RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Value of the central sensitisation inventory in patients with axial spondyloarthritis

Yvonne Maria van der Kraan ,[1] Davy Paap,[1,2] Hans Timmerman,[3] Freke Wink ,[4] Suzanne Arends ,[1] Michiel Reneman,[5] Anneke Spoorenberg[1]

To cite: van der Kraan YM, Paap D, Timmerman H, *et al*. Value of the central sensitisation inventory in patients with axial spondyloarthritis. *RMD Open* 2024;**10**:e004528. doi:10.1136/rmdopen-2024-004528

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/rmdopen-2024-004528).

This study has been presented at the SPARTAN Annual Meeting 19 May 2023–20 May 2023, Cleveland, USA, EULAR 31 May 2023–3 June 2023, Milan, Italy, International Forum for Back and Neck Pain Research in Primary Care 29 August 2023–1 September 2023, Groningen, the Netherlands and NVR najaarsdagen 28 September 2023–29 September 2023, Papendal, the Netherlands.

Received 14 May 2024
Accepted 10 October 2024

For numbered affiliations see end of article.

Correspondence to
Ms Yvonne Maria van der Kraan; y.m.van.der.kraan@umcg.nl

ABSTRACT

Background In many patients with axial spondyloarthritis (axSpA), pain persists despite anti-inflammatory medication. Quantitative sensory testing (QST) indirectly assesses altered somatosensory function, though its clinical practicality is limited. The Central Sensitisation Inventory (CSI) could be an alternative in the initial assessment of central sensitisation (CS). This study aimed to investigate the value of the CSI in evaluating CS in patients with axSpA by (1) assessing somatosensory function related to CS with QST and (2) exploring associations between CSI, QST, patient and disease characteristics and pain-related psychosocial factors.

Methods Consecutive outpatients from the Groningen Leeuwarden AxSpA cohort underwent QST, including pressure pain threshold (PPT), temporal summation (TS) and conditioned pain modulation (CPM). Participants completed questionnaires assessing CS (CSI), illness perception (Revised Illness Perception Questionnaire, IPQ-R), pain-related worrying (Pain Catastrophising Scale, PCS), fatigue (Modified Fatigue Impact Scale, MFIS), anxiety/depression (Hospital Anxiety and Depression Scale, HADS) and coping. QST measurements were stratified for CSI≥40.

Results 201 patients with axSpA were included; 63% male, 64% radiographic axSpA, median symptom duration 12 years (IQR 5–24), mean Axial Spondyloarthritis Disease Activity Score 2.1±1.0. Patients with CSI≥40 had significantly lower PPTs and higher TS than CSI<40 ($p<0.004$). No significant differences in CPM were observed. In multivariable linear regression, sex, PCS, IPQ-R Identity, MFIS and HADS anxiety were independently associated with CSI (78% explained variance).

Conclusion In this large cross-sectional study in patients with axSpA, the CSI appears as a useful initial CS assessment questionnaire. When CSI scores indicate CS, considering pain-related psychosocial factors is important. These results emphasise the need for a biopsychosocial approach to manage chronic pain in patients with axSpA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A significant proportion of patients with axial spondyloarthritis (axSpA) experience persistent back pain despite long-term anti-inflammatory treatment, which may be linked to central sensitisation (CS). Since quantitative sensory testing is limited in clinical practicality, the Central Sensitisation Inventory (CSI) could serve as an alternative in the initial assessment of CS.

WHAT THIS STUDY ADDS

⇒ This study highlights the CSI as a valuable initial assessment questionnaire in clinical practice for identifying CS in patients with axSpA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study results underscore the need for differentiation between pain phenotypes and the importance of adopting a multifactorial biopsychosocial perspective in the diagnosis and management of chronic pain in patients with axSpA. By incorporating pain phenotyping and multifactorial biopsychosocial perspective, a more personalised understanding of the pain of patients with axSpA can be gained, particularly those with substantial disease activity resistant to inflammation-focused treatments.

INTRODUCTION

Axial spondyloarthritis (axSpA) is characterised by chronic inflammation, particularly in the sacroiliac joints and the spine, causing chronic pain and stiffness. This chronic back pain is considered the most important primary and early presenting symptom of axSpA,[1] substantially impacting daily activities and health-related quality of life (QoL). Because pain is also considered an important indicator of disease activity, it is incorporated into the disease activity assessments Axial Spondyloarthritis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).[2 3] ASDAS and BASDAI primarily rely on patient-reported items to assess symptoms related to disease activity. ASDAS additionally incorporates C reactive protein (CRP) levels as a biomarker of inflammation. To target inflammation, pharmacological therapy, such as non-steroidal

anti-inflammatory drugs (NSAIDs) and biological disease-modifying antirheumatic drugs (bDMARDs), is considered the cornerstone of axSpA treatment.[4] However, pain and stiffness persist in 20%–40% of patients on long-term bDMARD therapy irrespective of the presence of inflammation.[5] Consequently, it is hypothesised that non-nociceptive pain mechanisms beyond inflammation contribute to chronic pain in patients with axSpA.

Nociceptive, neuropathic and nociplastic pain represent distinct pain phenotypes.[6] Inflammation is presumed to primarily cause nociceptive pain in axSpA.[1] Neuropathic pain is a lesion or disease of the somatosensory nervous system and nociplastic pain arises from altered nociception without clear evidence of tissue damage or disease or lesion of the somatosensory system.[7] However, pain does not strictly adhere to these phenotypes; a combination is also possible, known as mixed pain.[8] Within axSpA, chronic inflammation, for example, caused by proinflammatory TNF-α release, could result in neural hyperactivity, and therefore, be a potential source of developing central sensitisation (CS), whether or not remaining inflammation is present. CS is one of the underlying neurophysiological mechanisms of nociplastic pain[6] and is defined as 'an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity'.[9] Psychosocial factors play a role in the development and maintenance of CS,[10] in which CS acts as a mediator between psychological factors and the experienced pain intensity.[11] In patients with chronic low back pain, in addition to nociplastic pain mechanisms such as CS, psychosocial factors, including pain-related worrying, illness perceptions, depression and anxiety, are recognised as contributing factors to chronic pain.[12]

Both the (EULAR) recommendations for pain management and International Society of Pain state that the health professional should be able to differentiate between nociceptive and nociplastic pain.[13 14] Additionally, the presence of CS has been shown to predict poor treatment outcomes in some patient groups, including those with osteoarthritis and fibromyalgia, highlighting the clinical need for pain management strategies tailored to the involved pain phenotypes.[15] A gold standard for assessing CS is lacking, but the most reported validated method to assess altered somatosensory function related to CS is quantitative sensory testing (QST).[16] QST consists of pressure pain thresholds (PPTs) and temporal summation (TS), both reflecting pain facilitation pathways and conditioned pain modulation (CPM), which reflects pain inhibition pathways.[16] Widespread and low PPTs, high TS values and positive CPM values are considered to reflect CS. QST involves expensive specialised equipment, highly standardised procedures, experienced staff and extensive time and facilities and is, therefore, not easily applicable in daily clinical practice.[17] The Central Sensitisation Inventory (CSI) is a questionnaire developed and validated for the identification of CS.[18] Research in chronic pain conditions showed that a cut-off of ≥40 (range 0–100) is indicative of the presence of CS.[18]

In axSpA, cross-sectional studies showed that a high percentage of patients (45%–60%) score ≥40 on the CSI, indicating a high probability of CS.[19–22] These patients had significantly higher disease activity scores (ASDAS and BASDAI) and experienced lower QoL compared with patients with a CSI<40.[23] AxSpA patients with CSI≥40 showed significantly lower PPTs and less pain inhibition than patients with CSI<40.[21] Lower PPTs were also significantly associated with higher ASDAS, fatigue, depression and anxiety.[24] In summary, these findings suggest that CS plays a substantial role in chronic pain in patients with axSpA and is associated with disease activity assessments and psychosocial factors. To date, none of these studies have comprehensively integrated the multifaceted dimensions of CS in a single study, including CSI, QST, ASDAS and pain-related psychosocial factors.

To address this need, this study explores if the CSI can serve as an initial questionnaire to assess the potential presence of CS in patients with axSpA in daily clinical practice and research. We hypothesised that patients with axSpA with CSI≥40 will show significantly more hyperalgesia, increased pain facilitation and less pain inhibition measured with QST. Furthermore, we expected moderate to strong associations with pain-related psychosocial factors.

Therefore, our study aim was to investigate the value of the CSI to evaluate CS in patients with axSpA by (1) assessing somatosensory function related to CS with QST and (2) exploring associations between CSI, QST, patient-related and disease characteristics and pain-related psychosocial factors.

METHODS

AxSpA cohort and axSpA-related assessments

For this clinical cross-sectional study, participants from the Groningen Leeuwarden Axial Spondyloarthritis (GLAS) cohort were included between December 2021 and July 2022. GLAS is a prospective long-term observational cohort study of patients with axSpA from the University Medical Center Groningen and the Medical Center Leeuwarden. Patients in this cohort have been included since 2004 and undergo follow-up visits according to a standardised protocol. All participating patients were ≥18 years old and diagnosed with axSpA by their treating physician, meeting the ASAS classification criteria for axSpA. Reporting of results follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

The following patient and disease-related assessments were collected from the regular outpatient visits: age, sex, axSpA classification (radiographic axSpA (r-axSpA) or non-radiographic axSpA (nr-axSpA)), symptom duration, HLA-B27 status, current smoking status, educational level (categorised according to the International Standard Classification of Education), occupational status (employed, studying, retired or disabled due to axSpA), body mass index, history of extra-articular

manifestations (uveitis (AU), psoriasis (PsO), inflammatory bowel disease), current peripheral arthritis (≥1 swollen joint), current medication use (NSAIDs and bDMARDs), ASDAS, BASDAI, CRP, Bath Ankylosing Spondylitis Functional Index, Ankylosing Spondylitis QoL Index and modified-Short QUestionnaire to Assess Health-enhancing physical activity.[25–27]

Quantitative Sensory Testing

Participants underwent QST according to a standardised protocol, which included the assessment of PPT, TS and CPM in a sequential design. Participants marked their painful locations on a body diagram (front and back view) before testing, identifying the most painful area with an arrow. The reference area was located opposite the most painful area. Test sites were selected to encompass a range of anatomical locations and pain characteristics. QST was performed by three assessors (YvdK, MO and DP), of whom one is already an expert, who received 2-day in-person training sessions by two experts (HT and DP). All QST assessments, clinical assessments and additional questionnaires were performed on the same day.

PPT measurements were performed using a handheld pressure algometer (Algometer Wagner FPX50, Greenwich, USA). Initially, a demonstration was performed at the dominant deltoid muscle to familiarise the participant to the test. Then, PPT was performed at ten sites: thenar muscle bilateral, trapezius muscle bilateral (at the level of the third thoracic vertebra, 4 cm laterally), rectus femoris muscle bilateral (15 cm above the patella), abductor hallucis longus muscle bilateral, the reference area and the most painful area. Pressure was applied at a rate of 5 N/s until the participant reported a painful, burning, stinging drilling or pulling sensation. The pressure at this point represented the participant's PPT. To obtain an overall mean for the PPT, we averaged the PPTs from all sites (PPT sum). Widespread and low PPTs are indicative of CS.[9] Reproducibility parameters in PPT assessments were good, even in novice raters.[28] Studies have shown that test–retest reliability of PPT measurements was good to excellent in healthy volunteers.[28]

TS involves the increasing perception of pain when a sensory stimulus is repeatedly applied rapidly over a short time showing pain facilitation. TS was performed using a PinPrick 256 mN (MRC Systems, Heidelberg, Germany). Again, a demonstration was performed at the dominant forearm to familiarise the participant with the test. TS was performed at three sites: the non-dominant forearm, the reference area and the most painful area. A single stimulus was applied, followed by a series of ten stimuli, with a frequency of 1 s, within the same skin area, with a size of 1 cm^2 in total. Immediately after the single stimulus and again following the next series of stimuli, the participant rated the perceptual pain using a Visual Analogue Scale (VAS) on a scale of 0–100. This procedure was repeated a total of five times, and a mean value of all five pain ratings for the single stimuli and of the subsequent stimulus series was calculated as 'wind-up'.[29] High TS values are considered to reflect CS. Studies have shown that test–retest reliability was good to excellent in individuals with back pain and healthy participants.[30]

CPM refers to the phenomenon where one pain-inducing stimulus can reduce the perception of another pain stimulus, showing impaired pain inhibition. CPM was performed with an ice water bath test in a sequential design, which reflects descending inhibition pathways. CPM was performed at three sites: non-dominant rectus femoris muscle, the reference area and the most painful area. First, a test stimulus was applied using a pressure algometer at a rate of 5 N/s until the participant experienced a pain sensation corresponding to a VAS score of 40 (on a scale of 0–100). Following that, a conditioning stimulus was applied by immersing the participant's dominant hand in an ice water bath at approximately −10°C for a maximum of 60 s. Immediately after the conditioning stimulus, the test stimulus was repeated. CPM was presented as percentage change (relative CPM effect) and absolute values.[31] The relative CPM effect was calculated by subtracting the first amount of pressure from the second amount of pressure, with the baseline measurement used as the denominator, multiplied by 100%: $100\times(CPM2-CPM1)/CPM2$.[31] Absolute differences were calculated by subtracting the first amount of pressure from the second amount of pressure. Negative values indicate endogenous pain inhibition (pain inhibition), while positive values indicate altered endogenous pain inhibition (pain facilitation). Studies have shown that test–retest reliability was good to excellent in patients with chronic low back pain and healthy participants.[32]

CSI and pain-related psychosocial assessments

In addition to the standardised assessments collected in the GLAS cohort, participants were asked to complete the CSI, Revised Illness Perception Questionnaire (IPQ-R), Pain Catastrophising Scale (PCS), Modified Fatigue Impact Scale (MFIS), Hospital Anxiety and Depression Scale (HADS) and Coping with Rheumatic Stressors questionnaire (CORS).

Central Sensitisation Inventory

The CSI[18] consists of parts A and B. Part A comprises 25 items on a 5-point Likert scale, assessing the presence of symptoms associated with CS, with a total sum score ranging from 0 to 100. A score of ≥40 is associated with a high probability of CS.[33] Part B was not used in this study. The CSI has been shown to be a reliable and valid instrument.[18]

Psychosocial questionnaires

The IPQ-R includes 38 questions divided into 7 subscales of illness perception. It uses a 5-point Likert scale, ranging from 'strongly disagree' to 'strongly agree'. The domain scores range from 0 to 30, with higher scores within each domain signifying a stronger perception of the corresponding aspect of the illness.[34]

The PCS comprises 13 items that measure an individual's tendency to pain-related worrying. It uses a 5-point Likert scale, ranging from 'not at all' to 'all the time'. The total score ranges from 0 to 52, with higher scores indicating a greater tendency towards pain-related worrying.[35]

The MFIS includes 21 questions evaluating the impact of fatigue on various aspects of life. It employs a 5-point Likert scale, ranging from 'no problem' to 'extensive problem'. The total score ranges from 0 to 84, with higher scores indicating a greater level of perceived fatigue and its impact on daily functioning.[36]

The HADS includes 14 questions that screen for anxiety and depression. It employs a 4-point Likert scale, ranging from 'not at all' to 'most of the time'. The total scores range from 0 to 21, with higher scores indicating higher levels of anxiety or depression symptoms. HADS has demonstrated good reliability and validity across studies.[37]

The CORS consists of 20 items that assess coping strategies related to rheumatic stressors, divided into subscales for pain, limitations and dependence. It uses a 4-point Likert scale, ranging from 'not at all' to 'very much.' The domain scores range from 5 to 40, with higher scores indicating greater utilisation or preference for the coping strategies related to that specific domain.[38]

Statistical analysis

Data analysis was performed by using IBM SPSS Statistics for Windows V.28.0.0 (IBM). Descriptive statistics are presented as numbers of patients (%), mean (SD) or median (IQR) for categorical, normally distributed and non-normally distributed variables, respectively.

QST distribution analysis was stratified for CSI cut-off ≥40. For normally distributed data, the independent samples t-test was used and for non-normally distributed data, the Mann-Whitney U test was used. We applied Bonferroni correction to adjust for multiple comparisons (n=14), interpreting statistical significance at p<0.004.

Respectively, Pearson or Spearman's correlation coefficients were used to analyse the relationship between CSI, QST, patient-related and disease characteristics and pain-related psychosocial factors. Correlations ranging from 0.0 to 0.2 were interpreted as poor, >0.2–0.4 as fair, >0.4–0.6 as moderate, >0.6–0.8 as strong and >0.8–1.0 as excellent.[39]

Independent associations between CSI, QST, patient-related and disease characteristics and pain-related psychosocial factors were identified using multivariable linear regression analysis. All statistically significant variables (p<0.05) associated with the CSI were entered into a forward stepwise model. Potential confounding variables based on our univariable analysis and literature were added to the model. For QST measurements in the univariable and multivariable linear regression analysis, we used PPT sum values with and without the most painful area, TS at the non-dominant forearm and CPM at the non-dominant rectus femoris muscle. To assess the robustness of the results, we performed the same analysis using the enter model. Regression assumptions, including linearity of relationship (scatterplots), normal distribution of residuals (QQ-plots), homoscedasticity (plotting residuals vs predicted values) and the absence of multicollinearity (variance inflation factor <5), were tested.

The CSI contains questions with potential overlap with symptoms related to axSpA such as 'I have pain in my pelvic area', therefore, the multivariable linear regression analysis was also performed with CSI without items 2, 5, 8, 12, 14, 17 and 25. A sensitivity analysis was done for QST distribution stratified for CSI cut-off ≥30,[40] which recently was proposed as cut-off for the presence of CS.

RESULTS

Patient and disease characteristics

In total, 201 patients with axSpA were included in this study. Median age was 51 years (IQR 39–59), 64% were male, 64% were classified as r-axSpA, median symptom duration was 13.0 years (IQR 5.0–24.0), median diagnostic delay was 5.0 years (IQR 1.0–12.0), median CRP was 2.0 mg/L (1.0–4.2), 24% had elevated CRP (≥5 mg/L), mean ASDAS was 2.1±0.9 and 51% had ASDAS≥2.1. 49.3% of the participants reported either the left or right lower back as the most painful area. All sociodemographic and clinical patient characteristics are presented in table 1.

CSI and QST

Mean CSI score was 34.6±14.7 and 40% of the participants scored CSI≥40 indicating a high probability of CS (table 2). The PPT value was lowest at the most painful area (median 26.5 (17.8–41.5)) and left thenar (mean 33.3±16.6), respectively, and highest at left and right rectus femoris muscle (49.7±25.2; 47.3±26.1), respectively (table 3). Median TS values at the non-dominant forearm, reference area and most painful area were 0.7 (0.1–1.4), 0.8 (0.2–1.9) and 0.9 (0.2–2.1), respectively (table 3). Mean absolute CPM value at the non-dominant rectus femoris muscle was 1.9±12.0 (table 3), with a relative CPM effect of −1% (table 3).

QST measurements stratified for CSI

In patients with CSI≥40, PPTs at all sites were statistically significantly lower (p<0.004) and TS was statistically significantly higher (p<0.004), both within the non-painful areas and the most painful area, compared with patients with CSI<40. Although differences in TS at the non-dominant forearm and CPM at the non-dominant rectus femoris muscle were not statistically significant, the scores were in the expected direction (table 3). A CSI cut-off ≥30 yielded similar results to the cut-off ≥40 (online supplemental file 1).

Psychosocial assessments

Concerning illness perception, the results of IPQ-R domain 'identity' showed that few patients with axSpA perceived their symptoms as related to their disease

Table 1 Patient and disease characteristics (n=201)

	n (%) or mean±SD (median)
Age, years	49.5±13.4 (51.6)
Male	128 (64%)
Classified as r-axSpA	129 (64%)
Symptom duration, years	15.2±11.4 (13.0)*
Diagnostic delay, years	8.0±7.9 (5.0)*
HLA-B27 positive	153 (78%)
High education level†	68 (34%)
Occupational situation	
Employed	126 (63%)
Unemployed	18 (9%)
Studying	5 (3%)
Retired	18 (9%)
Not capable due to axSpA	32 (16%)
BMI, kg/m^2	27.8±5.8 (26.4)
Current smoker	51 (26%)
Current peripheral arthritis‡	6 (3%)§
History of IBD	16 (8%)
History of uveitis	52 (26%)
History of psoriasis	13 (7%)
BASDAI, 0–10 BASDAI≥4	3.9±2.2 (3.6) 93 (47%)
ASDAS ASDAS≥2.1	2.1±0.9 (2.2) 98 (51%)
CRP, mg/L CRP≥5, mg/L	4.1±5.9 (2.0) 49 (24%)
ASQoL, 0–18	5.4±4.8 (4.0)*
BASFI, 0–10	3.3±2.4 (2.9)*
mSQUASH activity total score	9202±5516 (8960)
Medication use	
NSAID use	117 (59%)
csDMARD use	25 (12%)
bDMARD use	104 (53%)

Values are presented in: n (%) or mean±SD (median). All % values exclude missing items for their respective characteristic. All missing values <5% unless otherwise specified.
*10-15% missing
†Defined as International Standard Classification of Education level >5.
‡Defined as a swollen joint count of ≥1.
§5-10% missing.
ASDAS, Axial Spondyloarthritis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life questionnaire; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; CRP, C reactive protein; csDMARD, conventional synthetic DMARD; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; mSQUASH, modified-Short Questionnaire to Assess Health-enhancing physical activity; NSAID, non-steroidal anti-inflammatory drug; r-axSpA, radiographic axial spondyloarthritis.

Table 2 Scores of CSI and psychosocial questionnaires (n=201)

	n (%) or mean±SD (median)
CSI, 0–100	34.6±14.7 (34.0)
CSI≥40	81 (40%)
IPQ-R	
Identity, 0–14	4.0±2.5 (4.0)
Timeline acute/chronic, 6–30	26.9±3.7 (28.0)
Timeline cyclical, 4–20	14.1±3.7 (15.0)
Personal control, 6–30	20.8±4.2 (21.0)
Treatment control, 6–30	18.2±3.2 (19.0)
Illness coherence, 5–25	19.1±4.2 20.0)
Consequences, 6–30	16.5±5.3 (16.0)
Emotional representations, 6–30	13.4±3.5 (13.0)
PCS, 0–52	13.2±9.5 (12.0)
MFIS, 0–84	32.0±16.9 (31.0)
HADS	
Anxiety, 0–21	4.5±3.2 (4.0)
Depression 0–21	6.3±3.7 (6.0)
CORS pain	
Comforting cognitions, 9–36	28.6±4.7 (29.0)
Decreasing activity, 8–31	19.6±4.5 (20.0)
Diverting attention, 8–30	20.9±4.6 21.0)
CORS Limitations	
Optimism, 5–20	16.4±31.3 (17.0)
Pacing, 10–40	26.8±6.8 (27.0)
Creative solution seeking, 8–32	23.2±5.2 (23.0)
CORS Dependence	
Acceptance, 6–24	15.7±4.8 (15.0)
Showing consideration, 7–28	21.3±3.8 (21.0)

Values are presented in: mean±SD (median).
CORS, Coping with Rheumatic Stressors questionnaire; CSI, Central Sensitisation Inventory; HADS, Hospital Anxiety and Depression Scale; IPQ-R, Revised Illness Perception Questionnaire; MFIS, Modified Fatigue Impact Scale; PCS, Pain Catastrophising Scale.

(median 4.0 (IQR 2.0–5.0), range 0–14). IPQ-R domain 'personal control' and 'treatment control' showed that patients overall felt some ability to have influence on their disease (mean 20.8±4.2, range 6–30) and treatment (mean 18.2±3.2, range 6–30). As expected, the IPQ-R domain 'timeline acute/chronic' showed most scores towards 'chronic', reflecting the chronic nature of axSpA (median 28 (26.0–29.0), range 6–30).

Pain-related worrying was relatively low, affecting only 4.5% of participants (median PCS 12.0 (5.0–20.0), range 0–52) and patients experienced a moderate level of fatigue (mean MFIS 32.0±16.9, range 0–84). Patients experienced relatively few feelings of anxiety and depression (HADS-anxiety median 4.0 (2.0–6.0) and HADS-depression 6.0 (3.0–8.0), range 0–21, respectively). For

Table 3 QST distributions of 201 patients with axSpA stratified for CSI score

		All patients (n=201)	CSI<40 (n=117)	CSI≥40 (n=81)
PPT				
Thenar	Left	33.3±16.6 (29.8)	37.2±18.2 (33.7)	27.7±12.3 (23.5)*
	Right	36.4±18.3 (32.6)	40.7±19.1 (38.8)	30.3±15.4 (26.8)*
m. trapezius	Left	35.3±20.9 (30.0)	38.6±20.0 (34.0)	30.4±21.4 (24.5)
	Right	34.8±19.8 (31.5)	38.2±20.0 (34.4)	30.1±18.7 (26.0)*
m. rectus femoris	Left	49.7±25.2 (46.0)	54.6±26.1 (49.1)	42.3±21.8 (36.8)*
	Right	47.3±26.1 42.0)	53.2±26.6 (47.2)	38.6±23.1 (32.0)*
m. abductor hallucis	Left	33.6±17.3 (31.2)	36.4±18.6 (33.8)	29.3±14.1 (28.0)*
	Right	35.1±18.8 (31.2)	38.3±19.7 (34.5)	30.0±16.2 (27.5)*
Reference area†		33.7±20.5 (28.5)	37.7±21.7 (31.7)	27.8±17.4 (23.0)*
Most painful area		32.4±20.8 (26.5)	36.9±21.9 (31.4)	25.7±17.2 (21.0)*
TS				
Non-dominant forearm		1.0±1.1 (0.7)	0.8±1.0 (0.5)	1.2±1.3 (0.8)
Reference area†		1.2±1.3 (0.8)	1.0±1.2 (0.6)	1.5±1.3 (1.3)†
Most painful area		1.4±1.5 (0.9)	1.1±1.3 (0.7)	1.8±1.6 (1.4)†
CPM				
Non-dominant m. rectus femoris		−1.9±12.0 (12.0)	−2.7±13.1 (2.6)	−0.3±9.7 (1.3)
		(−1%)	(−2%)	(2%)

Values are presented in: mean±SD (median).
*Statistically significant difference at p<0.004 (Bonferroni correction).
†Defined as area opposite to the most painful area.
axSpA, axial spondyloarthritis; CPM, conditioned pain modulation; CSI, Central Sensitisation Inventory; PPT, pain pressure threshold; QST, quantitative sensory testing; TS, temporal summation.

coping with pain, comforting cognitions were used most (CORS pain comforting cognitions: mean 28.6±4.7, range 9–36). All data from the psychosocial assessments are presented in table 2.

Associations between CSI, QST, patient-related and disease characteristics and pain-related psychosocial factors

Correlations between CSI and CRP, CORS limitations pacing, and CPM were (very) poor and not statistically significant. Statistical significant correlations, ranging from poor to strong, were observed between CSI and TS non-dominant forearm, PPT sum values with and without most painful area, CORS pain decreasing activities, HADS depression, IPQ-R emotional representations, IPQ-R consequences, ASDAS, PCS, IPQ-R identity, HADS anxiety and MFIS. All correlations are presented in online supplemental file 2.

Univariable and multivariable regression analyses

Results of the univariable and multivariable linear regression analysis are presented in table 4. A multivariable regression analysis (stepwise forward) was performed. In the model, HADS depression was removed due to multicollinearity with HADS anxiety and MFIS. For disease activity, ASDAS was used instead of BASDAI because it is the preferred assessment of disease activity. The final model revealed five variables (MFIS, IPQ-R Identity, sex, HADS anxiety and PCS) independently associated with CSI (table 4). These variables explained 78% of the variance in the CSI scores (R^2 of 0.78 p<0.001). Univariable and multivariable linear regression analysis using the sum of PPT values (PPT sum) excluding the most painful area did not yield significant differences (table 4). Correcting the model for potential overlap between the CSI questions and axSpA-related symptom questions did not significantly affect the model (online supplemental file 3).

DISCUSSION

This large cross-sectional study in patients with axSpA demonstrated that the CSI can serve as an initial questionnaire to assess the potential presence of CS in patients with axSpA in daily clinical practice and research.

Patients with CSI≥40 exhibited significantly higher hyperalgesia and increased pain facilitation reflected by lower PPTs at all assessed sites compared with patients with CSI<40. These results align with previous research in axSpA and other inflammatory rheumatic diseases, including rheumatic arthritis (RA) and psoriatic arthritis.[21 41] This suggests that patients with higher CSI scores experience increased sensitivity to pressure-induced pain across multiple body regions, which is associated with CS.[9] We also found increased

Table 4 Univariable and multivariable linear regression analysis with CSI as dependent variable with patient and disease characteristics, psychosocial assessments and QST (n=201)

	Univariable			Multivariable		
	R^2	B	95% CI	B	Standardised ß	95% CI
Age, years	0.02	−0.16*	−0.31, to 0.00			
Sex, male vs female	0.13	10.88*	6.89, 14.86	8.36*	0.27	5.98, 10.73
Diagnostic delay, years	0.00	0.03	−0.25, 0.31			
BMI, kg/m^2	0.00	0.16	−0.20,0.51			
CRP, mg/L	0.00	−0.02	−0.37, 0.33			
ASDAS	0.25	7.56*	5.71, 9.41			
BASDAI	0.44	4.46*	3.75, 5.16			
ASQoL, 0–18	0.50	2.20*	1.87, 2.54			
BASFI, 0–10	0.26	3.26*	2.42, 4.09			
mSQUASH total activity score	0.05	−0.01*	−0.01, 0.00			
Psychosocial assessments						
IPQ-R identity, 0–14	0.42	3.82*	3.18, 4.46	1.78*	0.28	1.19, 2.37
IPQ-R timeline acute/chronic, 6–30	0.00	0.29	−0.19, 0.94			
IPQ-R timeline cyclical, 4–20	0.03	0.28*	0.16, 1.27			
IPQ-R personal control, 6–30	0.03	0.25*	−1.12, to 0.14			
IPW-R treatment control, 6–30	0.08	0.32*	−1.94, to 0.68			
IPQ-R illness coherence, 5–25	0.09	0.24*	−1.49, to 0.56			
IPQ-R consequences, 6–30	0.25	1.37*	1.03, 1.71			
IPQ-R emotional representations, 6–30	0.24	2.05*	1.54, 2.57			
PCS, 0–52	0.38	0.95*	0.78, 1.12	0.28*	0.17	0.12, 0.44
MFIS, 0–84	0.61	0.04*	0.61, 0.76	0.29*	0.32	0.19, 0.39
HADS anxiety, 0–21	0.35	2.70*	2.18, 3.22	0.99*	0.23	0.54, 1.45
HADS depression, 0–21	0.18	0.26*	1.18, 2.20			
CORS pain comforting cognitions, 9–36	0.01	0.22	−0.76, 0.12			
CORS pain decreasing activities, 8–31	0.17	0.21*	0.90, 1.74			

Continued

Table 4 Continued

	Univariable		Multivariable
CORS pain diverting attention, 8–30	0.00	0.23	−0.25, 0.66
CORS limitations optimism, 5–20	0.05	0.33*	−1.64 to to 0.35
CORS limitations pacing, 10–40	0.01	0.15	−0.08, 0.52
CORS limitations creative solution seeking, 8–32	0.00	0.20	−0.28, 0.51
CORS dependence acceptance, 6–24	0.02	0.22	−0.86, 0.00
CORS dependence showing consideration, 7–28	0.00	0.28	−0.47, 0.63
QST measurements			
PPT sum values, N			
With most painful area	0.09	−0.24*	−0.35, 0.14
Without most painful area	0.09	−0.24*	−0.35, 0.13
TS non-dominant forearm, N	0.04	2.55*	0.77, 4.32
CPM non-dominant m. rectus femoris, N	0.00	−0.02	−0.19, 0.16

Order of inclusion CSI: (1) MFIS (R^2=0.60); (2) IPQ-R Identity (R^2=0.66); (3) Sex (R^2=0.71);(4) HADS anxiety (R^2=0.76); (5) PCS (R^2=0.78).
*p<0.05.
ASDAS, Axial Spondyloarthritis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life questionnaire; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; CORS, Coping with Rheumatic Stressors questionnaire; CPM, conditioned pain modulation; CRP, C reactive protein; CSI, Central Sensitisation Inventory; HADS, Hospital Anxiety and Depression Scale; IPQ-R, Revised Illness Perception Questionnaire; MFIS, Modified Fatigue Impact Scale; mSQUASH, modified-Short Questionnaire to Assess Health-enhancing physical activity; PCS, Pain Catastrophising Scale; PPT, pain pressure threshold; QST, quantitative sensory testing; TS, temporal summation.

pain facilitation shown by significantly higher TS values in both non-painful and painful areas in axSpA patients with CSI≥40 compared with those with CSI<40. Increased pain facilitation reflected by enhanced TS is also defined as a manifestation of CS.[9] We also expected less pain inhibition (CPM) in axSpA patients with probable CS according to CSI. Interestingly, overall there was little CPM effect in our study population, with no significant difference between the two groups stratified for CSI score. However, the direction of the change was as expected and patients with CSI<40 demonstrated a more pronounced CPM effect (pain inhibition) compared with those with CSI≥40. Only one other study in axSpA assessing CPM found a statistically significant difference stratified for CSI score.[21] Consequently, the evidence on the CPM effect in axSpA remains inconclusive, mirroring the situation observed in RA, where diverse results concerning the CPM effect have also been documented.[41] Our study results suggest that the CSI lacks discriminative value regarding the CPM effect. However, it is important to consider that peripheral inflammation in patients with axSpA can serve as an endogenous condition stimulus, activating

descending pain inhibition pathways.[42] Additionally, CPM is reflected by a different pain pathway than mechanical stimulation by PPT and TS. While PPT and TS reflect the facilitation of ascending nociceptive processing, CPM serves as an assessment of the descending inhibitory pain pathway.[43] Conducting longitudinal assessments of CPM before and after the start of anti-inflammatory treatment would provide valuable insights into how CPM changes in patients with and without inflammation.

Our study reaffirms the high correlation between CSI and psychological factors such as anxiety and depression. This emphasises the relevance of the CSI not only as an initial questionnaire for CS, but also for other psychological disorders that are associated with conditions sharing common pathophysiological mechanisms of CS.[44] The observed moderate to strong positive associations between CSI and pain-related worrying, fatigue, anxiety and depression align with our expectations. Similarly, we noted moderate to strong positive associations between CSI and negative illness beliefs. While a moderate positive association was observed between CSI and the evasive coping domain 'decreasing activities,' no significant association was found for the evasive coping domain 'pacing.' These findings align with previous studies reporting moderate to strong correlations between CSI and various psychological questionnaires.[45] The comprehensive assessment of QST measurements and psychological aspects enhances our understanding of the clinical utility of the CSI.

As expected, a moderate positive correlation was found between CSI and ASDAS, while no significant correlation was observed between CSI and CRP. This result is consistent with what is expected in a study population receiving treatment and supports the notion that, alongside inflammation, CS plays a role in pain in patients with axSpA. The associations found in our univariable and multivariable regression analysis could be attributed to the fact that these variables are related constructs and the presence of sex-related biopsychosocial differences in pain.[46] Women tend to have higher scores on (patient-reported) disease activity assessments than men in axSpA.[47] There is also growing evidence suggesting that there are considerable sex differences in disease presentation in patients with axSpA. Women generally experience a greater disease burden than men, including pain.[47] Moreover, within knee osteoarthritis a greater overall sensitivity to experimental pain in women compared with men was found, suggesting that sex may be an important mediator in CS.[48]

This study has some limitations, one of them is that there is currently no universally recognised gold standard for assessing CS. While a static cut-off value may not capture the diverse presentations of CS in individuals with different disorders,[18 33 40] the use of different CSI cut-offs in our study (eg, 30 and 40) yielded outcomes in the same expected direction, underscoring the value of the CSI in assessing CS in axSpA. Nonetheless, it is important to acknowledge that CS is dynamic and may change over time due to various factors, including disease-related factors. Therefore, longitudinal evaluations will be the next step to accurately capture changes and further validate the CSI and existing cut-off values for assessing CS in patients with axSpA. Furthermore, it is plausible that peripheral sensitisation is also involved in axSpA. Our study design did not allow us to fully distinguish between peripheral sensitisation and CS. QST assessments of hyperalgesia in a painful area of the body are not specific indicators of CS, as they may also reflect peripheral sensitisation. However, increased sensitivity to sensory input in non-painful areas of the body is generally accepted as a sign of CS.[15] Therefore, PPT sum values with and without the most painful area were used in our analysis and other studies.[49] However, different body regions may have different levels of sensitivity. This means that each different region will contribute a different amount to the summed PPT scale. The disadvantage of including each body region separately in the multivariable linear regression analysis is that it provides less clear impression of widespread sensitivity and results in a loss of power. Excluding the most painful area in our study protocol did not result in significant differences in the regression analysis. This is consistent with a recent meta-analysis by Neblett *et al*,[49] which found no notable differences in CSI-QST correlations between painful and non-painful areas of the body across different patient conditions, which may be related to patterns of widespread hyperalgesia.[49] Another possible limitation is that an inter-rater reliability assessment was not conducted in our study. However, recent studies using the same QST measurement tools reported good to excellent test–retest reliability (ICC 0.80–0.97).[28 30 32] Performing interobserver reliability assessments would have unnecessarily burdened our patients and resulted in a considerable loss of valuable data, as patients could not be tested twice. For CPM, the literature indicates variable reliability depending on methodology and parameters. To minimise this effect and ensure reliable results, we adhered to recommended standardisation protocols.[32]

This study is the first study integrating the multifaceted dimensions of CS combining CSI with QST including PPT, TS and CPM, patient-related and disease characteristics and pain-related psychosocial factors in patients with axSpA. This multifaceted approach provides insight into the complex interplay between biological, psychological and social factors in influencing pain experiences. Such understanding is needed to recognise the different pain phenotypes and associated factors. A comprehensive biopsychosocial perspective is needed when approaching pain in patients with axSpA. Treating clinicians should be

aware of nociplastic pain and CS in cases of chronic pain and persistent high disease activity scores measured with ASDAS. The CSI can be used as an initial CS assessment questionnaire in these patients. Notably, the CSI is not a diagnostic questionnaire. Based on this study, a high CSI score may suggest the presence of CS and pain-related psychosocial factors. In contrast to QST, which evaluates somatosensory function, the CSI primarily assess symptoms considered to be associated with CS. Nonetheless, the CSI provides valuable information to guide both healthcare providers and patients in making treatment decisions.

Due to the cross-sectional design, no definitive conclusions can be made about the effect of anti-inflammatory treatment on QST and CSI scores. The majority of patients in our study had stable disease, with approximately 50% receiving treatment with bDMARDs. Although 50% of the patients had an ASDAS score ≥2.1, indicating high disease activity, they had low overall CRP levels. It is important to note that, even in this group, clinically relevant pain persists. A separate longitudinal study is needed in patients with axSpA starting anti-inflammatory therapy to provide more insight into the effect of anti-inflammatory treatment on QST and CSI.

CONCLUSION

In conclusion, our large cross-sectional QST study in patients with axSpA reveals that CSI can be a valuable initial assessment questionnaire for identifying CS. For patients with CSI≥40, it is important to consider pain-related psychosocial factors such as fatigue, illness perception, anxiety and pain-related worrying, along with patient and disease characteristics, including sex and ASDAS. These insights will guide healthcare providers and patients in refining management plans, ultimately enhancing the overall care of patients with axSpA who experience chronic pain irrespective of anti-inflammatory treatment.

Author affiliations
[1]Department of Rheumatology and Clinical Immunology, University Medical Centre, Groningen, Netherlands
[2]Department of Physiotherapy, Saxion University of Applied Sciences, Enschede, Netherlands
[3]Department of Anaesthesiology, Pain Center, University Medical Centre, Groningen, Netherlands
[4]Department of Rheumatology, Medical Centre, Leeuwarden, Netherlands
[5]Rehabilitation Medicine, University Medical Centre, Groningen, Netherlands

Acknowledgements The authors would like to thank all patients who participated in the GLAS cohort and acknowledge Mrs. B. Toonder, Mrs. AAH van der Veen-Hebels, Mrs. M Boon-Middelkoop, Mrs. E Markenstein, Drs. SC Kieskamp and Mrs. DM van Ommen for their help in the study.

Contributors All authors have made substantial contributions to the conception or design of the work: Conceptualisation YvdK, DP, HT, MR and AS; Data curation YvdK and DP; Formal analysis YvdK, DP and AS; Methodology DP, HT and SA; Supervision DP, HT, MR and AS; Writing original draft YvdK; Writing review and Editing YvdK, DP, HT, FW, SA, MR and AS. The corresponding author, also acting as guarantor, attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding This study was funded by a ReumaNederland Grant.

Disclaimer The sponsor was not involved in the study design, in the collection, analysis and interpretation of the data, in the writing of the manuscript or in the decision to submit the manuscript for publication.

Competing interests None declared.

Patient and public involvement statement A representative of the GLAS cohort was involved during the design of the study.

Patient consent for publication Not applicable.

Ethics approval Approval for the GLAS cohort and an amendment for this study were obtained from the local ethics committees (RTPO 364/604). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data and the study protocol are available on reasonable request. Data are deidentified participant data. The data are available from the corresponding author (ORCiD iD: 0000-0001-6809-6799) on reasonable request. Reuse is not permitted.

ORCID iDs
Yvonne Maria van der Kraan http://orcid.org/0000-0001-6809-6799
Freke Wink http://orcid.org/0000-0003-0319-1247
Suzanne Arends http://orcid.org/0000-0002-4422-7640

REFERENCES

1 Navarro-Compán V, Sepriano A, El-Zorkany B, *et al*. Axial spondyloarthritis. *Ann Rheum Dis* 2021;80:1511–21.
2 Garrett S, Jenkinson T, Kennedy LG, *et al*. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21:2286–91.
3 Lukas C, Landewé R, Sieper J, *et al*. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009;68:18–24.
4 Braun J, van den Berg R, Baraliakos X, *et al*. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2011;70:896–904.
5 Arends S, Brouwer E, Efde M, *et al*. Long-term drug survival and clinical effectiveness of etanercept treatment in patients with ankylosing spondylitis in daily clinical practice. *Clin Exp Rheumatol* 2017;35:61–8.
6 Nijs J, Malfliet A, Nishigami T. Nociplastic pain and central sensitization in patients with chronic pain conditions: a terminology update for clinicians. *Braz J Phys Ther* 2023;27:100518.
7 Fitzcharles M-A, Cohen SP, Clauw DJ, *et al*. Nociplastic pain: towards an understanding of prevalent pain conditions. *The Lancet* 2021;397:2098–110.
8 Freynhagen R, Parada HA, Calderon-Ospina CA, *et al*. Current understanding of the mixed pain concept: a brief narrative review. *Curr Med Res Opin* 2019;35:1011–8.
9 Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011;152:S2–15.
10 Adams LM, Turk DC. Central sensitization and the biopsychosocial approach to understanding pain. *J Appl Biobehavioral Res* 2018;23.
11 Shigetoh H, Tanaka Y, Koga M, *et al*. The Mediating Effect of Central Sensitization on the Relation between Pain Intensity and Psychological Factors: A Cross-Sectional Study with Mediation Analysis. *Pain Res Manag* 2019;2019:3916135.

12 O'Keeffe M, George SZ, O'Sullivan PB, *et al*. Psychosocial factors in low back pain: letting go of our misconceptions can help management. *Br J Sports Med* 2019;53:793–4.
13 Geenen R, Overman CL, Christensen R, *et al*. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. *Ann Rheum Dis* 2017;annrheumdis–2017.
14 Perrot S, Cohen M, Barke A, *et al*. The IASP classification of chronic pain for ICD-11: chronic secondary musculoskeletal pain. *Pain* 2019;160:77–82.
15 Nijs J, George SZ, Clauw DJ, *et al*. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. *Lancet Rheumatol* 2021;3:e383–92.
16 den Boer C, Dries L, Terluin B, *et al*. Central sensitization in chronic pain and medically unexplained symptom research: A systematic review of definitions, operationalizations and measurement instruments. *J Psychosom Res* 2019;117:32–40.
17 Rolke R, Baron R, Maier C, *et al*. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain* 2006;123:231–43.
18 Mayer TG, Neblett R, Cohen H, *et al*. The development and psychometric validation of the central sensitization inventory. *Pain Pract* 2012;12:276–85.
19 Kieskamp SC, Paap D, Carbo MJG, *et al*. Central sensitization, illness perception and obesity should be considered when interpreting disease activity in axial spondyloarthritis. *Rheumatology (Oxford)* 2021;60:4476–85.
20 Aykurt Karlıbel I, Kasapoğlu Aksoy M. The relationship between central sensitization and disease activity, quality of life, and sleep quality among patients with axial spondyloarthritis. *Ir J Med Sci* 2023;192:481–9.
21 Yücel FN, Duruöz MT. Central sensitization in axial spondyloarthritis: An explorative study with quantitative sensory testing and clinical scales. *Mod Rheumatol* 2022;32:1137–45.
22 Guler MA, Celik OF, Ayhan FF. The important role of central sensitization in chronic musculoskeletal pain seen in different rheumatic diseases. *Clin Rheumatol* 2020;39:269–74.
23 Sariyildiz A, Coskun Benlidayi I, Turk I, *et al*. Biopsychosocial factors should be considered when evaluating central sensitization in axial spondyloarthritis. *Rheumatol Int* 2023;43:923–32.
24 Mogard E, Olofsson T, Bergman S, *et al*. Chronic Pain and Assessment of Pain Sensitivity in Patients With Axial Spondyloarthritis: Results From the SPARTAKUS Cohort. *J Rheumatol* 2021;48:1672–9.
25 Calin A, Garrett S, Whitelock H, *et al*. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994;21:2281–5.
26 Doward LC, McKenna SP, Meads DM, *et al*. Translation and validation of non-English versions of the Ankylosing Spondylitis Quality of Life (ASQOL) questionnaire. *Health Qual Life Outcomes* 2007;5:7.
27 Carbo MJ, Paap D, Maas F, *et al*. The mSQUASH; a valid, reliable and responsive questionnaire for daily physical activity in patients with axial spondyloarthritis. *Semin Arthritis Rheum* 2021;51:719–27.
28 Reezigt RR, Slager GEC, Coppieters MW, *et al*. Novice assessors demonstrate good intra-rater agreement and reliability when determining pressure pain thresholds; a cross-sectional study. *PeerJ* 2023;11:e14565.
29 Magerl W, Wilk SH, Treede R-D. Secondary hyperalgesia and perceptual wind-up following intradermal injection of capsaicin in humans. *Pain* 1998;74:257–68.
30 Mailloux C, Beaulieu L-D, Wideman TH, *et al*. Within-session test-retest reliability of pressure pain threshold and mechanical temporal summation in healthy subjects. *PLoS One* 2021;16:e0245278.
31 Yarnitsky D, Bouhassira D, Drewes AM, *et al*. Recommendations on practice of conditioned pain modulation (CPM) testing . *Eur J Pain* 2015;19:805–6.
32 Kennedy DL, Kemp HI, Ridout D, *et al*. Reliability of conditioned pain modulation: a systematic review. *Pain* 2016;157:2410–9.
33 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. *J Pain* 2013;14:438–45.
34 Moss-Morris R, Weinman J, Petrie K, *et al*. The Revised Illness Perception Questionnaire (IPQ-R). *Psychology & Health* 2002;17:1–16.
35 Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychol Assess* 1995;7:524–32.
36 Guidelines MSCP. Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis. 1998.
37 Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983;67:361–70.
38 Van Lankveld W, Naring G, Van der Staak C, *et al*. De ontwikkeling van de CORS: Coping met reuma stressoren. *Gedrag Gezond* 1993;21:40–8.
39 Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. *Biometrics* 1977;33:159.
40 Schuttert I, Wolff AP, Schiphorst Preuper RHR, *et al*. Validity of the Central Sensitization Inventory to Address Human Assumed Central Sensitization: Newly Proposed Clinically Relevant Values and Associations. *J Clin Med* 2023;12:4849.
41 Trouvin A-P, Attal N, Perrot S. Assessing central sensitization with quantitative sensory testing in inflammatory rheumatic diseases: A systematic review. *Joint Bone Spine* 2022;89:105399.
42 Lee YC, Bingham CO 3rd, Edwards RR, *et al*. Association Between Pain Sensitization and Disease Activity in Patients With Rheumatoid Arthritis: A Cross-Sectional Study. *Arthritis Care Res (Hoboken)* 2018;70:197–204.
43 Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. *Pain* 2015;156:S24–31.
44 Neblett R, Hartzell MM, Mayer TG, *et al*. Establishing Clinically Relevant Severity Levels for the Central Sensitization Inventory. *Pain Pract* 2017;17:166–75.
45 Adams GR, Gandhi W, Harrison R, *et al*. Do "central sensitization" questionnaires reflect measures of nociceptive sensitization or psychological constructs? A systematic review and meta-analyses. *Pain* 2023;164:1222–39.
46 Rusman T, van Bentum RE, van der Horst-Bruinsma IE. Sex and gender differences in axial spondyloarthritis: myths and truths. *Rheumatology (Oxford)* 2020;59:iv38–46.
47 Wright GC, Kaine J, Deodhar A. Understanding differences between men and women with axial spondyloarthritis. *Semin Arthritis Rheum* 2020;50:687–94.
48 Bartley EJ, King CD, Sibille KT, *et al*. Enhanced Pain Sensitivity Among Individuals With Symptomatic Knee Osteoarthritis: Potential Sex Differences in Central Sensitization. *Arthritis Care Res (Hoboken)* 2016;68:472–80.
49 Neblett R, Sanabria-Mazo JP, Luciano JV, *et al*. Is the Central Sensitization Inventory (CSI) associated with quantitative sensory testing (QST)? A systematic review and meta-analysis. *Neurosci & Biobehav Rev* 2024;161:105612.