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ORIGINAL ARTICLE

Pain sensitization in fibromyalgia. Cross-sectional associations between quantitative sensory testing of pain sensitization and fibromyalgia disease burden

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Abstract

Background: Whether fibromyalgia burden is related to measures of sensitization, assessed by quantitative sensory testing (QST), is not clear. We examine the associations between sensitization and fibromyalgia disease burden as measured by the polysymptomatic sistress scale (PDS) and the fibromyalgia impact questionnaire (FIQ) (range 0–100).

Materials and Methods: Participants were recruited from referrals to a rheumatology outpatient clinic and the fibromyalgia diagnosis was verified by a rheumatologist. They completed the PDS and FIQ and underwent QST of pressure pain threshold (PPT) at five sites, temporal summation (TS), and conditioned pain modulation (CPM) estimated as post-stimuli/pre-stimuli PPT. The associations between QST and disease burden were analysed in linear regression models adjusted for age, sex, and body mass index.

Results: A total of 78 individuals with clinically verified fibromyalgia (90% women, mean age 40.9 years (SD 7.3)) were recruited. Overall mean PPT was associated with the FIQ total score (β-2.1, 95% CI-4.3, −0.0) and the function component (β-2.1, (−4.3, −0.0)). When examining the associations between PPT at individual sites and fibromyalgia disease severity, PPTs at the distal interphalangeal joint and tibialis anterior muscle were associated with both FIQ total score and the FIQ fatigue component. All associations were weak and insignificant after Bonferroni corrections.

Conclusion: In this cohort of individuals with fibromyalgia, sensitization was not significantly associated with self-reported disease burden. Our results point to the multifactorial nature of fibromyalgia disease severity.

Significance: In patients with fibromyalgia, commonly used measures of sensitization do not explain the symptom burden or the functional impact.

1 | INTRODUCTION

Fibromyalgia is a prevalent condition which affects ~3% of the population, most frequently women (Hauser et al., 2021). The clinical hallmarks of fibromyalgia are widespread pain and widespread abnormal tenderness on examination. Patients experience a wealth of symptoms including fatigue, cognitive and somatic symptoms, and/or unrefreshing sleep that are part of the fibromyalgia disease complex (Wolfe et al., 2011).

Fibromyalgia disease burden is commonly measured by self-reported questionnaires. Two of the most frequently used instruments are the polysymptomatic distress scale (PDS) and the fibromyalgia impact questionnaire (FIQ). The PDS measures the degree of "fibromyalgianess" (Wolfe et al., 2011). The instrument consists of a symptom severity score and a widespread pain score that are added together from the PDS, a quantitative scale of fibromyalgia disease severity (Wolfe et al., 2011). PDS scores have been found to correlate with increased levels of pain, lower function, and a higher likelihood of depression and anxiety (Wolfe et al., 2015). The questionnaire may also be used for the diagnosis of fibromyalgia in epidemiological studies (Wolfe et al., 2011). The FIQ is a fibromyalgia-specific multidimensional questionnaire that captures health status, function and disease severity (Burckhardt et al., 1991). A revised version including additional dimensions was developed in 2009 (Bennett et al., 2009).

The pathophysiology of fibromyalgia is not fully understood. The lack of detectable tissue abnormalities and presence of mechanical hyperalgesia to deep tissue palpation and allodynia to non-noxious stimulation has directed interest towards concepts such as central augmented pain and sensory processing (Sluka & Clauw, 2016) and central sensitization (Sarzi-Puttini et al., 2020; Woolf, 2011), as key mechanism in fibromyalgia pathogenesis (Sarzi-Puttini et al., 2020; Sluka & Clauw, 2016; Woolf, 2011).

Quantitative sensory testing (QST) measures the individuals' self-reported responses to a battery of calibrated somatosensory stimuli (Edwards et al., 2016; Rolke et al., 2006). Previous studies have found differences in QST components between persons with fibromyalgia and healthy controls (Desmeules et al., 2003; Goubert et al., 2017; Julien et al., 2005; Staud et al., 2001) and studies have also confirmed that QST can be used to differentiate patients with fibromyalgia from healthy controls (Bourke et al., 2021). Despite this, the association between QST components and patient-perceived fibromyalgia disease burden is poorly understood. The aim of this study was thus to examine the associations between sensitization measured by QST and self-reported disease burden among patients with fibromyalgia.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This is a cross-sectional observational sub-study where the study sample participated in a randomized controlled trial that assessed the efficacy of a community-based multicomponent rehabilitation programme in patients with fibromyalgia (Haugmark et al., 2018). In brief, persons aged ≥18 years with anticipated fibromyalgia were referred from the primary health care services to a rheumatology outpatient clinic for confirmation of the fibromyalgia diagnosis and possible inclusion in the study between January 2016 and September 2018. The diagnosis was verified according to the 2016 fibromyalgia diagnostic Criteria (Wolfe et al., 2016) in all participants by one of two rheumatologists (SAP or IJB) after a clinical examination. Participants with comorbidities that could impact their pain condition, including arthritis, connective tissue disease, or osteoarthritis were excluded from the main study. Eligible participants were then asked to participate in the current study. The weight and height of participants were measured in lightweight clothing and body mass index (BMI kg/m^2) was calculated. All data for the current sub-study was collected at baseline prior to randomization. The study was approved by the Regional Ethical Committee of South-Eastern Norway (2015/2447).

2.2 | Assessments of fibromyalgia disease burden

In this article, we have used the term fibromyalgia disease burden to capture the combined consequence of fibromyalgia manifestations such as poor sleep quality and generalized pain, and also the loss of function that may be a consequence of fibromyalgia.

2.2.1 | Polysymptomatic distress scale

The PDS questionnaire is composed of variables used in the 2010 American College of Rheumatology fibromyalgia

criteria which were later modified for use in clinical research and epidemiological surveys (Wolfe et al., 2010, 2011, 2015). The PDS is thus both a diagnostic aid and a measure of fibromyalgia severity. The PDS symptoms severity scale (SSS) is based on a self-evaluation of the degree of fatigue, cognitive symptoms, and waking up unrefreshed during the past week, with each item being scored on a 0–3 numeric rating scale (NRS). There are three additional questions covering absence/presence of headaches, pain in the lower abdomen and/or depression during the past 6 months which are scored as 0 or 1. This gives a maximum SSS of 12. The PDS widespread pain index (WPI) asks the patient to indicate where he/she has experienced pain during the past week in 19 locations, corresponding to a maximum pain score of 19. The PDS score is the sum of the SSS and the WPI (range: 0–31). The PDS has been translated and validated in Norwegian (Fors et al., 2020). SSS and WPI have been used independently as measures of fibromyalgia symptoms and pain, while the composite PDS may be used as a measure of fibromyalgia disease severity (Salaffi et al., 2024). A sum score of 0–3 indicates no fibromyalgia symptoms, 4–7 mild, 8–11 moderate, 12–19 severe, and 20–31 very severe fibromyalgia disease (Wolfe et al., 2015).

2.2.2 | The fibromyalgia impact questionnaire

The FIQ measures the impact of fibromyalgia on the individual (Burckhardt et al., 1991). The questionnaire consists of 10 questions that concern difficulties performing everyday tasks such as making food or driving, each scored on a 0–3 NRS, and six visual analogue scales (range 0–10) that ask the respondent to estimate the level of pain, fatigue, stiffness, morning tiredness, anxiety, and depression during the past week (Burckhardt et al., 1991). The total FIQ score has a range of 0–100. The FIQ items have been found to correlate well with other instruments measuring physical function, pain, anxiety and depression, and previous studies have reported change in individual items following intervention in patients with fibromyalgia (Rasmussen et al., 2012; Williams & Arnold, 2011). The FIQ has been translated into multiple languages including Norwegian and the Norwegian version, which is used in the current study, has been used in a previous study (Tangen et al., 2020).

The revised FIQ (Bennett et al., 2009) has not yet been translated into Norwegian.

2.3 | Quantitative sensory testing (QST)

Participants included in this sub-study underwent QST. The senior author (SAP) was trained in the protocol prior to the start of the study and examined all participants according to a predefined protocol that was adapted from other studies performed in our department (Steen Pettersen et al., 2019). The examinations took place in one dedicated office between morning and noon. The examiner did not have knowledge of the patient's self-reported disease burden at the time of examination.

Pressure pain threshold (PPT) was tested at five predefined sites: A non-painful distal interphalangeal joint on the left hand, the left dorsal radio-ulnar joint (DRUJ), the lateral epicondyle of the left elbow, the middle surface of the left trapezius muscle and the left tibialis anterior muscle. A hand-held algometer (FPIX 25, 1.25 cm^2 flat rubber probe Wagner instrument) applied perpendicular pressure to each anatomic site, with pressure gradually increasing at 0.5 kg/s. A metronome was used in the initial stages to secure the correct escalation of pressure. The participants were instructed to report at what point they first experienced slight pain, and this pressure value was written down by the examiner. The procedure was performed three times at each site with ~1-min intervals and the mean PPT for each site was calculated. An overall mean PPT was calculated as the mean PPT of all five sites. Low PPTs indicate a higher degree of sensitization.

Mechanical temporal summation (TS) was estimated using punctate probes with increasing weight (8, 16, 32, 64, 126, 256, and 512 mN) (Rolke et al., 2006; Steen Pettersen et al., 2019). The participants were asked to close their eyes and enumerate the pain felt on an NRS of 0–10 as each probe was applied with a single touch in order of increasing weight on the left DRUJ. The probe that resulted in pain of NRS ≥4 was used for further testing of TS (or the highest weighted probe if none of them elicited NRS ≥4). TS was then assessed by touching the left DRUJ with the weighted probe 10 times with 1 s interval. Pain on the NRS was recorded for the 1st, 5th, and 10th tap (Graven-Nielsen & Arendt-Nielsen, 2010; Steen Pettersen et al., 2019). The maximum difference between the first, second, and third pain measurements was calculated. TS was analysed as a continuous variable and an increase in pain during repeated stimuli indicates TS.

Conditioned pain modulation (CPM) was evaluated using the forearm ischemia method as the conditioning stimulus, which involves the use of a blood pressure cuff to limit blood flow to the forearm contralateral to the site of the PPT assessment, as the conditioning stimulus. Specifically, the PPT was first assessed at the DRUJ. Then the blood pressure cuff on the contralateral arm was inflated to 20 mmHg above the systolic blood pressure (alternatively 200 mmHg). The participants then performed 10 hand grip exercises (in the hand with the cuff inflated)

and rated the pain in this forearm on a 0–10 NRS. The exercises continued according to a fixed protocol until the pain level was ≥4. The PPT at the original DRUJ was then repeated and the post-stimulus PPT was calculated as the average of three post-stimulus measurements. The CPM ratio was calculated at post-stimulus PPT/pre-stimulus PPT. A CPM ratio ≤1 suggests impaired CPM.

2.4 | Statistical methods

To examine the associations between pain sensitization and fibromyalgia disease burden, we examined the relations of PPT, TS, and CPM to the outcomes of PDS and FIQ total scores and PDS and FIQ components using separate linear regression models. In separate models, PDS and FIQ components were entered as dependent variables and PPT, TS, and CPM were examined as independent variables. Each model was adjusted for age, sex, and BMI. The distribution of all variables were visually inspected for normality prior to analyses and the distribution of residuals of each regression model were visually examined to ensure the validity of the models (Curtis & Drennan, 2013). The strength of associations/amount of variance of the dependent variable explained were classified as weak ($r<0.4$), moderate (r 0.40–0.59) and strong ($r\geq0.6$) (Swinscow 1976). A p-value of <0.05 was considered statistically significant. Bonferroni corrections were performed for each model due to multiple testing. All analyses were performed using STATA 17. This is a sub-study of a randomized controlled trial (Haugmark et al., 2021), and separate power analyses were not performed.

TABLE 1 Demographics of baseline data.

Variables	*N* = 78
Age in years, mean (SD) (range 24–50)	40.9 (7.3)
Female gender, *n* (%)	70 (89.7)
Symptom duration, median (IQR) years	6 (4–11)
BMI kg/m^2, mean (SD)	27.5 (4.7)
Currently working, *n* (%)[a]	55 (71)
Polysymptomatic distress scale mean (SD) (range 0–31)	19.9 (5.2)
Symptom severity score	8.2 (2.0)
Widespread pain index	11.7 (4.2)
FIQ sum score mean (SD) (range 0–100)	58.0 (19.0)
Pain VAS (0–10)[b]	6.8 (2.1)
Fatigue VAS (0–10)[b]	8.1 (1.7)
Anxiety VAS (0–10)[b]	5.4 (2.9)
Depression VAS (0–10)[b]	4.2 (3.1)
FIQ functional status only (0–10)	4.6 (2.6)
PPT median (IQR)	4.0 (2.7, 5.1)
PPT distal interphalangeal joint	5.7 (4.0, 7.8)
PPT radio-ulnar joint	3.6 (2.4, 5.0)
PPT elbow	2.7 (1.9, 3.8)
PPT trapezius	2.5 (1.9, 4.0)
PPT tibialis anterior	4.2 (3.0, 5.6)

Abbreviations: BMI, body mass index; FIQ, Fibromyalgia Impact Questionnaire; IQR, inter-quartile range; ns, non-significant of PPT for the comparison of temporal summation and conditioned pain modulation across categories of symptom duration; PPT, pain pressure threshold; SD, standard deviation; VAS, Visual Analogue Scale.

[a]Are you currently in paid employment.

[b]Questions in the Fibromyalgia Impact Questionnaire.

3 | RESULTS

A total of 78 participants (90% women, mean age 40.9 years (**SD** 7.3)) were recruited. Table 1 presents baseline demographics.

The median (IQR) PPT values varied across test sites with the lowest PPT at the trapezius muscle 2.5 (1.9–4.0) and the highest at the distal phalangeal joint 5.7 (4.0–7.8). The mean (SD) change in NRS pain during testing of TS was 2.0 (1.8), while the mean (SD) CPM ratio was 1.1 (0.3). The correlations between PPT at individual sites were strong. The weakest correlation was found between PPT at the trapezius and PPT at a distal interphalangeal joint ($r=0.60$), while the strongest correlation was found between the tibialis anterior muscle and the radio-ulnar joint ($r=0.83$).

The overall mean PPT was associated with the FIQ total score ($\beta-2.1$, 95% CI −4.3 to −0.0) and function ($\beta-0.4$, 95% CI-0.7 to −0.0), but the associations were not significant after Bonferroni adjustments for multiple comparisons and the strength of association was weak with R^2 adjusted <0.1 for all models (Table 2). There were no associations between any QST measures with PDS total score or PDS components. Neither TS nor CPM ratio were associated with self-reported fibromyalgia burden, except for a weak association between TS and depression scores (Table 2).

In the linear regression models examining the association between PPT at specific sites, the PPTs at the distal interphalangeal joint and the tibialis anterior muscle were associated with FIQ total scores and the fatigue component (Table 3). In addition, there were associations between PPT at the distal interphalangeal joint and the FIQ stiffness component, PPT at the tibialis anterior muscle and the FIQ component of depression and function and the PPT at the trapezius muscle and the FIQ component of function. None of the associations were statistically significant after Bonferroni corrections and the strength of all associations were again weak with R^2 adjusted <0.1 for all models (Table 3).

TABLE 2 Linear regression models associations between quantitative sensory tests and measures of fibromyalgia disease burden and symptoms.

	PPT (β (95% CI))	TS (β (95% CI))	CPM (β (95% CI))
Dependent variables			
Polysymptomatic Distress scale			
PDS	−0.4 (−1.1, 0.3)	0.1 (−0.6, 0.8)	3.5 (−1.1, 8.0)
SSS	−0.2 (−0.5, 0.1)	0.2 (−0.0, 0.5)	−0.1 (−1.9, 1.6)
WSP	−0.2 (−0.8, 0.3)	−0.1 (−0.7, 0.4)	3.6 (−0.0, 7.2)
Fibromyalgia Impact Questionnaire			
FIQ total	−2.1 (−4.3, −0.0)*	1.5 (−0.6, 3.7)	0.7 (−14.3, 15.6)
Pain	−0.2 (−0.5, 0.1)	0.1 (−0.2, 0.4)	1.2 (−0.6, 3.1)
Fatigue	−0.2 (−0.5, 0.0)	0.0 (−0.2, 0.3)	−0.2 (−1.7, 1.3)
Stiffness	−0.2 (−0.5, 0.2)	0.1 (−0.2, 0.4)	0.8 (−1.2, 2.9)
Anxiety	−0.3 (−0.7, 0.1)	0.3 (−0.1, 0.7)	0.8 (−1.8, 3.4)
Depression	−0.4 (−0.8, 0.0)	0.5 (0.1, 0.9)*	0.1 (−2.8, 3.1)
Function	−0.4 (−0.7, −0.0)*	0.1 (−0.3, 0.4)	1.5 (−0.9, 3.8)

Note: Linear regression models adjusted for age, gender and body mass index. R^2 adjusted <0.1 is not coloured. R^2 adjusted >=0.1 and <0.2. R^2 adjusted >=0.2 and <0.3.

Abbreviations: DIP, distal interphalangeal joint; DRUJ, dorsal radio-ulnar joint; PDS, polysymptomatic distress scale; PPT, Pressure pain threshold (lower values reflect greater pain sensitization); SSS, symptom severity score; tib ant, tibialis anterior muscle; WSP, widespread pain. All were statistically insignificant after corrections.

*$p < 0.05$ prior to Bonferroni corrections for multiple comparisons.

4 | DISCUSSION

In this cohort of individuals with clinically verified fibromyalgia, we found that higher PPT values, that is, less sensitization, were not significantly associated with scores of fibromyalgia disease burden measured by FIQ at alpha ≤0.05. The strengths of associations were negligible to weak in the entire cohort.

4.1 | Relationship between QST and composite measures in fibromyalgia

PDS and FIQ are both multidimensional composite instruments that purport to capture the burden of fibromyalgia, the former was developed as a measure of symptom burden and pain distribution, whereas the latter gives equal emphasis to function and symptom (Burckhardt et al., 1991; Wolfe et al., 2011). Indeed, whereas 61% of the total PDS score is derived from the widespread pain index, a maximum 10% of the FIQ score is derived from self-reported pain.

We found a weak association between PPT and the total FIQ and between PPT and the physical functioning component of the FIQ. PPT at the DIP joint and at the tibialis anterior muscle were also weakly associated with the FIQ total score. Our results are similar to the weak cross-sectional correlation found between PPT and FIQ in a study of 87 patients with fibromyalgia (Rehm et al., 2021).

Surprisingly, to the best of our knowledge, the associations between measures of QST and PDS has not been explored in homogenous populations of patients who fulfill the fibromyalgia diagnostic criteria, although some have been reported weak-to-moderate associations in populations of patients with rheumatoid arthritis and comorbid fibromyalgia. Joharatnam et al. reported a moderate and negative association between the PDS and PPT at three different sites (Joharatnam et al., 2015) and Moore et al. reported a weak inverse correlation between PDS and levels of PPT at multiple sites and TS at the wrist in 285 patients with RA (Moore et al., 2022).

4.2 | Association between QST and pain in fibromyalgia

In the current study, PPT, TS, and CPM scores were not associated with neither self-reported widespread pain nor the pain item of the FIQ, in patients with fibromyalgia. Again, we found few studies including patients with fibromyalgia specifically. Petzke et al. examined a mixed cohort of 47 women (65% healthy, 13% unspecified pain, 27% generalized pain) and reported significant but weak-moderate associations between self-reported pain according to the McGill questionnaire and PPT (r^2 0.13–0.25) performed at several sites, in adjusted analyses (Georgopoulos et al., 2019; Petzke et al., 2003; Rehm et al., 2021).

TABLE 3 Linear regression analyses: The association between PPT at individual sites and measures of fibromyalgia disease burden and symptoms.

	PPT trapezius (β (95% CI))	PPT elbow (β (95% CI))	PPT DRUJ (β (95% CI))	PPT DIP (β (95% CI))	PPT tib ant (β (95% CI))
Dependent variables					
Polysymptomatic Distress Scale					
PDS	−0.5 (−1.2, 0.2)	−0.1 (−0.8, 0.6)	−0.4 (−1.0, 0.2)	−0.4 (−0.9, 0.1)	−0.4 (−0.9, 0.2)
SSS	−0.2 (−0.5, 0.1)	−0.1 (−0.4, 0.1)	−0.1 (−0.4, 0.1)	−0.2 (−0.3, 0.0)	−0.2 (−0.4, 0.0)
WSP	−0.3 (−0.8, 0.3)	−0.0 (−0.6, 0.6)	−0.3 (−0.8, 0.2)	−0.2 (−0.6, 0.2)	−0.2 (−0.6, 0.2)
Fibromyalgia Impact Questionnaire					
FIQ total	−1.8 (−4.0, 0.4)	−1.1 (−3.4, 1.2)	−1.7 (−3.5, 0.2)	−1.9 (−3.4, −0.4)*	−2.0 (−3.6, −0.4)*
Pain	−0.1 (−0.4, 0.2)	−0.0 (−0.3, 0.3)	−0.2 (−0.4, 0.1)	−0.2 (0.4, 0.0)	−0.1 (−0.4, 0.1)
Fatigue	−0.2 (−0.4, 0.1)	−0.2 (−0.4, 0.0)	−0.2 (−0.4, 0.0)	−0.2 (−0.3, −0.0)*	−0.2 (−0.4, −0.0)*
Stiffness	−0.2 (−0.5, 0.1)	−0.1 (−0.4, 0.2)	−0.1 (−0.4, 0.1)	−0.2 (−0.4, −0.0)*	−0.1 (−0.3, 0.2)
Anxiety	−0.3 (−0.7, 0.1)	−0.2 (−0.6, 0.2)	−0.3 (−0.6, 0.1)	−0.2 (−0.4, 0.1)	−0.2 (−0.5, 0.1)
Depression	−0.3 (−0.7, 0.2)	−0.3 (−0.7, 0.1)	−0.3 (−0.6, 0.1)	−0.2 (−0.5, 0.1)	−0.4 (−0.7, −0.0)*
Function	−0.4 (−0.8, −0.1)*	−0.2 (−0.6, 0.1)	−0.3 (−0.6 0.0)	−0.2 (0.4, 0.1)	−0.3 (−0.6, −0.1)*

Note: Linear regression models adjusted for age, gender, and body mass index. All were statistically insignificant after corrections. R^2 adjusted >=0.1 and <0.2. R^2 adjusted >=0.2 and <0.3.

Abbreviations: DIP, distal interphalangeal joint; DRUJ, dorsal radio-ulnar joint; PDS, polysymptomatic distress scale; PT, Pressure pain threshold (lower values reflect greater pain sensitization); SSS, symptom severity score; tib ant, tibialis anterior muscle; WSP, widespread pain.

*$p < 0.05$ prior to Bonferroni corrections for multiple comparisons.

TS has been found to be associated with greater pain severity in RA and osteoarthritis (Heisler et al., 2020; Neogi et al., 2015; Steen Pettersen et al., 2019), but was not associated with self-reported pain in a small study of patients with fibromyalgia (Staud et al., 2007).

CPM was not related to pain severity in patients with RA (Heisler et al., 2020).

4.3 | Association between QST and anxiety and depression in fibromyalgia

We found no consistent association between measures of QST and the FIQ components of anxiety and depression although TS was associated with depression. Petzke et al. found a significant but weak association between distress and PPT in univariable models, but not in multivariable models that also included pain as a covariate (Petzke et al., 2003). The associations between pain sensitization and psychological symptoms such as depression and anxiety were explored in the systematic review performed by de la Coba et al. who identified 34 studies using QST in patients with fibromyalgia. The authors conclude that depression, anxiety, and pain catastrophizing have an important influence on the pain experiences that should be acknowledged in the interpretation of pain responses (de la Coba et al., 2022). Another review included 37 studies exploring QST in any musculoskeletal condition including injury and post-operative pain and found that QST may predict outcomes such as depression in patients with musculoskeletal pain (Georgopoulos et al., 2019).

Among the strengths of this study is that the fibromyalgia diagnosis in all participants was made after a clinical examination by one of two specialist rheumatologists (SAP, IJB) and that a comprehensive data collection was performed. For the QST, a clear strength is that all examinations were performed by one examiner (SAP) who was blinded to the results of the PDS and FIQ. There are however several weaknesses to report. Mean PPT calculated as the average measure of PPT across 18 tender-points sites has previously been used as a measure of central sensitization in patients with fibromyalgia (Petzke et al., 2003). In our study, PPT was measured at 5 sites in a protocol adapted from another study (Steen Pettersen et al., 2019). However, Petzke et al. have reported a very strong correlation between PPT at individual sites and the total average across all sites (18 tender-points and two control sites) in both females with fibromyalgia and female healthy controls (Petzke et al., 2001), and in our study, there were strong correlations between PPT measured at different sites.

Other weaknesses are the small study sample limiting the statistical power, the lack of healthy controls, and cross-sectional data collection, preventing inferences regarding causation. We also did not have a sufficient number of males in our study to perform sex-stratified analyses. Finally, we were not able to repeat the examinations and have thus not performed reliability testing.

In this cohort of patients with clinically verified fibromyalgia, self-reported disease burden was not significantly associated with pain sensitization. Our results point to the multifactorial nature of fibromyalgia and may also indicate that pain sensitization is not the sole driver of pain and disease burden in fibromyalgia. Our results should be confirmed in a larger study population where phenotypes of different pain mechanisms may be explored.

AUTHOR CONTRIBUTIONS

The study was conceptualized by P.S.P., H.A.Z., H.B.H., I.J.B., I.K.H., and S.A.P. The methodology was planned and the first draft prepared by P.S.P., I.K.H., T.N., and S.A.P. The following performed data curation and project administration H.A.Z., T.H., I.J.B., and S.A.P. P.S.P. and S.A.P. performed the statistical analysis. Funding was acquired by H.A.Z. All authors commented on the draft versions, participated in the editing process, and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

STATEMENT OF USE OF ARTIFICIAL INTELLIGENCE

AI has not been used during the preparation of this manuscript.

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