Systematic review

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Altered pain processing and sensitisation is evident in adults with patellofemoral pain: a systematic review including meta-analysis and meta-regression

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Abstract

Background and aims: Previous systematic reviews have reported manifestations of pain sensitisation as a feature of painful knee disorders, in particular osteoarthritis, with moderate evidence for pain sensitisation in patellofemoral pain (PFP). However, despite past studies recruiting female mostly adolescent PFP patients, it is unclear if sex or age plays a role. Investigation is required to determine if altered pain processing is a key feature of PFP and if a subgroup of patients is at an increased risk to help provide targeted management. The primary aim of this systematic review was to examine evidence investigating pain processing in PFP. Secondary aims were to evaluate the relationship between pain processing and (1) sex, (2) age and (3) symptom duration.

Methods: The protocol was prospectively registered with PROSPERO (CRD42019129851). PubMed, CINAHL, Web of Science and EMBASE were systematically searched from inception to April 2019 for studies investigating pain processing in PFP patients compared to controls using quantitative sensory testing. Each included paper was assessed for methodological quality using a modified version of Downs and Black. Means and standard deviations were extracted to calculate standardised mean differences (SMD) and 95% confidence intervals (95% CI). Where possible meta-analysis and meta-regression were performed using a random effects model.

Results: Eleven studies were identified, two medium and nine high quality. Meta-analysis indicates moderate evidence for decreased pressure pain thresholds (SMD −0.68, 95% CI −0.93 to −0.43), increased tactile detection thresholds (SMD 1.35, 95% CI 0.49–2.22) and increased warmth detection thresholds (SMD 0.61, 95% CI 0.30–0.92) in PFP patients compared to controls. Secondary analysis indicates moderate evidence for decreased pressure pain thresholds in female compared to male patients (SMD −0.75, 95% CI −1.34 to −0.16). Meta-regression indicates a moderate correlation between decreasing local and distal pressure pain thresholds and decreasing patient age (local $R^2 = 0.556$, $p = 0.0211$; distal $R^2 = 0.491$, $p = 0.0354$) but no correlation with symptom duration ($p > 0.05$).

Conclusions: Evidence from this systematic review with meta-analysis and meta-regression appears to suggest the presence of altered pain processing and sensitisation in patients with PFP with increased sensitivity indicated in female patients and younger patients.

Implications: With evidence of altered pain processing and sensitisation in PFP, it may be beneficial for clinicians to consider management approaches that aim specifically at adressing neuropathic pain, for example neuroscience education, to improve patients outcomes. With female patients and younger patients indicated as experiencing greater degree of sensitivity, this may be a good demographic to start screening for sensitisation, in order to better identify and treat those most affected.

Keywords: patellofemoral pain syndrome; pain processing; sensitisation; quantitative sensory testing.

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1 Introduction

Patellofemoral pain (PFP) is a challenging clinical condition seen regularly in primary and secondary care settings, with prevalence reported to be 22.7% in the general population [1–3]. PFP is characterised by insidious onset anterior or retropatellar knee pain that is exacerbated by activities associated with patellofemoral joint loading such as squatting, kneeling, stair ambulation, running

and jumping [4]. Symptoms often result in reduced participation in both activities of daily living and sports, with many experiencing recurrent or persistent pain [5, 6]. Long-term, only one in three persons with PFP are pain free after 12 months of treatment, with the potential risk of patellofemoral joint osteoarthritis development in later life in those with persistent pain [7–11]. With such chronicity, development of a greater understanding as to why pain persists is crucial to further current literature.

Despite the reported high prevalence and persistence of PFP there is little consensus concerning its aetiology [12]. Previous research often focusses on biomechanical deficits despite pain presentations varying considerably between patients and emerging evidence to suggest the contribution of neuropathic pain components [13–23]. Prolonged nociceptive firing may lead to manifestations of both peripheral sensitisation (increased responsiveness and reduced threshold of the nociceptive neurones in the periphery to stimulation of their receptive field) and central sensitisation (increased responsiveness of the nociceptive neurones in the central nervous system to their normal or subthreshold afferent input) causing pain hypersensitivity in patients [24, 25].

No tool currently exists to directly measure pain processing, with evidence of sensitisation identified through the use of quantitative sensory testing (QST) [25, 26]. QST uses a variety of non-noxious and noxious stimuli to evaluate the function of individual sensory responses, both peripherally and centrally [27, 28]. Pressure pain thresholds (PPTs) are commonly used, reflecting the function of myelinated Aβ-fibres and Aδ-fibres both around the painful knee (local hyperalgesia) and at remote sites (distal hyperalgesia) [28, 29]. Conditioned pain modulation (CPM) and temporal summation (TS) are two psychophysical tests to assess anti-nociceptive and pro-nociceptive elements of central sensitisation respectively [15]. CPM is thought to reflect the descending endogenous inhibitory system, a key contributor to persistent pain, through the net sum of inhibition and facilitation which normally allows painful stimuli to inhibit other painful stimuli [27, 30]. TS is related to "wind-up" of central nervous system neurones producing an increasing response to repeated C-fibre nociceptive input of the same intensity [27].

Previous systematic reviews by Fingleton et al. [28] and subsequently de Oliveira Silva et al. [31] have reported manifestations of pain sensitisation in knee osteoarthritis and painful knee disorders, respectively. Although the review by de Oliveira Silva et al. [31] explored pain sensitisation in PFP, it also investigated knee osteoarthritis, patellar tendinopathy and post-meniscectomy, lacking specificity to PFP with new publications emerging since this review was published [15, 32]. It remains unclear if females and males with PFP are affected by altered pain processing to the same degree or if changes are related to factors such as age or symptom duration. Addressing these knowledge gaps may help to determine if a particular patient demographic is greater affected allowing implementation of a more targeted management approach.

The primary aim of this systematic review was to examine evidence investigating pain processing in PFP. Secondary aims were to evaluate the relationship between pain processing and (1) sex, (2) age and (3) symptom duration.

2 Methods

This review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [33] and was prospectively registered with PROSPERO (CRD42019129851).

2.1 Search strategy

PubMed, CINAHL, Web of Science and EMBASE were systematically searched by one reviewer (CB) from inception to April 2019 using a comprehensive and reproducible search strategy outlined in Table 1. Each database was searched using two groups of keyword combinations,

Table 1: Search strategy.

Group one keywords	AND	Group two keywords
Patellofemoral pain OR PFP OR patellofemoral pain syndrome OR patellofemoral syndrome OR patellofemoral joint pain OR anterior knee pain OR retropatellar pain OR peripatellar pain OR parapatellar pain OR chondromalacia patellae		Pain sensitisation OR central sensitisation OR peripheral sensitisation OR hyperalgesia OR central hypersensitivity OR allodynia OR pain processing OR pain modulation OR pain threshold OR pressure pain threshold OR pain pathophysiology OR somatosensory OR neuropathic pain OR neuropathic-like pain OR central pain OR peripheral pain OR central nervous system sensitisation OR peripheral nervous system sensitisation

relating to PFP and pain processing, to identify all relevant literature. The electronic search was complemented by hand searching the reference lists of retrieved articles and the completion of citation tracking using Google Scholar.

2.2 Inclusion and exclusion criteria

Studies were eligible for inclusion if they investigated pain processing using QST in PFP participants compared to controls. QST measures included pressure pain thresholds, tactile detection thresholds, thermal detection thresholds (warmth and cold detection thresholds), vibration detection thresholds, CPM and TS. PFP participants were required to meet the diagnostic criteria of insidious onset anterior or retropatellar knee pain, exacerbated by activities associated with patellofemoral joint loading including squatting, kneeling, stair ambulation, running and jumping [4]. Mixed-sex and single-sex participant groups of all ages were included. Studies were required to involve only human subjects, full-text cohort, cross-section or case-control studies and published in peer-review journals in the English language.

Studies were excluded if they did not contain a control group or included participants with additional knee pathologies (including internal derangement or ligamentous instability) or previous knee surgery. The exclusion criteria also ruled out unpublished, non-peer reviewed, animal and studies not in the English language, in addition to case studies, reviews, letters, opinion articles, conference proceedings and thesis papers.

2.3 Review process

Studies identified through the search strategy were downloaded into Endnote X7.5 (Thomson Reuters Cooperation, New York, NY, USA), with duplicates subsequently deleted. Titles and abstracts were screened for eligibility with the full-texts of potentially relevant articles obtained for further review by one reviewer (CB). Full-texts were screened where eligibility could not be determined by the abstract alone, with any uncertainties resolved at a consensus meeting with a second reviewer (SL).

2.4 Quality assessment

Study methodological quality was evaluated using a modified version of the Downs and Black checklist [34] and a PFP diagnostic checklist [35]. Downs and Black [34] is a validated tool that is widely used in literature, with good reliability and validity reported [36, 37]. The modified version contained 16 criteria following the removal of criteria 4, 8, 9, 13, 14, 17, 19, 23, 24, 26 and 27 which have previously been deemed inappropriate for non-randomised studies [38]. As described by Hootman et al. [39], studies were scored out of a maximum of 17 points, with the score converted into a percentage to allow banding into low (≤33.3%), moderate (33.4–66.7%) or high (≥66.8%) quality. Studies scoring below 50% were excluded from subsequent analysis to prevent the inclusion of studies with a high risk of bias [35]. The PFP diagnostic checklist is a seven-item scale developed by Barton et al. [35] that identifies key inclusion and exclusion criteria for the diagnosis of PFP. A higher score indicates a higher number of criteria having been reported thus a more comprehensive diagnosis made. Both quality assessment tools were completed by two independent reviewers (CB and BN) with any discrepancies resolved at a consensus meeting. A third reviewer (SL) was available but not required.

2.5 Data extraction

Study details (primary author, year, study design), participant demographics (sample size, sex, age, height, weight, BMI), symptom duration and QST measures of pain processing (PPTs, tactile detection thresholds, vibration detection thresholds, thermal detection thresholds, CPM, TS), both locally and distally, were extracted and analysed from each study. Means and standard deviations were sourced from the papers or through contacting the authors via email. One study [16] presented data as median and interquartile range which were converted into mean and standard deviation following guidance from the Cochrane Handbook [40].

2.6 Data analysis

Data analysis was performed using the review manager software package RevMan 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Meta-analysis was completed where a minimum of two studies recorded comparable QST measures in PFP cases and controls. Data which could not be pooled was summarised in a narrative format and presented within tables. Means and standard deviations were inputted into RevMan to allow calculation of standardized mean difference (SMD) and 95% confidence interval (95% CI). SMDs were calculated for both pooled and unpooled data as all studies presented data as continuous scale.

A random effects model was used for meta-analysis. Calculated SMDs were categorised as small (≤0.59),

medium (0.60–1.19) or large (≥1.20) effect sizes, as recommended by Hume et al. [41]. The level of statistical heterogenicity for pooled data was established using χ^2 and I^2 statistics with the level of significance set at $p < 0.05$. PPT locations were categorised into local and distal sites, with the following definitions constructed to standardize analysis. Local was defined as either the most painful site reported at the patella or the site closest to the central patella, since this is thought to be the most prevalent site of pain in PFP [23]. Distal was defined as the site most anatomically distant from the primary area of pain [28].

Levels of evidence were established for each finding with the definitions based on the van Tulder Criteria [42].

(i) Strong: results derived from multiple studies, including at least two HQ studies, which are statistically homogenous ($I^2 < 50\%$).
(ii) Moderate: results derived from multiple studies, including at least one HQ study, which are statistically heterogeneous ($I^2 > 50\%$); or from multiple LQ studies which are statistically homogenous ($I^2 < 50\%$).
(iii) Limited: results derived from multiple LQ studies which are statistically heterogeneous ($I^2 > 50\%$); or from one HQ study.
(iv) Very limited: results derived from one LQ study.
(v) Conflicting: insignificant results derived from multiple statistically heterogeneous studies ($I^2 > 50\%$).

Initial planned analysis was to consider the relationship between PPTs before and after treatment, however, due to a paucity of studies presenting data for both time points this analysis was not possible. Instead, a random effects meta-regression was performed to explore the relationship between the SMDs of individual studies PPTs and both age and symptom duration. Meta-regression was completed using the comprehensive analysis and graphic software programme Prism 8.1.0 (GraphPad, San Diego, CA, USA). An α level was set a priori at <0.05. Calculated correlation coefficients (R^2) were categorised as negligible (0.00–0.10), weak (0.10–0.39), moderate (0.4–0.69), strong (0.7–0.89) and very strong (0.90–1.00) correlations, as outlined by Schober et al. [43].

3 Results

3.1 Search strategy

The results of the database searches are displayed in Fig. 1. The search identified 3,286 relevant papers and following the deletion of duplicates, 2,689 papers remained. After subsequent title and abstract screening, 21 papers remained and full-text assessment for eligibility identified 11 studies meeting the inclusion criteria [15–23, 32, 44]. The most common reasons for exclusion were a lack of specificity to PFP or the absence of a control group.

3.2 Study characteristics

Study characteristics are outlined in Table 2. All 11 included studies investigated pain processing in PFP patients compared to controls using QST measures. Three studies were case-control [18, 23, 32], six were cross-sectional [15, 19–22, 44] and two were cohort [16, 17].

3.3 Quality assessment

The results of the Downs and Black checklist [34] and PFP diagnostic checklist [35] are presented in Tables 3 and 4. The Downs and Black scores ranged from 64.7% [16, 18] to 88.2% [20–23], with nine studies rated high quality (HQ) [15, 17, 19–23, 32, 44] and two studies rated medium quality (MQ) [16, 18]. All studies exceeded the 50% threshold for inclusion. The most common reasons for methodological compromise were lack of detail concerning the population characteristics, lack of assessor blinding and inadequate adjustment for confounders. The PFP diagnostic checklist scores ranged from 3/7 points [17] to 7/7 points [21, 22, 32, 44]. Commonly, studies did not provide a clear definition of the location of pain or state that pain should be of insidious onset, unrelated to trauma.

3.4 Quantitative sensory testing measures

Data pooling for meta-analysis was possible for PPTs, tactile detection thresholds and thermal detection thresholds with forest plots displayed in Figs. 2–4, respectively. Results that could not be pooled are summarised in a narrative format in Table 5.

3.4.1 Pressure pain thresholds

Nine studies (8 HQ [15, 19–23, 31, 44] and 1 MQ [18]) assessed local and distal PPTs using handheld algometry (Fig. 2). Moderate evidence (8 HQ [15, 19–23, 31, 44] and 1 MQ [18]) of medium effect indicates decreased PPTs locally in PFP patients compared to controls (n = 567, SMD −0.80, 95% CI −1.21 to −0.39, $p = 0.0001$; $I^2 = 80\%$, $p < 0.00001$). Moderate

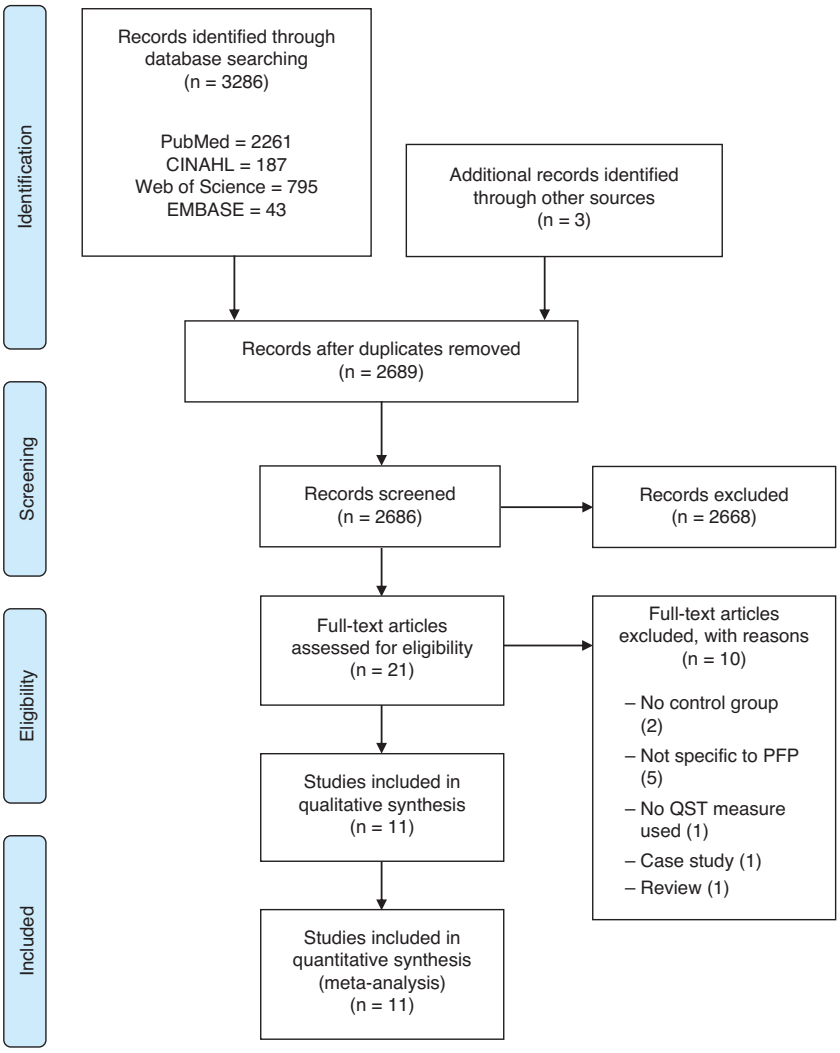

Fig. 1: PRISMA flow diagram.

evidence (8 HQ [15, 19–23, 31, 44] and 1 MQ [18]) of small effect indicates decreased PPTs distally in PFP patients compared to controls (n = 567, SMD −0.55, 95% CI −0.85 to −0.25, $p = 0.0003$; $I^2 = 64\%$, $p = 0.0004$). Overall, moderate evidence of medium effect indicates decreased PPTs in PFP patients compared to controls (n = 567, SMD −0.68, 95% CI −0.93 to −0.43, $p < 0.00001$; $I^2 = 75\%$, $p < 0.00001$).

3.4.2 Tactile detection thresholds

Three studies (1 HQ [17] and 2 MQ [16, 18]) assessed local tactile detection thresholds with two studies also assessing distal tactile detection thresholds (1 HQ [17] and 1 MQ [16]) using monofilament pressure. Moderate evidence (1 HQ [17] and 2 MQ [16, 18]) of large effect indicates increased tactile detection thresholds locally in PFP patients compared to controls (n = 225, SMD 1.67, 95% CI 0.33–3.01, $p = 0.01$; $I^2 = 94\%$, $p \leq 0.00001$). Moderate evidence (1 HQ [17] and 1 MQ [16]) of medium effect indicates increased tactile detection thresholds distally in PFP patients compared to controls (n = 225, SMD 0.82, 95% CI 0.46–1.17, $p < 0.00001$; $I^2 = 16\%$, $p = 0.27$). Overall, moderate evidence of large effect indicates increased tactile detection thresholds in PFP patients compared to controls (n = 225, SMD 1.35, 95% CI 0.49–2.22, $p = 0.002$; $I^2 = 93\%$, $p < 0.00001$).

3.4.3 Thermal detection thresholds

Two studies (1 HQ [17] and 1 MQ [16]) assessed warmth detection thresholds (WDTs) and cold detection thresholds (CDTs) using an adjustable thermal stimulator. Moderate evidence (1 HQ [17] and 1 MQ [16]) of medium effect indicates increased WDTs in PFP patients compared to controls (n = 185, SMD 0.61, 95% CI 0.30–0.92, $p = 0.0001$;

Table 2: Study characteristics.

Primary author, year, study design	Sample size (female:male)		Mean age ± SD (years)		Mean height ± SD (m)		Mean weight ± SD (kg)		Mean BMI ± SD (kg/m²)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Bartholomew, 2019, case-control [32]	11:2	10:10	30.0[a]	23.0[a]	1.69 ± 0.09	1.74 ± 0.09	68.9 ± 9.27	71.1 ± 15.5	23.9 ± 2.14	23.1 ± 2.83
Holden, 2018, cross-sectional [15]	36:0	29:0	22.8 ± 1.1	23.1 ± 1.2	1.69 ± 0.08	1.67 ± 0.06	69.2 ± 13.8	63.3 ± 11.1	24.1 ± 4.1	22.7 ± 4.1
Jensen, 2007, cohort [16]	16:9	12:11	32.2[a]	29.1[a]	NR	NR	NR	NR	23.8[a]	23.4[a]
Jensen, 2008, cohort [17]	35:56	12:11	31.2[a]	29.1[a]	NR	NR	NR	NR	25.3[a]	23.4[a]
Noehren, 2016, case-control [18]	20:0	20:0	23.2 ± 5.6	22.7 ± 5.0	1.64 ± 0.09	1.65 ± 0.06	67.2 ± 9.3	60.5 ± 8.0	NR	NR
Pazzinatto, 2016, cross-sectional [19]	20:0	20:0	25.6 ± 4.1	27.0 ± 5.6	1.63 ± 0.06	1.62 ± 0.04	58.3 ± 6.9	60.0 ± 7.4	NR	NR
Pazzinatto, 2017, cross-sectional [20]	38:0	33:0	21.6 ± 2.6	22.4 ± 3.5	1.64 ± 0.06	1.65 ± 0.10	61.9 ± 9.9	62.3 ± 10.6	NR	NR
Rathleff, 2013, cross-sectional [21]	57:0	22:0	17.3 ± 1.1	17.1 ± 0.9	1.68 ± 0.05	1.69 ± 0.05	58.5 ± 6.7	60.6 ± 9.0	20.5 ± 1.9	21.4 ± 3.1
Rathleff, 2016, cross-sectional [22]	20:0	20:0	20.0[a]	20.5[a]	1.70 ± 0.05	1.69 ± 0.05	63.8 ± 8.3	61.7 ± 7.4	NR	NR
Rathleff, 2017, cross-sectional [44]	23:10	22:10	28.5 ± 5.3	27.1 ± 5.2	1.69 ± 0.11	1.70 ± 0.09	69.7 ± 16.3	63.9 ± 13.1	24.2 ± 3.6	21.9 ± 3.0
van der Heijden, 2018, case-control [23]	35:29	41:29	23.4 ± 7.0	23.1 ± 5.9	NR	NR	NR	NR	23.6 ± 3.8	22.3 ± 3.0

SD = standard deviation; BMI = body mass index; NR = not recorded; [a]no SD value provided.

Table 3: Downs and Black quality assessment.

Primary author, year	1	2	3	5	6	7	10	11	12	15	16	18	20	21	22	25	Total score (out of 17)	Percentage score	Quality band
Bartholomew, 2019 [32]	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	14	82.4	HQ
Holden, 2018 [15]	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	14	82.4	HQ
Jensen, 2007 [16]	1	1	1	0	1	1	0	1	1	0	1	1	0	1	0	1	11	64.7	MQ
Jensen, 2008 [17]	1	1	1	0	1	1	0	1	1	0	1	1	1	1	0	1	12	70.6	HQ
Noehren, 2016 [18]	1	1	1	1	1	1	1	0	0	0	1	1	1	0	0	1	11	64.7	MQ
Pazzinatto, 2016 [19]	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	14	82.4	HQ
Pazzinatto, 2017 [20]	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	15	88.2	HQ
Rathleff, 2013 [21]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	15	88.2	HQ
Rathleff, 2016 [22]	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	15	88.2	HQ
Rathleff, 2017 [44]	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	14	82.4	HQ
van der Heijden, 2018 [23]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	15	88.2	HQ

1 = hypothesis/aim/objective clearly described; 2 = main outcomes clearly described in introduction or methods section; 3 = characteristics of included patients clearly described; 5 = distributions of principal confounders in each group to be compared clearly described; 6 = main findings clearly described; 7 = estimates for random variability for main outcomes provided; 10 = actual probability values reported for main outcomes; 11 = subjects representative of entire population from which they were recruited; 12 = subjects prepared to participate representative of entire population from which they were recruited; 15 = blinding of those measuring main outcomes; 16 = any results based on "data dredging" made clear; 18 = appropriate statistical tests used to assess the main outcomes; 20 = accurate (valid and reliable) main outcome measures used; 21 = cases and controls recruited from same population; 22 = cases and controls recruited over the same time period; 25 = adequate adjustment for confounders in analyses from which main findings drawn; UTD = unable to determine (scores 0); HQ = high quality; MQ = medium quality.

Table 4: PFP diagnostic checklist.

Primary author, year	Inclusion items			Exclusion items				Total score (out of 7)
	1	2	3	4	5	6	7	
Bartholomew, 2019 [32]	1	1	1	1	1	1	1	7
Holden, 2018 [15]	1	1	1	0	0	0	1	4
Jensen, 2007 [16]	1	1	1	1	1	1	0	6
Jensen, 2008 [17]	0	0	0	1	1	1	0	3
Noehren, 2016 [18]	0	0	0	1	1	1	1	4
Pazzinatto, 2016 [19]	0	1	1	1	1	1	1	6
Pazzinatto, 2017 [20]	0	1	1	1	1	1	1	6
Rathleff, 2013 [21]	1	1	1	1	1	1	1	7
Rathleff, 2016 [22]	1	1	1	1	1	1	1	7
Rathleff, 2017 [44]	1	1	1	1	1	1	1	7
van der Heijden, 2018 [23]	0	0	1	1	1	0	1	4

1 = clear definition of location; 2 = insidious onset unrelated to trauma; 3 = symptoms consistent with diagnosis; 4 = previous knee surgery; 5 = internal derangement; 6 = ligamentous instability; 7 = other sources of anterior knee pain.

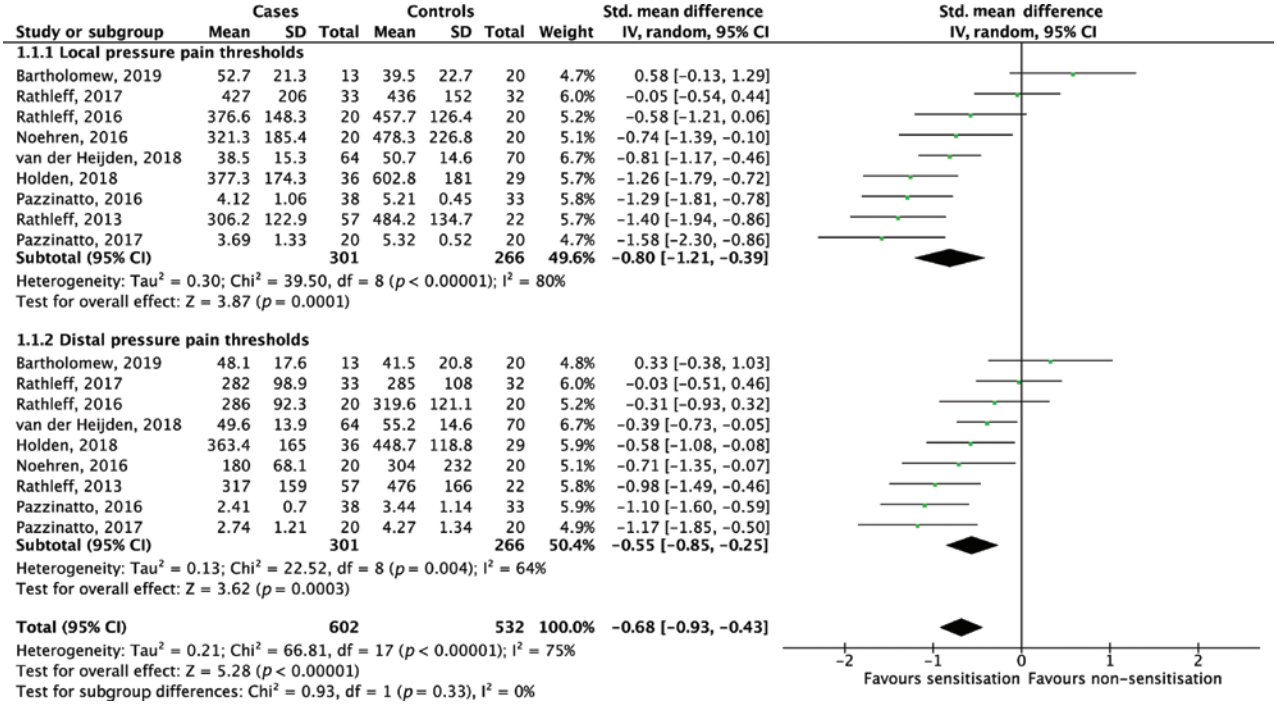

Fig. 2: Meta-analysis of local and distal pressure pain thresholds.

$I^2 = 0\%$, $p = 0.85$). Moderate evidence (1 HQ [17] and 1 MQ [16]) indicates no significant difference in CDTs in PFP cases compared to controls.

3.4.4 Vibration detection thresholds

One study (HQ [17]) assessed local vibration detection thresholds using a handheld vibrameter but only testing the painful and contralateral knee of patients and not controls. Very limited evidence (1 HQ [17]) indicates increased vibration detection thresholds in the painful compared to contralateral knee of patients (n = 91, painful knee median 1.9 µm, IQR 1.3–2.7; contralateral knee median 1.8 µm, IQR 1.0–2.2, $p = 0.003$). Twelve percent of patients reported an uncomfortable sensation descending distally in the leg when testing the vibration detection threshold on the painful side which was not experienced contralaterally.

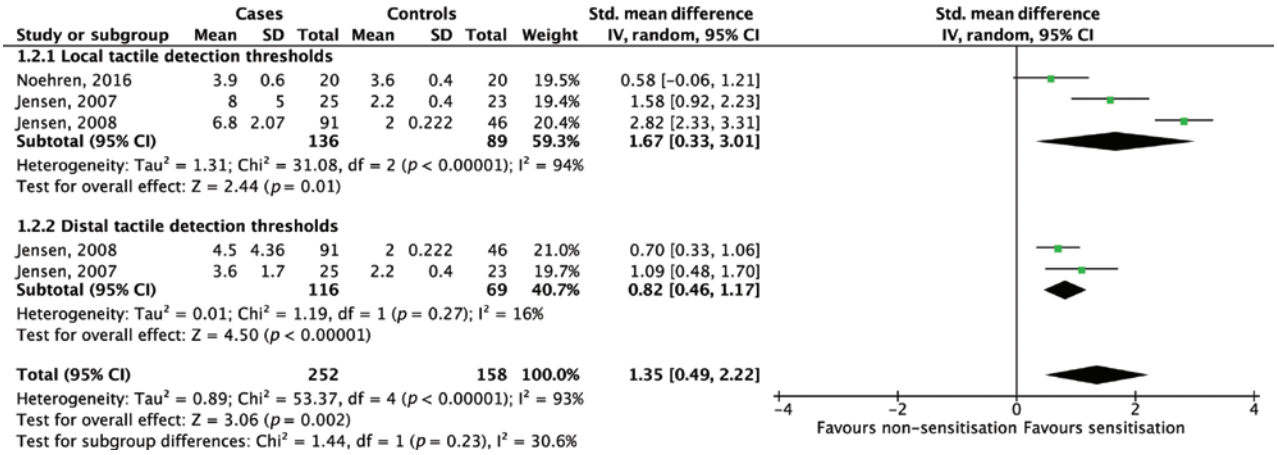

Fig. 3: Meta-analysis of local and distal tactile detection thresholds.

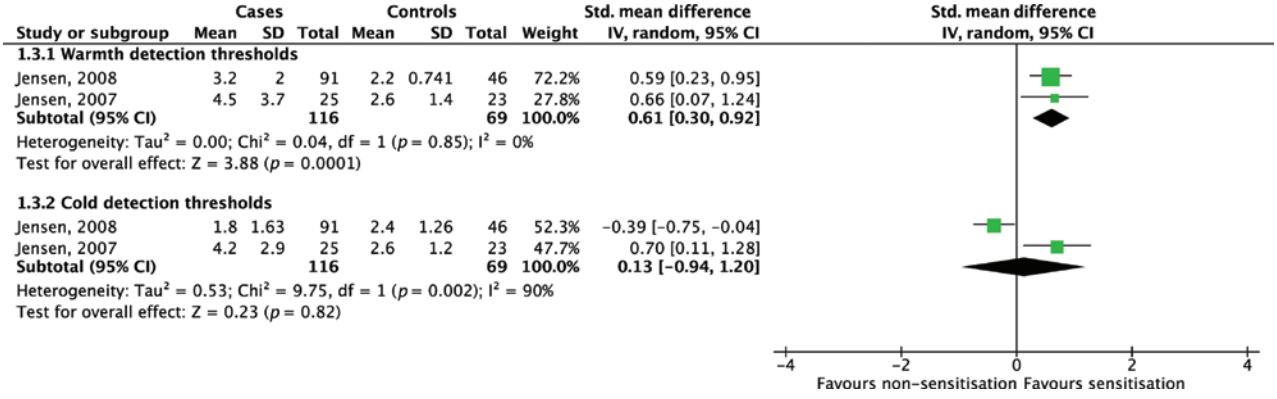

Fig. 4: Meta-analysis of warmth and cold detection thresholds.

3.4.5 Conditioned pain modulation

Three studies (3 HQ [15, 22, 44]) assessed CPM by measuring the change in pressure tolerance threshold (PTT) and pressure detection thresholds (PDT) from baseline to application of a painful stimulus. Different methodological approaches were utilised with Holden et al. [15] and Rathleff et al. [15, 22] using cuff algometry to induce pain and Rathleff et al. [44] using cold water immersion. Holden et al. [15] reported no significant difference in CPM between current-PFP patients compared to controls (n = 65, effect size Cohen's d = 0.4, 95% CI −0.1–0.5, $p > 0.05$). However, CPM effect was found to be reduced in current-PFP patients compared to recovered-PFP patients (n = 58, effect size Cohen's d = 0.7, 95% CI 0.2–1.3, $p < 0.05$). Rathleff et al. [22] reported a reduced CPM effect, based on PTTs, in PFP patients compared to controls (n = 40, percentage difference = 78%, 95% CI 4–151, $p < 0.04$). Similarly, results showed a reduced CPM effect, based on PDTs, in PFP patients compared to controls (n = 40, percentage difference = 20%, 95% CI 1–39%, $p < 0.04$) [22]. Rathleff et al. [44] reported no significant difference in CPM between PFP patients compared to controls (n = 65, $F(1,189) = 0.39$, $p = 0.89$).

3.4.6 Temporal summation

Two studies (2 HQ [15, 22]) assessed TS by delivering 10 cuff pressure stimuli at the level of the PTT with pain intensity rated using an electronic visual analogue scale. Holden et al. [15] reported that the current-PFP patients had a facilitated TS effect compared to controls (n = 65, mean difference 0.8 cm, 95% CI 0.3–1.4, $p < 0.01$). A similarly facilitated TS effect was identified in recovered-PFP patients compared to controls (n = 51, mean difference 0.7 cm, 95% CI 0.08–1.4, $p < 0.05$) with no significant difference between the current-PFP and recovered-PFP patients (n = 58, mean difference 0.1 cm, 95% CI −0.7 to 0.6, $p = 0.5$) [15]. Rathleff et al. [22] reported no significant difference in

Table 5: Main findings of each study.

Primary author, year	Peripheral sensitisation measures	Central sensitisation measures	Results summary
Bartholomew, 2019 [32]	1. PPTs using pressure algometry at six sites – five local (four peripatellar, one ipsilateral tibialis anterior) and one distal (contralateral tibialis anterior)	NR	1. No significant difference in PPTs in PFP patients compared to controls
Holden, 2018 [15]	1. PPTs using pressure algometry at three sites – two local (centre of patella, ipsilateral tibialis anterior) and one distal (contralateral lateral epicondyle)	2. CPM provoked by cuff-induced pain to arm. Change in cuff PDT and PTT recorded before and during stimulus 3. TS using computer-controlled cuff algometry to lower leg	1. Significantly decreased PPTs in PFP patients compared to controls 2. No significant difference in CPM in current-PFP patients compared to controls. Significantly decreased CPM effect in current-PFP patients compared to recovered-PFP patients 3. Significantly increased TS effect in both current-PFP and recovered-PFP patients compared to controls
Jensen, 2007 [16]	1. TDTs using von Frey monofilaments at two sites (most painful area of knee and same site contralaterally) 2. ThDTs (WDT, CDT) using computer-controlled thermotesting at two sites (most painful area of knee and same site contralaterally)	NR	1. Significantly increased TDTs in PFP patients compared to controls 2. Significantly increased WDTs in PFP patients compared to controls. Significantly increased CDTs in PFP patients compared to controls
Jensen, 2008 [17]	1. TDTs using von Frey monofilaments at two sites (most painful area of knee and same site contralaterally) 2. ThDTs (WDT, CDT) using computer-controlled thermotesting at two sites (most painful area of knee and same site contralaterally) 3. VDTs using a handheld vibrameter at two sites bilaterally (patella and medial malleolus)	NR	1. Significantly increased TDTs in PFP patients compared to controls 2. Significantly increased WDTs in PFP patients compared to controls. Significantly decreased CDTs in PFP patients compared to controls 3. Significantly increased VDTs in painful knee compared to non-painful knee of PFP patients. No significant difference at medial malleolus site
Noehren, 2016 [18]	1. PPTs using pressure algometry at three sites – two local (centre of patella, lateral retinaculum) and one distal (right lateral epicondyle of elbow) 2. TDTs using Semmes-Weinstein monofilaments at two sites (central patella, lateral retinaculum)	NR	1. Significantly decreased PPTs at all sites in PFP patients compared to controls 2. Significantly increased TDTs at the central patella site in PFP patients compared to controls. No significant difference at lateral retinaculum site
Pazzinatto, 2016 [19]	1. PPTs using pressure algometry at five sites – four local (all peripatellar) and one distal (contralateral upper limb)	NR	1. Significantly decreased PPTs at all local sites in PFP patients compared to controls. No significant difference at distal site

Table 5 (continued)

Primary author, year	Peripheral sensitisation measures	Central sensitisation measures	Results summary
Pazzinatto, 2017 [20]	1. PPTs using pressure algometry at five sites – four local (all peripatellar) and one remote (contralateral upper limb)	NR	1. Significantly decreased PPTs at all sites in PFP patients compared to controls
Rathleff, 2013 [21]	1. PPTs using pressure algometry at five sites locally (four peripatellar, one ipsilateral tibialis anterior)	NR	1. Significantly decreased PPTs at all sites in PFP patients compared to controls
Rathleff, 2016 [22]	1. PPTs using pressure algometry at three sites – two local (central patella, ipsilateral tibialis anterior) and one distal (contralateral lateral epicondyle of elbow)	2. CPM provoked by cuff-induced pain to arm. Change in cuff PDT and PTT recorded before and during stimulus 3. TS using computer-controlled cuff algometry to lower leg	1. Significantly decreased PPTs at all sites in PFP patients compared to controls 2. No significant difference in CPM in PFP patients compared to controls 3. No significant difference in TS in PFP patients compared to controls
Rathleff, 2017 [44]	1. PPTs using pressure algometry at three sites – two local (central patella, ipsilateral tibialis anterior) and one distal (contralateral lateral epicondyle of elbow)	2. CPM provoked by cold water immersion of hand. Change in PPT recorded before and after stimulus	1. No significant difference in PPTs in PFP patients compared to controls 2. No significant difference in CPM in PFP patients compared to controls
van der Heijden, 2018 [23]	1. PPTs using pressure algometry at three sites – one local (most painful area of knee) and two distal (same site on contralateral knee, contralateral dorsolateral midshaft of forearm)	NR	1. Significantly decreased PPTs at all sites in PFP patients compared to controls

PPT = pressure pain threshold; NR = not recorded; PFP = patellofemoral pain; CPM = conditioned pain modulation; PDT = pain detection threshold; PTT = pain tolerance threshold; TS = temporal summation; TDT = tactile detection threshold; ThDT = thermal detection threshold; WDT = warmth detection threshold; CDT = cold detection threshold; VDT = vibration detection threshold.

TS between the PFP patients compared to controls (n = 40, mean difference 0.9 cm, 95% CI −0.5 to 2.3, $p = 0.15$).

3.5 Relationship between pressure pain thresholds and sex

Three studies (3 HQ [23, 31, 44]) included mixed sex participants measuring local and distal PPTs. Results from these studies were pooled for PFP patients vs. controls (Fig. 5) and female vs. male PFP patients (Fig. 6).

Moderate evidence (3 HQ [23, 31, 44]) indicates no significant difference in PPTs locally (n = 222; SMD −0.14, 95% CI −0.92 to 0.64; $p = 0.72$; $I^2 = 86\%$, $p = 0.0007$) or distally (n = 222; SMD −0.12, 95% CI −0.51 to 0.27; $p = 0.56$; $I^2 = 48\%$, $p = 0.15$) in the mixed sex PFP patients compared to controls. The overall effect also indicates no significant difference (n = 222; SMD 0.13, 95% CI −0.52 to 0.26; $p = 0.51$; $I^2 = 74\%$, $p = 0.002$).

Moderate evidence (3 HQ [23, 31, 44]) indicates no significant difference in PPTs locally (n = 91; SMD −0.85, 95% CI −1.72 to 0.01; $p = 0.05$; $I^2 = 62\%$, $p = 0.07$) or distally (n = 91; SMD −0.59, 95% CI −1.62 to 0.43; $p = 0.26$; $I^2 = 74\%$, $p = 0.02$) in the female compared to male PFP patients. However, considering the overall effect, moderate evidence of medium effect indicates decreased PPTs in the female patients (n = 91; SMD −0.75, 95% CI −1.34 to −0.16; $p = 0.01$; $I^2 = 63\%$, $p = 0.02$).

3.6 Relationship between pressure pain thresholds and age

All nine studies (8 HQ [15, 19–23, 31, 44] and 1 MQ [18]) assessing local and distal PPTs provided mean ages of patients. Meta-regression was possible to evaluate the relationship between PPTs and age. Findings indicate a moderate correlation between decreasing local PTTs and

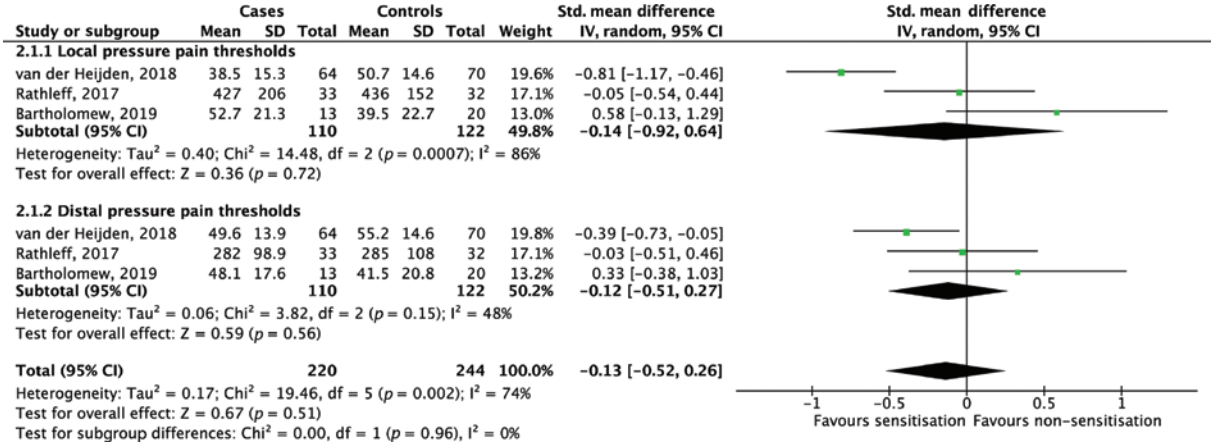

Fig. 5: Meta-analysis pressure pain thresholds in mixed sex studies.

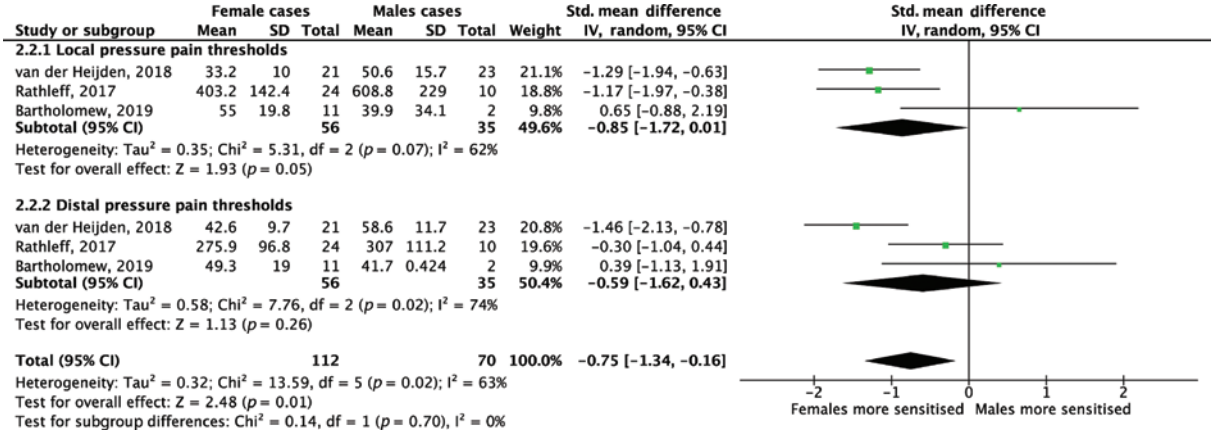

Fig. 6: Meta-analysis pressure pain thresholds in female cases compared to male cases in mixed sex studies.

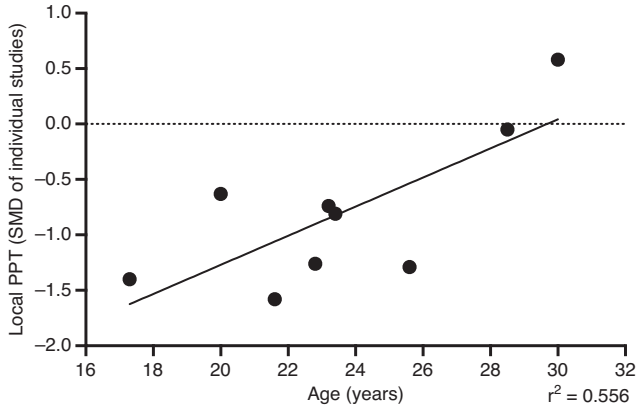

Fig. 7: Meta-regression scatterplot of local pressure pain thresholds and age.

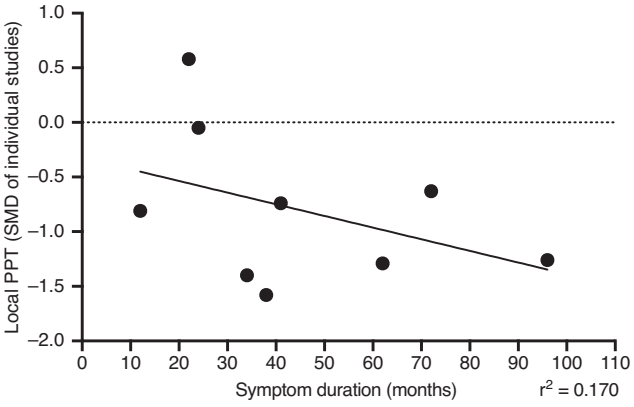

Fig. 9: Meta-regression scatterplot of local pressure pain thresholds and symptom duration.

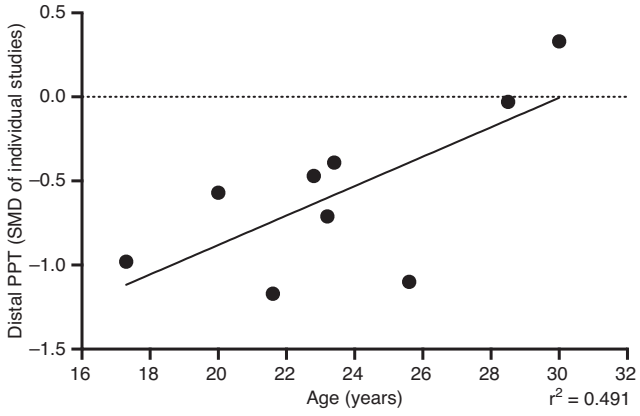

Fig. 8: Meta-regression scatterplot of distal pressure pain thresholds and age.

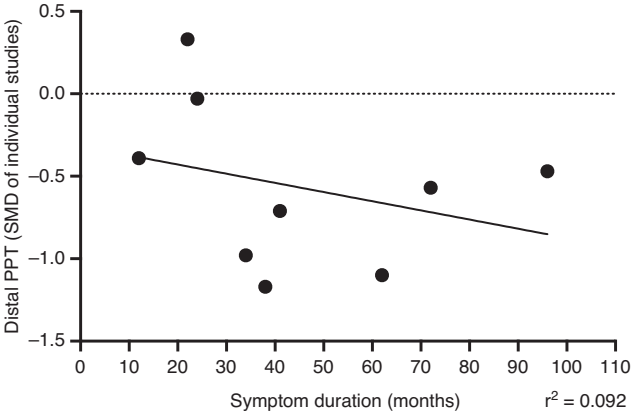

Fig. 10: Meta-regression scatterplot of distal pressure pain thresholds and symptom duration.

decreasing patient age ($R^2 = 0.556$, $\beta = -3.90$, 95% CI −6.40 to −1.40, $p = 0.0211$) (Fig. 7). Similarly, findings indicate a moderate correlation between decreasing distal PTTs and decreasing patient age ($R^2 = 0.491$, $\beta = -2.63$, 95% CI −4.54 to −0.728, $p = 0.0354$) (Fig. 8).

3.7 Relationship between pressure pain thresholds and symptom duration

All nine studies (8 HQ [15, 19–23, 31, 44] and 1 MQ [18]) assessing local and distal PPTs provided mean symptom durations of patients. Meta-regression analysis was possible to evaluate the relationship between PPTs and symptom duration. No significant association was identified between local pressure pain sensitivity and symptom duration ($R^2 = 0.170$, $\beta = -0.323$, 95% CI −1.41 to 0.759, $p = 0.270$) (Fig. 9). No significant association was identified between distal pressure pain sensitivity and symptom duration ($R^2 = 0.092$, $\beta = -0.318$, 95% CI −1.12 to 0.484, $p = 0.428$) (Fig. 10).

4 Discussion

This systematic review synthesises existing evidence from 11 studies investigating pain processing in PFP [15–23, 32, 44]. Findings addressed the primary aim, presenting moderate evidence to suggest altered pain processing and sensitisation, in agreement with current level one evidence that reported similar manifestations of pain sensitisation in other painful knee conditions including PFP, knee osteoarthritis, patellar tendinopathy and post-meniscectomy [28, 31]. Using meta-regression, the secondary aims were explored, indicating reduced PPTs in female patients with a correlation between decreasing PPTs and decreasing patient age.

4.1 Quantitative sensory testing measures

4.1.1 Pressure pain thresholds

The most robust evidence generated by this review is for pressure pain sensitivity providing moderate evidence for decreased local and distal PPTs in PFP patients compared to controls. This suggests the presence of widespread hyperalgesia which has been postulated to be the underlying reason for the longevity associated with PFP and other persistent pain conditions [17, 45]. Widespread hyperalgesia is common in other painful knee disorders and indicates an upregulation of the patient's nervous system beyond the painful area in isolation [28, 31].

4.1.2 Tactile detection thresholds

Similarly, we found moderate evidence for increased tactile detection thresholds in PFP patients compared to controls, indicating a reduced sensitivity to touch. It is thought that skin mechanoreceptors provide information about skin strain patterns induced by various joint positions, which can be used by the central nervous system to determine proprioception and joint movement [46–48]. Jensen et al. hypothesized that the cause of abnormal proprioception and disturbed muscle recruitment in some patients with PFP may be due to a dysfunction in mechanoreceptors which is possibly reflected in tactile detection thresholds [16, 49, 50]. Interventions that aim to address proprioceptive deficits, such as proprioceptive neuromuscular facilitation [51], have reported efficacy within the PFP population, and plausibly have these positive effects through modification of this pain mechanism.

4.1.3 Thermal detection thresholds

Results found moderate evidence for increased WDTs but no significant difference for CDTs in PFP patients compared to controls. Other reviews have found no evidence of significant thermal sensitivity in similar painful knee conditions [28, 31]. With just two studies reporting thermal detection thresholds, the extent to which thermal sensitivity contributes to the persistence of PFP is not well explored.

4.1.4 Vibration detection thresholds

One study found increased vibration detection thresholds on the painful compared to contralateral knee of PFP patients [17]. With no comparable control group this provides little insight as to whether vibration detection thresholds are altered in PFP patients with future studies required.

4.1.5 Conditioned pain modulation

Findings regarding CPM differed, with Holden et al. [15] and Rathleff et al. [44] finding no between-group difference but Rathleff et al. [22] finding a reduced CPM response in PFP patients compared to controls. This may be explained by the methodological variation used to evoke a conditioning stimulus with Holden et al. [15] and Rathleff et al. [22] using cuff algometry and Rathleff et al. [44] using cold water immersion. These variations mean the studies are not easily comparable and highlight the need to standardise methods of CPM assessment. Alternatively, this inconsistency may suggest a variable presence of impaired CPM amongst PFP patients which has been indicated in other painful knee conditions [31, 52]. Interestingly, Holden et al. [15] reported a more efficient CPM response in recovered-PFP patients compared to current-PFP patients. This was proposed to be potentially protective acting as a "buffer" against pain.

4.1.6 Temporal summation

Like CPM, findings regarding TS were not consistent, with Holden et al. [15] reporting an increased facilitation of TS in PFP patients compared to controls but Rathleff et al. [22] reporting no between-group difference. Remarkably, both studies recruited participants from the same population-based cohort (APA2011). With central pain mechanisms reported to worsen with increasing pain duration [15, 53], one reason for the differing findings may be the longer symptom duration in patients of Holden et al.'s study (median difference 2 years; Holden median 8 years, IQR 7–10; Rathleff et al. median 6 years, IQR 4.5–7) [15, 22]. Holden et al. also noted a similarly facilitated TS effect in current-PFP and recovered-PFP patients [15]. This suggests that features of central sensitisation may remain after treatment and symptom recovery, postulated to be due to the involvement of neuroplasticity of central pain mechanisms during pain-free periods [15]. This may explain why in other recurrent pain conditions, such as lower back pain [54] and musculoskeletal pain [52, 55], a history of pain is associated with an increased risk of new pain episodes [15]. With many studies reporting increased facilitation of TS in knee osteoarthritis [56–59]

it is likely that further research exploring TS in PFP may prove insightful.

4.2 Relationship between pressure pain thresholds and sex

With the prevalence of PFP twice as high in females compared to males [60], past research has often focused on females. Out of the nine studies assessing PPTs, just three studies recruited both female and male participants [23, 32, 44], with the remaining six studies recruiting female participants only [15, 18–22]. Interestingly, the mixed sex studies reported the lowest effect sizes, with two studies finding no significant difference in local or distal pressure pain thresholds in the PFP cases compared to controls [32, 44]. When data from these studies were pooled, this was confirmed, with the overall effect indicating no significant difference between the two groups. Extraction of PPT scores for female and male patients separately indicates an overall effect of reduced pressure pain thresholds in the female patients, hence increased pain sensitivity. Females with knee osteoarthritis are well documented to experience greater pain sensitivity to painful stimuli such as pressure pain thresholds when compared to male populations [61–63], with evidence suggesting less efficient endogenous pain mechanisms in females [64]. Certainly, further research to explore this potential link between increased pain sensitivity and sex is required to confirm findings and provide a more robust evidence base.

4.3 Relationship between pressure pain thresholds and age

A significant association was identified between decreasing PPTs and decreasing patient age, suggesting younger patients are more likely to experience pressure pain sensitivity. Evidence suggests that childhood and adolescence are critical periods where pain experience can prime nociceptors inducing long-lasting effects not seen amongst adults [65]. Consequently, pain sensitivity may be age dependent and amplified in a younger population [21, 22]. These findings further highlight the importance of effectively managing this common pain complaint within younger populations possibly to include components aimed at therapeutic neuroscience education [19] with involvement of the full multidisciplinary team to guide appropriate pain management interventions [66].

4.4 Relationship between pressure pain thresholds and symptom duration

No significant association was identified between pressure pain sensitivity and symptom duration. This remains in common with literature which reports symptom duration to be both positively and negatively associated with manifestations of hyperalgesia [21, 57]. Furthermore, the time taken to develop hyperalgesia varies greatly between conditions, for example, 1 month in whiplash [67] vs. 5 years in rheumatoid arthritis, but this time remains unclear in PFP.

4.5 Limitations and future research directions

This review is not without limitations, which must be considered when interpreting the results. Due to methodological heterogeneity and limited number of studies assessing pain processing in PFP, meta-analysis was not possible for all sensitisation measures. I^2 values were consistently high indicating significant heterogeneity between studies, however, a random effects model was used to help account for this. Due to a lack of available evidence, meta-analysis of tactile and thermal detection thresholds involved only several studies resulting in a high risk of bias and reduced methodological quality. The Downs and Black methodological quality assessment identified nine HQ studies [15, 17, 19–23, 32, 44] and two MQ studies [16, 18]. One common reason for methodological compromise was a lack of detail concerning the population characteristics which may introduce the risk of population bias. Furthermore, only four studies blinded the assessor during group assignment increasing the risk of detection bias [15, 20, 22, 44]. But despite these suggestions of bias, no study scored less than 50% during quality assessment requiring exclusion from subsequent analysis. However, there is no formally accepted quality assessment tool recommended for systematic reviews. Whilst Down and Black is a validated and widely used checklist, it is possible that using alternative tools may have generated different levels of evidence. PFP diagnostic checklist scores varied, ranging from 3/7 [23] to 7/7 points [16, 17, 19, 20], indicating large heterogeneity in the definition of PFP. Ensuring that the diagnostic approach is more uniform in future studies would be advisable to avoid the possibility of confounding pathologies. Furthermore, with sensitisation identified as a contributing factor, further research to consider whether manifestations of sensitisation are associated with treatment or prognosis may prove insightful to guide management approaches.

4.6 Conclusion

This systematic review presents moderate evidence to suggest the presence of altered pain processing and sensitisation in patients with PFP. Results indicate decreased PPTs, increased tactile detection thresholds and increased WDTs in PFP patients compared to controls. Furthermore, PPTs were found to be reduced in female patients with a correlation between decreasing PPTs and decreasing patient age. Although the exact aetiology of PFP remains elusive it is plausible that a combination of biomechanical and neuropathic dysfunction is responsible, possibly with the neuropathic elements contributing to the chronicity of PFP. With female patients and younger patients identified as being more likely to experience increased pressure pain sensitivity, this population may benefit most from a more targeted management approach incorporating components aimed specifically at neuropathic pain, including neuroscience education.

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