26.30	27.30
29	-0.86	0.21	26.68	27.68

30	-0.82	0.21	27.05	28.05
31	-0.77	0.21	27.41	28.41
32	-0.73	0.21	27.76	28.76
33	-0.68	0.20	28.11	29.11
34	-0.64	0.20	28.45	29.45
35	-0.60	0.20	28.78	29.78
36	-0.56	0.20	29.11	30.11
37	-0.52	0.20	29.43	30.43
38	-0.48	0.19	29.75	30.75
39	-0.44	0.19	30.07	31.07
40	-0.40	0.19	30.37	31.37
41	-0.36	0.19	30.68	31.68
42	-0.33	0.19	30.98	31.98
43	-0.29	0.19	31.28	32.28
44	-0.25	0.19	31.58	32.58
45	-0.22	0.19	31.86	32.86
46	-0.18	0.19	32.15	33.15
47	-0.14	0.19	32.44	33.44
48	-0.11	0.19	32.73	33.73
49	-0.07	0.19	33.02	34.02
50	-0.04	0.19	33.30	34.30
51	-0.00	0.18	33.59	34.59
52	0.02	0.18	33.87	34.87
53	0.06	0.19	34.15	35.15
54	0.10	0.19	34.44	35.44
55	0.13	0.19	34.72	35.72
56	0.17	0.19	35.01	36.01
57	0.20	0.19	35.29	36.29
58	0.24	0.19	35.58	36.58
59	0.27	0.19	35.88	36.88
60	0.31	0.19	36.17	37.17
61	0.35	0.19	36.47	37.47
62	0.38	0.19	36.76	37.76
63	0.42	0.19	37.07	38.07
64	0.46	0.19	37.38	38.38
65	0.50	0.19	37.69	38.69
66	0.54	0.20	38.01	39.01
67	0.58	0.20	38.33	39.33
68	0.62	0.20	38.67	39.67
69	0.66	0.20	39.01	40.01

70	0.71	0.21	39.35	40.35
71	0.75	0.21	39.70	40.70
72	0.80	0.21	40.07	41.07
73	0.84	0.21	40.44	41.44
74	0.89	0.22	40.83	41.83
75	0.94	0.22	41.23	42.23
76	0.99	0.23	41.64	42.64
77	1.05	0.23	42.07	43.07
78	1.10	0.23	42.52	43.52
79	1.16	0.24	42.99	43.99
80	1.22	0.25	43.47	44.47
81	1.28	0.25	43.99	44.99
82	1.35	0.26	44.52	45.52
83	1.42	0.27	45.09	46.09
84	1.50	0.27	45.69	46.69
85	1.58	0.28	46.33	47.33
86	1.66	0.29	47.01	48.01
87	1.75	0.30	47.74	48.74
88	1.85	0.31	48.52	49.52
89	1.95	0.33	49.37	50.37
90	2.07	0.34	50.30	51.30
91	2.20	0.36	51.32	52.32
92	2.34	0.38	52.46	53.46
93	2.50	0.41	53.75	54.75
94	2.68	0.44	55.24	56.24
95	2.90	0.49	57.00	58.00
96	3.17	0.55	59.18	60.18
97	3.53	0.65	62.04	63.04
98	4.06	0.82	66.31	67.31
99	5.29	1.38	76.18	77.18
100	8.13	3.15	99.00	100.00

CHAPTER 3 : STUDY 2

Assessing Validity of the Original and Rasch Versions of the Central Sensitization Inventory with Psychophysical Tests in People with Knee Osteoarthritis

Title:

Assessing Validity of the Original and Rasch Versions of the Central Sensitization Inventory with Psychophysical Tests in People with Knee Osteoarthritis

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Abstract

Background: We recently performed a Rasch analysis of the Central sensitization inventory (CSI) in people with KOA. This study aimed to determine the extent of agreement between the original CSI and the Rasch analyzed version (RC-CSI) and to explore the association of both versions with psychophysical tests and their respective sensitivity and specificity.

Methods: Patients with KOA enrolled in a multicenter cohort study completed the original CSI and RC-CSI and psychophysical tests i.e. Pressure pain thresholds (PPTs), Temporal Summation, Conditioned pain modulation using standardized protocols. Bland-Altman analyses assessed the agreement between the original CSI and the RC-CSI; Spearman correlations and chi-square analysis evaluated the association between the two CSI scores and psychophysical tests. A CSI cut point of 40 and the RC-CSI cut-point of 31.37 was used. Receiver Operating Characteristic curves and the resulting sensitivity and specificity with psychophysical tests were also analyzed.

Results: 293 participants were included (58.7% female, mean age of 63.6 and BMI 31.9 kg/m^2). The original CSI & RC-CSI mean difference 3.3/8.2, $t(292) = 8.84 (p < .001)$ was significantly different indicating a small bias. Small but significant inverse correlations were found for the original CSI and RC-CSI scores with PPTs at the forearm and patella. The largest area under the curve suggested cut-points of 23 (CSI) and 25 (RC-CSI) with 80.9% sensitivity and 38.5% specificity.

Conclusions: The Original CSI and RC-CSI should not be used interchangeably. Our results indicate little clinical value in using the RC-CSI in people with KOA.

3.1 Introduction:

Knee osteoarthritis (OA) is a major cause of disability that is slowly progressive (Driban et al., 2020) and highly prevalent among older adults (Cui et al., 2020a). KOA accounts for 83% of the total OA burden globally (Vos et al., 2012) and has doubled in prevalence since the mid-20th century (Wallace et al., 2017). In 2020, the pooled global prevalence of KOA was 22·9% (95% CI, 19·8%-26·1%) in individuals aged 40 and over (Cui et al., 2020b). The most common feature of KOA is moderate to severe persistent pain (Neogi, 2013). About 30% of people with KOA develop an increased sensitivity to pain which can result from altered excitability of neurons in the central nervous system leading to central sensitization (CS) (Woolf, 2011). The presence of CS in people with KOA is evidenced by hyperalgesia at local and remote sites (Fingleton et al., 2015). The intrinsic risk of developing CS in those with end-stage disease has been estimated to be approximately 20% (Petersen et al., 2015).

There is no gold standard for assessing CS in humans. Psychophysical tests such as pressure pain thresholds (PPT) and patient-reported methods known as Central Sensitization Inventory (CSI) are available (Boer et al., 2021). Psychophysical tests are valid and reliable, (Geber et al., 2011; Suokas et al., 2012) but these tests are time-consuming, and are rarely performed in clinical settings due to the high costs of equipment and challenges with interpretation with so many protocols being used (Lluch et al., 2013; Rankin et al., 2021). Therefore, patient-reported methods to measure CS have been developed as a clinician-friendly measure. The CSI was developed to describe the phenomenon of CS in patients with Central Sensitivity Syndromes, a group of nonspecific

disorders such as fibromyalgia, chronic low back pain, temporomandibular joint disorder, migraine and tension headache, myofascial pain syndrome, and some chronic pelvic pain disorders (Mayer et al., 2012a). CSI was originally developed as a screening tool (Mayer et al., 2012b) and is easy to administer in patients experiencing CS signs and symptoms (Caumo et al., 2017). The CSI has been reported to have strong internal consistency reliability (Cronbach alpha =0.92) (Cuesta-Vargas et al., 2018) and demonstrates construct validity (80%) with pain severity, physical function, and anxiodepressive symptoms in patients with chronic pain (Chiarotto et al., 2018): however, persons with KOA were not used in the development of the CSI.

Given the prevalence and risk of CS in people with KOA, the CSI could be a viable tool for clinicians to use with this population. Our previous studies of the CSI in people with KOA indicated better association of the CSI with somatization, anxiodepressive symptoms, and WSP compared to psychophysical tests (Gervais-Hupé et al., 2018). In addition, Receiver Operating Characteristic (ROC) analysis of the CSI with psychophysical tests suggested lower values for the CSI cut score with only moderate sensitivity and high specificity (Gervais-Hupé et al., 2018). In light of these results, we recently conducted a Rasch analysis of the CSI in people with KOA where we included variables specific to the pain experience such as pain catastrophizing, pressure pain thresholds, temporal summation and pain intensity. We found that the CSI was able to fit the Rasch model after rescoring several items while retaining all 25 items (Roby et al., 2022). We also found that the CSI was unidimensional. However, results suggested that the users of the CSI should be aware of the potential for differences in scoring across age groups for the frequent

urination item. Significant differences in CSI scores were found across different scores of the Pain Catastrophizing Scale (PCS) and pressure pain thresholds (PPT) at the knee. There is, therefore a need to assess the validity of the Rasch analyzed version of the CSI in people with KOA to evaluate its agreement with the original scale and its validity with psychophysical tests.

The objectives of this study were to determine (1) the extent of agreement between the original version of the CSI and the Rasch analyzed version. (2) the association between the original CSI or the RC-CSI with psychophysical tests, (3) the sensitivity (Sn) and specificity (Sp) of the original version of the CSI and the RC-CSI in identifying patients with signs of CS as measured by psychophysical tests.

3.2 Methods:

We performed a secondary analysis of data from a cross-sectional cohort study. Study participants were recruited from three major university-affiliated hospitals in Montreal, Quebec, Canada: Hôpital Maisonneuve-Rosemont (HMR), Hôpital Jean-Talon (HJT), and the Centre Hospitalier de l'Université du Montreal. Inclusion criteria were patients at least 40 years old, having a first-time consultation with an orthopedic surgeon, who was diagnosed with KOA according to American College of Rheumatology criteria. Exclusion criteria were any patients presenting with a systemic inflammatory condition disorder, severe cardiac or vascular condition, having suffered significant trauma to the affected knee in the previous year, or could not provide informed consent or understand study questionnaires.

Measures:

Self-report measures:

The Central sensitization inventory is a self-reported measure identifying symptoms associated with CS or central sensitivity syndromes (CSS) using 25 items scored on a five-point Likert scale from 0 to 4 with a total score of 100 (Mayer et al., 2012a). The questionnaire inquires about CS related symptoms such as widespread pain, abdominal pain, fatigue, poor sleep, headaches, anxiety, depression and poor memory or concentration (Mayer et al., 2012a; Neblett, 2018). A receiver operating characteristic analysis showed a CSI score of 40/100 in patients with CSS and chronic pain (area under the curve = 0.86, sensitivity = 81%, specificity = 75%) (Neblett et al., 2013a). For the purposes of the analysis, we used a Rasch recalibrated score of 31.37 (Roby et al., 2022).

Psychophysical Tests:

A research assistant was trained in a standardized testing protocol and all tests were conducted at the index knee and the volar aspect of the contralateral forearm with a delay of 3 min between tests to avoid temporal summation (TS).

Pressure pain thresholds (PPT) were used to measure deep muscular tissue sensitivity by an electronic hand-held algometer with a $1cm^2$ probe (Wagner Instruments, CT). Measurements were taken at the forearm and patella to assess central and peripheral sensitization (Neogi et al., 2015). The pressure was applied at a rate of 0.5 kg/s until respondents verbally indicated they felt the sensation change from pressure to pain (Neogi et al., 2016). The average of three trials generated a mean value. Tertiles were then created

where the lowest tertile represented the most sensitivity and the highest tertile indicated the least sensitivity. PPTs have demonstrated good relative and absolute test-retest reliability in patients with KOA (Srimurugan Pratheep et al., 2018).

Temporal summation is a measure of wind-up in the central nervous system whereby two or more weaker stimuli sum to create a stronger single stimuli (Eide, 2000; Staud et al., 2006). It was measured at the forearm and patella by a weighted Von Frey monofilament of 60g (1 stimulus/second) using a previously reported protocol (Neogi et al., 2015, 2016). An initial 4 taps were applied and the patient provided a pain rating out of 10. Next, a train of 30 consecutive stimuli were applied in the same manner after which a second pain rating was provided. TS was calculated by subtracting the initial pain rating from the second. Those with positive numbers were classified as having CS with scores≤0 considered normal (Neogi et al., 2016). TS has been shown to have moderate to good reliability (ICC range 0.69-0.91) for patients with musculoskeletal injury (Middlebrook et al., 2020).

Conditioned pain modulation (CPM) is a psychophysical experimental measure of the endogenous pain inhibitory pathway and consists of the evaluation of a painful test stimulus followed by a second painful conditioning stimulus (Yarnitsky et al., 2010). First, an ascending measure of PPT was evaluated at the anterior shin on the affected knee with a verbal pain rating of 4 out of 10. Next, a Medoc TSAII Neurosensory Analyzer was used for 1 min at the opposite volar forearm with conditioning stimulus in the form of cold pain to produce a minimum verbal pain rating of 6 out of 10. At the end, PPT was reevaluated in the same way and an index was created by subtracting the first PPT reading from the

last. The negative and positive values indicated pain inhibition and pain facilitation respectively where positive values indicated the presence of CS.

3.3 Analysis:

Descriptive analysis was performed using means and standard deviation for continuous variables and proportions for dichotomous variables. For our first objective, we assessed the agreement between the original version of the CSI and the Rasch analyzed version (RC-CSI) using a Bland-Altman analysis. This consisted of the one sample t-test which would inform examination of a scatterplot for bias. For our second objective, the association between the original CSI, RC-CSI, and psychophysical tests was evaluated using Spearman correlations and chi-square analysis. Lastly, we evaluated ROC curves and the resulting sensitivity and specificity for the scores of the CSI and RC-CSI and the presence or absence of CS as previously defined by PPT, TS, and CPM tests. The benchmarks for an area under the curve (AUC) analysis are considered as follows: excellent (0.9-1), good (0.8-0.9), fair (0.7-0.8), poor (0.6-0.7) and failed (0.5-0.6) (Akobeng, 2007; Metz, 1978; Vanderlooy et al., 2008). Chi-square analysis was used to evaluate the association between the CSI cut point of 40, the RC-CSI cut-point of 31.37 and the presence or absence of CS as identified by PPT, TS, and CPM. Fisher's exact test was used when the expected cell count is less than five. All analyses were conducted using SPSS Version 23.

3.4 Results:

A total of 293 KOA patients were included for the analysis; 58.7% of them were female with a mean age of 63.6. Almost half (49.1%) of the total participants met the criteria for obesity (mean 31.86kg/m^2 ±8.63) (CDC, 2012; Nuttall, 2015) The lowest tertiles of the

PPT scores at the forearm and patella indicating the presence of CS were 1.46 mean (±0.21) and 2.03 mean (±0.63) respectively. Moreover, 86% of the patients showed the presence of CS with positive TS values in patella and forearm. (Table-1)

Table 1 Descriptive statistics (n=293)

	Mean (SD)
Age	63.65(9.57)
BMI, kgm^2	31.86(8.63)
Sex, Female	172(58.7)
RC-CSI 0/100	27.51(7.27)
Original CSI 0/100	30.78(14.33)
PPT, forearm (n=271) most sensitive	1.46 (0.21)kg/cm^2
PPT, patella (n=274), most sensitive	2.03(0.63) kg/cm^2
TS, forearm (n=271), +CS	14.63(14.45)
TS, patella (n=273), +CS	15.25(13.09)
CPM (difference of PPT2- PPT1)	4.84(9.82) kg/cm^2

Bland Altman Analysis:

The original CSI & RC-CSI mean difference 3.3/8.2, $t(292) = 8.84 (p < .001)$ was significantly different indicating a small bias and a lack of agreement between the scores of the two versions. We proceeded with a confirmatory visual inspection of the

scatterplot which suggested the mean difference between the two versions increases as the average score of the Original CSI and RC-CSI increases (Appendix A figure 1). The appearance of overlapping data that are somewhat linear in shape (not scattered), along with the data not being close to 0 suggests the presence of bias and confirms a lack of agreement between the two measures.

The histogram (Appendix A) showed almost 78% of these data had a mean difference between 10 and -10. The chart further reveals that there are differing proportions of values above and below a difference of zero: 58.4% above and 41.6% below for the average CSI and RC-CSI. This is concordant with the scatter plot and suggested no agreement as most observations are different.

Association of the CSI and RC-CSI with Psychophysical Tests:

A small but significant inverse correlation was found such that higher original CSI scores were associated with lower PPTs at the forearm ($r = -0.25$, 95%CI [-0.35, -0.14], $p = 0.001$) and patella ($r = -0.34$, 95%CI [-0.44, -0.24], $p = 0.001$) and with CPM ($r = -0.12$, 95%CI [-0.23, -0.01], $p = 0.044$). Similarly, the higher RC-CSI scores were also small and negatively correlated with lower PPT patella ($rs = -0.29$, 95%CI [-0.39, -0.18], $p = 0.001$) and forearm ($r = -0.21$, 95%CI [-0.31, -0.10], $p = 0.001$) at the patella, but CPM was not significant. There was no significant association with TS at either site for both original CSI and RC-CSI. (Table 2)

Table 2 Association of CSI scores with PPT, TS and CPM

		PPT-forearm	PPT - patella	TS forearm-	TS patella	CPM
Original CSI	Pearson Correlation	-.25**	-.34**	-.01	.02	-.12*
RC-CSI)	Pearson Correlation	-.21**	-.29**	-.02	-.02	-.10

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Furthermore, similar results were found after Chi square analysis demonstrating significant associations between the original CSI or RC-CSI cut points and presence or absence of CS through PPT in both patella ($X^2 = 9.194$, $p = 0.002$) and forearm ($X^2 = 9.739$, $p = 0.002$). However, the strength of the relationship was positive and negligible Phi= $r<0.19$. Findings for TS at the forearm ($X^2 = 3.987$, $p = 0.046$) and CPM ($X^2= 0.411$, $p = 0.522$) with both CSI cut scores showed a non-significant negative association (Phi = $r<-0.19$). (Table 3)

Table:3 Chi square analysis between original CSI and RC-CSI cut points and signs of CS measured by psychophysical tests

CSI	QST	X^2 (P value)	Likelihood Ratio (P value)	Phi (p value)
CSI cut point 40 or RC- CSI cut point 31.37	PPT FA	9.194(0.002)	8.899(.003)	0.184(0.002)
	PPT PAT	9.739(0.002)	9.433(0.002)	0.189(0.002)
	TS FA	4.288(0.038)	3.987 (0.046)	-0.126(0.038)
	TS PAT	0.004(0.949)	0.004(0.949)	0.004(0.949)
	CPM	0.411(0.522)	0.407(0.524)	-0.039(0.522)

Sensitivity and Specificity of the CSI and the RC-CSI:

ROC curve analyses showed a statistically significant area under-the-curve (AUC) between the CSI cut point of 40 or RC-CSI cut point of 31.37 and PPT at the forearm (AUC = 0.646, p = 0.001) and PPT at the patella (AUC =0.631, p = 0.001). However, none of the AUC values met thresholds for acceptability. No other findings were statistically significant. The

AUC for PPT at the forearm suggested cut-points of 23 for the original CSI and 25 for the RC-CSI (Sn 80.9%, Sp 38.5%). Similarly for PPT at the patella, cut-points of 23 for the original CSI and 25 for the RC-CSI were observed (Sn 75.8%, Sp 36.1%). (Tables 4 and 5 and Fig. 2)

Table: 4 ROC curve analyses with AUC values

		AUC (P value)	95% CI
CSI cut point 40 or RC- CSI cut point 31.37	PPT FA	0.646(0.001)	0.576-0.715
	PPT PAT	0.631(0.001)	0.559-0.703
	TS FA	0.453(0.354)	0.347-0.558
	CPM	0.431(0.068)	0.360-0.501

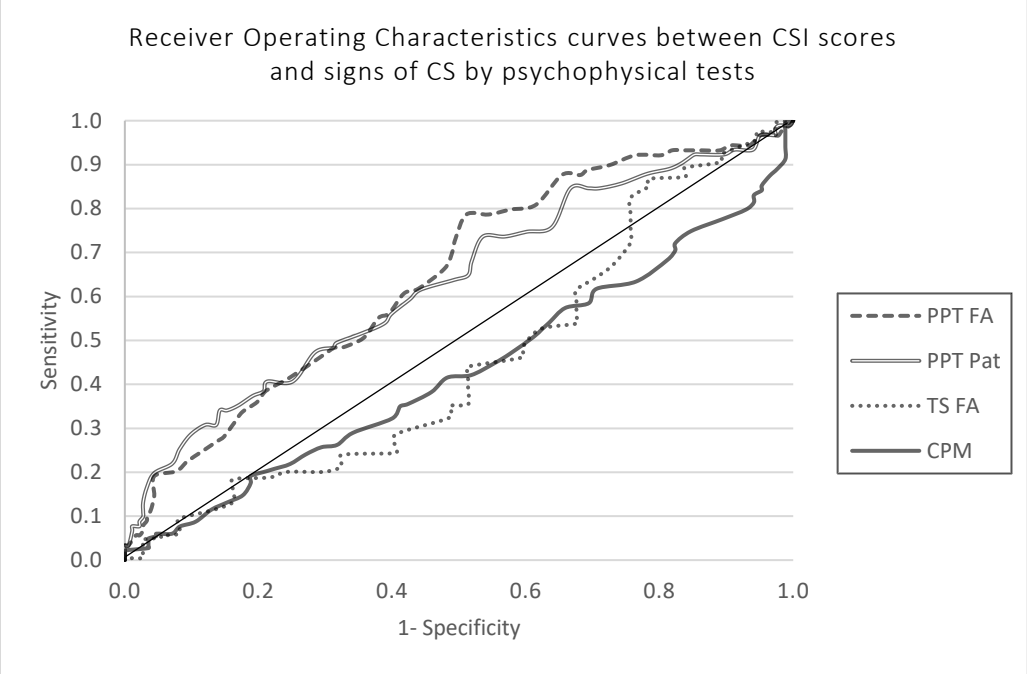

Fig:1 Receiver Operating Curves between CSI Scores and signs of CS measured by psychophysical tests. *PPT FA* pressure pain threshold at the forearm, *PPT PAT* pressure pain threshold at the patella, *TS FA* temporal summation at the forearm, *CPM* conditioned pain modulation.

Table 5: Sensitivity and specificity of versions of CSI and PPT using suggested cut-points

	PPT_FA	
	CS Present	CS Absent
Original CSI ≥23 or RC-CSI ≥25	72 **(80.9%)**	112 (61.5%)
Original CSI <23 or RC-CSI <25	17 (19.1)	70 **(38.5%)**
	PPT_PAT	
Original CSI ≥23 or RC-CSI ≥25	91 **(75.8%)**	117 (63.9%)
Original CSI <23 or RC-CSI <25	22 **(**24.2%)	66 **(36.1%)**

3.5 Discussion:

We found a lack of agreement between the original and Rasch calibrated CSI, as well as the small associations with psychophysical tests in a cohort of patients with KOA. Despite the Rasch analysis of the RC-CSI including pain related variables, our Bland-Altman analysis found that the original CSI and RC-CSI lacked agreement and showed the presence of bias. In considering the impact of the bias within a clinical context, the average discrepancy between the original CSI and RC-CSI was not sufficiently large at just over 3 points. However, the difference increased as the average increased, and the interval of the limits of agreement was quite wide spanning 30 points. This difference becomes concerning given previously established cut scores and subgroup scores to represent the

severity of CS (Neblett et al., 2013b), suggesting that a patient who is subclinical or mild could be misclassified as severe or extreme. Due to the size and unpredictable nature of the bias between measures, our findings therefore suggest that the two measures should not be used interchangeably. These differences could be due to the variations in the rescored items and the associated 'difficulty' level of the items.

Similar to our previous study of the original CSI, we found that both the original and RC-CSI scores had weak but significant correlations with PPT and CPM testing, but not TS. We had hypothesized that by specifically including person factor variables associated with pain in the Rasch version, we would see stronger correlations with psychophysical tests, but this was not the case. Similar findings in different MSK populations have been reported by others including those with nonspecific chronic spinal pain and shoulder pain (Kregel et al., 2018a; Coronado et al., 2018a) No associations with CPM were reported in the former. It is possible that any differences in our findings may be due to different sample sizes and populations, and that variances in correlations may reflect the CSI's lack of ability to identify changes to the nervous system related to CS: accordingly, several studies have reported it to be more strongly correlated with psychological constructs (Coronado et al., 2018b; Gervais-Hupé et al., 2018; Hendriks et al., 2020; Kregel et al., 2018b). Previous studies have shown robust evidence in identifying CS by QST (e.g PPT, TS, CPM) (Eckert et al., 2017; Siao et al., 2003; Zakir et al., 2016). The CSI was created and validated in people with central sensitivity syndrome (Neblett et al., 2013c, 2015) and has been validated with QST in different musculoskeletal conditions (Nishigami et al., 2018; Scerbo et al., 2018). Admittedly there are challenges to validating the CSI and QST against each

other as neither are gold standards for measuring CS. Both measures are based on differing definitions of CS, so it is not surprising that they may measure different aspects of CS. Validating the CSI and QST in this way provides clinicians with important information to consider when conducting a comprehensive assessment of CS, including awareness of each measures limitations.

Our ROC curve analyses indicated poor benchmark and cut-scores that are lower than the recommended threshold of the original CSI (cut point 40) or the corresponding RC-CSI (cut point 31.4). Our results suggest cut scores of 23 for the original CSI and 25 for the RC-CSI which provide identical sensitivity and specificity with PPT testing at the forearm and patella respectively. Our previous findings for the original CSI have similar sensitivity but slightly lower specificity with PPT patella in patients with KOA (Gervais-Hupé et al., 2018). Neblett et al. found high sensitivity (83%) and moderate specificity (55%) when testing the CSI's ability to detect central sensitivity syndrome (Neblett et al., 2015). These findings in combination with those of the Bland Altman analysis, lead us to conclude that there is no added benefit to using the RC-CSI. We therefore recommend that clinicians continue to use the original version of the CSI as part of a comprehensive toolkit to identify the multifaceted nature of CS.

The main strengths of this study are its assessment and consideration of the value of a Rasch calibrated version of the CSI compared to the original version in people with KOA. Our results further inform clinical practice by suggesting that the original version is preferable to use over the RC-CSI, however clinicians should be aware of the potential for false positives when using it which could lead to overtreatment and medicalization of

patients. Limitations of this work include the sample recruited from orthopaedic practices in a single city in Canada which restricts the generalizability of study findings. Typically, Rasch analysis leads to improved measures with increased precision for statistical calculations: but the low level of CS in the overall sample may have led to over-adjustment to impose the expected Guttman pattern due to a lack of variability across participants responses. The resultant lack of discrimination for cross-sectional screening of the Rasch version should not be interpreted to infer that interval level scaling is not important for evaluation over time. However, our results should be validated in an external cohort of patients with KOA.

3.6 Conclusion:

In conclusion, the original CSI should continue to be used with individual clients as our preliminary findings suggest that there is no added benefit to using the RC-CSI. Other studies are needed to confirm our findings in people with KOA. As this is the first comparison of the CSI and RC-CSI, future studies should examine their agreement and validity in external cohorts including the appropriateness of the lower cut score at identifying CS in people with KOA. This will help to minimize false positives to assure that patients with CS are provided with the most appropriate and effective treatment.

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Appendix A:

Fig 1- Scatter plot of mean CSI and RC-CSI

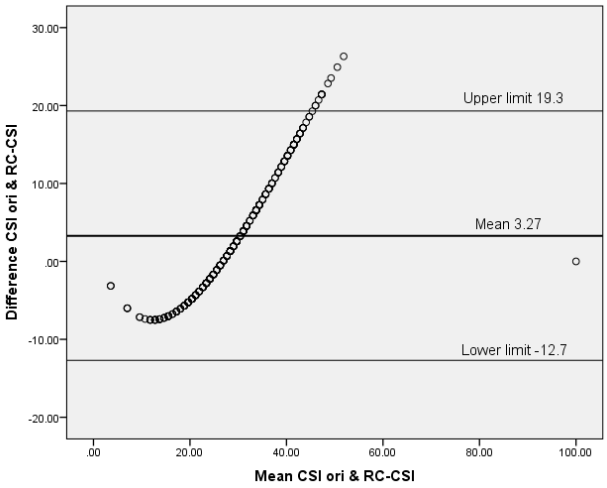
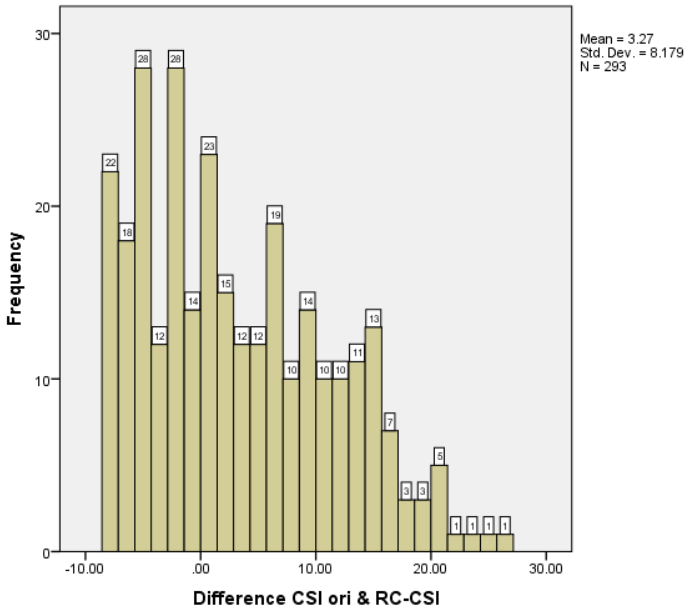


Fig 2- Histogram of mean CSI and RC-CSI



CHAPTER 4: DISCUSSION OF THESIS

The aim of this thesis was to validate the CSI in patients with KOA. Firstly, we used Rasch analysis to validate the CSI in people with KOA (chapter 2). Next using the Rasch analyzed version (RC-CSI), we compared it with the original version of the CSI and validated them both with psychophysical tests with same population (chapter 3). Our findings were illustrated in two manuscripts (Chapters 2 and 3).

In summary, our results suggest that CSI was able to fit Rasch model. After iterative analysis, we found the RC-CSI to be a singular construct with acceptable unidimensionality while retaining all the items. Moreover, we generated a new RC-CSI cut score of 31.37 that we used to compare with original cut score 40 in the second study. Our findings suggested a lack of agreement demonstrating small bias between two versions of the CSI. Finally, the RC-CSI showed little improved clinical value over the original CSI while exploring the association with psychophysical tests.

4.1 Summary of Chapter 2 (study 1)

The first study on the validity of the CSI through Rasch analysis in patients with KOA provided preliminary evidence suggesting that RC-CSI is a reliable tool in identifying CS in patient with KOA. We analyzed CSI responses using the Rasch model as it is a proven alternative framework to assess the accuracy and reliability of self-reported measures (Tennant et al., 2011). The literature has consistently reported that CS is a clinical feature of patients with KOA (Lluch et al., 2018) and that the CSI is a proven self-reported tool to measure it, however people with KOA were not part of the sample when the tool was developed (Mayer et al., 2012). In our study, the participating samples were experiencing KOA-related pain and were able to respond 25 questions of CSI. We also collected the

responses of other self-reported measures (i.e. NPRS, PCS) and psychophysical testing (i.e. PPT, TS) having a known association with pain in people with KOA to validate the CSI. Our findings suggested a lower average score than the recommended cut-score indicating a lower prevalence of CS in patients with KOA (Mayer et al., 2012). Other studies have reported a similar pattern of a low average score of the CSI (Gervais-Hupé et al., 2018; Zafereo et al., 2021).

Our study was the first study to conduct Rasch analysis in patients with KOA. Though the CSI was not initially able to fit in the Rasch model, we followed the iterative analysis plan. We found 11 items which displayed a disordered threshold, and we chose to rescore rather than reduce items. Other Rasch studies of people with chronic musculoskeletal pain have removed CSI items (Nishigami et al., 2018) . After reanalysis, we found the model misfit persisted. We then developed a subtest to address the local dependency of 6 items and finally achieved model fit. Therefore, we found RC-CSI could be used as a singular construct with acceptable unidimensionality in patients with KOA. We also found good reliability for the RC-CSI after sub-testing which was supported by other studies (Mayer et al., 2012; Nishigami et al., 2018).

Among all the 25 Items of CSI, we found two items, item 21- frequent urination and item 14-skin problems showed a pattern of uniform differential item functioning by age and sex respectively. Our findings suggested that younger patients answered item 21 differently than the older patients with KOA. Also, males and females with similar amounts of CS scored differently on item 14. Although, we found previous concordant supportive evidence for item 21 (Batmani et al., 2021; Potts & Payne, 2018) we are unaware of any

studies exploring sex differences in perceptions of skin issues. We can hypothesize that women may report skin concerns more frequently than men.

Moreover, this study adds that sex difference influences CSI scores. This is consistent with another study in people with musculoskeletal pain where patients showed differences in CSI cut scores by sex (Roldan-Jimenez et al., 2020). It is well accepted that females have an increased risk and prevalence of chronic pain (Emily et al., 2013; Smith et al., 2019). Bartley et al. have found that women exhibited greater pain sensitivity compared to men in people with symptomatic KOA (Emily et al., 2016). Collectively, this suggests that sex needs to be specifically considered when examining CS in KOA patients and all hypotheses should be assessed separately in both sexes to confirm that conclusions made are appropriate across sexes. Moreover, these requirements propose the need for a larger sample and prespecified sex analyses.

Lastly, we generated a new RC-CSI cut score from the original version of the CSI. We hypothesized that the new version can be used as an alternative to the original version. Thus, we planned for a second study (Chapter 3) to discern the agreement between the two versions and check the validity with other psychophysical tests.

4.2 Summary of Chapter 3 (study 2)

The final study of the thesis indicated a lack of agreement and a small amount of bias between the original CSI and RC-CSI. In addition, the bias and the difference between the two versions increased as the average increased, thereby suggesting that these two measures should not be used interchangeably in people with KOA.

Similar to a previous study (Gervais-Hupé et al., 2018), we found analogous results when we sought to evaluate the association of the original and RC-CSI scores with QST. We found weak significant correlations with PPT and CPM in people with KOA, which align with weak correlations found by studies of the CSI with QST in other MSK populations (Coronado & George, 2018; Hendriks et al., 2020). Our ROC curve analysis indicated that to detect sensitization based on QST findings, lower cut scores for the original and RC-CSI should be used. However these alternative cut scores resulted in good sensitivity, but relatively lower specificity with PPT testing at the forearm and patella respectively which is concordant with previous studies (Gervais-Hupé et al., 2018; Neblett et al., 2015). In brief, the cumulative results demonstrate little benefit of using the RC-CSI over the CSI in the clinical setting to identify CS in KOA patients.

4.3 List of Key Findings

The overarching goal of this thesis work was to explore the validity of the CSI in patients with KOA. We chose Rasch Analysis as it allows investigators to use a patient's raw test scores and articulate their performance with unequal difficulties throughout all test items (Boone, 2016). After a heuristic analysis process, the CSI was able to fit the Rasch model as a singular construct for patients with KOA. Moreover, we found only two items (item 21 and 14) with uniform differential item functioning by age and sex respectively. Rasch analysis enabled us to generate the RC-CSI version with a new cut-score and prompted us to make hypotheses for a second study. Following that we explored the agreement between the original CSI and the RC- CSI, to ultimately determine whether it was advantageous for clinicians to use the RC- CS version compared to the original to identify CS in patients

with KOA. Our analysis lead us to conclude that there is no additional benefit to use the RC-CSI in a clinical setting.

In summary, the initial study suggested a new version of the CSI with a lower cut score while the final study found no added benefit of using the new version in the clinical setting for the patients with KOA.

4.4 Limitations

The limitations of each study are described within each of the chapters (2 and 3). This section highlights some methodological considerations for interpreting the validity and generalizability of the dissertation as a whole. The main limitation of this study was the relatively small sample size for both studies, which was close to 300. A larger sample might add value by generating more responses on the CSI from people with KOA who are experiencing CS. Moreover, the samples were collected from a single city in Canada which restricts the generalizability of the study findings. It is a known fact that different races are considered to be risk modifiers in people with KOA (Chia et al., 2016; Johnson et al., 2021; Mat et al., 2019). Our study was unable to investigate the results of the CSI in different races as the majority of our sample was Caucasian.

Another limitation of this study was that we didn't collect the duration of patient's KOA or their pain. Literature suggested that higher CSI scores were associated with a longer duration of pain (Knezevic et al., 2018). If we collected the responses of different duration of pain in people with KOA, we might be able to validate the CSI scores for different stages of pain. Then we could possibly find an explanation for the extreme scores.

4.5 Knowledge Translation Recommendations

The studies summarized from this thesis add to the expanding literature on the use and validity of the CSI in people with KOA. This is an important knowledge building block in order to construct a foundation for improved insights into this population given that they were not included in the construction of the measure. It is the first study to our knowledge to perform a Rasch analysis of the CSI in people with KOA, modeling with pain-related variables known to have associations with CS. This study created the foundation for future studies to examine its use before clinical uptake. However, our second study found no added benefit to using the RC-CSI over the original CSI in this population. Further studies are needed to confirm our findings in people with KOA. Given that there is no gold standard for detecting CS in humans, our results support using the CSI as part of a comprehensive clinician toolkit to capture the spectrum of signs and symptoms associated with CS. As laboratory-based investigations are costly and require more time and training, it is challenging for clinicians to use them in the identification of CS (Zakir et al., 2016). Therefore, clinical descriptors of the pain experience may aid in identifying CS pain in patients with knee osteoarthritis (Lluch et al., 2018). During the subjective assessment, clinicians should consider data regarding the following pain-related factors: pain intensity, distribution, behavior, presence of neuropathic-like or centrally mediated symptoms, psychosocial factors and responsiveness to previous treatment (Lluch et al., 2018). Moreover, clinicians should also consider patient's response to clinical tests, the presence of widespread hyperalgesia, allodynia, hypoesthesia, reduced vibration sense and dynamic measures (e.g. temporal summation, conditioned pain modulation) of central sensitization

during physical examination in identifying CS (Lluch et al., 2018). Clinicians can use the above information in combination with the original CSI cut score to inform the presence/absence of CS in each patient, therefore, bridging the gap between research findings and clinical practice in identifying CS in KOA.

4.6 Conclusion

In summary, this dissertation offers initial research to explore the validity of the CSI in people with KOA experiencing CS-related symptoms. This dissertation research captures the importance of conducting Rasch analysis and its further implication in generating a new score. The first study established robust evidence by identifying the CSI model fit and a new RC-CSI score through Rasch analysis. While the second study suggested little importance of this RC-CSI over the original version of CSI with similar samples. Both studies suggested future research on a larger scale to explore the agreement and validity of both versions of CSI in an external KOA cohort thus expanding the opportunity to use CSI more effectively in the clinical setting.

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