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

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Abstract

Aims: 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 nonpainful 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 5966 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 multilocation 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.

KEYWORDS

central nervous system sensitization, lower urinary tract symptoms, musculoskeletal pain

1 | INTRODUCTION

Lower urinary tract symptoms (LUTS), which include symptoms of difficulty voiding or storing urine, affect 20% of adults worldwide.[1] 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.[2,3] Despite their health impact, knowledge about the pathophysiological mechanisms underlying LUTS is evolving and remains 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.[4] 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.[5] 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.[6] 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.[6]

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.[7–9] 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 nonpainful LUTS cases, then symptoms suggestive of sensitization, such as nonurologic 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,[7] 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[10–13] and may not apply to men.

There is a paucity 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.

2 | METHODS

2.1 | 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 US

men.[14] Eligible participants were identified through population-based lists (e.g., voting and motor vehicle registries) and recruited through mass mailings.[15] Between 2000 and 2002, 5994 community-dwelling men who were at least 65 years old and could walk without the assistance of another person were enrolled at six US 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.

2.2 | Independent variable: Lower urinary tract symptoms

LUTS were assessed with the American Urologic Association Symptom Index (AUA-SI) on the baseline questionnaire.[16] 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.

2.3 | 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, multilocation pain was defined as the sum of the number of "yes" responses to the four individual questions about back, neck, hip, or knee pain (0, 1, ≥ 2).

2.4 | 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.[14] Scores from the physical activity scale for the elderly[14] 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.[17] Height and weight were measured by study staff[14] 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.[18] 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 nonsteroidal 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 nonusers because results with this coding were similar to results excluding the missing observations. Study site was categorized as the participant's recruitment site.

2.5 | Analytic cohort

Of the 5994 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 5966 men.

2.6 | 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 multilocation 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, Texas, 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 S1) to guide our model building and variable selection,[19] 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.[20] 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 S1). 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.

2.7 | Sensitivity analyses

Prostatitis is a painful urinary condition that may have an underlying CS component.[9] 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 | 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

TABLE 1 Baseline characteristics of community-dwelling men aged ≥65 years according to lower urinary tract symptom (LUTS) severity: The MrOS study, USA ($N = 5966$)

	LUTS Severity			
	Mild	**Moderate**	**Severe**	***p* value**[a]
N (% in cohort)	3224 (54.4)	2346 (39.3)	396 (6.6)	
Age, years; mean (sd)	73.15 (5.75)	74.17 (5.90)	74.61 (6.18)	<.001
Race				.05
White	2889 (89.6%)	2124 (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	1704 (52.9%)	1271 (54.2%)	197 (49.7%)	.23
BMI				.51
Under/normal	901 (27.9%)	636 (27.1%)	98 (24.7%)	
Overweight	1640 (50.9%)	1214 (51.7%)	202 (51.0%)	
Obese	683 (21.2%)	496 (21.1%)	96 (24.2%)	
Smoking status				.01
Never	1,243 (38.6%)	861 (36.7%)	136 (34.3%)	
Past	1850 (57.4%)	1425 (60.7%)	247 (62.4%)	
Current	131 (4.1%)	60 (2.6%)	13 (3.3%)	
Alcohol consumption				.21
None	1108 (34.4%)	851 (36.3%)	152 (38.4%)	
1–7/week	1531 (47.5%)	1110 (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%)	<.001
Physical activity quartiles				<.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[b]	342 (10.6%)	387 (16.5%)	103 (26.0%)	<.001
Medication use				
Pain medications[c]	1514 (47.0%)	1172 (50.0%)	228 (57.6%)	<.001
Diuretic medications	578 (17.9%)	480 (20.5%)	78 (19.7%)	.06
LUTS medications[d]	349 (10.8%)	594 (25.3%)	157 (39.6%)	<.001
Antidepressant/anxiolytic medications[e]	237 (7.4%)	226 (9.6%)	59 (14.9%)	<.001
Medical history				
Prostatitis	645 (20.0%)	677 (28.9%)	170 (42.9%)	<.001
Diabetes	342 (10.6%)	248 (10.6%)	58 (14.6%)	.04
Hypertension	1309 (40.6%)	1060 (45.2%)	198 (50.0%)	<.001
Psychological distress[f]	414 (12.8%)	463 (19.7%)	93 (23.5%)	<.001
Any musculoskeletal pain	2520 (78.2%)	1986 (84.7%)	347 (87.6%)	<.001

(Continues)

TABLE 1 (Continued)

	LUTS Severity			
	Mild	Moderate	Severe	*p* value[a]
Multilocation pain				<.001
No pain	704 (21.8%)	360 (15.3%)	49 (12.4%)	
Pain at 1 Location	1090 (33.8%)	703 (30.0%)	90 (22.7%)	
Pain at ≥ 2 Locations	1430 (44.4%)	1,283 (54.7%)	257 (64.9%)	

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

[b]Defined as any difficulty walking 2–3 blocks or climbing 10 steps.

[c]Use of nonsteroidal anti-inflammatory drugs, opioids, acetaminophen, or aspirin.

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

[e]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).

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

[g]Physical activity assessed with the physical activity scale for the elderly.

Abbreviations: BMI, body mass index; BPH, benign prostatic hyperplasia; MrOS, osteoporotic fractures in men study; NSAIDS, nonsteroidal anti-inflammatory drugs; PASE, physical activity scale for the elderly.

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 one 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 one 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 multilocation pain (Supplementary Table 1).

3.1 | Sensitivity analyses

After excluding men with a history of prostatitis ($n = 1492$), prostate cancer ($n = 708$), either prostate cancer or prostatitis ($n = 1816$), or those with psychological distress ($n = 969$), our results were materially unchanged (Supplementary Table S2). Our results were also

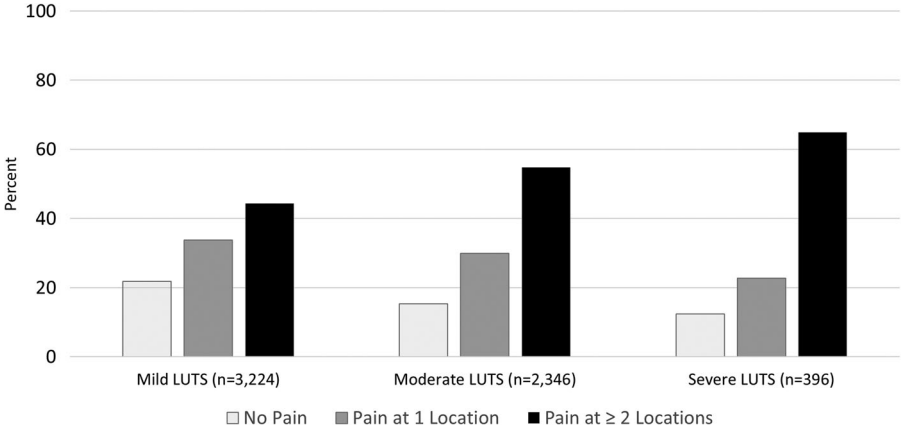

FIGURE 1 Unadjusted prevalence of the number of locations that pain was reported (back, neck, hip, or knee) within the last year among community-dwelling men ≥ 65 by severity of lower urinary tract symptoms. $p < .0001$ for a chi-square test for a difference in proportions across LUTS categories. The MrOS Study, USA ($N = 5966$)

TABLE 2 Association between lower urinary tract symptom (LUTS) severity and any musculoskeletal pain and among community-dwelling men aged ≥ 65 years: The MrOS Study, USA ($N = 5966$)

			Any Pain[a]		
	No pain (*n*)	Any pain (*n*)	Age-adjusted OR (95% CI)	Multivariable[b] OR (95% CI)	Multivariable[c] OR (95% CI)
Mild LUTS	704	2520	Ref.	Ref.	Ref.
Moderate LUTS	360	1986	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	1113	4853	–	–	–

[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.

Abbreviations: CI, confidence interval; MrOS, osteoporotic fractures in men study; OR, odds ratio.

unchanged after adjusting for all covariates described in the other independent variables section

4 | 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 with 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.[21,22] The majority of prior studies were cross-sectional, although two prospective studies suggest an association between back pain and urinary incontinence in women.[23,24] In men, back pain has been associated with LUTS progression over time.[18] 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.[25] 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.[13] Of those reporting co-occurring pelvic and nonpelvic pain, adults with BPS were significantly more likely to report nonpelvic pain in multiple locations compared to those with OAB, who in turn were more likely to report nonpelvic multilocation pain compared to controls. The authors hypothesized that the presence of bodily pain in multiple nonpelvic 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.[9] What remains unclear is whether CS also contributes to nonpainful LUTS. Most evidence in support of the latter is derived from studies of women with OAB and storage LUTS.[10–13] 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

TABLE 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 ($N = 5966$)

		Multilocation 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	1090	Ref.	Ref.	Ref.	1430	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)	1283	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	1113	1883	–	–	–	2970	–	–	–

[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.
Abbreviations: CI, confidence interval; MrOS, osteoporotic fractures in men study; OR, odds ratio.

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.[6] 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.[6] 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[26,27] 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.[28] 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.[29] 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,[8] it was not yet developed at the time the MrOS cohort was

TABLE 4 Association (OR and 95% CI) between LUTS and any musculoskeletal pain by severity of storage and voiding symptoms among community-dwelling men aged ≥ 65 years: The MrOS Study, USA (N = 5,966)

		Tertiles of voiding symptoms		
		T1 (0–1 point)	T2 (2–4 points)	T3 (5–20 points)
Tertiles of storage symptoms	T1 (0–3 points)	Ref.	1.47 (1.16,1.85)	1.49 (1.07,2.07)
	T2 (4–6 points)	1.50 (1.18,1.90)	1.46 (1.15,1.84)	1.86 (1.47,2.35)
	T3 (7–15 points)	1.29 (0.89,1.86)	1.87 (1.35,2.59)	2.26 (1.80,2.83)

Abbreviations: CI, confidence interval; MrOS, osteoporotic fractures in men study; OR, odds ratio.
ORs adjusted for age and mobility limitations.

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.[7]

5 | 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.

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AUTHOR CONTRIBUTIONS

Angela Senders, Scott R Bauer, Yiyi Chen, Barry Oken, Howard A Fink, and Lynn M Marshall helped with conception and design, acquisition of data, analysis, and interpretation of data, drafting and revising the article, final approval of the version to be published. Nancy E Lane and Kamran P Sajadi conception and design, analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Data from MrOS are available at ttps://mrosdata. sfcc-cpmc. net. The analysis data set for this specific manuscript is also available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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