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Review

Comparative effectiveness of various exercise interventions on central sensitisation indices: A systematic review and network meta-analysis

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ABSTRACT

Background: Central sensitisation (CS) increases musculoskeletal pain. Quantitative sensory testing (QST) or self-report questionnaires might indicate CS. Indices of CS might be suppressed by exercise, although the optimal exercise regimen remains unclear.
Objectives: We conducted a systematic review and network meta-analysis (NMA) to investigate effectiveness of different exercise regimens on these CS indices in adults.
Methods: We searched 6 electronic databases from inception to November 2023. Meta-analysis of randomised controlled trials (RCTs) investigated effects of exercise on all CS indices. Two independent reviewers assessed risk of bias. NMA of RCTs compared CS indices between exercise types. Sensitivity analysis using only high-quality studies was performed to verify the robustness of our results. Certainty was assessed using the GRADE approach.
Results: Of the 249 eligible studies identified, 164 were RCTs, of which 89 provided data suitable for NMA. Meta-analysis revealed large improvement of post-intervention CS indices compared to baseline (SMD −0.81, 95 % CI −0.93 to −0.70). All reported categories of exercise, except stretching exercise alone, were more effective than non-exercise controls. Combined exercises that include stretching together with strengthening exercises (SMD −1.67, 95 % Credible Interval (CrI) −2.41 to −0.97), or strengthening, stretching and aerobic components (SMD −1.61, 95 % CrI −2.74 to −0.56) were most effective at reducing CS indices compared to non-exercise controls. Sensitivity analysis confirmed the robustness of our findings, particularly for combined stretching and strengthening exercise.
Conclusions: Our meta-analysis suggested that various exercise interventions are effective in improving CS. Multi-component exercise tends to be the most effective, but some exercise combinations might be better than others. Combined exercise featuring strengthening and stretching components, with or without aerobic exercise, shows the greatest likelihood among other combinations of being the optimal exercise type. These findings might have utility informing future trials and personalising treatment strategies for people with CS features.

List of abbreviations

AMED	Allied and Complementary Medicine Database
AMSTAR2	Assessment of Multiple Systematic Reviews-2
CENTRAL	Cochrane Central Register of Controlled Trials
CINAHL	Cumulative Index to Nursing & Allied Health Literature
CNS	Central nervous system
CPM	Conditioned pain modulation
CrI	credible intervals
CS	Central sensitisation
CSI	Central Sensitisation Inventory
EMBASE	Excerpta Medica Database
EMG	Electromyography

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FIQ	Fibromyalgia Impact Questionnaire
GRADE	Grading of recommendation, assessment, development, and evaluation
MEDLINE	Medical Literature Analysis and Retrieval System Online
NMA	Network meta-analysis
PRISMA-P	Systematic Reviews and Meta-Analysis -Protocols guidelines
PROSPERO	The International Prospective Register of Systematic Reviews
QST	Quantitative Sensory Testing
REML	Restricted Maximum Likelihood
RCTs	Randomised control trials
RoB.2	The Cochrane risk-of-bias tool for randomised trials
SE	Standard error
SMD	Standardised mean difference
SUCRA	Surface Under the Cumulative Ranking
TS	Temporal summation
UNESCO	The United Nations Educational, Scientific and Cultural Organization

Introduction

Chronic pain is a major health problem globally, representing a huge economic and social burden [1]. There is often discrepancy between the extent of tissue damage and reported pain levels [2]. Hence, recent observations have widened the explanation of chronic pain to include pain modulation mediated by the central nervous system (CNS), which might be associated with central sensitisation (CS) [3]. Pain modulation by the CNS encompasses several mechanisms including neuronal plasticity, increased glial cell activity, enhanced activity of nociceptive facilitatory pathways, dysfunction of endogenous pain inhibitory pathways, alterations in grey and white matter structural integrity, and altered brain connectivity [4].

International Association for the Study of Pain defines CS as "increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold input" [5]. Evidence suggests that CS can develop independently of chronic pain and may be influenced by a variety of non-painful physiological and psychological factors [6,7]. Research indicates that CS can precede the onset of chronic pain conditions and that it interacts with these conditions in a bidirectional manner, contributing to both the initiation and maintenance of chronic pain [8,9]. Central neuronal responsiveness cannot be directly measured in humans, but several outcome measures (questionnaires, QST modalities, and neuroimaging) may function as CS indices. No single measurement modality provides a gold standard for assessing CS in humans [10]. The Central Sensitisation Inventory (CSI) [11] is a patient-reported outcome measure primarily assessing clinical features considered to be related to CS [12]. Other questionnaires could serve as indicators of CS including fibromyalgia severity questionnaires and classification [13,14].

Quantitative Sensory Testing (QST) assesses sensory responses to standardised stimuli and offers information about potential pain mechanisms. Increased sensitivity to stimuli in healthy or non-painful body areas has been proposed as an index for CS [12]. Several modalities are used in QST. Low pressure pain detection thresholds (PPT) at sites without demonstrable tissue pathology [15], high temporal summation (TS), and low conditioned pain modulation (CPM) [16,17] might respectively reflect widespread CNS sensitisation, spinal sensitisation, or deficient descending inhibitory control.

Electromyography (EMG) has been used to record motor unit electrical activity, then understand the effect of CNS processing on the ventral horn and motor control. This can help to assess the neural drive to the muscle [18]. Altered motor control has been associated with chronic pain [19,20].

Chronic pain treatment often focuses on peripheral nociception, which arises from damage to peripheral non-neural tissue. However, peripheral input is only one mechanism of pain, and modifying nociception might not adequately relieve chronic musculoskeletal pain [12]. CS indices are often associated with worse treatment outcomes, and so improving CS indices has the potential to improve outcomes for people with chronic pain [21].

Exercise has been defined by United Nations Educational, Scientific and Cultural Organisation (UNESCO) as "any bodily activity that is intended to enhance or maintain physical fitness and overall health and wellness" [22]. Exercise has the potential to reduce CS indices and produces short-term hypoalgesia in healthy, pain-free individuals [23].

However, exercise induced hypoalgesia is more variable in people with chronic pain and might be dependent on exercise type and dosage [23]. The mechanisms underlying exercise induced hypoalgesia are not completely understood, but might include activation of endogenous descending inhibitory (analgesic) pathways [24,25], and altered brain neurobiology [26]. Exercise might also inhibit spinal facilitatory pathways [27]. Acute exercise may alternatively cause pain flares in people with chronic pain and might increase joint inflammation [23]. Exercise therefore has the potential to reduce CS indices, but the optimal dose and type of exercise is not known. This systematic review aimed to address these unknowns to inform the design or selection of an optimal exercise intervention aiming to reduce CS indices, and therefore improve outcomes in people where CS contributes substantially to their pain. Therefore, the research questions for this systematic review were:

1. What are the effects of different exercise regimens on CS indices in adults?
2. Which type of exercise is the most effective?

Methods

This systematic literature review was designed and reported using the Preferred Reporting items for Systematic Reviews and Meta-Analysis Protocols guidelines (PRISMA-P) [28], (Additional Material), and the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [29]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42022312776 [30].

Search methods and eligibility criteria

We first developed the search strategy in the Medical Literature Analysis and Retrieval System Online (MEDLINE) and then adapted it to the other databases, Excerpta Medica Database (EMBASE), Allied and Complementary Medicine Database (AMED), Cumulative Index to Nursing & Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus, each from inception to November 2023. We also searched reference lists of the relevant systematic reviews to identify additional reports. The full research strategy is presented in Appendix A. All citations were exported to EndNote X9 for screening.

We included studies that reported the effect of exercise on CS indices in adult human populations (Table 1). The search was restricted to English language. We excluded studies when exercise was combined with any other intervention/s, other than education, studies with an intervention that does not meet the UNESCO exercise definition, and studies with only acute exercise (1 or 2 bouts). Cross-sectional studies, letters, reports, conference papers, and congress abstracts were excluded.

Study selection

Duplicate citations were removed. Titles and abstracts were screened against inclusion and exclusion criteria, and full texts of the

Table 1
Inclusion criteria for the systematic review.

Study design	Observational or interventional longitudinal studies (e.g., randomised controlled trials (RCTs), cohort studies)
Population	Any adult human population (aged 17 or more)
Intervention	Exercise interventions as defined by UNESCO "any bodily activity that is intended to enhance or maintain physical fitness and overall health and wellness". Three or more bouts of exercise within one or more weeks, as the minimum amount.
Comparison	For pairwise meta-analysis: Baseline measurements were used as comparators/ control to follow up measurements within study groups For NMA: passive controls were used as the common comparator to the intervention group.
Outcomes	Central sensitisation outcome measures including: - QST modalities: temporal summation, spatial summation, conditioned pain modulation, sensation, and detection threshold of sensory stimuli (heat, cold, pressure, electricity, or vibration). - EMG changes of motor unit associated with chronic pain. -Self-report questionnaires designed to measure indices of CS: Central sensitisation inventory (CSI), CSI-9, and Pain Sensitivity Questionnaire (PSQ). - Other questionnaires evaluating symptoms putatively associated with CS: Fibromyalgia Impact Questionnaire (FIQ), and PainDETECT questionnaire.

selected studies were assessed. The process of screening was conducted by one reviewer (AAI) for all studies (90,268) and then validation of 8800 randomly selected articles was conducted by 6 reviewers (DAW, DFM, SLS, WJC, VG, and AK; different articles were selected for each reviewer).

Data extraction

Data extraction for each trial was conducted by 2 reviewers using published data only (AAI performed data extraction for all eligible articles and validation extractions were done by SLS or MS). Any disagreements were discussed and resolved between reviewers, and a third reviewer (DAW) made the final decision. Data extraction followed the PICO framework (population, intervention, comparison, outcome) [31]. If measures were presented as figures or diagrams, we estimated the data using WebPlotDigitizer 4.6 [32].

Exercise interventions were classified based on the Physical Activity Guidelines for Americans [33] and other systematic reviews [34,35] into 5 broad categories; (1) aerobic exercise; (2) strengthening exercise; (3) stretching exercise; (4) mind-body exercise; (5) multi-component exercises [36]. The multi-component exercises were further classified according to the combinations that were used in the included studies ("Strengthening & stretching", "Aerobic & stretching", "Aerobic & strengthening", "Aerobic, strengthening & stretching").

Quality assessments

The Cochrane risk-of-bias tool for randomised trials (RoB.2) [29] was used to assess risk of bias for the trials used in meta-analysis. It contains 6 domains assessing performance bias, selection bias, detection bias, attrition bias, and selective outcome reporting. This tool categorises risk of bias of the studies into" low, high or some concern". All domains needed to have a low risk of bias in order for the trial to be categorised as "low". If one or more domains had some concerns or high risk of bias, the trial was categorised as "some concerns" or "high", respectively. Two independent reviewers (AAI and DFM) evaluated risk of bias. The inter-rater agreement for using RoB.2 tool was calculated with the Kappa statistics in R [33].

Data synthesis and analysis

Pairwise meta-analysis

Initially, we conducted a pairwise meta-analysis to estimate the effect of the various classes of exercise intervention on all CS indices. We used a random-effects model, using Restricted Maximum Likelihood (REML) estimation to accommodate both within-study and between-study variability. This method was chosen to provide unbiased estimates under the assumption of heterogeneity across studies. Studies were weighted using inverse variance weighting, which assigns more weight to studies with more precise estimates [37]. Multiple CS indices were measured on different scales, so we used standardised mean difference (SMD), with 95 % CIs, to combine effect sizes. SMD was calculated using the means and SDs of baseline and post-intervention. When no SDs were available, they were calculated from CIs, standard errors (SEs), t or *P* values [29,38]. A negative SMD denoted an improvement in the CS index. An SMD >0.8 was categorised as a large effect, >0.5 as moderate, and >0.2 as small [39]. Between-study heterogeneity was assessed using the I^2 statistic (25 %, low heterogeneity, 50 % medium, and ≥75 % high), Tau^2 (τ^2) (0, low heterogeneity, $0 \leq \tau^2 < 1$ moderate heterogeneity, and $\tau^2 \geq 1$ high heterogeneity), and the Cochran's Q test (a *P* value <0.05 indicating heterogeneity). The I^2 statistic is a descriptive measure indicating the percentage of total variation across studies that is due to heterogeneity rather than chance [40].

To assess publication bias, we initially conducted a visual inspection of a funnel plot (SMD plotted against SEs) in R, in addition to Egger's regression and rank correlation tests [41,42]. Upon identifying publication bias, we applied the trim-and-fill method to adjust for this bias [43]. This method estimates the number of missing studies that might exist due to publication bias and then imputes these missing studies to create a more symmetrical effect size distribution. The results of the trim-and-fill analysis are presented in Appendix B, where the funnel plot before and after adjustment illustrates any impact of addressing publication bias on our meta-analysis. Furthermore, we conducted, pre-specified subgroup analyses [30] (by exercise type, used outcome measure, exercise supervision, exercise setting, and follow-up measures at different time points) to explore potential sources of heterogeneity. We undertook a sensitivity analysis using only low risk of bias studies to verify the robustness of our results. Moreover, we performed a mixed effects meta-regression analysis to test for association between the SMDs of CS indices of individual studies and the reported exercise dose, age or sex. Meta-analysis and subgroup analyses were conducted using Revman manager 5.4. Additionally, meta-regression was conducted using the Meta [44], and Metafor [45] packages in R (Version: 4.2.2) (Appendix C). Additional R packages used were tidyverse (data manipulation and visualisation), devtools (supporting package installation and updating), irr (inter-rater reliability), MASS (dataset processing) and dmetar (diagnostic tests). We used 2 statistical software engines because of their complementary strengths. R offered advanced statistical capabilities, especially for meta-regression and network meta-analysis (NMA). Graphical representations used Revman manager, which provided high-quality figures when using large datasets, without truncating plots.

Network meta-analysis

We conducted an NMA to compare various exercise interventions using non-exercise controls (care as usual, placebo, education) as a common comparator. This involved combining both direct evidence from individual studies and indirect evidence obtained through shared comparators. SMDs were calculated in each study both for exercise and for control groups [46]. To validate the integration of populations with and without chronic pain in our network meta-analysis, we stratified the data to separately analyse the effects of exercise on CS in populations with and without chronic pain.

Two different models were used in the NMA to assess robustness of findings under different statistical frameworks. A Bayesian NMA analysis was conducted as the primary analysis (a probabilistic framework, accommodating prior information, using Markov Chain Monte Carlo (MCMC) methods for robust parameter estimation). Also, a Frequentist NMA was performed as a sensitivity analysis (using likelihood-based methods to attain point estimates and confidence intervals). The Bayesian model was chosen for the main analysis for its flexibility and capability of handling complex models.

For the Bayesian model, we conducted random-effects meta-analyses using MCMC methods. This approach considered both within-study and between-study heterogeneity, allowing for the possibility that direct and indirect estimates may exhibit inconsistency due to differences in study populations, methodologies, or other factors [47]. We ran 4 independent MCMC chains to enhance the robustness of our analysis. Each chain was updated with 100,000 simulated draws following a burn-in period of 5000 iterations. The convergence of these chains was assessed using the Gelman–Rubin diagnostic, which indicated satisfactory convergence (values close to 1) (Appendix D). The effect size of the posterior distribution, based on the combined 400,000 simulations was reported as the SMD, and the corresponding 95% credible intervals (CrIs).

To quantify network heterogeneity, we used the I^2 statistic and the tau^2 (τ^2) measure, which provided an estimate of the variance of true effect sizes across studies. Node splitting analysis, comparing direct and indirect estimates, was used to evaluate incoherence and inconsistency within the network. Additionally, the Cochran's Q statistic served as a supportive measure, not only assessing heterogeneity between comparisons but also aiding in loop-specific inconsistency tests and evaluating the overall consistency in the network [48]. We adopted a relaxed significance threshold of 0.10 for these assessments, enhancing our ability to detect subtle but potentially important inconsistencies [49]. Additionally, the robustness of our Bayesian model simulations was ensured through the Gelman–Rubin diagnostic, confirming the convergence and stability of our analyses.

To assess transitivity, we aimed for a consistent distribution of potential effect modifiers, such as average age, percentage of females, pain status, and risk of bias, across both trials and intervention arms. We then conducted a visual inspection of these factors using tables, forest plots, and scatter plots to identify any patterns or variations, providing a qualitative assessment of the consistency within the network (Appendix E). After that, we also attempted a quantitative assessment using meta-regression analysis to further explore the relationship between effect sizes and potential effect modifiers. In response to observed variabilities in these potential effect modifiers, additional sensitivity analyses were conducted by excluding outlier comparisons beyond the interquartile range (IQR) from the median for age, % female, and % with chronic pain, as per recent meta-analysis guidelines [25] (Appendix E).

All analyses were performed using R (Version: 4.3.2), using the rjags package [46] for Bayesian NMA, and the Metafor package [41] for Frequentist NMA (Appendix C). NMA results were visualised using forest plots. Possible publication biases were assessed through visual inspection of comparison-adjusted funnel plot [16]. Bayesian NMA ranks treatment using Surface Under the Cumulative Ranking (SUCRA) score, equivalent to P-score in frequentist NMA. These scores of 0 to 1 represent the certainty that one treatment is better than others, where score 1 represents the best treatment. Sensitivity analysis was performed to assess whether the exclusion of the studies with high risk of bias increased the certainty of evidence and maintained the treatment rank obtained from the primary network.

Certainty of evidence in NMA

We rated the confidence in estimates derived from NMA by applying the grading of recommendation, assessment, development, and evaluation (GRADE) approach [50]. In this approach, the rating of a direct estimate, derived from a trial, starts as high certainty and can be rated down based on risk of bias, indirectness, heterogeneity, imprecision, and publication bias. Possible ratings are high, moderate, low, and very low confidence. The indirect estimates (first-order loops) start at the lowest rating of the 2 direct, pairwise estimates that make up the indirect estimate; but could be rated down further for intransitivity or imprecision [50,51]. If direct and indirect estimates for a particular comparison were available, then the higher of the 2 certainty ratings was assigned to the NMA estimates [50]. The overall GRADE was categorised as high, moderate, low, and very low certainty of evidence for each intervention. Two independent reviewers (AAI and DFM) conducted this approach, and disagreements were discussed and resolved. The GRADE approach was re-applied in the sensitivity analysis after removal of studies with high risk of bias. More details of our GRADE approach can be found in Appendix F.

Narrative synthesis

We summarised characteristic analysis and included studies, including data that could not be pooled in quantitative analyses, and present them in Appendix G. Additionally, the dose of exercise was reported narratively because the main parameters used to quantify exercise dose (frequency, intensity, session duration and length of exercise program) were not consistently reported in a way that allowed pooling. For descriptive statistics, median (with IQR) and frequency (with percentage) were used as measures of central tendency and measures of exercise details frequency reporting, respectively (Appendix H). Box plots showing distribution of exercise dose parameters are in Appendix I. Classification of l large or major muscle groups comprised muscles around legs, hips, back, abdomen, chest, shoulders, and arms [52].

Results

Literature search and study characteristics

The search was completed on 17th November 2023, and identified a total of 101,655 potentially eligible studies, with 90,268 remaining after removal of duplicates. After title and abstract screening 89,413 studies were removed leaving 855 studies for full text screening. In total, 249 studies met our eligibility criteria and were included in the review. Of these studies, 164 studies (6118 participants, 68 % female) provided data suitable for meta-analysis, and 89 studies (6223 participants, including non-exercise and active treatment groups) provided data suitable for NMA. Fig. 1 depicts the selection process, and the characteristics of the included studies are in Appendix G. PPT (77 studies), and the Fibromyalgia Impact Questionnaire (FIQ) (83 studies) were the most used CS-related outcome measures in the included trials. Other outcome measures included CPM, TS, heat pain threshold, evoked potential, and CSI. Year of publication of studies eligible for inclusion ranged from 1994 to 2023. There were 5592 (92 %) participants diagnosed with chronic pain conditions (140 studies: 79 fibromyalgia, 18 neck and shoulder pain, 15 knee osteoarthritis, 8 low back pain, and 20 others), and 512 (9 %) classified as without chronic pain (23 studies).

Inter-rater agreement of the screening and risk of bias assessment

We measured inter-rater agreement of the screening and found 90 % (κ=0.94) agreement for all studies and 98% (κ=>0.99) agreement for randomised control trials (RCTs). This exceeded the Assessment of Multiple Systematic Reviews-2 (AMSTAR2) recommendation of > 80 % agreement [53]. Disagreements were discussed and resolved with co-authors (DAW, DFM, SLS, WJC, VG).

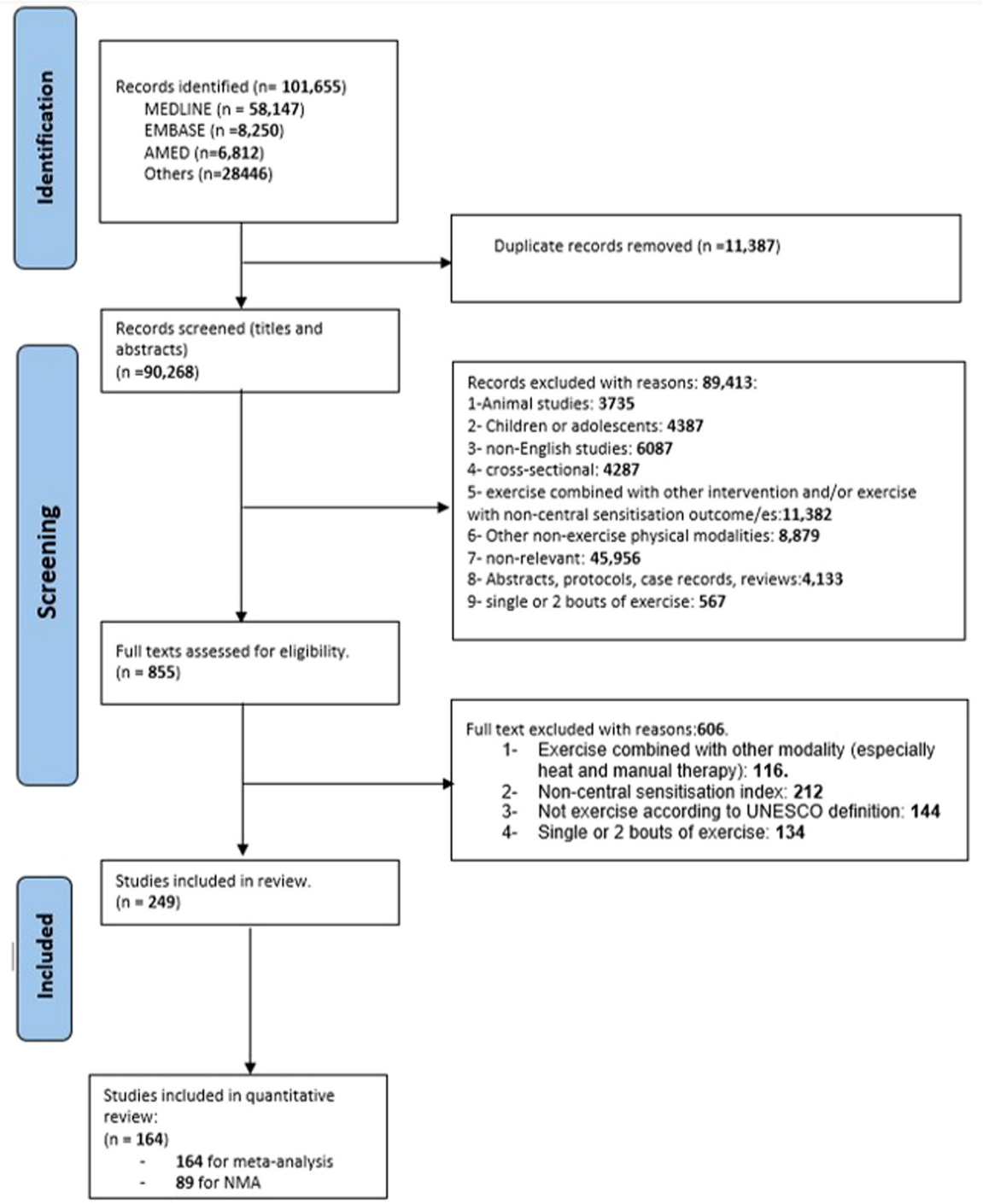

Fig. 1. PRISMA flow diagram: Illustrating the study selection process.

The inter-rater agreement for using the RoB.2 tool showed substantial reliability (91 % agreement, κ= 0.8) between the 2 reviewers. Disagreements were resolved by discussion and consulting a third reviewer (DAW).

Exercise modalities and doses

The most frequently reported type of exercise was strengthening exercise (32 studies, 892 participants), followed by aerobic exercise (26 studies, 997 participants), combined exercise featuring aerobic and strengthening components (18 studies, 467 participants), combined exercise featuring strengthening and stretching components (12 studies, 361 participants), stretching exercise (9 studies, 247 participants), mind-body exercise (10 studies, 262 participants), combined exercise featuring aerobic and stretching components (4 studies, 103 participants), and combined exercise featuring aerobic, strengthening and stretching components (4 studies, 110 participants).

The exercise dose parameters were recorded and summarised (according to criteria presented in Appendix H) in Appendix I. Studies reported a median of 3 (range 1;14) exercise sessions per week. The frequency of sessions was not reported in 8 of the selected studies. Sessions lasted a median of 45 (range 10;150) min. Duration of sessions was not reported in 33 studies. Duration of the exercise

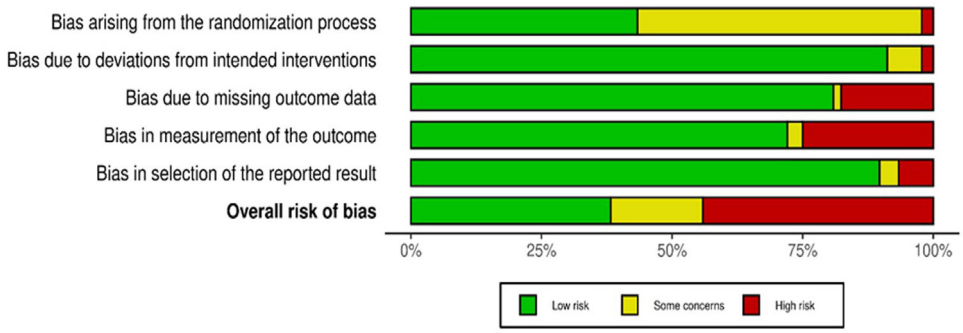

Fig. 2. Risk of bias graph: Summarising the methodological qualities of included RCTs using the Cochrane ROB.2 tool. Green for low risk, yellow for some concerns, and red for high risk of bias. 36 % of RCTs showed low risk of bias, and 43 % showed high risk of bias.(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

program was reported in 233 studies, with a median of 8 weeks (range 1 week; 2 years). For aerobic exercise, intensity was reported as % maximum heart rate (HR_{max}), or % maximum oxygen uptake (VO_{2max}). For strengthening exercise, intensity was expressed as number of sets and repetitions, or % one repetition maximum, which is the maximum amount of weight that a person can lift once. Intensity of exercise was not reported in 74 studies. Strengthening and/or stretching exercises targeted large muscle groups (102 studies) or small muscle groups (8 studies) or both (43 studies). Furthermore, exercise progression (gradual increase of exercise intensity as the body adapts to exercise over time) was reported in 192 studies (Appendix I). Boxplots for the distribution of reported exercise parameters are in Appendix J. Inconsistent reporting and lack of uniformity in exercise dose parameters precluded statistical analysis to determine the optimal exercise dose.

Effect of exercise on CS indices (Conventional meta-analysis)

Random-effects model meta-analysis was conducted on 164 trials (6110 participants) (Appendix G) investigating the effect of any exercise on any CS indices. We found a significant pooled effect of exercise to reduce CS indices (SMD = −0.81 95% CI= −0.93; −0.70, (I^2=88%, τ^2=0.44, $p < 0.0001$), (Appendix K).

Quality assessment

Of the 164 included trials, 58 (36 %) scored low risk of bias, 36 (22 %) raised some concerns, and 70 (42 %) had high risk of bias (Fig. 2). Study-level risk of bias assessment is shown in Appendix L. Sensitivity analysis performed using only low risk of bias trials confirmed an effect of exercise on CS indices, with a slightly lower effect size (SMD = −0.77, 95% CI −0.83 to −0.72, I^2 = 92 %, τ^2 = 0.55, $P < 0.0001$) than in the primary analysis.

Publication bias

Inspection of a funnel plot (Fig. 3) revealed asymmetry, skewed towards a favourable effect suggesting possible reporting biases. Egger regression ($z = -3.88$, $P < 0.001$) and rank correlation test (Kendall's tau = −0.12, $P = 0.02$) were significant, consistent with publication biases. After applying the trim-and-fill method, we recalculated the pooled effect size considering the hypothetical missing studies. This yielded a pooled effect size that was not substantially different from our initial findings (SMD = −0.74 95% CI −0.84 to −0.64, I^2 = 84%, τ^2 = 0.32, $P < 0.0001$), (Appendix B).

Subgroup analyses and meta-regression

Our conventional subgroup meta-analysis did not effectively address the heterogeneity observed in the data, as heterogeneity persisted across the different subsets analysed (Table 2, and Appendix M & N). Additionally, meta-regression analysis found no significant associations with age, sex, or exercise dosage on CS indices. No significant effects were found, indicating that these factors did not substantially influence the treatment outcomes for CS indices. The detailed meta-regression models are provided in Appendix O.

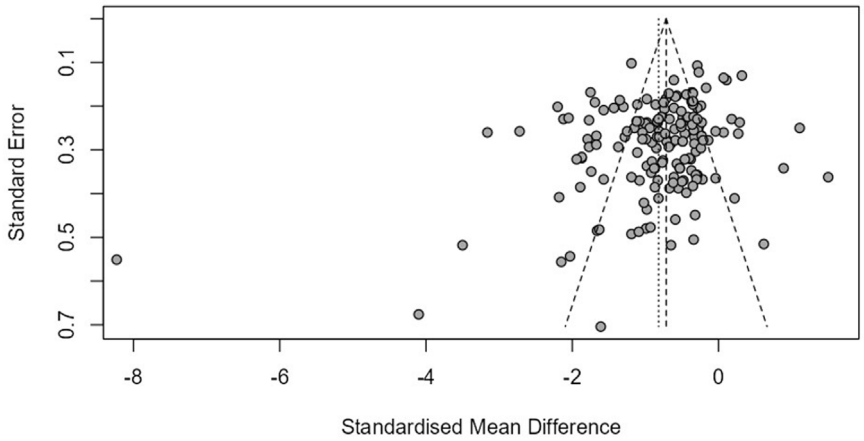

Fig. 3. Funnel plot: Assessing possible publication bias in the meta-analysis (Egger, $P < 0.01$). X-axis represents the magnitude of the effect size and Y-axis represents precision. The vertical dotted line represents "no effect"; to the left of this line, the effect favours exercise while to the right effect favours the control group. SMD: Standardised Mean Difference.

Table 2
Subgroup analyses.

Subgroup	Group number	Number of Participants	SMD (95% CI)	SMD *P* value	Heterogeneity	
					I^2	*P* value
Exercise type:	**159**	**8979**	**−0.79 [−0.89 to −0.69]**	**<0.0001**	**83 %**	
strength	56	4907	−0.79 [−0.96 to −0.62]	<0.0001	81 %	<0.0001
aerobic	33	1130	−0.99 [−1.27 to −0.70]	<0.0001	89 %	
stretch	18	465	−0.54 [−0.72 to −0.36]	<0.0001	41 %	
mind-body	14	438	−0.85 [−1.24 to −0.45]	<0.001	87 %	
balance	3	66	−0.07 [−0.47 to 0.32]	0.7200	22 %	
strength+ stretch +aerobic	13	329	−0.56 [−0.80 to −0.32]	<0.0001	55 %	
strength +aerobic	23	679	−0.89 [−1.17 to −0.61]	<0.0001	82 %	
strength +stretch	23	795	−0.85 [−1.18 to −0.53]	<0.0001	89 %	
aerobic +stretch	5	170	−0.51 [−0.73 to −0.30]	<0.0001	0 %	
Outcome measure:	**162**	**7089**	**−0.78 [−0.89 to −0.68]**	**<0.0001**	**88 %**	
PPT	77	2567	−0.76 [−0.95 to −0.57]	<0.0001	90 %	<0.0001
HPT	4	87	−0.37 [−0.79 to 0.06]	0.0900	47 %	
CPM	5	328	−0.72 [−1.44 to 0.01]	<0.0001	93 %	
TS	6	345	−0.21 [−0.37 to −0.06]	0.0070	0 %	
FIQ	83	3444	−0.89 [−1.03 to −0.74]	<0.0001	87 %	
CSI	2	120	−0.72 [−1.20 to −0.24]	<0.001	70 %	
Evoked potential	13	198	−0.70 [−1.04 to −0.36]	<0.0001	60 %	
Type of population	**164**	**6094**	**−0.82 [−0.93 to −0.71]**	**<0.0001**	**88 %**	
People with chronic pain	138	5611	−0.87 [−0.99 to −0.75]	<0.0001	89 %	<0.0001
People without chronic pain	24	483	−0.48 [−0.73 to −0.22]	<0.001	71 %	
Different time points	**166**	**11,349**	**−0.80 [−0.89 to −0.71]**	**<0.0001**	**87 %**	
after intervention	166	9378	−0.84 [−0.95 to −0.73]	<0.0001	87 %	
3-months follow-up	20	722	−0.75 [−1.10 to −0.41]	<0.0001	89 %	0.0020
6-months follow-up	12	784	−0.75 [−1.04 to −0.45]	<0.0001	86 %	
12-months follow-up	11	465	−0.46 [−0.61 to −0.30]	<0.0001	31 %	
Land or pool based.	**168**	**6029**	**−0.75 [−0.79 to −0.72]**	**<0.0001**	**86 %**	
land	151	5347	−0.75 [−0.79 to −0.71]	<0.0001	86 %	0.8800
pool	17	682	−0.76 [−0.87 to −0.65]	<0.0001	80 %	
Supervised or not.	**123**	**7827**	**−0.81 [−0.94 to −0.69]**	**<0.0001**	**87 %**	
supervised	23	6964	−0.89 [−1.04 to −0.75]	<0.0001	87 %	<0.0001
unsupervised	20	863	−0.47 [−0.67 to −0.27]	<0.0001	73 %	

Subgroup analyses showing the SMD (standardised mean difference) of each subgroup, heterogeneity of each subgroup analysis used I^2, with *P* value <0.05 representing significant heterogeneity. 95 % CI: 95% confidence interval.

Comparative effectiveness of exercise interventions (NMA)

Eighty-nine trials were included in the NMA comparing the effects of various exercise interventions on CS indices. Between 4 and 32 groups were available for each of the 8 exercise categories. The most common exercise category investigated was strengthening exercise (28%), followed by aerobic (23 %) and aerobic & strengthening combination (16 %) (Table 3). The NMA results included 24 pairwise comparisons as well as 36 with only indirect comparisons (89 trials, 187 groups, 6235 participants, 83 two-arm trials, 5 three-arm comparison trials, and 1 four-arm trial) (Appendix P). There was direct evidence available for 24 (66 %) of the possible treatment comparisons. Fig. 4 shows the network graphs and forest plots for the NMA. Improvement in CS indices was found for each exercise type, compared with controls, with SMDs ranging from −0.48 to −1.67. Combined exercises featuring strengthening and stretching, followed by strengthening combined with stretching and aerobic exercise, then aerobic combined with stretching exercise and mind-body exercise had largest improvements in CS indices. Our stratified analysis results, detailed in Appendix Q, supported the beneficial impact of exercise on CS indices across populations both with and without chronic pain.

To assess transitivity, we undertook visual inspection of tables, forest plots, and scatterplots which showed a varied distribution of potential effect modifiers across the comparisons between exercise interventions in the NMA. Potential outliers were identified for some comparisons for participant age, sex, and prevalence of chronic pain (Appendix E). The outliers were one comparison with no females (0 %), 2 comparisons with young men aged 24.3 and 25.4 years, and one comparison with no reported chronic pain (0%) (Appendix E). Quantitative assessment of transitivity through meta-regression analysis was not feasible due to very low numbers of studies per comparison. The sensitivity analyses revealed minimal differences compared to the primary analyses in the SMDs and no difference in the ranking of the top exercise interventions. Findings in our primary analyses were consistent with our sensitivity analyses, despite the presence of outlier studies (Appendix E). No asymmetry was observed in the funnel plot for the NMA (Fig. 5, Egger's test $p = 0.86$. Heterogeneity of the NMA was high ($\tau^2 = 0.6493$, $I^2 = 89\%$, $P < 0.0001$). Inconsistency between direct and indirect evidence was detected in 2 comparisons (Strengthening, stretching & aerobic combination exercise vs control and Strengthening, stretching & aerobic combination exercise vs aerobic exercise), (Appendix R). Forest plots illustrating net split results when comparing direct and indirect evidence are in Appendix S.

Frequentist NMA, undertaken as a sensitivity analysis, showed the same rank order of exercise categories as did the Bayesian NMA (Appendix T). Sensitivity analysis excluding studies with a high risk of bias showed that combined exercise featuring strengthening, stretching and aerobic components was ranked 1st, followed by strengthening combined with stretching exercise (Appendix U). Minor differences in the ranking of the lower-ranked exercise categories were found in this sensitivity analysis.

Discussion

First, we found using conventional meta-analysis that exercise has a large effect in reducing CS indices. After that, we pinpointed through NMA that exercise combinations that included stretching plus strengthening exercises were most effective for reducing CS indices.

Table 3
Group approach for rating the quality of treatment effect estimates from primary network meta-analysis (GRADE).

Classification	Intervention	Total studies: 89 RCTs Total participants:3398	Effect size SMD (95% CrI)	SUCRA score	Rank	Certainty (GRADE)
Very large beneficial effect (≥ 1.3)	Strength & stretch	11 arms (335 participants)	−1.67 (−2.41 to −0.97)	0.8389	**1st**	**Low**
	Strength & stretch& aerobic	4 arms (125 participants)	−1.61 (−2.74 to −0.56)	0.8146	**2nd**	**Moderate**
	Aerobic & stretch	4 arms (103 participants)	−1.55 (−2.74 to −0.42)	0.7870	**3rd**	**Low**
	Mind body	10 arms (413 participants)	−1.49 (−2.23 to −0.74)	0.7565	**4th**	**Low**
Large beneficial effect (<1.3, ≥0.8)	Aerobic & strength	18 arms (467 participants)	−0.92 (−1.50 to −0.42)	0.4479	**5th**	**Very low**
	Strength	32 arms (853 participants)	−0.85 (−1.42 to −0.45)	0.3839	**6th**	**Very low**
Moderate effect size (<0.8, ≥0.5)	Aerobic	25 arms (970 participants)	−0.60 (−1.13 to −0.13)	0.2796	**7th**	**Very low**
Small effect size (<0.5)	Stretch	9 arms (247 participants)	−0.48 (−1.22 to 0.23)	0.1868	**8th**	**Low**

High certainty: Further research is very unlikely to change our certainty in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our certainty in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our certainty in the estimate of effect and is likely to change the estimate.
Very low certainty: Any estimate of effect is very uncertain.
95 **%** CrI: 95 **%** credible interval.

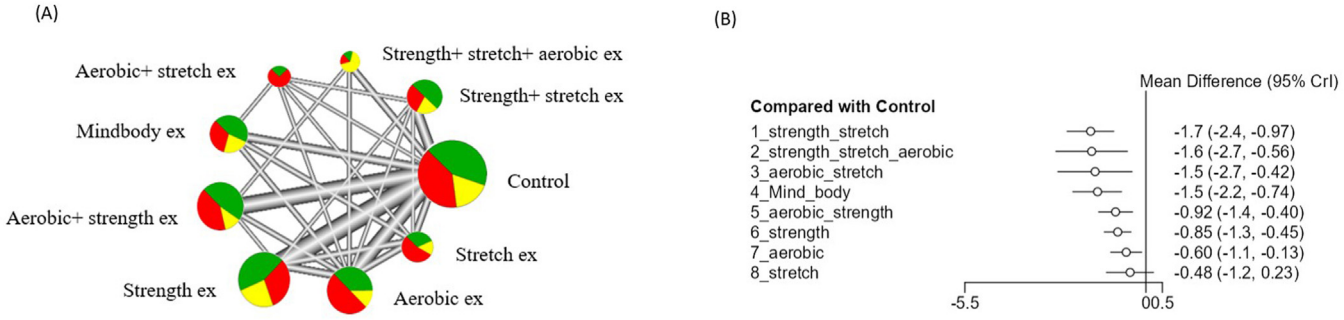

Fig. 4. (A) Network graphs: The size of the circle is proportional to the number of participants included in each intervention, and the width of the line is proportional to the number of trials directly comparing 2 interventions. Coloured areas within each node correspond to the proportion of RCTs with respect to risks of bias assessment as follows: green for low risk, yellow for some concerns, and red for high risk of bias. (B) Network forest plot: Showing the ranks of different types of exercise intervention in Bayesian network. ([strength & stretch & aerobic; k = 4, n = 125], [strength & stretch; k = 11, n = 335], [aerobic & stretch; k = 4, n = 103], [mind-body exercise; k = 10, n = 413], [aerobic & strength; k = 18, n = 467], [strength; k = 32, n = 853], [aerobic; k = 25, n = 970], [stretch; k = 9, n = 247], [control; k = 73, n = 2710] where k = number of trials, n = number of participants). SMD: Standardised Mean Difference, 95% CrI: 95% Credible interval, CS: central sensitisation.(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

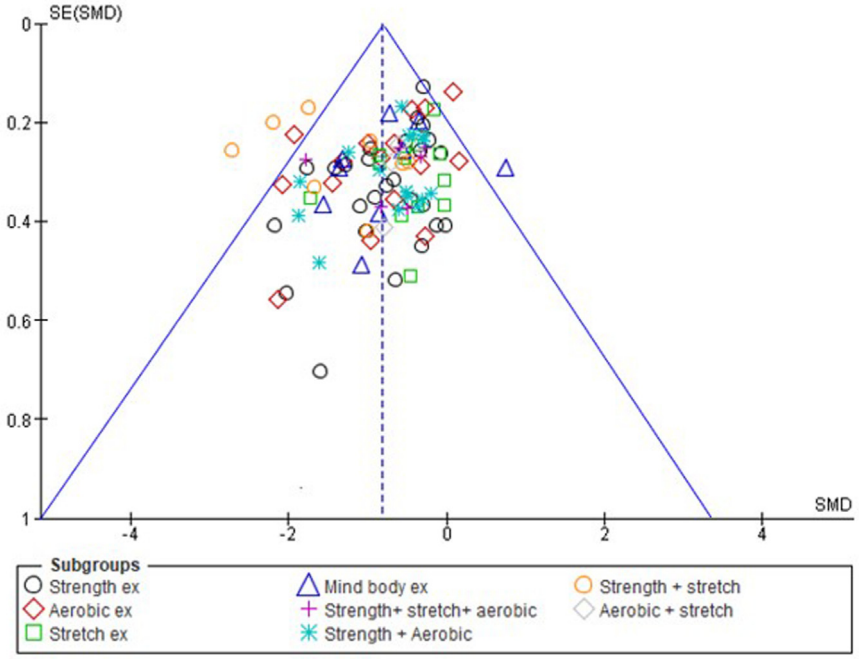

Fig. 5. Network Funnel plot: Assessing possible publication bias in the network meta-analysis (Egger, P = 0.83. X-axis represents the magnitude of the effect size and Y-axis represents precision. The vertical dotted line represents "no effect"; to the left of this line, the effect favours exercise whereas to the right effect favours the control group. SMD: Standardised Mean Difference, SE: Standard Error.

Overall effect of exercise on CS indices

The results of this meta-analysis are consistent with previous reviews reporting that exercise could reduce CS indices [54,55]. Different types of exercise reduced CS indices, particularly aerobic exercise, strength combined with aerobic exercise, and strength combined with stretch exercises. Our findings indicate that exercise can reduce pain sensitivity in individuals with or without chronic pain, but the effects were larger in people with chronic pain. People with chronic pain are more likely to display evidence of CS [12] and the greater effects of exercise in this group indicate the potential reversibility of CS.

We found that exercise could improve a wide range of CS indices, including FIQ, CSI, PPT and CPM. Several mechanisms might explain how exercise can modulate pain, however, the exact changes occurring in the pain pathways are unclear, as are their relative importance. Effects of exercise on CPM suggest restoration of deficient endogenous analgesic modulation by the CNS [56,57]. Effects on self-report measures such as FIQ and CSI might be explained by psychological benefit [58,59]. Maintenance of benefits from exercise will be important for chronic conditions associated with pain, where ongoing nociceptive drive might sustain or rekindle CS [8].

Comparative effects of different exercise categories on CS indices

Our NMA included 89 trials with 6223 participants and supported our initial findings that all exercise types, except stretching exercise alone, were more effective at reducing CS indices than were non-exercise controls. Combined exercise featuring strengthening and stretching components had the highest probability of being the most effective exercise type for reducing CS indices, followed by strengthening combined with stretching and aerobic exercise, then aerobic combined with stretching exercise, and then mind-body exercise. Differences between effect sizes for the 4 top-ranked exercise categories were small, and 95 % CrI were overlapping, therefore not permitting definitive conclusions on the superiority of any one of these top-ranked exercises. Indeed, in the sensitivity analysis using data only from trials graded as 'low' or 'some concern' risk of bias, combined exercise featuring aerobic, strengthening and stretching components emerged as the top-ranked intervention, followed closely by strengthening, stretching exercise combination. Despite this change in ranking, the narrower 95% CrI associated with strengthening, stretching exercise combination, as opposed to the wider 95 % CrI of combined exercise featuring aerobic, strengthening and stretching components, signals a more reliable and precise estimate. This suggests a higher degree of confidence in its effectiveness, potentially denoting a more consistent therapeutic benefit.

Previous systematic reviews of specific exercise types also found improvement of selected CS indices in response to aerobic, strengthening or mind-body exercises [54,55]. Our data update these findings with more recently published studies and extend them by showing the relative effects of different exercise categories and exercise combinations within a single NMA. This provides the current best evidence about which exercise categories are likely to have the greatest effect on CS indices. Our findings lead us to propose that a combination of stretching with strengthening exercise is most likely to relieve pain in people whose pain is predominantly driven by CS. A previous NMA reported that Pilates (strengthening + stretching) was the most effective reported exercise type for improving low back pain [60]. Chronic low back pain is often associated with high CS indices [61] and our data are consistent with suggestions that the benefits of Pilates in low back pain are, at least in part, mediated by reductions in CS. However other systematic reviews of exercise therapy for osteoarthritis pain [62] or fibromyalgia [63] indicated that aerobic combined with mind-body exercise, or aerobic combined with strengthening exercise were most effective in improving pain. This might suggest that factors other than CS influence analgesic responses to exercise in specific chronic pain conditions. Our finding that a broad range of exercise categories were associated with improvements in CS indices, is consistent with findings by De Zoete et al. that all studied exercise categories provided effective pain relief in people with chronic non-specific neck pain [64]. Such findings might suggest that uncontrolled contextual factors explain the analgesic benefits experienced by people undergoing exercise therapies. Our findings, alternatively suggest that the generic benefits of exercise on pain might be explained by shared effects on CS.

Strength and limitations

A key strength of our review is the large number of studies available for inclusion, which provided sufficient data to permit NMA and ranking of exercise categories. However, our findings are subject to several limitations. There was a relative scarcity in the research literature of trials comparing 2 exercise interventions head-to-head, rather than against a control. There was substantial statistical heterogeneity in the analyses. A wide variety of diagnoses and outcome variables were included, and the resulting heterogeneity might have concealed disease or outcome-specific effects. However, our subgroup and meta-regression analyses can contribute to a greater understanding of factors that might influence the effects of exercise on CS indices.

Our search was restricted to studies in the English language, although restricting reviews to English-language publications previously has been found to have little impact on effect estimates and conclusions [65]. High consistency between meta-analysis results using 2 different software packages suggests that our findings were not importantly influenced by the choice of package. Some baseline characteristics, other than age and sex, were not evaluated due to lack of data. Unreported characteristics might confound the effects of exercise and might conceal additional sources of bias. Moreover, 64% of trials included in our primary analyses had a high risk of at least one type of bias, especially performance bias. This might be an inevitable consequence of the inability to blind participants to exercise intervention. We attempted to overcome this limitation by conducting a sensitivity analysis with only low risk of bias studies, which yielded only a small reduction in the pooled effect estimate. There was heterogeneity in the follow-up periods for the intermediate and long-term effects of exercise interventions. Although the subgroup analyses highlighted differential effects in specific contexts, they did not effectively clarify the sources of heterogeneity. Therefore, it appears that other factors are responsible for the heterogeneity between studies. Most of the studies focused on the outcome at the end of interventions only and developed treatment recommendations based only on short-term data. For people with chronic pain, long-term outcomes might be more important than those immediately following an intervention. The lack of consistent reporting on exercise dose parameters made it difficult to conduct a comprehensive analysis to determine optimal exercise program recommendations. The use of exercise reporting templates [66] should be considered for future trials. We were unable to study anatomical targeting of exercise (eg, to sites of pain or pain-free regions), and future research might explore whether effects on CS indices depend on pain experienced during exercise or can be replicated if exercises can be targeted away from the area of pain. Some exercise combinations might be missing from our NMA, due to the unavailability of clinical trials; therefore, their effects on CS have not been studied. Our NMA revealed high heterogeneity, but our capacity to explore the underlying causes was limited due to constraints in the available data. Despite encountering high heterogeneity, we used the SMDs to enable meaningful comparisons across studies with diverse outcome measures and scales. This choice acknowledges some methodological limitations due to homogeneity assumptions but remains a practical

approach given our data constraints. We recognise the need for cautious interpretation of the NMA findings and see this as a groundwork for future research, which we hope will further refine methodologies in NMA as more homogeneous data become available. While visual inspection revealed some inconsistencies in the distribution of effect modifiers, these were addressed through sensitivity analyses to test the robustness of our findings. However, the lack of sufficient data for some comparisons limited our ability to perform meta-regression analysis, which remains a significant limitation. We recognise that future studies might wish to address this. Unmeasured factors might, therefore, have a greater impact on the comparisons between exercises than were revealed by our analyses. Most comparisons between interventions were judged to be of moderate or low certainty. Finally, we only addressed CS indices, and exercises can have additional benefits, for example cardiovascular, strength, mobility, balance, and psychological. Exercise might also have some adverse effects [67,68], which were not considered in this review. Translation into the clinic would need to take our findings within the context of other exercise goals, service delivery parameters such as cost and accessibility, as well as personal preference.

Clinical implications and conclusions

Our results provide evidence supporting the use of exercise for improving CS indices in people with chronic pain. All exercise types, except stretching exercise alone, were significantly more effective than non-exercise controls. We provide evidence, both from our main and sensitivity analyses, that a combination of stretching with strengthening exercise, with or without aerobic exercise, might be most effective at improving CS indices. High-quality reporting of exercise dose parameters is necessary to optimise personalised exercise prescription and improve evidence synthesis and replication. Future research should explore whether selecting exercise categories based on the presence of indices of CS, rather than necessarily on pathological diagnosis, might improve pain outcomes in people with evidence of CS.

Previous presentation of the research

Abstracts of earlier versions of this systematic review were presented at OARSI23 conference in Denver, USA, and BSR23 conference in Manchester, UK.

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Data availability

The data that support the findings of this study are available from the corresponding author, (Aya Abd Elkhabir Ibrahim), upon reasonable request.

Declaration of competing interest

Since 2015, DAW has undertaken consultancy through the University of Nottingham to AbbVie Ltd, Pfizer Ltd, Eli Lilly and Company, Love Productions, Reckitt Benckiser Health Limited and GSK (each non-personal, pecuniary). He has contributed to educational materials through the University of Nottingham, supported by Medscape Education, New York, International Association for the Study of Pain, and Osteoarthritis Research Society International (OARSI), each of which received financial support from commercial and non-commercial entities (each non-personal, pecuniary). He has received speaker fees from the Irish Society for Rheumatology (personal pecuniary). He has been responsible for research funded by Pfizer, Eli Lilly, UCB Pharma (non-personal, pecuniary). He receives a salary from the University of Nottingham, which has received funding for that purpose from Sherwood Forest Hospitals NHS Foundation Trust, Nottingham University Hospitals NHS Trust and UKRI/Versus Arthritis (personal, pecuniary). DM-grant support from Pfizer and Eli Lilly.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rehab.2024.101894.

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