Sex moderates the association between quantitative sensory testing and acute and chronic pain after total knee/hip arthroplasty

Paredes, Ana C; Arendt-Nielsen, Lars; Almeida, Armando; Pinto, Patrícia R

Published in:
Scandinavian Journal of Pain

DOI (link to publication from Publisher):
10.1515/sjpain-2024-0004

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

Clinical Pain Research

Ana C. Paredes, Lars Arendt-Nielsen*, Armando Almeida, Patrícia R. Pinto

Sex moderates the association between quantitative sensory testing and acute and chronic pain after total knee/hip arthroplasty

https://doi.org/10.1515/sjpain-2024-0004
received January 12, 2024; accepted April 05, 2024

Abstract

Objectives – Acute postsurgical pain (APSP) may persist over time and become chronic. Research on predictors for APSP and chronic postsurgical pain (CPSP) has produced inconsistent results. This observational study aimed to analyze psychological and psychophysical variables associated with APSP and CPSP after total knee or hip arthroplasty, and to explore the role of sex.

Methods – Assessments were conducted before surgery, 48 h, and 3 months postsurgery, including questionnaires (sociodemographic, pain related, and psychological) and quantitative sensory testing (QST). Hierarchical linear regression models analyzed potential predictors of APSP and CPSP, and moderation analyses evaluated the role of sex.

Results – The study included 63 participants undergoing total knee (34, 54%) or hip (29, 46%) arthroplasty. Thirty-one (49.2%) were female and 32 (50.8%) were male. APSP (48 h) was associated with impaired conditioned pain modulation (CPM) (β = 0.301, p = 0.019). CPSP (3 months) was associated with being female (β = 0.282, p = 0.029), longer presurgical pain duration (β = 0.353, p = 0.006), knee arthroplasty (β = −0.312, p = 0.015), higher APSP intensity (β = 373, p = 0.004), and impaired CPM (β = 0.126, p = 0.004). In multivariate analysis, these clinical variables were significant predictors of CPSP, unlike sex, and CPM (adj. R^2 = 0.349). Moderation analyses showed that wind-up ratio (WUR) was a significant predictor of APSP in men (WUR × sex: b = −1.373, p = 0.046) and CPM was a significant predictor of CPSP in women (CPM × sex: b = 1.625, p = 0.016).

Conclusions – Specific QST parameters could identify patients at risk for high-intensity APSP and CPSP, with sex as a moderator. This has important clinical implications for patient care, paving the way for developing tailored preventive pain management strategies.

Keywords: acute pain, chronic pain, postsurgical pain, sex, quantitative sensory testing

1 Introduction

Acute pain is an expected and adaptive event after surgery, which normally resolves during recovery [1]. However, postsurgical pain may persist over time and become chronic. Arthroplasty surgeries are consistently identified as procedures with a high prevalence of chronic postsurgical pain (CPSP) [2,3]. Given the relevant public health burden of CPSP, it is important to identify risk factors for its development. Several predictors (e.g., sociodemographic, clinical, pain mechanisms, psychological, pain sensitization) have been described, but a clear understanding of pain chronification mechanisms is still lacking [4]. Acute pain after surgery is recognized as one important predictor of CPSP, and thus, an important target for possibly preventing pain chronification [1]. In fact, prevention and treatment approaches can be improved by focusing on possible modifiable factors [4].

* **Corresponding author: Lars Arendt-Nielsen**, Department of Health Science and Technology, Faculty of Medicine, Center for Neuroplasticity and Pain (CNAP), SMI, Aalborg University, Selma Lagerløfs Vej 249, Gistrup 9260, Denmark, e-mail: lan@hst.aau.dk
Ana C. Paredes: Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; ICVS/3B's – PT Government Associate Laboratory, Braga, Guimarães, Portugal; 2CA-Braga, Clinical Academic Center, Hospital de Braga, Braga, Portugal, e-mail: anacristinamparedes@gmail.com
Armando Almeida: Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; ICVS/3B's – PT Government Associate Laboratory, Braga, Guimarães, Portugal; 2CA-Braga, Clinical Academic Center, Hospital de Braga, Braga, Portugal, e-mail: aalmeida@med.uminho.pt
Patrícia R. Pinto: Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; ICVS/3B's – PT Government Associate Laboratory, Braga, Guimarães, Portugal; 2CA-Braga, Clinical Academic Center, Hospital de Braga, Braga, Portugal, e-mail: patipinto@med.uminho.pt

Psychological variables can help outline patient profiles more prone to develop chronic pain [4,5]. Psychological variables, such as anxiety, depression, and pain catastrophizing, are generally associated with worst postsurgical pain and pain chronification [3,4,6–8]. Inversely, positive affect (pleasant moods and emotions) seems to be protective [9].

Along with psychological characteristics, research has been focusing on identifying quantitative sensory testing (QST) profiles that may be associated with postsurgical pain. Different QST modalities (e.g., mechanical, thermal, or dynamic tests) have been associated with acute [10] and chronic [11,12] pain after total joint arthroplasty but systematic reviews continue to point to inconsistent associations [13,14]. There is a promising role of QST, particularly temporal summation and conditioning pain modulation (CPM), to predict pain outcomes after surgery, but the current state-of-the-art is not yet sufficiently robust for high-level prediction [14].

Among sociodemographic predictors, being female is frequently associated with worse acute and chronic pain after surgery [3,7,8], though contrary findings have also been reported [6,15,16]. Women tend to demonstrate higher distress [17], but the positive association between distress and pain seems to be stronger for men [18–20]. Therefore, there is an apparent moderator role of sex in this relationship that warrants further investigation [18]. Results concerning sensitivity profiles also point towards increased sensitivity and endogenous pain facilitation in women [21,22]. Some studies control for the effect of sex on the statistical analyses [10–12], but it is striking that only a few investigate *how* sex influences the association between QST and postsurgical pain. For example, Bossmann et al. [23] hinted at an association between defective endogenous pain inhibition (assessed through CPM) and higher postsurgical pain in women, but not in men.

Sex differences in arthritis-related complaints are numerous and multifactorial, underlining the need to understand the association between presurgical sex disparities and surgical outcomes [24]. In fact, the relevance of sex and/or gender-based analyses has been strongly emphasized, with specific recommendations guiding the research community towards more equitable research and systematic account of this matter.

The aims of this study were: (1) to analyze psychological and psychophysical (QST) variables associated with acute and chronic pain after total knee or hip arthroplasty and (2) to explore if these associations are moderated by patients' sex.

2 Methods

2.1 Participants and procedure

Recruitment took place at the Orthopedics Unit of Hospital of Braga (Portugal), from June 2021 to December 2022. Inclusion criteria were as follows: (a) age >50; (b) unilateral total joint arthroplasty due to knee/hip osteoarthritis; and (c) ability to understand written information and give informed consent. Exclusion criteria were as follows: (a) revision surgery; (b) severe or disabling diseases; and (c) contralateral knee/hip arthroplasty in the previous 6 months. In case of acceptance, the participants signed the informed consent, followed by the baseline assessment. The study was approved by the Ethics Committee from the Hospital of Braga (Ref. 03_2021) and by the Ethics Committee for Research in Life and Health Sciences from the University of Minho (CEICVS 093/2020).

Patients were assessed before surgery, 48 h, and 3 months postsurgery. Presurgical (baseline) assessment focused on sociodemographic, clinical, pain-related, psychological, and QST assessment. The 48 h assessment took place during hospital stay and covered pain frequency, pain intensity, and anxiety. At 3 months, the evaluation focused on pain frequency, intensity, and interference.

This study includes 63 participants with complete baseline data. Assessments at 48 h and 3 months were completed in 62 and 60 participants, respectively. At 3 months, 2 participants were excluded due to revision surgery and 1 due to manipulation under general anesthesia.

2.2 Surgical and anesthetic procedures

Most total knee arthroplasties (TKA) were performed through the medial parapatellar approach (27, 79.4%) and most total hip arthroplasties (THA) were performed via the posterior approach (22, 75.9%).

Anesthetic and analgesic procedures were determined individually by the anesthesiologist in charge. Anesthesia was either locoregional only (subarachnoid block [58, 92.1%] or epidural block [1, 1.6%]), or locoregional plus general anesthesia (4, 6.3%). Spinal anesthesia (locoregional) was achieved with a combination of bupivacaine (0.5%/10 ml) or hyperbaric bupivacaine (20 mg/4 ml) and sufentanil (0.005 mg/ml). Peripheral nerve block was achieved using perineural ropivacaine (7.5 mg/ml) or lidocaine (10 mg/ml).

Postsurgical analgesia was administered by epidural or intravenous routes. Coadjuvant medication (detailed below) was delivered via oral or intravenous route, with indication to administer rescue analgesia if pain intensity was 3 or higher on a 0–10 numerical rating scale (NRS). Epidural analgesia was administered by continuous disposable infusion balloon (DIB [19, 30.2%]) or by patient-controlled epidural analgesia (11, 17.4%) with background infusion. These protocols included a combination of ropivacaine (0.15%) and fentanyl (1.5 µg/ml) and other analgesics such as paracetamol (1 g, 6/6 h) and non-steroidal anti-inflammatory drugs (NSAIDs: ketorolac 30 mg, parecoxib 40 mg, or diclofenac 50 mg, 12/12 h). Rescue analgesia was prescribed individually and administered as needed (ropivacaine 40 mg/20 ml, tramadol 100 mg, methimazole 2 g, pethidine 25 mg). Intravenous analgesia (26, 41.3%) consisted of different combinations of paracetamol (1 g, 6/6 h), ketorolac (30 mg, 12/12 h), and tramadol (100 mg, 8/8 h), and additional medication (pethidine, methamizol) delivered in case of uncontrolled pain (NRS >3). Some patients had an intravenous DIB protocol (7, 11.1%), with a 5 ml/hour drip of tramadol (400 mg) and droperidol (5 mg), along with coadjuvant medication (paracetamol and NSAIDs) and rescue analgesia (pethidine, 20 mg).

Antiemetic treatment (metoclopramide or ondansetron) was used as needed and all patients underwent infection prophylaxis with antibiotics (cefazolin) and thromboembolism prophylaxis with LMWH (low molecular weight heparin – enoxaparin).

2.3 Measures

2.3.1 Questionnaires

- S*ociodemographic and clinical questionnaire*: developed by the research team to collect sociodemographic and clinical information (Supplementary File 1).
- *Brief Pain Inventory* (BPI) [25]: evaluated pain intensity and interference, according to a 0–10 NRS (0 = no pain/does not interfere; 10 = worst pain imaginable/completely interferes). The "pain at its worst" item was used as a measure of pain intensity. A mean score was computed for pain interference, to achieve a global value considering general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.
- *Coping Strategies Questionnaire-Revised* (CSQ-R) subscale [26]: used to assess pain catastrophizing. Possible scores range from 1 to 5, with higher values indicating greater pain catastrophizing.
- *Hospital Anxiety and Depression Scale* (HADS) [27]: evaluated anxiety and depression, with subscale scores ranging from 0 to 21. Higher values translate higher symptomatology.
- *Life Orientation Test-Revised* (LOT-R) [28]: derived an optimism score ranging from 0 to 24 with higher values translating to more optimistic expectations.

2.3.2 QST

Sensory sensitivity was evaluated according to recommendations [29,30]. Measures were performed on a distal control site (dominant hand, for evaluating generalized pain hypersensitivity) and on the affected joint (joint that was being replaced, for evaluating localized pain hypersensitivity). Specifically, the assessment site of the knee was 5 cm medial to the center of patella and the assessment site of the hip was 5 cm medial to the greater trochanter.

- *Mechanical detection threshold* (MDT): measured with a standardized set of modified von Frey filaments (Optihair2, Marstock Nervtest, Germany), with exerted forces varying between 0.25 and 512 mN. The stimuli were delivered in a series of ascending and descending intensities and the participants indicated if they could perceive them. Five supra- and sub-threshold determinations were made and the final MDT is the average of all values [29].
- *Wind-up ratio* (WUR): evaluated the temporal summation of pain. WUR was tested using a 512 mN modified von Frey filament (Optihair2, Marstock Nervtest, Germany). A single application of the stimulus was followed by a set of 10 repetitive applications of the same stimulus. Participants rated the intensity of the single stimulus and of the 10-stimuli series, according to a 0–100 NRS (0 = no pain, 100 = most intense pain imaginable). This procedure was repeated 5 times and a ratio was calculated by dividing each pain rating of the series by the rating of the single stimulus. The final score is the average of these 5 ratios [29].
- *Pressure pain threshold* (PPT): assessed using a digital pressure algometer (FPN 100, Wagner Instruments, USA), exerting a constant ascending pressure of 50 kPa/s (≈0.5 kg/cm^2 s) [29]. Participants indicated the point at which the pressure became painful. The final score is the average of 3 measurements.
- CPM: assessed by first administering a painful stimulus (test stimulus – PPT) by itself and then administering it again after a different painful condition

(conditioning stimulus – cold water bath) had been administered on a different body site. After PPT, the participants immersed their hand in cold water (10–12°C) for 1 min. CPM score was calculated by subtracting the mean score of the 3 post-conditioning PPT (after water immersion) from the mean score of the 3 pre-conditioning PPT ("first-minus-last" calculation). Therefore, negative values (increase in PPT) indicate pain inhibition and positive values (decrease in PPT) denote pain facilitation [30]. Participants with negative (<0) CPM values were classified as "CPM responders" (anti-nociception) and participants with positive (≥0) CPM values as "CPM non-responders" (pro-nociception).

2.4 Statistical analyses

All analyses were conducted in IBM SPSS Statistics v.29, with statistical significance set at $p < 0.05$. Data are reported as absolute and relative frequencies (n, %), or mean and standard deviation (mean ± SD). A logarithmic transformation (base 10) was performed to MDT, WUR, and PPT tests to achieve a secondary normal distribution [29]. Data distribution was analyzed through skewness (Sk ± 2) and kurtosis (Ku ± 7), with no substantial differences from a normal distribution [31].

Between-sex differences were explored through independent samples' t-tests or chi-square (χ^2) tests. Cohen's d and Phy (ϕ) coefficient were computed as measures of effect size. Pearson correlation or point-biserial testes analyzed the association of study variables with two outcomes: acute and chronic pain (worst pain intensity at 48 h and 3 months). For acute pain, no further analyses were performed because there was only one variable significantly associated with it. The variables significantly associated with chronic pain entered a hierarchical linear regression model, wherein a minimum of 10 events per variable was considered for predictor selection [32]. Multicollinearity was analyzed through the tolerance coefficient (>0.4) and the independence of errors through Durbin–Watson value (2 ± 0.2) [33]. There were no violations of these assumptions.

Moderation models analyzed if sex (moderator, W) interacted with psychological/psychophysical characteristics (independent variables, X) in their influence on postsurgical pain (dependent variables, Y) [34]. The independent variables were psychological and psychophysical characteristics that differed between men and women. Worst pain intensity (48 h and 3 months) was set as dependent variable. Type of arthroplasty was included as a covariate in all models given its relevance for the acute and chronic pain experience after total joint replacement. Additionally, presurgical pain duration and acute postsurgical pain (APSP) were included as covariates in the moderation models with pain at 3 months, given their strong association with that outcome. The continuous predictors were z-transformed. Moderation analyses were performed using PROCESS macro for SPSS [34] (model 1) with 95% bias-corrected confidence intervals and 5,000 bootstrap samples.

The present work is part of a larger study focusing on predictors of pain chronification, and thus, there were no specific power calculations for the analyses. From the larger sample, only a subset of patients completed the QST assessment. Thus, only those with QST at baseline were selected for the present analyses.

3 Results

3.1 Sample characterization and between-sex differences

This study included 63 participants undergoing TKA (34, 54%) or THA (29, 46%), with a mean age of 64.5 years (SD = 7.43). Thirty-one (49.2%) were female and 32 (50.8%) were male. Baseline sample information and between-sex differences are detailed in Table 1. There were statistically significant differences in body mass index (BMI, $t = -2.726$, $p = 0.008$), type of arthroplasty ($\chi^2 = 21.967$, $p < 0.001$), pain duration ($t = -2.59$, $p = 0.013$), presurgical pain intensity ($t = -2.181$, $p = 0.033$), and interference ($t = -2.88$, $p = 0.006$). Most women had TKA, while most men had THA. BMI was higher among women, who also had longer pain duration, more intense pain, and higher pain interference before surgery. ASA score (American Society of Anesthesiologists physical status classification) was retrieved from the clinical record and included 1 (1.6%) case of ASA I, 48 (76.2%) ASA II, and 14 (22.2%) ASA III.

Concerning psychological variables, there were significant differences in anxiety ($t = -2.261$, $p = 0.027$) and optimism ($t = 3.199$, $p = 0.002$), with women showing more anxiety symptoms and less optimism than men. For QST, there were significant differences in hand MDT ($t = -2.667$, $p = 0.010$), WUR (hand: $t = -3.646$, $p = 0.001$; joint: $t = -2.208$, $p = 0.033$), and CPM at the affected joint ($t = -2.061$, $p = 0.044$). Women showed lower mechanical sensitivity (higher MDT) at the hand, higher pain facilitation (higher WUR) at the hand and at the affected joint, and lower pain inhibition (higher CPM) assessed at the affected joint. Individual analysis of the CPM effect revealed the proportion of participants with effective pain inhibition (CPM responders)

Table 1: Description of baseline patient characteristics and between-sex differences

Variable	Total sample (n = 63)	Male (n = 32)	Female (n = 31)	Test statistics		
				t/χ^2 (df)	p	d/ϕ [95% CI]
Sociodemographic						
Age	64.57 ± 7.43	63.53 ± 8.00	65.65 ± 6.75	−1.131 (61)	0.262	−0.29 [−0.78; 0.21]
Marital status (married)	50 (79.4%)	28 (87.5%)	22 (71.0%)	2.628 (1)	0.105	−0.20 [−0.46; 0.05]
Education (>4th grade)	30 (47.6%)	17 (53.1%)	16 (51.6%)	0.014 (1)	0.904	−0.02 [−0.26; 0.23]
Occupation (employed)	19 (30.2%)	11 (34.4%)	8 (25.8%)	0.549 (1)	0.459	−0.09 [−0.34; 0.15]
Clinical						
BMI (kg/m^2)	29.22 ± 4.48	27.78 ± 4.21	30.71 ± 4.32	−2.726 (61)	**0.008**	−0.69 [−1.19; −0.18]
Nr. comorbidities	2.51 ± 1.45	2.66 ± 1.52	2.35 ± 1.38	0.825 (61)	0.413	0.21 [−0.28; 0.70]
Type of arthroplasty (knee)	34 (54%)	8 (25%)	26 (83.9%)	21.967 (1)	<**0.001**	−0.59 [−0.66; −0.52]
Pain and function						
Pain duration (months)	85.51 ± 84.76	59.22 ± 45.98	112.65 ± 105.66	−2.588 (40.7)	**0.013**	−0.66 [−1.16; −0.15]
Presurgical pain intensity (worst pain, NRS)	8.35 ± 1.57	7.94 ± 1.70	8.77 ± 1.31	−2.181 (61)	**0.033**	−0.55 [−1.05; −0.044]
Pain interference (BPI)	5.20 ± 1.99	4.53 ± 2.10	5.89 ± 1.62	−2.877 (61)	**0.006**	−0.73 [−1.23; −0.21]
Psychological						
Pain catastrophizing (CSQ-R)	1.85 ± 0.90	1.77 ± 0.87	1.94 ± 0.932	−0.750 (61)	0.456	−0.19 [−0.68; 0.31]
Depression (HADS)	2.67 ± 2.16	2.22 ± 2.06	3.13 ± 2.20	−1.695 (61)	0.095	−0.43 [−0.93; 0.074]
Anxiety (HADS)	4.89 ± 3.73	3.88 ± 3.58	5.94 ± 3.65	−2.261 (61)	**0.027**	−0.57 [−1.07; −0,064]
Optimism (LOT-R)	17.25 ± 4.97	19.09 ± 4.12	15.35 ± 5.12	3.199 (61)	**0.002**	0.81 [0.29; 1.32]
Psychophysical (QST)						
MDT, mN (hand)	4.58 ± 5.97	3.39 ± 5.77	5.81 ± 6.00	−2.668 (61)	**0.010**	−0.67 [−1.18; −0.16]
MDT, mN (joint)	12.05 ± 19.92	9.48 ± 9.90	14.69 ± 26.54	−0.067 (61)	0.947	−0.02 [−0.51; 0.48]
WUR (hand)	3.78 ± 6.45	1.74 ± 0.58	5.88 ± 8.76	−3.646 (33.8)	**0.001**	−0.96 [−1.50; −0.42]
WUR (joint)	5.14 ± 9.00	2.80 ± 1.94	7.63 ± 12.4	−2.208 (41.4)	**0.033**	−0.58 [−1.10; −0.062]
PPT, kg (hand)	3.51 ± 1.05	3.60 ± 1.15	3.42 ± 0.95	0.466 (61)	0.643	0.12 [−0.38; 0.61]
PPT, kg (joint)	2.76 ± 1.19	3.01 ± 1.30	2.44 ± 1.00	1.938 (61)	0.057	0.49 [−0.02; 0.99]
CPM (hand)	−0.14 ± 0.57	−0.16 ± 0.60	−0.13 ± 0.56	−0.225 (59)	0.823	−0.06 [−0.56; 0.45]
CPM (joint)	−0.17 ± 0.52	−0.30 ± 0.52	−0.03 ± 0.49	−2.061 (58)	**0.044**	−0.53 [−1.05; −0.02]
CPM responder (hand)	33 (54.1%)	14 (46.7%)	19 (61.3%)	1.313 (1)	0.252	0.15 [−0.10; 0.40]
CPM responder (joint)	41 (68.3%)	23 (76.7%)	18 (60%)	1.926 (1)	0.165	−0.18 [−0.43; 0.07]

Categorical variables are presented as n (%) and continuous variables are presented as mean ± SD.

Note: Bold values are statistically significant at $p < 0.05$.

Abbreviations: CI, confidence interval; BMI, body mass index; NRS, numerical rating scale; BPI, brief pain inventory; CSQ-R, coping strategies questionnaire-revised; HADS, hospital anxiety and depression scale; LOT-R, life orientation test-revised; QST, quantitative sensory testing; MDT, mechanical detection threshold; WUR, wind-up ratio; PPT, pressure pain threshold; CPM, conditioned pain modulation.

(Figure 1). An anti-nociceptive effect was shown in 33 (54.1%) participants at the hand (14 [46.7%] males and 19 [61.3%] females), and in 41 (68.3%) participants at the affected joint (23 [76.7%] males and 18 [60%] females).

3.2 Surgical outcomes at 48 h and 3 months after total knee/hip arthroplasty

The mean length of hospital stay after surgery was 4.51 days (SD = 1.23), with women having significantly longer hospitalizations than men (t = −2.393, p = 0.02). At 48 h postsurgery, there were no significant between-sex differences in the analyzed variables. However, 3 months after surgery, there were statistically significant differences in pain intensity (t = 2.239. p = 0.029), with women reporting more intense pain than men (Table 2).

3.3 Variables associated with pain intensity at 48 h and 3 months after surgery

The correlation tests did not reveal demographic or clinical variables significantly associated with APSP (Table 3).

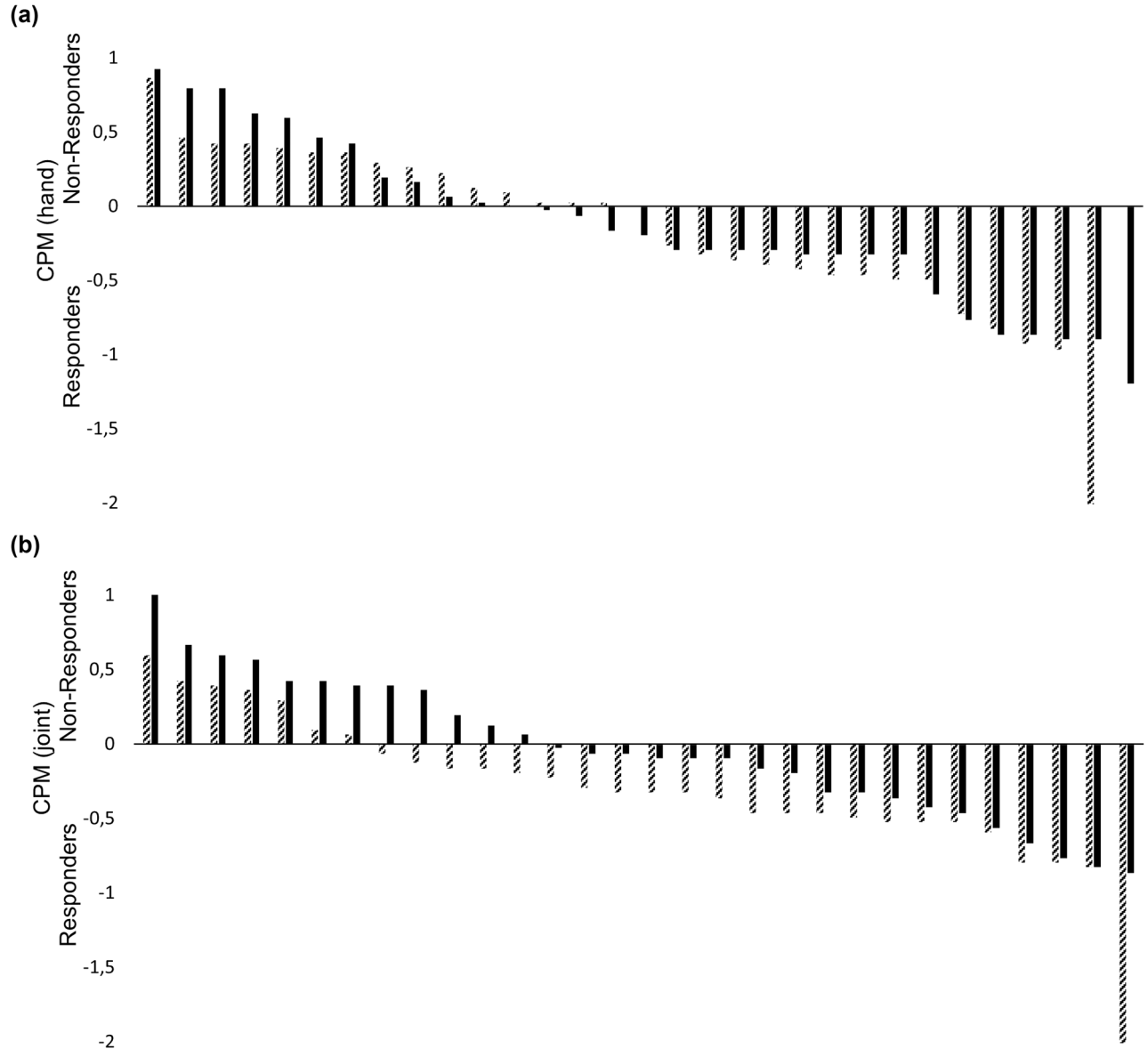

Figure 1: Individual CPM effect at the hand (a) and affected joint (b) (each bar represents a participant's score). Men are represented as dashed bars and women are represented as solid bars.

However, pain at 3 months was significantly associated with sex (r_{pb} = 0.282, p = 0.029), type of arthroplasty (r_{pb} = −0.312, p = 0.015), presurgical pain duration (r = 0.353, p = 0.006), and APSP intensity (r = 373, p = 0.004). More intense pain at 3 months was associated with being female, having longer presurgical pain duration, undergoing TKA, and experiencing higher pain at 48 h after surgery. CPM (at the affected joint) was the only QST measure with significant results for either time point, with CPM at the hand being associated with acute pain (r = 0.301, p = 0.019) and CPM at the joint being associated with chronic pain (r = 0.126, p = 0.004). At both moments, pain intensity was higher among patients with less effective pain inhibition (higher CPM score). The analysis of CPM responders *vs.* non-responders showed comparable results. Participants with effective CPM at the hand had less pain at 48 h (r_{pb} = −0.288, p = 0.026), and those with effective CPM at the joint had less pain at 3 months (r_{pb} = −0.353, p = 0.007). None of the psychological variables were associated with pain at 48 h or 3 months after surgery.

Table 4 shows the results of the hierarchical linear regression model combining the previously significant individual predictors of chronic pain. Sex and CPM cease to be significant predictors when the clinical variables are included in the model. Presurgical pain duration (β = 0.276, p = 0.023), type of arthroplasty (β = −0.300, p = 0.034), and APSP intensity

Table 2: Postsurgical outcomes and between-sex differences

Variable	Total sample	Male	Female	Test statistics		
				t/χ^2 (df)	p	d/ϕ [95% CI]
Length of stay (days)	4.51 ± 1.23	4.16 ± 0.92	4.87 ± 1.41	−2.393 (61)	**0.020**	−0.60 [−1.11; −0.10]
48 h postsurgery	n = 62	n = 31	n = 31			
Pain frequency (MPQ): continuous	19 (31.1%)	8 (25.8%)	11 (36.7%)	0.838 (1)	0.360	0.12 [−0.13; 0.37]
Postsurgical pain intensity (Worst pain, NRS)	7.63 ± 2.07	7.71 ± 1.90	7.55 ± 2.26	0.304 (60)	0.762	0.08 [−0.42; 0.58]
Anxiety (HADS)	1.97 ± 2.33	1.68 ± 1.94	2.26 ± 2.66	−0.983 (60)	0.330	−0.25 [−0.75; 0.25]
3 months postsurgery	n = 60	n = 30	n = 30			
Presence of pain: Yes	37 (61.7%)	15 (50%)	22 (73.3%)	3.455 (1)	0.063	0.24 [−0.01; 0.49]
Chronic pain intensity (Worst pain, NRS)	3.18 ± 3.04	2.33 ± 2.77	4.03 ± 3.10	−2.239 (58)	**0.029**	−0.58 [−1.09; −0.06]
Pain interference (BPI)[†]	2.13 ± 1.98	1.50 ± 1.84	2.54 ± 1.99	−1.612 (35)	0.116	−0.54 [−1.20; 0.13]

Categorical variables are presented as n (%) and continuous variables are presented as mean ± SD.

Note: Bold values are statistically significant at $p < 0.05$.

Abbreviations: CI, confidence interval; MPQ, McGill Pain Questionnaire; NRS, numerical rating scale; HADS, hospital anxiety and depression scale; BPI, brief pain inventory.

[†]n = 37 (patients with pain at 3 months).

(β = 0.370, p = 0.002) are significant predictors of pain at 3 months, with the final model explaining 35% of the variance in CPSP intensity.

3.4 The moderator role of sex

Table 5 shows that sex is a significant moderator in the relationship between WUR (assessed at the joint) (int: b = −1.373, p = 0.046) and acute pain. In males, increased pain facilitation (higher WUR scores) is associated with more intense pain at 48 h (b = 1.486, p = 0.016). For females, there is no relationship between WUR and acute pain (Figure 2a). For this time point, moderation analysis also shows a statistically significant interaction between sex and optimism (int: b = 1.191, p = 0.048), but there are no significant conditional effects revealed (Figure 2b).

There is a moderation effect of sex in the association of CPM (at the joint) and CPSP (int: b = 1.625, p = 0.016). Women with less effective pain inhibition (higher CPM scores) have more intense pain three months after surgery (b = 1.543, p = 0.002). The conditional effect for males is nonsignificant (Figure 2c). The effect of the remaining variables on postsurgical pain is not dependent on sex.

4 Discussion

This study analyzed psychological and psychophysical variables associated with acute and chronic pain after total knee or hip arthroplasty and explored the moderator role of sex. Higher APSP was associated with impaired CPM. Higher CPSP was associated with being female, longer presurgical pain duration, TKA, more intense APSP, and impaired CPM. The clinical variables were significant predictors of CPSP in a multivariate analysis. Sex moderated the association between psychophysical variables and postsurgical pain. Increased WUR was associated with higher APSP in men, and impaired CPM was associated with higher CPSP in women.

4.1 Sex differences

Women had higher pain intensity before and 3 months after surgery than men. Indeed, sex has been suggested as a risk factor for pain chronification [2,3], despite some equivocal evidence [35,36]. It is worth noting that most women in the present study underwent knee surgery, while most men had hip surgery, and it is known that THA has a lower incidence of CPSP than TKA [37]. Since TKA is also associated with more severe postoperative pain and lower improvement rates [38,39], it is possible that the sex-related differences in CPSP are at least partially accounted for by surgery-specific characteristics. Also, women undergo surgery at more advanced arthritis stages than men [40,41], which may contribute to higher presurgical pain intensity and interference in this group. Indeed, this hypothesis is partially supported by longer presurgical pain duration in female participants, though there are no differences in reported disability.

Sex differences in psychological variables are well documented, with different reports in the general population [42]

Table 3: Association of study variables with acute and chronic postsurgical pain

Variable	Worst pain at 48 h		Worst pain at 3 months	
	r [95% CI]	*p*	*r* [95% CI]	*p*
Sociodemographic				
Sex[†]	−0.039 [−0.286; 0.213]	0.762	0.282 [0.028; 0.498]	**0.029**
Age	−0.160 [0.393; 0.094]	0.213	−0.096 [−0.341; 0.163]	0.465
Clinical and pain-related				
BMI	−0.040 [−0.286; 0.212]	0.759	0.102 [−0.157; 0.346]	0.437
Nr. comorbidities	0.124 [0.131; 0.362]	0.337	−0.018 [−0.270; 0.237]	0.893
ASA score	−0.038 [−0.285; 0.214]	0.767	−0.066 [−0.314; 0.192]	0.616
Type of arthroplasty[†]	0.038 [−0.214; 0.284]	0.772	−0.312 [−0.522; −0.060]	**0.015**
Presurgical pain duration	0.041 [−0.211; 0.288]	0.749	0.353 [0.106; 0.555]	**0.006**
Presurgical pain intensity (Worst pain)	−0.009 [−0.258; 0.241]	0.943	0.049 [−0.208; 0.298]	0.713
Presurgical pain interference (BPI)	−0.048 [−0.294; 0.205]	0.711	0.079 [−0.179; 0.326]	0.547
Psychological				
Pain catastrophizing (CSQ-R)	0.110 [−0.145; 0.349]	0.395	0.106 [−0.153; 0.350]	0.420
Depression (HADS)	0.108 [−0.147; 0.347]	0.405	0.123 [−0.136; 0.365]	0.348
Anxiety (HADS)	0.110 [−0.145; 0.349]	0.395	0.130 [−0.130; 0.370]	0.324
Optimism (LOT-R)	0.052 [−0.201; 0.298]	0.687	−0.032 [−0.283; 0.224]	0.811
Psychophysical (QST)				
MDT (hand)	0.114 [−0.141; 0.353]	0.378	0.202 [−0.057; 0.432]	0.122
MDT (joint)	0.195 [0.059; 0.423]	0.128	−0.026 [−0.278; 0.230]	0.844
WUR (hand)	0.085 [−0.178; 0.335]	0.528	0.152 [−0.114; 0.396]	0.258
WUR (joint)	0.164 [−0.098; 0.402]	0.215	0.047 [−0.214; 0.301]	0.726
PPT (hand)	0.102 [−0.152; 0.342]	0.430	0.005 [−0.249; 0.259]	0.970
PPT (joint)	0.166 [−0.089; 0.398]	0.198	0.127 [−0.132; 0.368]	0.334
CPM (hand)	0.301 [0.048; 0.514]	**0.019**	0.096 [−0.167; 0.345]	0.474
CPM (joint)	0.238 [−0.021; 0.4654]	0.069	0.376 [0.125; 0.578]	**0.004**
CPM responder (hand)[†]	−0.288 [−0.503; −0.034]	**0.026**	−0.034 [−0.290; 0.226]	0.798
CPM responder (joint)[†]	−0.129 [−0.372; 0.133]	0.331	−0.353 [−0.560; −0.099]	**0.007**
48 h postsurgery				
Pain frequency (MPQ)[†]	—	—	0.071 [−0.191; 0.323]	0.597
Postsurgical pain intensity (worst pain)	—	—	0.373 [0.1269; 0.572]	**0.004**
Postsurgical anxiety (HADS)	—	—	0.008 [−0.248; 0.264]	0.951

[†]For dichotomic variables, the value zero corresponds to male sex, TKA, CPM non-responder and intermittent or brief pain (*vs* continuous).
Note: Bold values are statistically significant at $p < 0.05$.
Abbreviations: CI, confidence interval; BMI, body mass index; ASA, American Society of anesthesiologists physical status classification; BPI, brief pain inventory; CSQ-R, coping strategies questionnaire-revised; HADS, hospital anxiety and depression scale; LOT-R, life orientation test-revised; QST, quantitative sensory testing; MDT, mechanical detection threshold; WUR, wind-up ratio; PPT, pressure pain threshold; CPM, conditioned pain modulation; MPQ, McGill pain questionnaire; TKA, total knee arthroplasty.

and chronic pain patients [43] showing higher prevalence of anxiety and mood disorders in women. Poorer emotional well-being in women was confirmed in this study in terms of higher anxiety and lower optimism among females but without any differences in depression. There were also no differences in pain catastrophizing, which in some studies was higher in women [44]. Concerning optimism, there are apparently contradictory findings in other studies, which show higher levels in women than men [45]. However, among patients undergoing joint arthroplasty, the results have matched ours [46].

In QST, women showed lower sensitivity to touch (MDT) and increased pain facilitation (assessed by WUR and CPM). Generally, studies do not report sex differences for non-noxious stimuli [47], which makes our finding concerning MDT at the hand rather unexpected, particularly because women were found to be less sensitive than men. It is possible that the inhibitory systems activated to counteract the hyperexcitability of peripheral afferents in the affected joints also contribute to reduced tactile sensitivity [48,49]. In our sample, it could be hypothesized that this phenomenon is more pronounced in women due to longer pain duration and more intense pain in this group.

The absence of differences in PPT was somehow surprising, since studies generally conclude that women are more sensitive to pressure pain than men [22,47]. However, the effect of age

Table 4: Results of hierarchical linear regression model to predict chronic postsurgical pain

Variable	*B* [95% CI]	SE	*β*	*p*	Adj. R^2	*F*	*p*	Sig. *F* change
1st block					0.058	4.368	**0.041**	**0.041**
Sex[†]	1.654 [0.067; 3.241]	0.791	0.274	**0.041**				
2nd block					0.130	3.733	**0.017**	**0.047**
Sex	0.112 [−1.915; 2.139]	1.010	0.019	0.912				
Presurgical pain duration	0.010 [0.000; 0.019]	0.005	0.277	**0.046**				
Type of arthroplasty [†]	−1.527 [−3.452; 0.398]	0.959	−0.252	0.117				
3rd block					0.313	7.261	<**0.001**	<**0.001**
Sex	−0.036 [−1.840; 1.768]	0.899	−0.006	0.968				
Presurgical pain duration	0.009 [0.001; 0.018]	0.004	−0.264	**0.033**				
Type of arthroplasty	−1.860 [−3.580; −0.140]	0.857	−0.307	**0.035**				
Postsurgical pain intensity (worst pain)	0.625 [0.299; 0.950]	0.162	0.433	<**0.001**				
4th block					0.349	6.906	<**0.001**	0.055
Sex	−0.349 [−2.135; 1.436]	−0.889	−0.058	0.696				
Presurgical pain duration	0.010 [0.001; 0.018]	0.004	0.276	**0.023**				
Type of arthroplasty	−1.820 [−3.495; −0.145]	0.834	−2.183	**0.034**				
Postsurgical pain intensity (worst pain)	0.533 [0.203; 0.863]	0.164	0.370	**0.002**				
CPM (joint)	1.337 [−0.030; 2.704]	0.681	0.229	0.055				

Note: Bold values are statistically significant at $p < 0.05$.
[†]For dichotomic (dummy) variables, the value zero corresponds to male sex and TKA.
Abbreviations: CI, confidence interval; SE, standard error; CPM, conditioned pain modulation.

Table 5: Results of moderation analyses to explore the interaction of sex with baseline variables and postsurgical pain

Variable	Worst pain at 48 h				Worst pain at 3 months			
	B [95% CI]	SE	*t*	*p*	*B* [95% CI]	SE	*t*	*p*
Psychological								
Anxiety								
HADS_A	0.004 [−0.810; 0.811]	0.405	0.001	0.999	−0.381 [−1.576; 0.814]	0.595	−0.640	0.525
Sex	−0.209 [−1.578; 1.160]	0.684	−0.306	0.761	0.469 [−1.471; 2.408]	0.967	0.485	0.630
HADS_A × sex	0.523 [−0.619; 1.665]	0.570	0.918	0.363	0.608 [−1.013; 2.228]	0.808	0.753	0.455
Optimism								
LOT-R	−0.629 [−1.543; 0.284]	0.456	−1.379	0.173	−0.057 [−1.249; 1.136]	0.594	−0.095	0.925
Sex	−0.208 [−1.571; 1.155]	0.681	−0.306	0.761	0.318 [−1.565; 2.200]	0.938	0.339	0.736
LOT-R × sex	1.191 [0.011; 2.371]	0.589	2.022	**0.048**	0.501 [−1.065; 2.066]	0.780	0.642	0.524
Psychophysical (QST)								
MDT (hand)								
MDT (hand)	0.387 [−0.474; 1.249]	0.430	0.900	0.372	−0.643 [−1.729; 0.443]	0.541	−1.188	0.240
Sex	−0.212 [−1.585; 1.162]	0.686	−0.308	0.759	0.021 [−1.786; 1.827]	0.900	0.023	0.982
MDT (hand) × sex	−0.156 [−1.358; 1.047]	0.6005	−0.259	0.797	1.066 [−0.433; 2.565]	0.747	1.428	0.159
WUR (hand)								
WUR (hand)	0.754 [−1.309; 2.817]	1.029	0.733	0.467	1.565 [−1.216; 4.345]	1.384	1.131	0.264
Sex	−0.635 [−2.278; 1.007]	0.819	−0.776	0.441	−0.583 [−2.877; 1.710]	1.141	−0.511	0.612
WUR (hand) × sex	−0.519 [−2.688; 1.650]	1.081	−0.480	0.633	−1.788 [−4.682; 1.107]	1.440	−1.241	0.221
WUR (joint)								
WUR (joint)	1.486 [0.294; 2.678]	0.595	2.498	**0.016**	−0.042 [−1.695; 1.610]	0.823	−0.052	0.959
Sex	−0.662 [−2.00; 0.677]	0.668	−0.991	0.326	0.684 [−1.236; 2.605]	0.956	0.716	0.478
WUR (joint) × sex	−1.373 [−2.722; −0.023]	0.673	−2.039	**0.046**	−0.357 [−2.198; 1.484]	0.917	−0.389	0.699
CPM (joint)								
CPM (joint)	0.387 [−0.406; 1.180]	0.395	0.979	0.332	−0.082 [−1.001; 0.836]	0.457	−0.180	0.858
Sex	−0.173 [−1.570; 1.225]	0.697	−0.248	0.805	−0.224 [−1.925; 1.478]	0.847	−0.264	0.793
CPM (joint) × sex	0.307 [−0.839; 1.452]	0.571	0.537	0.593	1.625 [0.321; 2.929]	0.649	2.505	**0.016**

Note: Bold values are statistically significant at $p < 0.05$.
Abbreviations: CI, confidence interval; SE, standard error; HADS_A, hospital anxiety and depression scale (anxiety subscale); LOT-R, life orientation test-revised; QST, quantitative sensory testing; WUR, wind-up ratio; CPM, conditioned pain modulation.

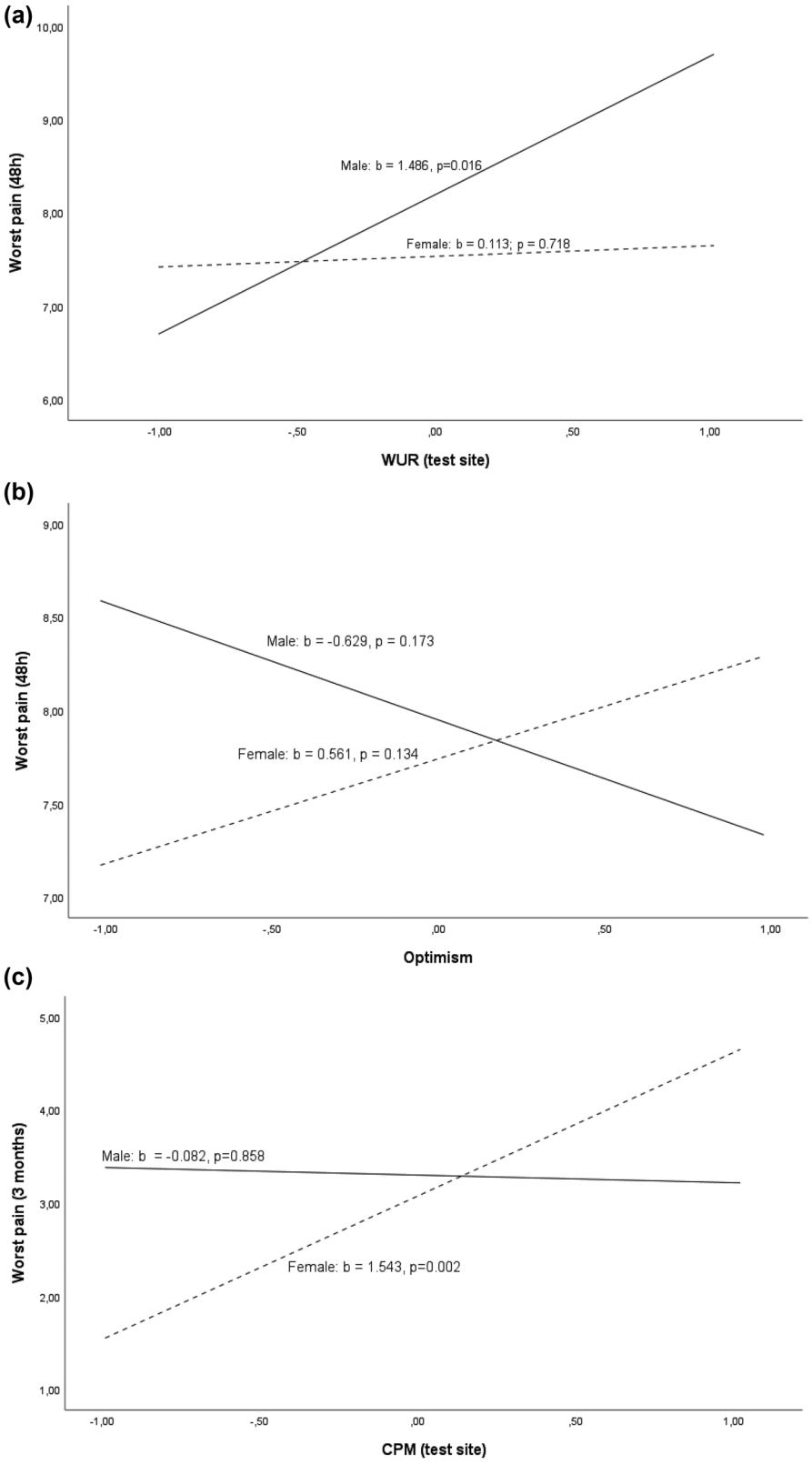

Figure 2: Visual representation of the moderator role of sex on the association between WUR (joint) and acute pain (a), optimism and acute pain (b), and CPM (joint) and chronic pain (c).

should be accounted for, as PPT differences seem to disappear in older age groups [22], in line with our findings.

Women also showed facilitated central integration (WUR at the hand and joint) and more impaired descending modulation (CPM at the joint). Gender differences at this level have been analyzed in a variety of studies, with some evidence of greater facilitation and less effective inhibition in women. However, some non-significant findings in individual studies make these conclusions somewhat inconsistent [50,51]. In the present sample, it is conceivable that women have increased sensitization due to longer pain duration and more intense pain [52].

4.2 Variables associated with APSP and CPSP

Pain-related variables were associated with chronic but not with acute pain. Indeed, pain itself is one of the strongest predictors of future pain [53], with different sources indicating that both presurgical pain and APSP are relevant risk factors for pain chronification [2,36]. The type of arthroplasty should also be accounted for, since TKA is usually associated with higher postsurgical pain intensity than THA [54].

Psychological variables are another relevant category of protective/risk factors, with characteristics such as anxiety, depression, pain catastrophizing, and optimism being frequently associated with postsurgical pain [3,6,7]. Nonetheless, findings concerning psychological domains remain equivocal, with systematic reviews highlighting that many studies fail to find significant associations [36]. Particularly in this study, it is possible that the sample size, along with the globally low levels of emotional distress and low variance in questionnaire scores, accounts for the absence of statistically significant results.

CPM was the only QST measure associated with postsurgical pain, and only in correlation analysis. A recent report also showed that CPM was associated with pain 12 months after TKA but was not a significant predictor in a multivariate model [55]. Nonetheless, less effective CPM still shows a trend towards higher CPSP in this study (p = 0.055), when controlling for the clinical variables. Based on previous reports, it is possible to hypothesize that the predictive value of QST differs according to arthroplasty type [12]. This seems may be visible in the present results since CPM was not a significant predictor when 'type of arthroplasty' was included in the regression model.

4.3 The moderator role of sex

Sex was not a moderator in the association between emotional states and postsurgical pain. Previous studies have shown such an effect in chronic pain [19,20] and TKA patients [18], but this was not confirmed by a meta-analysis focusing on postsurgical pain [56].

A significant effect of sex was seen for the association between two QST measures (WUR and CPM) and postsurgical pain. Interestingly, WUR was associated with acute pain in men and CPM with chronic pain in women. The wind-up phenomenon translates a state of neuronal hyperexcitability at the spinal cord that causes a progressive increase in the magnitude of pain evoked by repetitive noxious inputs of the same intensity, being a marker of pain sensitization [47,57]. Indeed, the acute postsurgical period is characterized by continuous nociceptive transmission due to damage and inflammation at the operated joint. Our findings seem to suggest that the impact of increased pain facilitation before surgery on APSP is more pronounced in men.

On the other hand, impaired presurgical descending inhibition seems to be associated with pain chronification only in women. A similar trend was reported by Bossmann et al. [23], reinforcing that accounting for sex may be relevant to improve the predictive value of QST. Our results support the utility of CPM to predict CPSP, at least in a subgroup of patients. CPM is a proxy measure of endogenous inhibitory pain pathways [58], which are important for pain chronification [59]. In patients undergoing thoracotomy, CPM was also shown to predict chronic, but not acute pain [60]. It is likely that endogenous modulation does not have much expression in the acute phase, when the injury itself is likely more relevant [60]. At this stage, the continuous activation of nociceptors (WUR) seems to play a major contribution to increased pain perception.

4.4 Limitations

In this study, the relatively small sample size may have hindered statistical power and limited the ability to detect otherwise significant associations in some analyses.

There are relevant sex differences in clinical variables, which were circumvented by including them as covariates in the moderation analyses (type of arthroplasty, presurgical pain duration, and APSP). Nonetheless, future studies should aim to achieve larger TKA and THA samples, to analyze them independently. The type of arthroplasty

may have significant implications for postsurgical pain experience, which deserves more detailed exploration.

Joint pain was not assessed in terms of localized *vs.* spreading location [61]. Since spreading pain may be associated with greater pain hypersensitivity, this would be relevant to consider in future studies.

Pain medication can affect QST results but, due to the nature of the underlying pathology, patients were not asked to refrain from taking analgesics before the assessment. Subsequent analyses confirmed that there were no differences in QST outcomes between patients who did or did not take medication, so this is also not likely to have influenced results. On the other hand, the variability in pharmacological treatments and analgesic strategies did not allow their inclusion in the statistical models and its influence was not controlled for. The single-center nature of this study limits the generalizability of findings.

5 Conclusions

This study showed that specific QST parameters predicted higher intensity of APSP and CPSP, depending on sex. It is likely that risk factors are not equally generalizable to all patients, and it is thus crucial to determine *for whom* the predictive models may be most useful.

The moderator role of sex that was evidenced in this study may help explain the variable and apparently contradictory findings reported in QST literature. To identify clinically relevant predictors of pain, efforts should be made to acknowledge all chains of causal paths and identify subgroups of patients for whom these may be more relevant. In the future, separate consideration of TKA/THA samples will be crucial to determine the applicability of the present findings.

Research ethics: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by research ethical committee: Ethics Committee from Hospital of Braga (Ref. 03_2021) and Ethics Committee for Research in Life and Health Sciences from the University of Minho (CEICVS 093/2020).

Informed consent: Informed consent has been obtained from all individuals included in this study.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Lars Arendt-Nielsen is an editorial team member of Scandinavian Journal of Pain. The remaining authors have no conflicts of interest to declare.

Research funding: This work has been funded by Portuguese National funds, through the Foundation for Science and Technology (FCT) – project UIDB/50026/2020 (DOI 10.54499/UIDB/50026/2020), UIDP/50026/2020 (DOI 10.54499/UIDP/50026/2020), and LA/P/0050/2020 (DOI 10.54499/LA/P/0050/2020) and by the project NORTE-01-0145-FEDER-000039, supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF). ACP has a PhD scholarship (SFRH/BD/146135/2019, DOI 10.54499/SFRH/BD/146135/2019; and COVID/BD/153639/2024) funded by the Portuguese Foundation for Science and Technology. The Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121). The Center for Mathematical Modeling of Knee Osteoarthritis (MathKOA) is funded by the Novo Nordic Foundation (NNF21OC0065373) and Danish Rheumatism Association provided additional support.

Data availability: The raw data can be obtained on request from the corresponding author.

Supplementary material: This article contains supplementary material (followed by the link to the article online).

References

[1] Deumens R, Steyaert A, Forget P, Schubert M, Lavand'homme P, Hermans E, et al. Prevention of chronic postoperative pain: cellular, molecular, and clinical insights for mechanism-based treatment approaches. Prog Neurobiol. 2013;104:1–37. doi: 10.1016/j.pneurobio.2013.01.002.

[2] Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet. 2019;393:1537–46. doi: 10.1016/s0140-6736(19)30352-6.

[3] Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. Pain Rep. 2017;2:e627. doi: 10.1097/pr9.0000000000000627.

[4] Chadwick A, Frazier A, Khan TW, Young E. Understanding the psychological, physiological, and genetic factors affecting precision pain medicine: A narrative review. J Pain Res. 2021;14:3145–61. doi: 10.2147/jpr.S320863.

[5] Li Q, Dai W, Chen X, Su D, Yu W, Gu X. Publication trends and hot spots in chronic postsurgical pain (CPSP) research: A 10-year bibliometric analysis. J Pain Res. 2021;14:2239–47. doi: 10.2147/jpr.S300744.

[6] Lewis GN, Rice DA, McNair PJ, Kluger M. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. Br J Anaesth. 2015;114:551–61. doi: 10.1093/bja/aeu441.

[7] Ashoorion V, Sadeghirad B, Wang L, Noori A, Abdar M, Kim Y, et al. Predictors of persistent post-surgical pain following total knee arthroplasty: A systematic review and meta-analysis of observational studies. Pain Med. 2022;24:369–81. doi: 10.1093/pm/pnac154.
[8] Schnabel A, Yahiaoui-Doktor M, Meissner W, Zahn PK, Pogatzki-Zahn EM. Predicting poor postoperative acute pain outcome in adults: an international, multicentre database analysis of risk factors in 50,005 patients. Pain Rep. 2020;5:e831. doi: 10.1097/pr9.0000000000000831.
[9] Hanssen MM, Peters ML, Boselie JJ, Meulders A. Can positive affect attenuate (persistent) pain? State of the art and clinical implications. Curr Rheumatol Rep. 2017;19:80. doi: 10.1007/s11926-017-0703-3.
[10] Abrecht CR, Cornelius M, Wu A, Jamison RN, Janfaza D, Urman RD, et al. Prediction of pain and opioid utilization in the perioperative period in patients undergoing primary knee arthroplasty: Psychophysical and psychosocial factors. Pain Med. 2019;20:161–71. doi: 10.1093/pm/pny020.
[11] Arendt-Nielsen L, Simonsen O, Laursen MB, Roos EM, Rathleff MS, Rasmussen S, et al. Pain and sensitization after total knee replacement or nonsurgical treatment in patients with knee osteoarthritis: Identifying potential predictors of outcome at 12 months. Eur J Pain. 2018;22:1088–102. doi: 10.1002/ejp.1193.
[12] Wylde V, Sayers A, Lenguerrand E, Gooberman-Hill R, Pyke M, Beswick AD, et al. Preoperative widespread pain sensitization and chronic pain after hip and knee replacement: a cohort analysis. Pain. 2015;156:47–54. doi: 10.1016/j.pain.0000000000000002.
[13] Paredes AC, Pinto JM, Almeida A, Pinto PR. Predictive value of quantitative sensory testing for acute and chronic postsurgical pain after total joint arthroplasty: a systematic review. Pain. 2022;163:e385–400. doi: 10.1097/j.pain.0000000000002385.
[14] Petersen KK, Vaegter HB, Stubhaug A, Wolff A, Scammell BE, Arendt-Nielsen L, et al. The predictive value of quantitative sensory testing: a systematic review on chronic postoperative pain and the analgesic effect of pharmacological therapies in patients with chronic pain. Pain. 2021;162:31–44. doi: 10.1097/j.pain.0000000000002019.
[15] Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL. Sex, gender, and pain: A review of recent clinical and experimental findings. J Pain. 2009;10:447–85. doi: 10.1016/j.jpain.2008.12.001.
[16] García-López J, Polanco-García M, Montes A. Factors associated with the risk of developing moderate to severe acute postoperative pain after primary total knee arthroplasty: Results from the PAIN OUT registry. J Arthroplasty. 2021;36:1966–73. doi: 10.1016/j.arth.2021.02.005.
[17] Ferraro KF, Nuriddin TA. Psychological distress and mortality: are women more vulnerable. J Health Soc Behav. 2006;47:227–41. doi: 10.1177/002214650604700303.
[18] Nandi M, Schreiber KL, Martel MO, Cornelius M, Campbell CM, Haythornthwaite JA, et al. Sex differences in negative affect and postoperative pain in patients undergoing total knee arthroplasty. Biol Sex Differ. 2019;10:23. doi: 10.1186/s13293-019-0237-7.
[19] Robinson ME, Dannecker EA, George SZ, Otis J, Atchison JW, Fillingim RB. Sex differences in the associations among psychological factors and pain report: A novel psychophysical study of patients with chronic low back pain. J Pain. 2005;6:463–70. doi: 10.1016/j.jpain.2005.02.007.
[20] Speed TJ, Richards JM, Finan PH, Smith MT. Sex moderates the effects of positive and negative affect on clinical pain in patients with knee osteoarthritis. Scand J Pain. 2017;16:66–73. doi: 10.1016/j.sjpain.2017.03.005.
[21] Bulls HW, Freeman EL, Anderson AJB, Robbins MT, Ness TJ, Goodin BR. Sex differences in experimental measures of pain sensitivity and endogenous pain inhibition. J Pain Res. 2015;8:311–20. doi: 10.2147/JPR.S84607.
[22] Magerl W, Krumova EK, Baron R, Tölle T, Treede R-D, Maier C. Reference data for quantitative sensory testing (QST): Refined stratification for age and a novel method for statistical comparison of group data. Pain. 2010;151:598–60545. doi: 10.1016/j.pain.2010.07.026.
[23] Bossmann T, Brauner T, Wearing S, Horstmann T. Predictors of chronic pain following total knee replacement in females and males: an exploratory study. Pain Manag. 2017;7:391–403. doi: 10.2217/pmt-2017-0023.
[24] Novicoff WM, Saleh KJ. Examining sex and gender disparities in total joint arthroplasty. Clin Orthop Relat Res. 2011;469:1824–8. doi: 10.1007/s11999-010-1765-y.
[25] Cleeland C, Ryan K. Pain assessment: global use of the brief pain inventory. Ann Acad Med Singapore. 1994;23:129–38.
[26] Riley JL, 3rd Robinson ME. CSQ: five factors or fiction? Clin J Pain. 1997;13:156–62. doi: 10.1097/00002508-199706000-00010.
[27] Zigmond A, Snaith R. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70. doi: 10.1111/j.1600-0447.1983.tb09716.x.
[28] Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the life orientation test. J Pers Soc Psychol. 1994;67:1063–78. doi: 10.1037//0022-3514.67.6.1063.
[29] Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain. 2006;10:77–88. doi: 10.1016/j.ejpain.2005.02.003.
[30] Yarnitsky D, Bouhassira D, Drewes AM, Fillingim RB, Granot M, Hansson P, et al. Recommendations on practice of conditioned pain modulation (CPM) testing. Eur J Pain. 2015;19:805–6. doi: 10.1002/ejp.605.
[31] West S, Finch J, Curran P. Structural equation models with non-normal variables: problems and remedies. In: Hoyle R, editor. Structural equation modeling: Concepts, issues and applications. Thousand Oaks, CA: Sage; p. 1995. 56–75.
[32] Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49:1373–9. doi: 10.1016/s0895-4356(96)00236-3.
[33] Chan YH. Biostatistics 201: linear regression analysis. Singapore Med J. 2004;45:55–61.
[34] Hayes A. Introduction to mediation, moderation and conditional process analysis. A regression-based approach. New York: The Guilford Press; 2013.
[35] VanDenKerkhof EG, Peters ML, Bruce J. Chronic pain after surgery: time for standardization? A framework to establish core risk factor and outcome domains for epidemiological studies. Clin J Pain. 2013;29:2–8. doi: 10.1097/AJP.0b013e31824730c2.
[36] Ghoshal A, Bhanvadia S, Singh S, Yaeger L, Haroutounian S. Factors associated with persistent postsurgical pain after total knee or hip joint replacement: a systematic review and meta-analysis. Pain Rep. 2023;8:e1052. doi: 10.1097/pr9.0000000000001052.
[37] Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective

studies in unselected patients. BMJ Open. 2012;2:e000435. doi: 10.1136/bmjopen-2011-000435.
[38] Pinto PR, McIntyre T, Ferrero R, Araújo-Soares V, Almeida A. Persistent pain after total knee or hip arthroplasty: differential study of prevalence, nature, and impact. J Pain Res. 2013;6:691–703. doi: 10.2147/jpr.S45827.
[39] O'Brien S, Bennett D, Doran E, Beverland DE. Comparison of hip and knee arthroplasty outcomes at early and intermediate follow-up. Orthopedics. 2009;32:168.
[40] Katz JN, Wright EA, Guadagnoli E, Liang MH, Karlson EW, Cleary PD. Differences between men and women undergoing major orthopedic surgery for degenerative arthritis. Arthritis Rheum. 1994;37:687–94. doi: 10.1002/art.1780370512.
[41] Borkhoff CM, Hawker GA, Wright JG. Patient gender affects the referral and recommendation for total joint arthroplasty. Clin Orthop Relat Res. 2011;469:1829–37. doi: 10.1007/s11999-011-1879-x.
[42] Boyd A, Van de Velde S, Vilagut G, de Graaf R, O'Neill S, Florescu S, et al. Gender differences in mental disorders and suicidality in Europe: results from a large cross-sectional population-based study. J Affect Disord. 2015;173:245–54. doi: 10.1016/j.jad.2014.11.002.
[43] Morales-Fernández Á, Jiménez Martín JM, Vergara-Romero M, Morales-Asencio JM, Mora-Bandera AM, Gomez-Ortigosa MI, et al. Gender differences in perceived pain and health-related quality of life in people with chronic non-malignant pain: a cross-sectional study. Contemp Nurse. 2021;57:280–9. doi: 10.1080/10376178.2021.1999836.
[44] Sullivan MJL, Tripp DA, Santor D. Gender differences in pain and pain behavior: The role of catastrophizing. Cognit Ther Res. 2000;24:121–34. doi: 10.1023/A:1005459110063.
[45] Yue XD, Hiranandani NA, Jiang F, Hou Z, Chen X. Unpacking the gender differences on mental health:The effects of optimism and gratitude. Psychol Rep. 2017;120:639–49. doi: 10.1177/0033294117701136.
[46] Pinto PR, McIntyre T, Ferrero R, Almeida A, Araújo-Soares V. Predictors of acute postsurgical pain and anxiety following primary total hip and knee arthroplasty. J Pain. 2013;14:502–15. doi: 10.1016/j.jpain.2012.12.020.
[47] Yarnitsky D, Pud D. Quantitative sensory testing. In: Binnie C, Cooper R, Mauguiere F, Osselton J, Prior P, Tedman B, editors. Clinical Neurophysiology, EMG, Nerve Conduction and Evoked Potentials. Vol. 1. Amsterdam: Elsevier; 2004. p. 205–332.
[48] Hendiani JA, Westlund KN, Lawand N, Goel N, Lisse J, McNearney T. Mechanical sensation and pain thresholds in patients with chronic arthropathies. J Pain. 2003;4:203–11. doi: 10.1016/s1526-5900(03)00557-1.
[49] Geber C, Magerl W, Fondel R, Fechir M, Rolke R, Vogt T, et al. Numbness in clinical and experimental pain–a cross-sectional study exploring the mechanisms of reduced tactile function. Pain. 2008;139:73–81. doi: 10.1016/j.pain.2008.03.006.
[50] Ramaswamy S, Wodehouse T. Conditioned pain modulation-A comprehensive review. Neurophysiol Clin. 2021;51:197–208. doi: 10.1016/j.neucli.2020.11.002.
[51] Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choinière M. A systematic literature review of 10 years of research on sex/gender and pain perception - part 2: do biopsychosocial factors alter pain sensitivity differently in women and men? Pain. 2012;153:619–35. doi: 10.1016/j.pain.2011.11.026.
[52] Arendt-Nielsen L, Egsgaard LL, Petersen KK, Eskehave TN, Graven-Nielsen T, Hoeck HC, et al. A mechanism-based pain sensitivity index to characterize knee osteoarthritis patients with different disease stages and pain levels. Eur J Pain. 2015;19:1406–17. doi: 10.1002/ejp.651.
[53] Katz JN, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother. 2009;9:723–44. doi: 10.1586/ern.09.20.
[54] Bourne RB, Chesworth B, Davis A, Mahomed N, Charron K. Comparing patient outcomes after THA and TKA: is there a difference? Clin Orthop Relat Res. 2010;468:542–6. doi: 10.1007/s11999-009-1046-9.
[55] Larsen DB, Laursen M, Edwards RR, Simonsen O, Arendt-Nielsen L, Petersen KK. The combination of preoperative pain, conditioned pain modulation, and pain catastrophizing predicts postoperative pain 12 months after total knee arthroplasty. Pain Med. 2021;22:1583–90. doi: 10.1093/pm/pnaa402.
[56] Jackson T, Tian P, Wang Y, Iezzi T, Xie W. Toward identifying moderators of associations between presurgery emotional distress and postoperative pain outcomes: A meta-analysis of longitudinal studies. J Pain. 2016;17:874–88. doi: 10.1016/j.jpain.2016.04.003.
[57] Cheng JC, Erpelding N, Kucyi A, DeSouza DD, Davis KD. Individual differences in temporal summation of pain reflect pronociceptive and antinociceptive brain structure and function. J Neurosci. 2015;35:9689–700. doi: 10.1523/jneurosci.5039-14.2015.
[58] Petersen KK, McPhee ME, Hoegh MS, Graven-Nielsen T. Assessment of conditioned pain modulation in healthy participants and patients with chronic pain: manifestations and implications for pain progression. Curr Opin Support Palliat Care. 2019;13:99–106. doi: 10.1097/spc.0000000000000419.
[59] Miranda J, Lamana SMS, Dias EV, Athie M, Parada CA, Tambeli CH. Effect of pain chronification and chronic pain on an endogenous pain modulation circuit in rats. Neuroscience. 2015;286:37–44. doi: 10.1016/j.neuroscience.2014.10.049.
[60] Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, et al. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. Pain. 2008;138:22–8. doi: 10.1016/j.pain.2007.10.033.
[61] Thompson LR, Boudreau R, Hannon MJ, Newman AB, Chu CR, Jansen M, et al. The knee pain map: reliability of a method to identify knee pain location and pattern. Arthritis Rheum. 2009;61:725–31. doi: 10.1002/art.24543.