An Epidemiologic Study of Lower Urinary Tract Symptoms and Central Sensitization in Men: Investigations of a Mechanistic Hypothesis

By

Angela Senders, ND, MCR

A dissertation presented to the

Oregon Health & Science University-Portland State University School of Public Health

in partial fulfillment of the requirements for the degree of:

Doctor of Philosophy in Epidemiology

School of Public Health

Oregon Health & Science University – Portland State University

---

CERTIFICATE OF APPROVAL

This is to certify that the PhD dissertation of

Angela J. Senders, ND, MCR

has been approved.

Committee Chair: Lynn M. Marshall, ScD

Committee Member: Scott R. Bauer, MD

Committee Member: Barry Oken, MD, PhD

Committee Member: Yiyi Chen, PhD

Acknowledgments

This work would not have been possible without the support and guidance from several important individuals. I extend the deepest gratitude to each of them, including my primary academic mentor and dissertation committee chair, Dr. Lynn Marshall, who has spent countless hours over many years training me to be a thoughtful and precise epidemiologist; my dissertation committee, Drs. Scott Bauer, Yiyi Chen, and Barry Oken, who graciously volunteered their time to share their expertise and guide me in this work; Dr. Jonathan Snowden who invited me to return to office hours week after week and whose passion for this work is a continued inspiration to me; Dr. Willi Horner-Johnson who funded part of my studies and whose mentorship forever shifted my world view of disability and health; and the dedicated faculty and staff in the School of Public Health. I am also eternally grateful for the friendships forged by this program, including my Epi Girl Gang of Otters who are always available with encouragement, reassurance, advice, and epidemiologic brilliance and Menolly Kaufman who has provided never-ending support from our qualifying exam to the finish line. Finally, my husband and family who never once questioned or complained about the extraordinary amount of time I chose to spend on this pursuit. Thank you for standing by me.

Abstract

Approximately 20% of adults worldwide experience lower urinary tract symptoms (LUTS). The prevalence of LUTS increases with age, and in the US, over a quarter of adults older than 50 years of age are affected. Increasingly severe LUTS are associated with decreased physical and mental quality of life, stigma and psychological distress, and falls among older adults. As the US population ages, 42 million US adults are projected to have LUTS by 2025. Current LUTS treatments target the lower urinary tract yet are limited by modest efficacy, and a substantial proportion of individuals with LUTS do not respond to these interventions. This variable response to conventional treatment suggests that non-urologic factors may be an important underlying mechanism in some LUT cases. If true, these individuals will require an alternative approach to care.

Central sensitization (CS) has been proposed as a non-urologic mechanism of LUTS. CS is generally accepted as an underlying mechanism in painful urologic conditions such as interstitial cystitis/bladder pain syndrome, chronic pelvic pain, and prostatitis. However, it is unknown whether CS is associated with non-painful LUTS. Emerging evidence supports an association between CS and non-painful LUTS, although the majority of studies have been conducted among small clinical samples of women with overactive bladder. Whether the findings from these studies apply to men or to other LUTS etiologies is unclear. Therefore, we undertook three research aims to investigate CS as a possible mechanism of non-painful LUTS in men.

In Aim 1, we used musculoskeletal pain as symptom suggestive of CS to determine whether the prevalence of musculoskeletal pain was greater among men with LUTS compared to men without LUTS. Using data from a large US cohort of older, community-dwelling men, we observed that musculoskeletal pain, especially at multiple locations, is associated with greater LUTS severity. In Aim 2, we again used musculoskeletal pain as a proxy measure of CS and asked whether musculoskeletal pain increases the risk for LUTS progression. Using prospectively collected data from the same large cohort of community-dwelling men, we found that the presence of musculoskeletal pain and the extent to which it interferes with daily activities is associated with worsening LUTS. Finally, in Aim 3, we administered a validated self-report measure of CS-related symptoms to men with a recent history of urodynamic study for LUTS. We observed a strong positive association between symptoms suggestive of CS and LUTS severity, irrespective of LUTS etiology.

This dissertation presents some of the first studies to investigate CS as a possible mechanism of LUTS in men. We observed that symptoms suggestive of CS are positively associated with increasingly severe LUTS and increase the risk of worsening LUTS over time. Our work expands the current literature base of CS-LUTS investigations to include understudied populations: non-painful LUTS and LUTS etiologies other than over active bladder. Our findings support the hypothesis that CS may represent a novel and currently untargeted mechanism of LUTS, and suggest that future investigations of CS and LUTS should include men with non-painful LUTS and a range of LUTS pathologies.

Table of Contents

List of Tables

Chapter 2

Chapter 3

Chapter 4

Chapter 5

List of Figures

List of Abbreviations

AUA-SI	American Urologic Association Symptom Index
BPH	Benign prostatic hyperplasia
BMI	Body mass index
BOO	Bladder outlet obstruction
BPS	Bladder pain syndrome
CI	Confidence interval
CS	Central sensitization
CSI	Central Sensitization Inventory
IBS	Irritable bowel syndrome
I-PSS	International Prostate Symptoms Score
LUT	Lower urinary tract
LUTS	Lower urinary tract symptoms
MrOS	The Osteoporotic Fractures in Men (MrOS) Study
OAB	Overactive bladder
OR	Odds ratio
QST	Quantitative sensory testing
SD	Standard deviation
UDS	Urodynamic study

Chapter 1. Introduction and Research Aims

Approximately 20% of adults worldwide experience moderate to severe lower urinary tract symptoms (LUTS).[1–3] LUTS are a constellation of symptoms that make it challenging to void or difficult to store urine, including straining, incomplete emptying, frequency, urgency, and incontinence.[4] Increasingly severe LUTS are associated with decreased quality of life, and the stigma associated with urinary symptoms often leads to negative self-image and psychological distress.[5–9] By 2025, 42 million US adults are projected to have LUTS.[9] Despite their health impact, the pathophysiological mechanisms underlying LUTS remain poorly understood. As a result, it is not uncommon for LUTS cases to be deemed idiopathic, with no identifiable cause. Thus, urologic experts have called for an expansion of LUTS research to determine the biologic, behavioral, neurologic, and psychosocial factors that may contribute to LUTS etiology.[10]

One pathway ripe for examination pertains to a neurological phenomenon called central sensitization (CS). CS occurs when the nervous system's threshold for responding to sensory stimuli is lowered. Under acute stress or heightened arousal, CS is a temporary and adaptive phenomenon.[11] For example, when faced with repeated or intense noxious stimuli, the nervous system can amplify pain signals to generate a reflex withdrawal from the stimulus and engage behaviors to avoid potential harm. In the absence of harm, the system will return to baseline sensitivity over time.[12,13] However, several situations can lead to persistent CS in the absence of harm or tissue damage. Under these circumstances, hypersensitivity to sensory signals continues but is no

longer protective. In this way, CS is considered one of the mechanisms by which acute sensations become chronic, thereby promoting and maintaining a variety of symptoms in the absence of the original trigger.

Recently, CS has been proposed as a mechanism of idiopathic LUTS.[14] While CS is most often conceptualized as disordered pain processing, it can also cause the intensification of non-painful sensory stimuli such as light, odor, and sound.[15] Thus, it has been suggested that CS may amplify bladder sensations such as stretch, warmth, and pressure such that they result in common LUTS, including urgency, frequency, and nocturia. Emerging evidence supports this hypothesis, yet most studies have been conducted in small clinical samples of women.[16–18] There is a paucity of epidemiologic information on this potential mechanistic pathway in men.

The overarching objective of this dissertation research was to investigate CS as a possible mechanism of LUTS in men. An appropriate first step in this line of inquiry is to measure the association between CS and LUTS in men. Therefore, we conducted an epidemiologic investigation using two data sources, a national prospective cohort of community-dwelling men (The Osteoporotic Fractures in Men (MrOS) study) and primary data collected in a clinical urologic setting. To investigate the association between CS and LUTS, we completed the following aims:

Aim 1 (Chapter 3). **Determine the extent to which the prevalence of musculoskeletal pain is greater among community-dwelling older men with LUTS compared to men**

without LUTS. Using baseline data from the MrOS study, we used musculoskeletal pain as a proxy measure of CS. We hypothesized that the prevalence of musculoskeletal pain at any of four locations (back, neck, hip, or knee; yes/no) within 12 months prior to baseline would be significantly higher among men with LUTS compared to those without.

Aim 2 (Chapter 4). Determine whether musculoskeletal pain is positively associated with the progression of LUTS severity. Using prospectively collected data from the MrOS study, we again used musculoskeletal pain as a proxy measure of CS. We hypothesized that men who reported baseline musculoskeletal pain at any of four locations (back, neck, hip, or knee; yes/no) would be more likely to experience worsening LUTS over a 2- and 4-year follow-up period compared to men without pain.

Aim 3 (Chapter 5). Assess the association between symptoms suggestive of central sensitization and LUTS severity in a clinical sample of men. Using a validated self-report measure of symptoms commonly experienced by people of CS, we hypothesized that symptoms suggestive of CS would be positively associated with LUTS severity, independent of LUTS etiology or lower urinary tract (LUT)/pelvic pain.

Chapter 2: Review of the Literature

2.1 LUTS: Epidemiology

2.1.a Measurement

Lower urinary tract symptoms are typically measured with self-report surveys. The most widely used surveys in clinical practice and epidemiologic studies are the American Urological Symptom Index and the International Prostate Symptom Score.

American Urological Association Symptoms Index (AUA-SI)

The AUA-SI is the most widely used measure of male LUTS in clinical care and research worldwide.[19] It is a validated, 8-item Likert-type questionnaire of symptom frequency and bother. Three items pertain to storage symptoms (urgency, frequency, nocturia), three items pertain to voiding symptoms (straining, weak stream, intermittency), one item asks about post-micturition (incomplete emptying), and one item measures LUTS-related quality of life (*How would you feel if you had to live with your urinary condition the way it is now, no better, no worse, for the rest of your life?*). The seven symptom-related items are summed for a total score (range 0-35 points). Scores 0-7 points are typically categorized as mild symptoms, 8-19 points as moderate symptoms, and scores 20-35 points as severe LUTS. The AUA-SI has demonstrated good internal consistency (Cronbach's alpha = 0.86) and test-retest reliability (r = 0.92).[19]

International Prostate Symptoms Score (I-PSS)

The I-PSS and the AUA-SI are nearly identical questionnaires. The World Health Organization and the International Scientific Committee used the first seven items of the AUA-SI to create the I-PSS. The wording of eighth item about quality of life was slightly modified from that of the AUA-SI to read: *If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?* The scoring system is the same for both instruments and they are considered interchangeable. The I-PSS has been translated and validated for use in many languages, including Danish, Dutch, Flemish, French, German, Italian, Norwegian, Spanish, Swedish, Korean, Thai, and Mandarin.[20–22]

2.1.b Case Definition

LUTS are common, and having a few symptoms (e.g. nocturia 1-2 times a night) may not be bothersome to some individuals. Thus, a score of ≥ 8 points on the AUA-SI (moderate to severe symptoms) is the generally accepted definition of LUTS in clinical and epidemiologic studies. A 3-4 point change on the AUA-SI is generally accepted as a clinically relevant change in LUTS.[23,24] Urinary bother due to LUTS is measured by the one quality of life item on the AUA-SI: *How would you feel if you had to live with your urinary condition the way it is now, no better, no worse, for the rest of your life?* The 7-point Likert-scale item responses range from delighted (0) to terrible (6) and are often categorized as satisfied (0, 1, 2), mixed (3), or unsatisfied (4, 5, 6). Clinically relevant urinary bother is often defined as a score of > 3.[25]

2.1.c Prevalence

Worldwide, approximately 20% of adults experience moderate to severe lower urinary tract symptoms (Table 2.1). In the US, the estimated prevalence of moderate to severe LUTS is similar among US men and women (18.7% and 18.6%, respectively), and across racial/ethnic groups (White 18.9%, Black 19.3%, and Hispanic 16.2%).[1] The prevalence of urinary symptoms increases with age, and LUTS are associated with injuries that drive disability and death among older adults (e.g. falls).[26–28] By 2025, 42 million US adults are projected to have moderate to severe LUTS.[9]

Table 2.1. Prevalence estimates of lower urinary tract symptoms (LUTS) from population-based studies around the world.

COUNTRY	N	AGE RANGE (years)	LUTS DEFINED AS	MEN	WOMEN
Denmark[29]	5,379	≥50	≥ 8 AUA-SI	28.0	20.0
United States[1]	5,506	≥30	≥ 8 AUA-SI	18.7	18.6
Norway[30]	21,694	≥20	≥ 8 AUA-SI	15.8	-
Sweden[3]	39,928	45-79	≥ 8 AUA-SI	18.5	-
France[2]	1,829	40-79	≥ 8 AUA-SI	16.1	11.0
Netherlands[2]	2,299	40-79	≥ 8 AUA-SI	17.3	15.0
United Kingdom[2]	1,891	40-79	≥ 8 AUA-SI	20.0	19.5
South Korea[2]	2,720	40-79	≥ 8 AUA-SI	12.5	16.6

2.2 LUTS: Clinical Perspective

2.2.a The Micturition Response

Both somatic and autonomic nervous systems are involved in bladder control. As part of the autonomic system, one of the primary functions of sensory receptors located in the bladder is to manage bladder fullness. The detrusor, smooth muscle that makes up the bladder wall, must be relaxed in order to expand and hold urine. As the bladder fills, sensory receptors in the detrusor respond to stretch and convey a sense of bladder fullness to the central nervous system (CNS).[14] Specifically, sensory information is relayed from the bladder to the Barrington's nucleus, a cluster of neurons in the brain stem responsible for managing the micturition reflex.[31] When sensory information from the periphery reaches the Barrington's nucleus, neurons release corticotropin releasing factor into the locus coeruleus, a part of the brain responsible for attention, arousal, and stress.[32] The result is increased arousal and enhanced attention to both bladder stimuli and the environment.

Some Barrington's neurons descend and synapse with bladder motor neurons in the sacral spinal cord which subsequently innervate the bladder wall. Stimulation of the Barrington's nucleus neurons in this direction results in detrusor muscle contraction and micturition. This bidirectional pathway allows for the Barrington's nucleus to regulate both bladder tone and one's response to stimuli, coordinating micturition and voiding behaviors.[33] One must decide "Do I need to urinate?" and if so engage in a variety of actions that move toward that activity without voiding until appropriately situated.

2.2.b Medical Management

While a score of ≥ 8 points on the AUA-SI is considered clinically relevant LUTS in research studies, the amount of bother that an individual experiences as a result of their symptoms typically drives medical management. Thus, the bother question on the AUA-SI can be a useful tool to guide conversations about treatment.[34] LUTS that cause little to no bother are often managed with patient education, lifestyle changes (e.g. alteration in type, timing, and volume of fluid intake), and watchful waiting.[35] Bothersome LUTS are treated with first-line medical interventions, and individuals who do not improve are typically referred for additional testing to inform second-line or surgical interventions.[36] The majority of current pharmacological therapies target the prostate or bladder and are limited by side effects, inconsistent outcomes, and the need for ongoing treatment.[10,37] The long-term use of LUTS medications can be costly over time, and medications may interact with other drugs, a concern in aging populations where polypharmacy is common.

The most widely prescribed class of medication for LUTS is an α-adrenergic receptor antagonist, followed by a 5α-reductase inhibitor.[38] α-adrenergic receptor antagonists, also known as alpha-blockers, work by relaxing smooth muscle in the prostate and the bladder neck; 5α-reductase inhibitors prevent the conversion of testosterone to dihydrotestosterone, reducing prostate size over time. The effectiveness of these pharmaceutical interventions for LUTS is variable. In a one-year observation of 2,351

European men who newly-presented to primary care with LUTS suggestive of BPH, at least 25% of men prescribed an α-adrenergic receptor antagonist or 5α--reductase inhibitor did not experience a clinically relevant improvement of symptoms.[39] In a cohort of US men with LUTS followed for a median 13.7 years, some men were treated with an α-adrenergic receptor antagonist (n=155) or 5α-reductase inhibitor (n=92) *after* a median of 8.2 years of observation.[40] Before the pharmaceutical intervention, median symptom scores increased (worsened) over time. After the intervention, median symptom scores stabilized for a period and then continued to rise, albeit more gradually than before treatment. The variable response to prostate-centric treatment suggests that, for some men, LUTS may be a manifestation of non-prostatic causes that require a different approach to care.

2.2.c Progression

A substantial number of people do not respond to pharmacologic treatment and LUTS often worsen over time.[39,41,42] Among 1,740 US community-dwelling men initially free from LUTS/BPH treatment and followed for a mean (sd) 6.9 (0.4) years, 73% experienced a stable symptom severity profile, whereas 20% of men experienced progression, 6% remittance of symptoms, and 1% had a mixed symptom pattern (worsening followed by improvement).[41] Similarly, in a prospective study of 5,634 German men with untreated LUTS, 80% reported similar symptom severity scores after

four-years of follow-up, whereas 16% had worsened and 3.6% reported symptom improvement.[43] Frequencies remained similar when an additional 2,187 men treated with medication or surgery were included in the analyses: 77% remained stable, 17% worsened, and 6.1% improved. Identifying causes of LUTS progression and non-response to therapy is essential to inform new therapeutic targets.

2.3 Central Sensitization: Clinical Presentation

As previously described, central sensitization is an increased responsiveness of central nervous system neurons to afferent sensory stimuli. Several conditions exhibit features of CS, including fibromyalgia, irritable bowel syndrome, endometriosis, migraines, and painful urinary conditions such as interstitial cystitis/bladder pain syndrome, chronic pelvic pain, and prostatitis.[44,45] People with these conditions often experience high levels of distress about their health, as well as overlapping symptom profiles, including pain (e.g. during sex, intercourse, or urination), gastrointestinal complaints (nausea, bloating, constipation), sexual or reproductive symptoms (painful or irregular menses, premature ejaculation), or neurological deficits (difficulty swallowing, lump in throat, urinary retention).[46] A hallmark of these symptoms is that they often present in the absence of any detectable organic cause. LUTS often co-occur with CS-related conditions and a subset of LUTS cases also present in the absence of organic pathology. Whether CS is a contributing mechanism to these cases is unknown.

2.3.a Possible Pathways Linking CS and LUTS

There are several ways in which CS could cause LUTS. First, repeated, noxious sensory stimuli and/or tissue damage can result in a sensory processing system that "gets stuck" in a state of elevated reactivity.[14,47] In the urinary tract, ongoing changes in local pH, mechanical or chemical trauma, and repeated infections can compromise urothelial tissues.[48] It is hypothesized that these insults could cause CS, resulting in chronic abnormalities in lower urinary tract sensation and function.[48]

A second way in which CS could result in LUTS is through pelvic organ crosstalk. There is considerable overlap in the neurological pathways that transmit sensory information from the pelvic organs to the CNS. Pain can be enhanced between any two organs in which sensory projections innervate the spinal cord at a common location.[49] For example, both bladder and bowel sensory neurons converge in similar thoracic and sacral regions of the spinal cord and it is suspected that pelvic organ crosstalk may explain the well-established co-occurrence of IBS and urinary symptoms.[50–53] Bladder-bowel crosstalk has been induced in animal studies and is also observed clinically. For example, constipation can impair bladder emptying and increase the severity of LUTS, and rectal distention can cause changes in bladder capacity, sensation, and activity.[14]

Finally, adverse early life experiences may predispose individuals to CS and LUTS in later life. A wide body of literature demonstrates that the chronic increase in physiologic arousal required to manage early life adversity can lead to long-lasting changes in neural, endocrine, immune, and metabolic physiology.[54] For example, a threatening

external environment causes a sympathetic stress response that can also influence how safe one perceives their internal environment to be. In this way, early life adversity may influence whether signals that originate within the body can be trusted or are cause for worry. Continued worry about one's own bodily integrity will maintain a general perception of threat that can amplify the processing of sensory-related information, resulting in CS.[55–57] Recent findings support an association between adverse early life events and CS, chronic conditions that exhibit features of CS,[58] and LUTS later in life.[59,60]

2.3.b Measurement

Because CS is a function of neuronal activity it can be difficult to detect and quantify. There are three general ways in which CS, or features of CS, are measured.

Quantitative Sensory Testing

The first method used to detect CS is a laboratory technique called quantitative sensory testing (QST).[61] During QST, laboratory participants receive a quantifiable physical stimulus (e.g. heat, pressure, electric shock) and their perceptual response (e.g. subjective report of pain, neural response on electroencephalogram) is measured. QST is used to assess the nervous system's ability to both enhance and mitigate the perception of pain.

In response to a repetitive painful stimulus, the nervous system can mitigate the perception of pain and pain-related reactions through a process called pain

habituation.[62] Conversely, with repeated or constant noxious stimuli the nervous system has the capacity to increase the perception of pain through a process called temporal summation. Both pain habituation and temporal summation can be elicited by differentiating the strength, frequency, and timing of a repeated stimulus during QST. Compared to healthy controls, people with CS-related conditions like fibromyalgia, temporomandibular joint disorder, and migraines often demonstrate decreased pain habituation and heightened temporal summation on QST.[63]

Co-occurrence of Symptoms/Conditions with a Known CS *Component*

A second method often used to detect the possible presence of CS involves identifying a co-occurrence of the condition of interest with other symptoms/conditions that have a known CS component.[47] Several conditions that demonstrate features of CS on QST frequently co-occur with one another, including fibromyalgia, irritable bowel, migraines, chronic fatigue, chronic musculoskeletal pain, and other pain syndromes.[64]

Central Sensitization Inventory (CSI)

The CSI is a validated 25-item Likert-type questionnaire that quantifies subjective experiences commonly reported among people with CS.[44] Respondents indicate their level of agreement with statements such as “I feel pain all over my body”, “I do not sleep well”, “I have difficulty concentrating”, and “I am sensitive to bright lights”. Items are summed for an overall score (range 0-100). The questionnaire was developed based

on the lived experience of people with chronic pain, QST was not used in questionnaire development or initial validation.

A CSI score of ≥ 40 is often used in research investigations to identify individuals with an increased likelihood of underlying CS.[65] This cut point was derived from a study of patients from a multidisciplinary pain clinic with at least one functional diagnosis indicative of CS (n=89) and a non-clinical sample of undergraduate students (n=129). A CSI cut score of 40 distinguished chronic pain patients from graduate students with a sensitivity of 81% and specificity of 75%.[66]

Few studies have assessed the association between CSI scores and the presence of CS determined by QST. In a sample of people with knee osteoarthritis (n=129), the sensitivity and specificity of the CSI to correctly identify those with CS diagnosed by validated laboratory measures was 75% and 63.4%, respectively, with an optimal cut point of 36.[67] Authors observed that the CSI was more strongly associated with psychological factors (e.g. anxiety and depressive symptoms ($r=0.58$, $p<0.005$) and pain catastrophizing ($r=0.30$, $p<0.005$) than QST findings. They concluded that among people with knee osteoarthritis pain, the CSI is better at identifying psychological symptoms associated with CS rather than physical nervous system adaptations. In a mixed clinical sample of people with and without chronic pain conditions (n=77), Caumo et al. observed an association between CSI scores and QST. Patients who were able to modulate their pain response on QST had significantly lower mean CSI scores compared to patients who were unable to modulate their pain response. In contrast, Mibu et al.

did not observe any correlation between CSI scores and objective QST measures among individuals with chronic low back pain (n=104) or knee osteoarthritis (n=50).[68] Similarly, among patients with shoulder pain (n=78), CSI scores were not correlated with QST findings.[65] The inconsistent association between CSI scores and QST findings may be a result of vast differences in QST methods, as well as variable clinical samples across studies.

2.3.c Evidence of an Association between CS and LUTS

There is literature to suggest that non-painful LUTS co-occur with conditions that have a known CS component. The co-occurrence of IBS and urinary symptoms is well established.[50–53] More recently, evidence of co-occurring LUTS with back pain,[69,70] fibromyalgia,[18,71,72] chronic fatigue,[71] and migraine[18,73] has emerged, suggesting that CS may be a possible common underlying pathway among these conditions. Much of the co-occurrence literature stems from small, cross-sectional surveys administered to women in a clinical setting. Men are underrepresented in these investigations. Moreover, those who seek healthcare may not be representative of all community-dwelling adults, and investigations in non-clinical samples, such as community-dwelling older adults, are needed.

CS is accepted by many as an underlying mechanism of *painful* urinary conditions (distinct from LUTS, which are not considered painful). To date, the majority of QST has been conducted in people with interstitial cystitis/bladder pain syndrome and chronic

pelvic pain. Compared to controls, individuals with painful urinary conditions exhibit decreased pain tolerance to mechanical and thermal stimuli,[74–76] diminished habituation to repetitive noxious stimuli,[77] hyperalgesia to bladder filling,[77] and hypersensitivity to auditory stimuli.[78]

We are aware of three studies that used QST to investigate the presence of CS in individuals with overactive bladder (OAB), a condition that is not generally associated with urologic pain. Two of these studies provided evidence in support of a CS-OAB association. First, women with OAB (n=20) exhibited stronger temporal summation to thermal stimuli applied to the forearm compared to healthy controls (n=23).[16] Second, women with OAB who were refractory to treatment and presented to clinic for third-line interventions (botulinum toxin bladder injection or sacral neuromodulation (n=39)) had stronger temporal summation to thermal stimuli applied to the forearm compared to women with OAB who were not seeking third-line interventions (n=55).[79] In contrast, a third study recently reported that, despite 191 participants with OAB scoring significantly higher than 106 non-OAB controls on a number of self-report symptoms associated with CS, investigators observed no difference in temporal summation to thumbnail pressure between the two groups.[80]

To our knowledge, the CSI has only been used in one study of lower urinary tract symptoms. In 177 women with chronic pelvic pain, higher CSI scores were significantly associated with more severe LUTS.[81] We are not aware of any studies that have administered the CSI to men or to people with non-painful LUTS.

Chapter 3. Lower urinary tract symptoms are associated with musculoskeletal pain among older men: Preliminary evidence for central sensitization as a mechanism?

Angela Senders, Scott R Bauer, Yiyi Chen, Barry Oken, Howard A Fink, Nancy E Lane, Kamran P Sajadi, Lynn M Marshall for the Osteoporotic Fractures in Men (MrOS) Study Group.

This work has previously been published:

Citation: Senders A, Bauer SR, Chen Y, Oken B, Fink HA, Lane NE, Sajadi KP, Marshal LM for the Osteoporotic Fractures in Men Study. Lower urinary tract symptoms are associated with musculoskeletal pain among older men: Preliminary evidence for central sensitization as a mechanism? *Neurourology and Urodynamics*. 2021;40(8):1929-1938. doi:10.1002/nau.24767

Funding: This work was supported by the National Center for Complementary and Integrative Health (grant number K23AT008211 to AS] and the National Center for Advancing Translational Sciences (NCATS) National Institutes of Health (grant number UL1TR002369). This work was also supported by grants and awards to SRB from the National Institute of Diabetes, Digestive, and Kidney Disorders (grant number 1K12DK111028), the National Institute on Aging (grant number 1R03AG067937), and the UCSF Claude D. Pepper Older Americans Independence Center funded by National

Institute on Aging (grant number P30 AG044281). MrOS is supported by the National Institute on Aging (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Center for Advancing Translational Sciences (NCATS), and the National Institutes of Health Roadmap for Medical Research (grant numbers U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01AG042168, U01 AR066160, and UL1 TR000128). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Data source: Data used in this project are publicly available at https://mrosonline.ucsf.edu/

3.1 Abstract

Background: Features of central sensitization (CS) are present in almost all chronic pain conditions, including painful urinary conditions and back pain. Recently CS was proposed as a mechanism of non-painful lower urinary tract symptoms (LUTS). Using musculoskeletal pain as an indicator of CS, we investigated whether the prevalence of musculoskeletal pain is greater among community-dwelling men with moderate or severe LUTS compared to those with mild LUTS.

Methods: We conducted a cross-sectional study of 5,966 men ≥ 65 years who attended the Osteoporotic Fractures in Men Study baseline visit. LUTS were assessed with the American Urological Association Symptom Index (AUA-SI) and categorized as none/mild (0-7), moderate (8-19), or severe (≥20). Self-reported back, neck, hip, or knee pain within the 12 months before baseline was categorized as any pain and multi-location pain. We tested our hypothesis using odds ratios (OR) and 95% confidence intervals (CI) estimated from multivariable logistic regression models.

Results: The adjusted odds of any pain were higher among men with moderate (OR 1.49, 95% CI: 1.29-1.72) and severe LUTS (OR 1.76, 95% CI: 1.28-2.40) compared to those with no/mild LUTS. The adjusted odds of pain at ≥ 2 locations were 69% higher among men with moderate (OR 1.69, 95% CI: 1.45-196) and more than double among men with severe LUTS (OR 2.24, 95% CI: 1.62-3.10) compared to men with no/mild LUTS.

Conclusions: Musculoskeletal pain, especially at multiple locations, is associated with greater LUTS severity among older men. CS may represent a novel shared mechanism of pain and LUTS.

3.2 Introduction

Lower urinary tract symptoms (LUTS), which include symptoms of difficulty voiding or storing urine, affect 20% of adults worldwide.[2] The stigma associated with urinary symptoms often leads to psychological distress and LUTS are associated with decreased quality of life of a similar magnitude to diabetes and heart disease.[6,7] Despite their health impact, knowledge about the pathophysiological mechanisms underlying LUTS are evolving and remain incompletely understood.

The bladder is controlled by both the somatic and autonomic nervous systems, making it logical to investigate contributions of autonomic nervous system function to LUTS etiology. One possible explanation pertains to how the nervous system develops increased responsiveness to primarily noxious stimuli, known as sensitization. Sensitization is a temporary and adaptive phenomenon.[11] For example, when faced with repeated or intense noxious stimuli, the nervous system can amplify signals, which are often perceived as pain, to motivate behaviors to avoid potential harm. In the absence of harm, the system will return to a physiologic baseline sensitivity over time.[13] However, sensitization can become impaired, such that even in the absence of harm the amplification of sensory signals continues but is no longer protective. This impairment in the processing of sensory information is called central sensitization (CS). Recently, CS was proposed as a mechanism of storage LUTS.[14] Specifically, it has been proposed that the sensory amplification of bladder stretch or pressure may be perceived as a signal of harm and translated into common LUTS of urgency, frequency, and nocturia.[14]

CS is recognized as an underlying mechanism in painful urinary conditions such as bladder pain syndrome and chronic prostatitis, as well as several other chronic conditions, including fibromyalgia, irritable bowel syndrome, low back pain, and osteoarthritis.[15,44,74] These diagnoses tend to co-occur and people with these conditions often experience overlapping symptom profiles, including depression, anxiety, fatigue, poor concentration, and pain. What is unknown is whether CS is a mechanism of non-painful LUTS. We reasoned that if CS is responsible for a portion of non-painful LUTS cases, then symptoms suggestive of sensitization, such as non-urologic chronic musculoskeletal pain, would be more prevalent among people with LUTS compared to those without. Moreover, because widespread bodily pain indicates a disruption in central nervous system pain regulation,[15] we would also expect a strong association between LUTS and musculoskeletal pain in multiple sites. These hypotheses have not been adequately tested. The emerging evidence supporting a possible association between CS and non-painful urologic conditions is based on inference from studies conducted in small clinical samples of women[16–18,82] and may not apply to men.

There is a lack of epidemiologic information on CS as a potential mechanism of LUTS in men. Therefore, using musculoskeletal pain as an indicator of CS, the objective of this study was to determine if the prevalence of musculoskeletal pain is associated with LUTS among community-dwelling older men using baseline data from the Osteoporotic Fractures in Men (MrOS) study. We hypothesized that the prevalence of

musculoskeletal pain, particularly pain in multiple sites, would be higher with increasing LUTS severity.

3.3 Methods

Data Source

We conducted a cross-sectional study with data collected at the baseline visit of the MrOS cohort. MrOS is designed to identify risk factors for falls, fractures, and prostate conditions among community-dwelling older U.S. men.[83] Eligible participants were identified through population-based lists (e.g. voting and motor vehicle registries) and recruited through mass mailings.[84] Between 2000 and 2002, 5,994 community-dwelling men who were at least 65 years old and could walk without the assistance of another person were enrolled at 6 U.S. academic medical centers in Birmingham, Minneapolis, Palo Alto, Pittsburgh, Portland and San Diego. At the baseline visit, all men completed a comprehensive self-administered questionnaire and an in-person study visit. All participants gave written informed consent and Institutional Review Boards at each participating institution approved the study.

Independent Variable: Lower Urinary Tract Symptoms

LUTS were assessed with the American Urologic Association Symptom Index (AUA-SI) on the baseline questionnaire.[19] The AUA-SI includes seven items on urinary urgency, frequency, nocturia, straining, weak stream, intermittency, and/or incomplete emptying

in the previous 30 days. Item scores are summed for a total score (range 0-35 points). AUA-SI scores were categorized according to standard practice as no/mild (0-7 points), moderate (8-19 points), or severe (≥ 20 points) LUTS.

We also assessed AUA-SI subscales for storage (frequency, urgency, nocturia) and voiding symptoms (straining, incomplete emptying, intermittency, and weak stream). For each subscale, we categorized the total subscale score into tertiles because there are no established thresholds.

Dependent Variables: Musculoskeletal Pain

In four separate questions on the baseline questionnaire, MrOS participants reported on back, neck, hip, and knee pain within the previous 12 months. We defined two primary dependent variables for this study. First, any musculoskeletal pain was defined as a response of "yes" to any of the four pain locations (back, neck, hip, or knee) versus "no" for all locations. Second, multi-location pain was defined as the sum the number of "yes" responses to the four individual questions about back, neck, hip, or knee pain (0, 1, ≥ 2).

Other Independent Variables

Race was categorized as White, Black, or Other because there were too few men to examine other racial/ethnic categories separately. Education was categorized as college degree (yes/no). Cigarette smoking status was categorized as current, former, or never.

Alcohol consumption was assessed as average intake in a typical week and categorized as none, >0-7, and >7 drinks per week. Problem drinking was defined as a score of ≥ 2 on the CAGE Substance Abuse Screening Tool.[83] Scores from the Physical Activity Scale for the Elderly[83] were categorized into quartiles. Mobility limitation was defined as self-report of any difficulty walking two to three blocks outside on level ground or any difficulty climbing ten steps without resting. Self-reports of physician-diagnosed hypertension, diabetes, prostatitis, and prostate cancer were also obtained. We defined psychological distress as a score of ≤50 points on the mental health component of the SF-12 questionnaire.[85] Height and weight were measured by study staff [83] and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). BMI was assessed as a continuous variable and as categories of normal/underweight (<25.0) overweight (25.0-29.9), and obese (≥30). Prescription medication use was documented from labels on products brought by participants and classified using the Iowa Drug Information System.[41] Current LUTS medication use was coded as a binary variable indicating use of any alpha-1 adrenergic antagonist, 5-alpha reductase inhibitor, anticholinergic for storage symptoms, or phosphodiesterase-5 inhibitor. Current pain medication use was coded as binary variable indicating use of non-steroidal anti-inflammatory drugs, opioids, acetaminophen, or aspirin. Current antidepressant or anxiolytic medication use was coded as a binary variable indicating use of selective serotonin receptor inhibitors, serotonin-norepinephrine reuptake Inhibitors, tri/tetracyclic antidepressants, monoamine oxidase inhibitors,

benzodiazepines, barbiturates, or pharmaceuticals indicated for treatment of depression or anxiety that do not belong to one of these categories (e.g. trazodone, buspirone). Men with missing antidepressant or anxiolytic medication information (n=239) were coded as non-users, because results with this coding were similar to results excluding the missing observations. Study site was categorized as the participant's recruitment site.

Analytic Cohort

Of the 5,994 participants enrolled at baseline, men who had missing data for LUTS (n=4) or other independent variables of interest (BMI n=2, smoking status n=1, drinks per week n=7, physical activity n=3, mobility limitation n=8, psychological distress n=3) were excluded. The final analytic sample consisted of 5,966 men.

Statistical Analysis

We compared characteristics of the analytic cohort according to LUTS severity using one-way analysis of variance for continuous variables or chi-square tests for categorical variables. We also computed the unadjusted prevalence of multi-location pain among those with no/mild, moderate, and severe LUTS.

Odds ratios (OR) and 95% confidence intervals (CI) were estimated as the measure of association between LUTS severity and musculoskeletal pain prevalence. For the outcome variable any musculoskeletal pain, logistic regression for a binary variable was

used. For the outcome variable multi-location pain with three categories, multinomial logistic regression with a reference outcome of no pain and a robust variance estimator was used to estimate OR for the categories of pain at 1 location and pain at ≥ 2 locations. Stata 14.2 (StataCorp LLC, College Station, TX, USA) was used for all analyses.

We hypothesize that musculoskeletal pain and LUTS do not mutually cause each other, but rather are associated through a common underlying mechanism, CS, a phenomenon for which there is no standardized physiologic measure. Therefore, we created a causal diagram (Supplementary Figure 1) to guide our model building and variable selection,[86] summarized briefly as follows. First, we defined potential confounders as variables associated with LUTS, musculoskeletal pain, or both and that are unlikely to be caused by CS, including age, race, education, smoking status, alcohol consumption, physical activity, limited mobility, BMI, diabetes, hypertension, prostate cancer, and study site. Second, we created base models adjusted for age. Third, the remaining potential confounders were added to the age-adjusted model in a systematic and iterative fashion using well-established change in estimate methods.[87] Briefly, each variable was added to the age-adjusted model one at a time and ranked according to the strength of confounding. Variables that resulted in ≥ 10% change in the OR were considered candidate confounders. The candidate confounder that produced the greatest percentage change in the estimate was retained first. The process was repeated with the remaining candidate confounders until all variables that produced confounding were assessed in the presence of variables already in the model. As a result

of these procedures, age and mobility limitations were retained in the final model as confounding variables.

Because CS may be a common mechanism of musculoskeletal pain and LUTS, additional factors may mediate the (unmeasured) associations between CS and pain or between CS and LUTS (Supplementary Figure 1). Therefore, we added the following variables separately one at time to the final multivariable model: pain medication use, LUTS medication use, psychological distress, and prostatitis. The two variables that resulted in ≥ 10% change in any OR were use of LUTS medications and history of prostatitis. We present the OR before and after adjustment for these variables.

Finally, we examined whether the association between LUTS and pain varied across levels of storage and voiding symptom severity. To perform this analysis, we created a 9-level categorical variable by cross-tabulating storage symptom tertiles and voiding symptom tertiles. We then repeated our analyses using this as our primary independent variable; the referent group was men in the lowest tertile of both storage and voiding symptoms.

Sensitivity Analyses

Prostatitis is a painful urinary condition that may have an underlying CS component.[74] Prostate cancer is a risk factor for LUTS and metastasis can result in musculoskeletal pain. Therefore, we repeated our analyses after excluding men with a history of prostatitis, prostate cancer, or either condition. Second, because psychological

comorbidities are common among individuals with CS, pain, and LUTS, we explored whether the association between LUTS and pain was consistent among men without psychological distress symptoms by excluding those with psychological symptoms from the final models. Finally, we assessed the sensitivity of our model estimates to the inclusion of all independent variables described in *Other Independent Variables*.

3.4 Results

Nearly half (46%) of the men had moderate or severe LUTS (Table 1). Compared to men with no/mild LUTS, those with moderate or severe LUTS were on average slightly older, less physically active, and more likely to have mobility limitations, to use medications for LUTS and for pain, and to report diabetes, hypertension, and symptoms of depression/anxiety.

The prevalence of any musculoskeletal pain was greater among men with moderate or severe LUTS than among men with no/mild LUTS (Figure 1). After adjustment for confounders, the odds of reporting any musculoskeletal pain were 49% higher among men with moderate LUTS (OR 1.49, 95% CI: 1.29-1.72) and 76% higher among men with severe LUTS (OR 1.76, 95% CI: 1.28-2.40) compared to those with no/mild LUTS (Table 2). Further adjustment for a history of prostatitis and use of LUTS medication did not change the association with moderate LUTS and attenuated the OR for severe LUTS to 1.55 (95% CI: 1.13,2.13), although all associations remained statistically significant.

With increasing LUTS severity, the unadjusted prevalence of pain at 1 location decreased and the prevalence of pain at ≥ 2 locations increased (Figure 1). Compared to men with no/mild LUTS, adjusted odds of reporting pain at 1 location were higher among men with moderate LUTS, but not among men with severe LUTS (Table 3). However, compared to men with no/mild LUTS, the adjusted odds of reporting pain at ≥ 2 locations were 69% higher among men with moderate LUTS (OR 1.69, 95% CI: 1.45-196) and more than twice as high among men with severe LUTS (OR 2.24, 95% CI: 1.62-3.10). Further adjustment for LUTS medication use and prostatitis history did not materially change the ORs for pain at 1 location, but did attenuate the ORs for pain at ≥ 2 locations to 1.57 (95% CI: 1.35-1.83) for moderate LUTS and 1.91 (95% CI: 1.37-2.65) for severe LUTS.

When men were simultaneously classified by storage and voiding symptom severity, results were consistent with our primary analysis (Table 4). The association was strongest among men in the highest tertiles of both storage and voiding subscores; the odds of reporting any pain were nearly double for this group compared to men with the lowest storage and voiding scores (OR 2.25, 95% CI: 1.80-2.83). We observed a similar pattern for the outcome of multi-location pain (Supplementary Table 1).

Sensitivity Analyses

After excluding men with a history of prostatitis (n=1,492), prostate cancer (n=708), either prostate cancer or prostatitis (n=1,816), or those with psychological distress

(n=969), our results were materially unchanged (Supplementary Table 2). Our results were also unchanged after adjusting for all covariates described in the Other Independent Variables section (Supplementary Tables 3 and 4).

3.5 Discussion

In this large US cohort of community-dwelling older men, the prevalence of any musculoskeletal pain, and particularly pain at multiple locations, rose with increasing severity of LUTS. Both the presence and number of locations of musculoskeletal pain were associated with greater LUTS severity independently of age, mobility limitations, LUTS medication use, and history of prostatitis. The association was strongest for men with pain at multiple locations and similar for men who reported predominantly storage symptoms versus predominantly voiding symptoms. These findings lend support to the hypothesis that LUTS and musculoskeletal pain may be associated through a common underlying mechanism of CS.

There is some prior evidence of a positive association between musculoskeletal pain and LUTS, albeit mostly among women with low back pain and urinary incontinence.[88,89] The majority of prior studies were cross-sectional, although two prospective studies suggest an association between back pain and urinary incontinence in women.[69,90] In men, back pain has been associated with LUTS progression over time.[41] These studies only assessed back pain at a single site. Our observation that any musculoskeletal pain is

associated with greater LUTS severity is consistent with these earlier findings and extends these works by assessing not only back pain but pain at other locations, as well.

Very few studies have assessed an association between LUTS and musculoskeletal pain at multiple locations. Nearly half of older adults with urinary incontinence report pain in more than one musculoskeletal location.[91] In a clinical sample of adults with bladder pain syndrome (BPS; n=27), overactive bladder (OAB; n=51), or no/mild LUTS (n=30), participants were asked to indicate where they experienced pain on a whole body map.[82] Of those reporting co-occurring pelvic and non-pelvic pain, adults with BPS were significantly more likely to report non-pelvic pain in multiple locations compared to those with OAB, who in turn were more likely to report non-pelvic multi-location pain compared to controls. The authors hypothesized that the presence of bodily pain in multiple non-pelvic locations indicates a disruption in central systems of pain regulation and suggests that CS may contribute to a subset of BPS and OAB cases. Our finding that musculoskeletal pain is most strongly associated with LUTS severity among men who report pain at more than one location provides further support for this hypothesis.

Features of CS are present in painful urinary conditions.[74] What remains unclear is whether CS also contributes to non-painful LUTS. Most evidence in support of the latter is derived from studies of women with OAB and storage LUTS.[16–18,82] However, we found that the association between musculoskeletal pain and LUTS severity was similar between men with predominantly storage symptoms and men with predominantly voiding symptoms. Moreover, the strength of association between musculoskeletal pain

and LUTS was greatest among men with the highest storage and voiding subscores. Thus, CS may not only be an underlying mechanism of storage symptoms indicative of OAB as previously suggested, but it may also contribute to the sensory amplification of voiding LUTS associated with benign prostatic or other obstructive pathologies.

Our observation that musculoskeletal pain is associated with greater LUTS severity supports the hypothesis that musculoskeletal pain and LUTS may be associated through a common cause, CS, as described in our supplementary figure. Although our study employs a cross-sectional design and uses musculoskeletal pain as a proxy of CS rather than measuring CS directly, some consideration of the mechanisms by which CS could contribute to LUTS is warranted. Possible ways in which CS may contribute to storage symptoms and OAB have been well-articulated.[14] Briefly, it is suggested that repetitive mechanical, inflammatory, and/or chemical stimuli that increase urinary afferent signaling above normal thresholds can, in turn, cause central sensitization.[14] Sensitized neurons may then interpret greater bladder fullness at reduced bladder volumes, resulting in urinary symptoms of urgency or frequency. We posit that the same pathophysiologic changes hypothesized to occur with OAB might also occur with obstructive pathologies such as bladder outlet obstruction (BOO). For example, early in the course of BOO, increased resistance in urinary outflow can cause bladder inflammation and tissue remodeling[92,93] which could, in turn, cause increased afferent signaling and central sensitization. Thus, it is possible that CS is caused early in the course of obstruction and contributes to the storage symptoms that accompany voiding

dysfunction. Indeed, most men with BOO present with a mix of voiding and storage symptoms - rarely are symptoms purely obstructive.[94] If CS is associated with both storage and voiding pathologies, then prospective investigations are needed to determine whether CS, or conditions indicative of CS, are positively associated with worsening LUTS.

Our study has limitations. Recall of pain over 12 months may be prone to measurement error. If inaccurate recall of pain was similar across all categories of LUTS severity, the ORs we observed could have been underestimated. Alternatively, if men with moderate or severe LUTS were more likely than men with no/mild LUTS to recall other somatic symptoms like pain, our observed ORs could be overestimated. Nevertheless, the accuracy of pain recall over the past 12 months is generally high on average, particularly for questions similar to those used in this study (e.g. "did it happen") as opposed to more complex constructs like pain intensity, duration, or interference.[95] Second, chronic pain is more indicative of CS than acute pain; but we were unable to differentiate acute from chronic pain in these analyses. We have no reason to believe that the reporting of acute pain would be systematically different across categories of LUTS severity, therefore the inclusion of acute pain in our analyses could have resulted in an underestimation of ORs. Third, we lacked a measure of urinary pain and therefore were unable to determine if differences in musculoskeletal pain prevalence exist among men with painful and non-painful LUTS. Finally, although a validated measure of CS symptoms now exists,[44] it was not yet developed at the time

the MrOS cohort was assembled. Nevertheless, musculoskeletal pain in multiple locations is a marker of disordered central pain regulation and therefore is an appropriate surrogate for the presence of CS.[15]

3.6 Conclusion

Musculoskeletal pain, especially at multiple locations, is associated with greater LUTS severity among older men. CS may represent a novel and currently untargeted shared mechanism of pain and LUTS. Prospective studies and those that objectively investigate the presence of CS among older men with LUTS are warranted.

Table 3.1. Baseline characteristics of community-dwelling men aged ≥ 65 years according to lower urinary tract symptom (LUTS) severity: The MrOS study, USA (N=5,966).

	LUTS Severity			
	Mild	**Moderate**	**Severe**	***P* value[a]**
N (% in cohort)	3,224 (54.4)	2,346 (39.3)	396 (6.6)	
Age, years; mean (sd)	73.15 (5.75)	74.17 (5.90)	74.61 (6.18)	<0.001
Race				0.05
White	2,889 (89.6%)	2,124 (90.5%)	350 (88.4%)	
Black/African American	125 (3.9%)	90 (3.8%)	26 (6.6%)	
Other	210 (6.5%)	132 (5.6%)	20 (5.1%)	
College Degree	1,704 (52.9%)	1,271 (54.2%)	197 (49.7%)	0.23
BMI				0.51
Under/Normal	901 (27.9%)	636 (27.1%)	98 (24.7%)	
Overweight	1,640 (50.9%)	1,214 (51.7%)	202 (51.0%)	
Obese	683 (21.2%)	496 (21.1%)	96 (24.2%)	
Smoking Status				0.01
Never	1,243 (38.6%)	861 (36.7%)	136 (34.3%)	
Past	1,850 (57.4%)	1,425 (60.7%)	247 (62.4%)	
Current	131 (4.1%)	60 (2.6%)	13 (3.3%)	
Alcohol consumption				0.21
None	1,108 (34.4%)	851 (36.3%)	152 (38.4%)	
1-7/week	1,531 (47.5%)	1,110 (47.3%)	183 (46.2%)	
>7/week	585 (18.1%)	385 (16.4%)	61 (15.4%)	
Problem Drinking	456 (14.1%)	463 (19.7%)	80 (20.2%)	<0.001
Physical activity quartiles				<0.001
Q1 (Least active)	718 (22.3%)	646 (27.5%)	128 (32.3%)	
Q2	783 (24.3%)	610 (26.0%)	99 (25.0%)	
Q3	813 (25.2%)	589 (25.1%)	89 (22.5%)	
Q4 (Most active)	910 (28.2%)	501 (21.4%)	80 (20.2%)	
Mobility Limitations[c]	342 (10.6%)	387 (16.5%)	103 (26.0%)	<0.001
Medication Use				
Pain Medications[d]	1,514 (47.0%)	1,172 (50.0%)	228 (57.6%)	<0.001
Diuretic Medications	578 (17.9%)	480 (20.5%)	78 (19.7%)	0.06
LUTS Medications[e]	349 (10.8%)	594 (25.3%)	157 (39.6%)	<0.001
Antidepressant/anxiolytic Medications[f]	237 (7.4%)	226 (9.6%)	59 (14.9%)	<0.001

Medical History				
Prostatitis	645 (20.0%)	677 (28.9%)	170 (42.9%)	<0.001
Diabetes	342 (10.6%)	248 (10.6%)	58 (14.6%)	0.04
Hypertension	1,309 (40.6%)	1,060 (45.2%)	198 (50.0%)	<0.001
Psychological distress[g]	414 (12.8%)	463 (19.7%)	93 (23.5%)	<0.001
Any Musculoskeletal Pain	2,520 (78.2%)	1,986 (84.7%)	347 (87.6%)	<0.001
Multi-location Pain				<0.001
No Pain	704 (21.8%)	360 (15.3%)	49 (12.4%)	
Pain at 1 Location	1,090 (33.8%)	703 (30.0%)	90 (22.7%)	
Pain at ≥ 2 Locations	1,430 (44.4%)	1,283 (54.7%)	257 (64.9%)	

BMI: Body mass index; BPH: benign prostatic hyperplasia; MrOS: Osteoporotic Fractures in Men Study; NSAIDS: Non-steroidal anti-inflammatory drugs; PASE: Physical Activity Scale for the Elderly

[a] p-values estimated from chi-square test for categorical variables or one-way analysis of variance for continuous variables

[b] Physical activity assessed with the Physical Activity Scale for the Elderly

[c] Defined as any difficulty walking 2-3 blocks or climbing 10 steps

[d] Use of non-steroidal anti-inflammatory drugs, opioids, acetaminophen, or aspirin

[e] Use of any alpha-1 adrenergic antagonist, 5-alpha reductase inhibitor, anticholinergic for storage symptoms, or phosphodiesterase-5 inhibitor

[f] Use of selective serotonin receptor inhibitors, serotonin-norepinephrine reuptake Inhibitors, tri/tetracyclic antidepressants, monoamine oxidase inhibitors, benzodiazepines, barbiturates, or pharmaceuticals indicated for treatment of depression or anxiety that do not belong to one of these categories (e.g. trazodone, buspirone).

[g] Defined as a mental health component score of ≤ 50 on the SF-12

Table 3.2. Association between lower urinary tract symptom (LUTS) severity and any musculoskeletal pain among community dwelling men aged ≥ 65 years: The MrOS Study, USA (N=5,966).

			Any Pain[a]		
	No Pain (*n*)	Any Pain (*n*)	Age-Adjusted OR (95% CI)	Multivariable[b] OR (95% CI)	Multivariable OR (95% CI)
Mild LUTS	704	2,520	Ref.	Ref.	Ref.
Moderate LUTS	360	1,986	1.55 (1.35,1.79)	1.49 (1.29,1.72)	1.41 (1.22,1.63)
Severe LUTS	49	347	2.00 (1.46,2.73)	1.76 (1.28,2.40)	1.55 (1.13,2.13)
Column Total	1,113	4,853	-	-	-

MrOS: Osteoporotic Fractures in Men Study; OR: Odds ratio; CI: Confidence interval

[a] Report of any back, neck, hip, or knee pain in the previous 12 months.

[b] Adjusted for age and mobility limitations.

[c] Adjusted for age, mobility limitations, use of medications to treat LUTS, and history of prostatitis.

Table 3.3. Association between lower urinary tract symptom (LUTS) severity and musculoskeletal pain at multiple locations among community dwelling men aged ≥ 65 years: The MrOS Study, USA (N=5,966).

		Multi-location Pain[a]							
		1 Location				≥ 2 Locations			
	No Pain (n)	*Pain at 1 location (n)*	Age-Adjusted OR (95% CI)	Multivariable[b] OR (95% CI)	Multivariable[c] OR (95% CI)	*Pain at ≥ 2 Locations (n)*	Age-Adjusted OR (95% CI)	Multivariable[b] OR (95% CI)	Multivariable[c] OR (95% CI)
Mild LUTS	704	1,090	Ref.	Ref.	Ref.	1,430	Ref.	Ref.	Ref.
Moderate LUTS	360	703	1.27 (1.08,1.49)	1.25 (1.07,1.47)	1.22 (1.04,1.44)	1,283	1.77 (1.52,2.05)	1.68 (1.45,1.96)	1.57 (1.35,1.83)
Severe LUTS	49	90	1.20 (0.83,1.72)	1.15 (0.80,1.65)	1.08 (0.75,1.56)	257	2.61 (1.90,3.59)	2.24 (1.62,3.11)	1.91 (1.37,2.65)
Column Total	1,113	1,883	-	-	-	2,970	-	-	-

MrOS: Osteoporotic Fractures in Men Study; OR: Odds ratio; CI: Confidence interval

[a] Number of locations that pain was reported in the previous 12 months; includes back, neck, hip, or knee.

[b] Adjusted for age and mobility limitations.

[c] Adjusted for age, mobility limitations, use of medications to treat LUTS, and history of prostatitis.

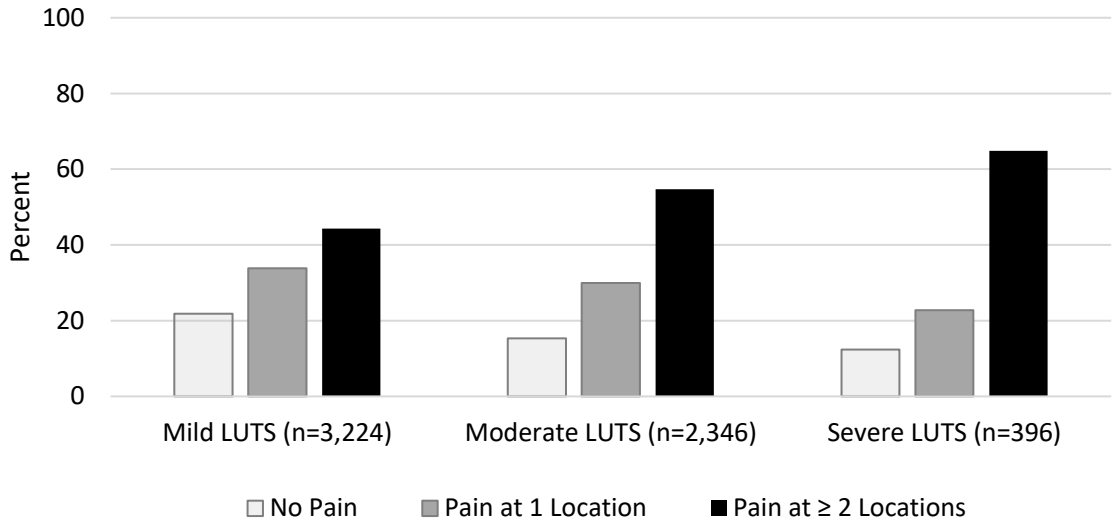


Figure 3.1. Unadjusted prevalence of the number of locations that pain was reported (back, neck, hip, or knee) within the last year among community-dwelling men ≥ 65 by severity of lower urinary tract symptoms. P<0.0001 for a chi square test for a difference in proportions across LUTS categories. The MrOS Study, USA (N=5,966).

Chapter 4. Musculoskeletal pain, as possible indicator of central sensitization, is positively associated with lower urinary tract symptom progression in community dwelling older men

Angela Senders, ND, MCR[1,5]; Scott R Bauer, MD[2,3]; Yiyi Chen, PhD[4]; Barry Oken, MD, PhD[5]; Howard A Fink, MD, MPH[6,7]; Nancy E Lane, MD[8]; Kamran P Sajadi, MD[9]; Lynn M Marshall, ScD[1] for the Osteoporotic Fractures in Men (MrOS) Study Group

1. Oregon Health & Science University-Portland State University School of Public Health, Portland, OR, USA
2. Departments of Medicine and Urology, University of California San Francisco, San Francisco, CA, USA
3. San Francisco VA Healthcare System, San Francisco, CA, USA
4. Seagen, Inc., Bothell, WA, USA
5. Department of Neurology, Oregon Health & Science University, Portland, OR, USA
6. Geriatric Research Education and Clinical Center, VA Health Care System, Minneapolis, MN
7. Department of Medicine, University of Minnesota, Minneapolis, MN, USA.
8. Department of Medicine, University of California, Davis, CA, USA
9. Department of Urology, Oregon Health & Science University, Portland, OR, USA

Funding: This work was supported by the National Center for Complementary and Integrative Health (grant number K23AT008211 to AS] and the National Center for

Advancing Translational Sciences (grant number UL1TR002369) at the National Institutes of Health (NIH). This work was also supported by grants and awards to SRB from the National Institute of Diabetes, Digestive, and Kidney Disorders at NIH (grant number 1K12DK111028), the National Institute on Aging at NIH (grant number 1R03AG067937), and the UCSF Claude D. Pepper Older Americans Independence Center funded by National Institute on Aging (grant number P30 AG044281). MrOS is supported by the National Institute on Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Center for Advancing Translational Sciences, and the National Institutes of Health Roadmap for Medical Research at the NIH (grant numbers U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01AG042168, U01 AR066160, and UL1 TR000128). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Data source: Data used in this project are publicly available at https://mrosonline.ucsf.edu/

4.1 Abstract

Background: Musculoskeletal pain, a possible marker of central sensitization, is associated with higher prevalence of lower urinary tract symptoms (LUTS) among older men. We investigated whether musculoskeletal pain is independently associated with LUTS progression.

Methods: We conducted prospective cohort study among 5,569 men age ≥65 years enrolled in the Osteoporotic Fractures in Men (MrOS) Study. Self-reported musculoskeletal pain within 12 months before baseline was categorized as any pain and as multi-location pain. Pain interference with normal activities was assessed with the SF-12 questionnaire. LUTS were assessed with the American Urological Association Symptom Index (AUA-SI). Men with severe LUTS at baseline were excluded. LUTS progression was defined as the first occurrence of a ≥4-point AUA-SI increase during a two-year follow-up interval. We estimated adjusted incident rate ratios (IRR) and 95% confidence intervals (CI) using multivariable pooled logistic regression.

Results: LUTS progression was 37% higher among men with any baseline musculoskeletal pain compared to men without pain (IRR 1.37, 95%CI: 1.21, 1.54). Positive associations were also observed between LUTS progression and baseline pain at 1 (IRR 1.31, 95%CI: 1.13, 1.48) and ≥2 locations (IRR 1.42, 95%CI: 1.24, 1.60). Compared to men without pain, men with at least moderate pain interference were the most likely

to experience LUTS progression (minimal interference IRR 1.40, 95%CI: 1.21, 1.60; ≥ moderate interference IRR 1.62, 95%CI: 1.38, 1.86).

Conclusions: Among men initially without severe LUTS, musculoskeletal pain is associated with an increased risk of LUTS progression. Studies using validated measures of central sensitization and LUTS progression among men are warranted.

4.2 Introduction

Approximately 25% of US adults older than 50 years experience lower urinary tract symptoms (LUTS).[1] LUTS are a constellation of symptoms experienced during storage or voiding of urine. Not only are LUTS associated with psychological distress and decreased quality of life,[8] they are associated with greater risk of falls among older men.[26] Symptoms often worsen over time[96] and, in a substantial proportion of people, LUTS do not respond to pharmacologic treatment.[39,97] The variable response to pharmacologic interventions that target the lower urinary tract suggests that, for some individuals, LUTS may be a manifestation of non-LUT causes that require a different approach to care.[10] Despite their high prevalence and health impact among older adults, the pathophysiological mechanisms underlying LUTS onset and progression are not fully understood.

Central sensitization (CS) is proposed as a mechanism of LUTS.[14] CS occurs when the central nervous system amplifies noxious sensory signals resulting in hypersensitivity to painful stimuli.[15] Features of CS have been identified in almost all chronic pain conditions, including painful urinary conditions such as bladder pain syndrome and chronic prostatitis. What is unknown is whether CS also might contribute to a portion of non-painful LUTS cases or to LUTS progression. CS generally results in the amplification of painful stimuli and may increase the degree to which pain interferes with an individual's ability to engage in physical, social, emotional, or cognitive activities. However, many people with CS also exhibit hypersensitivity to non-painful stimuli such

as sound, light, and odor.[15] Specifically, it has been proposed that the sensory amplification of bladder stretch or pressure may be translated into storage LUTS, such as urinary urgency, frequency, and nocturia.[14]

Chronic conditions that exhibit features of CS, such as fibromyalgia and low back pain, tend to co-occur.[15,44] The term chronic overlapping pain conditions (COPCs) is used to describe the comorbid nature of these conditions and to indicate that CS likely plays a prominent role in their pathogenesis.[98] The co-occurrence of COPCs and painful urinary conditions like bladder pain syndrome has been documented.[99,100] Emerging evidence demonstrates overlap in the prevalence of COPCs, or symptoms suggestive of CS/COPCs, and non-painful LUTS,[17,82,88,89] although the majority of these studies were conducted in women. Recently, we showed that the prevalence of musculoskeletal pain is greater among community dwelling men with moderate or severe LUTS compared to those with no/mild LUTS.[101] Further, there was a strong positive association with multi-location pain and LUTS severity. Together, these findings suggest that CS may be associated with the presence of LUTS, but whether CS is associated with LUTS progression remains an unanswered question.

Building on our initial work using musculoskeletal pain as a possible indicator of CS, the objective of this study was to investigate whether musculoskeletal pain may be a risk factor for LUTS progression among community dwelling men. We hypothesized that men who reported musculoskeletal pain and those with higher levels of pain

interference would be more likely to experience worsening LUTS over time compared to men without pain.

4.3 Methods

Data Source

The Osteoporotic Fractures in Men (MrOS) study is a multicenter, prospective cohort study designed to identify risk factors for fracture and other conditions of aging in men.[83] After identification through population-based lists (e.g. motor vehicle and voting registries), eligible individuals were recruited through mass mailings.[84] Participants were enrolled at 6 academic medical centers in Birmingham, Minneapolis, Palo Alto, Pittsburgh, Portland OR and San Diego. Between March 2000 and April 2002, 5,994 community dwelling men who were at least 65 years old and could walk without the assistance of another person were enrolled in MrOS. At baseline, all men completed a comprehensive self-administered questionnaire and an in-person study visit. The questionnaire was repeated approximately two (July 2002 – March 2004) and four (March 2005 – May 2006) years after each participant's baseline enrollment date. All participants gave written informed consent, and Institutional Review Boards at each participating institution approved the study.

Exposure Variables: Musculoskeletal Pain

We defined three primary exposure variables for this study: any musculoskeletal pain, multi-location pain, and pain interference. In separate questions on the baseline assessment, MrOS participants reported whether they had any back, neck, hip, or knee pain within the previous 12 months. We defined any musculoskeletal pain as a response of "yes" to any of the four pain locations versus "no" for all locations. Multi-location pain was defined as the sum the number of "yes" responses to the four individual questions about back, neck, hip, or knee pain (0, 1, ≥ 2). Pain interference was assessed with the following question from the SF-12 questionnaire: "During the past 4 weeks, how much did pain interfere with your normal work (including work outside the home and housework)?"[102] Possible responses included "not at all", "a little bit", "moderately", "quite a bit", or "extremely". We combined each participant's response to this question with their musculoskeletal pain status (yes or no) to create the following categories for analysis: no pain, pain with no interference, pain with a little bit of interference, or pain with at least moderate interference.

Other Independent Variables

Other Independent Variables

Race was categorized as white, Black, or other because there were too few men to examine other racial and ethnic categories separately. Education was categorized as college degree (yes/no). Study site was categorized as one of the six academic medical center recruitment sites.

Height and weight were measured at the in-person baseline study visit using calibrated scales and a stadiometer[83] and used to calculate a standard body mass index (BMI). BMI was assessed as categories of normal (<25.0 kg/m^2) overweight (25.0-29.9 kg/m^2), and obese (≥30 kg/m^2). Cigarette smoking status was categorized as current, former, or never. Current alcohol consumption was assessed as average intake in a typical week and categorized as none, 1-7, and >7 drinks per week. Problem drinking was defined as a score of ≥ 2 on the CAGE Substance Abuse Screening Tool.[83] Physical activity was assessed with the Physical Activity Scale for the Elderly;[83] scores were categorized into quartiles. Mobility limitation was defined as self-report of any difficulty walking two to three blocks outside on level ground or any difficulty climbing ten steps without resting. Prescription medication use was derived from labels on products brought to the study visits by participants. Product information was entered into an electronic medications inventory (San Francisco Coordinating Center, San Francisco, CA). Each medication was matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).[103] For this study, LUTS medications were assessed as current use of any alpha-1 adrenergic antagonist, 5-alpha reductase inhibitor, anticholinergic, or phosphodiesterase-5 inhibitor. Pain medications were assessed as current use of non-steroidal anti-inflammatory drugs, opioids, acetaminophen, or aspirin. Current antidepressant or anxiolytic medication use was coded as a binary variable indicating use of selective serotonin receptor inhibitors, serotonin-norepinephrine reuptake Inhibitors, tri/tetracyclic antidepressants, monoamine oxidase inhibitors, benzodiazepines, barbiturates, or pharmaceuticals indicated for treatment of depression or anxiety that do not belong to one of these categories (e.g. trazodone, buspirone). Men with missing antidepressant or anxiolytic medication information (n=239) were coded as non-users, because results with this

coding were similar to results excluding the missing observations. We also assessed the use of diuretics. Self-report of physician-diagnosed hypertension, diabetes, prostatitis, and prostate cancer were also obtained. A multimorbidity score was defined as the number of physician-diagnosed chronic conditions, including: angina, myocardial infarction, heart failure, stroke, chronic obstructive pulmonary disease, diabetes mellitus, Parkinson's disease, osteoporosis, osteoarthritis, hyperthyroidism or hypothyroidism.[104] Self-report history of prostate surgery was categorized as yes/no. We defined psychological distress as a score of ≤50 on the mental health component of the SF-12 questionnaire (which does not include the pain interference question).[85]

Outcome Variable: Incident LUTS Progression

LUTS were assessed with the American Urologic Association Symptom Index (AUA-SI) at baseline and two- and four-years of follow-up. The AUA-SI includes seven items on urinary urgency, frequency, nocturia, straining, weak stream, intermittency, and/or incomplete emptying in the previous 30 days. Items are summed for a total score of 0-35 points and LUTS were categorized as no/mild (0-7 points), moderate (8-19 points), or severe (≥ 20 points) according to standard practice.[105] A 3-4 point change on the AUA-SI is generally accepted as a clinically relevant change in LUTS.[23] We defined incident LUTS progression as a ≥ 4-point increase from the previous score such that the current AUA-SI score was at least 8 points. Men who did not experience LUTS progression at the two-

year follow-up remained at risk for incident LUTS progression at the four-year follow-up assessment.

Men who withdrew from the study, were lost, or died prior to completing a follow-up assessment could not be observed for LUTS progression. For men who remained enrolled in the study, ascertainment of LUTS progression was over 98% complete at each follow-up assessment.

Analytic Cohort

Of the 5,994 MrOS participants, men with missing data for LUTS severity (n=4) and other independent variables of interest (n=23) were excluded. Men with severe LUTS at baseline (AUA-SI ≥ 20; n=398) were also excluded because of a potential ceiling effect with the AUA-SI and symptom progression may represent a different physiologic process for them compared to men who progress from mild or moderate LUTS. The analytic sample consisted of 5,569 men. Each participant contributed follow-up time from baseline until LUTS progression, date of death, withdrawal, last known contact, or the four-year follow-up assessment occurred, whichever came first.

Statistical Analysis

We compared characteristics of the analytic cohort according to any musculoskeletal pain status using one-way analysis of variance (ANOVA) for continuous variables or chi-square tests of independence for categorical variables. We also computed the

unadjusted prevalence of pain interference among those with any musculoskeletal pain, pain at one location, and pain at ≥ 2 locations.

To estimate the association between musculoskeletal pain and LUTS progression we used multivariable pooled logistic regression for grouped failure times[106] and a sandwich variance estimator. We used this established pooled method because the exact date of each participant's LUTS progression was unknown. We then used output from the pooled logistic regression to estimate the adjusted incidence rate of LUTS progression.[107] Specifically, the incident rate of LUTS progression for each category of musculoskeletal pain can be calculated by dividing the pooled number of LUTS progression events by the pooled person-years at risk in each pain category. The IRR is then calculated as the incidence rate in the pain category of interest divided by the incidence rate for the reference category of no musculoskeletal pain.

We hypothesize that musculoskeletal pain, as a proxy for CS, is associated with LUTS progression. If true, musculoskeletal pain and LUTS progression would be associated through a common cause, CS, that was not measured in this study. Therefore, we created a conceptual framework to guide our analysis (Supplementary Figure).[86] We adjusted for factors that confounded the association between musculoskeletal pain and LUTS progression *independent* of CS using a change in estimate approach.[87] All base models were adjusted for age. Additional covariables were selected in a series of iterative and systematic steps,[87] First, we specified four groups of candidate confounders: demographics (race, education), health behaviors (smoking status, alcohol

consumption, physical activity), health status (mobility limitation, BMI, diabetes, hypertension, prostate cancer, prostate surgery) and medications (diuretics). We constructed a full multivariable model adjusted for age and all four candidate confounder groupings. Then, we removed each candidate grouping from the full model one at a time and calculated the percentage change in the IRR for each musculoskeletal pain category. Any group that resulted in ≥ 10% change in the measures of association was retained in the model. We then followed a similar process to determine which individual variables confounded the measure of association. Specifically, for every confounder grouping retained in the model, each variable within the group was removed from the model one at a time. If the change in the measures of association was <1%, the variable was permanently removed. This step was repeated until each group contained only variables that confounded the final measure of association. As a result of these procedures, age, history of prostate surgery, hypertension, multimorbidity, and mobility difficulties were retained in the final model.

Additional factors, including pain medication use, LUTS medication use, psychological distress, and prostatitis, may lie on the causal pathway between CS and pain or CS and LUTS progression (Figure 2). To assess the impact of further adjusting for these factors, we created a second multivariable model. We added the four variables to the final model simultaneously. We then removed each variable one at a time and retained only those whose removal resulted in ≥ 1% change in the measure of association. As a result, age, history of prostate surgery, hypertension, multimorbidity,

mobility difficulties, prostatitis, psychological distress, and LUTS medication use were retained in this second model. We updated baseline values with responses from the two-year assessment to account for changes during follow-up in smoking status, drinks per week of alcohol, history of prostate surgery, history of prostatitis, and LUTS medication status.

We anticipated that the loss of data from men who died, withdrew, or were lost to follow-up during the observation period might induce selection bias in our analytic sample. Therefore, we used inverse probability of censoring weighting to assign extra weight to men who were not censored yet had similar covariate patterns to those who were censored. We used logistic regression to calculate the cumulative probability of censoring in each follow-up interval as a function of covariate and exposure status.[108] We then applied stabilized weights to each non-censored observation and repeated our analyses.[108] A *p* value of ≤ 0.05 was considered significant for all statistical tests; Stata 14.2 (StataCorp LLC, College Station Tx, USA) was used for all analyses.

Sensitivity Analysis

Our primary analysis estimates the incidence of LUTS progression over a two-year period, and thus may miss men whose symptoms progress more slowly over a longer period of time. Therefore, we also assessed whether musculoskeletal pain is associated with LUTS progression over four years. Specifically, for this analysis, incident LUTS progression was evaluated at the four-year follow-up assessment and was defined as a ≥

4-point increase since the baseline AUA-SI measurement such that the four-year follow-up AUA-SI score was at least 8 points.

4.4 Results

The majority of men (81%) reported musculoskeletal pain at baseline (Table 1). Compared to men without pain, those with any musculoskeletal pain were proportionally less likely to have a college degree, more likely to be obese, report mobility limitations, and to use medications for pain and LUTS. Men with musculoskeletal pain were also more likely to report hypertension, prostatitis, a history of prostate surgery, psychological distress, and had higher mean multimorbidity scores than men who did not report pain.

Among men with any musculoskeletal pain, nearly half (47%) reported no pain interference, 30% reported a little interference, and 23% reported at least moderate pain interference (Table 2). Among men with pain at one location, 64% reported no pain interference and 12% reported at least moderate interference. In comparison, men with pain at two or more locations were less likely to report no interference (36%) and more likely to report at least moderate interference (30%).

In total, 1,838 men experienced LUTS progression over 17,936 observed person-years at risk (Table 3). Musculoskeletal pain was positively associated with LUTS progression. After adjusting for potential confounders, the incidence rate of LUTS

progression was 37% higher among men with any musculoskeletal pain compared to men with no pain (IRR 1.37, 95% CI: 1.21, 1.54). The association of musculoskeletal pain at one and ≥ 2 locations with LUTS progression was of a similar magnitude and direction (one location: IRR 1.31, 95% CI: 1.13, 1.48; ≥2 locations: IRR 1.42, 95% CI: 1.24, 1.60). The incidence of LUTS progression rose with increasing levels of pain interference. Men with at least moderate pain interference were the most likely to experience LUTS progression compared to men with no pain (IRR 1.62, 95% CI: 1.38, 1.86). Further adjustment for history of prostatitis, psychological distress, and LUTS medication use did not materially change these results.

The odds ratios and 95% confidence intervals for these associations estimated after the application of stabilized weights (Supplementary Table) were nearly identical to the estimates reported in Table 3.

Sensitivity Analysis

Among men who completed the four-year follow-up, those with any pain were 42% more likely to experience LUTS progression over four years compared to men with no pain (adjusted cumulative incidence ratio (CIR): 1.42, 95% CI: 1.20, 1.65), as were men with pain at one and two or more locations (CIR 1.30, 95% CI: 1.07, 1.52; CIR 1.52, 95% CI: 1.27, 1.76, respectively). Similar to our primary analyses, men with at least moderate pain interference were the most likely to experience LUTS progression compared to men with no pain (CIR 1.71, 95% CI: 1.38, 2.03).

4.5 Discussion

In this large US cohort of community dwelling older men, individuals with musculoskeletal pain had an increased rate of LUTS progression over two years, independent of age, prostatitis, prostate surgery, hypertension, mobility difficulties, psychological distress, and LUTS medication use. The association between musculoskeletal pain and LUTS progression was similar among men with pain at one and two or more bodily locations. The rate of LUTS progression rose with increasing levels of pain interference and was highest for those with at least moderate pain interference. Our results lend further support to the hypothesis that musculoskeletal pain is a risk factor for progression of non-painful LUTS in older community-dwelling men, perhaps via CS mechanisms.

There is some prior evidence of a positive association between musculoskeletal pain and LUTS progression. Two prospective studies suggest an association between incident back pain and urinary incontinence in older women (mean age 72.5 (SD 1.5) years).[69,90] In older men, those with progressing LUTS trajectories were more likely to have back pain compared to those with stable trajectories.[41] Our observation that musculoskeletal pain is associated with LUTS progression is consistent with these earlier findings and extends these works by assessing pain at multiple locations as well as pain interference. The consistency in associations we observed between musculoskeletal pain outcomes of

any pain, multi-location pain, and pain interference and LUTS progression further strengthens the evidence in support of this relationship.

Most of the evidence suggesting CS may play a role in urinary conditions stems from cross-sectional studies.[14] Because CS mechanisms are located in the central nervous system, the effects of CS are not limited to the anatomic location in which symptoms present. For example, compared to healthy controls, individuals with painful urinary conditions exhibit hypersensitivity to pain on laboratory bladder filling[77] as well as decreased pain tolerance to non-pelvic mechanical and thermal stimuli.[74–76] Studies suggest that women with overactive bladder also exhibit similar findings.[16,79] Together these results suggest that features of CS are associated with the presence of painful and non-painful urinary symptoms. Evidence from COPC studies also suggests that CS may contribute to symptom progression. CS is implicated in the progression of episodic to chronic migraine[109] and tension type headaches.[110] Additionally, having one COPC may increase the risk of developing future COPCs.[111] Thus, the presence of CS might contribute not only to the worsening of a singular condition such as LUTS, but could also promote the onset and progression of non-urological symptoms in which CS plays a role.

The majority of current medications for male LUTS have pharmacologic mechanisms that target the prostate or bladder and are limited by side effects, modest efficacy, and the need for chronic therapy.[10] If CS contributes to a subset of progressive LUTS cases, these individuals may benefit from interventions that also target the nervous system.

For example, repetitive transcranial magnetic stimulation (rTMS) is a non-invasive intervention that stimulates cortical neurons and, over time, can result in structural and functional synaptic changes.[112] Clinically, rTMS is used to treat pain conditions and it has been hypothesized that some analgesic effects of rTMS may be derived by acting on CS mechanisms.[113] Emerging evidence suggests that rTMS applied to cortical areas associated with the pelvic region may improve LUT function as well as voiding and storage symptoms in people with multiple sclerosis, Parkinson's disease, and bladder pain syndrome.[114] Mind-body interventions such as mindfulness training can also alter neural circuits related to the integration of pain and other sensory signals.[115] While we are aware of only small mindfulness-based interventions that have been piloted for women with urge incontinence,[116,117] the approach has improved symptoms in other conditions with a CS component and could hold promise for LUTS in older men.

Our study has limitations. First, although a validated measure of CS symptoms now exists,[44] it was not yet developed at the time the MrOS cohort was assembled so we used musculoskeletal pain as an proxy for CS. Nevertheless, musculoskeletal pain in multiple locations is a marker of disordered central pain regulation making it a suitable surrogate for the presence of CS.[15] Further, as a measure of emotional reactivity to pain, pain interference may be a better indication of CS than the number of locations in which pain occurred.[118] Second, CS is thought to be more likely a mechanism of chronic rather than acute pain and we were unable to differentiate chronic from acute pain in these analyses. We have no reason to believe that the reporting of acute pain would be

systematically different among men whose LUTS subsequently progressed and those whose LUTS did not, therefore the inclusion of acute pain in our analyses could have resulted in an underestimation of IRRs. Third, we lacked a measure of lower urinary tract pain and therefore were unable to determine if the association between musculoskeletal pain and LUTS progression exists among men with painful urinary conditions and non-painful LUTS, although we were able to adjust for prostatitis – a condition that often causes pelvic pain and dysuria. Fourth, LUTS fluctuate over time, complicating the measurement of symptom change over prolonged periods. Nevertheless, we observed consistent results when assessing change over two- and four-year intervals, suggesting our definition was a reasonable measure of LUTS progression. Finally, MrOS is a cohort of older men and some inevitably died during the observation period. Our sensitivity analysis, however, suggests that deaths in the follow-up interval did not affect our findings.

4.6 Conclusion

The presence of musculoskeletal pain and the extent to which it interferes with daily activities is associated with worsening LUTS among older men. Musculoskeletal pain and LUTS may share an underlying mechanism, CS. Studies that investigate whether the validated presence of CS is associated with LUTS progression among older men are warranted. If future studies identify CS as a risk factor for LUTS progression, then

opportunities for new non-pharmacologic treatment targets for individuals with specific LUTS phenotypes or those who do not respond to current LUTS interventions may arise.

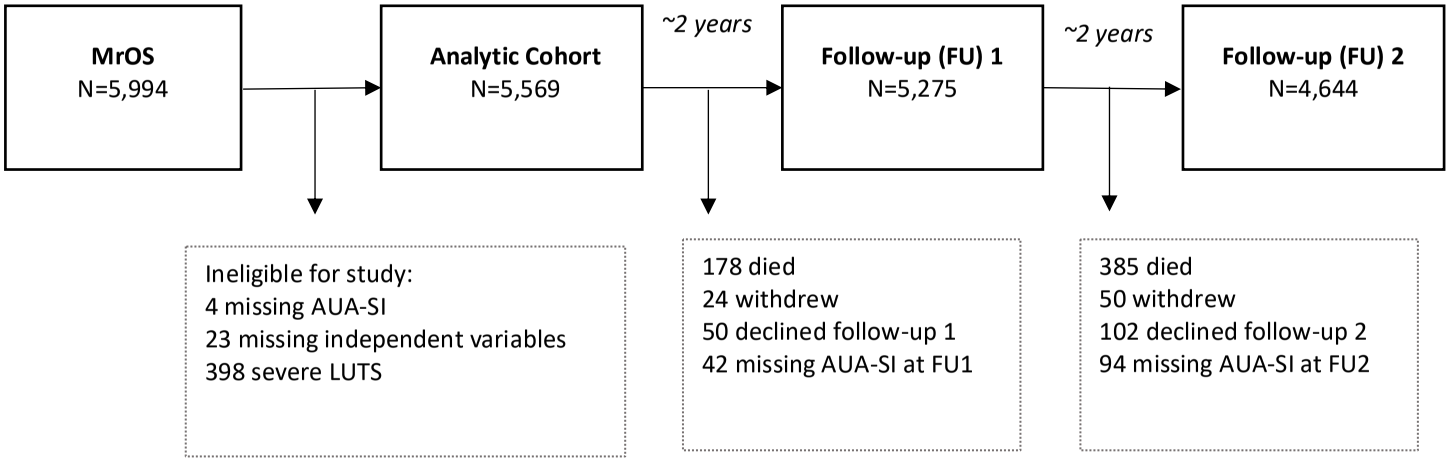


Figure 4.1. Timeline of follow-up assessments in the MrOS study. N at each study assessment represents number of participants with complete exposure and outcome assessments. Abbreviations: AUA-SI, American Urological Association Symptoms Index; FU, follow-up; LUTS, lower urinary tract symptoms.

Table 4.1. Baseline characteristics of community-dwelling men aged ≥ 65 years by musculoskeletal pain status within the previous 12 months: The MrOS study, USA.

	No Pain	**Any Pain**	***P* value[a]**
N (% in cohort)	1,064 (19.1)	4,505 (80.9)	
Age, years; mean (sd)	73.71 (5.76)	73.54 (5.85)	0.39
Race			0.16
White	949 (89.2%)	4,063 (90.2%)	
Black/African American	37 (3.5%)	178 (4.0%)	
Other	78 (7.3%)	264 (5.9%)	
College Degree	619 (58.2%)	2,355 (52.3%)	<0.001
Body Mass index			<0.001
Under/Normal (<25.0 kg/m^2)	347 (32.6%)	1,190 (26.4%)	
Overweight (25.0-29.9 kg/m^2)	543 (51.0%)	2,310 (51.3%)	
Obese (≥30 kg/m^2)	174 (16.4%)	1,005 (22.3%)	
Smoking Status			0.01
Never	448 (42.1%)	1,655 (36.7%)	
Past	580 (54.5%)	2,695 (59.8%)	
Current	36 (3.4%)	155 (3.4%)	
Alcohol consumption[b]			0.82
None	383 (36.0%)	1,575 (35.0%)	
1-7/wk	367 (34.5%)	1,578 (35.0%)	
>7/wk	314 (29.5%)	1,352 (30.0%)	
Problem Drinking	155 (14.6%)	764 (17.0%)	0.06
Physical activity quartiles[c]			0.37
Q1 (Least active)	274 (25.8%)	1,124 (25.0%)	
Q2	244 (22.9%)	1,144 (25.4%)	
Q3	267 (25.1%)	1,125 (25.0%)	
Q4 (Most active)	279 (26.2%)	1,112 (24.7%)	

Mobility Limitations[d]	47 (4.4%)	682 (15.1%)	<0.001
Medication Use			
Pain Medications[e]	384 (36.1%)	2,202 (48.9%)	<0.001
LUTS Medications[f]	144 (13.5%)	867 (19.2%)	<0.001
Diuretic Medications	170 (16.0%)	868 (19.3%)	0.01
Antidepressant/Anxiolytic Medications[g]	52 (4.9%)	411 (9.1%)	<0.001
Medical History			
Diabetes	114 (10.7%)	476 (10.6%)	0.89
Hypertension	378 (35.5%)	1,990 (44.2%)	<0.001
Prostatitis	191 (18.0%)	1,131 (25.1%)	<0.001
Prostate Cancer	107 (10.1%)	544 (12.1%)	0.07
Prostate surgery	152 (14.3%)	827 (18.4%)	0.002
Multimorbidity; mean (sd)[h]	0.66 (0.89)	0.96 (1.10)	<0.001
Psychological Distress[i]	100 (9.4%)	776 (17.2%)	<0.001

MrOS: Osteoporotic Fractures in Men Study; PASE: Physical Activity Scale for the Elderly

[a] p-values estimated from a chi-square test for categorical variables or one-way analysis of variance for continuous variables

[b] Defined as a score of ≥ 2 on the CAGE Substance Abuse Screening Tool

[c] Physical activity assessed with the Physical Activity Scale for the Elderly

[d] Defined as any difficulty walking 2-3 blocks or climbing 10 steps

[e] Use of non-steroidal anti-inflammatory drugs, opioids, acetaminophen, or aspirin

[f] Use of any alpha-1 adrenergic antagonist, 5-alpha reductase inhibitor, anticholinergic for storage symptoms, or phosphodiesterase-5 inhibitor

[g] Use of selective serotonin receptor inhibitors, serotonin-norepinephrine reuptake Inhibitors, tri/tetracyclic antidepressants, monoamine oxidase inhibitors, benzodiazepines, barbiturates, or pharmaceuticals indicated for treatment of depression or anxiety that do not belong to one of these categories (e.g. trazodone, buspirone).

[h] Mean number of the following physician-diagnosed conditions: thyroid disease, diabetes, angina, myocardial infarction, congestive heart failure, stroke, , chronic obstructive pulmonary disease, Parkinson's disease, osteoarthritis, and osteoporosis.

[i] Defined as a mental health component score of <=50 on the SF-12

Table 4.2. Pain interference according to musculoskeletal pain status at baseline in community dwelling men aged ≥ 65 years: The MrOS Study, USA.

		Pain Interference[a]		
		none	**a little**	**≥ moderate**
	n	n (%)	n (%)	n (%)
No musculoskeletal pain	1,064	na	na	na
Any musculoskeletal pain	4,505	2,113 (46.9)	1,355 (30.1)	1,037 (23.0)
Pain at 1 location	1,793	1,142 (63.7)	439 (24.5)	212 (11.8)
Pain at ≥ 2 locations	2,712	971 (35.8)	916 (33.8)	825 (30.4)

MrOS: Osteoporotic Fractures in Men Study; na: Not applicable

[a] Original answers for pain interference were “not at all”, “a little bit”, “moderately”, “quite a bit”, or “extremely”.

Table 4.3. Association between musculoskeletal pain and the progression of lower urinary tract symptoms (LUTS) among community dwelling men aged >= 65 years: The MrOS Study, USA. Progression was measured at two- and four-years follow-up.

		LUTS Progression				
	n	**Person-years of follow-up**	**No. Progressed**	**Age-Adjusted** IRR (95% CI)	**Multivariable**[a] IRR (95% CI)	**Multivariable**[b] IRR (95% CI)
Any Pain						
No Pain	1,064	3,580	272	ref	ref	ref
Any Pain	4,505	14,356	1,566	1.45 (1.27, 1.62)	1.37 (1.21, 1.54)	1.33 (1.17, 1.49)
Multi-location pain						
No Pain	1,064	3,580	272	ref	ref	ref
Pain at one location	1,793	5,768	579	1.33 (1.15, 1.51)	1.31 (1.13, 1.48)	1.28 (1.11, 1.45)
Pain at ≥ 2 locations	2,712	8,588	987	1.52 (1.33, 1.71)	1.42 (1.24, 1.60)	1.37 (1.19, 1.54)
Pain Interference						
No Pain	1,064	3,580	272	ref	ref	ref
Pain, no interference	2,113	6,916	666	1.28 (1.11, 1.45)	1.27 (1.10, 1.44)	1.24 (1.07, 1.40)
Pain, minimal interference	1,355	4,368	480	1.46 (1.26, 1.66)	1.40 (1.21, 1.60)	1.37 (1.18, 1.56)
Pain, ≥ moderate interference	1,037	3,072	420	1.80 (1.55, 2.05)	1.62 (1.38, 1.86)	1.54 (1.31, 1.77)

AUA-SI: American Urological Association Symptom Index; IRR: Incidence rate ratio; CI: Confidence interval

[a] Adjusted for age, hypertension, mobility difficulties, and history of prostate surgery.

[b] Adjusted for age, hypertension, mobility difficulties, history of prostate surgery, history of prostatitis, psychological distress, and LUTS medication use.

Chapter 5. Symptoms of central sensitization are associated with worse lower urinary tract symptoms in men

Angela Senders[1], Kamran P Sajadi[2], Thu Le[1], Ryan Wexler[3], Alex Wang[2], Scott R Bauer[4,5], Yiyi Chen[6], Barry Oken[7], Lynn M Marshall[1]

1. Oregon Health & Science University-Portland State University School of Public Health, Portland, OR, USA
2. Department of Urology, Oregon Health & Science University, Portland, OR, USA
3. Helfgott Research Institute, National University of Natural Medicine, Portland, OR, USA
4. Departments of Medicine and Urology, University of California San Francisco, San Francisco, CA, USA
5. Veterans Affairs Medical Center, San Francisco, CA, USA
6. Seagen, Inc., Bothell, WA, USA
7. Department of Neurology, Oregon Health & Science University, Portland, OR, USA

Funding: This work was supported by the National Center for Complementary and Integrative Health (grant number K23AT008211 to AS] and the National Center for Advancing Translational Sciences (NCATS) National Institutes of Health (grant number

UL1TR002369). This work was also supported by grants and awards to SRB from the National Institute of Diabetes, Digestive, and Kidney Disorders (grant number 1K12DK111028), the National Institute on Aging (grant numbers 1R03AG067937 and 1K76AG074903), and the UCSF Claude D. Pepper Older Americans Independence Center funded by National Institute on Aging (grant number P30 AG044281). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Acknowledgments: We thank our study participants for sharing their time and experience with us.

5.1 Abstract

Aims: Central sensitization (CS) has been examined as a possible mechanism of lower urinary tract symptoms (LUTS) among women, but studies among men are lacking. Our objective was to determine the association between symptoms suggestive of CS and LUTS severity among men.

Methods: We conducted a cross-sectional survey and medical record review of 87 men, age 18 years or older, who had received a urodynamic study (UDS) for LUTS in the past 3 years. We collected demographic and clinical characteristics, the American Urological Association Symptom Index (AUA-SI), and the Central Sensitization Inventory (CSI). We used multivariable linear regression to model the association between symptoms suggestive of CS (CSI ≥ 40) and AUA-SI score, adjusting for age, neurologic diagnosis, LUTS etiology on UDS, and history of urologic procedure between UDS and survey completion.

Results: The mean (standard deviation, SD) age of the sample was 66 (14) years, 29% had CSI scores ≥ 40, and the mean (SD) AUA-SI score was 15 (9) points. The adjusted mean AUA-SI score was 6.5 (95%CI: 2.6,10.4) points higher among men with symptoms suggestive of CS compared to those without. Results were materially unchanged after excluding men with a neurologic diagnosis or those with urologic/pelvic pain.

Conclusions: Symptoms suggestive of CS were common among men with a recent history of urodynamic study for LUTS and were significantly associated with higher AUA-

SI scores, independent of existing neurologic and chronic pain conditions. Studies that use objective measures to assess for CS among men with LUTS are warranted.

5.2 Introduction

Lower urinary tract symptoms (LUTS) are common, affecting approximately 25% of US adults older than 50 years of age.[1] Severe LUTS are associated with decreased quality of life[8] and pharmacologic treatments are often limited by modest efficacy, side effects, and the need for long-term therapy.[10] Despite this high prevalence and public health burden, the pathophysiological mechanisms underlying LUTS onset and progression are not fully understood. Clinically, urodynamic testing is used to assess how well the bladder, urethra, and sphincters store and release urine. However, there are non-urologic factors that can also contribute to LUTS, even among individuals with pathologic findings on urodynamic study (UDS).[10] Accordingly, in an effort to improve our understanding of LUTS risk, prevention, and management, experts have highlighted the importance of investigating possible effects of psychological and behavioral factors, comorbid conditions, and non-urologic physiologic processes on LUTS.[10]

Central sensitization (CS) has been proposed as a non-urologic mechanism of LUTS.[14] CS occurs when the central nervous system amplifies sensory signals, resulting in hypersensitivity to painful stimuli, as well as non-painful stimuli such as sound, light, and odor.[15] Although CS is recognized as an underlying mechanism in painful urinary conditions such as bladder pain syndrome and chronic prostatitis, whether it also plays a role in non-painful LUTS is unknown. For example, CS-related sensory amplification of bladder stretch or pressure could result in storage LUTS, such as urinary urgency, frequency, and nocturia.[14] Studies conducted among women with overactive bladder

provide emerging evidence that supports an association between CS and non-painful LUTS.[16–18,79,82] However, it is unclear if inferences made from these studies also apply to men or to LUTS resulting from other etiologies.

The objective of this study was to evaluate the association between symptoms suggestive of CS and LUTS severity in a clinical sample of men who had received urodynamic testing for LUTS. We hypothesized that symptoms suggestive of CS would be positively associated with LUTS severity, independent of LUTS etiology or urologic/pelvic pain.

5.3 Methods

Study Sample

Participants were recruited from the Oregon Health & Science University (OHSU) Department of Urology in Portland, Oregon between June-August, 2020. Cis-gendered men ≥ 18 years of age who underwent UDS to evaluate LUTS within the three years prior to recruitment received an email or hard copy invitation to complete a survey. Those who agreed to participate gave permission for study personnel to extract relevant information from their medical record. The study was approved by the OHSU Institutional Review Board. All participants provided written informed consent.

Primary Independent Variable: Central Sensitization Symptoms

Symptoms suggestive of CS were assessed with the validated Central Sensitization Inventory (CSI).[44] The CSI includes 25 subjective experiences commonly reported by people with CS. Respondents indicate their level of agreement with statements such as "I feel pain all over my body", "I do not sleep well", "I have difficulty concentrating", and "I am sensitive to bright lights". Item scores are summed for an overall score (range 0-100 points). When scoring the CSI, we removed one item that overlapped with our measure of LUTS severity, "I have to urinate frequently", and summed for an overall score of 0-96. CSI scores were categorized as unlikely to have CS (0-30 points) or symptoms suggestive of CS (>= 40 points).[66]

Dependent Variable: Lower Urinary Tract Symptom Severity

LUTS were assessed with the American Urologic Association Symptom Index (AUA-SI).[19] The AUA-SI includes seven items on urinary urgency, frequency, nocturia, straining, weak stream, intermittency, and/or incomplete emptying in the previous 30 days. Item scores are summed for a total score (range 0-35 points). For descriptive analyses, AUA-SI scores were categorized as no/mild (0-7 points), moderate (8-19 points), or severe (≥ 20 points) LUTS according to standard practice. A change of 3.1 points on the AUA-SI represents a minimally important difference.[23]

Other Independent Variables

Age was assessed as a continuous variable. Length of time with LUTS was categorized as a binary variable of more than two years (yes/no). Painful urologic/pelvic symptoms in the last week (yes/no) included any pain in the perineum, testicles, tip of the penis, pubic or bladder area, or pain during urination or ejaculation.[119] Respondents reported (yes/no) whether they had ever been told by a healthcare provider that they had a painful urologic diagnosis, including chronic prostatitis, chronic pelvic pain syndrome, or bladder pain syndrome/interstitial cystitis. LUTS medication was categorized as a binary variable indicating current use of any alpha-1 adrenergic antagonist, 5-alpha reductase inhibitor, anticholinergic, phosphodiesterase-5 inhibitor, or beta-3 adrenergic agonist.

Additional data were extracted from the medical record in duplicate (TL, AW, AS) using a standardized extraction guide. We extracted any AUA-SI score recorded at the time of UDS, whether or not respondents had a neurological diagnosis that may interfere with urinary function (yes/no), and whether participants received a urologic procedure between the time of their UDS and survey completion (e.g. prostatectomy, sacral neuromodulation, etc.). We also recorded the diagnostic impression of the physician (KS) who conducted all of the urodynamic studies. From this, we categorized LUTS etiology as pathologic (e.g. bladder outlet obstruction due to stricture or enlarged prostate, neurogenic bladder, etc.), idiopathic, or unclear. Due to sparse data, we categorized LUTS etiology as a binary variable (pathologic vs. idiopathic/unclear) for regression analyses.

Missing Data

Twelve respondents left one item on the CSI blank, two respondents left two items blank, and one respondent left three items blank. To generate a total CSI score for these individuals, we conservatively assumed that they did not endorse the blank item statement and set the item score to 0.

Five respondents left one item on the AUA-SI blank. To generate a total AUA-SI score for these individuals, we replaced their missing item value with the sample median for that item. One respondent with multiple missing items on the AUA-SI was excluded from this analysis.

Statistical Analysis

As a descriptive analysis, we compared age and length of time between UDS and study recruitment between men who did and did not participate in this study. Among participants, we compared characteristics across categories of LUTS severity and across categories of CSI score using one-way analysis of variance (ANOVA) for continuous variables or Fisher's exact test for categorical variables. We computed the proportion of the sample with symptoms suggestive of CS. We also explored change in AUA-SI score among men who had a urologic procedure between UDS and survey completion.

We used multivariable linear regression to estimate beta coefficients (β) and 95% confidence intervals (CI) as the measure of association between CSI and AUA-SI scores. To guide our analyses, we followed a conceptual framework (Figure 1).[86] Our first model

estimated the unadjusted association between CSI and AUA-SI scores. Coefficients from model 2 were adjusted for potential confounding by age, neurologic diagnosis, and LUTS etiology. Model 3 coefficients were further adjusted for a history of urologic procedure. Model 4 coefficients were further adjusted for variables that may mediate the association between CS and LUTS severity, including painful urologic/pelvic symptoms, history of a painful urologic diagnosis, and current use of LUTS medication. We adjusted for urologic procedure separately in Model 3 because it could be a confounding factor or an intermediate variable. Adjusting for urologic procedure could account for any residual confounding as a result of incomplete adjustment for LUTS etiology, because LUTS etiology informs the clinical recommendation for a therapeutic procedure. Alternatively, individuals with CS may be less likely to be prescribed, or agree to, a procedural intervention for LUTS, which would place urologic procedure in the pathway between CS and LUTS severity.

As a sensitivity analysis, we re-fitted the models by excluding certain groups of individuals from the analysis. We excluded men with 1) a neurologic diagnosis, 2) idiopathic or unclear LUTS etiologies, 3) a urologic procedure between UDS and survey completion, 4) urologic/pelvic pain symptoms within the week prior to survey, 5) a history of a painful urologic diagnosis, or 6) either urologic/pelvic pain symptoms or a history of a painful urologic diagnosis. We reasoned that any observed association of CSI and AUA-SI score among men with a pathologic diagnosis might vary according to whether men had a urologic procedure between UDS and the time of survey

completion. Therefore, we performed a separate sensitivity analysis stratifying by procedure status among men with a pathologic diagnosis. Due to small sample sizes, we only adjusted for age in this analysis. Finally, we explored the association between CSI and AUA-SI scores among men with a pathologic LUTS etiology who did not have a neurologic diagnosis, representing a subsample of men for whom bladder outlet obstruction was the primary reason for their LUTS. Due to small sample sizes, we present the unadjusted difference in mean AUA-SI scores for those with and without symptoms suggestive of CS.

Stata 14.2 (StataCorp LLC, College Station, TX, USA) was used for all analyses.

5.4 Results

We invited 204 eligible men to participate in this study. Forty-three declined, 73 did not respond to recruitment efforts, and one was excluded for missing data resulting in a study sample of 87 men (response 43%). Among respondents and non-respondents, respectively, average time between UDS and recruitment was 1.97 years and 2.00 years ($p=0.80$), whereas average age was 65.6 years and 55.8 years ($p<0.0001$).

Nearly one third (32%) of participants had severe LUTS, 47% reported moderate LUTS, and 21% reported no or mild LUTS (Table 1). Men with severe LUTS were more likely to report painful urologic/pelvic symptoms in the prior week compared to men with no/mild or moderate LUTS; there was no difference in a history of painful urologic diagnosis across categories of LUTS severity. Men with no/mild LUTS were more likely

to have a pathologic LUTS etiology on UDS, and they were also more likely to have had a urologic procedure between UDS and survey completion. Of the 27 men who had a urologic procedure, 19 had an AUA-SI score on record at the time of their UDS. For these men, the mean change (SD) in AUA-SI score was a decrease of 8.4 (8.4) points ($p < 0.001$) between UDS and our survey.

Compared to men unlikely to have CS, men with symptoms suggestive of CS were on average younger, more likely to report painful urologic symptoms in the prior week, more likely to have a neurologic diagnosis, and less likely to have had a urologic procedure between UDS and study enrollment (Supplementary Table).

The mean (SD) AUA-SI score for the analytic sample was 15.0 (8.8) points. Symptoms suggestive of CS were observed for 25 respondents, which was 28.7% (95% CI: 19.5%, 39.4%) of the sample. Symptoms suggestive of CS were observed among 26.6% of men with a pathologic LUTS etiology and among 33.3% of men with idiopathic or unclear LUTS etiologies.

Men with symptoms suggestive of CS scored an average of 6.7 points higher on the AUA-SI than men unlikely to have CS (95% CI: 2.7, 10.6) after adjusting for age, neurologic diagnosis, and LUTS etiology (Table 2). Men with symptoms suggestive of CS were less likely to have had a urologic procedure than men unlikely to have CS (16% vs. 37%, $p=0.05$); however, further adjustment for urologic procedure slightly attenuated the β coefficient to 6.5 (95% CI: 2.6, 10.4). Adjustment for suspected mediators led to further modest attenuation of the β coefficient to 6.1 (95% CI: 2.1, 10.1).

The magnitude of the β coefficient remained relatively stable in the sensitivity analysis with restricted samples (Table 3). For example, after excluding men with a neurological diagnosis, the β coefficient was 6.1 (95% CI: 1.1, 11.07; n=57). Upon excluding men with an idiopathic or unclear LUTS etiology the β coefficient was 8.2 (95% CI: 3.5, 12.9; n=60). Likewise, after excluding men who reported urologic/pelvic pain or a history of painful urologic diagnosis, the β coefficient was 6.3 (95% CI: 0.8, 11.8; n=52).

The β coefficient also remained stable when we restricted to men with a pathologic etiology and stratified by urologic procedure. The age-adjusted β coefficient was 7.4 (95% CI: 1.5, 13.2; n=35) for men who did not have a urologic procedure and 10.6 (95% CI: 3.4, 18.1; n=25) for those who had. Among men with a pathologic etiology who did not have a neurologic diagnosis, the mean AUA-SI score was 12.7 points higher among those with symptoms suggestive of CS compared to those unlikely to have CS (95% CI: 5.4, 20.1; n=33).

5.5 Discussion

Using a validated measure of CS symptoms in a clinical sample of men with a history of UDS, we observed that men with symptoms suggestive of CS on average reported higher AUA-SI scores compared to those without symptoms suggestive of CS, independent of age, neurologic diagnosis, LUTS etiology, and history of urologic procedure. The association between symptoms suggestive of CS and LUTS severity persisted after excluding men with idiopathic LUTS and those with urologic/pelvic pain. Our results are

consistent with emerging evidence that CS may be an underlying mechanism for some men with LUTS.[14]

Several studies have documented the co-occurrence of LUTS with conditions that have an underlying CS component.[17,82,88,89] Additionally some,[16,79] although not all,[80] laboratory studies have demonstrated that individuals with overactive bladder (OAB) tend to exhibit decreased pain tolerance to non-pelvic mechanical and thermal stimuli compared to healthy controls. Because the majority of these studies were conducted among women, it is unknown whether features of CS are also associated with LUTS in men. Recently, we used musculoskeletal pain as a proxy for CS and showed that the prevalence of musculoskeletal pain in multiple anatomic locations is greater among community dwelling men with moderate or severe LUTS compared to those with no/mild LUTS.[120]

Our current study extends the prior literature by administering a validated measure of CS-related symptoms to men with LUTS. To date, only one other study has examined the CSI in relation to LUTS severity. Specifically, in a clinical sample of 177 women with chronic pelvic pain, the adjusted odds of moderate to severe LUTS were 4.5 times greater among women with symptoms suggestive of CS (CSI ≥ 40) than women unlikely to have CS.[81] Our study furthers this work by including men and demonstrating that the association between CSI and AUA-SI scores exists even among those without urologic/pelvic pain.

It has been unclear whether LUTS etiology would impact any association of symptoms suggestive of CS and AUA-SI scores, which our study also addresses. We observed a strong association between CSI and AUA-SI scores in this heterogenous sample of men with neurologic, obstructive, and/or idiopathic findings on UDS. There is evidence that CS may contribute to urinary symptoms among people with neurologic conditions, including spinal cord injury, Parkinson's disease, and multiple sclerosis.[19–21] However, after removing men with these neurologic diagnoses from our sample, the association between CSI and AUS-SI scores persisted among men with obstructive or idiopathic LUTS etiologies. Moreover, a hallmark of conditions in which CS plays a prominent role (e.g. fibromyalgia, irritable bowel syndrome) is that symptoms often present in the absence of suggestive organic pathology. For this reason, it is hypothesized that CS may contribute to idiopathic LUTS, as well.[14] Yet in our study, the strong positive association between CSI and AUA-SI scores remained among a subset of men for whom most LUTS were attributed to bladder outlet obstruction. Because symptoms suggestive of CS were positively associated with LUTS regardless of the exclusions we made, we propose that CS may be associated with a wider range of LUTS etiologies than has previously been discussed in the literature.

The association of symptoms suggestive of CS and LUTS subtypes among men also warrants consideration. The ways in which CS may contribute to storage symptoms associated with OAB have been well-articulated,[6] yet little attention has been paid to the possible role of CS in voiding symptoms which typically are associated with

obstructive pathologies. Our results suggest that CS is associated with obstructive pathologies, and by extension, may contribute to the severity of voiding symptoms that often accompany these conditions. While we did not differentiate between storage and voiding symptoms in this study, in our prior work using musculoskeletal pain as a proxy for CS we found that the association between musculoskeletal pain and LUTS severity was similar between men with predominantly storage symptoms and men with predominantly voiding symptoms.[17] Moreover, the strength of association between musculoskeletal pain and LUTS was greatest among men with the highest storage and voiding subscores. Taken together, our findings suggest that CS may contribute to the sensory amplification of voiding LUTS associated with obstructive pathologies.

This study has limitations. This was a small cross-sectional study, causality cannot be inferred from our findings. The sample size was large enough, however, to identify important signals of an association between CS symptoms and LUTS severity in men, an understudied population. Our survey response was 43%. We had limited information on non-respondents and could only discern that they tended to be younger, on average, than study participants. Several studies have observed similar or lower mean CSI scores among older compared to younger adults,[121–123] thus it is difficult to conceive of a scenario in which the inclusion of older respondents in this study would have produced an association between CSI and AUA-SI scores if one truly does not exist. The time between UDS and survey completion could have been as long as 3 years and the etiology of an individual's LUTS may have changed during this time. Further, we were

able to determine and account for urologic procedures subsequent to UDS that occurred at our institution, but if men had a procedure at a different location they would have been misclassified. Finally, we had a heterogeneous sample in terms of age, comorbidities, and LUTS pathology. Nevertheless, our findings were robust to sample size limitations and heterogeneity, suggesting that CS may be associated with a broader set of LUTS cases than has previously been hypothesized.

5.6 Conclusion

We observed a strong positive association between symptoms suggestive of CS and LUTS severity in a clinical sample of men. Our results suggest that CS could contribute to non-painful LUTS and LUTS in men with abnormal UDS. Future investigations of CS and LUTS should include men with a range of LUTS pathologies.

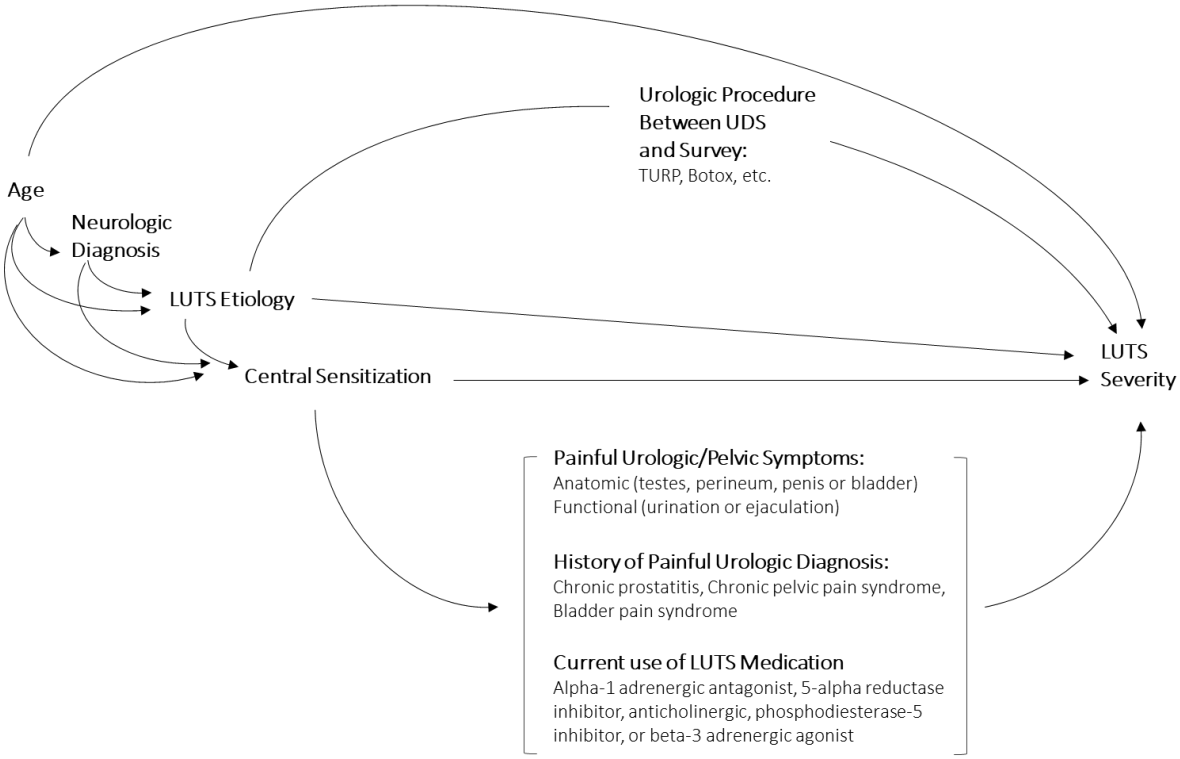


Figure 5.1. Conceptual framework for the association between central sensitization (CS) and lower urinary tract symptom (LUTS) severity. We assessed factors that were associated with CS, LUTS, or both for potential confounding, including age, neurologic diagnosis, and LUTS etiology. LUTS etiology informs the clinical recommendation for a therapeutic procedure. However, individuals with CS may be less likely to be prescribed or agree to a procedural intervention for LUTS. Thus, an alternative location for urologic procedure could be on the pathway between CS and LUTS severity.

Table 5.1. Characteristics of the analytic sample (n=87) according to lower urinary tract symptom (LUTS) severity.

		LUTS Severity			
	Full Sample	**None/Mild**	**Moderate**	**Severe**	*p* value[a]
N (%) of study sample	87 (100%)	18 (21%)	41 (47%)	28 (32%)	
Age, mean (SD), years	65.6 (14.0)	65.0 (16.5)	66.3 (12.5)	65.9 (14.8)	0.95
Had LUTS > 2 years	69 (82%)	15 (88%)	30 (77%)	24 (86%)	0.61
Painful urologic/pelvic symptoms	21 (24%)	2 (11%)	8 (20%)	11 (39%)	0.07
History of painful urologic diagnosis	22 (25%)	5 (28%)	10 (24%)	7 (25%)	0.95
Current LUTS medication use	35 (40%)	4 (22%)	20 (49%)	11 (39%)	0.17
Neurologic diagnosis[b]	30 (34%)	6 (33%)	14 (34%)	10 (36%)	0.99
LUTS Etiology					0.06
Pathologic[c]	60 (69%)	16 (89%)	30 (73%)	14 (50%)	
Idiopathic	13 (15%)	1 (6%)	4 (10%)	8 (29%)	
Unclear	14 (16%)	1 (6%)	7 (17%)	6 (21%)	
Urologic procedure since UDS	27 (31%)	11 (61%)	13 (32%)	3 (11%)	0.001

UDS: Urodynamic study

[a]P values comparing the characteristic according to LUTS severity are derived from ANOVA for continuous variables and Fisher's exact test for categorical variables.

[b]Neurologic diagnoses included Parkinson's (n=11), spinal cord injury (n=7), multiple sclerosis or transverse myelitis (n=6), spina bifida (n=2), neurogenic bladder as a result of prior surgery (n=2), autoimmune encephalitis (n=1), and Charcot-Marie-Tooth (n=1).

[c]Pathologic LUTS etiologies included benign prostatic obstruction (n=27), neurogenic bladder (n=19), bladder outlet obstruction (n=8), bladder diverticula (n=2), hostile neuropathic bladder (n=1), complex LUT dysfunction (n=1), post-prostatectomy complication (n=1), and radical pelvic surgery (n=1).

Table 5.2. Association between symptoms suggestive of central sensitization syndrome and lower urinary tract symptom (LUTS) severity in a clinical sample of men with a history of urodynamic testing (N=87).

		Model 1 - Crude		Model 2[a]		Model 3[b]		Model 4[c]	
Independent Variable	**n (%)**	β	**95% CI**	β	**95% CI**	β	**95% CI**	β	**95% CI**
CSI (0-39 points)	62 (71.3)	ref	-	ref	-	ref	-	ref	-
CSI (≥ 40 points)	25 (28.7)	7.0	3.1,10.9	6.7	2.7,10.6	6.5	2.6,10.4	6.1	2.1,10.1

β: Regression coefficient; CI: Confidence interval; CSI: Central Sensitization Inventory

[a]Adjusted for age, neurologic diagnosis, and LUTS etiology.

[b]Adjusted for age, neurologic diagnosis, LUTS etiology, and urologic procedure.

[c]Adjusted for age, neurologic diagnosis, LUTS etiology, urologic procedure, painful urologic/pelvic symptoms in the previous week, history of painful urologic diagnosis (chronic prostatitis, chronic pelvic pain syndrome, or bladder pain syndrome), and current use of LUTS medication (including any alpha-1 adrenergic antagonist, 5-alpha reductase inhibitor, anticholinergic, phosphodiesterase-5 inhibitor, or beta-3 adrenergic agonist).

Table 5.3. A sensitivity analysis in which various, non-sequential exclusions were applied.

	Independent Variable	n (%)	β	95% CI
Complete Analytic Sample[a] (n=87)	CSI (0-39 points)	62 (71)	6.5	2.6,10.4
	CSI (≥ 40 points)	25 (28)		
Excludes neurological diagnoses[b] (n=57)	CSI (0-39 points)	46 (81)	6.1	1.1,11.1
	CSI (≥ 40 points)	11 (19)		
Excludes idiopathic/unclear LUTS etiologies[c] (n=60)	CSI (0-39 points)	44 (73)	8.2	3.5,12.9
	CSI (≥ 40 points)	16 (27)		
Excludes urologic procedure[d] (n=60)	CSI (0-39 points)	39 (65)	6.1	1.5,10.7
	CSI (≥ 40 points)	21 (35)		
Excludes urologic/pelvic pain symptoms (n=66)	CSI (0-39 points)	52 (79)	7.5	2.9,12.2
	CSI (≥ 40 points)	14 (21)		
Excludes history of painful urologic diagnosis (n=65)	CSI (0-39 points)	46 (71)	5.4	0.9,9.9
	CSI (≥ 40 points)	19 (29)		
Excludes both urologic/pelvic pain symptoms and history of painful urologic diagnosis[a] (n=52)	CSI (0-39 points)	42 (81)	6.3	0.8,11.8
	CSI (≥ 40 points)	10 (19)		

β: Regression coefficient; CI: Confidence interval; CSI: Central Sensitization Inventory

[a] Reported as Model 3 in Table 2. Adjusted for age, neurologic diagnosis, LUTS etiology, and urologic procedure

[b] Adjusted for age, LUTS etiology, and urologic procedure

[c] Adjusted for age, neurologic diagnosis, and urologic procedure

[d] Adjusted for age, neurologic diagnosis, and LUTS etiology

Chapter 6. Discussion

6.1 Overview of Dissertation Objectives

The objective of this dissertation research was to investigate CS as a possible mechanism of non-painful LUTS in men. Emerging evidence supports an association between CS and LUTS, although the majority of studies have been conducted in small clinical samples of women with overactive bladder. To our knowledge, the studies conducted for this dissertation are among the first to specifically interrogate the association between CS and LUTS among men.

If CS plays a role in LUTS etiology among males, then positive associations among features of CS and LUTS outcomes should be observable in population-based and clinical epidemiologic studies. Due to the paucity of existing research, a cross-sectional study design is an appropriate first step to investigate distributional patterns of variables of interest. Therefore, we assessed the cross-sectional association between symptoms suggestive of CS and LUTS severity among community-dwelling men in Aim 1 and a clinical sample of men in Aim 3. In Aim 1, we hypothesized that the prevalence of symptoms suggestive of CS would be significantly higher among men with LUTS compared to those without. In Aim 3, we hypothesized that symptoms suggestive of CS would be positively associated with LUTS severity.

If symptoms suggestive of CS are more prevalent among men with increasingly severe LUTS, it raises the question of whether CS might also be a risk factor for LUTS

progression. Because a cross-sectional design cannot determine if sensitization precedes the worsening of LUTS symptoms, we utilized a prospective study design in Aim 2 to investigate the temporal association between CS and LUTS. We hypothesized that symptoms suggestive of CS would be positively associated with the worsening of LUTS symptoms over time. Using the same national sample of community-dwelling men from our first aim, we conducted a prospective cohort study to investigate the association between CS and LUTS progression.

6.2 Summary of Findings

In our first cross-sectional study (Aim 1, Chapter 3), we measured the association between musculoskeletal pain, a symptom suggestive of CS, and LUTS severity in a large US cohort of community-dwelling men. We observed that the prevalence of any musculoskeletal pain rose with increasing severity of LUTS, independent of age, mobility limitations, LUTS medication use, and history of prostatitis. The association was strongest for men with pain in multiple locations and similar for men who reported predominantly storage symptoms and those who reported predominantly voiding symptoms.

In our second cross-sectional study (Aim 3, Chapter 5), we administered a validated measure of symptoms suggestive of CS to a clinical sample of men with a recent history of urodynamic testing. We observed that, on average, men with symptoms suggestive of CS reported higher AUA-SI scores compared to those with unlikely CS, independent of

age, neurologic diagnosis, LUTS etiology, and history of urologic procedure. This association remained strong, even after excluding men with idiopathic LUTS and those with urologic/pelvic pain.

Finally, in our prospective cohort study (Aim 2, Chapter 4), we returned to using musculoskeletal pain as symptom suggestive of CS among community-dwelling older men. In this study, individuals with musculoskeletal pain had an increased risk of LUTS progression over two years, independent of age, prostatitis, prostate surgery, hypertension, mobility difficulties, psychological distress, and LUTS medication use. In contrast to our Aim 1 results, the association between musculoskeletal pain and LUTS progression was similar among men with pain at one and two or more bodily locations. However, the risk of LUTS progression rose with increasing levels of pain interference and was highest for those with at least moderate pain interference. Together, the evidence generated from Aims 1 and 2 suggest that there is an association between the presence of musculoskeletal pain and LUTS severity and progression. These findings are consistent with emerging evidence that CS may contribute to a portion of LUTS cases.

Our work expands on the current CS-LUTS literature in three important ways. First, the majority of studies to investigate an association between CS and LUTS have been conducted in women.[16–18,82] We present some of the first studies to support this hypothesis in men. Second, CS has rarely been explored as a risk factor for non-painful LUTS. As a mechanism of chronic pain conditions, evidence suggests CS contributes to painful urinary conditions such as chronic pelvic pain and bladder pain syndrome. Only

recently has the concept of CS come to include a hypersensitivity not only to painful stimuli, but other sensations like stretch, warmth, light, and sound, as well. Our work capitalizes on this recent understanding and provides evidence that symptoms suggestive of CS are highly prevalent among men with non-painful LUTS. Third, prior studies of CS and non-painful LUTS have primarily been limited to one type of LUTS etiology: storage symptoms related to OAB. Our work suggests that CS may be associated with LUTS, independent of LUTS etiology. In Aim 1, we observed that musculoskeletal pain was just as prevalent among men with primarily storage symptoms as it was among men with predominantly voiding symptoms. In Aim 3, we found that symptoms suggestive of CS were associated with AUA-SI scores, even after restricting our study sample to men with obstructive pathologies on UDS. Taken together, our findings suggest that future CS-LUTS investigations should not be limited to OAB but instead include a wide range of LUT etiologies, including obstructive/voiding pathologies that have received little research attention thus far.

6.3 Limitations and Future Directions

Our Aim 1 and 2 studies were limited in two important ways. First, musculoskeletal pain was limited as a proxy for CS in that we were unable to verify that pain was current at the baseline measurement, nor could we distinguish acute from chronic pain. Second, we were unable to fully assess the association between musculoskeletal pain and *non-painful* LUTS because painful urologic conditions were not assessed in the MrOS cohort.

The MrOS cohort was established in 1998, well before the current interest in CS as a potential mechanism of non-painful LUTS and prior to development of a validated measure of CS-related symptoms. Based on our findings, future studies that are specifically designed to assess for the presence of CS among men with and without LUTS are essential to advancing the field. A large, prospective cohort that employs validated qualitative and quantitative measures of CS would be the most appropriate next step to study the possible effects of CS on LUTS onset, progression, and treatment response.

In Aim 3, we were able to address the primary shortcomings of Aims 1 and 2 by administering a validated measure of CS-related symptoms and assessing for the presence or history of painful urologic symptoms or diagnoses. In this way, our Aim 3 findings strengthen our interpretation of our Aims 1 and 2 results. For example, chronic musculoskeletal pain is likely a stronger indicator of CS than acute musculoskeletal pain. Had we been able to replace our proxy measure, which did not distinguish between acute and chronic pain, with the CSI, we would expect the association between CSI and LUTS severity and progression to be stronger than what we observed for musculoskeletal pain.

While we were able to address some of the limitations from Aims 1 and 2 in Aim 3, the latter also had weaknesses that should inform future study design. First, the data collection for Aim 3 was originally intended to be prospective; men were to be recruited as they presented to the OHSU urology clinic for UDS. However, early in the COVID-19 pandemic OHSU postponed UDS procedures. We responded to this challenge by instead

recruiting men who had received UDS in the 3 years prior to recruitment. With this design, the etiology of an individual's LUTS may have changed in the time between UDS and our survey and some men may have been misclassified. A stronger cross-sectional study design would have been to administer the survey at the time of the UDS.

Additionally , we began recruiting participants in late summer 2020, just as one of Oregon's most destructive wildfire seasons on record was underway.[124] More than 1.2 million acres and over 5,000 homes and commercial structures were destroyed across the state. Fires and toxic smoke displaced thousands of Oregonians, and more than one study recruit shared with us that they were unable to participate as a result of needing to evacuate their home. The COVID-19 pandemic and destructive wildfire season highlight the limited control we had over the recruitment process and may partially explain why only 43% of recruited individuals took part in the study. We had limited information to assess differences between non-respondents and study participants and were thus unable to fully investigate potential selection bias. Additionally, our sample size was too small to fully interrogate our original hypothesis that the association between CSI and AUA-SI scores would be stronger among men with idiopathic LUTS than those with LUTS that appear to have an organic cause on UDS. A future clinical study that prospectively recruits a larger study sample under less uncertain circumstances is an appropriate next step. This study should include both qualitative and quantitative measures of CS and collect data such that respondents and non-respondents may be compared and potential selection bias assessed.

6.4 Public Health Impact

LUTS are highly prevalent and pose substantial medical and economic burden in the US. Approximately one quarter of men ≥ 65 experience moderate to severe symptoms that often progress over time.[1,42] LUTS of increasing severity are associated with decreased mental and physical quality of life.[6 7,8] Compared to similarly aged men, those with severe LUTS report lower mean quality of life scores than those with hypertension, gout, angina, or diabetes.[7] Many men do not respond to pharmacological treatment,[39] and for others, the modest improvement afforded by LUTS pharmaceuticals is limited by side effects and the need for long-term treatment.[10,125] The direct medical costs of benign prostatic hyperplasia alone have been estimated to exceed 1 billion dollars annually, and this estimate excludes the cost of LUTS medications.[126] The direct and indirect costs of LUTS are expected to grow as the population ages. By 2030, 20% of the population is projected to be ≥ 65,[127] making LUTS a relevant public health concern.

Despite the high prevalence and profound personal and public health burden, there is still a somewhat common perception that LUTS are a consequence of aging that little can be done to prevent.[125] However, a modest literature base suggests that modifiable factors, including obesity, physical activity, alcohol consumption, diet, anxiety, depression, and cardiovascular and/or metabolic comorbidities are associated with LUTS risk, treatment response, or progression.[41,128–130] Our work contributes to the bourgeoning literature in this area and provides evidence in support of CS as a

neurobiological mechanism of LUTS severity and progression. A complete understanding of the mechanisms that contribute to LUTS etiology and natural history is important for public health because this knowledge may lead to new treatments and approaches to prevent this highly prevalent and burdensome condition.

6.5 Clinical Urology Impact

Patients with CS and related conditions often struggle with uncertain diagnoses and feel misunderstood in their search for symptom relief.[131,132] These encounters can also frustrate doctors, delay appropriate care, and increase medical costs.[133–135] If CS is a driver of some LUTS cases, then screening, diagnosis, and treatment of CS could improve a subset of LUTS clinical encounters for patients and doctors alike. We demonstrated a strong association between symptoms suggestive of CS and LUTS using the CSI, a validated measure of CS-related symptoms. The CSI is freely available[136] and easy to administer in a clinical setting, making it a useful tool to screen for individuals who might benefit from additional CS workup.[137] Patients with idiopathic LUTS and/or LUTS that do not respond to standard of care could benefit from understanding how CS might contribute to their symptoms.

If CS is a driver of some LUTS cases, then the nervous system may be an appropriate adjunctive or alternative treatment target for these men. The evidence in support of repetitive transcranial magnetic stimulation and mindfulness-based interventions to treat LUTS with a possible CS component was presented in Chapter 4.

While it has yet to be used in a study of LUTS, cognitive behavioral therapy (CBT) has shown benefit for conditions in which CS plays a prominent role, including fibromyalgia, migraine, IBS, and somatoform disorders.[138–141] Of note, individuals with comorbid anxiety or depression, limited self-efficacy, decreased symptom acceptance, or excessive worry about their symptoms are less likely to experience a positive CBT outcome.[142] Thus, addressing cognitive, emotional, behavioral, and social factors that influence how patients perceive, manage, and respond to their symptoms may improve their response to CBT and other psychosocial interventions.[142] Ultimately, our work suggests that a wholistic, multidisciplinary approach for individuals with high CSI scores and LUTS that do not respond to first-line interventions may be warranted.

6.6 Conclusions

This dissertation presents some of the first studies to investigate CS as a possible mechanism of LUTS among men. Our findings suggest a possible association between CS and LUTS in both older, community-dwelling men from a geographically diverse sample and those who presented to a urology clinic for evaluation and treatment. We observed that symptoms suggestive of CS occur with increasingly greater prevalence among men with mild, moderate, and severe LUTS and are associated with worsening LUTS over time. Our results expand the current literature base of CS-LUTS investigations to include non-painful LUTS and LUTS in men with abnormal UDS. Future investigations of CS and LUTS should include men with non-painful LUTS and a range of LUTS etiologies.

References

1. Kupelian V, Wei JT, O'Leary MP, et al. Prevalence of Lower Urinary Tract Symptoms and Effect on Quality of Life in a Racially and Ethnically Diverse Random Sample: The Boston Area Community Health (BACH) Survey. *Arch Intern Med*. 2006;166(21):2381-2387. doi:10.1001/archinte.166.21.2381

2. Boyle P, Robertson C, Mazzetta C, et al. The prevalence of lower urinary tract symptoms in men and women in four centres. The UrEpik study. *BJU International*. 2003;92(4):409-414. doi:10.1046/j.1464-410X.2003.04369.x

3. Andersson SO, Rashidkhani B, Karlberg L, Wolk A, Johansson JE. Prevalence of lower urinary tract symptoms in men aged 45–79 years: a population-based study of 40 000 Swedish men. *BJU International*. 2004;94(3):327-331. doi:10.1111/j.1464-410X.2004.04930.x

4. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology*. 2003;61(1):37-49. doi:10.1016/S0090-4295(02)02243-4

5. Elstad EA, Taubenberger SP, Botelho EM, Tennstedt SL. Beyond incontinence: the stigma of other urinary symptoms. *J Adv Nurs*. 2010;66(11):2460-2470. doi:10.1111/j.1365-2648.2010.05422.x

6. Coyne KS, Wein AJ, Tubaro A, et al. The burden of lower urinary tract symptoms: evaluating the effect of LUTS on health-related quality of life, anxiety and depression: EpiLUTS. *BJU International*. 2009;103(s3):4-11. doi:10.1111/j.1464-410X.2009.08371.x

7. Welch G, Weinger K, Barry MJ. Quality-of-life impact of lower urinary tract symptom severity: results from the Health Professionals Follow-up Study. *Urology*. 2002;59(2):245-250. doi:10.1016/S0090-4295(01)01506-0

8. Robertson C, Link CL, Onel E, et al. The impact of lower urinary tract symptoms and comorbidities on quality of life: the BACH and UREPIK studies. *BJU International*. 2007;99(2):347-354. doi:10.1111/j.1464-410X.2007.06609.x

9. Litman HJ, McKinlay JB. The future magnitude of urological symptoms in the USA: projections using the Boston Area Community Health survey. *BJU International*. 2007;100(4):820-825. doi:10.1111/j.1464-410X.2007.07018.x

10. Bavendam TG, Norton JM, Kirkali Z, et al. Advancing a Comprehensive Approach to the Study of Lower Urinary Tract Symptoms. *J Urol*. 2016;196(5):1342-1349. doi:10.1016/j.juro.2016.05.117

11. Latremoliere A, Woolf CJ. Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. *J Pain*. 2009;10(9):895-926. doi:10.1016/j.jpain.2009.06.012

12. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature*. 1983;306(5944):686-688. doi:10.1038/306686a0

13. Woolf CJ, Salter MW. Neuronal Plasticity: Increasing the Gain in Pain. *Science*. 2000;288(5472):1765-1768. doi:10.1126/science.288.5472.1765

14. Reynolds WS, Dmochowski R, Wein A, Bruehl S. Does central sensitization help explain idiopathic overactive bladder? *Nature Reviews Urology*. 2016;13(8):481-491. doi:10.1038/nrurol.2016.95

15. Harte SE, Harris RE, Clauw DJ. The neurobiology of central sensitization. *Journal of Applied Biobehavioral Research*. 2018;23(2):e12137. doi:10.1111/jabr.12137

16. Reynolds WS, Brown ET, Danford J, et al. Temporal summation to thermal stimuli is elevated in women with overactive bladder syndrome. *Neurourol Urodyn*. 2017;36(4):1108-1112. doi:10.1002/nau.23059

17. Reynolds WS, Mock S, Zhang X, et al. Somatic syndromes and chronic pain in women with overactive bladder. *Neurourol Urodyn*. 2017;36(4):1113-1118. doi:10.1002/nau.23060

18. Altman D, Nyman AI, Lundholm C, Milsom I, Pedersen NL. Somatic comorbidity in women with overactive bladder syndrome. *J Urol*. 2016;196(2):473-477. doi:10.1016/j.juro.2016.02.076

19. Barry MJ, Fowler FJ, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*. 1992;148(5):1549-1557; discussion 1564.

20. Badía X, García-Losa M, Dal-Ré R. Ten-language translation and harmonization of the International Prostate Symptom Score: developing a methodology for multinational clinical trials. *Eur Urol*. 1997;31(2):129-140. doi:10.1159/000474438

21. Nontakaew K, Kochakarn W, Kijvika K, Viseshsindh W, Silpakit C. Reliability of a Thai version of the International Prostate Symptom Score (IPSS) for the Thai population. *J Med Assoc Thai*. 2014;97(6):615-620.

22. Quek KF, Chua CB, Razack AH, Low WY, Loh CS. Construction of the Mandarin version of the International Prostate Symptom Score inventory in assessing lower urinary tract symptoms in a Malaysian population. *Int J Urol*. 2005;12(1):39-45. doi:10.1111/j.1442-2042.2004.00988.x

23. Barry MJ, Williford WO, Chang Y, et al. Benign Prostatic Hyperplasia Specific Health Status Measures in Clinical Research: How Much Change in the American Urological Association Symptom Index and the Benign Prostatic Hyperplasia Impact Index is Perceptible to Patients? *The Journal of Urology*. 1995;154(5):1770-1774. doi:10.1016/S0022-5347(01)66780-6

24. McConnell JD, Roehrborn CG, Bautista OM, et al. The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia. *New England Journal of Medicine*. 2003;349(25):2387-2398. doi:10.1056/NEJMoa030656

25. Parsons JK, Wilt TJ, Wang PY, et al. Progression of lower urinary tract symptoms in older men: a community based study. *J Urol*. 2010;183(5):1915-1920. doi:10.1016/j.juro.2010.01.026

26. Parsons JK, Mougey J, Lambert L, et al. Lower urinary tract symptoms increase the risk of falls in older men. *BJU International*. 104(1):63-68. doi:10.1111/j.1464-410X.2008.08317.x

27. Morris V, Wagg A. Lower urinary tract symptoms, incontinence and falls in elderly people: time for an intervention study. *International Journal of Clinical Practice*. 2007;61(2):320-323. doi:10.1111/j.1742-1241.2006.01174.x

28. von Renteln-Kruse W, Krause T. [Fall events in geriatric hospital in-patients. Results of prospective recording over a 3 year period]. *Z Gerontol Geriatr*. 2004;37(1):9-14. doi:10.1007/s00391-004-0204-7

29. Nørby B, Nordling J, Mortensen S. Lower Urinary Tract Symptoms in the Danish Population: A Population-Based Study of Symptom Prevalence, Health-Care Seeking Behavior and Prevalence of Treatment in Elderly Males and Females. *European Urology*. 2005;47(6):817-823. doi:10.1016/j.eururo.2005.01.011

30. Seim A, Hoyo C, Østbye T, Vatten L. The prevalence and correlates of urinary tract symptoms in Norwegian men: The HUNT Study. *BJU International*. 2005;96(1):88-92. doi:10.1111/j.1464-410X.2005.05573.x

31. Valentino RJ, Sheng C, Yan Z, Aston-Jones G. Evidence for divergent projections to the brain noradrenergic system and the spinal parasympathetic system from Barrington's nucleus. *Brain Research*. 1996;732(1):1-15. doi:10.1016/0006-8993(96)00482-9

32. Benarroch EE. The locus ceruleus norepinephrine system: Functional organization and potential clinical significance. *Neurology*. 2009;73(20):1699-1704. doi:10.1212/WNL.0b013e3181c2937c

33. Valentino RJ, Wood SK, Wein AJ, Zderic SA. The bladder–brain connection: putative role of corticotropin-releasing factor. *Nature Reviews Urology*. 2011;8(1):19-28. doi:10.1038/nrurol.2010.203

34. O'Leary MP. Validity of the "Bother Score" in the Evaluation and Treatment of Symptomatic Benign Prostatic Hyperplasia. :10.

35. Black L, Naslund MJ, Gilbert TD, Davis EA, Ollendorf DA. An examination of treatment patterns and costs of care among patients with benign prostatic hyperplasia. *Am J Manag Care*. 2006;12(4 Suppl):S99-S110.

36. Abrams P, Chapple C, Khoury S, Roehrborn C, de la Rosette J. Evaluation and Treatment of Lower Urinary Tract Symptoms in Older Men. *The Journal of Urology*. 2013;189(1, Supplement):S93-S101. doi:10.1016/j.juro.2012.11.021

37. Norton JM, Bradley CS, Brady SS, et al. Individualizing Urinary Incontinence Treatment: Research Needs Identified at NIDDK Workshop. *Journal of Urology*. 2018;199(6):1405-1407. doi:10.1016/j.juro.2017.11.118

38. Oelke M, Bachmann A, Descazeaud A, et al. EAU Guidelines on the Treatment and Follow-up of Non-neurogenic Male Lower Urinary Tract Symptoms Including Benign Prostatic Obstruction. *European Urology*. 2013;64(1):118-140. doi:10.1016/j.eururo.2013.03.004

39. Hutchison A, Farmer R, Verhamme K, Berges R, Navarrete RV. The Efficacy of Drugs for the Treatment of LUTS/BPH, A Study in 6 European Countries. *European Urology*. 2007;51(1):207-216. doi:10.1016/j.eururo.2006.06.012

40. Krambeck AE, Jacobson DJ, McGree ME, et al. Effectiveness of medical and surgical therapies for lower urinary tract symptoms in the community setting. *BJU Int*. 2012;110(9):1332-1337. doi:10.1111/j.1464-410X.2012.10998.x

41. Marshall LM, Holton KF, Parsons JK, Lapidus JA, Ramsey K, Barrett-Connor E. Lifestyle and Health Factors Associated with Progressing and Remitting Trajectories of Untreated Lower Urinary Tract Symptoms among Elderly Men. *Prostate Cancer Prostatic Dis*. 2014;17(3):265-272. doi:10.1038/pcan.2014.22

42. Sarma AV, Jacobsen SJ, Girman CJ, et al. Concomitant Longitudinal Changes in Frequency of and Bother From Lower Urinary Tract Symptoms in Community Dwelling Men. *The Journal of Urology*. 2002;168(4, Part 1):1446-1452. doi:10.1016/S0022-5347(05)64471-0

43. Rohrmann S, Katzke V, Kaaks R. Prevalence and Progression of Lower Urinary Tract Symptoms in an Aging Population. *Urology*. 2016;95:158-163. doi:10.1016/j.urology.2016.06.021

44. Mayer TG, Neblett R, Cohen H, et al. The Development and Psychometric Validation of the Central Sensitization Inventory. *Pain Practice*. 2012;12(4):276-285. doi:10.1111/j.1533-2500.2011.00493.x

45. Gasperi M, Krieger JN, Forsberg C, Goldberg J, Buchwald D, Afari N. Chronic prostatitis and comorbid non-urological overlapping pain conditions: A co-twin control study. *J Psychosom Res*. 2017;102:29-33. doi:10.1016/j.jpsychores.2017.09.005

46. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013. https://doi.org/10.1176/appi.books.9780890425596.dsm09

47. Yunus MB. Fibromyalgia and Overlapping Disorders: The Unifying Concept of Central Sensitivity Syndromes. *Seminars in Arthritis and Rheumatism*. 2007;36(6):339-356. doi:10.1016/j.semarthrit.2006.12.009

48. Birder L, de Groat W, Mills I, Morrison J, Thor K, Drake M. Neural control of the lower urinary tract: peripheral and spinal mechanisms. *Neurourol Urodyn*. 2010;29(1):128-139. doi:10.1002/nau.20837

49. Giamberardino MA, Costantini R, Affaitati G, et al. Viscero-visceral hyperalgesia: Characterization in different clinical models. *PAIN®*. 2010;151(2):307-322. doi:10.1016/j.pain.2010.06.023

50. Averbeck MA, Madersbacher H. Constipation and LUTS - how do they affect each other? *Int Braz J Urol*. 2011;37(1):16-28.

51. Malykhina AP, Brodie KE, Wilcox DT. Genitourinary and gastrointestinal co-morbidities in children: The role of neural circuits in regulation of visceral function. *J Pediatr Urol*. 2017;13(2):177-182. doi:10.1016/j.jpurol.2016.04.036

52. Zingone F, Iovino P, Santonicola A, Gallotta S, Ciacci C. High risk of lower urinary tract symptoms in patients with irritable bowel syndrome. *Tech Coloproctol*. 2017;21(6):433-438. doi:10.1007/s10151-017-1653-5

53. Li Z, Huang W, Wang X, Zhang Y. The relationship between lower urinary tract symptoms and irritable bowel syndrome: a meta-analysis of cross-sectional studies. *Minerva Urologica e Nefrologica*. 2018;70(4). doi:10.23736/S0393-2249.18.03044-8

54. Berens AE, Jensen SKG, Nelson CA. Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. *BMC Med*. 2017;15(1):1-12. doi:10.1186/s12916-017-0895-4

55. Brown CA, El-Deredy W, Jones AKP. When the brain expects pain: common neural responses to pain anticipation are related to clinical pain and distress in fibromyalgia and osteoarthritis. *Eur J Neurosci*. 2014;39(4):663-672. doi:10.1111/ejn.12420

56. Carriere JS, Martel MO, Meints SM, Cornelius MC, Edwards RR. What do you expect? Catastrophizing mediates associations between expectancies and pain-facilitatory processes. *European Journal of Pain*. 2019;23(4):800-811. doi:10.1002/ejp.1348

57. Meints SM, Mawla I, Napadow V, et al. The relationship between catastrophizing and altered pain sensitivity in patients with chronic low-back pain: *PAIN*. 2019;160(4):833-843. doi:10.1097/j.pain.0000000000001461

58. You DS, Meagher MW. Childhood Adversity and Pain Sensitization: *Psychosomatic Medicine*. 2016;78(9):1084-1093. doi:10.1097/PSY.0000000000000399

59. Link CL, Lutfey KE, Steers WD, McKinlay JB. Is Abuse Causally Related to Urologic Symptoms? Results from the Boston Area Community Health (BACH) Survey. *European Urology*. 2007;52(2):397-406. doi:10.1016/j.eururo.2007.03.024

60. Lai HH, Morgan CD, Vetter J, Andriole GL. Impact of Childhod and Recent Traumatic Events on the Clinical Presentation of Overactive Bladder. *Neurourol Urodyn*. 2016;35(8):1017-1023. doi:10.1002/nau.22872

61. Arendt-Nielsen L. Central Sensitization in Humans: Assessment and Pharmacology. In: Schaible HG, ed. *Pain Control*. Handbook of Experimental Pharmacology. Springer Berlin Heidelberg; 2015:79-102. doi:10.1007/978-3-662-46450-2_5

62. Rennefeld C, Wiech K, Schoell ED, Lorenz J, Bingel U. Habituation to pain: Further support for a central component. *PAIN®*. 2010;148(3):503-508. doi:10.1016/j.pain.2009.12.014

63. Staud R, Cannon RC, Mauderli AP, Robinson ME, Price DD, Vierck CJ. Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. *Pain*. 2003;102(1):87-95. doi:10.1016/s0304-3959(02)00344-5

64. Yunus MB. Editorial Review: An Update on Central Sensitivity Syndromes and the Issues of Nosology and Psychobiology. :16.

65. Coronado RA, George SZ. The Central Sensitization Inventory and Pain Sensitivity Questionnaire: An exploration of construct validity and associations with widespread pain sensitivity among individuals with shoulder pain. *Musculoskeletal Science and Practice*. 2018;36:61-67. doi:10.1016/j.msksp.2018.04.009

66. Neblett R, Cohen H, Choi Y, et al. The Central Sensitization Inventory (CSI): Establishing Clinically Significant Values for Identifying Central Sensitivity Syndromes in an Outpatient Chronic Pain Sample. *The Journal of Pain*. 2013;14(5):438-445. doi:10.1016/j.jpain.2012.11.012

67. Gervais-Hupé J, Pollice J, Sadi J, Carlesso LC. Validity of the central sensitization inventory with measures of sensitization in people with knee osteoarthritis. *Clinical Rheumatology*. 2018;37(11):3125-3132. doi:10.1007/s10067-018-4279-8

68. Mibu A, Nishigami T, Tanaka K, Manfuku M, Yono S. Difference in the impact of central sensitization on pain-related symptoms between patients with chronic low back pain and knee osteoarthritis. *Journal of Pain Research*. Published online May 29, 2019. doi:10.2147/JPR.S200723

69. Smith MD, Russell A, Hodges PW. The Relationship Between Incontinence, Breathing Disorders, Gastrointestinal Symptoms, and Back Pain in Women: A Longitudinal Cohort Study. *The Clinical Journal of Pain*. Published online March 2013:1. doi:10.1097/AJP.0b013e31828b10fe

70. Cassidy T, Fortin A, Kaczmer S, Shumaker JTL, Szeto J, Madill SJ. Relationship Between Back Pain and Urinary Incontinence in the Canadian Population. *Phys Ther*. 2017;97(4):449-454. doi:10.1093/ptj/pzx020

71. Nickel JC, Tripp DA, Pontari M, et al. Interstitial Cystitis/Painful Bladder Syndrome and Associated Medical Conditions With an Emphasis on Irritable Bowel Syndrome, Fibromyalgia and Chronic Fatigue Syndrome. *The Journal of Urology*. 2010;184(4):1358-1363. doi:10.1016/j.juro.2010.06.005

72. Clemens JQ, Meenan RT, O'Keeffe Rosetti MC, Kimes TA, Calhoun EA. Case-Control Study of Medical Comorbidities in Women With Interstitial Cystitis. *The Journal of Urology*. 2008;179(6):2222-2225. doi:10.1016/j.juro.2008.01.172

73. Ramos ML, García-Cabo C, Leira R, et al. Comorbidity between idiopathic overactive bladder and chronic migraine. *Cephalalgia*. 2018;38(3):581-584. doi:10.1177/0333102417690127

74. Harte S, Schrepf A, Gallop R, et al. Quantitative assessment of nonpelvic pressure pain sensitivity in urologic chronic pelvic pain syndrome: a MAPP Research Network study. *Pain*. 2019;160(6):1270-1280. doi:10.1097/j.pain.0000000000001505

75. Lai HH, Gardner V, Ness TJ, Gereau RW. Segmental Hyperalgesia to Mechanical Stimulus in Interstitial Cystitis/Bladder Pain Syndrome: Evidence of Central Sensitization. *The Journal of Urology*. 2014;191(5):1294-1299. doi:10.1016/j.juro.2013.11.099

76. Ness TJ, Lloyd LK, Fillingim RB. An endogenous pain control system is altered in subjects with interstitial cystitis. *J Urol*. 2014;191(2):364-370. doi:10.1016/j.juro.2013.08.024

77. FitzGerald MP, Koch D, Senka J. Visceral and cutaneous sensory testing in patients with painful bladder syndrome. *Neurourology and Urodynamics*. 2005;24(7):627-632. doi:10.1002/nau.20178

78. Clemens JQ, Mullins C, Ackerman AL, et al. Urologic chronic pelvic pain syndrome: insights from the MAPP Research Network. *Nat Rev Urol*. 2019;16(3):187-200. doi:10.1038/s41585-018-0135-5

79. Reynolds WS, Kowalik C, Cohn J, et al. Women Undergoing Third Line Overactive Bladder Treatment Demonstrate Elevated Thermal Temporal Summation. *J Urol*. 2018;200(4):856-861. doi:10.1016/j.juro.2018.05.007

80. Harte SE, Wiseman J, Wang Y, et al. Experimental Pain and Auditory Sensitivity in Overactive Bladder Syndrome: A Symptoms of the Lower Urinary Tract Dysfunction Research Network (LURN) Study. *J Urol*. Published online August 25, 2021:101097JU0000000000002147. doi:10.1097/JU.0000000000002147

81. Sammarco A, Kobernik E, Haefner H, Till S, Berger M. Lower Urinary Tract Symptoms in a Chronic Pelvic Pain Population. *Female Pelvic Medicine & Reconstructive Surgery*. 2019;Publish Ahead of Print. doi:10.1097/SPV.0000000000000689

82. Thu JHL, Vetter J, Lai HH. The Severity and Distribution of Nonurologic Pain and Urogenital Pain in Overactive Bladder are Intermediate Between Interstitial Cystitis and Controls. *Urology*. 2019;130:59-64. doi:10.1016/j.urology.2019.03.030

83. Orwoll E, Blank JB, Barrett-Connor E, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study — A large observational study of the determinants of fracture in older men. *Contemporary Clinical Trials*. 2005;26(5):569-585. doi:10.1016/j.cct.2005.05.006

84. Blank JB, Cawthon PM, Carrion-Petersen ML, et al. Overview of recruitment for the osteoporotic fractures in men study (MrOS). *Contemporary Clinical Trials*. 2005;26(5):557-568. doi:10.1016/j.cct.2005.05.005

85. Gill SC, Butterworth P, Rodgers B, Mackinnon A. Validity of the mental health component scale of the 12-item Short-Form Health Survey (MCS-12) as measure of common mental disorders in the general population. *Psychiatry Research*. 2007;152(1):63-71. doi:10.1016/j.psychres.2006.11.005

86. Greenland S, Pearl J, Robins JM. Causal Diagrams for Epidemiologic Research: *Epidemiology*. 1999;10(1):37-48. doi:10.1097/00001648-199901000-00008

87. Greenland S. Modeling and variable selection in epidemiologic analysis. *American Journal of Public Health*. 1989;79(3):340-349. doi:10.2105/AJPH.79.3.340

88. Welk B, Baverstock R. Is there a link between back pain and urinary symptoms? *Neurourology and Urodynamics*. Published online January 3, 2020. doi:10.1002/nau.24269

89. Nuotio M, Jylhä M, Luukkaala T, Tammela TLJ. Health problems associated with lower urinary tract symptoms in older women. *Scandinavian Journal of Primary Health Care*. 2005;23(4):209-214. doi:10.1080/02813430500227626

90. Smith MD, Russell A, Hodges PW. Do Incontinence, Breathing Difficulties, and Gastrointestinal Symptoms Increase the Risk of Future Back Pain? *The Journal of Pain*. 2009;10(8):876-886. doi:10.1016/j.jpain.2009.03.003

91. Thapa S, Shmerling RH, Bean JF, Cai Y, Leveille SG. Chronic multisite pain: evaluation of a new geriatric syndrome. *Aging Clin Exp Res*. 2019;31(8):1129-1137. doi:10.1007/s40520-018-1061-3

92. Bosch R, Abrams P, Averbeck MA, et al. Do functional changes occur in the bladder due to bladder outlet obstruction? - ICI-RS 2018. *Neurourology and Urodynamics*. 2019;38(S5):S56-S65. doi:10.1002/nau.24076

93. Fusco F, Creta M, Nunzio CD, et al. Progressive bladder remodeling due to bladder outlet obstruction: a systematic review of morphological and molecular evidences in humans. *BMC Urol*. 2018;18(1):1-11. doi:10.1186/s12894-018-0329-4

94. Dmochowski RR. Bladder Outlet Obstruction: Etiology and Evaluation. *Rev Urol*. 2005;7(Suppl 6):S3-S13.

95. Rasmussen CDN, Holtermann A, Jørgensen MB. Recall Bias in Low Back Pain Among Workers: Effects of Recall Period and Individual and Work-Related Factors. *SPINE*. 2018;43(12):E727-E733. doi:10.1097/BRS.0000000000002457

96. Platz EA, Joshu CE, Mondul AM, Peskoe SB, Willett WC, Giovannucci E. Incidence and Progression of Lower Urinary Tract Symptoms in a Large Prospective Cohort of United States Men. *The Journal of Urology*. 2012;188(2):496-501. doi:10.1016/j.juro.2012.03.125

97. Chancellor MB, Migliaccio-Walle K, Bramley TJ, Chaudhari SL, Corbell C, Globe D. Long-Term Patterns of Use and Treatment Failure With Anticholinergic Agents for Overactive Bladder. *Clinical Therapeutics*. 2013;35(11):1744-1751. doi:10.1016/j.clinthera.2013.08.017

98. Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD. Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification. *The Journal of Pain*. 2016;17(9, Supplement):T93-T107. doi:10.1016/j.jpain.2016.06.002

99. Rodríguez MÁB, Afari N, Buchwald DS. Evidence for Overlap Between Urological and Nonurological Unexplained Clinical Conditions. *The Journal of Urology*. 2013;189(1, Supplement):S66-S74. doi:10.1016/j.juro.2012.11.019

100. Krieger JN, Stephens AJ, Landis JR, et al. Relationship between chronic nonurological associated somatic syndromes and symptom severity in urological

chronic pelvic pain syndromes: baseline evaluation of the MAPP study. *J Urol*. 2015;193(4):1254-1262. doi:10.1016/j.juro.2014.10.086

101. Senders A, Bauer SR, Chen Y, et al. Lower urinary tract symptoms are associated with musculoskeletal pain among older men: Preliminary evidence for central sensitization as a mechanism? *Neurourology and Urodynamics*. n/a(n/a). doi:10.1002/nau.24767

102. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34(3):220-233. doi:10.1097/00005650-199603000-00003

103. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug Data Coding and Analysis in Epidemiologic Studies. *European Journal of Epidemiology*. 1994;10(4):405-411.

104. Cauley JA, Cawthon PM, Peters KE, et al. Risk Factors for Hip Fracture in Older Men: The Osteoporotic Fractures in Men Study (MrOS). *Journal of Bone and Mineral Research*. 2016;31(10):1810-1819. doi:10.1002/jbmr.2836

105. Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK. Correlation of the American Urological Association symptom index with self-administered versions of the Madsen-Iversen, Boyarsky and Maine Medical Assessment Program symptom indexes. Measurement Committee of the American Urological Association. *J Urol*. 1992;148(5):1558-1563; discussion 1564. doi:10.1016/s0022-5347(17)36967-7

106. Ngwa JS, Cabral HJ, Cheng DM, et al. A comparison of time dependent Cox regression, pooled logistic regression and cross sectional pooling with simulations and an application to the Framingham Heart Study. *BMC Med Res Methodol*. 2016;16. doi:10.1186/s12874-016-0248-6

107. Muller CJ, MacLehose RF. Estimating predicted probabilities from logistic regression: different methods correspond to different target populations. *Int J Epidemiol*. 2014;43(3):962-970. doi:10.1093/ije/dyu029

108. Fewell Z, Hernán MA, Wolfe F, Tilling K, Choi H, Sterne JAC. Controlling for Time-dependent Confounding using Marginal Structural Models. *The Stata Journal: Promoting communications on statistics and Stata*. 2004;4(4):402-420. doi:10.1177/1536867X0400400403

109. Louter MA, Bosker JE, van Oosterhout WPJ, et al. Cutaneous allodynia as a predictor of migraine chronification. *Brain*. 2013;136(11):3489-3496. doi:10.1093/brain/awt251

110. Bendtsen L, Ashina S, Moore A, Steiner TJ. Muscles and their role in episodic tension-type headache: implications for treatment. *European Journal of Pain*. 2016;20(2):166-175. doi:https://doi.org/10.1002/ejp.748

111. Warren JW, Langenberg P, Clauw DJ. The number of existing functional somatic syndromes (FSSs) is an important risk factor for new, different FSSs. *Journal of Psychosomatic Research*. 2013;74(1):12-17. doi:10.1016/j.jpsychores.2012.09.002

112. Lenz M, Galanis C, Müller-Dahlhaus F, et al. Repetitive magnetic stimulation induces plasticity of inhibitory synapses. *Nature Communications*. 2016;7(1):10020. doi:10.1038/ncomms10020

113. Jodoin M, Rouleau D, Larson-Dupuis C, Gosselin N, De Beaumont L. The clinical utility of repetitive transcranial magnetic stimulation in reducing the risks of transitioning from acute to chronic pain in traumatically injured patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;87(Pt B):322-331. doi:10.1016/j.pnpbp.2017.07.005

114. Nardone R, Versace V, Sebastianelli L, et al. Transcranial magnetic stimulation and bladder function: A systematic review. *Clinical Neurophysiology*. 2019;130(11):2032-2037. doi:10.1016/j.clinph.2019.08.020

115. Gibson J. Mindfulness, Interoception, and the Body: A Contemporary Perspective. *Front Psychol*. 2019;10. doi:10.3389/fpsyg.2019.02012

116. Felsted KF, Supiano KP. Mindfulness-Based Stress Reduction Versus a Health Enhancement Program in the Treatment of Urge Urinary Incontinence in Older Adult Women: A Randomized Controlled Feasibility Study. *Research in Gerontological Nursing*. 2019;12(6):285-297. doi:10.3928/19404921-20190702-02

117. Baker J, Costa D, Guarino JM, Nygaard I. Comparison of Mindfulness-Based Stress Reduction Versus Yoga on Urinary Urge Incontinence: A Randomized Pilot Study. With 6-Month and 1-Year Follow-up Visits. *Female Pelvic Medicine & Reconstructive Surgery*. 2014;20(3):141-146. doi:10.1097/SPV.0000000000000061

118. Karayannis NV, Sturgeon JA, Chih-Kao M, Cooley C, Mackey SC. Pain interference and physical function demonstrate poor longitudinal association in people living with pain: a PROMIS investigation. *PAIN*. 2017;158(6):1063-1068. doi:10.1097/j.pain.0000000000000881

119. Litwin MS, McNaughton-Collins M, Fowler FJ, et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. *J Urol*. 1999;162(2):369-375. doi:10.1016/s0022-5347(05)68562-x

120. Senders A, Bauer SR, Chen Y, et al. Lower urinary tract symptoms are associated with musculoskeletal pain among older men: Preliminary evidence for central sensitization as a mechanism? *Neurourology and Urodynamics*. 2021;40(8):1929-1938. doi:10.1002/nau.24767

121. Ohashi Y, Fukushima K, Inoue G, et al. Central sensitization inventory scores correlate with pain at rest in patients with hip osteoarthritis: a retrospective study. *BMC Musculoskeletal Disorders*. 2020;21(1):595. doi:10.1186/s12891-020-03630-6

122. Roldán-Jiménez C, Pérez-Cruzado D, Neblett R, Gatchel R, Cuesta-Vargas A. Central Sensitization in Chronic Musculoskeletal Pain Disorders in Different Populations: A Cross-Sectional Study. *Pain Medicine*. 2020;21(11):2958-2963. doi:10.1093/pm/pnaa069

123. Sasaki E, Ota S, Chiba D, et al. Association Between Central Sensitization and Increasing Prevalence of Nocturnal Knee Pain in the General Population with Osteoarthritis from the Iwaki Cohort Study. *JPR*. 2021;Volume 14:2449-2458. doi:10.2147/JPR.S318038

124. Governor's Wildfire Economic Recovery Council. *Recovering & Rebuilding from Oregon's 2020 Wildfires: Key Findings & Recommendations*.; 2021:1-32. Accessed January 16, 2022. https://www.oregon.gov/gov/policy/Documents/WERC-2020/Wildfire%20Report%20FINAL.pdf

125. Parsons JK. Commentary on BPH and Public Health-Have We Lost the Forest Through the Trees? *Journal of Urology*. 2008;179(5).

126. Wei JT, Calhoun E, Jacobsen SJ. Urologic Diseases in America Project: Benign Prostatic Hyperplasia. *The Journal of Urology*. 2005;173(4):1256-1261. doi:10.1097/01.ju.0000155709.37840.fe

127. Bureau UC. Older People Projected to Outnumber Children. The United States Census Bureau. Accessed January 16, 2019. https://www.census.gov/newsroom/press-releases/2018/cb18-41-population-projections.html

128. Calogero AE, Burgio G, Condorelli RA, Cannarella R, Vignera SL. Epidemiology and risk factors of lower urinary tract symptoms/benign prostatic hyperplasia and

erectile dysfunction. *The Aging Male*. 2019;22(1):12-19. doi:10.1080/13685538.2018.1434772

129. Parsons JK, Sarma AV, McVary K, Wei JT. Obesity and Benign Prostatic Hyperplasia: Clinical Connections, Emerging Etiological Paradigms and Future Directions. *The Journal of Urology*. 2013;189(1, Supplement):S102-S106. doi:10.1016/j.juro.2012.11.029

130. Parsons J. Lifestyle factors, benign prostatic hyperplasia, and lower urinary tract symptoms: *Current Opinion in Urology*. 2011;21(1):1-4. doi:10.1097/MOU.0b013e32834100c9

131. Cournoyea M, Kennedy AG. Causal explanatory pluralism and medically unexplained physical symptoms. *Journal of Evaluation in Clinical Practice*. 2014;20(6):928-933. doi:10.1111/jep.12238

132. Lian OS, Robson C. "It´s incredible how much I´ve had to fight." Negotiating medical uncertainty in clinical encounters. *Int J Qual Stud Health Well-being*. 2017;12(sup2):1392219. doi:10.1080/17482631.2017.1392219

133. Fried D, McAndrew LM, Helmer DA, Markowitz S, Quigley KS. Interrelationships between symptom burden and health functioning and health care utilization among veterans with persistent physical symptoms. *BMC Fam Pract*. 2020;21(1):124. doi:10.1186/s12875-020-01193-y

134. Konnopka A, Kaufmann C, König HH, et al. Association of costs with somatic symptom severity in patients with medically unexplained symptoms. *J Psychosom Res*. 2013;75(4):370-375. doi:10.1016/j.jpsychores.2013.08.011

135. Barsky AJ, Orav EJ, Bates DW. Somatization Increases Medical Utilization and Costs Independent of Psychiatric and Medical Comorbidity. *Arch Gen Psychiatry*. 2005;62(8):903-910. doi:10.1001/archpsyc.62.8.903

136. Central Sensitisation Inventory. Physiopedia. Accessed January 23, 2022. https://www.physio-pedia.com/Central_Sensitisation_Inventory

137. den Boer C, Terluin B, van der Wouden JC, Blankenstein AH, van der Horst HE. Tests for central sensitization in general practice: a Delphi study. *BMC Family Practice*. 2021;22(1):206. doi:10.1186/s12875-021-01539-0

138. van Dessel N, den Boeft M, van der Wouden JC, et al. Non-pharmacological interventions for somatoform disorders and medically unexplained physical

symptoms (MUPS) in adults. *Cochrane Database Syst Rev*. 2014;(11):CD011142. doi:10.1002/14651858.CD011142.pub2

139. Bae J yong, Sung HK, Kwon NY, et al. Cognitive Behavioral Therapy for Migraine Headache: A Systematic Review and Meta-Analysis. *Medicina (Kaunas)*. 2021;58(1):44. doi:10.3390/medicina58010044

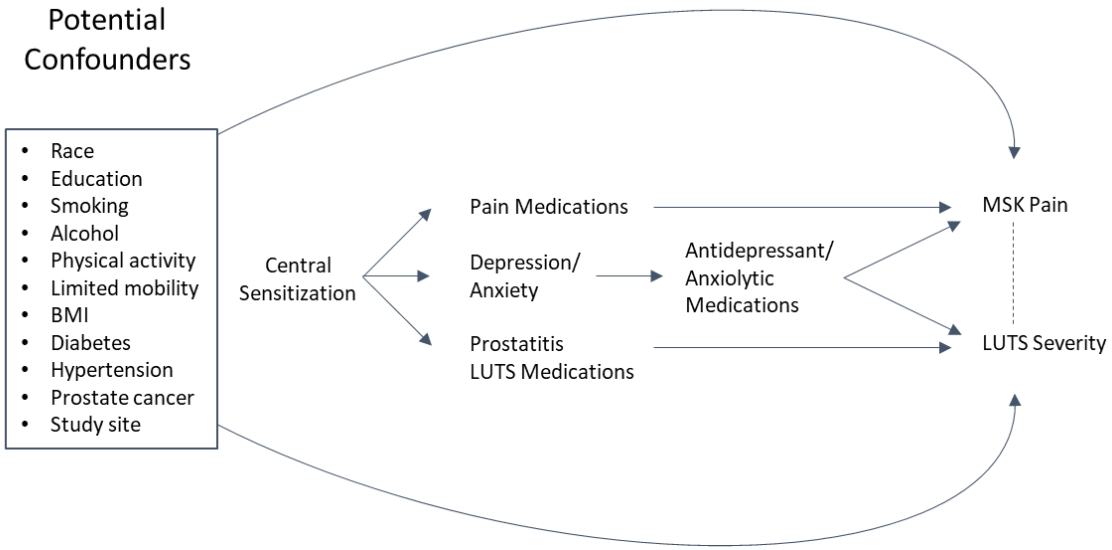
140. Black CJ, Thakur ER, Houghton LA, Quigley EMM, Moayyedi P, Ford AC. Efficacy of psychological therapies for irritable bowel syndrome: systematic review and network meta-analysis. *Gut*. 2020;69(8):1441-1451. doi:10.1136/gutjnl-2020-321191

141. Mascarenhas RO, Souza MB, Oliveira MX, et al. Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia. *JAMA Intern Med*. 2021;181(1):1-9. doi:10.1001/jamainternmed.2020.5651

142. Sarter L, Heider J, Kirchner L, et al. Cognitive and emotional variables predicting treatment outcome of cognitive behavior therapies for patients with medically unexplained symptoms: A meta-analysis. *J Psychosom Res*. 2021;146:110486. doi:10.1016/j.jpsychores.2021.110486

Appendices

Appendix A. Supplementary materials for Chapter 3



Supplementary Figure. Modified causal diagram for the association between musculoskeletal (MSK) pain and lower urinary tract symptom (LUTS) severity. Dotted line represents a non-causal association that would result from central sensitization (CS) as a common cause. To assess whether CS may be a common underlying mechanism of musculoskeletal pain and LUTS severity, we assessed factors that were associated with LUTS, musculoskeletal pain, or both and that were unlikely to be caused by CS for potential confounding (variables in the box). We statistically adjusted for variables that confounded the association between musculoskeletal pain and LUTS severity. Additional factors may lie on the causal pathway between CS and musculoskeletal pain or CS and LUTS. For example, depression/anxiety symptoms may occur as a result of CS, and individuals with sensitization may be more likely to present for care and receive medical treatment for somatic complaints such as pain or LUTS. And, evidence suggests that sensitization may be cause of chronic painful urinary conditions, such as prostatitis. Therefore, we assessed the potential for these variables to confound the association between musculoskeletal pain and LUTS in a separate model.

Appendix B. Supplementary materials for Chapter 4

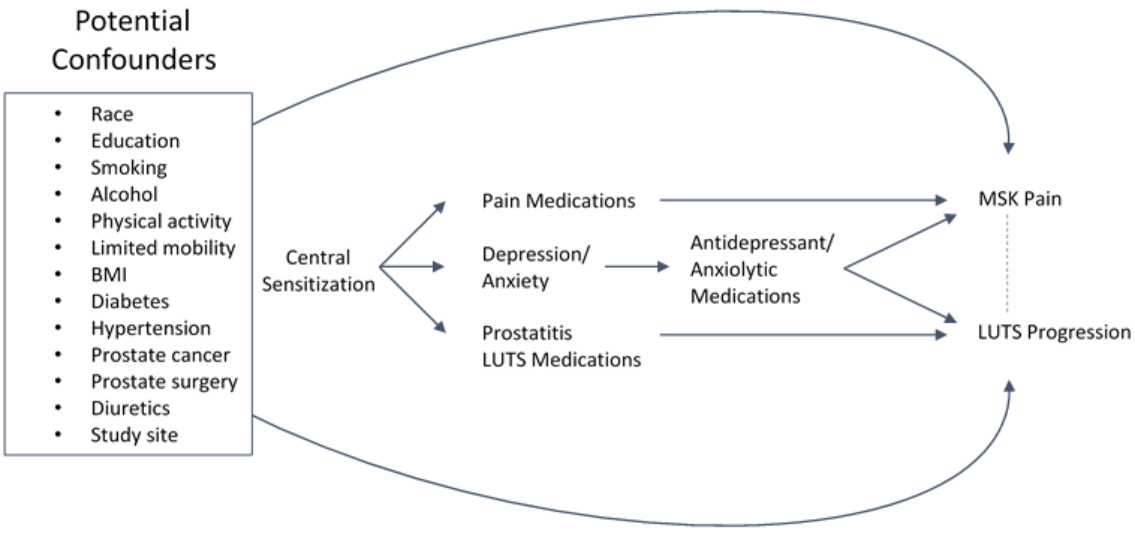
Supplementary Table. Association between musculoskeletal pain and the progression of lower urinary tract symptoms (LUTS) over two years among community-dwelling men aged >= 65 years: The MrOS Study, USA. Estimates were generated using stabilized inverse probability of censoring weights.

		LUTS Progression			
	n	**Person-years of follow-up**	**No. Progressed**	**Multivariable[a]** IRR (95% CI)	**Multivariable[b]** IRR (95% CI)
Any Pain					
No Pain	1,064	3,580	272	ref	ref
Any Pain	4,505	14,356	1,566	1.37 (1.21, 1.54)	1.33 (1.17, 1.49)
Multi-location pain					
No Pain	1,064	3,580	272	ref	ref
Pain at one location	1,793	5,768	579	1.31 (1.13, 1.48)	1.28 (1.11, 1.45)
Pain at ≥ location	2,712	8,588	987	1.42 (1.24, 1.60)	1.37 (1.19, 1.54)
Pain Interference					
No Pain	1,064	3,580	272	ref	ref
Pain, no interference	2,113	6,916	666	1.27 (1.11, 1.44)	1.24 (1.08, 1.40)
Pain, minimal interference	1,355	4,368	480	1.40 (1.21, 1.60)	1.37 (1.18, 1.56)
Pain, ≥ moderate interference	1,037	3,072	420	1.62 (1.38, 1.86)	1.54 (1.31, 1.77)

AUA-SI: American Urological Association Symptom Index; IRR: Incidence rate ratio; CI: Confidence interval

[a] Adjusted for age, hypertension, multimorbidity, mobility difficulties, and history of prostate surgery.

[b] Adjusted for age, hypertension, multimorbidity, mobility difficulties, history of prostate surgery, history of prostatitis, psychological distress, and LUTS medication use.



Supplementary Figure. Conceptual diagram for the association between musculoskeletal (MSK) pain and lower urinary tract symptom (LUTS) progression. Dotted line represents a non-causal association that would result from central sensitization (CS) as a common cause. To assess whether CS may be a common underlying mechanism of musculoskeletal pain and LUTS severity, we assessed factors that were associated with LUTS, musculoskeletal pain, or both and that were unlikely to be caused by CS for potential confounding (variables in the box). We statistically adjusted for variables that confounded the association between musculoskeletal pain and LUTS severity. Additional factors may lie on the causal pathway between CS and musculoskeletal pain or CS and LUTS. For example, depression/anxiety symptoms may occur as a result of CS, and individuals with sensitization may be more likely to present for care and receive medical treatment for somatic complaints such as pain or LUTS. And, evidence suggests that sensitization may be a cause of chronic painful urinary conditions, such as prostatitis. Therefore, we assessed the potential for these variables to confound the association between musculoskeletal pain and LUTS in a separate model.

Appendix C. Supplementary materials for Chapter 5

Supplementary Table. Characteristics of the study sample (n=87) across categories of the Central Sensitization Inventory (CSI) score.

	CSI Score		
	0-39 points	**≥ 40 points**	p value
N (%) of study sample	62 (71.3%)	25 (28.7%)	
Age, mean (sd), years	68.0 (13.0)	60.8 (15.3)	0.03
Had LUTS > 2 years	50 (85%)	19 (76%)	0.34
Painful LUT/pelvic symptoms	10 (16%)	11 (44%)	0.01
History of painful LUT diagnosis	16 (26%)	6 (24%)	0.86
Current LUTS medication use	28 (45%)	7 (28%)	0.14
Neurologic diagnosis	16 (26%)	14 (56%)	0.01
LUTS Etiology			0.43
Pathologic	44 (71%)	16 (64%)	
Idiopathic	10 (16%)	3 (12%)	
Unclear	8 (13%)	6 (24%)	
LUT procedure since UDS	23 (37%)	4 (16%)	0.05

[a]P values comparing the characteristics across categories of the CSI score are derived from ANOVA for continuous variables and Fisher's exact test for categorical variables.

Appendix D. Institutional review board documentation

IRB MEMO

Research Integrity Office
3181 SW Sam Jackson Park Road - L106RI
Portland, OR 97239-3098
(503)494-7887 irb@ohsu.edu

APPROVAL OF SUBMISSION

June 10, 2020

Dear Investigator:

On 6/10/2020, the IRB reviewed the following submission:

IRB ID:	STUDY00021449
Type of Review:	Initial Study
Title of Study:	Awareness and Perception of Internal Sensation Among Men with Lower Urinary Tract Symptoms: A Cross-sectional Survey
Principal Investigator:	Lynn Marshall
Funding:	None
IND, IDE, or HDE:	None
Documents Reviewed:	• Questionnaire - Contact Information.pdf • Protocol - v1.2_6.5.20.doc • Recruitment - Letter v1.1_5.13.20.pdf • Recruitment - Reminder Phone Script_v1.0_4.10.20.pdf • Questionnaire - ACEs.pdf • Questionnaire - AUASI.pdf • Questionnaire - Brief Medical Hx.pdf • Questionnaire - CSI.pdf • Questionnaire - LURN10.pdf • Questionnaires - MAIA.pdf • Recruitment - Email Text_v1.1_5.13.20.pdf • PPQ • HIPAA- Prep-to-Research Form_5.31.20.docx • Consent - Information Sheet_v1.2_5.31.20.pdf • Recruitment - Phone Script_v1.0_4.10.20.pdf • Questionnaire - CSQ.pdf

The IRB granted final approval on 6/10/2020. The study requires you to submit a check-in before 6/8/2023.

Review Category Exempt Categories # 2 & 4

Even though there is IRB approval for this activity, study teams must continue to follow institutional policy regarding COVID-19 restrictions.

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB.

Ongoing IRB submission requirements:

- Six to ten weeks before the eIRB system expiration date, submit a check-in..
- Any changes to the project must be submitted for IRB approval prior to implementation.
- Reportable New Information must be submitted per OHSU policy.
- Submit a check-in to close the study when your research is completed.

Guidelines for Study Conduct

In conducting this study, you are required to follow the guidelines in the document entitled, "Roles and Responsibilities in the Conduct of Research and Administration of Sponsored Projects," as well as all other applicable OHSU IRB Policies and Procedures.

Requirements under HIPAA

If your study involves the collection, use, or disclosure of Protected Health Information (PHI), you must comply with all applicable requirements under HIPAA. See the HIPAA and Research website and the Information Privacy and Security website for more information.

IRB Compliance

The OHSU IRB (FWA00000161; IRB00000471) complies with 45 CFR Part 46, 21 CFR Parts 50 and 56, and other federal and Oregon laws and regulations, as applicable, as well as ICH-GCP codes 3.1-3.4, which outline Responsibilities, Composition, Functions, and Operations, Procedures, and Records of the IRB.

Sincerely,

The OHSU IRB Office

TITLE: Awareness and Perception of Internal Sensation Among Men with Lower Urinary Tract Symptoms: A Cross-sectional Survey

PRINCIPAL INVESTIGATOR: Lynn Marshall, ScD (503) 494-3990

CO-INVESTIGATORS: Angela Senders, ND, MCR (503) 552-1765

Kamran Sajadi, MD (503) 346-1500

WHY IS THIS STUDY BEING DONE?

You have been invited to be in this research study because you have been seen for evaluation of urinary symptoms at the OHSU Urology Clinic. The purpose of this study is to learn more about how lower urinary tract symptoms are perceived by the nervous system.

Data collected from/about you in this study will not be used and/or shared for future research.

WHAT PROCEDURES ARE INVOLVED IN THIS STUDY?

This study consists of several questionnaires. You will be asked questions about your medical history, adverse experiences you may have had as a child, symptoms that you currently experience (including urinary), how you feel when you experience these symptoms, and whether symptoms cause you a great deal of worry or not. You can answer the questionnaires at home, they will take about 30 minutes to complete.

If you agree to participate in this study we will obtain information about you from your medical record, including the results of cystoscopy or urodynamic testing. Examples of these measures include prostate size and volume, how much urine the bladder can hold, bladder pressure upon filling, and how full it is when the urge to urinate begins. We will also verify some of the information you share with us, including information about your medical history and any medications you might take.

If you have any questions, concerns, or complaints regarding this study now or in the future, contact Lynn Marshall at (503) 494-3990 or Angela Senders at (503) 552-1765.

WHAT RISKS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

Although we have made every effort to protect your identity, there is a minimal risk of loss of confidentiality. Some of the questions on the questionnaires may seem sensitive or personal. They may upset you. You may refuse to answer any of the questions that you do not wish to answer.

WHAT ARE THE BENEFITS OF TAKING PART IN THIS STUDY?

You will not benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future.

WHAT ARE THE ALTERNATIVESTO TAKING PART IN THIS STUDY? You may choose not to be in this study.

WILL I RECEIVE RESULTS FROM THIS STUDY?

The results of research tests will not be made available to you because the research is still in an early phase and the reliability of the results is unknown.

WHO WILL SEE MY PERSONAL INFORMATION?

We will take steps to keep your personal information confidential, but we cannot guarantee total privacy. Information that you share with use is stored in a secure

research data-base that only study staff have access to. Any paper copies of questionnaires that you provide will be labeled with a number and not your name.

We may have to release this information to others for example, if the study is audited. However, we would try to do so without information that could identify you. This release could be to the Institutional Review Board (ethics review committee) at OHSU or Office of Human Research Protection (agency that oversees research).

If your information goes outside of OHSU, it might not be protected under federal law from being used or further shared. Your information will be maintained indefinitely but will be destroyed at the end of the study. If you decide you don't want us to use your name and information for this research, you can request this by contacting us at:

Angela Senders

2220 SW 1st Avenue

Portland, OR 97201

senders@ohsu.edu

Your request will be effective as of the date we receive it. However, health information collected before your request is received may continue to be used and disclosed to the extent that we have already acted based on your authorization.

You do not have to allow the use and disclosure of your health information in the study, but if you do not, you cannot be in the study. If you choose not to participate, or if you decide to stop at any time, that will not affect your ability to receive health care at OHSU or insurance coverage.

WILL ANY OF MY INFORMATION FROM THIS STUDY BE USED FOR ANY COMMERCIAL PROFIT? Information about you or obtained from you in this research may be used for commercial purposes, such as making a discovery that could, in the future, be patented or licensed to a company, which could result in a possible financial benefit to that company, OHSU, and its researchers. There are no plans to pay you if this happens. You will not have any property rights or ownership or financial interest in or arising from products or data that may result from your participation in this study. Further, you will have no responsibility or liability for any use that may be made of your information.

WHERE CAN I GET MORE INFORMATION?

This research is being overseen by an Institutional Review Board ("IRB"). You may talk to the IRB at (503) 494-7887 or irb@ohsu.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get more information or provide input about this research.

You may also submit a report to the OHSU Integrity Hotline online at https://secure.ethicspoint.com/domain/media/en/gui/18915/index.html or by calling toll-free (877) 733-8313 (anonymous and available 24 hours a day, 7 days a week).

DO I HAVE TO TAKE PART IN THIS STUDY?

You do not have to join this or any research study. If you do join, and later change your mind, you may quit at any time. If you refuse to join or withdraw early from the study, there will be no penalty or loss of any benefits to which you are otherwise entitled.

HOW DO I TELL YOU IF I WANT TO TAKE PART IN THIS STUDY?

Please indicate whether you provide your consent to participate in this study:

(__) Yes, I AGREE to participate in the study.

(__) I do not agree to participate in the study.