


High Prevalence of Pain Sensitization in Knee Osteoarthritis: A Meta-Analysis with Meta-Regression

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Abstract

Objective. The aim of this meta-analysis was to study the evidence on pain sensitization in knee osteoarthritis (OA), providing a quantitative synthesis of its prevalence and impact. Factors associated with pain sensitization were also investigated. **Methods.** Meta-analysis; PubMed (MEDLINE), Cochrane Central Register (CENTRAL), and Web of Science were searched on February 2021. Level I to level IV studies evaluating the presence of pain sensitization in patients with symptomatic knee OA, documented through a validated method (questionnaires or quantitative sensory testing), were included. The primary outcome was the prevalence of pain sensitization. Factors influencing the prevalence were also evaluated, as well as differences in terms of pain thresholds between knee OA patients and healthy controls. **Results.** Fifty-three articles including 7,117 patients were included. The meta-analysis of proportion documented a prevalence of pain sensitization of 20% (95% confidence interval [CI] = 16%-26%) with a significant heterogeneity of results ($I^2 = 89\%$, $P < 0.001$). The diagnostic tool used was the main factor influencing the documented prevalence of pain sensitization ($P = 0.01$). Knee OA patients presented higher pain sensitivity compared with healthy controls, both in terms of local pressure pain threshold (standardized mean difference [SMD] = -1.00 , 95% CI = -1.67 to -0.32 , $P = 0.007$) and distant pressure pain threshold (SMD = -0.54 , 95% CI = -0.76 to -0.31 , $P < 0.001$). **Conclusions.** Knee OA pain presents features that are consistent with a significant degree of pain sensitization. There is a high heterogeneity in the reported results, mainly based on the diagnostic tool used. The identification of the best methods to detect pain sensitization is warranted to correctly evaluate and manage symptoms of patients affected by knee OA.
 Registration: PROSPERO CRD42019123347.

Keywords

knee osteoarthritis, OA, pain, pain sensitization, neuropathic, nociplastic, prevalence

Introduction

Pain is the main symptom of knee osteoarthritis (OA), as well as the most relevant cause of disability and poor quality of life in the affected patients.^{1,2} Current treatments can only partially address patient symptoms, often offering a limited improvement with persistent pain regardless of the treatment strategy. Structural changes are traditionally considered the trigger of the noxious stimuli and, as such, are the most common target of pain treatment, but the latest studies on this topic led to conflicting results regarding the association between structural damage and pain.³⁻⁶ This documented discrepancy could be related to an altered pain perception mechanism, with pain sensitization being increasingly recognized as a key determinant in knee OA-related pain.⁷⁻¹⁰

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Pain sensitization is defined as an altered pain perception caused by increased impulses from peripheral nervous tissues (peripheral sensitization) and/or by the amplification of the pain signals within the central nervous system (central sensitization).¹¹⁻¹⁴ As a consequence, patients present a change in the characteristics of pain including local allodynia and hyperalgesia, as well as in the distribution of pain, as these changes can lead to widespread hypersensitivity, which extends beyond local anatomic changes.¹⁵ The involvement of the nervous system with changes in nervous transmission and cerebrospinal fluid composition affecting level and characteristics of perceived pain leads to the use of the term “neuropathic pain,” to distinguish it from “nociceptive pain” historically considered related to knee OA.¹⁶⁻¹⁸ As “neuropathic” pain is a broader concept pertaining different pathologic conditions outside the OA field¹⁹ (i.e., neuropathies, central poststroke pain, etc.) and entailing the presence of a demonstrable neurologic lesion, the term “nociplastic pain” has been introduced to account for the possible involvement of the nervous system in musculoskeletal diseases.^{20,21} However, neuropathic pain diagnostic tools proved effective in identifying knee OA patients with peripheral and central pain sensitization.^{22,23} Validated methods such as questionnaires and quantitative sensory testing (QST) protocols evaluating pressure and thermal pain threshold and pain modulating mechanism, such as conditioned pain modulation (CPM) and temporal summation (TS), have been used to investigate the presence of local and widespread pain sensitization in the clinical setting avoiding invasive procedure such as cerebrospinal fluid collection.²⁴ Although with sometimes controversial findings, recent awareness on this important pain determinant fueled a significant research effort to shed new light in knee OA mechanisms.^{25,26}

The primary aim of this meta-analysis was to provide a quantitative synthesis of the prevalence of pain sensitization in knee OA determining the percentage of patients that present features of pain sensitization according to tools available in the outpatient setting such as questionnaires or QST. The impact of pain sensitization was evaluated comparing pain thresholds—documented with QST—of affected patients and healthy controls. Furthermore, possibly associated factors were investigated through a meta-regression to better identify and manage patients affected by pain sensitization in knee OA.

Materials and Methods

Data Source and Study Selection

After the registration of the protocol on PROSPERO (CRD42019123347), PubMed (MEDLINE), the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science were systematically searched with no time

limitation on February 2, 2021, using the following string: (Osteoarthritis OR OA) AND (pain) AND (neuropathic OR nociceptive OR sensitisation OR sensitization OR DN4 OR painDETECT OR S-LANSS OR QST).

After the removal of duplicates, all titles and abstracts were checked to retrieve all eligible articles. Subsequently, if not enough information could be obtained from the abstract, the full-text article was read. Level I to level IV studies on humans reporting the prevalence of pain sensitization in patients with symptomatic knee OA (as a primary or secondary outcome) documented through a validated method (questionnaires or QST), or reporting a comparison of QST between knee OA patients and healthy subjects, were included. Systematic reviews, meta-analyses, narrative reviews, expert opinions, and case reports were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used.²⁷ Two authors (D.P., G.C.) independently performed the article selection process, with disagreement on study eligibility solved by a third author (C.C.).

Data Extraction, Study Outcomes, and Quality Assessment

Extracted information on methodology from all eligible studies included level of evidence, study design, technique of pain sensitization assessment, inclusion/exclusion criteria, origin of data, number of patients included, and follow-up length. Information from all eligible studies on characteristics of the study population included sex, age, body mass index (BMI), comorbidities, PROMs (Patient-Reported Outcome Measures), length of symptoms, prevalence of pain sensitization, QST protocol results, and OA stage. Two authors (D.P., G.C.) independently extracted trial information. If data were not available from the published studies, the corresponding authors were contacted. The primary outcome was the prevalence of pain sensitization determined as the percentage of patients that presented features of pain sensitization according to questionnaires or QST. Study and patient characteristics influencing the documented prevalence of pain sensitization in knee OA were also evaluated, as well as differences in terms of pain thresholds—measured with QST—between patients and healthy controls to quantify the impact of pain sensitization in knee OA pain perception.

A previously validated checklist, specifically developed for systematic reviews and meta-analyses addressing prevalence,²⁸ was used to assess the risk of bias and the quality of the included studies. The evaluation was performed independently by 2 reviewers (D.P., G.C.), and interrater variability was quantified through Cohen’s kappa. Discrepancies were discussed and resolved by a third author (C.C.).

Statistical Analysis

To compute the adequate sample size to detect a prevalence of 20%, the formula of Naing *et al.*²⁹ was used and it was determined that at least 246 patients were required. Continuous data were expressed as means and standard deviations and compared as mean differences, whereas binary data were expressed as frequencies and compared as risk ratios. A meta-analysis of proportions was performed to quantify the prevalence of pain sensitization in patients with knee OA with sub-analyses based on the detection method.³⁰ When a score adopts more than 1 threshold to classify patients (i.e., unlikely, ambiguous, likely), the most conservative class (i.e., likely) was considered in the evaluation of prevalence. Both fixed and random effects were used, with the results of the random effect preferred in case of heterogeneity of the included studies. A linear meta-regression was performed to identify the source of the documented heterogeneity and evaluate the study characteristics influencing the reported prevalence of pain sensitization. Multiple meta-regression, with the variable identified as significantly associated to the documented prevalence, was then performed. Moreover, a meta-analysis was performed to compare the local and distant pressure pain thresholds (PPTs) between knee OA patients and healthy controls. The random effect model with Knapp-Hartung-Sidik-Jonkman adjustment was used, and results were expressed as standardized mean differences (SMDs). The statistical analysis was performed with the packages *meta* (v4.9-7) and *metafor* (v2.1-0) in RStudio (v1.2.5019).

Results

Characteristics of the Included Studies and Patients

Out of the 3,405 articles retrieved, 53 were selected (Fig. 1).^{5,22,23,25,26,31-80} All these articles reported pain sensitization prevalence in the included patients, but only 12 studies had the evaluation of the prevalence of pain sensitization in knee OA as a primary aim. Thirty-five studies were focused on other relevant features of pain sensitization, such as its association with patient characteristics and clinical outcomes (19 studies), the detection of pain threshold (5 studies), the effect of a specific treatment on it (5 studies), the development of a new index to evaluate it (3 studies), the evaluation of the different pain phenotypes (2 studies), and the evaluation of the reliability of the QST protocols (1 study). In the remaining 6 studies, pain sensitization was only documented as baseline patient characteristic. All of them used a validated method to detect the presence of pain sensitization in knee OA (some of the studies used more than 1 method to evaluate sensitization): painDETECT questionnaire in 24 studies (4 of which used a modified format), Douleur Neuropathic 4 (DN4) in 4

studies, central sensitization index (CSI) in 3 studies, S-LANSS (Leeds Assessment of Neuropathic Symptoms and Signs) in 2 studies, a newly developed index in 2 studies, and QST in 32 studies. Out of the 32 studies evaluating pain sensitization in knee OA, 10 reported an analysis of the prevalence of pain sensitization. Different methods were used to determine the prevalence of pain sensitization in their samples: Cardoso *et al.* and Osgood *et al.* used a cluster analysis of the results of QST protocol; Hochmann *et al.*, Kurien *et al.*, Wright *et al.*, and Wylde *et al.* created cutoffs based on QST of healthy controls; Bossmann *et al.* used cutoff values published for healthy subject by the German Research Network on Neuropathic Pain; Lewis *et al.* considered abnormal a CPM <10% and a TS >10 on a 0 to 100 Visual Analogue Scale; and Courtney *et al.* and Fingleton *et al.* considered abnormal a CPM with no change or an increase in pain perception. Patients were recruited from the community in 7 studies, from outpatient settings in 21 studies, from both the community and outpatient settings in 6 studies, from the surgery list in 14 studies, and from both the outpatient settings and the surgery list in 1 study, whereas 4 studies did not report the method of patient recruitment. Overall, 7,117 patients were included, with a male/female ratio ranging from 0 to 3.3, a mean age ranging from 51 to 76, a mean BMI ranging from 25 to 38, and a mean pain duration ranging from 273 days to 11.9 years. Table 1 reports detailed information on studies and patient characteristics.

Pain Sensitization in Knee OA

The meta-analysis of proportion (Fig. 2) considering all the detection methods documented a prevalence of pain sensitization of 20% (95% confidence interval [CI] = 16%-26%), with a significant heterogeneity of results ($I^2 = 89%$, $P < 0.001$). Sub-analyses were performed for the different detection methods used. PainDETECT was the most commonly used questionnaire and documented an overall prevalence of 17% (18% in the studies using the original PainDETECT and 11% in the studies using a modified form). Regarding the other questionnaires, the documented prevalence was 25% with DN4, 31% with S-LANSS, and 33% with CSI. Among the studies that used static QST protocols to evaluate pain sensitization, the documented prevalence was 29% using PPT, 27% using cold pain threshold (CPT), and 10% using heat pain threshold (HPT). In the studies evaluating pain response with dynamic QST protocols, a prevalence of 17% and 55% was reported in terms of abnormal TS and abnormal CPM, respectively.

In the meta-analysis comparing pain sensitivity of knee OA patients and healthy controls (Fig. 3), a lower PPT was documented in the affected subjects, both in terms of local PPT (SMD = -1.00, 95% CI = -1.67 to -0.32, $P = 0.007$)

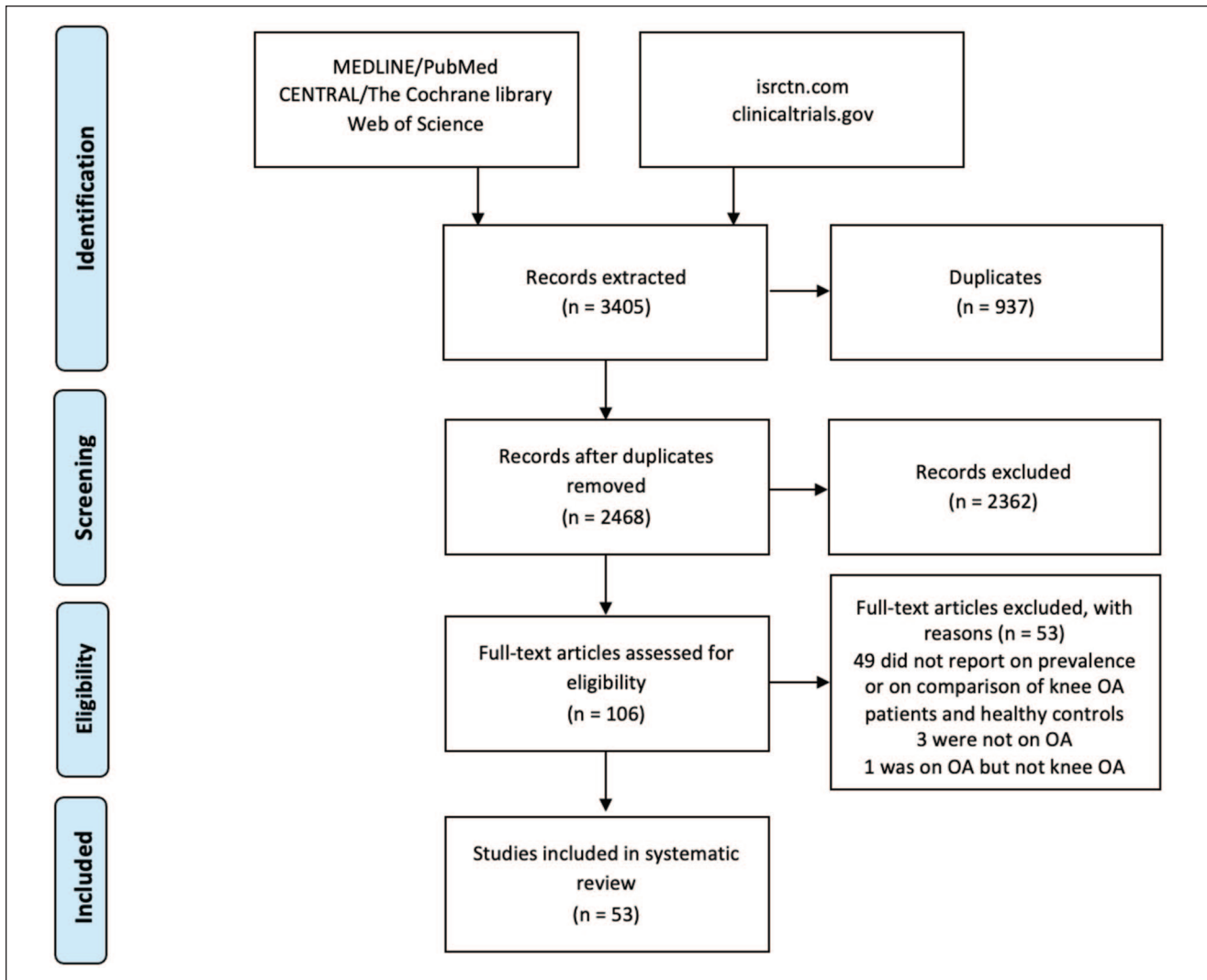


Figure 1. PRISMA flowchart of the study selection process. OA = osteoarthritis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

and distant PPT (SMD = -0.54 , 95% CI = -0.76 to -0.31 , $P < 0.001$).

Factors Associated with Pain Sensitization

To evaluate the effect of study and patient characteristics on the prevalence of pain sensitization, a meta-regression analysis was performed. The diagnostic tool used ($R^2 = 41\%$, $P = 0.01$) and the aim of the study ($R^2 = 35\%$, $P = 0.01$) were associated with the documented prevalence. There was an association tendency also for pain duration ($R^2 = 21\%$, $P = 0.07$) and the category of the journal ($R^2 = 37\%$, $P = 0.07$). Number of patients included, publication year, country of the study, appropriateness of the inclusion criteria, recruitment technique, and patient characteristics such as sex, age, BMI, baseline pain intensity, and related

symptoms were not significantly associated with the reported prevalence. A multiple meta-regression model was created with the identified associated factors (diagnostic tool, aim of the study, year, category of the journal). The only variable, whose significance was confirmed by multiple regression, was the diagnostic tool used, being the use of PainDETECT significantly associated with a lower documented prevalence ($P = 0.03$).

Quality of the Included Studies

The sample was considered representative in all included studies, except for the studies of Kim *et al.* and Imamura *et al.*, which enrolled only women, and the study of Rabuille *et al.*, which did not specify if the 50 patients included were recruited progressively or differentiated by the presence of

Table 1. Characteristics of the Included Studies and Patients.

Study	Origin of Patients	Inclusion Criteria	Exclusion Criteria	Diagnostic Tool	Study Aim	# pts (#Knees) (M, F)	Age, Mean ± SD (Range)	BMI, Mean ± SD (Range)	Pain Duration, Mean ± SD (Range)
Alshuft <i>et al.</i> ³¹	Outpatients + community	Radiologic KOA with >3 mo chronic pain	Comorbidities, ^a age <18, pregnancy, previous TKA or MRI contraindications	PDQ	NeuP ^b	40 (19 M, 21 F)	66.1 ± 8.5 (45.4-83.0)	28.8 ± 4.9 (20-41.1)	8.5 (1-38)
Arendt-Nielsen <i>et al.</i> ³³	Outpatients + community	ACR KOA criteria, discontinuation of analgesic	Secondary KOA, comorbidities, ^a pregnancy	New index, QST	NeuP ^b	217 (102 M, 115 F)	63.8	28.3	NR
Arendt-Nielsen <i>et al.</i> ³²	Outpatients	ACR KOA criteria, K-L 1-3, worst pain 4-9 analgesic discontinuation	Comorbidities, ^a allergy to medications, normal ECG and labor, changed FKT (14 d)	PDQ, QST	Oth ^c	37 (14 M, 23 F)	63.3 ± 7.6	28.2 ± 4.1	10.9 ± 7.5
Arendt-Nielsen <i>et al.</i> ³⁴	NR	ACR KOA criteria, K-L 1-3, worst pain 4-9, age 40-75, stable knee pain ≥6 mo	Secondary KOA, rheumatic diseases, prior treatment with IA HA (≤24 w) steroid (≤12 w), botulinum toxin (any time)	PDQ, QST	Oth ^c	121 (59 M, 62 F)	62.3 ± 8.6	28 ± 3.9	8.6 ± 6.6
Askin, <i>et al.</i> ³⁵	NR	ACR KOA criteria, chronic pain	Previous knee surgery, active inflammation, comorbidities, ^a pregnant	PDQ, DN4	NeuP Prev ^d	60 (14 M, 46 F)	56.2 ± 10.0 (32-82)	29.8 ± 4.8 (20.3-39.5)	9.1 ± 10.9
Blikman <i>et al.</i> ³⁶	Outpatients	age > 18 y, primary painful KOA (K-L >1)	Comorbidities, ^a hip/knee surgery (6 mPDQ mo), no Dutch speakers	6 mPDQ	NeuP ^b	138 (66 M, 72 F)	61.9 ± 10.5	28.7 ± 5.4	2.4 ± 0.4
Bossmann <i>et al.</i> ³⁷	Surgery-List	Painful KOA	Major knee surgery (2 y), comorbidities ^a	QST	NeuP ^b	56 (19 M, 37 F)	68 ± 9.3 (39-87)	NR	7.5
Cardoso <i>et al.</i> ³⁸	Community	Age 45-85 y, African American or non-Hispanic whites. ACR KOA criteria	Daily opioids use, major knee surgery, comorbidities ^a	QST	NeuP ^b	292 (36.5% M, 63.5% F)	57	NR	NR
Courtney <i>et al.</i> ³⁹	Outpatients	KOA, K-L ≥II	TKA, ligament deficit, comorbidities ^a	QST	NeuP ^b	40 (13 M, 27 F)	59.1 ± 8.3	36.9 ± 13.5	11.9 ± 9.0
Dua <i>et al.</i> ⁴⁰	Outpatients	Painful KOA, ACR OA criteria, walk pain ≥20/100, K-L ≥2	Other painful joints, comorbidities, ^a TKA	QST	NeuP ^b	42 (13 M, 29 F)	54 ± 8	NR	NR
Fingleton <i>et al.</i> ⁴¹	Outpatients	ACR KOA criteria fulfilled, NRS >3	Comorbidities, ^a antidepressant, anticonvulsant TKA, <90° of flexion	QST	NeuP ^b	40 (22 M, 18 F)	63.7 ± 10.3	NR	NR
Fitzsimmons <i>et al.</i> ⁴²	SurgeryList	> 18 y, medically safe to undergo surgery. English speaking	TKA, comorbidities ^a	S-LANSS	NeuP ^b	99 (32 M, 67 F)	65.1 ± 8.9	NR	NR
Garip <i>et al.</i> ⁴³	Outpatients	ACR KOA criteria, >1 mo knee pain	Comorbidities ^a	PDQ	NeuP Prev ^d	50 (21 M, 29 F)	50.9 ± 5.1 (41-65)	NR	NR
Graven-Nielsen <i>et al.</i> ⁴⁵	Outpatients + SurgeryList	ACR KOA criteria, >3 mo knee pain (VAS >4)	Comorbidities, ^a no pain medications (48 h)	QST	NeuP	48 (12 M, 36 F)	65 (40-86)	NR	6.6 ± 0.9
Golob <i>et al.</i> ⁴⁴	Outpatients	ACR KOA criteria, >12 mo knee pain	Major knee surgery, knee infection, RA	PDQ	NeuP Prev ^d	122 (36 M, 86 F)	64.6	NR	NR
Hendiani <i>et al.</i> ⁴⁶	Outpatients	ACR KOA criteria, >3 mo	Comorbidities, ^a history of trauma, prior surgery, use of recreational drugs (1 y)	QST	NeuP ^b	28 (4 M, 24 F)	53.2 ± 2.1 (33-70)	NR	4.0 ± 0.6 (0.5-2.1)
Hochmann <i>et al.</i> ⁴⁸	Community	Knee pain, no TKA	Inflammatory arthritis, knee surgery	mPDQ	NeuP Prev ^d	171 (39 M, 132 F)	76 (67-99)	NR	NR

(continued)

Table 1. (continued)

Study	Origin of Patients	Inclusion Criteria	Exclusion Criteria	Diagnostic Tool	Study Aim	# pts (#Knees) (M, F)	Age, Mean ± SD (Range)	BMI, Mean ± SD (Range)	Pain Duration, Mean ± SD (Range)
Hochmann et al. ⁴⁷	Outpatients + community	Symptomatic KOA x-ray confirmed OA	Chronic non-OA pain, comorbidities; ^a history of trauma or surgery	mPDQ, QST	Neup ^b	36 (57) (6 M, 30 F)	60.7 ± 6.8	29.8 (19.5-62.3)	10.1 (0.2-55.0)
Imamura et al. ⁴⁹	Surgery-List	Women, ACR KOA criteria, K-L2-4, VAS ≥4/10	Other joints OA, comorbidities ^a	QST	Neup ^b	62 (0 M, 62 F)	71.1 ± 6.6	NR	8.3 ± 6.3
Jakorinne et al. ⁵⁰	Outpatients + community	Painful KOA, K-L1-4, age > 18, Finnish speaking	Lesion at QST site, previous surgery, comorbidities, ^a analgesic	QST	Neup ^b	33	(50-70)	NR	NR
Kavchak et al. ⁵¹	Outpatients + community	K-L ≥2	TKA, comorbidities ^a	QST	Neup ^b	16 (3 M, 13 F)	52 ± 8 (39-61)	38.3 ± 7.1	4.1 ± 4.0
Kim et al. ⁵²	Surgery-List	Unilateral degenerative KOA	Inflammatory arthritis, ROM limitation > 20°, history of knee surgery, comorbidities ^a	CSI	Neup ^b	161 (22 M, 139 F)	71.2 ± 6.7 (53-85)	25.6 ± 3.2 (16.0-38.2)	7.5 ± 5.3 (0.5-25)
Kim et al. ²⁶	Surgery-List	KOA	ASA ≥III, drug or alcohol abuse, opioid (4 w), change in analgesic (2 w) obesity, spinal fusion, neurological disorders	CSI	Neup ^b	91 (0 M, 91 F)	70.2 ± 5.7	NR	NR
King et al. ⁵³	Community	Age 45-85, African American or non-Hispanic whites, ACR KOA criteria	Daily opioids use, major knee surgery, comorbidities ^a	QST	Neup ^b	209 (63 M, 146 F)	57.3 (54.8-59.5)	31.2 (27.9-35.1)	3.3 (1.0-6.0)
Koh et al. ⁷⁹	Surgery-List	Patients undergone TKA for primary knee OA	Postoperative complications, ASA > 2, centrally acting drugs, comorbidities ^a	CSI	Neup ^b	222 (21 M, 201 F)	70 (57-83)	26.4 (17.8-38.1)	NR
Kuni et al. ⁵⁴	Surgery-List	Patients undergoing TKA	Neurological and psychiatric diseases, infection of the joints, chronic low back pain	QST	Neup ^b	50 (23 M, 27 F)	66 (44-77)	NR	7
Kurien et al. ⁵⁵	Surgery-List	Chronic KOA	Hip OA, comorbidities ^a contraindication to MRI	PDQ, QST	Neup ^b	50 (20 M, 30 F)	66.4 ± 8.3	30 (27-39)	4.7 (2.9-7.2)
Lee et al. ⁵⁶	Outpatients	Painful KOA	Anxiety, pregnancy, infections, no neuropathy, no cardiovascular or AI disease	QST	Neup ^b	26 (6 M, 20 F)	59.0 ± 7.5	27.5 (24.8-32.6)	NR
Lewis et al. ⁵⁷	Surgery-List	KOA pain >3	Contraindications to MRI, neurological conditions, non-English speakers	QST	Neup ^b	29 (15 M, 14 F)	68 ± 10	31 ± 5.7	NR
Lluch Girbes et al. ⁵⁸	Outpatients	Chronic KOA pain (3 mo)	Previous joint replacement, comorbidities ^a	PDQ, QST	Neup ^b	53 (19 M, 34 F)	70.2 ± 7.4	29.9 ± 3.9	7.5 ± 6
Mesci et al. ⁵⁹	Outpatients	Age >40, knee pain, KOA according to ACR criteria	History of trauma or surgery, comorbidities ^a	PDQ, QST	Neup ^b	60 (14 M, 46 F)	62.9 ± 10.5	29.6 ± 4.9	4.5 (1-20)
Moreton et al. ²²	Outpatients	Radiographic painful KOA (>3 mo)	Inflammatory rheumatic condition, knee surgery (3 mo), non-English speakers.	PDQ, S-LANSS, QST	Neup ^b	192 (90 M, 102 F)	67 ± 10	NR	9 ± 9
Moss et al. ⁶²	Community	KOA based on ACR	Comorbidities ^a	QST	Neup ^b	23 (10 M, 13 F)	68.5 ± 8.5 (55-82)	26.9 ± 4.5	8.26 (2-10)
Moss et al. ⁶⁰	Community	Painful KOA (VAS >3/10)	Comorbidities, ^a lower limb injury or surgery	PDQ, QST	Oth ^c	80 (36 M, 44 F)	65 (50-86)	28.3 (20.3-38.3)	(2-30)
Moss et al. ⁶¹	Community	KOA based on ACR criteria, pain >4/10	Comorbidities, ^a lower limb injury or surgery	PDQ, QST	Neup ^b	130 (62 M, 68 F)	66 (50-88)	NR	NR
Othori et al. ⁶⁴	Outpatients	Knee pain > 1 mo, radiographic KOA	History of knee surgery, infection, and RA	PDQ	Neup ^b Prev ^d	92 (21 M, 71 F)	70.3 ± 8.0 (53-81)	NR	3.1 ± 0.7 (0.1-15)

(continued)

Table 1. (continued)

Study	Origin of Patients	Inclusion Criteria	Exclusion Criteria	Diagnostic Tool	Study Aim	# pts (#Knees) (M, F)	Age, Mean ± SD (Range)	BMI, Mean ± SD (Range)	Pain Duration, Mean ± SD (Range)
Othori et al. (2) ⁶³	Outpatients	Knee pain > 1 mo, radiographic KOA	Previous knee surgery, infection, or RA	PDQ	Oth ^c	89 (26 M, 63 F)	70.0 ± 8.0	NR	3.0 ± 0.7
Osgood, et al. ⁶⁵	Community	Age > 21, painful KOA, NR pain 3/10	NR	New index QST	NeuP ^b	20 (6 M, 14 F)	59.5 (30-83)	NR	11.9 ± 7
Oteo-Alvaro et al. ⁶⁶	Outpatients	Age ≥ 65 KOA (K-L 0-4)	Previous surgery, other source of pain	DN4	NeuP Prev ^d	2,167 (2,992) (762 M, 1,405 F)	73.1 ± 5.4	28.7 ± 4.0	7.3 ± 5.5
Petersen et al. ⁶⁷	SurgeryList	Severe KOA, scheduled for TKA	Fibromyalgia, RA, previous fractures	QST	NeuP	135 (51 M, 84 F)	67.6 ± 5.5 (44-89)	30.2 ± 5.2	NR
Phillips et al. ²⁵	SurgeryList	KOA	NR	PDQ	NeuP Prev ^d	96 (42 M, 54 F)	70.6 (48-89)	NR	NR
Polat et al. ⁶⁸	Outpatients	Painful KOA (>3 mo)	Previous surgery, infection, comorbidities; ^a medical treatment for NP	PDQ	NeuP Prev ^d	109 (16 M, 93 F)	62.5 ± 8.5 (44-81)	33.7 ± 6.0	4.2 ± 3.5
Power et al. ⁶⁹	SurgeryList	End-stage KOA, age > 18 English speaking	TKA, posttraumatic or inflammatory forms of arthritis	PDQ	NeuP Prev ^d	437 (184 M, 253 F)	NR	NR	NR
Pujol et al. ⁷¹	Outpatients	KOA based on ACR criteria, >44 y, knee pain > 3 mo, VAS pain 8-11	Analgesic for 3 d, stable pain, steroids (3 mo) or HA (6 mo), antidepressants or anticonvulsive, comorbidities ^a	QST	NeuP ^b	60 (17 M, 43 F)	66.7 ± 7.8	NR	NR
Radwan et al. ⁷²	Outpatients	KOA based on ACR criteria	Knee infection or surgery, comorbidities; ^a medical treatment for NP	DN4	NeuP Prev ^d	165 (319) (21 M, 144 F)	53.1	NR	39.5
Rakel et al. ⁷³	Outpatients/ community	Age 18-95, KOA	Inability to walk, change in medication (3 w); VAS ≤ 2; knee surgery, knee infection (4 w), comorbidities ^a	QST	NeuP ^b	75 (14 M, 61 F)	56 ± 1.4	36.3 ± 0.9	6 ± (3-10)
Rouille et al. ⁷⁴	Outpatients	Age ≥ 40, primary KOA, according to ACR criteria, K-L 2-3, walk VAS ≥ 40 mm	Other bone or joint diseases, comorbidities restricting knee function, contraindication to MRI, steroids (12 w), HA (26 w)	PDQ	NeuP ^b	50 (17 M, 33 F)	64.2 ± 8.6	31.2 ± 5.1	7.8 ± 2.8
Soni et al. ²³	SurgeryList	NR	NR	mPDQ, QST	NeuP ^b	24 (13 M, 11 F)	68.3 ± 8.9	NR	3.4 (1.5-9.0)
Tiendrebego et al. ⁸⁰	Outpatients	Age 40-85, KOA based on ACR criteria, VAS 3-8, non-responsive to NSAID or weak opioids	KOA with Flares, hip OA, rheumatic comorbidities, knee misalignment, steroids (3 mo) or HA (9 mo)	DN4	Oth ^c	187 (83 M, 104 F)	64.7 (63.2-66.2)	27.7 (27.0-28.4)	46.5 (37.1-56.0)
Valdes et al. ⁷⁶	Outpatients	KOA (K-L > 2), age ≥ 40	No TKR or THA	PDQ	NeuP ^b	139 (55 M, 84 F)	63.9 ± 9.2	29.4 ± 4.81	10.7 ± 9.9
Vas et al. ⁷⁵	NR	Pain, stiffness, function compromised in both knees	NR	PDQ	Oth ^c	10 (20) (1 M, 9 F)	61 ± 10.6 (49-82)	NR	NR
Wright, et al. ⁷⁷	NR	Painful KOA (VAS > 3/10)	Comorbidities; ^a lower limb injury or surgery (< 6 m)	QST	NeuP Prev ^d	80 (36 M, 44 F)	64 (50-86)	38% obese	NR
Wylde et al. ⁷⁸	SurgeryList	KOA, being pain free in their right forearm	Cognitive impairment	QST	NeuP Prev ^d	107 (56 M, 51 F)	69 ± 8.5	NR	6 (3-10)

M = males; F = females; SD = standard deviation; BMI = body mass index; KOA = knee osteoarthritis; TKA = total knee arthroplasty; MRI = magnetic resonance imaging; PDQ = PainDETECT questionnaire; ACR = American College of Rheumatology; QST = quantitative sensory testing; NR = not reported; ECG = electrocardiogram; K-L = Kellgren-Lawrence; d = days; w = weeks; DN4 = Douleur Neuropathic 4; y = years; mPDQ = modified PainDETECT questionnaire; mo = months; NRS = Numeric Rating Scale; S-LANSS = Leeds Assessment of Neuropathic Symptoms and Signs; VAS = Visual Analogue Scale; RA = rheumatoid arthritis; OA = osteoarthritis; CSI = central sensitization index; ASA = American Society of Anesthesiologists; pts = patients; Oth = Pain sensitization was documented only as baseline patient characteristic; NeuP Prev = Evaluation of the prevalence of pain sensitization in knee OA as a primary aim; FKT = Physiotherapy; IA = intra-articular; HA = hyaluronic acid; ROM = range of motion; NP = neuropathic pain; NSAID = non-steroidal antiinflammatory drugs; THA = total hip arthroplasty.

^aMajor medical, rheumatologic, neurological, or psychiatric comorbidities that may influence pain perception.

^bStudies focused on relevant features of pain sensitization but not on its prevalence.

^cPain sensitization was documented only as baseline patient characteristic.

^dEvaluation of the prevalence of pain sensitization in knee OA as a primary aim.

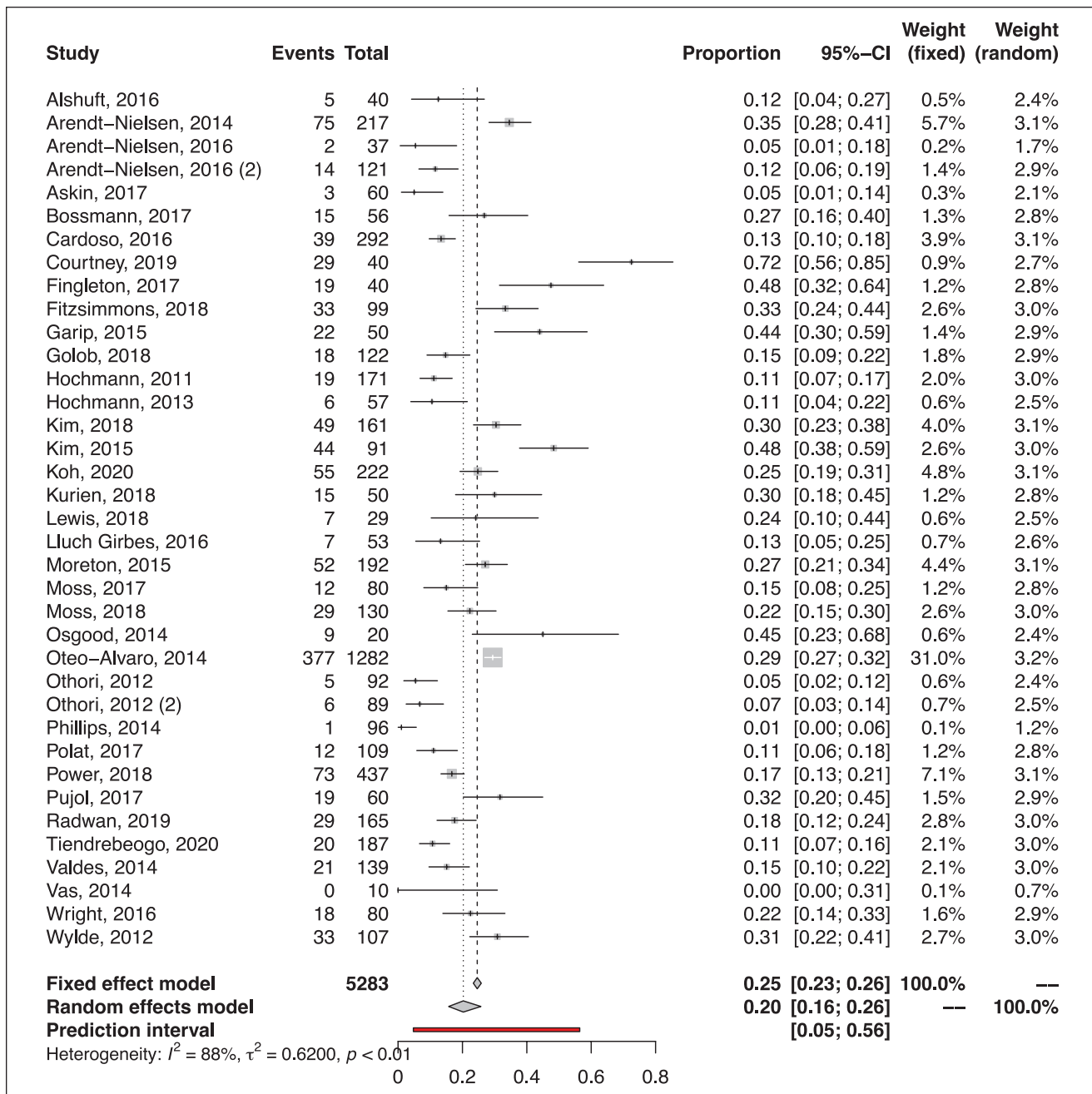


Figure 2. Prevalence of pain sensitization in the patients with knee osteoarthritis (forest plot). Both the fixed and random effect analyses are reported. The results of the random effect analysis are considered more reliable due to the documented heterogeneity in the included studies.

neuropathic pain to create 2 groups with 25 patients each. The recruitment technique was appropriate in all but 4 studies, which did not specify how patients were recruited. Only 3 out of 46 studies had an adequate sample size (estimated as at least 246 patients; please refer to “Materials and Methods” section). A complete description of the study sample was reported in 24 studies. In 6 studies, there were missing data

at follow-up, although it was not clear if this could influence the documented results. There is no standard measure to evaluate the presence of pain sensitization; thus, no study had the possibility to satisfy this criterium. All but 11 studies used a reliable measure to document the presence of pain sensitization: Only PainDETECT and QST protocols of the affected patients compared with those of healthy controls

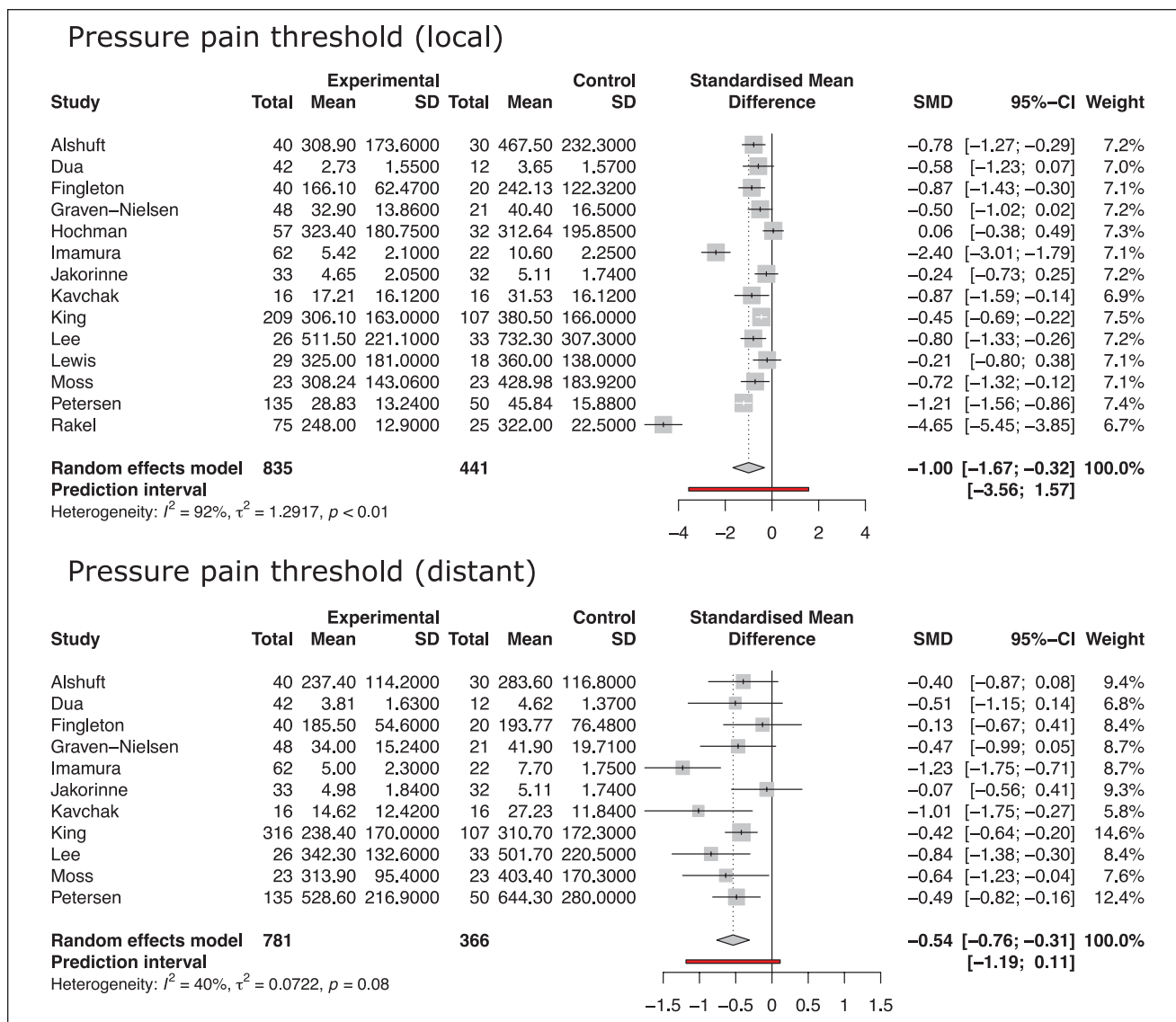


Figure 3. Forest plot of the comparisons of local and distant pressure pain threshold in patients with knee osteoarthritis and healthy controls. Results are reported as standardized mean difference (SMD). The random effect model was used.

were considered reliable because the reliability of other self-reported questionnaires has never been confirmed by the literature.^{22,81} In 15 studies, the number of patients with pain sensitization was not available; thus, their statistical analysis was considered inappropriate. Most of the confounding factors were identified and accounted for in 36 studies, excluding patients with comorbidities that may influence the prevalence of pain sensitization. None of the studies evaluated the prevalence of pain sensitization in specific sub-populations.

Discussion

The main finding of this meta-analysis is that pain sensitization has a high prevalence in knee OA, representing a

relevant component of symptoms suffered by many patients. Depending on the diagnostic tool used, the documented prevalence ranges from 10% in studies testing the decrease in HPTs to 56% in studies evaluating the reduction of CPM, underlining the differences based on the various tested pathways and, thus, the need to pursue exhaustive and standardized methods to evaluate pain sensitization.

Pain sensitization should not be overlooked when managing knee OA and its presence should always be considered to properly address this burdening condition. According to the results of this meta-analysis, up to one-fifth of patients with knee OA presents an altered pain processing mechanism that, if disregarded, may lead to treatment failure and patient dissatisfaction. Indeed, several studies have shown that the presence of a “neuropathic” component of pain in

musculoskeletal diseases may lead to an increased risk of pain chronicity and to worse outcomes after treatment.⁸²⁻⁸⁵ Patients identified as “sensitized” probably represents a sub-group of knee OA patients with a specific pain phenotype that could take advantage of a targeted approach.⁸⁶ Treatments specifically addressing pain sensitization have been developed and tested to improve the results of traditional approaches to OA.^{70,87} In particular, duloxetine, a serotonin and norepinephrine reuptake inhibitor acting on the central nervous system as analgesic drug, showed initial promising results in treating a part of the patients with pain poorly controlled with traditional analgesic drugs.^{88,89} The fact that these treatments, developed with the intention of managing the neuropathic component of pain, have also an effect in tempering knee OA pain in some patients, is often considered a proof of the involvement of pain sensitization in OA symptoms.⁹⁰ However, it is still not clear if the advantages of these approaches rely on their overall good results as analgesic treatments or on their specific effectiveness in sensitized patients, as the improvement of the evidence in this field is hindered by the difficulties in detecting pain sensitization in musculoskeletal conditions.^{90,91}

The diagnosis of pain sensitization, in the absence of a gold standard, is based on physical exam, questionnaires, and QST protocols.⁹² Questionnaires evaluate the presence of signs and symptoms, such as dull pain, tingling, prickling, and widespread diffusion of pain with allodynia, that differ from those present in patients suffering from nociceptive musculoskeletal pain.^{93,94} QST protocols can be divided into static and dynamic tests. Static tests measure the pain threshold of patients related to a specific noxious stimuli, commonly pressure, heat, or cold.⁹⁵ Dynamic tests are aimed at quantifying the active response of the nervous system to pain: CPM is estimated computing the difference between pain threshold at rest and pain threshold during a peripheral noxious stimulation⁹⁶; TS is measured as the difference between patient-reported pain severity at first and last noxious stimuli of a series of supra-threshold stimuli with a constant intensity.⁹⁷ This pool of examinations evaluates most of the features of abnormal pain processing, and the combination of these tests has been included in comprehensive protocols aimed at investigating the presence of pain sensitization.^{98,99} In this light, the meta-analysis on the comparison between knee OA patients and healthy controls confirmed the presence of a hypersensitivity state in affected patients. Nonetheless, a great variability of reported prevalence of pain sensitization in association to the different diagnostic tools used was documented not only among different trials but also when different tests were used in the same study.^{35,38}

The literature reports conflicting findings regarding the correlation between the results of the QST protocols and that of the most used questionnaires. Even though they are frequently used to evaluate the neurological involvement in

knee OA pain, such questionnaires have been developed to evaluate the presence of neuropathic-like symptoms⁹³ or to suspect a neuropathy,^{100,101} whose presence in knee OA has never been confirmed.¹⁹ Other authors also suggested that some of the questionnaires used to assess the presence of pain sensitization rely on questions that may reflect a broader definition of sensitivity which includes depression, anxiety, stress, and neuroticism.¹⁰² Moreover, while for painDETECT a correlation with an increased pain sensitivity has been documented, this was never reported for DN4 and S-LANSS, and no correlation was found for CSI, whose results appear to be mainly influenced by the psychologic profile of the patients.^{47,81} This raises questions on the suitability of available diagnostic methods, as underlined by the meta-regression, which identified the diagnostic tool used as the greatest source of heterogeneity in the meta-analysis of prevalence. In this light, new attempts to identify a new subset of individual phenotypic traits that correlate with the presence of pain sensitization are ongoing, but new research confirming the relevance of the identified factors is needed.¹⁰³

The linear meta-regression also showed that the aim of the article resulted to be significantly associated with the reported prevalence: The highest prevalence was reported by studies aimed at evaluating features of pain sensitization that were not directly related to its prevalence, an intermediate value was reported by studies specifically focused on the prevalence of pain sensitization, whereas the lowest prevalence was documented by studies where pain sensitization was only one of the outcomes reported in a trial aimed at evaluating other aspects of knee OA. The highest prevalence documented in the first group of studies could be due to selection bias: Being the aim of these studies the evaluation of a feature of pain sensitization, it could be possible that patients suspected to have hypersensitivity were more easily recruited than other patients. On the contrary, the lack of attention and, probably, of experience in evaluating pain sensitization could be the cause of the lower prevalence documented in trials that were not focused on this aspect. The meta-regression also found a tendency toward association between the documented prevalence and the category of the journal with a higher prevalence for those on orthopedic and rehabilitation, followed by articles published in pain category, in rheumatology category, and in medicine category journals. A possible explanation could be the difference among patients visited by different practitioners: Patients with more severe knee OA pain have been suggested to be more likely to be seen by an orthopedic surgeon than by a rheumatologist or a general practitioner, and greater pain severity has been previously linked to higher prevalence of pain sensitization.^{33,104,105} Finally, the meta-regression found a tendency toward the association between symptoms' duration and the prevalence of pain sensitization with an increase of the reported prevalence in

the studies, including patients with a greater symptoms' duration. Pain chronicity is considered a key factor for developing pain sensitization.¹⁰⁶ The constant noxious stimulation from the affected peripheral tissues is considered the trigger necessary to develop hypersensitivity,¹⁰⁷ and this could explain why the duration of pain was associated with a higher reported prevalence of pain sensitization. However, while these aspects are interesting insights for further investigation, the multiple meta-regression found that the only independent variable associated with the documented prevalence was the diagnostic tool used.

The meta-regression also evaluated patient-related characteristics that could explain the reported heterogeneity and identify patients that are more prone to develop pain sensitization. This could be extremely helpful to delineate a group of patients that should be tested with the available protocols that are otherwise considered too expensive and time-consuming to be used for all patients in the daily clinical practice.¹⁰⁸ Unfortunately, most of the patient-related characteristics evaluated with the meta-regression were not associated with the reported prevalence, thus hindering the possibility to identify a phenotype of patients with knee OA more prone to present pain sensitization. Patient characteristics, such as female sex and older age, or symptom characteristics, such as pain intensity, that are traditionally reported as distinctive of sensitized patients were not found to be associated with a higher prevalence of pain sensitization in knee OA.^{109,110} Moreover, some factors that may be related to the presence of pain sensitization, such as the degree of knee OA, could not be analyzed in the meta-regression due to the paucity of data available in the included studies.

The impossibility to perform a characterization of sensitized patients represents a limitation of the current literature that is reflected in the present meta-regression. Some of the included trials lacked data on patient characteristics that could have been useful to strengthen this evaluation. This is indicative of the unyielding need to improve the quality of the existing literature on the topic, as also underlined by the evaluation of the risk of bias of the included studies. Moreover, even though some of the sources of heterogeneity were identified and accounted for, there was still a high residual heterogeneity in the results of this meta-analysis. Besides this, it should be noted that the reliability of questionnaires and QST protocols in determining the presence of pain sensitization is still debated. This limited the precision of estimate of the exact prevalence of pain sensitization. Regarding the comparison of healthy subjects and knee OA patients, meta-analyses on thermal pain thresholds and dynamic QST could have been useful to provide more interesting insight on the topic. Unfortunately, the literature lacks studies providing data on this comparison and, with the number of studies available (3 on HPTs, 2 on CPTs, and none on dynamic QST), a meta-analysis could have led to

misleading conclusions. Moreover, the recent literature reported changes in cerebrospinal fluid composition that may be helpful in characterizing knee OA patients with pain sensitization, but the evaluation of these issues was besides the focus of this meta-analysis that was focused on altered pain perception.¹⁸ Finally, in the meta-analysis comparing PPT of affected patients and healthy controls, the use of healthy controls without knee OA or pain as comparators does not allow for clear understanding of whether structural pathology versus pain symptomatology (or both) are relevant for the development of pain sensitization.

Nonetheless, this meta-analysis was able to document that pain sensitization plays a key role in OA pain and should be the focus of more research efforts to further understand how to evaluate and address this component in the symptoms of patients affected by knee OA. Knee OA pain presents features that are consistent with a significant degree of pain sensitization. There is a high heterogeneity in the reported results, mainly based on the diagnostic tool used. The identification of the best methods to detect pain sensitization is warranted to correctly evaluate and manage symptoms of patients affected by knee OA.

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Ethical Approval

No ethical approval needed for the present study.

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