Pain Science Education Plus Exercise Therapy in Chronic Nonspecific Spinal Pain: A Systematic Review and Meta-analyses of Randomized Clinical Trials

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Abstract: **Exercise therapy and education are recommended from several guidelines for managing symptoms in chronic nonspecific spinal pain (CNSP) patients. However, no systematic reviews have previously analyzed the effectiveness of pain science education (PSE) plus exercise therapy for managing CNSP related symptoms. Systematic searches were conducted on 10 databases looking for randomized control trials (RCTs) aimed to evaluate the effectiveness on pain, disability, kinesiophobia, and catastrophizing. Data were analyzed using random-effects meta-analyses and studies were appraised using the Cochrane ROB tool and GRADE. A total of eight RCTs (n = 622) were included in the qualitative-analysis and five were selected for meta-analysis. PSE plus exercise therapy showed improvements in pain (5RCTs: short-term: SMD: -0.53 [-0.86,-0.2]; 4RCTs: intermediate-term: SMD: -0.57 [-1.01,-0.14]; low quality), disability (4RCTs: short-term: SMD: -0.24 [-0.53,0.05]; 4RCTs: intermediate-term: SMD: -0.93 [-1.08,-0.03]; low-to-very-low quality), kinesiophobia (3RCTs: short-term: SMD: -0.7 [-1.51,0.11]; 4RCTs: intermediate-term: SMD: -0.93 [-1.57,-0.30]; moderate-to-very-low quality), and catastrophizing (2RCTs: short-term: MD: -3.26 points [-6.15,-0.37]; 3RCTs: intermediate-term: MD: -4.94 points [-8.08,-1.81]; low-to-very-low quality) compared to exercise alone. A qualitative-analysis showed improvements in the experimental group compared to multimodal physiotherapy (1RCT; low-to-very-low quality), whereas no clear benefits were reported compared to PSE alone (1RCT; very-low quality) or no intervention (1RCT; very-low quality). There is low to very-low certainty of the evidence suggesting that PSE plus exercise therapy reduces CNSP related-symptoms.**

Perspective: ***Based on low-quality data from small samples, PSE plus exercise therapy reduces CNSP related symptoms. The evidence requires further investigation due to the limited number of studies with short follow-up periods (CRD42020168968).***

Key words: *Chronic pain, exercise, pain education, cognitive behavioral therapy, pain neuroscience education.*

Chronic nonspecific spinal pain (CNSP) is defined as a chronic pain experienced in musculoskeletal structures of the spine. CNSP is characterized by a significant emotional distress or functional disability which cannot be attributed directly to a known disease or damage process.[39] CNSP represents the leading worldwide cause of years lived with disability[16] and it is responsible for a high social and financial burden in developed countries.[11,20] Findings from literature accounted that one-fifth of overall workers with CNSP takes some absence over a period of 6 months.[50] Factors associated to the likelihood of return to work include emotional distress such as catastrophizing and fear of pain like kinesiophobia, both of them represent important contributors of pain and disability in people with CNSP.[19,29]

Several guidelines for managing pain and disability in CNSP patients include exercise and educational

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strategies as primary treatment options.[2,3,30] Exercise programs may include general aerobic or strengthening exercises, muscle stretching exercises, or different combinations of these elements which have shown moderate to strong evidence.[30] However, educational programs based on self-care, general behavior and information have shown moderate to very low evidence for managing CNSP symptoms.[30] These educational programs have been mostly based on traditional educational models focused on anatomical damage and biomechanical alterations as underlying causes of pain which have reported trivial results (eg, The Back School approach).[6,38]

An educational approach for managing chronic pain conditions called pain science education (PSE) has been well received by practitioners.[33] This approach relates that both biological and psychological processes are involved in pain experiences and it is focused on facilitating individuals to reconsider their beliefs on pain-tissue damage relationship,[34] since there does not seem to be a clear relationship between pain and tissue or structural alterations in CNSP patients.[10,18] In the last years several systematic reviews have been conducted on this topic supporting the use of PSE for reducing pain and disability in CNSP patients.[9,26,46,48,49] However, these sources of knowledge have pooled the effect of PSE interventions in isolation or combined with wide range of treatments such as manual therapy interventions, dry needling, neural self-mobilization, or exercise interventions, making its conclusions and recommendations imprecise and indirect for clinical practice. Exercise therapy and PSE improves pain and physical function at short-, intermediate- and long-term when applied in isolation.[2,17,26,44,46] However, PSE was never intended to be used in isolation but in combination with exercise therapy.[34,45] From our knowledge, no systematic reviews have been previously published about the effectiveness of PSE plus exercise therapy for managing CNSP related symptoms at short- and long-term. The aim of this review was to evaluate the evidence for effectiveness of PSE plus exercise therapy on pain, disability, kinesiophobia, and catastrophizing in CNSP patients.

Methods

Design and Protocol Registration

This systematic review was designed according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA)[25] and the 2015 updated method guidelines for systematic reviews of the Cochrane Back and Neck Group.[13] The protocol was previously registered on the International Prospective Register of Systematic Reviews (PROSPERO) in the Centre for Reviews and Dissemination (University of York, United Kingdom): CRD42020168968.

published systematic review on related-topics were reviewed in order to select appropriate key terms for minimizing publication bias.[26,46,48,49] The search strategies were used in the databases Academic Search Complete, CENTRAL, CINHAL complete, IBECS, Lilacs, PsycInfo, Pubmed, Scielo, SportDiscus, and Web of Science. Last search was run at March 01, 2021. References from included studies were checked looking for potential articles of interest (see Supplementary Material for additional information about search strategies).

Eligibility Criteria

Randomized controlled clinicals trials focusing on the effects of PSE plus exercise therapy compared to non-intervention, education, exercise therapy or multimodal physiotherapy on pain, disability, kinesiophobia or catastrophizing in patients with CNSP were included. Studies combining PSE and exercise therapy with other types of therapy were excluded.

Study Selection and Data Extraction

From the initial search, the titles and abstracts were reviewed to exclude any irrelevant study. The full texts of the remaining studies were then read in full by 2 blinded independent reviewers (B.L. & FA.L.) to determine whether the studies met the inclusion criteria. Disagreements were resolved by consensus with a third author (RJ.JJ.).

Data extraction was performed by a single author (B. L.) in a spreadsheet and then cross-checked point by point from the original papers by a second author (RC. JD.). We extracted data about patient characteristics (age, sex, pain localization and duration), interventions (PSE content, resources, exercise type, duration, repetitions, sets, sessions), characteristics of the comparison group, outcomes analyzed, drop-out rate and study design according to PICOS strategy. Additionally, a template for intervention description and replication (TIDIeR)[23] guideline was used.

Risk of Bias and Quality of Evidence

Two independent authors (B.L. & RJ.JJ.) assessed the risk of bias of individual studies using the Cochrane Collaboration Risk of Bias Tool[21] which evaluates selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential of bias.

The quality of evidence was evaluated using Grading Recommendation Assessment, Development and Evaluation (GRADE) approach which take into account risk of bias, inconsistency, indirectness, imprecision, publication bias, magnitude of effect, dose–response gradient, and plausible residual confounding.

Statistical Analysis

A set of meta-analyses using a random effect model were performed in order to analyze the effects of PSE plus exercise therapy compared to exercise interventions

on pain, disability, catastrophizing, and kinesiophobia. Statistical heterogeneity between studies was assessed by I^2 statistic which may be interpreted with caution as not important (< 40%), moderate (30-60%), substantial (50-90%) and considerable (75-100%).[22] Additionally, when a study performed assessment at multiple time-points of follow-up, these time-points were combined into a single effect size and entered into the analysis as only once.[5] All statistical analyses were performed using RevMan 5.4 (Review manager [Computer program]. Version 5.4, The Cochrane Collaboration, 2020) and the level of statistical significance was set at $P \leq .05$.

Due to the lack of studies analyzing the effects of PSE plus exercise therapy compared to other types of intervention, a meta-analysis was not possible, but a qualitative analysis was reported. Mean differences (MD) or standardized mean difference (SMD) were calculated for each study. Additionally, the number needed to treat (NNT) was calculated according to Furukawa et al (2005),[14] considering as responders patients with a reduction of 30% or greater in pain, disability, kinesiophobia or catastrophizing from baseline scores. This cut-off value was selected according to IMMPACT guidelines for chronic pain trials.[12]

Results

Study Selection

A total of 552 hits were identified across selected databases and one potentially eligible article was retrieved after analyzing the reference lists of those identified through the search strategy. After removing duplicates, 264 hits were screened reading title and abstract. Finally, a total of 19 hits were full text analyzed and 11 hits were excluded due to combined treatments in the experimental group (n = 4), protocol studies (n = 2), case reports (n = 3), no population of interest (n = 1), or secondary analysis of an already included study (n = 1). Therefore, a total of eight articles were included in the qualitative synthesis and five in the quantitative synthesis (Fig 1). Agreement between researchers during study selection was almost perfect (κ = 0.87; 95% Confidence Interval (95% CI): 0.6 to 1).

Study Characteristics and Risk of Bias

All included studies were randomized clinical trials published in English language and delivered between 2010 and 2021. Studies were monocentric conducted in Portugal,[1,28,40] Spain,[4,15] United Kingdom,[43] Iran[41] and Belgium.[27] Two studies were delivered in school setting[1,28] and 1 in primary care,[15] no information was provided for the remaining studies. Studies follow-up after the treatment periods were 3 months,[4,28,40,43] 6 months,[15] and 1 year.[27] Two studies did not perform a follow-up period.[1,41]

Studies were considered at high risk of bias overall because all studies had a high risk of bias in at least 2 domains (Fig 2). Random sequence generation was considered at low risk in most of included studies (7 of 8 studies).[1,4,15,27,28,41,43] Several studies (5 of 8 studies) did not provide sufficient information about allocation concealment which was considered at unclear risk.[1,15,27,28,43] Blinding of personnel and participants was considered at high risk in all studies due to the characteristics of the intervention. Some studies reported that outcome assessor was blinded to allocation group[15,28,40,41]; however, the measures of pain, disability, kinesiophobia, and catastrophizing were based on self-reports by the participants, who were not themselves blinded. Therefore, blinding of outcome assessment was considered at high risk in all studies. Incomplete outcome data was rated as low risk of bias in all of included studies. Three studies were rated as unclear risk of bias in other sources of bias because some authors may benefit financially from the promotion of PSE methods,[4,15,27] whereas one trial was rated as high risk due to inadequate comparison.[1]

Agreement between researchers during risk of bias assessment was substantial (κ = 0.69; 95% CI: 0.5 to 0.9). Additional information about risk of bias is provided in the Supplementary Material.

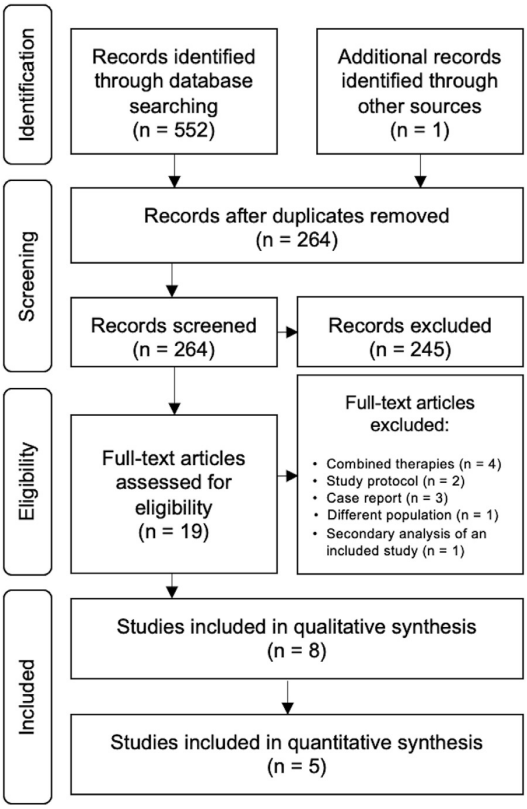

Figure 1. Flow chart of the selection process of the studies.

Participant Characteristics

The total sample of included studies was composed by 621 participants (69% woman) mean age ranged between 40 to 51 years,[4,15,27,40,41,43] with the exception of those studies delivered in school setting which

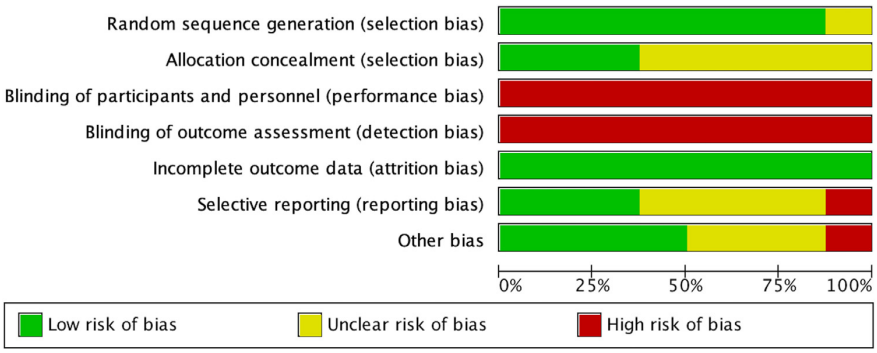

Figure 2. Risk of bias of included studies.

ranged between 16 to 21 years.[1,28] Patients had a minimum of 3 months of symptoms duration characterized in most of cases by low back pain (~50% of cases),[4,40,41,43] overall spinal pain (~25% of cases had a combination of neck, thoracic and low back pain),[15,27] or neck pain (~25% of cases)[1,28] (Table 1).

Drop-out rate was 14% (89 from 621) from initial enrolled. A total of 55 participants were drop-out from the control groups (18% drop-out rate) whereas 34 participants were drop-out from the experimental groups (11% drop-out rate).

Characteristics of the Intervention

Experimental protocol was based on a combination of PSE plus exercise therapy. PSE programs were based on similar concepts among studies which included explications about the function of the central nervous system, the role of psychosocial factors on CNSP, and the transition from acute to chronic pain, among others. Many authors[1,4,28,40,43] used the book "Explain pain" in 2003[7] and 2013[8] editions as framework for the PSE protocol. All studies used pictures, diagrams and other pedagogical resources as recommended by some authors.[34] In order to increase the effect of the intervention, books copies or booklets with the main concepts of PSE sessions were delivered in three studies.[4,40,43] The sessions were usually conducted in group format before the exercise therapy program. Only 2 studies performed one-to-one sessions.[4,27] The interventions were usually provided by physiotherapists[1,4,15,28,41] and the number of sessions varied across studies; one-off session,[43] two sessions,[4,40] three sessions,[27,41] four sessions[28] or six sessions.[15]

Exercise therapy programs were composed by aerobic exercises,[43] strengthening exercises,[1,28,41] or a combination of aerobic, strengthening and stretching exercises.[4,15,40] One study performed mobilization exercises of the spine plus motor control training using "time-contingent" approach and stretching exercises.[27] Only one study reported exercise intensity which was called as "somewhat hard".[43] These programs were supervised, and the number of sessions ranged between 1 to 3 per week from 4 to 12 weeks with a session duration of 15 to 60 minutes. Only 1 study was semi-supervised and instructed the patients to perform the exercise program daily during 12 weeks[4] (Table 1).

Outcome Characteristics

Primary outcomes were pain and disability. Four studies used the Visual Analogue Scale (VAS) in centimeters[1,28,41] or millimeters[15,40] whereas three studies used the Numeric Rating Scale (NRS) ranging from 0-10 points[4,27] or 0-100 points[43] for pain measurements. Disability was measured using the Roland Morris Disability Questionnaire (RMDQ),[4,41,43] Neck Disability Index (NDI),[28] Quebec Back Pain Disability Scale (QBPDS),[40] and Pain Disability Index (PDI).[27]

Secondary outcomes were kinesiophobia and catastrophizing. A total of six studies analyzed kinesiophobia using different versions of the Tampa Scale for Kinesiophobia (TSK)[4,15,27,28,40,43] whereas catastrophizing was measured using the Pain Catastrophizing Scale (PCS) in 5 studies.[1,4,15,27,28]

Effectiveness of PSE plus Exercise Therapy Compared to PSE

Only one study[43] compared the experimental protocol to PSE alone. The results showed greater reduction in pain in favor of the PSE group at 8 weeks (MD: 15.5 points; $P < .05$, very-low quality evidence; NNT 2), but no differences were detected at follow-up period (3 months, very-low quality evidence). Disability and kinesiophobia did not change over time (very-low quality evidence) (Table 2).

Effectiveness of PSE plus Exercise Therapy Compared to Exercise Therapy

Our meta-analysis found that PSE plus exercise therapy improved pain at short-term (SMD: -0.53; 95% CI: -0.86 to -0.20; $P = .002$; low quality evidence; NNT 5) and at intermediate-term (SMD: -0.57; 95% CI: -1.01 to -0.14; $P = .01$; low quality evidence; NNT 6) compared to exercise therapy alone with moderate heterogeneity at both time periods (Fig 3 and Table 3).

Table 1. Characteristics of the Included Studies.

	Intervention									Comparison	
	Exercise Therapy				PSE Therapy					Control group	
Studies	Subjects	Protocol	Duration	Therapist	PSE Content	Modality	Therapist	Duration	Treatment Order	Subjects	Protocol
Ryan et al, 2010 [43]	EG: n20 (70% F) 45.2 (11.9) yrs. Low back pain: 7.6 (7) months	Warm-up followed by an aerobic phase at an intensity "somewhat hard", and a cool-down phase.	1x week (55 min) total 6 weeks	ND (supervised)	Based on Explain pain, focused on reshaping the participant's beliefs and attitudes about their back pain.	Verbal communication, prepared diagrams, and free-hand drawings, and "The back book" copy [42].	ND	One session (150 min)	PSE before ET	CG: n18 (60% F) 45.5 (9.5) yrs. Low back pain: 13.7 (10.2) months	Same PSE protocol than EG
Pires et al, 2014 [40]	EG: n30 (67% F) 50.9 (6.2) yrs. Low back pain: 80% > 24 months	Aquatic exercise program including aerobic and strengthening exercises. No intensity reported.	2x week (30-50 min) total 6 weeks	ND (supervised)	Transition from acute to chronic pain; central sensitization; role of the brain in the perception of pain; psychosocial factors	Group sessions: Metaphors and pictures.	ND	Two sessions (90 min)	PSE before ET	CG: n32 (63% F) 51 (6.3) yrs. Low back pain: 75% > 24 months	Same ET protocol than EG
Andias et al, 2018 [1]	EG: n21 (57% F) 17.4 (1.4) yrs. Neck pain: > 3 months	Strengthening exercises of neck muscles (3 series of 10 rep.) and scapular stabilizers. No intensity reported.	1x week (15-30 min) total 4 weeks	Physiotherapist (supervised)	Transition from acute to chronic pain, and the nervous system ability to modulate the pain experience.	Small groups at the school setting, booklet with the contents of session was given to participants.	Physiotherapists with 2, 15, and 17 years of PSE experience.	Four sessions (15-45 min)	ND	GC: n22 (76% F) 15.9 (1) yrs. Neck: < 3 months	No intervention
Pardo et al, 2018 [4]	EG: n28 (78% F) 44.9 (9.6) yrs. Low back pain: ≥ 6 months	Core isometric exercises Stretching of back and gluteal region muscles at a tolerable muscle tension.	Every day. Total 3 months	Physiotherapist (Semi-supervised)	Based on Explain pain [7] and Pain in Motion content	Group sessions conducted using verbal and visual presentation. At the end of the session, participants received a leaflet	Physiotherapist	Two sessions one month apart (30-50 min)	PSE before ET	CG: n28 (78% F) 49.2 (10.5) yrs. Low back pain: ≥ 6 months	Same ET protocol than EG
Malfliet et al, 2018 [27]	EG: n60 (63% F) 39.9 (11.9) yrs. Spine pain: 121.5 (100.7) months	Cognition-targeted motor control training, using a time-contingent approach.	15 sessions in 12 weeks	ND (supervised)	Explanation of neuron, synapse, top-down, bottom-up and wing up phenomenas	Group sessions, home-based online module, and individual sessions.	ND	Three sessions in 12 weeks	ND	CG: n60 (58% F) 40.5 (12.9) yrs. Spine pain: 103.4 (82.9) months	General exercise, symptom contingent and traditional education.
Matias et al, 2019 [28]	EG: n25 (88% F) 20.7 (1.9) yrs. Neck pain: ≥ 3 months	Strengthening of neck and shoulder muscles.	1x week (30 min) total 4 weeks	ND (supervised)	Transition from acute to chronic pain and the nervous system's ability to modulate the pain.	Group session, accompanied by pictures and diagrams	Physiotherapist with 1 year of PSE.	Four sessions (5-30 min)	ND	CG: n27 (78% F) 21.3 (2.1) yrs. Neck pain: ≥ 3 months	Same ET protocol than EG but fewer repetitions.
Galán et al, 2020 [15]	EG: n89 (73% F) 50 (10.7) yrs. Spine pain: 93.1 (85.5) months	Coordination, aerobic and strengthening exercises followed by stretching and relaxation exercises.	3x week (60 min) total 6 weeks	Physiotherapist (supervised)	Protective function of pain. Differences between acute and chronic pain, functional and structural caused by pain.	Group education, pedagogical resources are used to simplify the process, explanatory videos.	Physiotherapist with 30 hours of training,	Six sessions. Total 10 hrs.	PSE - ET - PSE	CG: n81 (88% F) 49.1 (12.4) yrs. Spine pain: 93.9 (84.9) months	15 sessions (60min) of thermotherapy and electrotherapy plus ET.
Rabiei et al, 2021 [41]	EG: n40 (56% F) 42.5 (9.7) yrs. Low back pain: 78% > 12 months	Deep spinal muscles and pelvic floor muscles contraction and diaphragmatic breath. Fearful movement were trained.	2x week (30-60 min) total 8 weeks	Physiotherapist (supervised)	Conceptualize negative beliefs about pain, nature of pain, Differences between acute and chronic pain.	Individual interview, pedagogical resources are used to simplify the process, drawing and diagrams, and verbal instructions.	Physiotherapist trained in PSE	Three sessions (30-60 min)	PSE - ET	CG: n40 (50% F) 44.2 (8.8) yrs. Low back pain: 64% > 12 months	16 sessions (60 min): Strengthening (45 min) Intensity based on subjective effort.

Abbreviation. EG, Experimental Group; CG, Control Group; F, Female; PSE, Pain Science Education; ET, Exercise Therapy; ND, No defined; min, minutes; yrs, years.
Note. Data are given as mean (standard deviation) or number (percent).

Table 2. PSE Plus Exercise Therapy Compared to PSE for Chronic Spinal Pain.

Patient or population: Chronic Spinal Pain at Short-term
Setting: No information provided

Outcomes	№ of Participants (Studies)	Certainty of the Evidence (GRADE)	Anticipated Absolute Effects	
			Risk With PSE	Risk Difference With PSE Plus Exercise Therapy
Short-term analyses				
Pain assessed with: NRS Scale from: 0 to 100 follow up: 8 weeks	34 (1 RCT)	⨁x̂x̂x̂ VERY LOW *,†,‡	The mean pain was 8.4 points	MD 15.5 points higher (3.1 higher to 27.9 higher)
Disability assessed with: RMDQ Scale from: 0 to 24 follow up: 8 weeks	34 (1 RCT)	⨁x̂x̂x̂ VERY LOW *,†,‡	The mean disability was 3.3 points	MD 2.3 points higher (0.15 lower to 4.75 higher)
Kinesiophobia assessed with: TSKe13 Scale from: 13 to 52 follow up: 8 weeks	34 (1 RCT)	⨁x̂x̂x̂ VERY LOW *,†,‡	The mean kinesiophobia was 21.3 points	MD 0.6 points higher (4.61 lower to 5.81 higher)
Intermediate-term analyses				
Pain assessed with: NRS Scale from: 0 to 100 follow up: 3 months	27 (1 RCT)	⨁x̂x̂x̂ VERY LOW *,†,‡	The mean pain was 22.6 points	MD 3.5 points lower (23.3 lower to 16.3 higher)
Disability assessed with: RMDQ Scale from: 0 to 24 follow up: 3 months	27 (1 RCT)	⨁x̂x̂x̂ VERY LOW *,†,‡	The mean disability was 4.3 points	MD 2.1 points higher (1.6 lower to 5.8 higher)
Kinesiophobia assessed with: TSK-13 Scale from: 13 to 52 follow up: 3 months	27 (1 RCT)	⨁x̂x̂x̂ VERY LOW *,†,‡	The mean kinesiophobia was 23.7 points	MD 2.2 points lower (7.87 lower to 3.47 higher)

Abbreviation. MD, Mean difference.
*Personnel, participants and outcome assessors not blinded to allocation group. Unclear risk of bias for selective reporting and selection bias.
†The participants involved in this study were only focused on low back pain.
‡< 400 participants and wide confidence intervals for the outcome assessed.

Disability showed no difference between groups comparison at short-term (SMD: -0.24; 95% CI: -0.53 to 0.05; P = .18, low quality evidence) with no heterogeneity, whereas the results were favorable to the experimental group at intermediate-term (SMD: -0.93; 95% CI: -1.08 to -0.03; P = .04; very-low quality evidence; NNT 5) with substantial heterogeneity (I^2 = 76%; P = .04) (Fig 4 and Table 3).

Regarding secondary outcomes, kinesiophobia showed no difference at short-term (SMD: -0.70; 95%

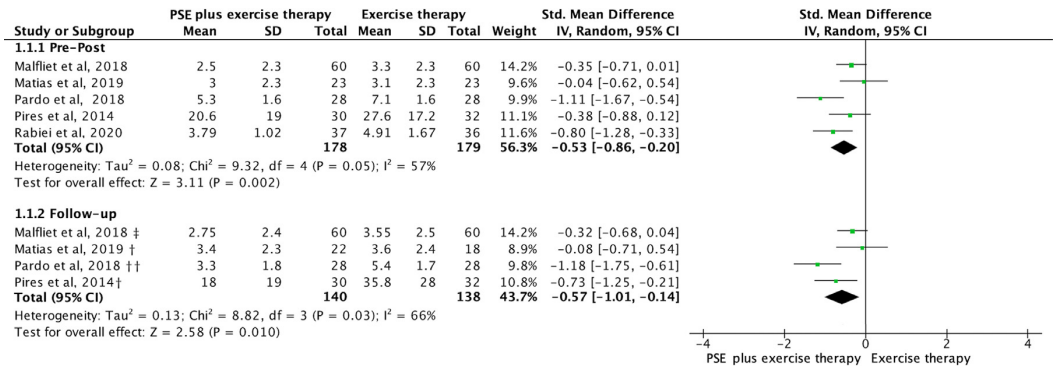

Figure 3. Forest plot of comparison: Pain science education (PSE) plus Exercise Therapy versus Exercise Therapy, outcome: Pain. Follow-up at 3 months (†), multiple time-points at 1 and 3 months combined (††), multiple time-points at 6 months and 1 year combined (‡).

Table 3. PSE plus Exercise Therapy Compared to Exercise Therapy in Chronic Spinal Pain.

Patient or Population: Chronic Spinal Pain at Short-term
Setting: No Information Provided

Outcomes	№ of Participants (studies)	Certainty of the Evidence (GRADE)	Anticipated Absolute Effects	
			Risk with Exercise Therapy	Risk difference with PSE plus Exercise Therapy
Short-term analyses				
Pain assessed with: NRS (0-10 or 0-100), VAS (0-10 or 0-100) follow up: range 4 weeks to 6 months	357 (5 RCTs)	⨁⨁◯◯ LOW *,†	-	SMD 0.53 SD lower (0.86 lower to 0.2 lower)
Disability assessed with: NDI, QBPDS, PDI follow up: range 4 weeks to 6 months	301 (4 RCTs)	⨁⨁◯◯ LOW *,†	-	SMD 0.24 SD lower (0.53 lower to 0.05 higher)
Kinesiophobia assessed with: TSK follow up: range 4 weeks to 6 months	228 (3 RCTs)	⨁◯◯◯ VERY LOW *,†,‡	-	SMD 0.7 SD lower (1.51 lower to 0.11 higher)
Catastrophizing assessed with: PCS Scale from: 0 to 52 follow up: range 4 weeks to 6 months	166 (2 RCTs)	⨁◯◯◯ VERY LOW *,†	-	MD 3.26 Point lower (6.15 lower to 0.37 lower)
Intermediate-term analyses				
Pain assessed with: NRS (0-10 or 0-100), VAS (0-10 or 0-100) follow up: range 1 months to 12 months	278 (4 RCTs)	⨁⨁◯◯ LOW *,†	-	SMD 0.57 SD lower (1.01 lower to 0.14 lower)
Disability assessed with: RMDQ, NDI, QBPDS, PDI follow up: range 1 months to 12 months	278 (4 RCTs)	⨁◯◯◯ VERY LOW *,†,‡	-	SMD 0.56 SD lower (1.08 lower to 0.03 lower)
Kinesiophobia assessed with: TSK follow up: range 1 months to 12 months	278 (4 RCTs)	⨁⨁⨁◯ MODERATE *,†,‡	-	SMD 0.93 SD lower (1.57 lower to 0.30 lower)
Catastrophizing assessed with: PCS Scale from: 0 to 52 follow up: range 3 months to 12 months	216 (3 RCTs)	⨁⨁◯◯ LOW *,†	-	MD 4.94 lower (8.08 lower to 1.81 lower)

Abbreviation. SMD, Standardized mean difference; MD, Mean difference.
*Personnel, participants and outcome assessors not blinded to allocation group. Unclear risk of bias for selective reporting and selection bias.
†< 400 participants and wide confidence intervals for the outcome assessed.
‡Chi-squared test ($P < .05$) and high heterogeneity.

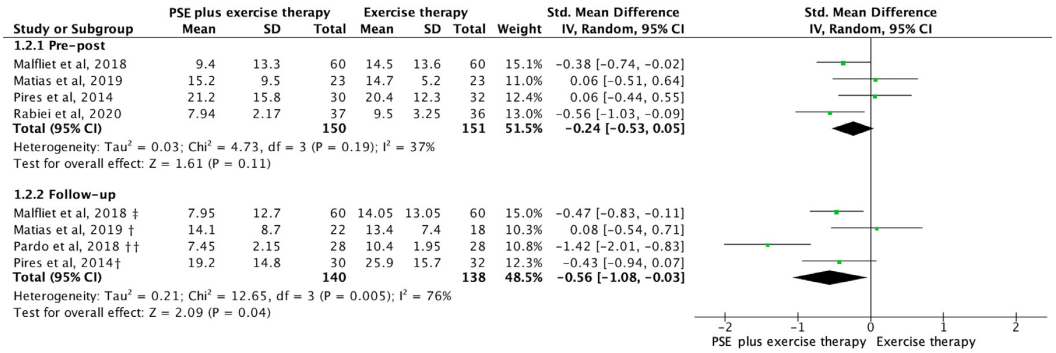

Figure 4. Forest plot of comparison: Pain science education (PSE) plus Exercise Therapy versus Exercise Therapy, outcome: Disability. Follow-up at 3 months (†), multiple time-points at 1 and 3 months combined (††), multiple time-points at 6 months and 1 year combined (‡).

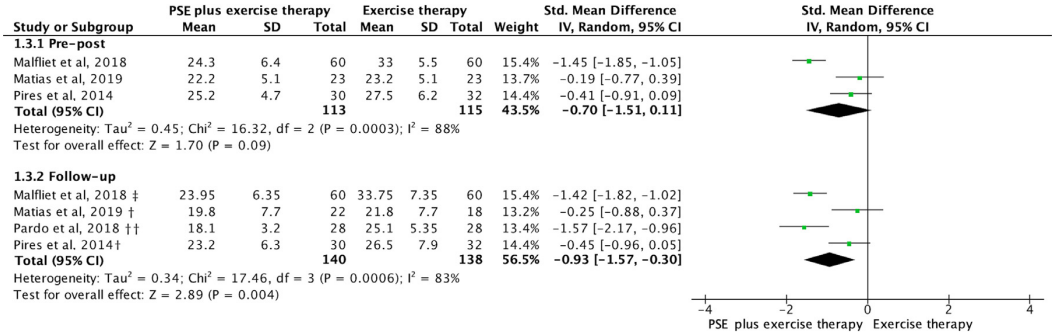

Figure 5. Forest plot of comparison: Pain science education (PSE) plus Exercise Therapy versus Exercise Therapy, outcome: Kinesiophobia. Follow-up at 3 months (†), multiple time-points at 1 and 3 months combined (††), multiple time-points at 6 months and 1 year combined (‡).

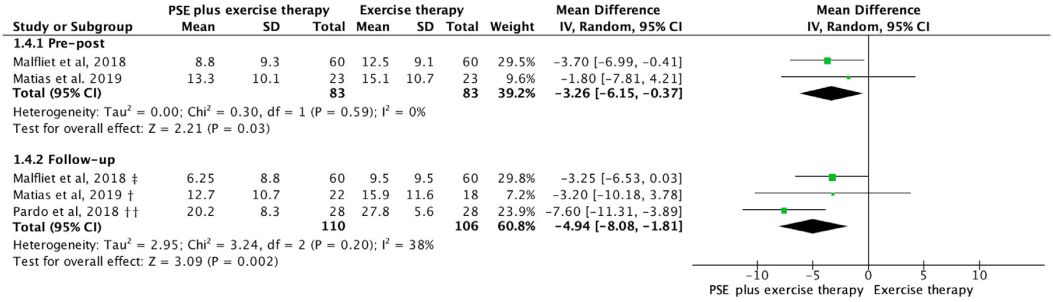

Figure 6. Forest plot of comparison: Pain science education (PSE) plus Exercise Therapy versus Exercise Therapy, outcome: Catastrophizing. Follow-up at 3 months (†), multiple time-points at 1 and 3 months combined (††), multiple time-points at 6 months and 1 year combined (‡).

CI: -1.51 to 0.11; *P* = .09, very-low quality evidence), whereas the results were favorable to the experimental group at intermediate-term (SMD: -0.93; 95% CI: -1.57 to -0.30; *P* < .01; moderate quality evidence; NNT 4) with substantial heterogeneity at both time periods (Fig 5 and Table 3).

The results for catastrophizing were favorable for the experimental group at short-term (MD: -3.26; 95% CI: -6.15 to -0.37; *P* = .03; very-low quality evidence; NNT 5) and at intermediate-term (MD: -4.94; 95% CI: -8.08 to -1.81; *P* < .01; low quality evidence; NNT 5) with no heterogeneity at both time periods (Fig 6 and Table 3).

Effectiveness of PSE plus Exercise Therapy Compared to Multimodal Physiotherapy

Galan-Martin et al[15] compared experimental protocol to multimodal physiotherapy and the results showed between-group differences in favor of the experimental group for pain at intermediate-term (MD: 32.7 points; *P* < .01; low quality evidence; NNT 2), disability at intermediate-term (MD: 4.4 points; *P* < .01, very-low quality evidence; NNT 3), kinesiophobia at intermediate-term (MD: 9.1 points; *P* < .01, low quality evidence; NNT 2), and catastrophizing at intermediate-term (MD: 8.7 points; *P* < .01; very-low quality evidence; NNT 3). Short-term analyses were not reported in this study (Table 4).

Effectiveness of PSE Plus Exercise Therapy Compared to No Intervention

Andias et al[1] compared experimental protocol to no intervention. The results showed no between-group differences for pain and catastrophizing at short-term (very-low quality evidence). This study did not perform a follow-up period (Table 5).

Discussion

The objective of this systematic review and meta-analysis was to evaluate the evidence for effectiveness of PSE plus exercise therapy on pain, disability, kinesiophobia, and catastrophizing in CNSP patients.

The results of this study showed that PSE plus exercise therapy was usually superior to other forms of intervention such as exercise therapy or multimodal physiotherapy for improving pain, disability, kinesiophobia, and catastrophizing at short- and intermediate-term. These results were more evident at intermediate-term (3 to 12 months) than at short-term (< 3 months) and suggested that the intervention dose used in the included studies was sufficient for improving symptoms during the follow-up period in CNSP patients.

These results were similar to those summarized in a Cochrane review by Kamper et al,[24] examining the

Table 4. PSE plus Exercise Therapy Compared to Multimodal Physiotherapy for Chronic Spinal Pain at Intermediate-term.

Patient or Population: Chronic Spinal Pain at Intermediate-term
Setting: Primary Care

Outcomes	№ of Participants (Studies)	Certainty of the Evidence (GRADE)	Anticipated Absolute Effects	
			Risk with Multimodal Physiotherapy	Risk difference with PSE plus Exercise Therapy
Pain assessed with: VAS Scale from: 0 to 100 follow up: 6 months	170 (1 RCT)	⊕⊕x̂x̂ LOW *,†,‡	The mean pain was 59.7 mm	MD 40.9 mm lower (46.7 lower to 35.2 lower)
Disability assessed with: RMDQ Scale from: 0 to 24 follow up: 6 months	170 (1 RCT)	⊕x̂x̂x̂ VERY LOW *,†,‡	The mean disability was 7.7 points	MD 5.6 points lower (6.7 lower to 4.5 lower)
Kinesiophobia assessed with: TSK Scale from: 11 to 44 follow up: 6 months	170 (1 RCT)	⊕⊕x̂x̂ LOW *,†,‡	The mean kinesiophobia was 26.3 points	MD 10.6 points lower (12.4 lower to 8.7 lower)
Catastrophizing assessed with: PCS Scale from: 0 to 52 follow up: 6 months	170 (1 RCT)	⊕x̂x̂x̂ VERY LOW *,†,‡	The mean catastrophizing was 24.2 points	MD 11 points lower (13.6 lower to 8.4 lower)

Abbreviation. MD, Mean difference.
*Personnel, participants and outcome assessors not blinded to allocation group. Unclear risk of bias for selective bias and other sources of bias.
†Only one study analyzing middle-age participants.
‡< 400 participants.

effect of a multidisciplinary biopsychosocial rehabilitation program composed by cognitive behavior therapy, exercise and education for chronic low back pain. They reported small improvements at short-term for pain and disability in the experimental group compared to exercise and active physiotherapy, and these improvements were maintained at intermediate-term (3 to 12 months). Similarly, in a systematic review by O'Keeffe et al,[37] analyzing behavioral therapy plus exercise compared to exercise alone in chronic spinal pain showed small differences for pain and disability at short- (12 weeks to < 6 months) and long-term (≥ 12 months) in favor of the

Table 5. PSE Plus Exercise Therapy Compared to No Intervention for Chronic Spinal Pain at Short-term.

Patient or Population: Chronic Spinal Pain at Short-term
Setting: School Setting

Outcomes	№ of Participants (studies)	Certainty of the Evidence (GRADE)	Anticipated Absolute Effects	
			Risk with No Intervention	Risk Difference With PSE Plus Exercise Therapy
Pain assessed with: VAs Scale from: 0 to 10 follow up: 5 weeks	43 (1 RCT)	⊕x̂x̂x̂ VERY LOW *,†,‡	The mean pain was 3.4 cm	MD 1.9 cm lower (2.59 lower to 6.39 higher)
Catastrophizing assessed with: PCS Scale from: 0 to 52 follow up: 5 weeks	43 (1 RCT)	⊕x̂x̂x̂ VERY LOW *,†,‡	The mean catastrophizing was 13.5 points	MD 1.5 points higher (4.19 lower to 7.19 higher)

Abbreviation. MD, Mean difference.
*Personnel, participants and outcome assessors not blinded to allocation group. Unclear risk of bias for selection bias. High risk of bias for other sources of bias.
†Only one study analyzing young-age participants with chronic non-specific neck pain.
‡< 400 participants and wide confidence intervals for the outcome assessed.

combined intervention. However, despite the reported improvements in the combined intervention, between-group differences were small. Indeed, the decision to choose a combined intervention should be balanced against the time and resources available, especially in absence of large improvements. In contrast to the small differences observed in the above-mentioned literature, the results of our systematic review showed moderate to large differences for the combined interventions (PSE plus exercise therapy) compared to exercise therapy alone or even when it was compared to a multimodal physiotherapy approach, reinforcing educational interventions plus exercise therapy as a promising tool for managing symptoms in CNSP patients. Specifically, the NNT ranged from 4 to 6 patients for pain, disability, catastrophizing, and kinesiophobia when PSE plus exercise therapy was compared to exercise therapy alone. This means that 1 in every 4 to 6 patients treated could get additional benefit from the combined intervention compared to exercise therapy alone. In other words, a range between 193 to 326 patients (it depends on the outcome) per 1,000 treated may get a reduction of 30% or greater in symptoms compared to exercise therapy alone. This is remarkable since exercise therapy represents the leading conservative treatment reported by several guidelines for managing CNSP related symptoms.[2,3,30]

Controversial results were observed in this systematic review when PSE plus exercise therapy was compared to no intervention or PSE alone. Andias et al 2018[1] compared PSE plus exercise therapy to no intervention and the results showed no between-group differences for pain or catastrophizing at short-term (4 weeks). These results could be due to the younger age group included in this study or the very low exposure to the treatment (1 session per week), as well as the small sample size used in this study, since a positive effect was evident in favor of the combined intervention, but differences did not reach statistical significance. Another study compared PSE plus exercise therapy to PSE alone.[43] The results showed improvements in pain at short-term (8 weeks) for the PSE group, but not between-group differences were detected at follow-up (3 months) neither for pain, disability, and kinesiophobia. It is unclear as to why the PSE alone had better short-term outcomes in this study, however, there are some possible explanations. Among others, the purpose of the PSE intervention is to shift attitudes towards a self-management approach in order to improve patient autonomous care. However, attending the exercise classes with a clinical class instructor (physiotherapist) may have detracted from that message and reinforced the concept of the participants being patients. Moreover, it is likely that the combinations of interventions present any dissonance in explanatory models. The "back to fitness" exercise classes[31] in this study could provide some advices that differed somewhat from the PSE sessions leading to cognitive dissonance to the patient and poor outcomes. Indeed treatment credibility have major impacts on outcome results.[32] Another possible explanation could be the very low attendance rate to exercise classes: two patients were dropped-out prior to beginning the exercise classes and 3 attended zero classes from a total of six patients in a considerable small sample size (n = 20). Further studies are required to clarify the elements of PSE treatment that determine success, and investigate possible interactions between PSE and multidisciplinary management such as exercise therapy.

Despite of promising findings about the use of PSE plus exercise therapy for the managing of CNSP symptoms, these results should be interpreted cautiously due to the certainty of the evidence which, in most cases, was low to very low. Limitations affecting the certainty of the evidence of this systematic review were due to the small number of studies included and their small sample size which impact the precision of the results. Most studies included a population with cervical or lumbar pain with a narrow range of age which could represent an indirect condition to the research question addressed in this study. Additionally, although the studies were well conducted, lack of blinding of participants and personnel, as well as of outcome assessment were the main reasons for downgraded the quality of the evidence. Due to the small number of studies included in the meta-analysis, publication bias was not possible to be assessed through statistical evaluation. In absence of this, publication bias can be suspected when the body of evidence consists of only small positive studies or when studies are reported in trial registries but not published, which was not the case of this systematic review. Moreover, publication bias is more likely if the search strategies are not comprehensive.[35] Our search strategy was developed using terms of previous published systematic reviews about similar topics and was conducted in ten databases in order to minimize publication bias. Therefore, risk of publication bias was not suspected in this review. Despite the published guidelines for reporting core outcomes in chronic pain research,[12] most of included studies did not reported all of them, in particular avoiding sleep disturbance assessment which was accounted as an important factor in chronic pain field.[36] Further studies should take into account core outcomes and larger follow-up period with more rigorous methodological assessment to clarify the results of the present systematic review.

Despite a rigorous approach towards data collection and synthesis, this review is not without limitations. Two deviations from the original protocol were done. First, kinesiophobia was considered as secondary outcome rather than primary outcome based on Higgins and Green (2011)[22] and Vetter and Masha (2017)[47] (type of deviation: organization). Second, preregistration indicated that the comparison groups will be PSE alone or exercise alone, however in order to provide a broad overview of the treatment, two additional comparisons were added such as non-intervention and multimodal physiotherapy (type of deviation: addition).

In conclusion, there is low to very-low certainty of the evidence suggesting that PSE plus exercise therapy reduces pain, disability, kinesiophobia, and catastrophizing compared to exercise therapy or multimodal physiotherapy at short- and intermediate-term. The

evidence is very uncertain about the effect of PSE plus exercise therapy on pain, disability, kinesiophobia, and catastrophizing compared to PSE alone or no-intervention neither short- or intermediate-term.

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Supplementary data

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