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Effectiveness of treatments for acute and subacute mechanical non-specific low back pain: a systematic review with network meta-analysis

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ABSTRACT

Objective To assess the effectiveness of interventions for acute and subacute non-specific low back pain (NS-LBP) based on pain and disability outcomes.

Design A systematic review of the literature with network meta-analysis.

Data sources Medline, Embase and CENTRAL databases were searched from inception until 17 October 2020.

Eligibility criteria for selecting studies Randomised clinical trials (RCTs) involving adults with NS-LBP who experienced pain for less than 6 weeks (acute) or between 6 and 12 weeks (subacute).

Results Forty-six RCTs (n=8765) were included; risk of bias was low in 9 trials (19.6%), unclear in 20 (43.5%), and high in 17 (36.9%). At immediate-term follow-up, for pain decrease, the most efficacious treatments against an inert therapy were: exercise (standardised mean difference (SMD) −1.40; 95% confidence interval (CI) −2.41 to −0.40), heat wrap (SMD −1.38; 95% CI −2.60 to −0.17), opioids (SMD −0.86; 95% CI −1.62 to −0.10), manual therapy (SMD −0.72; 95% CI −1.40 to −0.04) and non-steroidal anti-inflammatory drugs (NSAIDs) (SMD −0.53; 95% CI −0.97 to −0.09). Similar findings were confirmed for disability reduction in non-pharmacological and pharmacological networks, including muscle relaxants (SMD -0.24; 95% CI -0.43 to -0.04). Mild or moderate adverse events were reported in the opioids (65.7%), NSAIDs (54.3%) and steroids (46.9%) trial arms.

Conclusion With uncertainty of evidence, NS-LBP should be managed with non-pharmacological treatments which seem to mitigate pain and disability at immediate-term. Among pharmacological interventions, NSAIDs and muscle relaxants appear to offer the best harm–benefit balance.

BACKGROUND

Low back pain is a common symptom in people of all ages and socioeconomic status. The worldwide point prevalence of low back pain (acute, subacute and chronic) was 7.83% (95% CI 7.04 to 8.64) in 2017, with 577 million people affected at any one time.[1] In 2017, low back pain was responsible for around 65 million years lived with disability, representing a deterioration of about 17.5% since 2007 mainly owing to population growth and ageing, with the greatest increase recorded for low-income and middle-income countries.[2] People more often leave their job because of low back pain than diabetes, hypertension, neoplasm, asthma, heart and respiratory disease combined.[3] About one in four adults in the USA had low back pain that lasted for at least 24 hours within the previous 3 months, with 7.6% adults reporting at least one episode of severe acute low back pain within a 1-year period.[4] Moderate-to-severe pain and impairment of motor and psychological functions due to low back pain are the primary reasons for seeking medical consultation from a general practitioner.[5]

Despite its high prevalence, low back pain has a generally good prognosis. While a specific cause of low back pain can seldom be identified, the most prevalent type is mechanical, non-specific low back pain (NS-LBP).[6] Most episodes of acute and subacute NS-LBP improve significantly within 6 weeks, and the average pain intensity is moderate (6 on a 100-point scale; 95% CI 3 to 10) by 12 months. However, two-thirds of people with low back pain still experience pain at 3 months (67%, 95% CI 50% to 83%) and at 12 months (65%, 95% CI 54% to 75%).[7]

Most guidelines agree on the first line of care in case of acute episode: advice, reassurance and encouragement to engage in light physical activity.[8] When second-line treatment is needed, a range of therapeutic interventions (pharmacological and physiotherapy) for acute NS-LBP are available. The relative effects of various treatment options, when each option is compared against all others, are not well known. This uncertainty is reflected in the variety of recommendations in recent guidelines for acute NS-LBP.[8 9] We explored the relative efficacy of currently available treatments for acute and subacute mechanical NS-LBP in terms of benefit and harm via a systematic review of the literature and network meta-analysis (NMA).

METHODS

Protocol

The systematic review protocol was developed using guidance from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement,[10] registered in the PROSPERO database (CRD42018102527, available at: http://www.crd.york.ac.uk/) and published.[11] The methods have been described in the published protocol and are reported briefly here. We followed the PRISMA extension for NMA for reporting of the results.[12] Additional sections specific to NMA are reported according to Chaimani *et al*[13] (see online supplemental A).

Eligibility criteria

Randomised controlled trials (RCTs) had to involve both adult men and women who had experienced pain for up to 12 weeks due to acute or subacute NS-LBP.[14] Non-pharmacological treatments (eg, manual therapy) including acupuncture and dry needling or pharmacological treatments for improving pain and/or reducing disability considering any delivery parameters were included. The comparator was an inert treatment encompassing sham/placebo treatment or no treatment.

Outcomes

The primary outcomes were pain intensity and disability. The secondary outcomes were any occurrence of adverse events (eg, number of events, number of participants who experienced an event). Follow-up was classified as immediate-term (closest to 1 week), short-term (closest to 1-month assessment), medium-term (closest to 3–6 months) and long-term effects (closest to 12 months).

Data sources

We searched the following electronic databases since the inception date up to 27 February 2019 and updated on 17 October 2020: Medline (PubMed), CENTRAL and Embase (Elsevier, EMBASE.com) using the appropriate Thesaurus and free-text terms (see the study protocol for the search strategy).[11] Additional studies were identified by scanning the reference lists of relevant reviews and contacting the study authors. No restriction on language or publication period was applied. Studies published in a language other than English for which no translation could be obtained were classified as potentially eligible but were not entered in the final review.

Study selection

We tested the eligibility criteria by piloting a small sample (10 trials). Two independent reviewers screened the title and the abstract of the publications retrieved by the search strategy and assessed the full text for potential inclusion. Studies not meeting the inclusion criteria were discarded. Disagreements between reviewers were resolved by discussion and consultation with a third reviewer, if necessary. Covidence software[15] was used to manage this phase.

Data extraction

We designed and piloted a data collection form created with Excel (Microsoft). Two reviewers independently extracted the study characteristics and outcome data. Disagreements were resolved through discussion or with assistance from a third reviewer, if necessary. From each study we extracted: name of first author, year of publication, setting, number of centres and population definition (acute/subacute), number, sex and age of participants, type of intervention and its duration, primary and secondary study outcomes data at interested time point of follow-up.

All relevant arm-level final value scores were extracted. When these were lacking, the final value data were derived from the difference between the baseline and the mean change values. The SDs were imputed (eg, using the average of the available SD for the same instrument or baseline SD for the same intervention within study when different instruments are used).[16] Not enough information was present to perform a secondary analysis using mean change values.

When per-protocol and intention-to-treat analyses were reported, we prioritised intention-to-treat data as the effect of assignment to intervention might be more appropriate to inform stakeholder about effects of interventions in a healthcare perspective.[17] When population had a duration of pain exceeding for a few weeks over the definition of subacute NS-LBP and when the outcomes of interest were missing, we contacted the corresponding study authors to obtain data.

Risk of bias (RoB) within individual studies

Two reviewers independently assessed the RoB of the included trials. We assessed the RoB for each study using the following RoB assessment tools recommended by the Cochrane Collaboration[16]: random sequence generation, allocation concealment, blinding of participants, providers and outcome assessment, incomplete outcome data (dropouts) and selective outcome reporting. In the selective outcome data, we accounted for a broader assessment considering also the selective non-reporting RoB due to missing results in index meta-analyses (eg, missing or unavailable outcome results crosschecked from method plans) according to published criteria by Page *et al*.[18–20] For each study, the items were scored as high, low or unclear (not enough information reported) RoB.[16]

In order to obtain an overall RoB assessment,[21] the certainty of evidence of the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach, allocation concealment, blinding of outcome assessment and incomplete outcome data were all carefully examined to classify each study as: low RoB when all three criteria are met; high risk when at least one criterion was not met and moderate in the remaining cases. Since allocation concealment, blinding of outcome assessment and incomplete outcome data were not expected to vary in importance across the primary outcomes, we summarised the RoB of each study. Disagreements were resolved through discussion or arbitration with a third review author.

Small study effects

Small study effects were assessed for each outcome (when >10 RCTs were available) using the *netfunnel* command in Stata 15[22] generating a comparison-adjusted funnel plot for a network of interventions. In the absence of small study effects, the comparison-adjusted funnel plot should be symmetric around the zero line.

Certainty of evidence

We assessed the certainty of evidence contributing to the network estimate of the main outcomes by means of the GRADE framework. The five GRADE domains were applied: study limitations, indirectness, inconsistency (heterogeneity and incoherence), imprecision and publication bias by Confidence in Network Meta-Analysis (CINeMA), a web application that simplifies evaluation of confidence in the findings from an NMA.[23] The framework combines judgments about direct evidence with their statistical contribution to NMA results, enabling evaluation of the credibility of NMA treatment effects. Online supplemental P and Q include the operational criteria used to form judgements for each domain.

Data synthesis and analysis

Pairwise comparisons

Conventional pairwise meta-analysis for each outcome was performed using a random effects model for each treatment comparison with at least two studies.[24]

Summary of the network

For the network analysis, according to the PRISMA-NMAs,[12] the eligible interventions are reported in the study protocol[11] and the process leading to node grouping and nodes adopted is described in online supplemental D, box 1 and box 2, respectively.[25]

Assumption of transitivity

To ensure transitivity and enough statistical power for robust conclusions, a sufficient number of trials and treatment comparisons with sufficient data were evaluated. Judgement of treatments' network connection was presented and evaluated graphically by network plot.

Transitivity is the assumption that the distributions of effect modifiers (covariates associated with intervention effects) are balanced across comparisons in the network in order to allow the estimation effects for indirect comparisons.[26 27] To our knowledge, no robust effect modifiers are established in NS-LBP trials,[28] thus we supposed the following potential effect modifiers based on clinical and methodological experience: stage of low back pain, presence of leg pain or sciatica, mean age, percentage of male participants, baseline severity, length of treatment, number of randomised subjects and psychological assessment. Judgement of transitivity was based on visualisation of tables and box plots of these variables by trials, by interventions and by head-to-head comparisons (online supplemental E) in order to assess any dissimilarity between comparisons in the network that could threaten the assumption of transitivity. We assessed the insufficient reporting of effect modifiers and the pairwise comparisons containing few studies as limitation of the transitivity assessment.[29] In fact, outlier treatment comparisons (ie, insufficiently study's characteristics reported) were carefully appraised. Non-eligible treatment arms (eg, bed rest advice) or non-eligible comparisons (eg, head-to-head comparison of the same intervention) were not considered.[30]

Network meta-analysis

After checking the shared nodes in the compared interventions and covariates for any effect modifiers, we assumed that people with NS-LBP meeting the inclusion criteria were, in principle, equally likely to be randomised to any of the eligible NS-LBP interventions.

Random effects NMA within frequentist setting was conducted for connected networks.[26 31–33] We presented the interval plot results for each intervention compared with reference standard (inert treatment) and the league table for estimates of all interventions against all by outcomes. Then, in order to identify the superiority of the interventions, we estimated the probability of being the best, the mean rank and the surface under cumulative ranking (SUCRA) which expresses the percentage of effectiveness or safety of a treatment that can be ranked first without uncertainty.[34] We estimated all cumulative ranking probabilities (line plots of the cumulative probabilities vs ranks) for each treatment and outcome[35] setting up to 8780 draws and 50 000 replicates. All analyses were performed using Stata V.15 with *mvmeta* command and network graphs package.[22 32 36 37]

Results were summarised using the standardised mean differences (SMDs) when different outcome measurements were reported for each trial. The uncertainty of all estimates is expressed with their 95% CI. Details on the analyses are provided in the published protocol.[11] Difference in the methods between the protocol and the present review are reported in online supplemental B.

Assessment of network inconsistency (heterogeneity and incoherence)

Variation in treatment effects between studies (ie, heterogeneity) and variation between direct and indirect sources of evidence (ie, incoherence) are two concepts related to the inconsistency.[27 29]

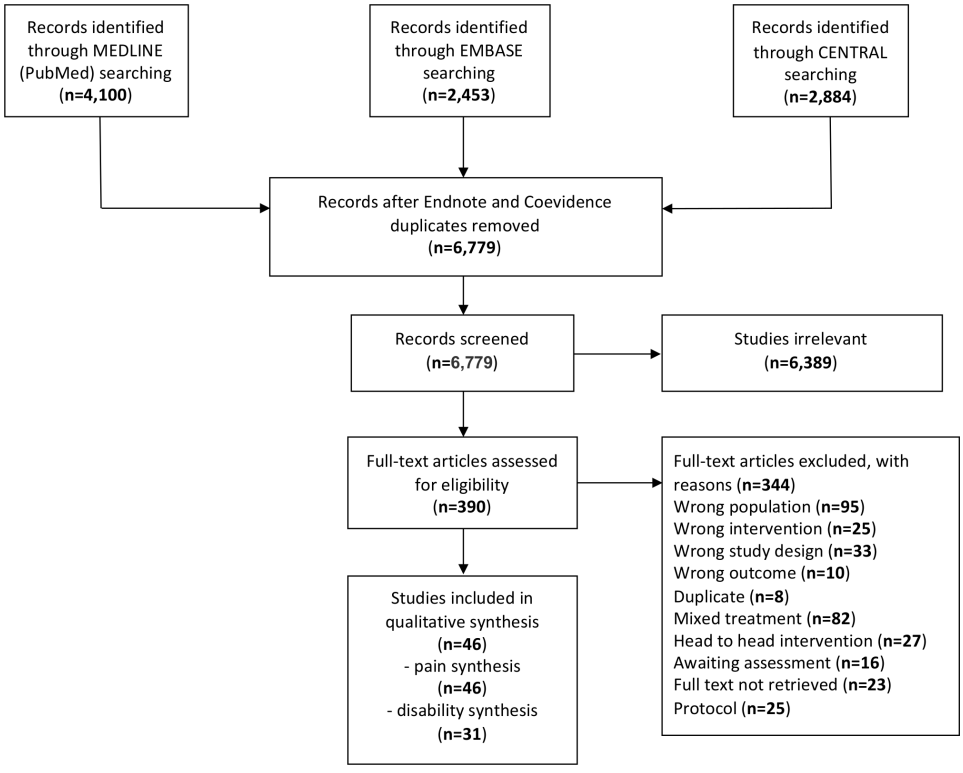

Figure 1 Flow chart of study selection.

Table 1 General characteristics

Study characteristic	No. (%) of RCTs (N=46)
Year of publication	
1961–1970	1 (2.2)
1971–1980	2 (4.3)
1981–1990	7 (15.2)
1991–2000	8 (17.4)
2001–2010	16 (34.8)
2011–2019	12 (26.1)
Intervention*	
Acupuncture	2 (1.7)
Back school	2 (1.7)
Cognitive behavioural therapy	4 (3.3)
Education	5 (4.2)
Exercise	7 (5.8)
Heat wrap	5 (4.2)
Inert treatment	34 (28.3)
Manual therapy	12 (10.0)
Muscle relaxant	10 (8.3)
NSAIDs	18 (15.0)
Opioids	3 (2.5)
Paracetamol	5 (4.2)
Physical therapy	1 (0.8)
Steroids	3 (2.5)
Usual care	9 (7.5)
Length of treatment*	
≤7 days	66 (55)
>7 days	29 (24.2)
Not reported	25 (20.8)
Stage of NS-LBP	
Acute NS-LBP	30 (65.2)
Subacute NS-LBP	2 (4.4)
Acute and subacute	14 (30.4)
Presence of leg pain or sciatica†	
Yes	15 (31.2)
No	19 (39.6)
Not stated	14 (29.2)
Study setting	
Multicentre	22 (47.8)
Single centre	24 (52.2)
Outcomes and follow-up	
Pain (n=46)	
At immediate-term (1 week)	35 (76.1)
At short-term (1 month)	16 (34.8)
At medium-term (3–6 months)	13 (28.3)
At long-term (12 months)	9 (19.6)
Disability (n=31)	
At immediate-term (1 week)	21 (67.7)
At short-term (1 month)	14 (45.2)
At medium-term (3–6 months)	11 (35.5)
At longterm (12 months)	7 (22.6)
Any adverse event	26 (56.5)

*The total number of interventions is higher due to multiarms trials (n=120).
†One study involved three patient subgroups (one with leg pain, two without leg pain) (n=48).
NSAIDs, non-steroidal anti-inflammatory drugs; NS-LBP, non-specific low back pain.

The assessment of statistical heterogeneity in the entire network was based on the magnitude of the heterogeneity variance parameter (τ2) estimated by using NMA models.[38] We assumed equal heterogeneity across all treatment comparisons accounting for correlations induced by multiarm studies.[39 40] Then, to assess presence of global inconsistency, we used a full design-by-treatment interaction random effects model (global χ^2 test). If the null hypothesis of inconsistency parameters being equal to zero was not rejected, we fit a consistency model. We presented local inconsistency estimates using forest plots and side-splitting for direct and indirect estimates in each available comparison (online supplemental I and J). When global significant inconsistency was found,[26 32 33] multiple strategies were explored.[33] We first checked the dataset for data extraction errors or outlier effect sizes among comparisons (visually inspected by pairwise meta-analysis). Then, we tried to interpret the significant inconsistency parameters separating indirect from direct evidence (side-splitting) and finally we explored the observed inconsistency using prespecified covariates in network meta-regression analyses and subgroup analyses. If any strategy explained the inconsistency, we presented only forest plots grouped into direct and indirect estimates (network forests).[33]

Meta-regression and subgroup analyses

We performed network meta-regression random effects within a frequentist framework with *metareg* command in Stata using aggregate-level data to examine relationship between treatments effects and each specified covariate (age, percentage of male, stage of low back pain, baseline severity of pain, presence of leg pain or sciatica, RoB).[41]

When inconsistency remains unexplained by meta-regression, we explored the treatments effects performing subgroup analyses into pharmacological and non-pharmacological interventions groups.[42]

RESULTS

Study selection

After removal of duplicates, 6779 records were retrieved and 6389 records were discarded. The full text of the remaining 390 records was examined and 344 did not meet the inclusion criteria: 95 involved a different study population (eg, chronic pain), 82 had mixed treatments (eg, manual therapy plus usual care), 25 described interventions not pertinent to the present study (eg, bed rest), 27 were head-to-head interventions (eg, exercise vs exercise), 10 reported outcomes not pertinent to the present study (eg, cost-effectiveness related to pain), 33 had a study design other than RCT, 8 were further duplicates, 25 were protocols, 16 were awaiting assessment for language (original not in English or Italian) and in 23 instances the full text could not be retrieved. In total, 18 authors were contacted; four of the eight who responded provided useful data for our analysis. Finally, 46 studies were included (citations in References in online supplemental C). The study flow diagram is illustrated in figure 1.

Study and participant characteristics

A total of 8765 participants were included in 46 trials. The sample size of trials ranged between 21.5 and 91.3 participants (IQR) with a median of 39.5 participants each. Most studies involved people with acute NS-LBP (n=30 trials). Overall, 22 were multicentre and 24 were single-centre trials. The median year of publication of RCTs was 2003 (IQR 1995–2013). The median age of participants was 40.4 years old (IQR: 37–43) and the median percentage of males was 52% (IQR 43.7%–60%)

Table 1 presents the general characteristics of the studies and the participants. No important concerns were raised regarding the violation of the transitivity assumption when the potential

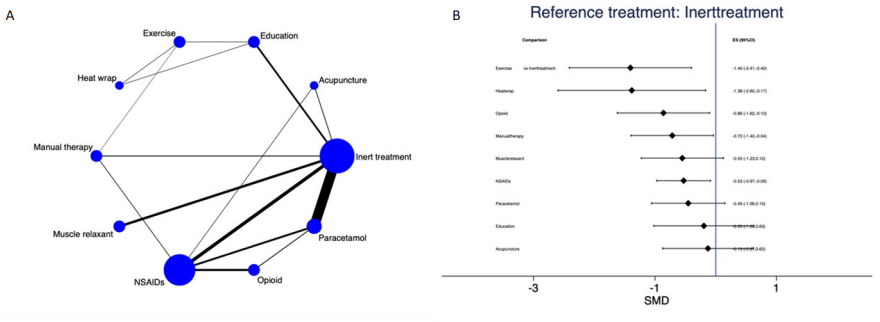

Figure 2 Pain at immediate-term (1 week): network plot (A) and interval plot (B). NSAIDs, non-steroidal anti-inflammatory drugs; SMD, standardised mean difference.

effect modifiers were evaluated. Studies and participants characteristics stratified by trials, by interventions and by head-to-head comparisons are summarised in online supplemental E. The inconsistency assessment is reported globally and locally in online supplemental J, table 1 and table 2, respectively.

RoB assessment

Online supplemental F, table 1 and figure 1 summarise the RoB assessments. Of the 46 studies, 9 (19.6%) had low RoB, 20 (43.5%) unclear RoB and 17 (36.9%) high RoB.

Pain

Pain was assessed in 35 studies at immediate-term (1 week) of follow-up, in 16 studies at 1 month, in 13 studies at 3–6 months and in 9 studies at 12 months. No evidence of publication bias was present (online supplemental N). Under consistency (p value=0.52), the NMA of pain at 1 week (16/35 studies involving 2905 subjects with data provided for 15 direct comparisons between 10 different treatment nodes, figure 2A) showed that exercise (SMD −1.40; 95% CI −2.41 to –0.40), heat wrap (SMD −1.38; 95% CI −2.60 to –0.17), opioids (SMD −0.86; 95% CI −1.62 to –0.10), manual therapy (SMD −0.72; 95% CI −1.40 to –0.04) and non-steroidal anti-inflammatory drugs (NSAIDs) (SMD −0.53; 95% CI −0.97 to –0.09) significantly reduced pain compared with inert treatment (figure 2B). The contribution matrix of direct and indirect evidence is depicted in online supplemental O, figure 1A. Pairwise meta-analyses and forest plot of NMA data are presented in online supplemental H, table 1 and online supplemental I, figure 1, respectively. Table 2 presents NMA estimates of all interventions against all. The ranking of treatments based on cumulative probability plots and SUCRAs is presented in online supplemental M, figure 1 and table 2. The most effective treatment was exercise (89.2%) and the least effective was inert treatment (10.7%).

Under consistency (p value=0.36), the NMA of pain at short-term (1 month) (11/16 studies involving 2378 subjects with data provided for 10 direct comparisons between nine different treatment nodes, online supplemental G, figure 1A) showed that manual therapy (SMD −0.83; 95%CI −1.44 to –0.22) significantly reduced pain compared with inert treatment (online supplemental L, figure 1A). The contribution matrix of direct and indirect evidence is presented in online supplemental O, figure 1B. Pairwise meta-analyses and forest plot of NMA data are presented in online supplemental H, table 2 and online supplemental I, figure 2, respectively. Online supplemental M, table 1A presents NMA estimates of all interventions against all. The ranking of treatments based on cumulative probability plots and SUCRAs is presented in online supplemental M, figure 2 and table 2. The most effective treatment was manual therapy (91.1%) and the least effective was education (4.9%).

The NMA of pain at medium-term (3–6 months) (11/13 studies involving 2458 subjects with data provided for 10 different treatment nodes, online supplemental G, figure 1B) showed a disconnected network. Pairwise meta-analyses are presented in online supplemental H, table 3: manual therapy was superior to inert treatment in reducing pain at 3–6 months.

Under consistency (p value=1), the NMA of pain at long-term (12 months) (5/9 studies involving 938 subjects with data for four direct comparisons between five different treatment nodes, online supplemental G, figure 1C) showed no statistically significant intervention against inert treatment (online supplemental L, figure 1B). The contribution matrix of direct and indirect evidence is presented in online supplemental O, figure 1C. Pairwise meta-analyses and forest plot of NMA data are presented in online supplemental H, table 4 and online supplemental I, figure 3, respectively. Online supplemental M, table 1B presents NMA estimates of all interventions against all. The ranking of treatments based on cumulative probability plots and SUCRAs is presented in online supplemental M, figure 3 and table 2. The most effective treatment was cognitive behavioural therapy (CBT) (73.7%) and the least effective was inert treatment (15.3%).

Disability

Disability was assessed in 21 studies at 1 week of follow-up, in 14 studies at 1 month, in 11 studies at 3–6 months and in 7 studies at 12 months. No evidence of publication bias was present (online supplemental N).

The NMA of disability at immediate-term (1 week) (15/21 studies involving 4167 subjects with data provided for 16 direct comparisons between nine different treatment nodes, figure 3A) showed sources of inconsistency (p value=0.001). Pairwise meta-analyses and forest plot of NMA data are presented in online supplemental H, table 5 and online supplemental I, figure 4, respectively. Strategies to explore inconsistency are reported in online supplemental J for meta-regression and in online supplemental K for subgroup analysis. Inconsistency was explained by subgroup analysis. In the non-pharmacological group, exercise (SMD −0.71; 95% CI −1.16 to –0.26), heat wrap (SMD −0.59; 95% CI −0.82 to –0.36), manual therapy (SMD −0.52; 95% CI −0.89 to –0.16) and education (SMD −0.28; 95% CI −0.53 to –0.03) were statistically significant compared with inert treatment (figure 3B). Online supplemental K, table 1A presents NMA estimates of all interventions against all. The ranking of treatments based on cumulative probability plots and SUCRAs showed that the most effective treatment was

Table 2 League table presenting all network meta-analysis estimates of pain outcome at immediate-term (1 week)

Inert treatment									
0.13 (−0.62, 0.87)	Acupuncture								
0.20 (−0.63, 1.02)	0.07 (−1.04, 1.17)	Education							
1.40 (0.40, 2.41)	**1.28 (0.04, 2.51)**	**1.21 (0.31, 2.11)**	Exercise						
1.38 (0.17, 2.60)	1.25 (−0.16, 2.67)	**1.19 (0.17, 2.20)**	−0.02 (−1.03, 0.99)	Heat wrap					
0.72 (0.04, 1.40)	0.59 (−0.38, 1.55)	0.52 (−0.44, 1.48)	−0.69 (−1.67, 0.29)	−0.67 (−1.92, 0.58)	Manual therapy				
0.55 (−0.12, 1.23)	0.42 (−0.58, 1.43)	0.36 (−0.71, 1.42)	−0.85 (−2.07, 0.36)	−0.83 (−2.22, 0.56)	−0.17 (−1.12, 0.79)	Musde relaxant			
0.53 (0.09, 0.97)	0.40 (−0.35, 1.15)	0.33 (−0.58, 1.25)	−0.88 (−1.93, 0.18)	−0.85 (−2.12, 0.41)	−0.19 (−0.89, 0.51)	−0.02 (−0.83, 0.78)	NSAIDs		
0.86 (0.10, 1.62)	0.73 (−0.25, 1.71)	0.67 (−0.44, 1.77)	−0.54 (−1.77, 0.68)	−0.52 (−1.93, 0.89)	0.15 (−0.80, 1.09)	0.31 (−0.71, 1.33)	0.33 (−0.32, 0.98)	Opioids	
0.45 (−0.15, 1.06)	0.32 (−0.57, 1.22)	0.26 (−0.75, 1.26)	−0.95 (−2.10, 0.19)	−0.93 (−2.27, 0.41)	−0.26 (−1.11, 0.58)	−0.10 (−1.00, 0.81)	−0.08 (−0.63, 0.48)	−0.41 (−1.15, 0.34)	Paracetamol

Interventions are reported in alphabetical order from left to right except for reference treatment (inert treatment). The estimate is in the cell where the column-defining treatment and the row-defining treatment intersect. For efficacy SMD>0 favours the row-defining treatment whereas SMD<0 favours the column-defining treatment. Significant results are given in bold.
NSAIDs, non-steroidal anti-inflammatory drugs; SMD, standardised mean difference.

manual therapy (80.3%) and the least effective was inert treatment (2.9%) (online supplemental K, table 2A). In the pharmacological group, NSAIDs (SMD −0.33; 95% CI −0.55 to -0.11) and muscle relaxants (SMD −0.24; 95% CI −0.43 to -0.04) were statistically significant compared with inert treatment (figure 3C). Online supplemental K, table 1B presents NMA estimates of all interventions against all. The ranking of treatments based on cumulative probability plots and SUCRAs showed that the most effective treatment was NSAIDs (94.6%) and the least effective was inert treatment (7.9%) (online supplemental K, table 2B).

The NMA of disability at short-term (1 month) (11/14 studies involving 2463 subjects with data provided for 13 direct comparisons between 10 different treatment nodes, online supplemental G, figure 2A) showed sources of inconsistency (p value=0.0107). Pairwise meta-analyses and forest plot of NMA data are presented in online supplemental H, table 6 and online supplemental I, figure 5, respectively. Manual therapy was statistically significant compared with education and exercise and a positive trend was found in favour of low-dose steroids compared to NSAIDs.

Strategies to explore inconsistency are reported in online supplemental J for meta-regression and in online supplemental K for subgroup analysis. Inconsistency was not explained by any strategy.

The NMA of disability at medium-term (3–6 months) (9/11 studies involving 1404 subjects with data provided for nine different treatment nodes, online supplemental G, figure 2B) was disconnected; pairwise meta-analyses are presented in online supplemental H, table 7: low-dose steroids were statistically significant compared to NSAIDs as well as manual therapy compared to education and exercise.

Under consistency (p value=0.77), the NMA of disability at long-term (12 months) (6/7 studies involving 1031 subjects with data provided for five intervention nodes, online supplemental G, figure 2C) showed that no intervention was statistically significant against inert treatment (online supplemental L, figure 2A). The contribution matrix of direct and indirect evidence is presented in online supplemental O, figure 2A. Pairwise meta-analyses and forest plot of NMA data are presented in online supplemental H, table 8 and online supplemental I, figure 6, respectively. Online supplemental M, table 3A presents NMA estimates of all interventions against all. The ranking of treatments based on cumulative probability plots and SUCRAs is presented in online supplemental M, figure 4 and table 4. The most effective treatment was CBT (68.5%) and the least effective was inert treatment (22.7%).

Adverse events

Twenty-six studies (56.5%) reported adverse events. No events were reported for acupuncture, education, exercise or manual therapy. Mild-moderate events occurred with the use of heat wrap, muscle relaxants, NSAIDs, opioids, paracetamol, steroids and inert treatment. No study reported treatment-related disabling events or death and only one reported three severe adverse events (one in the NSAIDs arm and two in the inert treatment arm). Mild or moderate adverse events occurred most often in the opioids (65.7%), the NSAIDs (54.3%) and the steroids arm (46.9%). But because adverse events reporting was heterogeneous for number of people with NS-LBP and number of events, we cannot quantitate these data (table 3).

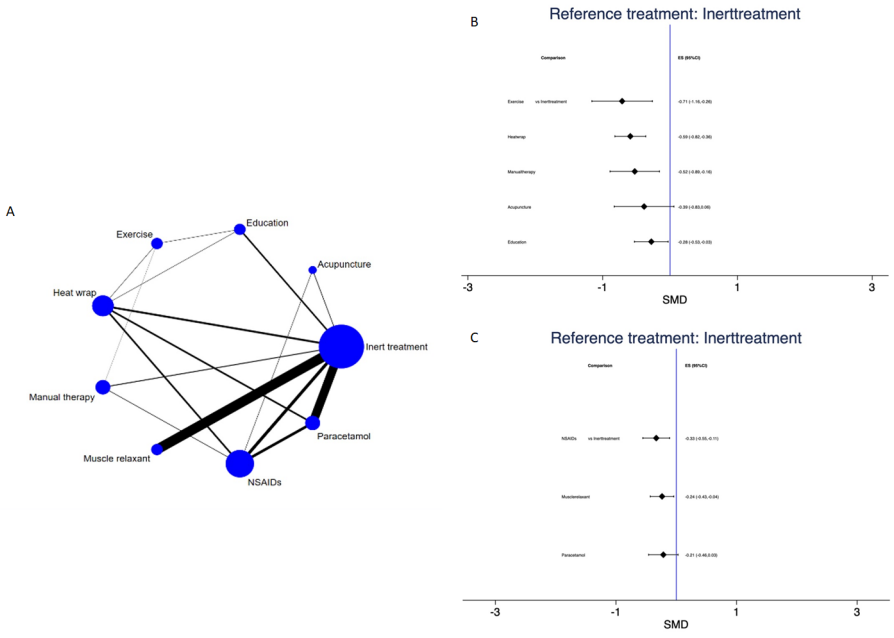

Figure 3 Disability at immediate-term (1 week): network plot (A) and interval plot (B) for non-pharmacological interventions and (C) for pharmacological interventions. NSAIDs, non-steroidal anti-inflammatory drugs; SMD, standardised mean difference.

Grading of evidence

We incorporated the GRADE judgments in online supplemental P and Q. The certainty of evidence for the treatment effects of efficacy varied.

DISCUSSION

To our knowledge, this is the largest NMA to date in the field of low back pain (46 RCTs involving 8765 participants assigned to pharmacological, non-pharmacological or inert treatment). We found that pharmacological and non-pharmacological interventions were more efficacious than inert treatment for reducing pain intensity and disability due to acute and subacute mechanical NS-LBP. Overall, the certainty of evidence ranged from very low to moderate, with high certainty of evidence for manual therapy compared with usual care and education.

For reducing pain intensity, the most efficacious interventions at immediate-term follow-up (close to 1 week) were heat wrap, manual therapy, exercise, NSAIDS and opioids, whereas at short-term follow-up (closest to 1 month), the most efficacious treatment was manual therapy. For reducing disability, similar findings are found in the subgroup analysis showing that heat wrap, manual therapy, exercise and education for non-pharmacological group and muscle relaxants and NSAIDs for pharmacological group are effective at immediate-term follow-up. Manual therapy confirmed the effects also for decreasing disability at short-term follow-up (closest to 1 month). Limited evidence was found for steroids when compared with NSAIDs (one study) to reduce disability.

The present analysis highlights a potentially minor role for medicines in the management of NS-LBP: initial treatment should be non-pharmacological as confirmed by the SUCRA. However, only a minority of pharmacological interventions are included in the networks. In particular, steroids and opioids are under-represented (only three studies) and their desirable effects should be weighed against side effects. In fact, mild or moderate adverse events were most often recorded for the opioids, the NSAIDs and the steroids arms. This observation is shared by recent systematic reviews that found that at least 50% of people with NS-LBP taking opioids withdrew from the study owing to adverse events or lack of efficacy,[43 44] with trends noted for higher harm rates and higher percentages of severe harm.[45]

Given that paracetamol offer limited or no benefit, its clinical value might be questionable. This finding is not reflected in all current guidelines, however.[9 46] A recent Cochrane systematic review[47] found that paracetamol does not result in better outcomes compared to placebo in people with acute low back pain reporting evidence from a large multicentre RCT included in our NMA (1652 randomised people with NS-LBP) that showed no benefit of any dose of paracetamol (until 4000 mg) compared with placebo in people with moderate intensity acute low back pain.[48]

Also, our data support the National Institute for Health and Care Excellence (NICE) 2016 guideline which recommend the use of NSAIDs for acute low back pain and weak opioids when NSAIDs are ineffective or poorly tolerated.[49] In fact, we found significant reduction of pain and disability at 1 week for NSAIDs. The evidence associated with NSAIDs goes beyond the trials included in this analysis because they have a well-established role in pain management.[50–52]

Moreover, two recent systematic reviews that found evidence for reducing pain and disability with the use of muscle relaxants recommended caution in interpretation of the findings as the evidence cannot be generalised because only two muscle relaxants were studied.[43 53] Our analysis included a heterogeneous group of muscle relaxants (carisoprodol, thiocolchicoside, tizanidine) administered at different doses and for a short time.

Although the authors of previous published systematic reviews on spinal manipulation,[54–57] exercise[58] and heat wrap[59 60] did not conduct NMA, their results overlap with ours: exercise (eg, motor control exercise, McKenzie exercise), heat wrap and manual therapy (eg, spinal manipulation, mobilisation, trigger points or any other technique) were found to reduce pain intensity and disability in adults with acute and subacute phases of NS-LBP. Such treatments should be tailored to the patient's needs and preferences. In fact, in our analysis, there was large variability in delivering the interventions for each node. A

Table 3 Adverse events reported as number of people with NS-LBP experiencing adverse events and number of events classified from grade 1–5

		Adverse events						
Study (Author, year)	Category of intervention	n	%	AE 1 (mild), n	AE 2 (moderate), n	AE 3 (severe), n	AE 4 (disabling), n	AE 5 (death), n
Shin, 2013	Acupuncture	0	0	–	–	–	–	–
Mayer, 2005	Education	0	0	0	0	0	0	0
Traeger, 2019	Education	0	0	–	–	–	–	–
Mayer, 2005	Exercise	0	0	0	0	0	0	0
Mayer, 2005	Heat wrap	0	0	0	0	0	0	0
Nadler, 2002	Heat wrap	–	6.2	–	–	–	–	–
Nadler, 2003b	Heat wrap	–	15	–	–	–	–	–
Nadler, 2003a	Heat wrap	1	1.1	–	–	–	–	–
Santilli, 2006	Manual therapy	0	0	–	–	–	–	–
Takamoto, 2015	Manual therapy	0	0	–	–	–	–	–
Takamoto, 2015	Manual therapy	0	0	–	–	–	–	–
von Heymann, 2013	Manual therapy	0	0	–	–	–	–	–
Berry, 1988	Muscle relaxant	25	42,4	–	–	–	–	–
Hindle, 1972	Muscle relaxant	0	0	0	0	0	0	0
Ketenci, 2005	Muscle relaxant	–	18; 10; 5; 5*	–	–	0	0	0
Ketenci, 2005	Muscle relaxant	–	28; 3; 15*	–	–	0	0	0
Ralph, 2008	Muscle relaxant	–	–	74	–	–	–	–
Serfer, 2009	Muscle relaxant	–	–	69	–	–	–	–
Serfer, 2009	Muscle relaxant	–	–	85	–	–	–	–
Tuzun, 2003	Muscle relaxant	–	–	4	–	–	–	–
Amlie, 1987	NSAIDs	18	13	14	6	1	–	–
Dreiser, 2003	NSAIDs	15	12.1†	–	–	0	0	0
Dreiser, 2003	NSAIDs	17	13.9†	–	–	0	0	0
Eken, 2014	NSAIDs	4	8.7	4	–	–	–	–
Goldie, 1968	NSAIDs	8	32	–	–	–	–	–
Miki, 2018	NSAIDs	5	7.9†	–	–	–	–	–
Nadler, 2002	NSAIDs	–	10.4	–	–	–	–	–
Nadler, 2003b	NSAIDs	–	25	–	–	–	–	–
Nadler, 2003a	NSAIDs	0	0	–	–	–	–	–
Sae-Jung, 2016	NSAIDs	4	12	–	–	–	–	–
Shin, 2013	NSAIDs	0	0	–	–	–	–	–
Szpalski, 1994	NSAIDs	1	2.7	–	–	–	–	–
Veenema, 2000	NSAIDs	–	–	8	–	–	–	–
Videman, 1984	NSAIDs	19	54.3	–	–	–	–	–
von Heymann, 2013	NSAIDs	0	0	–	–	–	–	–
Eken, 2014	Opioid	7	15.5	6	1	–	–	–
Veenema, 2000	Opioid	–	–	41	–	–	–	–
Videman, 1984	Opioid	23	65.7	–	–	–	–	–
Eken, 2014	Paracetamol	4	8.7	4	–	–	–	–
Miki, 2018	Paracetamol	1	1.6†	–	–	–	–	–
Nadler, 2002	Paracetamol	–	4.4	–	–	–	–	–
Williams, 2014	Paracetamol	99	18.0†	–	–	–	–	–
Williams, 2014	Paracetamol	99	18.0†	–	–	–	–	–
Eskin, 2014	Steroids	–	–	0	0	0	0	0
Sae-Jung, 2016	Steroids	15	46.9†	–	–	–	–	–
Amlie, 1987	Inert treatment	24	17	19	8	2	–	–
Berry, 1988	Inert treatment	12	22.6	–	–	–	–	–
Dreiser, 2003	Inert treatment	25	19.8†	–	–	0	0	0
Eskin, 2014	Inert treatment	–	–	0	0	0	0	0
Goldie, 1968	Inert treatment	5	20	–	–	–	–	–
Hindle, 1972	Inert treatment	0	0	0	0	0	0	0
Ketenci, 2005	Inert treatment	–	22; 4*	–	–	0	0	0
Nadler, 2003b	Inert treatment	–	12	–	–	–	–	–
Nadler, 2003a	Inert treatment	0	0	–	–	–	–	–
Nadler, 2003a	Inert treatment	0	0	–	–	–	–	–

Continued

Table 3 Continued

Study (Author, year)	Category of intervention	Adverse events						
		n	%	AE 1 (mild), n	AE 2 (moderate), n	AE 3 (severe), n	AE 4 (disabling), n	AE 5 (death), n
Ralph, 2008	Inert treatment	–	–	26	–	–	–	–
Santilli, 2006	Inert treatment	0	0	–	–	–	–	–
Serfer, 2009	Inert treatment	–	–	34	–	–	–	–
Szpalski, 1994	Inert treatment	–		–	–	–	–	–
Takamoto, 2015	Inert treatment	0	0	–	–	–	–	–
Traeger, 2019	Inert treatment	0	0	–	–	–	–	–
Tuzun, 2003	Inert treatment	–	–	4	–	–	–	–
von Heymann, 2013	Inert treatment	0	0	–	–	–	–	–
Williams, 2014	Inert treatment	98	18.0	–	–	–	–	–

All references of included studies are provided in online supplemental C.
*Percentage of people with NS-LBP reporting specific adverse events (eg, headache, diarrhea, dyspepsia).
†Percentages were reported slightly different in the primary studies (unclear about randomised people with NS-LBP).
NS-LBP, non-specific low back pain.

gap exists between the current scientific literature on NS-LBP and the global actions undertaken to contrast musculoskeletal disorders.[61 62] To date, the largest discrepancies between RCTs and global care initiatives are the new directions in classification systems, which have changed from time contingent (acute, subacute, chronic) to risk contingent (class 0–class V).[61] In the new frameworks, treatment is targeted to the whole spine and prescribed according to the patient's risk class regardless of the time since NS-LBP onset.[62] A direct consequence in meta-analysing the results of RCTs, in which enrolment is mainly time-contingent based, is that patients in different risk classes may be assigned to the same group, potentially confounding the effects of the intervention. This limitation might explain the inconsistency of the results from the RCTs included in our NMA, as well as in future secondary analyses for a long time to come.

We noted other limitations in our analysis. We excluded head-to-head comparisons of the same intervention since we did not aim to inspect different characteristics of delivery (eg, intensity, dose, techniques). This was an example of our narrow inclusion criteria, set at the protocol stage, in order to obtain a homogenous sample, preventing intransitivity.[63] Nevertheless, the studies were published over a 40-year period, during which the characteristics of interventions undoubtedly changed and thus created heterogeneity. We incorporated the certainty of evidence in the main results to highlight the most robust findings for further use in clinical judgement. We inspected potentially important clinical and demographical modifiers of treatment response at the individual patient level (eg, stage of low back pain, presence of leg pain or sciatica, mean age, percentage of male participants, baseline severity, length of treatment, number of randomised subjects and psychological assessment). We found inconsistency at 1 month for disability that remained unresolved despite exploring different strategies to resolve it. We appraised no important limitation in the transitivity evaluation even if few potential confounders were poorly reported (eg, psychological assessment) and unobserved covariates could possibly affect the global assessment.[26] Our results should be cautiously interpreted: people with NS-LBP subgroups with different characteristics could play an important role, though such did not emerge from our analyses. We found some large estimates at immediate-term for pain that could inflate the overall effects. Small sample size (around 24% of the included trials had a sample smaller than 30 patients per arm) and study limitation (such as inadequate reporting data) could lead to doubtful pairwise estimates.

We addressed clinically important endpoints for recovery from episodes of low back pain; however, we did not include other endpoints possibly relevant for people with NS-LBP, such as health-related quality of life, social participation or return to work.[64] Further studies should broaden outcome evaluation. Furthermore, we did not explore the combination of interventions with multidisciplinary approaches often provided in clinical settings.[65] Taken together, the data from our NMA indicate potential successful treatments, along with ineffective interventions that contribute to waste of time and resources.

CONCLUSION

Ultimately, understanding the balance between benefits and harms of non-pharmacological and pharmacological interventions is a key step to better serving people with NS-LBP. After first line of care, NS-LBP should be managed with non-pharmacological treatments which seem to mitigate pain and disability in the first week. Among pharmacological interventions, NSAIDs and muscle relaxants appear to offer the best net balance at immediate-term for pain and disability.

What is already known

- Non-specific low back pain (NS-LBP) is a leading cause of pain and disability worldwide.
- Among the therapeutic interventions for NS-LBP, it is not clear which intervention offers the best benefit–harm balance.
- Uncertainty in the management of NS-LBP is reflected in the often discordant guideline recommendations.

What are the new findings

- Among non-pharmacological interventions, pain and disability reduction were best achieved by heat wrap, manual therapy and exercise at immediate-term of follow-up.
- Among pharmacological interventions, pain and disability reduction were best achieved by NSAIDs and muscle relaxants at immediate-term of follow-up.
- Paracetamol had no benefit over inert treatments at any follow-up assessment; evidence was largely uncertain.

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Contributors SG and GC designed the study, developed the search strategies and wrote the first draft of the manuscript. SG, SB, GC and GDC extracted the data. SG, SB and GC performed the analyses. All authors provided feedback on early and advanced drafts of the manuscript and approved the final version.

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Effectiveness of treatments for acute and subacute mechanical non-specific low back pain: a systematic review with network meta-analysis

Supplementary materials

Supplement A. PRISMA NMA Checklist

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	*1*
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	***4***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	***5***
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***7***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	7
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	7
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**7**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	***7***
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***10-11***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	***10-11***

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	***10-11***
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	***10-11-14***
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	***10-11***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	10-11
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	***10-11***
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	16-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***19***

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Supplement B. Difference between protocol and review

We extracted some important intervention details as suggested by the TIDieR checklist [1] in order to create consistent nodes, however, the poor reporting of included trials prevent the full reporting of their descriptions. We summarized some items in Table 1 of **Supplement E** (Assessment of transitivity) and full details are reported in the online repository OSF at the following link https://osf.io/q24xh.

We transparently edit the nodes according to the statement declaration in the published protocol [2]. For instance, we build a new subgroup category "heat wrap" separated from "physical therapy" category. We also noted that "physical therapy" is represented only by TENS improving the homogeneity of treatment's node. Then, we merged "Inert treatment" (e.g., placebo drug, sham therapy) and "No treatment" since only one study (Malmivaara 1995) reported no intervention in this control group described as: "the continuation of ordinary activities as tolerated."

Supplement C. References of Included Studies

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Supplement D. Interventions and Nodes

Box 1. Planned description interventions

Class	Example of individual treatments
Pharmacological	
Antidepressant drugs	Any kind of SSRI/SNRI or tryciclic drug
Muscle relaxants drugs	Any kind of skeletal muscle relaxant drug (e.g. flupirtin, orphenadrine, dantrolene, carisoprodol, tizanidine, incobotulinumtoxinA, cyclobenzaprine, metaxalone, baclofen, methocarbamol, chlorzoxazone)
Non-steroidal anti-inflammatory drugs (NSAIDs)	Any kind of NSAIDs drug, including COX-2 inhibitors (e.g. ibuprofen, naproxen, sulindac, ketoprofen, tolmetin, etodolac, fenoprofen, diclofenac, flurbiprofen, piroxicam, ketorolac, indomethacin, meloxicam, nabumetone, oxaprozin mefenamic acid, diflunisal)
Opiod drugs	Any kind of strong or weak opiod analgesics (e.g. morphine, hydromorphone, oxycodone, fentanyl, methadone, buprenorphine, diamorphine, tapentadol, codeine, hydrocodone, tramadol, pentazocine, tilidine)
Paracetamol	
Steroids	Any kind of steroid drug (e.g dexamethasone, methylprednisolone, prednisone)
Non-pharmacological treatments	
Acupuncture and dry needling	
Biopsychosocial rehabilitation	Any kind of cognitive behavioral treatment, multidisciplinary biopsychological rehabilitation and back school
Education	Any kind of advice to stay active, booklet, reassurance, ergonomics, workplace intervention, pain education (neurobiology and neurophysiology of pain)
Exercise	Any kind of exercise (aerobic or resistance training) single supervised or home exercise, including stretching and McKenzie therapy
Manual therapy	Any kind of mobilization or spinal manipulation (high velocity thrust techniques at or near to the end of the range of motion or low-grade velocity movements within the range of motion), myofascial therapy/trigger point, soft tissue massage
Physical Therapy	Any physical therapy (low-laser therapy, diathermy, transcutaneous electrical nerve stimulation, ultrasound therapy, heat wrap)
Taping	Kinesiotaping
Usual care	Any kind of treatment suggested by general medicine (minimal intervention: advice to stay active or to take drugs as needed)
Inert treatment	Any kind of sham or placebo therapy
No treatment	No treatment, waiting list control

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Box 2. Nodes

Treatments	Nodes	Evidence and assumptions
Muscle relaxant drugs (Baclofen, Carisoprodol, Dantrolene, Tizanidine Thiocolchicoside)	Muscle relaxant	Separate assessment for muscle relaxants and for Benzodiazepines[3]. A metanalysis shown similar effects across muscle relaxant drugs versus placebo, I^2=55%[4].
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), including COX-2 inhibitors (diclofenac, diflunisal, ibuprofen, indomethacin, loxoprofen, piroxicam, tenoxicam)	NSAIDs	Separate assessment for all NSAIDs[3]. No clear difference in short-term pain reduction when comparing selective COX-2 inhibitors to non-selective NSAIDs[5].
Opioid analgesics (meptazinol)	Opioids	Separate assessment for opiods[3]. Inclusion criteria of SR: morphine, diamorphine, fentanyl, alfentanil, remifentanil, methadone, oxycodone, pethidine, tapentadol, tramadol, codeine, dihydrocodeine, meptazinol)[6]. Inclusion criteria of SR: various opioid analgesics[7].
Paracetamol	Paracetamol	Separate assessment for paracetamol [3 8].
Steroids drugs (dexamethasone, methylprednisolone, prednisone)	Steroids	Separate assessment for steroids [3]. Systematic reviews found no evidence to suggest that a series of epidural injections was any more effective than a single injection (see Appendix 1 Table 3). Individual RCTs found no evidence of improvement in steroid benefits with increasing dose (see Appendix 1 Table 4) [9]. Individual RCTs found no consistent evidence of superior efficacy of one steroid over the others (see Appendix 1 Table 4) [9]. A meta-analysis included all type of steroids. [10].
Acupuncture	Acupuncture	
Cognitive behavioural treatment/multidisciplinary biopsychological rehabilitation (MBR) with or without exercise	Cognitive behavioral therapy	Inclusion criteria of Cochrane review, MBR program: the intervention included a physical component (e.g., pharmacological, physical therapy, exercise) in combination with either a psychological, social, or occupational component (or any combination of these)[11].
Back school	Back school *	
Booklet, Information, ergonomics, any kind of advice, workplace intervention, pain education	Education	Findings suggest positive effects for education even if differ in terms of its contents such as health education, self-management, video education, and postural education[12].

		Many different types of patient education are widely used [13].
McKenzie Any kind of exercise (aerobic or resistance training) Stretching	Exercise	No superior type of physical exercise for people with chronic non-specific neck pain [14]. Various exercise training approaches are effective [15].
Spinal manipulation Manual therapy (mobilization) Trigger point/myofascial therapy/massage	Manual therapy	Inclusion crtieria of SR: Studies investigating manual therapy using HVLA or non-HVLA techniques such as: joint mobilization, soft tissue focused techniques, myofascial release, longitudinal sliding, soft tissue mobilizations, deep-pressure massage, muscle energy, massage, hold relaxation technique, ischemic compression, and functional/fascial technique. therapy technique(s)[16]. Different forms of manual therapy did not lead to different outcomes in older persons with chronic LBP [17].
Heat wrap	Heat wrap**	
TENS	Physical therapy	
Usual care or minimal treatment (general prescription such as drugs as needed, advice stay active)	Usual care	Usual care is a term used to describe the full spectrum of patient care practices in which clinicians have the opportunity (which is not necessarily seized) to individualize care [18]. Treatment reported: education and reassurance, exercise, bed rest, return to work[19].
Sham therapy Placebo therapy No treatment	Inert treatment	

* This node was assessed only in the qualitative synthesis because of insufficient data (e.g., not reported outcome data)
**According to the protocol [2] since we obtained a sufficient number of studies sharing the same description of the intervention, we created a new node (heat wrap) separated from the physical therapy node.

Supplement E. Assessment of transitivity

Before conducting the statistical analysis, we assessed whether the trials included in the NMA were on average similar in terms of characteristics that might modify the treatment effect (so that the transitivity assumption is plausible). Indirect comparisons, in contrast to direct comparisons, are not protected by randomisation and may be confounded by differences between the trials. In our analysis we deemed the following parameters as possible confounders [20] which were displayed as cumulative frequencies, boxplots or bar charts when appropriate: stage of NS-LBP, presence of leg pain or sciatica, mean age, percentage of male participants, baseline severity, length of treatment, number of randomized, psychological assessment. The plausibility of the transitivity assumption was evaluated by comparing the distribution of these potential effect modifiers across trials, interventions and heah-to-head comparisons

Assessment of transitivity by trials

Table 1. Study and Patient characteristics (n=46)

ID	Author	Year	Setting	Stage of LBP	Presence of leg pain or sciatica	Length of treatment	Outcomes	Week of FU	Sample size	Treatments	Nodes	Age mean	Age variance (SD)	% of male
1	Amlie*	1987	Multi-center	Acute LBP (less than 6 weeks)	Not stated	1 week	Pain; disability	3 days; 7 days	282	1.Piroxicam 2. Placebo	NSAIDs Inert treatment	37,3 38,5	NA	58,6 59,2
2	Bergquist-ullman*	1977	Single center	Mixed LBP (less than 12 weeks)	Yes	2 weeks Max 10 trt	Pain; disability	10 days; 3 weeks; 6 weeks	145	1.Back school 2. Placebo	Back school Inert treatment	NA	NA	91,4 86,7
3	Berry	1988	Single center	Acute LBP (less than 6 weeks)	Yes	1 week	Pain	1 week	112	1.Tizanidine 2. Placebo	Muscle relaxant Inert treatment	44 38	13 13	51 50,9
4	Bertalanffy	2005	Single center	Acute LBP (less than 6 weeks)	No	1 day	Pain	30 minutes	63	1. TENS 2. Sham TENS	Physical therapy Inert treatment	47 49	7 14	53,3 51,5
5	Casale*	1988	Single center	Acute LBP (less than 6 weeks)	Not stated	4 days	Pain	Day 4	20	1.Dantrolene sodium 2. Placebo	Muscle relaxant Inert treatment	46,7 47,1	2,3 2,2	70 80
6	Cherkin*	1996	Single center	Mixed LBP (less than 12 weeks)	Yes	1 session	Pain; disability	1 week	299	1. Nurse education 2. Booklet 3. Usual care	Education Education Usual care	40,8 44,1 43,0	NA	57 49 51
7	Cherkin**	1998	Multi-center	Mixed LBP (less than 12 weeks)	No	1 month	Pain; disability	4 weeks; 12 weeks; 12 months	321	1. McKenzie 2. Manipulation 3. Booklet	Exercise Manual therapy Education	41,8 39,7 40,1	11,5 9,4 11,2	53 47 58
8	Dapas*	1985	Multi-center	Acute LBP (less than 6 weeks)	Not stated	14 days	Pain; disability	Day 4; Day 10	123	1. Baclofen 2. Placebo	Muscle relaxant Inert treatment	42,7 41,8	NA	52 44
9	Dreiser	2003	Multi-center	Acute LBP (less than 6 weeks)	No	1 week	Pain; disability	Day 3; day 8	372	1. Diclofenac-K 2. Ibuprofen 3. Placebo	NSAIDs NSAIDs Inert treatment	40,9 40,6 41	10,9 11,6	48,4 52,5 47,2

												11,3	
10	Eken*	2014	Silgle center	Acute LBP (less than 6 weeks)	No	1 day	Pain	30 minutes	137	1. Paracetamol 2. Dexketoprofen 3. Morphine	Paracetamol NSAIDs Opioid	31,5* 	9,5* 	60,6*
11	Eskin*	2014	Single center	Acute LBP (less than 6 weeks)	Not stated	5 days	Pain	Day 5-7	79	1. Prednisone 2. Placebo	Steroids Inert treatment	39 41	8 9	67 73
12	Faas*	1995	Multi-center	Acute LBP (less than 6 weeks)	Yes	5 weeks	Pain	1 week; 1 month; 12 month	363	1. Exercise 1. Usual care 2. Sham ultrasound	Exercise Usual care Inert treatment	35 34 37	NA	62 71 66
13	Goldie*	1968	Single center	Acute LBP (less than 6 weeks)	Yes	14 days	Pain	1 week; 2 weeks	50	1. Indomethacin 2. Placebo	NSAIDs Placebo	NA	NA	52 52
14	Haimovic*	1986	Single center	Acute LBP (less than 6 weeks)	Yes	7 days	Pain	1 week; 12 months	33	1. Dexamethasone 2. Placebo	Steroids Inert treatment	NA	NA	NA
15	Hasegawa	2014	Single center	Acute LBP (less than 6 weeks)	No	1 week	Pain; disability	7 days; 28 days	80	1. Acupuncture 2. Sham acupuncture	Acupuncutre Inert treament	47 43,9	9,8 10,9	37,5 35
16	Hindle*	1972	Single center	Acute LBP (less than 6 weeks)	Not stated	4 days	Pain; disability	2 days; 4 days	32	1. Carisoprodol 2. Placebo	Muscle relaxant Inert treatment	37 43,5	NA NA	56 62
17	Jellema	2005	Multi-center	Mixed LBP (less than 12 weeks)	Not stated	5 days	Pain; disability	6, 26, 52 weeks	314	1.Behavioral therapy 2. Usual care	Cognitive behavioral therapy Usual care	43,4 42	11,1 12	52,4 52,6
18	Ketenci	2005	Single center	Acute LBP (less than 6 weeks)	Not stated	1 week	Pain	Day 5-7	97	1.Thiocolchicoside 2. Tizanidine 3.Placebo	Muscle relaxant Muscle relaxant Inert treatment	37 37 40	NA NA NA	57,9 37,5 48,1
19	Kettenmann *	2007	Single center	Mixed LBP (less than 12 weeks)	Not stated	4 days	Pain	Day 4	30	1. Heat wrap 2. Usual care	Heatwrap Usual care	56,2 57,9	14,9 11,7	46,7 25
20	Lindstrom	1995	Single center	Subacute LBP (6-12 weeks)	Not stated	Until recover y	Pain; disability	12 months	103	1. Cognitive behavioral therapy 2. Usual care	Cognitive behavioral therapy Usual care	39,4 42,4	10,7 10,9	76,5 61,5

21	Malmivaara	1995	Multi-center	Acute LBP (less than 6 weeks)	Yes	Not reported	Pain; disability	3 weeks; 12 weeks	119	1. Exercise 2. No treatment	Exercise Inert treatment	41,1 39,1	NA NA	29 30
22	Mayer	2005	Multi-center	Mixed (acute and subacute)	No	5 days	Pain; disability	1 week	76	1. Heat wrap 2. Exercise 3. Booklet	Heat wrap Exercise Education	29,3 32,6 31,3	9,9 10,3 10,9	32 40 7,7
23	Miki	2018	Single center	Acute LBP (less than 6 weeks)	No	4 weeks	Pain; disability	2 weeks, 1 month	127	1. Acetaminophen 2. Loxoprofen	Paracetamol NSAIDs	66,7 63,5	2,3 19,4	32,8 34,9
24	Nadler**	2002	Multi-center	Mixed (acute and subacute)	No	2 days o 1 day??	Pain; disability	4 days	371	1. Heat wrap 2. Acetaminophen 3. Ibuprofen 4. Unheated wrap 5. Oral placebo	Heat wrap Paracetamol NSAIDs Inert treatment Inert treatment	35,8 34,9 36,6 36,8 38,0	10,5 11,3 10,4 9,3 9,1	41,6 43,4 40,6 42,1 40
25	Nadler**	2003b	Multi-center	Mixed (acute and subacute)	No	3 days	Pain; disability	Days 2-4	76	1.Heat wrap 2. Oral placebo 3. Ibuprofen 4. Unheated wrap	Heat wrap Inert treatment NSAIDs	42,2 41,5 42,5 34,0	9,4 9,8 2,7 8,4	36,4 38,2 25 20
26	Nadler**	2003 a	Multi-center	Mixed (acute and subacute	No	3 days	Pain; disability	Day 5	219	1. Heat wrap 2. Oral placebo 3. Ibuprofen 4. Unheated wrap	Heat wrap Inert treatment NSAIDs Inert treatment	35,6 36,7 36,3 34,9	11,6 10,8 11,6 11,3	45,7
27 a	Postacchini *	1988	Multi-center	Acute LBP (less than 6 weeks)	No	4 weeks 10-14 days 1 or 2 weeks	Pain; disability	3 weeks; 6 months	46	1. Manipulation 2. Diclofenac 3. Placebo gel	Manual therapy NSAIDs Inert treatmnt	36,3	NA	55
27 b	Postacchini *	1988	Multi-center	Acute LBP (less than 6 weeks)	No	4 weeks 10-14 days 1 week 1 or 2 weeks	Pain; disability	3 weeks; 6 months	66	1. Manipulation 2. Diclofenac 3. Back school 4. Placebo gel	Manual therapy NSAIDs Back school Inert treatment	40,3	NA	51,2
27 c	Postacchini *	1988	Multi-center	Acute LBP (less than 6 weeks)	Yes	4 weeks 10-14 days 1 or 2 weeks	Pain; disability	3 weeks; 6 months	53	1. Manipulation 2. Diclofenac 3. Placebo gel	Manual therapy NSAIDs Inert treatment	37,7	NA	45,8

28	Ralph*	2008	Multi-center	Acute LBP (less than 6 weeks)	No	7 days	Pain; disability	1 week	562	1. Carisoprodol 2. Placebo	Muscle relaxant Inert treatment	39,3 41,5	11,82 11,7	51,3 45
29	Sae-Jung	2016	Single center	Mixed (acute and subacute)	No	2 weeks	Pain; disability	1 month; 3 months	65	1. Diclofenac 2. Methylprednisolone	NSAIDs Steroids	49 44	8,7 9,3	55 53,1
30	Santilli	2006	Multi-center	Acute LBP (less than 6 weeks)	Yes	Until recover y (max 4 weeks)	Pain	15 days; 1, 3, 6 months	102	1. Active manipulation 2. Simulated manipulation	Manual therapy Inert treatment	NA	NA	69,8 55,1
31	Schrenk	2003	Single center	Mixed (acute and subacute)	Yes	Not reporte d	Pain; disability	3 visits	25	1. Exercise (McKenzie) 2. Mobilization	Exercise Manual therapy	40,1 44,8	17,1 12,7	46,7 80
32	Schneider	2015	Single center	Mixed (acute and subacute)	No	4 weeks	Pain; disability	4 weeks; 3 months; 6 months	112	1. Manual manipulation 2. Mechanical assisted manipulation 3. Usual care	Manual therapy Manual therapy Usual care	41,4 40,4 41,3	15,3 15,9 11,6	32,4 40 40
33	Seferlis	1998	Single center	Acute LBP (less than 6 weeks)	Yes	8 weeks	Pain; disability	1 months; 3 months; 12 months	180	1. Exercise 2. General pratictionnaire program-usual care	Exercise Usual care	39	19-64 range	52,7
34	Serfer*	2009	Multi-center	Acute LBP (less than 6 weeks)	No	1 week	Pain; disability	1 week	828	1.Carisoprodol 250 mg 2. Carisoprodol 350 mg 3. Placebo	Muscle relaxant Muscle relaxant Inert treatment	40,9 40,5 40,7	11,7 12,4 13,1	47,7 44,3 39,4
35	Shin	2013	Multi-center	Acute LBP (less than 6 weeks)	Yes	1 day	Pain; disability	2 weeks; 4 weeks; 24 weeks	58	1. Acupuncture 2. Diclofenac	Acupuncture NSAIDs	37,9 38,7	7,4 8,6	66 52
36	Storheim	2003	Single center	Subacute LBP (6-12 weeks)	No	15 weeks 1 week	Pain; disability	18 weeks; 48 weeks	93	1. Exercise 2. Cognitive intervention 3. Usual care	Exercise Cognitive behavioral therapy Usual care	42,3 41,3 38,9	9,2 9,4 11,9	46,7 52,9 44,8
37	Suni*	2006	Multi-center	Mixed (acute and subacute)	Not stated	12 monhts	Pain; disability	6 months; 12 monhts	106	1. Exercise with cognitive goals 2. Control group	Cognitive behavioral therapy Usual care	47,6 46,9	5,8 5,3	100 100
38	Szpalski	1994	Single center	Acute LBP (less than 6 weeks)	Yes	1-2 weeks	Pain	8 days; 15 days	73	1. Tenoxicam 2. Placebo	NSAIDs Inert treatment	37,5 38,9	9,2 10,4	62,2 66,7

39	Takamoto	2015	Multi-center	Acute LBP (less than 6 weeks)	No	2 weeks	Pain; disability	1 week; 1 month	63	1. Compression at TP 2. Sham compression 3. Effleurage massage	Manual therapy Inert treatment Manual therapy	38 38,1 35,6	3 3,8 3	45,4 47,1 37,5
40	Traeger	2019	Multi-center	Acute LBP (less than 6 weeks)	Yes	2 sessions	Pain; disability	1 week, 3, 6, 12 months	202	1. Education 2. Sham education	Education Inert treatment	46,5 43,8	14,7 14,1	47,5 50,5
41	Tuzun	2003	Multi-center	Acute LBP (less than 6 weeks)	Not stated	Until recover y, max 5 days	Pain	5 days	149	1.Thiocolchicoside 2. Placebo	Muscle relaxant Inert treatment	40,7 41	10,3 11	50 42
42	Veenema	2000	Single center	Acute LBP (less than 6 weeks)	Not stated	1 day	Pain	60 minutes	155	1. Meperidine 2. Ketorolac	Opioid NSAIDs	35,5 36,0	12,8 12,1	63,0 60,0
43	Videman*	1984	Single center	Acute LBP (less than 6 weeks)	No	Until recover y, max 3 weeks	Pain; disability	1 week; 3 weeks	70	1. Meptazinol 2. Diflunisal	NSAIDs Opioid	38,0 35,0	14,0 11,0	60,0 57,1
44	von Heymann**	2013	Multi-center	Acute LBP (less than 6 weeks)	Not stated	Not reporte d	Pain; disability	9 days	100	1. Manipulation 2. Diclofenac 3. Placebo-sham	Manual therapy NSAIDs Inert treatment	34,1* 37,5* 39,3* (medi an values)	9,5 10,9 10,2	63,9 10,9 10,2
45	Williams	2014	Multi-center	Acute LBP (less than 6 weeks)	Yes	Until recover y, max 4 weeks	Pain; disability	1week; 1 month; 3 months;	165 2	1. Paracetamol 2. Paracetamol as needed 3. Placebo	Paracetamol Paracetamol Inert treatment	44,1 45,5 45,4	14,8 16,7 15,9	52,0 53,0 55,0
46	Younes*	2017	Single center	Mixed (acute and subacute)	Not stated	1 week	Pain	1 week	22	1. Manipulation 2. Sham manipulation	Manual therapy Inert treatment	31,0 28,0	9,0 7,0	100,0 100,0 100,0

*studies were not included in quantitative analysis due to different reasons such as median and IQR, missing outcome data.

**not all treatment arms are reported in quantitative analysis (e.g., multi-arm trial reported 2 out 3 treatment arms with available outcome data).

Assessment of transitivity by interventions

Table 2. Stage of LBP

	FREQUENCIES (%)		
TREATMENT	Acute	Subacute	Mixed
A	76,5	0,0	23,5
B	100,0	0,0	0,0
C	50,0	0,0	50,0
D	0,0	50,0	50,0
E	20,0	0,0	80,0
F	42,9	14,3	42,9
G	0,0	0,0	100,0
H	58,3	0,0	41,7
I	100,0	0,0	0,0
J	77,8	0,0	22,2
K	100,0	0,0	0,0
L	80,0	0,0	20,0
M	100,0	0,0	0,0
N	66,7	0,0	33,3
O	22,2	22,2	55,6

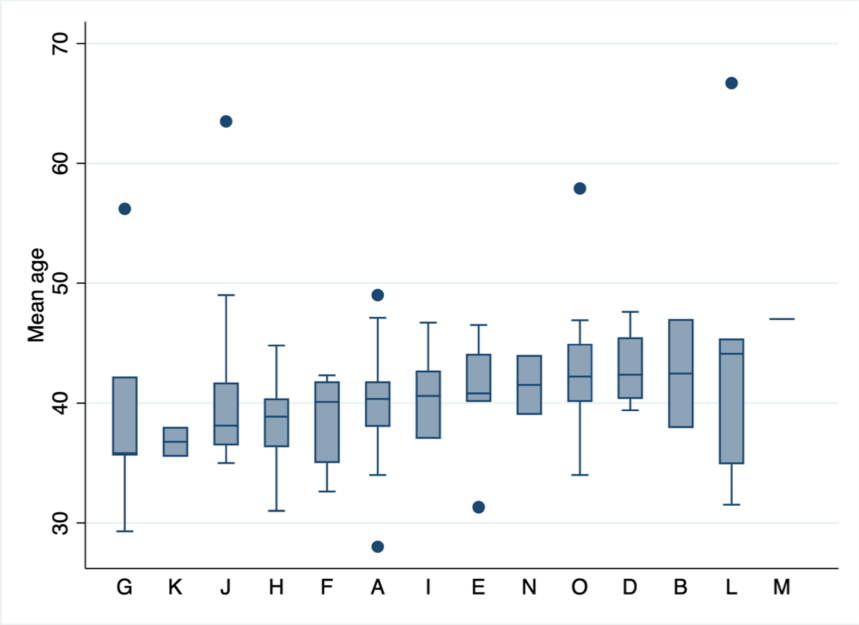
Legend: A=Inert treatment; B=Acupuncture; C=Back school; D=Cognitive behavioral therapy; E=Education; F=Exercise; G=Heat wrap; H=Manual therapy; I=Muscle relaxant; J=NSAIDs; K=Opioids; L=Paracetamol; M=Physical therapy; N=Steroids; O=Usual care

Table 3. Presence of leg pain or sciatica

	FREQUENCIES (%)		
TREATMENT	Yes	No	Not stated
A	32,4	41,2	26,5
B	50,0	50,0	0,0
C	50,0	50,0	0,0
D	0,0	25,0	75,0
E	60,0	40,0	0,0
F	57,1	42,9	0,0
G	0,0	80,0	20,0
H	25,0	58,3	16,7
I	10,0	30,0	60,0
J	22,2	61,1	16,7
K	0,0	66,7	33,3
L	40,0	60,0	0,0
M	0,0	100,0	0,0
N	33,3	33,3	33,3
O	33,3	22,2	44,4

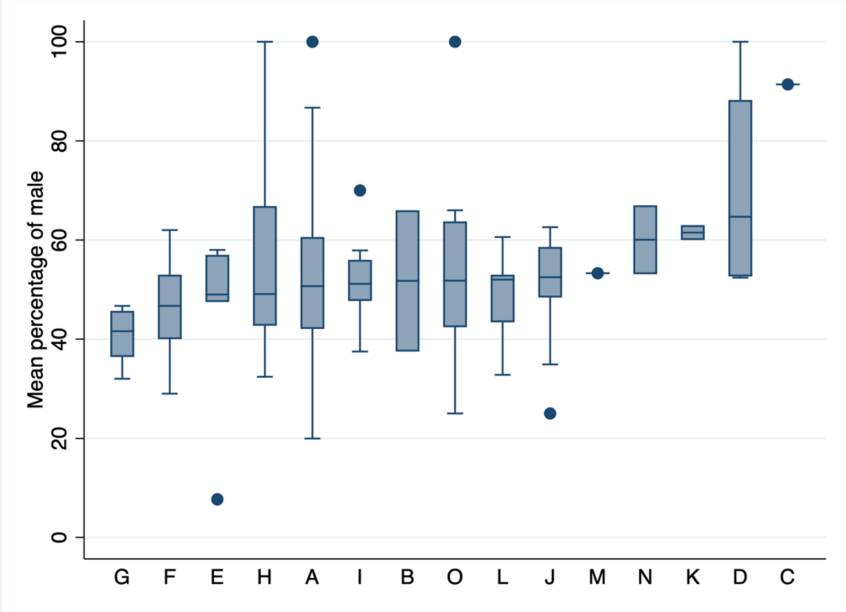
Legend: A=Inert treatment; B=Acupuncture; C=Back school; D=Cognitive behavioral therapy; E=Education; F=Exercise; G=Heat wrap; H=Manual therapy; I=Muscle relaxant; J=NSAIDs; K=Opioids; L=Paracetamol; M=Physical therapy; N=Steroids; O=Usual care

*Presence of leg pain or sciatica was reported in 15 studies out of 46 (31%) of which 6 were not included in quantitative analysis (qualitative analysis).
*Leg pain or sciatica is present in 32% (median, IQR 5-45%) of studies whereas 17% of studies did not report information (median, 0-33%).



Median age ranged from 35 to 48 years old with overlapping of 25-75 percentiles across interventions as already known by the Global Burden of Disease. [21]

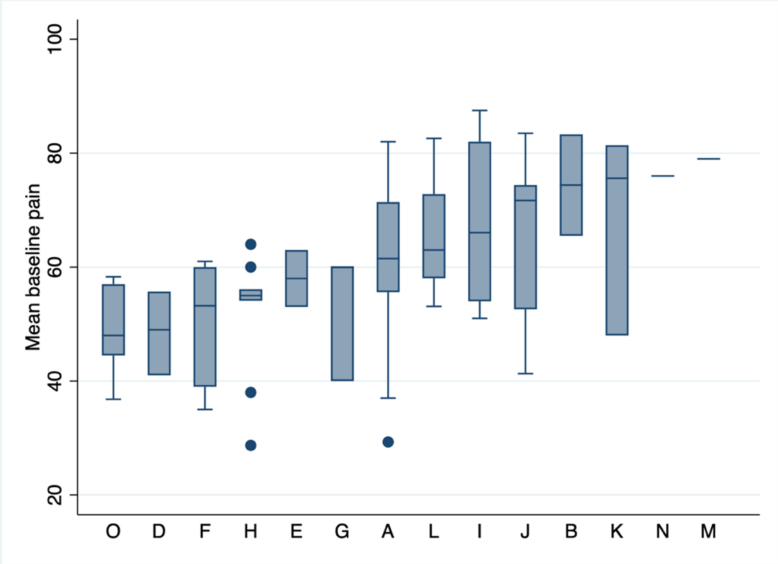
Figure 1. Mean age



Median percentage of male ranged from 42% to 90% with overlapping of 25-75 percentiles across interventions.*

Figure 2. Percentage of male participants

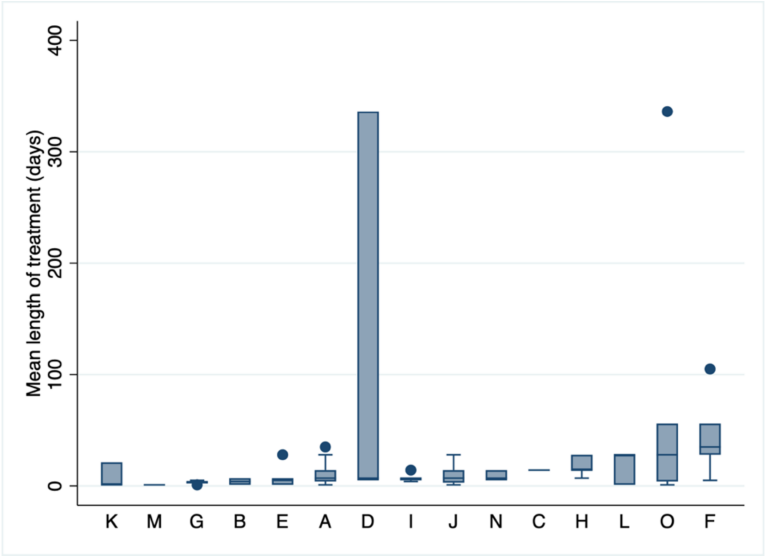
*Five studies did not report geder; outliers referts to 2 studies with a 100% male; however, these trials did not report outcome data and were not included in quantitative analysis (qualitative analysis). Excluding them, male and female can be equally distributed across interventions.



Median baseline pain ranged from 37 to 78 with overlapping of 25-75 percentiles across interventions.

Figure 3. Baseline severity (pain)

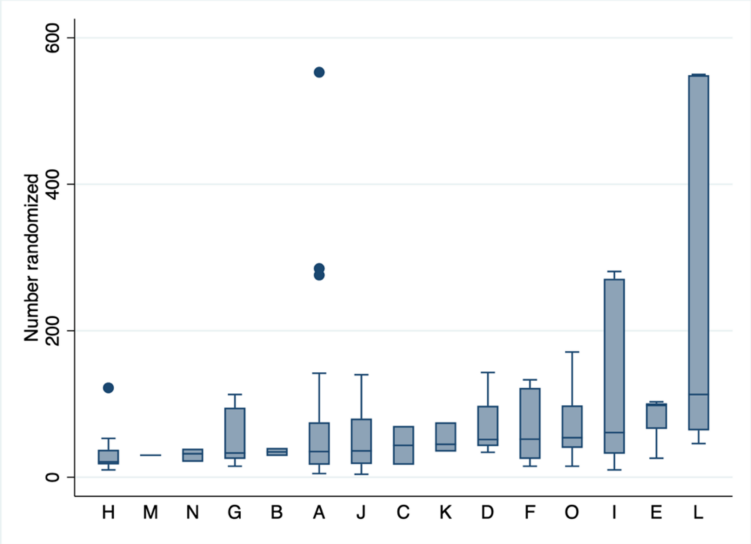
*A: 1 trial out of 34 had an outlier mean baseline value of 29.3, however this trail did not report outcome data and was not included in quantitative analysis (qualitative analysis);
**H: 1 trial out of 12 had an outlier mean baseline value of 28.7, however this trail did not report outcome data and was not included in quantitative analysis (qualitative analysis)
Severity of pain based on adapted scale 0-100



Median length of treatment ranged from 1 to 40 days with overlapping of 25-75 percentiles across interventions.

Figure 4. Length of treatment

*D: 1 trial out of 4 had an outlier mean length of treatment of 336 days, however this trail did not report outcome data and was not included in quantitative analysis (qualitative analysis); **O: 1 trial had out of 9 an outlier median lenght of treatment of 336 days, however this trail did not report outcome data and was not included in quantitative analysis (qualitative analysis)



Median number of randomized ranged from 30 to 90 with overlapping of 25-75 percentiles across interventions.

Figure 5. Number of randomized

*L: 1 trial out of 4 had an outlier number of randomized of 550, which represents less than 5% of the overall sample. However, we judged this reason insufficient to affect transitivity across interventions.
**A: 1 trial out of 34 had an outlier number of randomized of 545, which represents less than 5% of the overall sample. However, we judged this reason insufficient to affect transitivity across interventions.

Legend: A=Inert treatment; B=Acupuncture; C=Back school; D=Cognitive behavioral therapy; E=Education; F=Exercise; G=Heat wrap; H=Manual therapy; I=Muscle relaxant; J=NSAIDs; K=Opioids; L=Paracetamol; M=Physical therapy; N=Steroids; O=Usual care

Table 4. Pshycological assessment

Overall, 10 RCTs (22%) reported a psychological assessment as baseline characteristics of samples. We found heteroegeneity and poor reporting in outcome measurements with missing data; thus, we did not explore the heterogeneity across all included studies. We reported the phsychological assessment in a table format.

PSYCHOLOGICAL ASSESSMENT

ID	Author	Category of Intervention	Scores at baseline	Mean (SD)
4	Bertalanffy 2005	Physical therapy	Anxiety score[a]	82,0 (8,0)
4	Bertalanffy 2005	Inert treatment	Anxiety score[a]	85,0 (6,0)
6	Cherkin 1996	Education	Worry about pain[b]	6,0
6	Cherkin 1996	Education	Worry about pain[b]	6,0
6	Cherkin 1996	Usual care	Worry about pain[b]	5,7
12	Faas 1995	Usual care	NHP (emotion)[c]	7,4
12	Faas 1995	Inert treatment	NHP (emotion)[c]	7,2
12	Faas 1995	Exercise	NHP (emotion)[c]	7,7
16	Hindle 1972	Muscle relaxant	Anxiety and tension[d]	2,6
16	Hindle 1972	Inert treatment	Anxiety and tension[d]	2,2
17	Jellema 2005	Cognitive behavioral therapy	FABQpa[e]	14,3 (5,6)
			CSQ[f]	10,3 (6,6)
17	Jellema 2005	Usual care	FABQpa[e]	15,3 (5,2)
			CSQ[f]	11,2 (6,9)
23	Miki 2018	Paracetamol	PCS[g]	24,5 (1,5)
23	Miki 2018	NSAIDs	PCS[g]	30,7 (1,7)
32	Schneider 2015	Manual therapy	FABQ[h]	32,7 (15,3)
32	Schneider 2015	Manual therapy	FABQ[h]	33,0 (18,6)
32	Schneider 2015	Usual care	FABQ[h]	33,0 (17,8)
36	Storheim 2003	Exercise	FABQpa[e]	13,3 (5,2)
			FABQw[i]	25,9 (9,7)
36	Storheim 2003	Cognitive behavioral therapy	FABQpa[e]	14,1 (4,4)
			FABQw[i]	26,7 (9,1)
36	Storheim 2003	Usual care	FABQpa[e]	14,6 (3,8)
			FABQw[i]	29,1 (8,2)
40	Traeger 2019	Education	PCS[g]	18,3 (12)
			DASS[j]	4,1 (3,7)
40	Traeger 2019	Inert treatment	PCS[g]	19,9 (11,2)
			DASS[j]	5,1 (5)
45	Williams 2014	Paracetamol	Feelings of depression[k]	3,2 (2,9)
45	Williams 2014	Paracetamol	Feelings of depression[k]	3,1 (2,9)
45	Williams 2014	Inert treatment	Feelings of depression[k]	3,1 (2,9)

[a] Visual analogue scale from 0 (no anxiety) to 100 (highest anxiety)
[b] Numeric rating scale from 0 (no worry) to 10 (extremely worried)
[c] NHP: Nottingham Health Profile – emotional reactions domains from 0 (good subjective health status) to 100 (poor subjective health status)
[d] Four step severity rating scale from 1 (none) to 4 (severe)
[e] FABQpa: Fear-avoidance belief questionnaire - four item physical activity subscale from 0 to 24, with higher score indicating more strongly held fear avoidance beliefs
[f] CSQ: Coping strategies questionnaire - six item subscale from 0 to 36, with higher scores indicating greater use of coping strategies
[g] PCS: Pain catastrophizing scale from 0 to 52, with higher scores indicating higher levels of catastrophizing
[h] FABQ: Fear-avoidance belief questionnaire from 0 to 96, with higher score indicating more strongly held fear avoidance beliefs
[i] FABQw: Fear-avoidance belief questionnaire - seven item physical activity subscale from 0 to 42, with higher score indicating more strongly held fear avoidance beliefs
[j] DASS: Depression severity scale of Depression, Anxiety and Stress Scale with range from 0 (no depressive symptoms) to 42 (high depressive symptoms)
[k] Feelings of depression from 0 (not at all) to 10 (extremely).

Assessment of transitivity by head-to-head comparisons

Table 5. Stage of LBP

	FREQUENCIES (%)		
COMPARISONS	Acute	Subacute*	Mixed (acute and subacute)
AB	100,0	0,0	0,0
AC	50,0	0,0	50,0
AE	100,0	0,0	0,0
AF	100,0	0,0	0,0
AG	0,0	0,0	100,0
AH	85,7	0,0	14,3
AI	100,0	0,0	0,0
AJ	72,7	0,0	27,3
AL	50,0	0,0	50,0
AM	100,0	0,0	0,0
AN	100,0	0,0	0,0
AO	100,0	0,0	0,0
BJ	100,0	0,0	0,0
CH	100,0	0,0	0,0
CJ	100,0	0,0	0,0
DF	0,0	**100,0**	0,0
DO	0,0	**50,0**	50,0
EF	0,0	0,0	100,0
EG	0,0	0,0	100,0
EH	0,0	0,0	100,0
EO	0,0	0,0	100,0
FG	0,0	0,0	100,0
FH	0,0	0,0	100,0
FO	66,7	**33,3**	0,0
GJ	0,0	0,0	100,0
GL	0,0	0,0	100,0
GO	0,0	0,0	100,0
HJ	100,0	0,0	0,0
HO	0,0	0,0	100,0
JK	100,0	0,0	0,0
JL	66,7	0,0	33,3
JN	0,0	0,0	100,0
KK	100,0	0,0	0,0

Legend: A=Inert treatment; B=Acupuncture; C=Back school; D=Cognitive behavioral therapy; E=Education; F=Exercise; G=Heat wrap; H=Manual therapy; I=Muscle relaxant; J=NSAIDs; K=Opioids; L=Paracetamol; M=Physical therapy; N=Steroids; O=Usual care

*only 3 comparisons investigated subacute population:
DO: 50% was due to 2 studies (Lindstrom 1995 and Storheim 2003)
DF: 100% was due to 1 study (Storheim 2003)
FO: 33% was due to 1 study (Storheim 2003)
Generally, covariates were equally distributed acrosss comparisons except for a very little percentage of comparisons (0.09%) represented by subacute population.
Moreover, these comparisons are present only in medium and long-terms of follow-ups:

- For both pain and disability at medium term no NMA was performed due to a disconnected network;
- For pain at long term, subacute population is present in 1 out of 4 head-to head comparisons;
- For disaibility at long term, subacute population is present in 3 out 5 head-to head comparisons.

Moreover, there is no consensus on the time-contingent traditional classification (acute, subacute, chronic) because this classificiation does not adequately reflect the prognostically highly important process of chronification [22].
For all these reasons, stage of pain can not be considered a potential effect modifier.

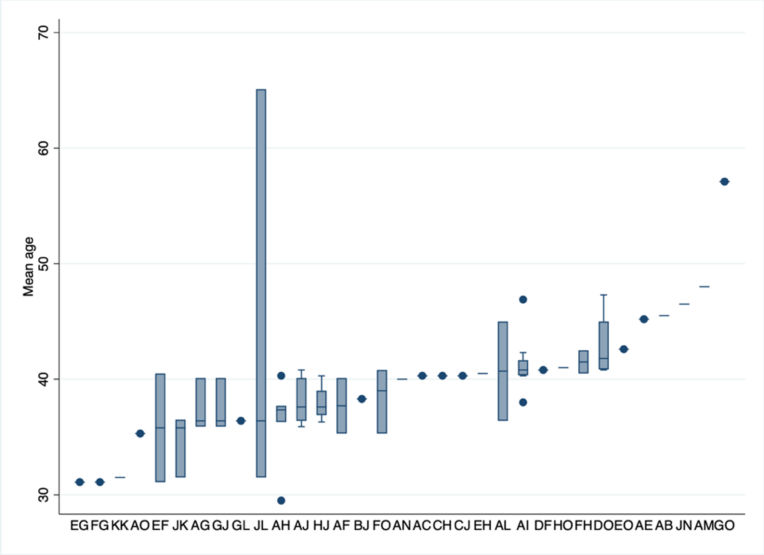
Table 6. Presence of leg pain or sciatica

	FREQUENCIES (%)		
COMPARISONS	Yes*	No	Not stated
AB	0,0	100,0	0,0
AC	50,0	50,0	0,0
AE	**100,0**	0,0	0,0
AF	**100,0**	0,0	0,0
AG	0,0	100,0	0,0
AH	28,6	42,9	28,6
AI	12,5	25,0	62,5
AJ	27,3	54,6	18,2
AL	50,0	50,0	0,0
AM	0,0	100,0	0,0
AN	50,0	0,0	50,0
AO	**100,0**	0,0	0,0
BJ	**100,0**	0,0	0,0
CH	0,0	100,0	0,0
CJ	0,0	100,0	0,0
DF	0,0	100,0	0,0
DO	0,0	25,0	75,0
EF	0,0	100,0	0,0
EG	0,0	100,0	0,0
EH	0,0	100,0	0,0
EO	**100,0**	0,0	0,0
FG	0,0	100,0	0,0
FH	50,0	50,0	0,0
FO	**66,7**	33,3	0,0
GJ	0,0	100,0	0,0
GL	0,0	100,0	0,0
GO	0,0	0,0	100,0
HJ	25,0	50,0	25,0
HO	0,0	100,0	0,0
JK	0,0	66,7	33,3
JL	0,0	100,0	0,0
JN	0,0	100,0	0,0
KK	0,0	100,0	0,0

Legend: A=Inert treatment; B=Acupuncture; C=Back school; D=Cognitive behavioral therapy; E=Education; F=Exercise; G=Heat wrap; H=Manual therapy; I=Muscle relaxant; J=NSAIDs; K=Opioids; L=Paracetamol; M=Physical therapy; N=Steroids; O=Usual care

Presence of leg pain or sciatica was reported in 15 studies out of 46 (31%) of which 6 were not included in quantitative analysis.

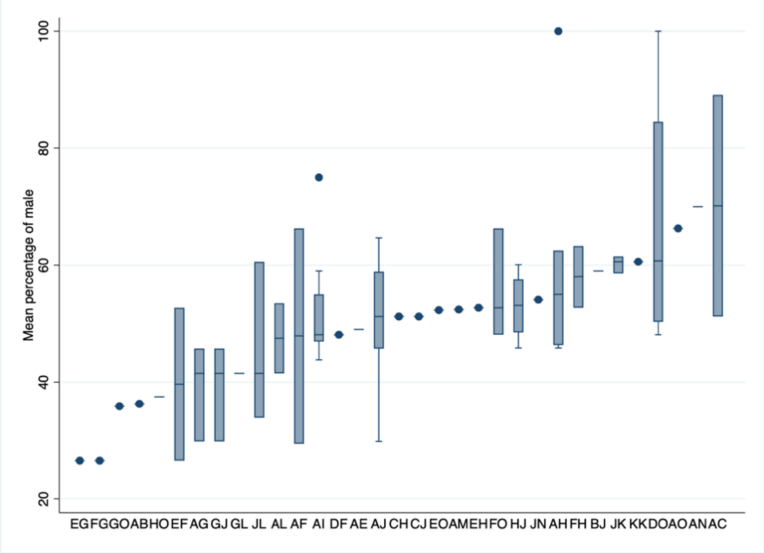
*AE: 1 study
*AF: 2 studies, of which 1 was not included in quantitative analysis (qualitative analysis).
*EO: 1 study not included in quantitative analysis (qualitative analysis).
*BJ: 1 study
*AO: 1 study not included in quantitative analysis (qualitative analysis).
*FO: 2 studies of which 1 was not included in quantitative analysis (qualitative analysis).
Overall, a very little percentage of leg pain or sciatica (0.09%) impact on global assessment.



Median of mean age ranged from 32 to 57 years old as already known by the Global Burden of Disease [21]

Figure 6. Mean age

*JL: 1 out of 3 trials has a mean age of 65.1

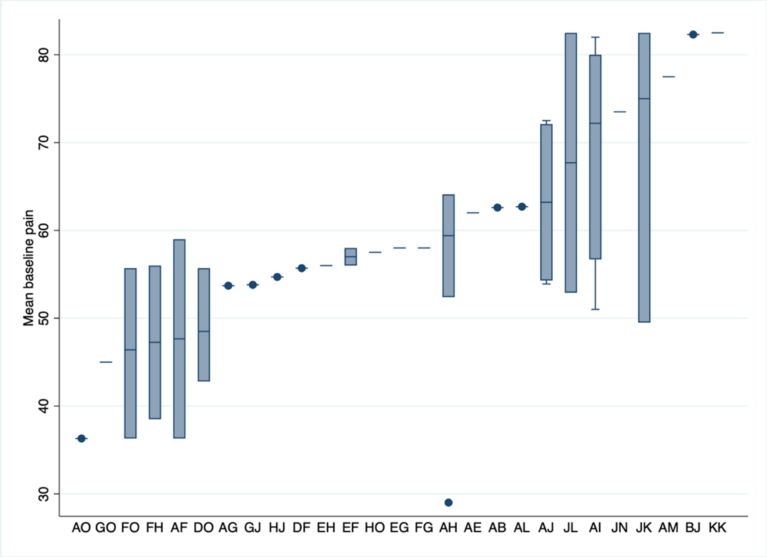


Median percentage of male ranged from 27 to 70 percent with overlapping of 25-75 percentiles across comparisons.

Figure 7. Percentage of male participants

*Five studies did not report gender

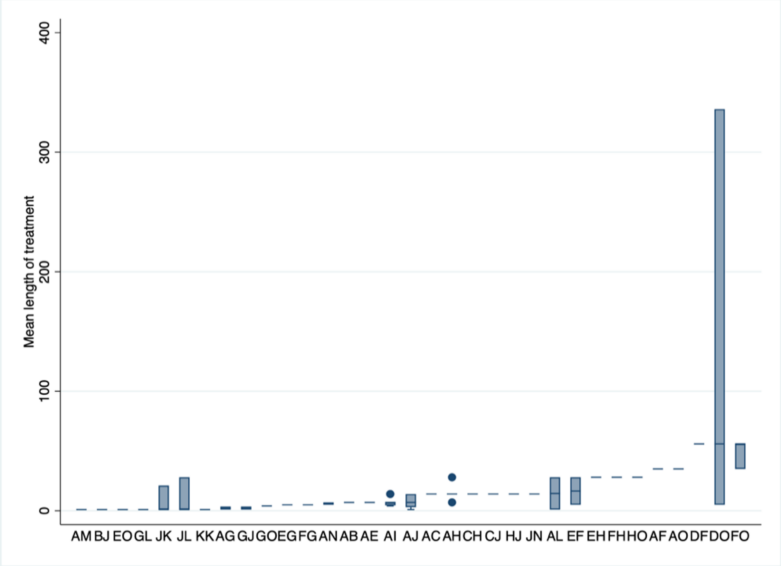
**AH and DO: outliers refer to 2 studies with a 100% male; however, these trials did not report outcome data and were not included in quantitative analysis (qualitative analysis). Excluding them, male and female can be equally distributed across interventions.



Median baseline pain ranged from 37 to 82 with overlapping of 25-75 percentiles across comparisons.

Figure 8. Baseline severity (pain)

*AH: 1 trial had an outlier mean baseline value of 29, however this trail did not report outcome data and was not included in quantitative analysis (qualitative analysis)



Median length of treatment ranged from 1 to 40 days with overlapping of 25-75 percentiles across comparisons.

Figure 9. Length of treatment

*DO: 1 trial had an outlier mean lenght of treatment of 336 days, however this trail did not report outcome data and was not included in quantitative analysis (qualitative analysis)

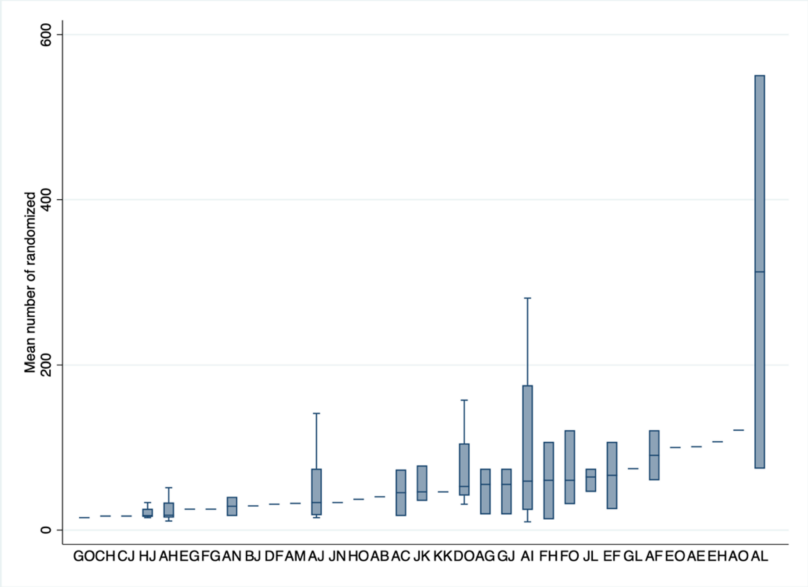


Figure 10. Number of randomized

*AL: 1 trial had an outlier number of randomized of 550, which represents less than 5% of the overall sample. However, we judged this reason insufficient to prejudice transitivity across interventions.

Legend: A=Inert treatment; B=Acupuncture; C=Back school; D=Cognitive behavioral therapy; E=Education; F=Exercise; G=Heat wrap; H=Manual therapy; I=Muscle relaxant; J=NSAIDs; K=Opioids; L=Paracetamol; M=Physical therapy; N=Steroids; O=Usual care

Supplement F. Risk of Bias

Figure 1. Aggregate Cochrane Risk-of-bias appraisal results

Risk of bias appraisal.[23]

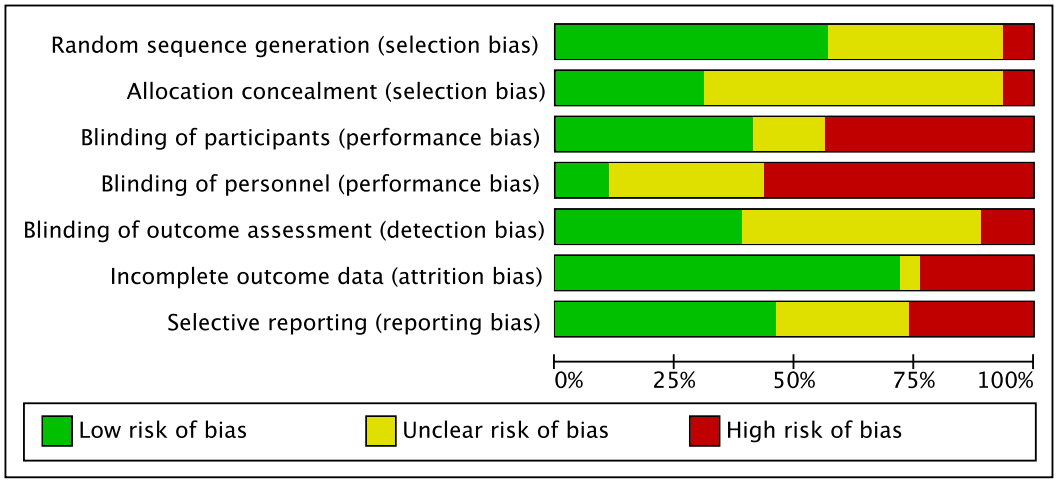


Table 1. Cochrane Risk-of-bias global judgement

Author, year	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel/ care providers (performance bias)	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting	FINAL JUDGEMENT
Amlie 1987	unclear	unclear	low	unclear	unclear	low	low	unclear
Bergquist-Ullman 1977	low	unclear	high	high	unclear	high	low	high
Berry 1988	unclear	unclear	unclear	unclear	unclear	low	low	unclear
Bertalanffy 2005	low	low	low	high	low	low	low	low
Casale 1988	unclear	unclear	low	unclear	unclear	low	high	unclear
Cherkin 1996	high	unclear	high	high	low	low	unclear	unclear
Cherkin 1998	unclear	low	high	high	low	low	unclear	low
Dapas 1985	unclear	unclear	low	unclear	unclear	high	high	high
Dreiser 2003	low	low	low	unclear	unclear	low	low	unclear
Eken 2014	low	low	low	low	unclear	low	low	unclear
Eskin 2014	low	unclear	unclear	low	low	low	low	unclear
Faas 1995	high	unclear	high	high	high	low	low	high
Goldie 1968	unclear	unclear	low	low	unclear	low	low	unclear
Haimovic 1986	low	unclear	low	unclear	unclear	high	unclear	high
Hasagawa 2014	low	unclear	low	high	low	low	low	unclear
Hindle 1972	low	high	unclear	unclear	unclear	low	high	high
Jellema 2005	low	unclear	high	high	unclear	low	unclear	unclear
Ketenci 2005	unclear	unclear	low	unclear	unclear	low	low	unclear
Kettenmann 2007	high	high	high	unclear	high	high	unclear	high
Lindstrom 1995	unclear	unclear	high	unclear	unclear	low	high	unclear
Malmivaara 1995	low	low	high	high	low	low	low	low
Mayer 2005	low	unclear	high	high	unclear	low	high	unclear
Miki 2018	low	unclear	high	high	unclear	high	high	high
Nadler 2002	unclear	unclear	high	high	unclear	low	unclear	unclear
Nadler 2003b	unclear	unclear	high	high	unclear	low	unclear	unclear
Nadler 2003a	unclear	unclear	high	high	unclear	high	unclear	high
Postacchini 1988	unclear	unclear	unclear	unclear	unclear	unclear	high	unclear
Ralph 2008	unclear	unclear	unclear	unclear	unclear	low	high	unclear

Sae-Jung 2016	low	low	unclear	high	high	low	low	high
Santilli 2006	low	low	low	high	low	low	unclear	low
Schenk 2003	low	unclear	high	high	high	low	unclear	high
Schneider 2015	low	low	high	high	low	low	high	low
Seferlis 1998	unclear	unclear	high	high	unclear	high	low	high
Serfer 2010	low	unclear	low	low	high	low	low	high
Shin 2013	low	low	high	high	low	low	low	low
Storheim 2003	low	low	high	high	low	high	low	high
Suni 2006	low	unclear	high	high	low	unclear	unclear	unclear
Szpalski 1994	unclear	unclear	unclear	unclear	unclear	low	low	unclear
Takamoto 2015	low	unclear	high	high	low	high	high	high
Traeger 2019	low	low	low	high	low	low	low	low
Tuzun 2003	low	low	low	unclear	low	low	low	low
Veenema 2000	unclear	high	low	high	low	low	unclear	high
Videman 1984	unclear	unclear	low	unclear	unclear	low	unclear	unclear
Von Heymann 2013	low	low	low	high	low	high	high	high
Williams 2014	low	low	low	low	low	low	low	low
Younes 2017	low	unclear	low	high	low	high	high	high

Supplement G. Network Plots

Figure 1. Network Plot- Pain outcome

Note: The size of the nodes is proportional to the number of studies evaluating each intervention, and the thickness of the edges is proportional to the precision (the inverse of the variance) of each direct comparison.

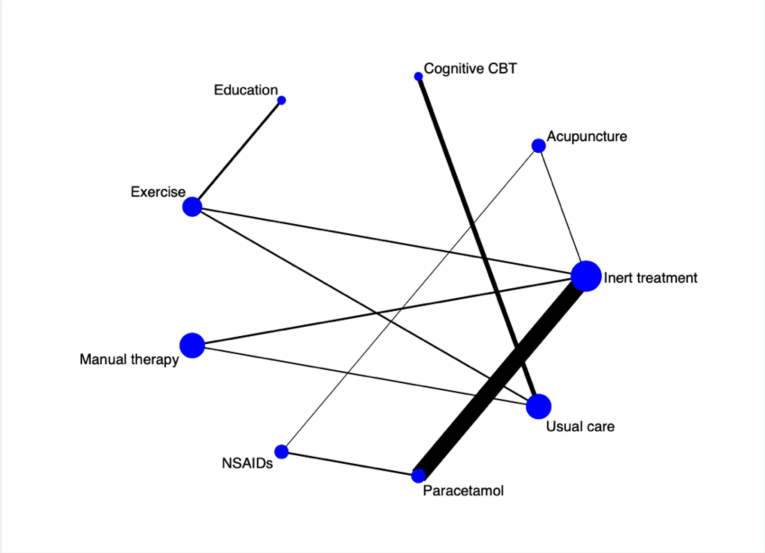


Figure 1a. Network for pain outcome at 1 month of FU

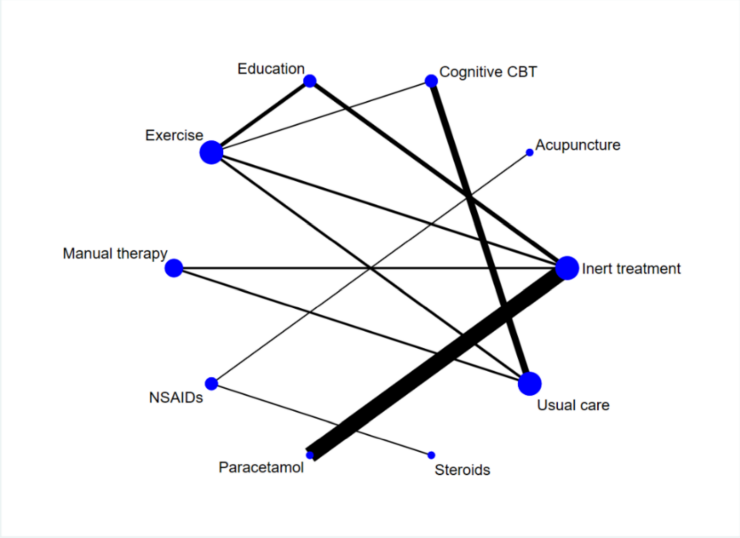


Figure 1b. Network for pain outcome at 3-6 months of FU

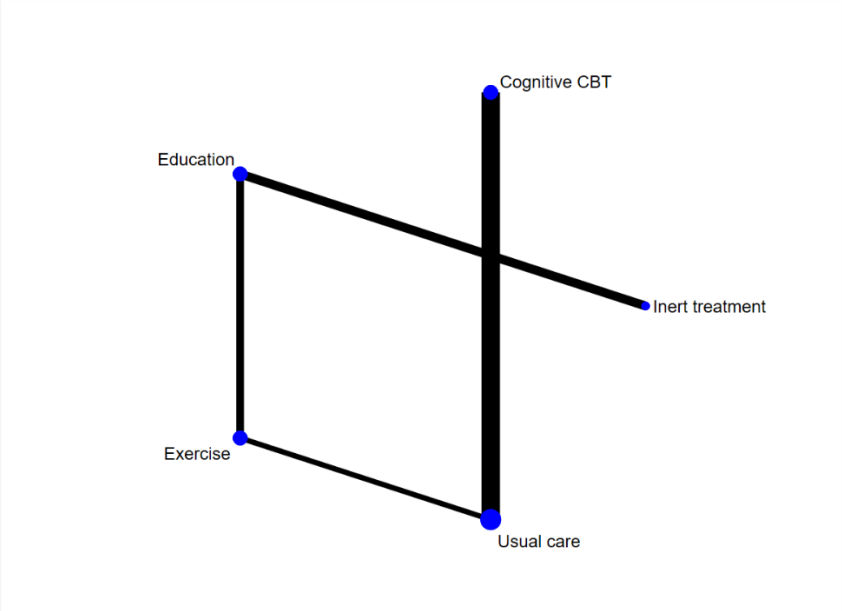


Figure 1c. Network for pain outcome at 12 months of FU

Figure 2. Network Plot- Disability outcome

Note: The size of the nodes is proportional to the number of studies evaluating each intervention, and the thickness of the edges is proportional to the precision (the inverse of the variance) of each direct comparison.

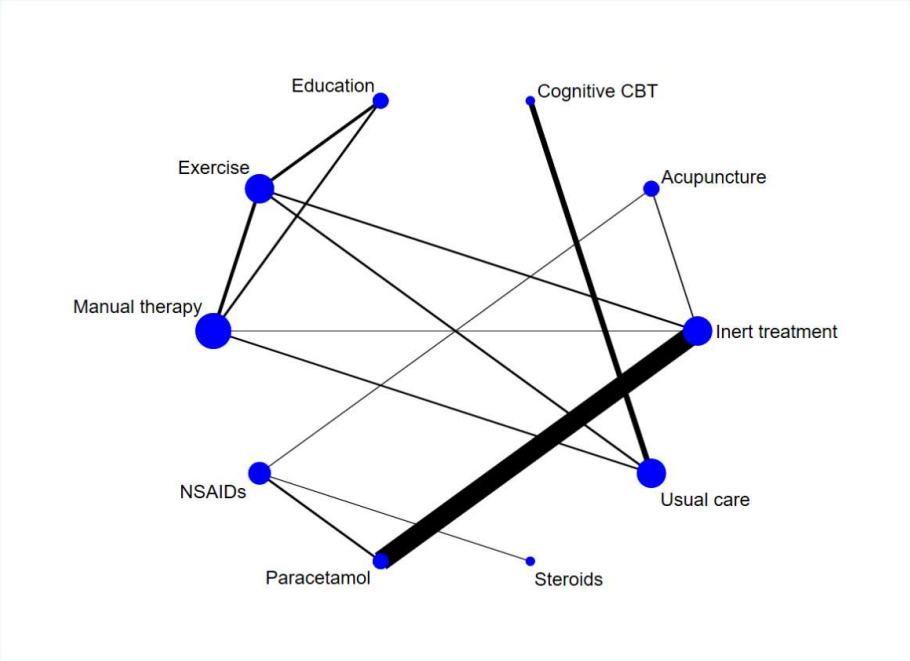


Figure 2a. Network for disability outcome at 1 month of FU

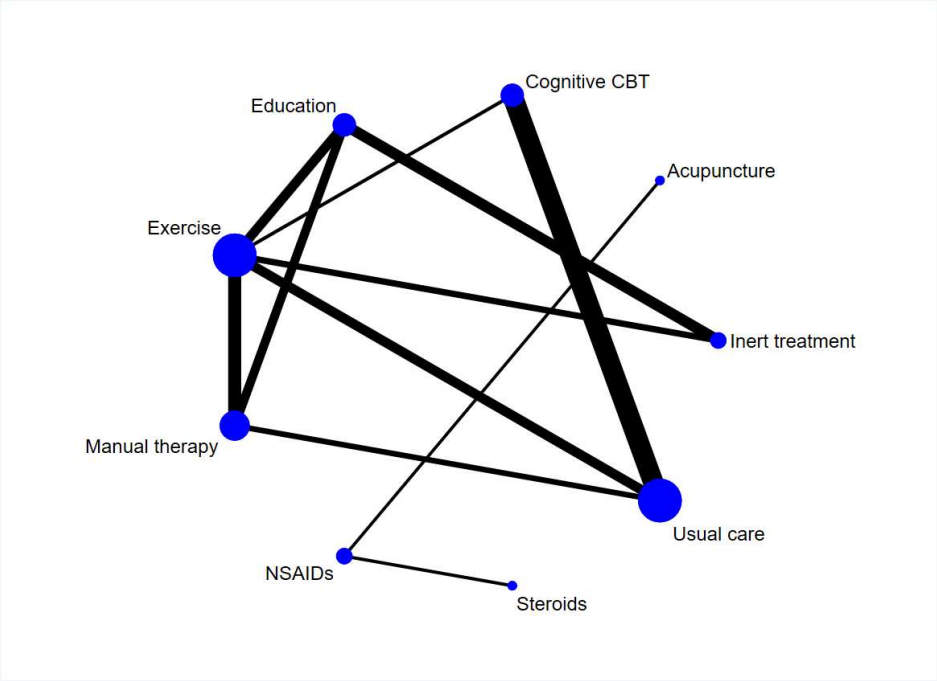


Figure 2b. Network for disability outcome at 3-6 months of FU

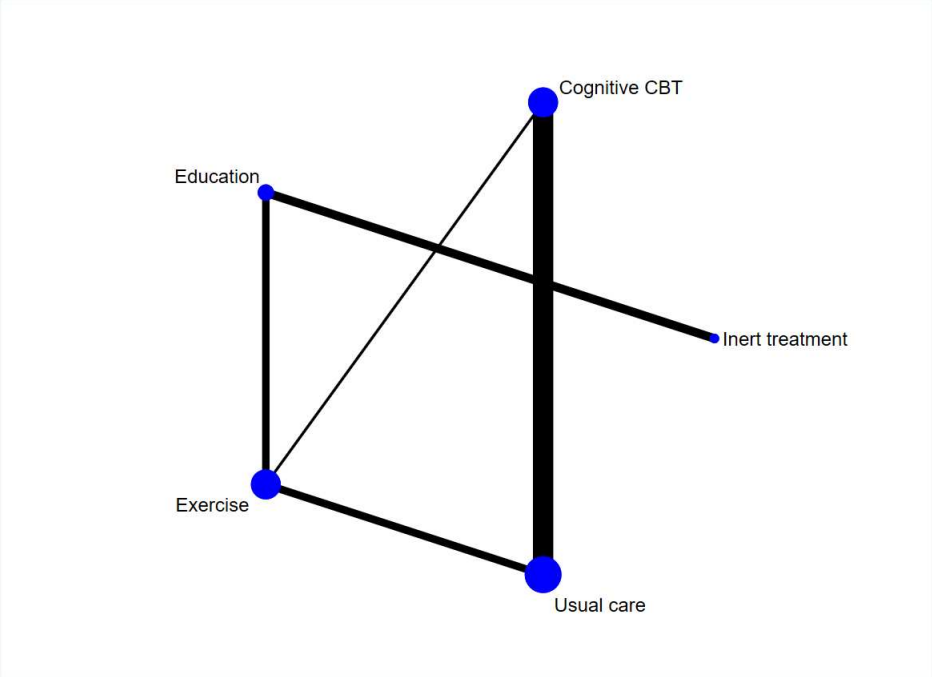


Figure 2c. Network for disability outcome at 12 months of FU

Supplement H. Assessment of pairwise Meta-Analyses

Pairwise meta-analyses –Pain Outcome

Table 1. Pairwise meta-analyses at 1 week of FU for pain

	Comparison	Number of studies	Effect size	Lower limit 95%	Upper limit 95%	Heterogeneity (I^2)	P value
1	Muscle relaxants vs Inert treatment	4	-1.06	-1.89	-0.24	91.1%	0.0000
2	Physical therapy vs Inert treatment	1	-2.85	-3.57	-2.14	Na	Na
3	NSAIDs vs Inert treatment	3	-0.84	-1.15	-0.53	54.2%	0.112
4	Opioid vs NSAIDs	2	-0.43	-0.71	-0.14	20.3%	0.263
5	Paracetamol vs NSAIDs	2	-0.21	-0.62	0.20	56.9%	0.128
6	Paracetamol vs Opioid	1	0.18	-0.24	0.59	Na	Na
7	Acupuncture vs Inert treatment	1	-0.30	-0.74	0.14	Na	Na
8	Exercise vs Education	1	-0.90	-1.47	-0.33	Na	Na
9	Heat wrap vs Education	1	-1.03	-1.60	-0.46	Na	Na
10	Heat wrap vs Exercise	1	-0.13	-0.68	0.43	Na	Na
11	Heat wrap vs Inert treatment	1	-4.77	-5.72	-3.81	Na	Na
12	Manual therapy vs Inert treatment	2	-1.20	-2.59	0.19	91.1%	0.000
13	Manual therapy vs Exercise	1	1.12	0.25	1.99	Na	Na
14	NSAIDs vs Acupuncture	1	-0.58	-1.11	-0.06	Na	Na
15	Education vs Inert treatment	1	0.04	-0.23	0.32	Na	Na
16	NSAIDs vs Manual therapy	1	0.67	0.20	1.13	Na	Na
17	Paracetamol vs Inert treatment	1	0.04	-0.08	0.16	Na	Na

Table 2. Pairwise meta-analyses at 1 month of FU for pain

	Comparison	Number of studies	Effect size	Lower limit 95%	Upper limit 95%	Heterogeneity (I^2)	P value
1	Exercise vs Education	1	-0.84	-1.14	-0.53	Na	Na
2	Acupuncture vs Inert treatment	1	-0.63	-1.08	-0.18	Na	Na
3	Usual care vs Cognitive CBT	1	0.04	-0.18	0.26	Na	Na

4	Exercise vs Inert treatment	1	0.00	-0.36	0.36	Na	Na
5	Paracetamol vs NSAIDs	1	-0.08	-0.43	0.27	Na	Na
6	Steroids vs NSAIDs	1	-1.51	-2.06	-0.95	Na	Na
7	Manual therapy vs Inert treatment	2	-0.86	-1.45	-0.27	59.7%	0.115
8	Usual care vs Manual therapy	2	0.61	-0.15	1.37	72.6%	0.056
9	Usual care vs Exercise	1	0.00	-0.36	0.36	Na	Na
10	NSAIDs vs Acupuncture	1	-0.55	-1.07	-0.02	Na	Na
11	Paracetamol vs Inert treatment	1	0.00	-0.12	0.12	Na	Na

Table 3. Pairwise meta-analyses at 3-6 months of FU for pain

	Comparison	Number of studies	Effect size	Lower limit 95%	Upper limit 95%	Heterogeneity (I^2)	P value
1	Exercise vs Education	1	-0.17	-0.47	0.13	Na	Na
2	Usual care vs Cognitive CBT	1	0.00	-0.22	0.22	Na	Na
3	Manual therapy vs Inert treatment	1	-0.80	-1.20	-0.40	Na	Na
4	Usual care vs Manual therapy	2	0.06	-0.62	0.73	66.6%	0.084
5	Usual care vs Exercise	1	0.00	-0.36	0.36	Na	Na
6	Exercise vs Cognitive CBT	1	-0.47	-0.97	0.03	Na	Na
7	Education vs Inert treatment	1	-0.08	-0.36	0.19	Na	Na
8	Paracetamol vs Inert treatment	1	-0.04	-0.16	0.07	Na	Na

Table 4. Pairwise meta-analyses at 12 months of FU for pain

	Comparison	Number of studies	Effect size	Lower limit 95%	Upper limit 95%	Heterogeneity (I^2)	P value
1	Exercise vs Education	1	-0.39	-0.68	-0.09	Na	Na
2	Usual care vs Cognitive CBT	2	0.09	-0.40	0.58	79.3%	0.028
3	Usual care vs Exercise	1	0.00	-0.36	0.36	Na	Na
4	Education vs Inert treatment	1	-0.30	-0.58	-0.03	Na	Na

Pairwise meta-analyses – Disability Outcome

Table 5. Pairwise meta-analyses at 1 week of FU for disability

	Comparison	Number of studies	Effect size	Lower limit 95%	Upper limit 95%	Heterogeneity (I^2)	P value
1	NSAIDs-Inert treatment	2*(3)	-0.432	-0.664	-0.199	22.3%	0.000
2	Acupuncture- Inert treatment	1	-0.385	-0.828	0.057	Na	0.088
3	Exercise-Education	1	-0.291	-0.842	0.260	Na	0.300
4	Heat Wrap-Education	1	-0.414	-0.967	0.140	Na	0.143
5	Heat Wrap-Exercise	1	-0.122	-0.677	0.432	Na	0.666
6	Paracetamol-NSAIDs	2	0.010	-0.201	0.221	0.0%	0.924
7	NSAIDs –Heat Wrap	1	-0.512	-0.780	-0.244	Na	0.000
8	Paracetamol–Heat Wrap	1	-0.466	-0.729	-0.202	Na	0.001
9	Heat Wrap- Inert treatment	1	-0.544	-0.792	-0.295	0.0%	0.000
10	Muscle Relaxant-Inert treatment	2*(3)	-0.235	-0.439	-0.031	70.6%	0.024
11	Manual therapy-Exercise	1	0.772	-0.063	1.606	Na	0.070
12	NSAIDs – Acupuncture	1	-0.732	-1.265	-0.199	Na	0.007
13	Manual therapy-Inert treatment	2	-0.660	-1.099	-0.221	19.6%	0.003
14	Education-Inert treatment	1	-0.271	-0.548	0.006	Na	0.055
15	NSAIDs –Manual Therapy	1	0.793	0.327	1.260	Na	0.001
16	Paracetamol-Inert treatment	1	-0.092	-0.210	0.026	Na	0.126

*3 comparisons from 2 studies

Table 6. Pairwise meta-analyses at 1 month of FU for disability

	Comparison	Number of studies	Effect size	Lower limit 95%	Upper limit 95%	Heterogeneity (I^2)	P value
1	Usual care – Manual therapy	1 *(2)	0.239	-0.333	0.810	53.5%	0.413
2	Acupuncture – Inert treatment	1	-0.709	-1.162	-0.257	Na	0.002
3	Usual care – Cognitive CBT	1	0.019	-0.203	0.241	Na	0.868
4	Exercise - Inert treatment	1	0.674	0.302	1.047	Na	0.000
5	Paracetamol - NSAIDs	1	-0.128	-0.476	0.220	Na	0.472
6	Steroids - NSAIDs	1	-1.215	-1.747	-0.682	Na	0.000

7	Usual care – Exercise	1	0.000	-0.358	0.358	Na	1.000
8	NSAIDs Acupuncture	1	-0.640	-1.169	-0.111	Na	0.018
9	Manual therapy - Inert treatment	1	-0.819	-1.438	-0.201	Na	0.009
10	Paracetamol - Inert treatment	1	-0.019	-0.137	0.099	Na	0.747
11	Exercise - Education	1	-0.426	-0.723	-0.129	Na	0.005
12	Manual therapy - Education	1	-2.158	-2.502	-1.815	Na	0.000
13	Manual therapy - Exercise	1	-1.732	-2.012	-1.452	Na	0.000

*2 comparisons from 1 study

Table 7. Pairwise meta-analyses at 3-6 months of FU for disability

	Comparison	Number of studies	Effect size	Lower limit 95%	Upper limit 95%	Heterogeneity (I^2)	P value
1	Usual care – Manual Therapy	1 *(2)	0.039	-0.348	0.426	0%	0.844
2	Usual care – Cognitive CBT	2	0.212	-0.333	0.757	75.4%	0.446
3	Exercise - Inert treatment	1	0.312	-0.052	0.677	Na	0.093
4	Steroids - NSAIDs	1	-0.794	-1.300	-0.287	Na	0.002
5	Usual care - Exercise	2	0.159	-0.229	0.547	38.0%	0.422
6	NSAIDs - Acupuncture	1	0.435	-0.087	0.956	Na	0.102
7	Exercise- Cognitive CBT	1	0.135	-0.356	0.627	Na	0.590
8	Education - Inert treatment	1	-0.096	-0.372	0.180	Na	0.496
9	Exercise- Education	1	-0.052	-0.347	0.243	Na	0.731
10	Manual therapy - Education	1	-0.896	-1.204	-0.588	Na	0.000
11	Manual therapy - Exercise	1	-0.844	-1.099	-0.590	Na	0.000

*2 comparisons from 1 study

Table 8. Pairwise meta-analyses at 12 months of FU for disability

	Comparison	Number of studies	Effect size	Lower limit 95%	Upper limit 95%	Heterogeneity (I^2)	P value
1	Exercise - Education	1	-0.437	-0.735	-0.138	Na	0.004
2	Usual care - Cognitive CBT	3	0.332	-0.142	0.806	80.4%	0.170
3	Usual care - Exercise	2	0.185	-0.249	0.619	49.5%	0.403
4	Exercise - Cognitive CBT	1	0.086	-0.405	0.577	Na	0.732
5	Education - Inert treatment	1	-0.163	-0.439	0.114	Na	0.249

Supplement I. Forest plot of network meta-analysis (network forest)

Figure 1. Network forest – pain outcome 1 week

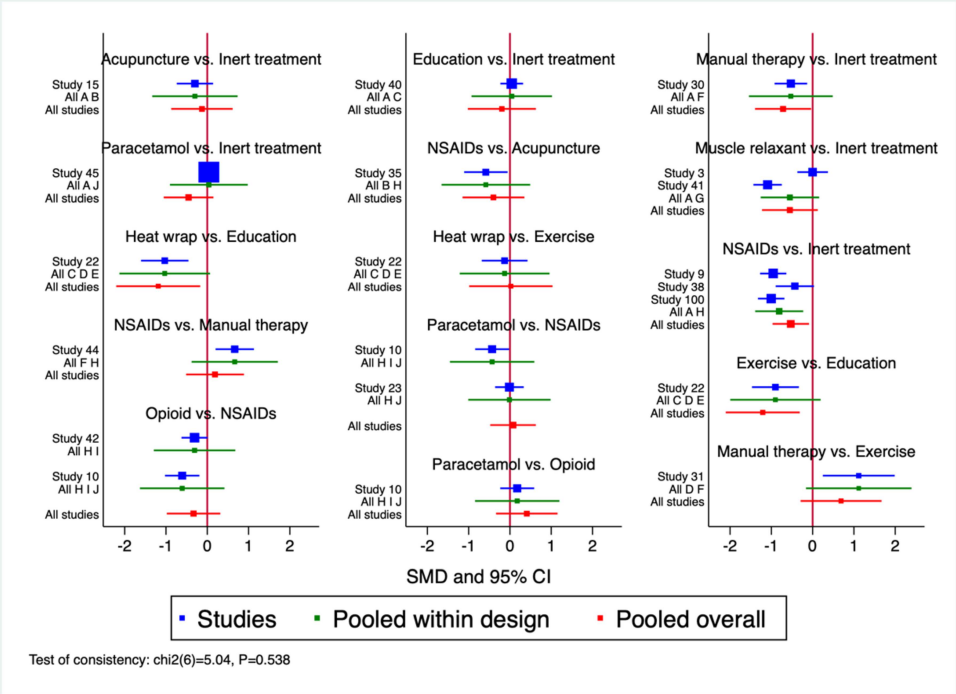


Figure 2. Network forest – pain outcome 1 month

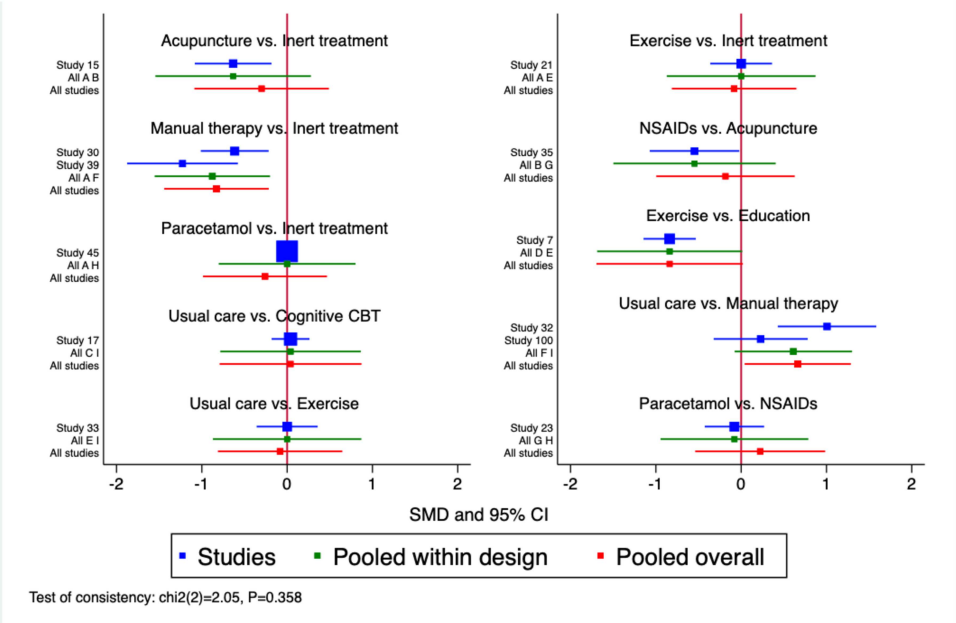


Figure 3. Network forest – pain outcome 12 months

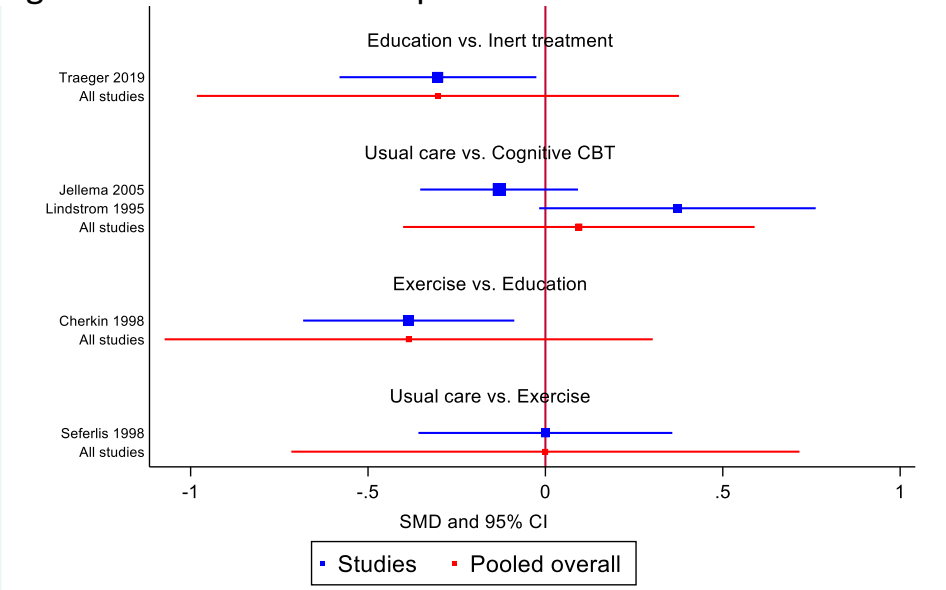


Figure 4. Network forest – disability outcome 1 week

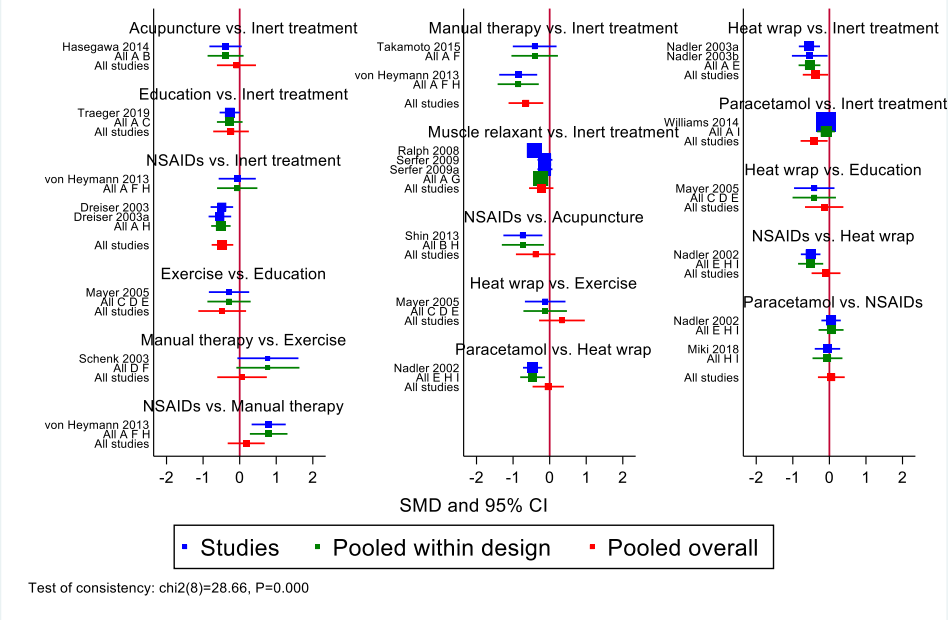
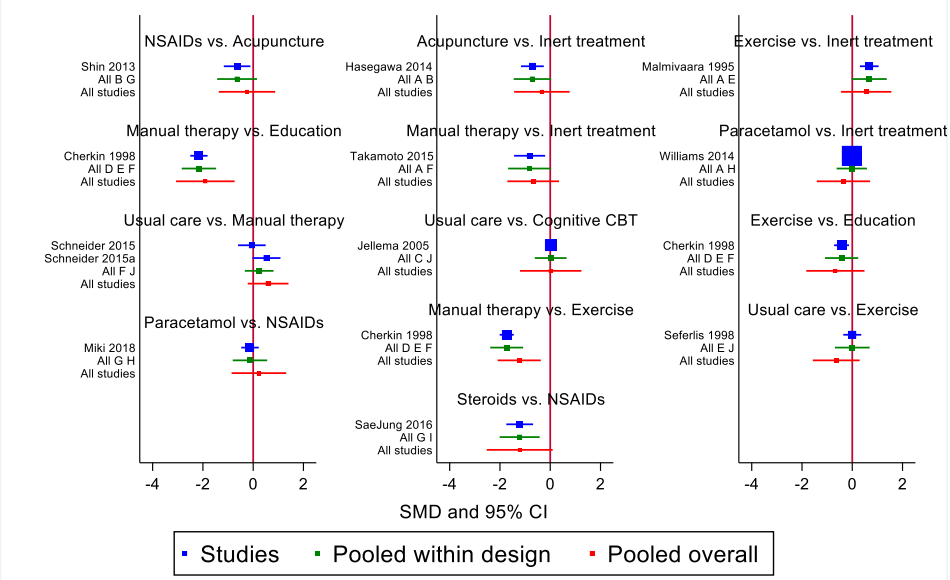
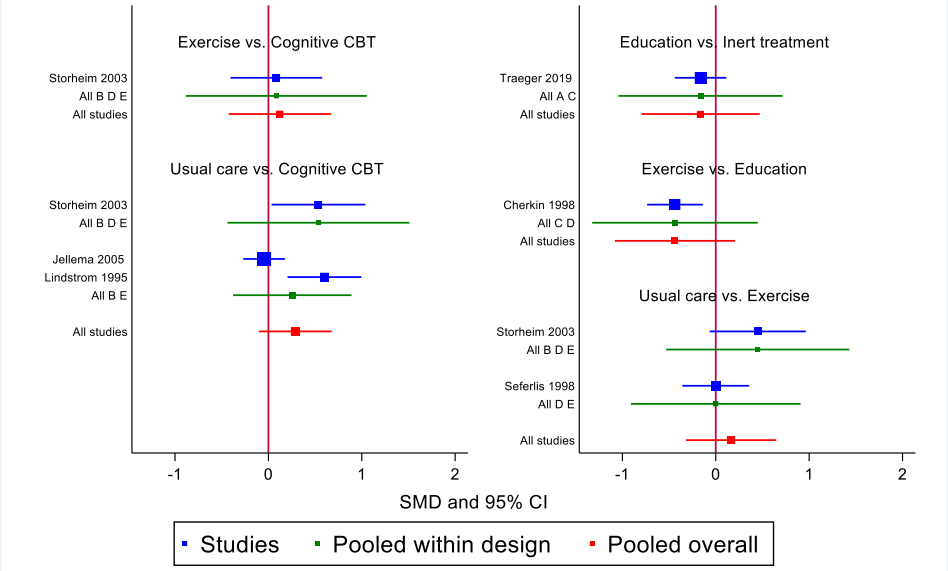


Figure 5. Network forest – disability outcome 1 month



Test of consistency: chi2(3)=11.19, P=0.011

Figure 6. Network forest – disability outcome 12 months



Test of consistency: chi2(2)=0.51, P=0.774

Supplement J. Incoherence estimation and evaluation

Table 1. Estimated Global Inconsistency in Networks

OUTCOME	FOLLOW UP	Chi square	Prob > chi2	tau
PAIN	1 week	chi2 (7) = 9.48	Prob > chi2 = 0.5383	0.234
	1 month	chi2 (2) = 2.05	Prob > chi2 = 0.3583	0.169
	3-6 months	disconnected		-
	12 months	chi2 (1) = 0.00	Prob > chi2 = 1**	0.1
DISABILITY	1 week	chi2 (8) =28.66	Prob > chi2 = 0.0004*	-
	1 month	chi2 (3) =11.20	Prob > chi2 = 0.0107*	-
	3-6 months	disconnected		-
	12 months	chi2 (2) = 0.51	Prob > chi2 = 0.7737	0.097

* Global consistency is tested here using the 'design-by-interaction' test that infers consistency across an entire treatment network, using a chi square test. A p value <0.05 is taken to infer evidence of global inconsistency in the network. [24 25]
**all the evidence about these contrasts comes from the trials which directly compare them

Table 2. Estimated Local Inconsistency for each pairwise comparison (side splitting) – pain outcome

Table 2a. Nodesplit pain 1 week

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>z	
Inert treatment - Acupuncture	-.2987834	.5246669	.0931138	.5981655	-.3918972	.7956616	0.622	.4740148
Inert treatment - Education	.0432741	.4689486	-1079062,00	.9044266	1122337,00	1018774,00	0.271	.4473322
Inert treatment - Manual therapy	-.5280427	.5132268	-.8939374	.5025075	.3658947	.7182726	0.610	.4719181
Inert treatment - Muscle relaxant	.	.	.	.	.	.	.	.

Inert treatment - NSAIDs	-.8159915	.2426794	-.0329156	.3199731	-.7830758	.4018672	0.051	.3754527
Inert treatment - Paracetamol	.0384353	.4065262	-.8652568	.3777104	.9036921	.5549132	0.103	.4020402
Acupuncuture - NSAIDs	-.5837083	.5448436	-.1918109	.5798476	-.3918974	.7956619	0.622	.4740148
Education – Exercise *	-.9012443	.5332432	-2023588,00	.8680764	1122343,00	1018776,00	0.271	.4473321
Education - Heat wrap *	-1029994,00	.5348997	-3274667,00	1963983,00	2244673,00	2037546,00	0.271	.4473318
Exercise - Heat wrap *	-.1287492	.5293618	2115939,00	1968485,00	-2244688,00	2037552,00	0.271	.4473321
Exercise - Manual therapy	1117072,00	.6305311	-.005282	.8002101	1122354,00	1018777,00	0.271	.4473321
Manual therapy - NSAIDs	.6652757	.4944677	-.2694296	.4841419	.9347054	.69202	0.177	.4335961
NSAIDs - Opiod *	-.4512816	.3356582	.9098231	1082583,00	-1361105,00	1133386,00	0.230	.4358473

* All the evidence about these contrasts comes from the trials which directly compare them.

Table 2b. Nodesplit pain 1 month

Side	**Direct**		**Indirect**		**Difference**			**tau**
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>z	
Inert treatment - Acupuncture	-.6327764	.3567964	.6254979	.5752867	-1.258.274	.6769479	0.063	.273273
Inert treatment - Exercise	-4.80e-12	.5233844	-.2740767	.7685576	.2740767	.9298451	0.768	.4896684
Inert treatment - Manual therapy	-.8871542	.3955099	-.613068	.8416375	-.2740862	.9298405	0.768	.4896674
Inert treatment - Paracetamol	-2.90e-12	.2798297	-1.258.269	.6164035	1.258.269	.6769475	0.063	.273273
Acupuncture - NSAIDs	-.5466608	.3826874	.7116145	.5583996	-1.258.275	.6769489	0.063	.2732733
Cognitive CBT - Usual care *	.0399034	.4245035	-.3263798	6.354.628	.3662832	6.354.629	1.000	.4090962
Education - Exercise *	-.8383118	.4379943	-.4467205	6.328.197	-.3915912	6.328.198	1.000	.4090963
Exercise - Usual care	-2.29e-08	.5225983	-.2740773	.7690965	.2740772	.9298486	0.768	.489669
Manual therapy - Usual care	.6130723	.4016588	.8871557	.8387265	-.2740834	.9298459	0.768	.4896684
NSAIDs - Usual care	-.078838	.3258861	1.179.435	.5933446	-1.258.273	.6769487	0.063	.2732733

* All the evidence about these contrasts comes from the trials which directly compare them.

Table 2c. Nodesplit pain 12 months

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>z	
Inert treatment - Education*	-.3029187	.34666	.3777316	158.3944	-.6806503	158.3948	0.997	.3164487
Cognitive CBT - Usual care*	.0943039	.2527336	-1.379709	447.7409	1.474013	447.7409	0.997	.316448
Education - Exercise*	-.385339	.3509876	.3660218	174.4564	-.7513608	174.4568	0.997	.3164487
Exercise - Usual care*	-9.18e-11	.3653395	.8080591	209.9836	-.8080591	209.9839	0.997	.3164485

* All the evidence about these contrasts comes from the trials which directly compare them.

Table 3. Estimated Local Inconsistency for each pairwise comparison (side splitting) – disability outcome

Table 3a. Nodesplit disability 1 week

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>z	
Inert Treatment-Acupuncture	-0.3850695	0.3512901	0.318208	0.412454	-0.7032775	0.541778	0.194	0.269133
Inert Treatment- Education	-0.2712998	0.3261325	-0.18365	0.424351	-0.0876449	0.535197	0.87	0.293896
Inert Treatment-Heat wrap	-0.5423379	0.2294745	-0.17954	0.253958	-0.3627932	0.342356	0.289	0.259164
Inert Treatment-Manual therapy	-0.664142	0.2886231	-0.59046	0.501075	-0.0736865	0.581203	0.899	0.292533
Inert Treatment-Muscle relaxant	.	.	.	.	.	.	.	.
Inert Treatment-NSAIDs	-0.387447	0.2022145	-0.59797	0.251741	0.2105194	0.324018	0.516	0.293991
Inert Treatment-Paracetamol	-0.0922448	0.2390906	-0.67043	0.219723	0.5781899	0.324719	0.075	0.231374
Acupuncture- NSAIDs	-0.731988	0.38266	-0.02871	0.383529	-0.7032779	0.541778	0.194	0.269133
Education- Exercise	-0.2919225	0.4040913	-0.93469	0.632299	0.6427636	0.750304	0.392	0.290215
Education- Heat wrap	-0.4121889	0.3985883	0.083842	0.365582	-0.4960307	0.540926	0.359	0.281415
Exercise-Heat wrap	-0.1227089	0.3721725	1.177.067	0.505458	-1.299.776	0.627943	**0.038**	0.241674
Exercise- Manual therapy	0.7716	0.4925257	-0.52044	0.434413	1.292.041	0.656732	**0.049**	0.24743

Heat wrap- NSAIDs	-0.5127726	0.274752	0.1945	0.237414	-0.7072724	0.36315	0.051	0.238334
Heat wrap- Paracetamol	-0.4646165	0.2367674	0.3788	0.239479	-0.8434166	0.336712	**0.012**	0.195007
Manual therapy- NSAIDs	0.7923256	0.328629	-0.40012	0.328938	1.192.444	0.463877	**0.01**	0.226649
NSAIDs-Paracetamol	-0.0008166	0.2354043	0.15986	0.348297	-0.1606761	0.420353	0.702	0.293809

* All the evidence about these contrasts comes from the trials which directly compare them; inconsistency in bold constrast are >5% of the all comparisons

Table 3b. Nodesplit disability 1 month

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>z	
Inert Treatment -Acupuncture	-0.7093169	0.6236239	0.7481728	1.055.844	-145.749	122.626	0.235	0.579317
Inert Treatment-Exercise	0.6744899	0.7305522	0.3343372	0.9563461	0.3401527	1.203.455	0.777	0.705391
Inert Treatment-Manual Therapy	-0.819488	0.772666	-0.4793281	0.92265	-0.34016	1.203.452	0.777	0.705389
Inert Treatment- Paracetamol	-0.0194038	0.5824383	-1.476.859	1.079.109	1.457.455	1.226.259	0.235	0.579317
Acupuncture-NSAIDs	-0.6397983	0.6390752	0.8176958	1.046.569	-1.457.494	1.226.264	0.235	0.579317
Cognitive CBT-Usual care *	0.0188224	0.6228875	-0.1682687	6.329.995	0.1870911	6.329.998	1.000	0.612493
Education-Exercise *	-0.4262689	0.5999444	-2.366.002	1.562.167	1.939.733	1.667.265	0.245	0.580495
Education-Manual therapy *	-2.158.292	0.6063919	-0.2185552	155.468	-1.939.737	1.667.265	0.245	0.580495
Exercise- Manual therapy *	-1.732.024	0.5978718	-0.7621531	0.5809457	-0.9698712	0.8336358	0.245	0.580497
Exercise- Usual care	-1.82E-10	0.4822981	-1.423.537	0.5431255	1.423.537	0.7263586	0.05	0.446406
Manual Therapy-Usual care	0.2390929	0.3731235	1.662.631	0.6231943	-1.423.538	0.7263602	0.05	0.446407
NSAIDs- Paracetamol	-0.127779	0.6059484	1.329.688	1.066.091	-1.457.467	1.226.264	0.235	0.579317
NSAIDs- Steroids *	-1.214.723	0.6700337	1.142.942	630.608	-2.357.665	6.306.084	0.997	0.612493

* All the evidence about these contrasts comes from the trials which directly compare them.

Table 3c. Nodesplit disability 12 months

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>z	
Inert treatment-Education*	-0.162517	0.323069	0.382189	141.004	-0.54471	1.410.044	0.997	0.290697
Cognitive CBT-Exercise	0.088617	0.446814	0.174454	0.492926	-0.08584	0.6648704	0.897	0.369949
Cognitive CBT-Usual care*	0.3264051	0.226606	-0.35701	1.060.696	0.683413	1.086.459	0.529	0.336763
Education-Exercise*	-0.436679	0.328125	0.151605	1.535.627	-0.58828	153.563	0.997	0.290697
Exercise-Usual care *	0.2022777	0.296387	-0.12221	0.932483	0.32449	0.9785033	0.74	0.354265

* All the evidence about these contrasts comes from the trials which directly compare them.

Table 4. Strategy to explore global inconsistency – disability 1 week

	Study removed	**Chi square**	**Prob > chi2**	**Resolving inconsistency**
All studies		chi2 (8) = 28.66	Prob > chi2 = 0.0004*	
STRATEGY 1: nodesplitting				
All studies without inconsistent constast (Exercise-Heat wrap)	Mayer 2005	chi2 (6) = 21.33	Prob > chi2 = 0.0016*	Not resolved
All studies without inconsistent constast (Exercise- Manual therapy)	Shrenk 2003	chi2 (7) = 22.93	Prob > chi2 = 0.0018*	Not resolved
All studies without inconsistent constast (Heat wrap-Paracetamol)	Nadler 2002	chi2 (6) = 14.38	Prob > chi2 = 0.0257*	Not resolved
All studies without inconsistent constast (Manual therapy-NSAIDs)	von Heymann 2013	chi2 (6) = 19.47	Prob > chi2 = 0.0034*	Not resolved
All studies without the four previous inconsistent constasts	All studies above	chi2 (2) = 6.03	Prob > chi2 = 0.0491*	Not resolved
STRATEGY 2: inspection of covariates				
Metaregression	The effects of the investigated co-variates were not statistically significant. See Table 6a			Not resolved
STRATEGY 3: inspection of subgroups				
Subgroup analysis (splitting pharmacological from non-pharmacological intervention)	Dreiser 2003; Miki 2018; Nadler 2002; Ralph 2008; Serfer 2009; Shin 2013; von Heymann 2013 (arm NSAIDs); Williams 2014	chi2 (2) = 3.19	Prob > chi2 = 0.2030	Resolved
Subgroup analysis (splitting non-pharmacological from pharmacological intervention)	Hasegawa 2014; Mayer 2005; Nadler 2002 (arm heat wrap); Nadler 2003a; Nadler 2003b; Schenk 2003; Shin 2013; Takamoto 2015; Traeger 2019; von Heymann 2013 (arm manual therapy)	chi2 (1) = 2.14	Prob > chi2 = 0.1432	Resolved

* Global consistency is tested here using the 'design-by-interaction' test that infers consistency across an entire treatment network, using a chi square test. A p value <0.05 is taken to infer evidence of global inconsistency in the network. [24 25]

Table 5. Strategy to explore global inconsistency – disability 1 month

	Study removed	**Chi square**	**Prob > chi2**	**Resolving inconsistency**
All studies		chi2 (3) =11.20	Prob > chi2 = 0.0107*	See network meta forest
STRATEGY 1: nodesplitting				
All studies without inconsistent constast	No contrast statistically significant			Not resolved
STRATEGY 2: inspection of covariates				
Metaregression	The effects of the investigated co-variates were not statistically significant. See Table 6b			Not resolved
STRATEGY 3: inspection of subgroups				
Subgroup analysis (splitting pharmacological from non-pharmacological intervention)	Miki 2008, Sea-Jung 2016; Shin 2013, Williams 2014	chi2 (2) = 7.15	Prob > chi2 = 0.0280*	Not resolved; See network meta forest
Subgroup analysis (splitting non-pharmacological from pharmacological intervention)	Cherkin 1998, Hasegawa 2014, Jellema 2005, Malmivaara 1995, Schneider 2015, Seferlis 1998, Shin 2013, Takamoto 2015	chi2 (1) = 19.69	Prob > chi2 = 0.0000*	Not resolved; See network meta forest

* Global consistency is tested here using the 'design-by-interaction' test that infers consistency across an entire treatment network, using a chi square test. A p value <0.05 is taken to infer evidence of global inconsistency in the network. [24 25]

Table 6a. Metaregression disability 1 week

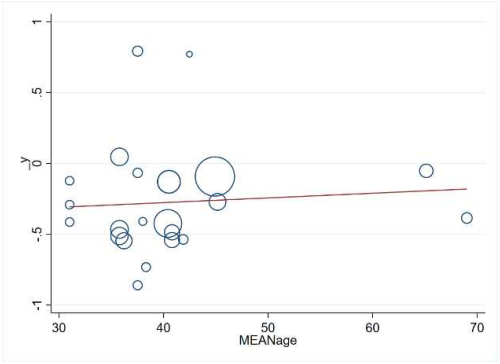
Variable	Coeff.	St. error	P>[t]	Tau2	95% CI	
Age	0.003	0.008	0.699	0.067	-0.014	0.021
Gender	0.005	0.007	0.477	0.067	-0.010	0.021
Patients with subacute/acute pain	-0.022	0.077	0.782	0.067	-0.181	0.138
Baseline value of pain	-0.008	0.007	0.244	0.098	-0.023	0.006
Presence of leg pain or sciatica	-0.039	0.143	0.783	0.069	-0.337	0.257
Risk of bias	0.124	0.104	0.246	0.067	-0.092	0.342

Table 6b. Metaregression disability 1 month

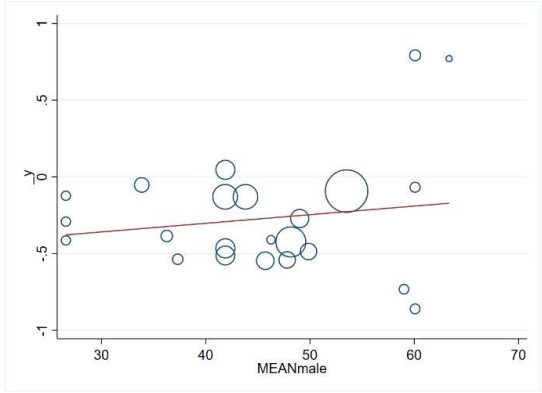
Variable	Coeff.	St. error	P>[t]	Tau2	95% CI	
Age	0.014	0.034	0.677	0.664	-0.059	0.088
Gender	-0.043	0.022	0.071	0.504	-0.090	0.004
Patients with subacute/acute pain	-0.257	0.213	0.252	0.591	-0.721	0.207
Baseline value of pain	-0.017	0.026	0.533	0.651	-0.073	0.039
Presence of leg pain or sciatica	-0.113	0.235	0.638	0.660	-0.624	0.398
Risk of bias	0.008	0.259	0.976	0.674	-0.571	0.555

Figure 1. Bubble plot disability 1 week

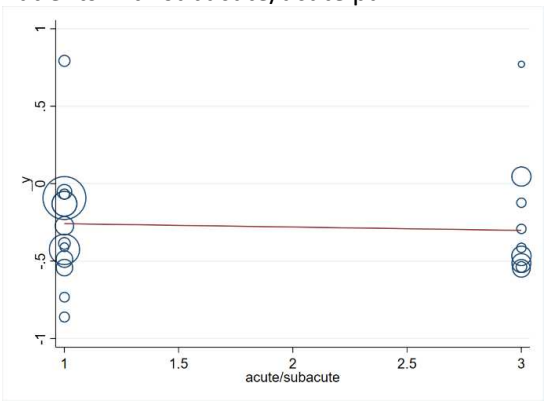
Age



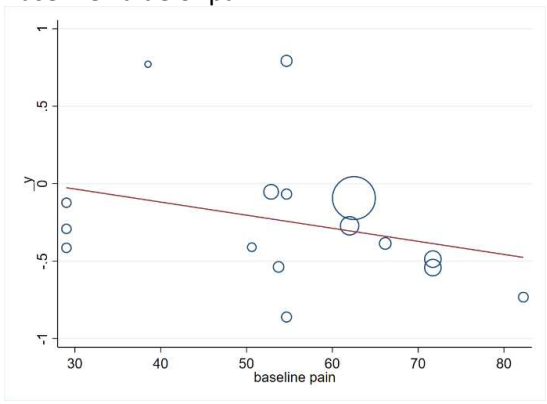
Gender



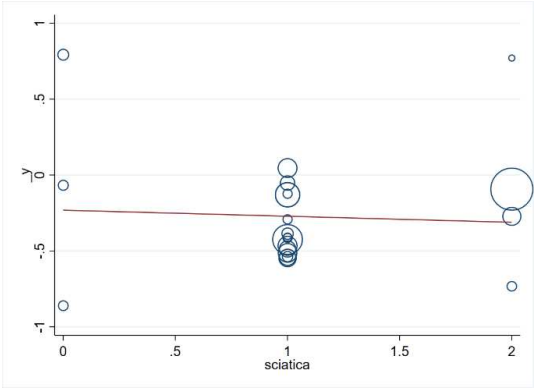
Patients with subacute/acute pain



Baseline value of pain



Presence of leg pain or sciatica



Risk of bias

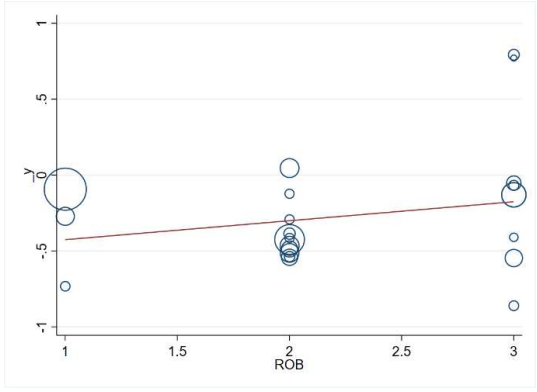
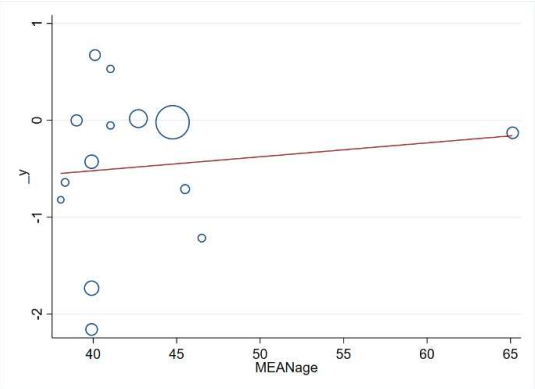
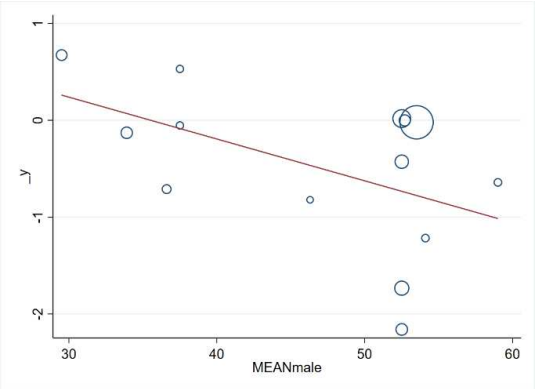


Figure 2. Bubble plot disability 1 month

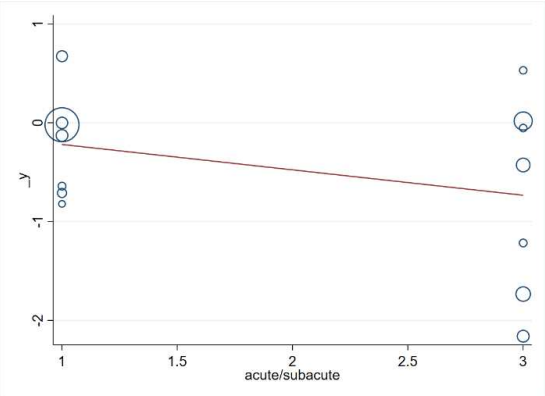
Age



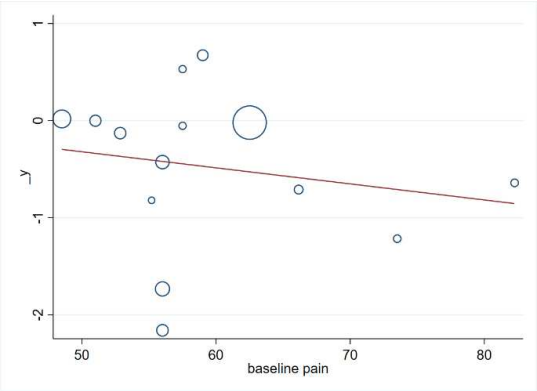
Gender



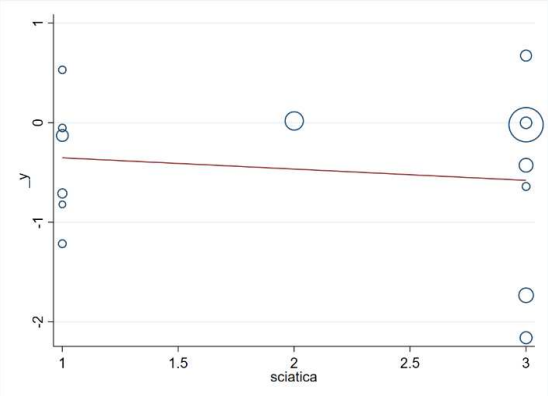
Patients with subacute/acute pain



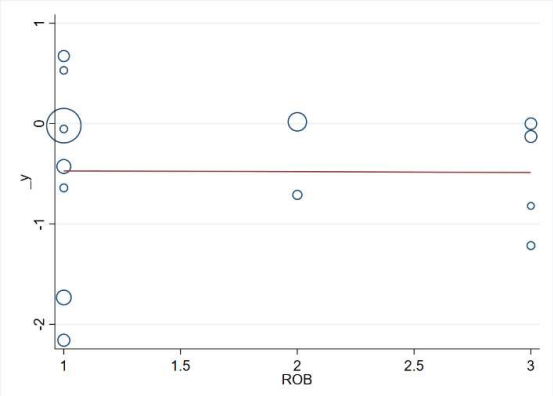
Baseline value of pain



Presence of leg pain or sciatica



Risk of bias

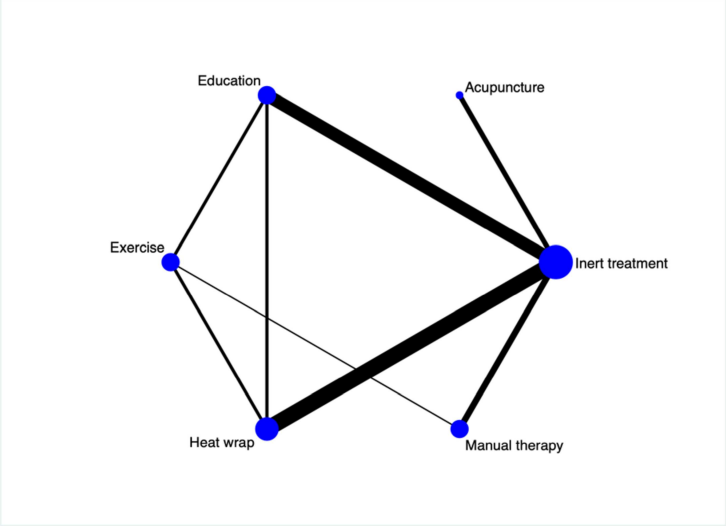


Supplementary K. Subgroup analysis results

1. Subgroup meta-analysis (pharmacological and non-pharmacological)

Disability 1 week – non pharmacological treatments

Figure 1a. Network plot of non-pharmacological treaments



Testing for inconsistency: chi2(2) = 3.19; Prob > chi2 = 0.2030

Figure 2a. Network forest of non-pharmacological treaments

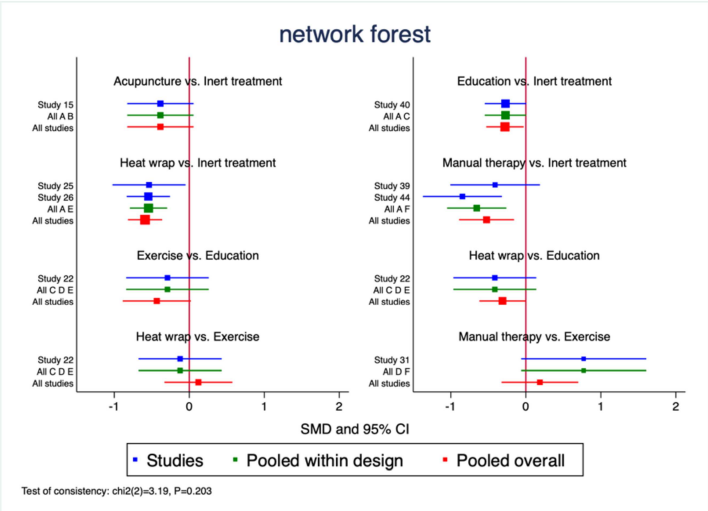


Table 1a. Netleague of non-pharmacological treaments

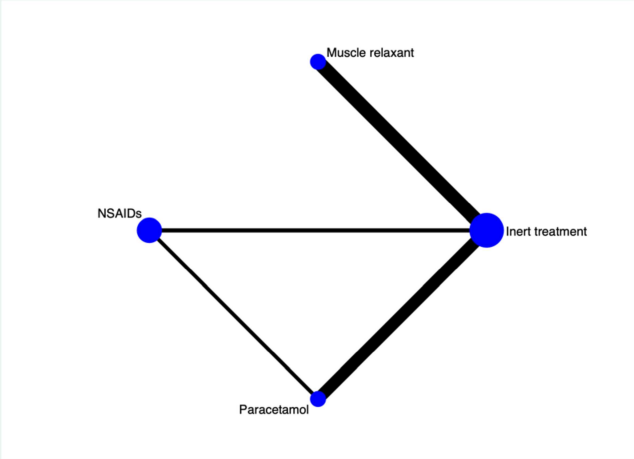
Inert treatment	-0.39 (-0.83,0.06)	-0.28 (-0.53,-0.03)	-0.71 (-1.16,-0.26)	-0.59 (-0.82,-0.36)	-0.52 (-0.89,-0.16)
0.39 (-0.06,0.83)	Acupuncture	0.11 (-0.40,0.61)	-0.33 (-0.96,0.30)	-0.20 (-0.70,0.29)	-0.14 (-0.71,0.44)
0.28 (0.03,0.53)	-0.11 (-0.61,0.40)	Education	-0.43 (-0.89,0.02)	-0.31 (-0.62,-0.00)	-0.25 (-0.68,0.19)
0.71 (0.26,1.16)	0.33 (-0.30,0.96)	0.43 (-0.02,0.89)	Exercise	0.12 (-0.33,0.57)	0.19 (-0.32,0.70)
0.59 (0.36,0.82)	0.20 (-0.29,0.70)	0.31 (0.00,0.62)	-0.12 (-0.57,0.33)	Heatwrap	0.07 (-0.36,0.49)
0.52 (0.16,0.89)	0.14 (-0.44,0.71)	0.25 (-0.19,0.68)	-0.19 (-0.70,0.32)	-0.07 (-0.49,0.36)	Manual therapy

Table 2a. SUCRA of non-pharmacological treaments

Treatment	SUCRA	PrBest	MeanRank
Manual therapy	80,3	43,6	2
Exercise	69,4	35,4	2,5
Heatwrap	67,9	12,6	2,6
Acupuncture	48,4	8,4	3,6
Education	31,2	0	4,4
Inert treatment	2,9	0	5,9

Disability 1 week – pharmacological treatments

Figure 1b. Network plot of pharmacological treaments



Testing for inconsistency: chi2(1) = 2.14; Prob > chi2 = 0.1432

Figure 2b. Network forest of pharmacological treaments

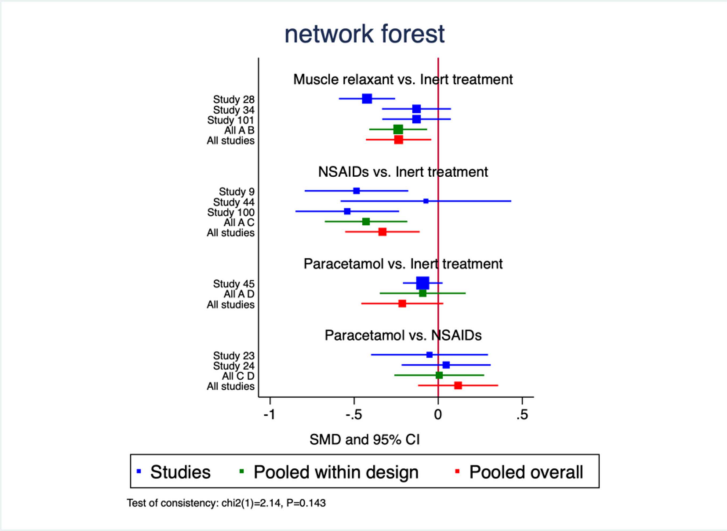


Table 1b. Netleague of pharmacological treaments

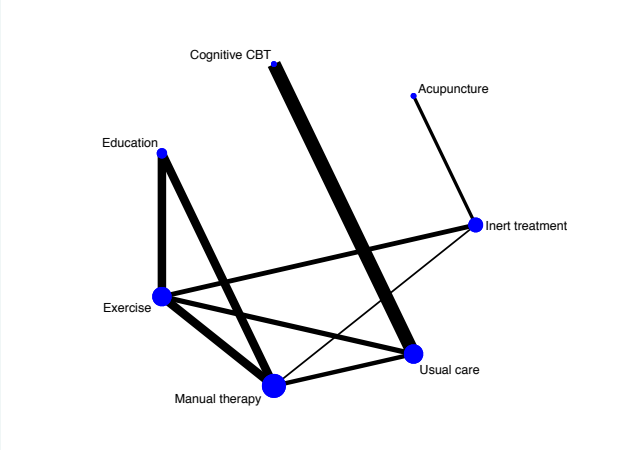
Inert treatment	-0.24 (-0.43,-0.04)	-0.33 (-0.55,-0.11)	-0.21 (-0.46,0.03)
0.24 (0.04,0.43)	Muscle relaxant	-0.10 (-0.39,0.20)	0.02 (-0.29,0.34)
0.33 (0.11,0.55)	0.10 (-0.20,0.39)	NSAIDs	0.12 (-0.12,0.36)
0.21 (-0.03,0.46)	-0.02 (-0.34,0.29)	-0.12 (-0.36,0.12)	Paracetamol

Table 2b. SUCRA of pharmacological treaments

Treatment	SUCRA	PrBest	MeanRank
NSAIDs	94,6	86	1,2
Muscle relaxant	64,1	11	2,1
Paracetamol	33,3	3	3
Inert treatment	7,9	0	3,8

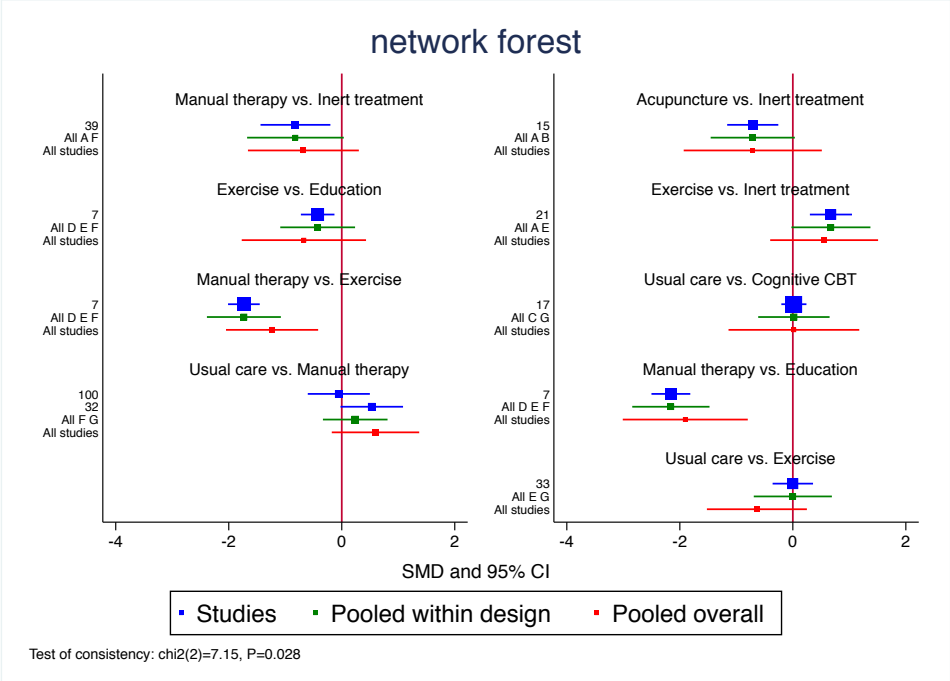
Disability 1 month – non pharmacological treatments

Figure 3a. Network plot of non-pharmacological treaments



Since we found sources of inconsistency (Prob > chi2 =0.0280) in non-pharmacological network, we presented only pairwise meta-analyses and NMA

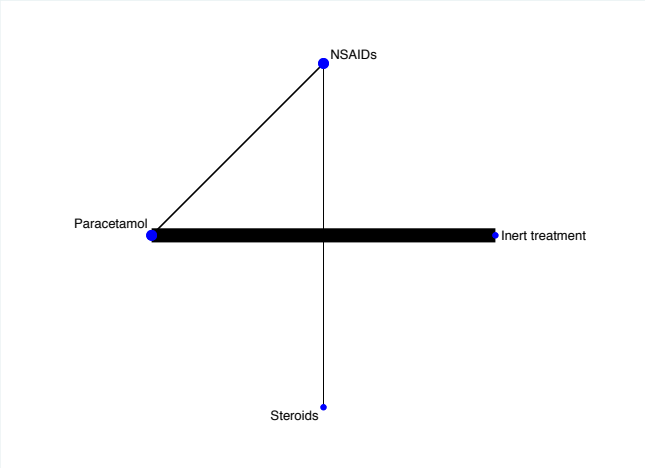
Figure 4a. Network forest of non-pharmacological treaments



Comparison	*ES*	*[95% Conf.*	*Interval]*	*z*	*p value*	*I2*	*Tau-squared*
Usual care-Manual Therapy							
2 studies	-0.052	-0.601	0.497				
	0.531	-0.022	1.085				
overall	0.239	-0.333	0.81	z= 0.82	p = 0.413	53.5%	0.0910
Acupuncture-Inert treatment							
1 study	-0.709	-1.162	-0.257	z= 3.07	p = 0.002		
Usual care-Cognitive CBT							
1 study	0.019	-0.203	0.241	z= 0.17	p = 0.868		
Exercise-Inert treatment							
1 study	0.674	0.302	1.047	z= 3.55	p = 0.000		
Usual care-Exercise							
1 study	0	-0.358	0.358	z= 3.55	p = 0.000		
Manual Therapy-Inert treatment							
1 study	-0.819	-1.438	-0.201	z= 2.60	p = 0.009		
Exeercise-Education							
1 study	-0.426	-0.723	-0.129	z= 2.81	p = 0.005		
Manual Therapy - Education							
1 study	-2.158	-2.502	-1.815	z= 12.31	p = 0.000		
Manual Therapy-Exercise							
1 study	-1.732	-2.012	-1.452	z= 12.10	p = 0.000		

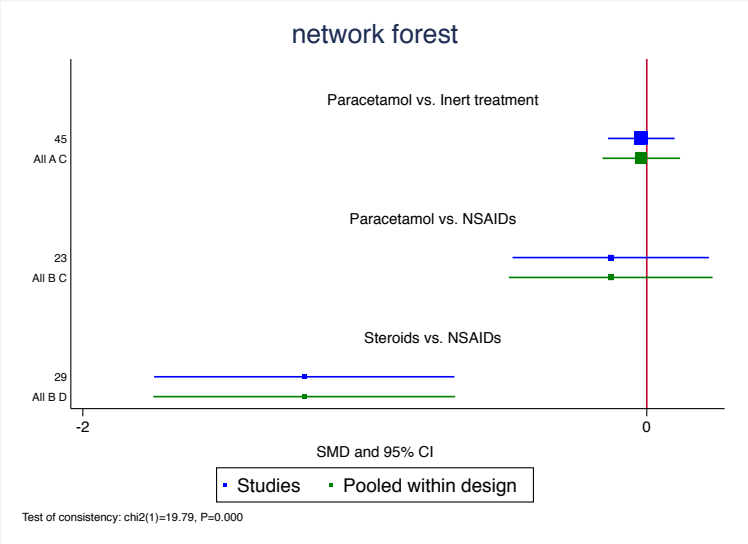
Disability 1 month – pharmacological treatments

Figure 3b. Network plot of pharmacological treaments



Since we found sources of inconsistency (Prob > chi2 = 0.000) in non-pharmacological network, we presented only pairwise meta-analyses and NMA

Figure 4b. Network forest of pharmacological treaments



Comparisons	*ES*	*[95% Conf.*	*Interval]*	*z*	*p-value*
Paracetamol-NSAIDs					
1 study	-0.128	-0.476	0.22	z= 0.72	p = 0.472
Steroids-NSAIDs					
1 study	-1.215	-1.747	-0.682	z= 4.47	p = 0.000
Paracetamol-Inert treatment					
1 study	-0.019	-0.137	0.099	z= 0.32	p = 0.747

Supplementary L. Network meta-analysis results- Interval plot

Figure 1. Interval Plot -Network Meta-Analyses – Pain outcome

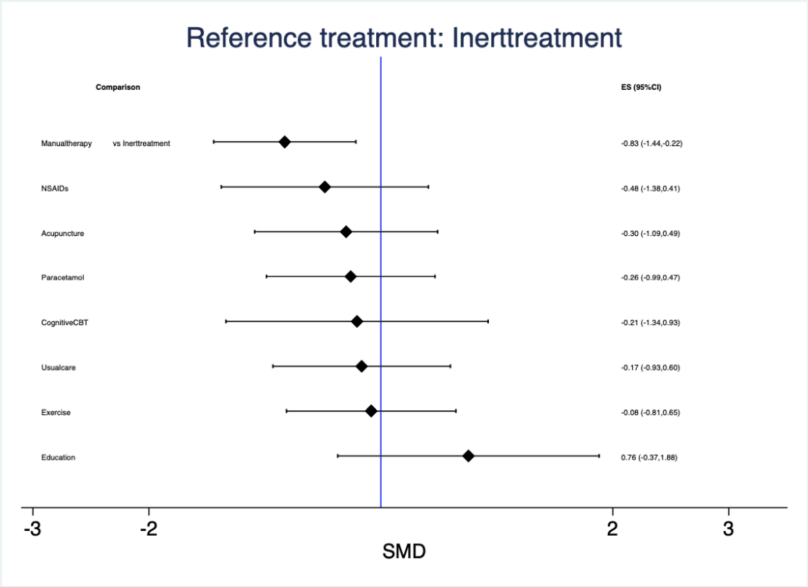


Figure 1a. Interval plot all treatments against inert treatment for pain outcome at 1 month of FU

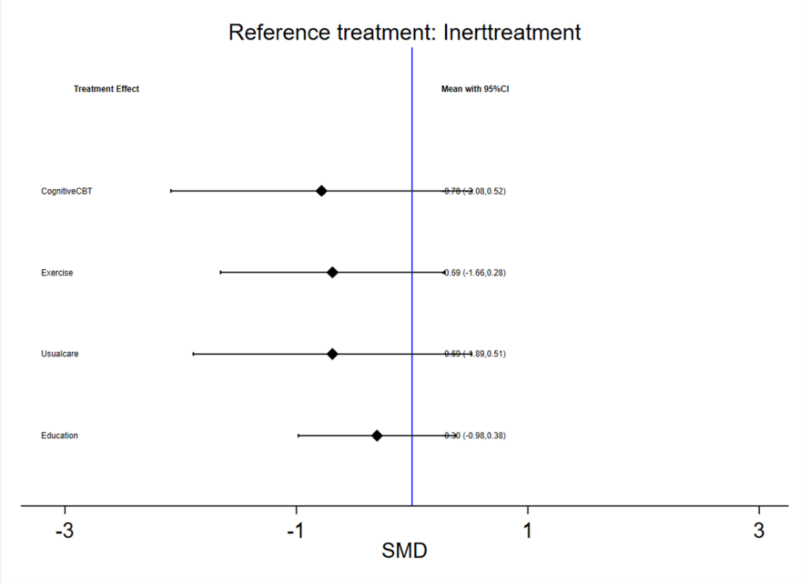


Figure 1b. Interval plot all treatments against inert treatment for pain outcome at 12 months of FU

Figure 2. Interval Plot -Network Meta-Analyses – Disability Outcome

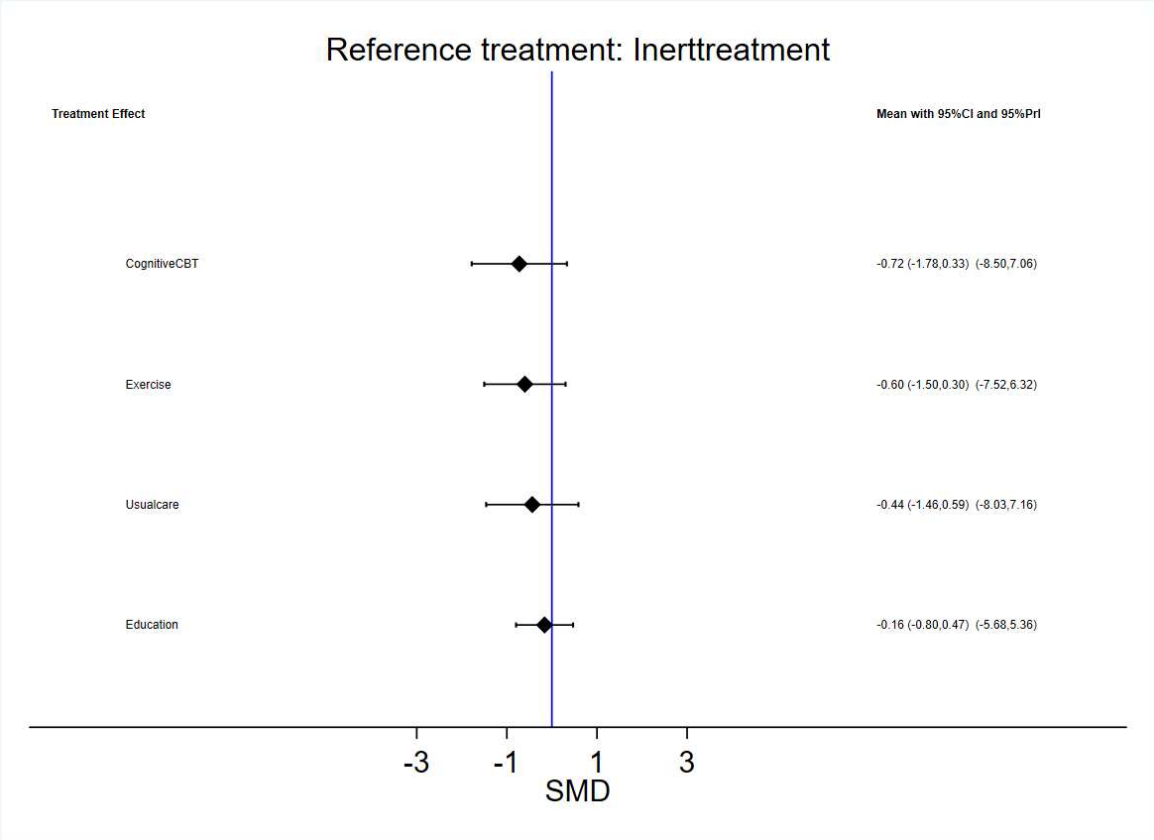


Figure 2a. Interval plot all treatments against inert treatment for disability outcome at 12 months of FU

Supplement M. All treatments against all treatments

Table 1. League table - pain

Table 1a. League table pain 1 month

Inert treatment	-0.30 (-1.09,0.49)	-0.21 (-1.34,0.93)	0.76 (-0.37,1.88)	-0.08 (-0.81,0.65)	-0.83 (-1.44,-0.22)	-0.48 (-1.38,0.41)	-0.26 (-0.99,0.47)	-0.17 (-0.93,0.60)
0.30 (-0.49,1.09)	Acupuncture	0.09 (-1.28,1.47)	1.05 (-0.32,2.43)	0.22 (-0.86,1.29)	-0.53 (-1.53,0.47)	-0.18 (-1.00,0.63)	0.04 (-0.85,0.93)	0.13 (-0.96,1.23)
0.21 (-0.93,1.34)	-0.09 (-1.47,1.28)	Cognitive CBT	0.96 (-0.44,2.36)	0.12 (-0.98,1.23)	-0.62 (-1.66,0.42)	-0.28 (-1.71,1.16)	-0.05 (-1.40,1.29)	0.04 (-0.79,0.87)
-0.76 (-1.88,0.37)	-1.05 (-2.43,0.32)	-0.96 (-2.36,0.44)	Education	-0.84 (-1.70,0.02)	-1.58 (-2.75,-0.42)	-1.24 (-2.67,0.20)	-1.02 (-2.35,0.32)	-0.92 (-2.05,0.21)
0.08 (-0.65,0.81)	-0.22 (-1.29,0.86)	-0.12 (-1.23,0.98)	0.84 (-0.02,1.70)	Exercise	-0.75 (-1.53,0.04)	-0.40 (-1.55,0.75)	-0.18 (-1.21,0.85)	-0.08 (-0.81,0.65)
0.83 (0.22,1.44)	0.53 (-0.47,1.53)	0.62 (-0.42,1.66)	1.58 (0.42,2.75)	0.75 (-0.04,1.53)	Manual therapy	0.35 (-0.73,1.42)	0.57 (-0.38,1.51)	0.66 (0.04,1.29)
0.48 (-0.41,1.38)	0.18 (-0.63,1.00)	0.28 (-1.16,1.71)	1.24 (-0.20,2.67)	0.40 (-0.75,1.55)	-0.35 (-1.42,0.73)	NSAIDs	0.22 (-0.54,0.99)	0.32 (-0.85,1.49)
0.26 (-0.47,0.99)	-0.04 (-0.93,0.85)	0.05 (-1.29,1.40)	1.02 (-0.32,2.35)	0.18 (-0.85,1.21)	-0.57 (-1.51,0.38)	-0.22 (-0.99,0.54)	Paracetamol	0.09 (-0.96,1.15)
0.17 (-0.60,0.93)	-0.13 (-1.23,0.96)	-0.04 (-0.87,0.79)	0.92 (-0.21,2.05)	0.08 (-0.65,0.81)	-0.66 (-1.29,-0.04)	-0.32 (-1.49,0.85)	-0.09 (-1.15,0.96)	Usual care

Table 1b. League table pain 12 months

Inert treatment	-0.69 (-1.89,0.51)	-0.69 (-1.66,0.28)	-0.30 (-0.98,0.38)	-0.78 (-2.08,0.52)
0.69 (-0.51,1.89)	Usual care	-0.00 (-0.72,0.72)	0.39 (-0.61,1.38)	-0.09 (-0.59,0.40)
0.69 (-0.28,1.66)	0.00 (-0.72,0.72)	Exercise	0.39 (-0.30,1.07)	-0.09 (-0.96,0.78)
0.30 (-0.38,0.98)	-0.39 (-1.38,0.61)	-0.39 (-1.07,0.30)	Education	-0.48 (-1.59,0.63)
0.78 (-0.52,2.08)	0.09 (-0.40,0.59)	0.09 (-0.78,0.96)	0.48 (-0.63,1.59)	Cognitive CBT

Table 2. Pain SUCRA

1 week of FU (immediate-term)			
Treatment	**SUCRA**	**PrBest**	**MeanRank**
Exercise	89,2	40,8	2
Heat wrap	85,8	45,2	2,3
Opioid	68,6	9,6	3,8
Manual therapy	60	1,4	4,6
Muscle relaxant	50,2	2	5,5
NSAIDs	47,9	0,2	5,7
Paracetamol	40,7	0,6	6,3
Education	25,1	0	7,7
Acupuncture	21,8	0,2	8
Inert treatment	10,7	0	9
1 month of FU (short-term)			
Treatment	**SUCRA**	**PrBest**	**MeanRank**
Manual therapy	91,1	57,2	1,7
NSAIDs	71,4	20,8	3,3
Acupuncture	55,7	7,4	4,5
Paracetamol	55,3	5	4,6
Cognitive CBT	50,8	8,6	4,9
Usual care	46,3	0,2	5,3
Exercise	40,3	0,6	5,8
Inert treatment	34,2	0	6,3
Education	4,9	0,2	8,6
12 months (long term)			
Treatment	**SUCRA**	**PrBest**	**MeanRank**
Cognitive CBT	73.7	45.0	2.1
Exercise	66.0	26.0	2.4
Usual care	61.4	16.8	2.5
Education	33.6	8.4	3.7
Inert treatment	15.3	3.8	4.4

Figure 1. Cumulative ranking curve of pain 1 week

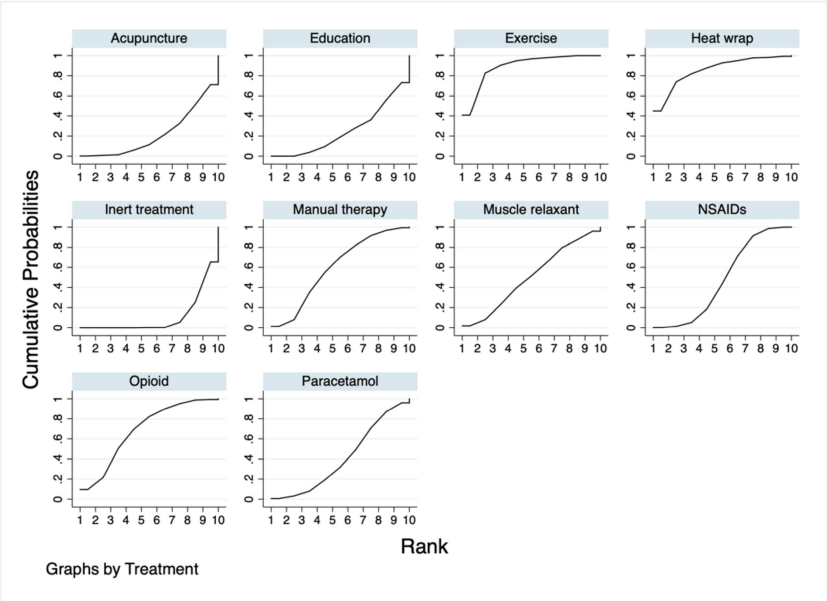


Figure 2. Cumulative ranking curve of pain 1 month

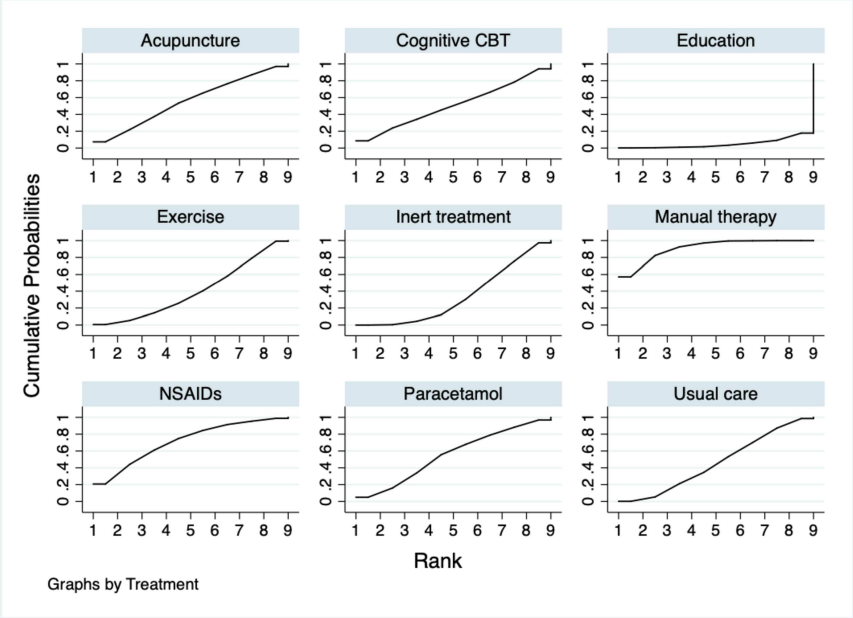


Figure 3. Cumulative ranking curve of pain 12 months

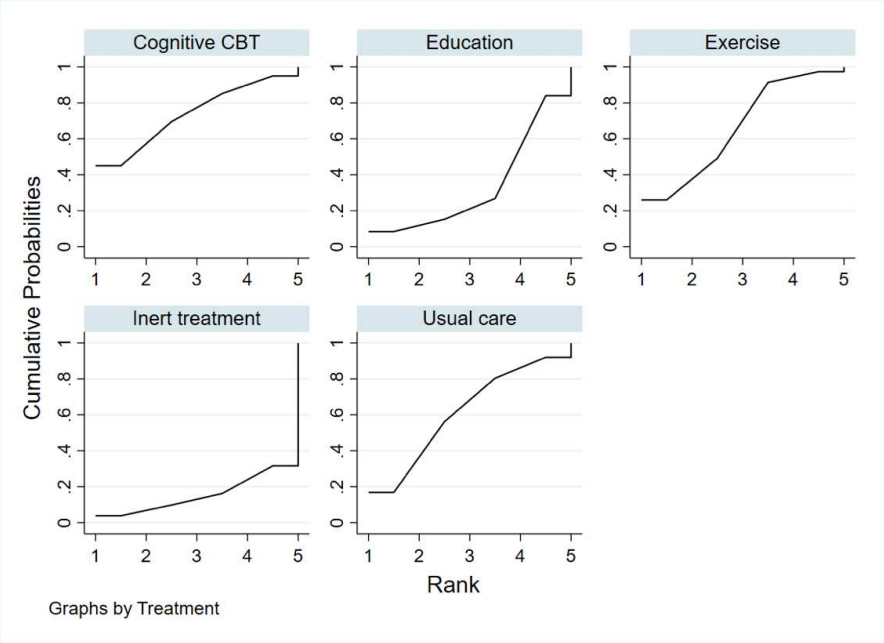


Table 3. League table - disability

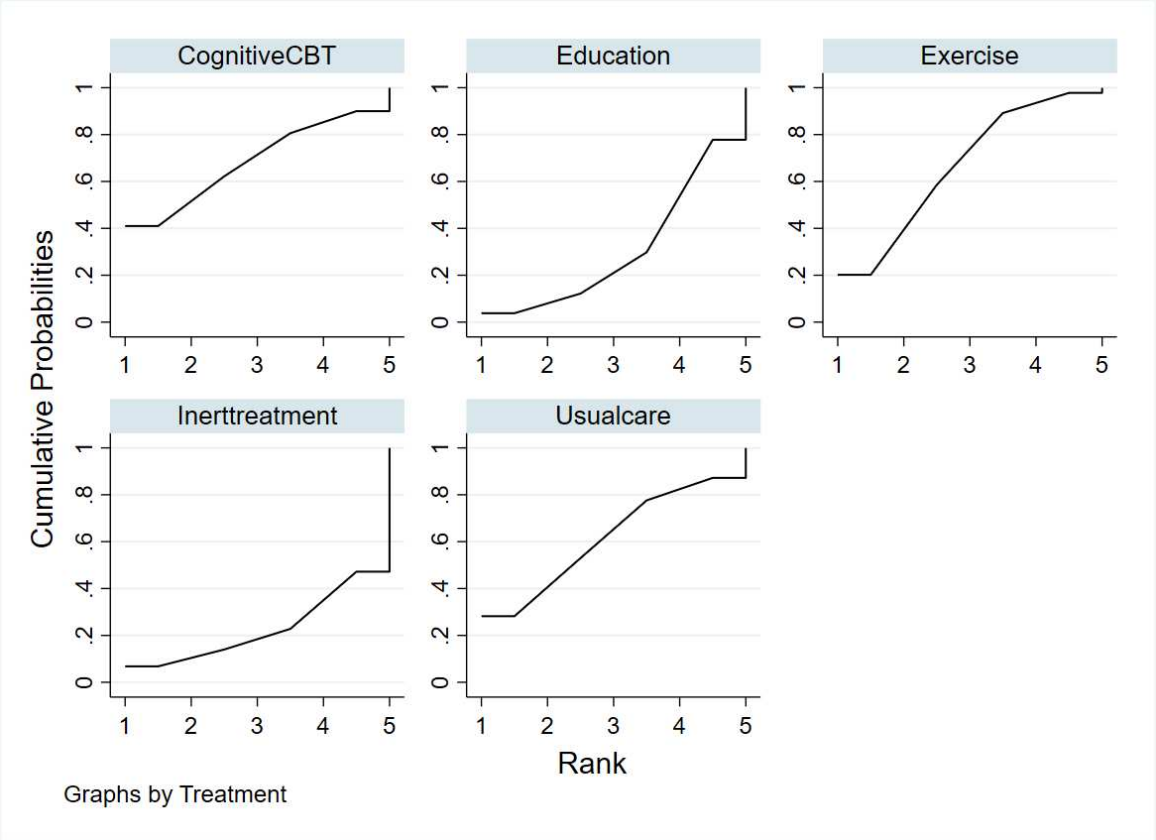
Table 3a. League table disability 12 months

Inert treatment	-0.44 (-1.46,0.59)	-0.60 (-1.50,0.30)	-0.16 (-0.80,0.47)	-0.72 (-1.78,0.33)
0.44 (-0.59,1.46)	Usual care	-0.16 (-0.65,0.32)	0.27 (-0.53,1.08)	-0.29 (-0.68,0.10)
0.60 (-0.30,1.50)	0.16 (-0.32,0.65)	Exercise	0.44 (-0.21,1.08)	-0.12 (-0.67,0.42)
0.16 (-0.47,0.80)	-0.27 (-1.08,0.53)	-0.44 (-1.08,0.21)	Education	-0.56 (-1.41,0.28)
0.72 (-0.33,1.78)	0.29 (-0.10,0.68)	0.12 (-0.42,0.67)	0.56 (-0.28,1.41)	Cognitive CBT

Table 4. Disability SUCRA

12 month of FU (long term)			
Treatments	**SUCRA**	**PrBest**	**MeanRank**
Cognitive CBT	68.5	41	2.3
Exercise	66.5	20.2	2.3
Usual care	61.5	28.2	2.5
Education	30.9	3.8	3.8
Inert treatment	22.7	6.8	4.1

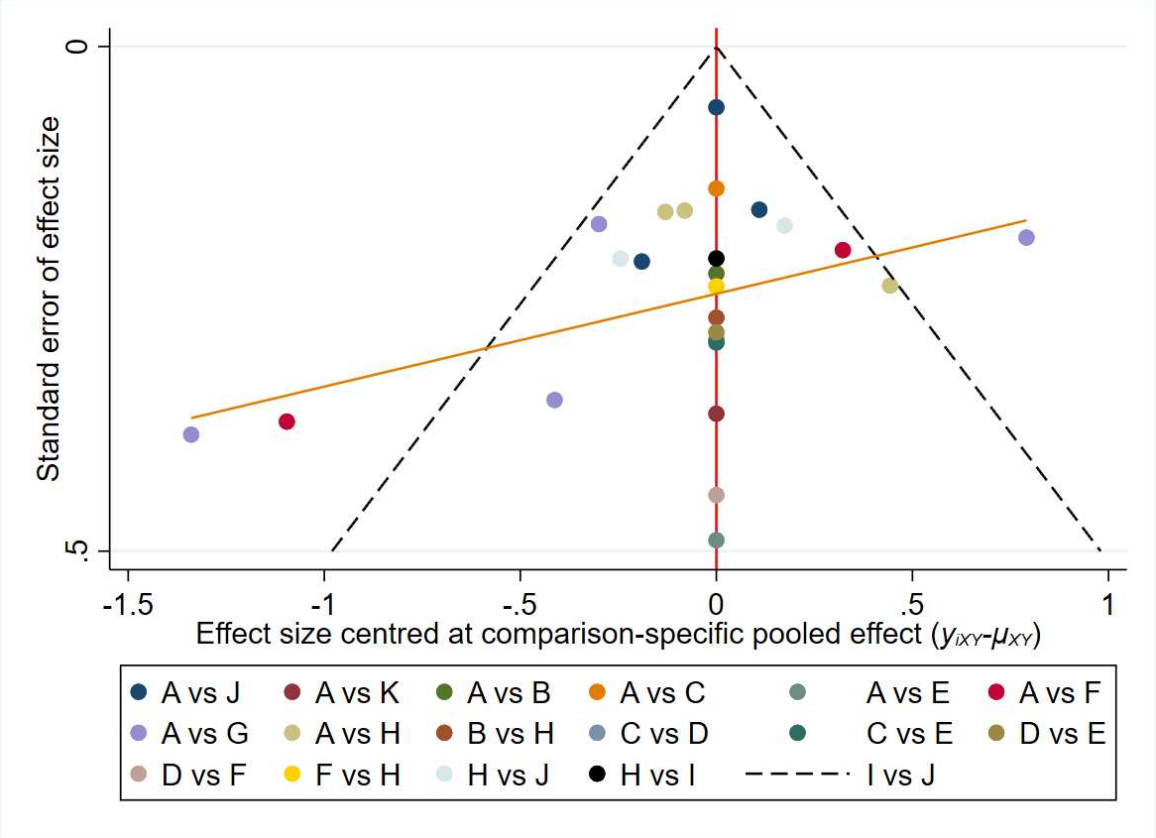
Figure 4. Cumulative ranking curve of disability 12 months



Supplement N. Funnel Plot

Funnel plot asymmetry was used to assess publication bais containing 10 or more trials reporting the outcome of interest. Thus, this was possibile only for pain and disability outcomes at 1 week and 1 month of follow-up.

Figure 1. Funnel plot-pain



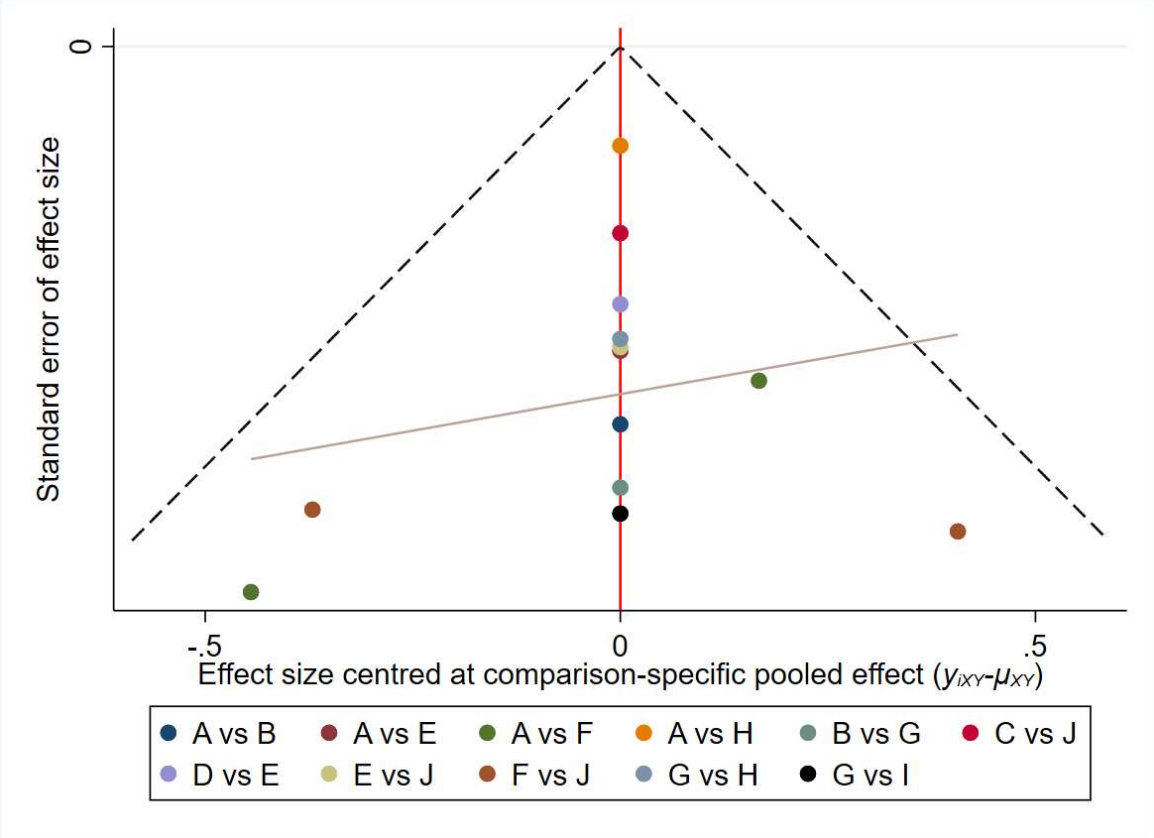
The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The orange line is the regression line.

Figure 1a. Pain Outcome 1 week

legend: Treatments used

A (reference):	Inert treatment
B:	Acupuncture
C:	Education
D:	Exercise
E:	Heat wrap
F:	Manual therapy
G:	Muscle relaxant

H: NSAIDs
I: Opioid
J: Paracetamol
K: Physical therapy

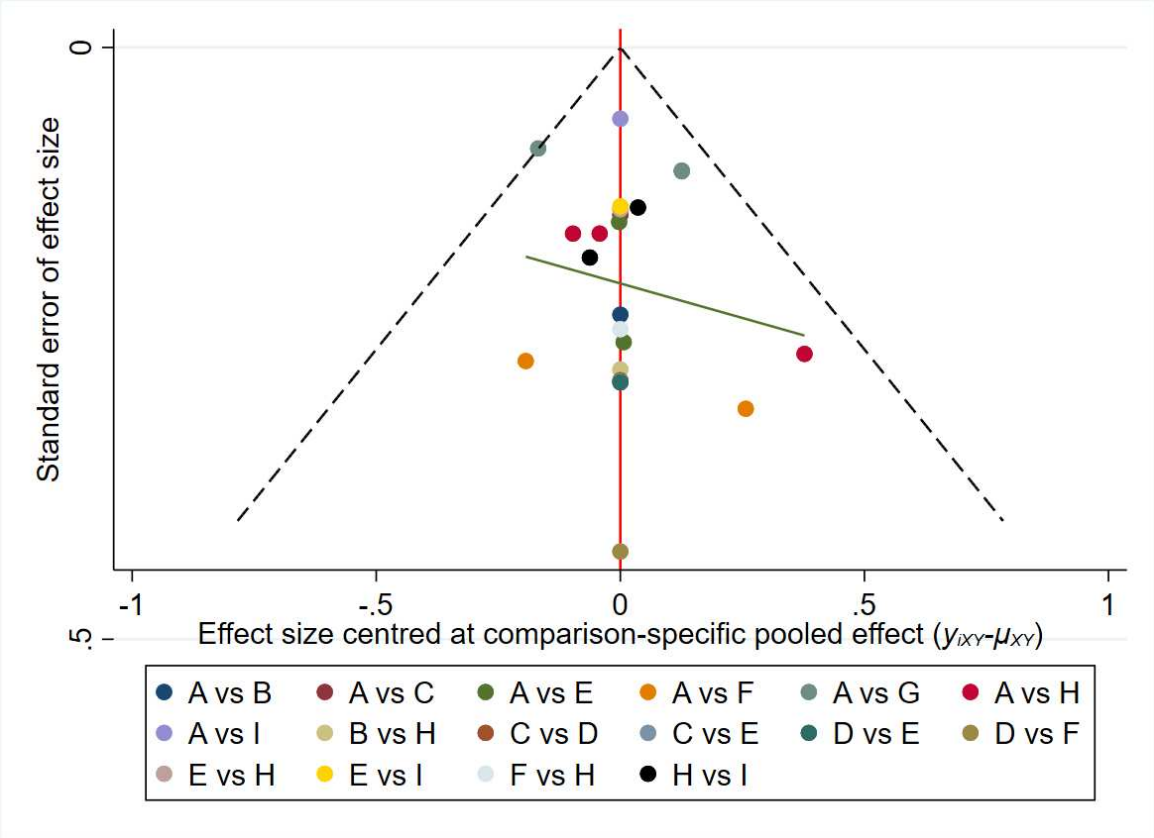


The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The gray line is the regression line.

Figure 1b. Pain Outcome 1 month

Legend: Treatments used
A (reference): Inert treatment
B: Acupuncture
C: Cognitive CBT
D: Education
E: Exercise
F: Manual therapy
G: NSAIDs
H: Paracetamol
I: Steroids
J: Usual care

Figure 2. Funnel plot- disability



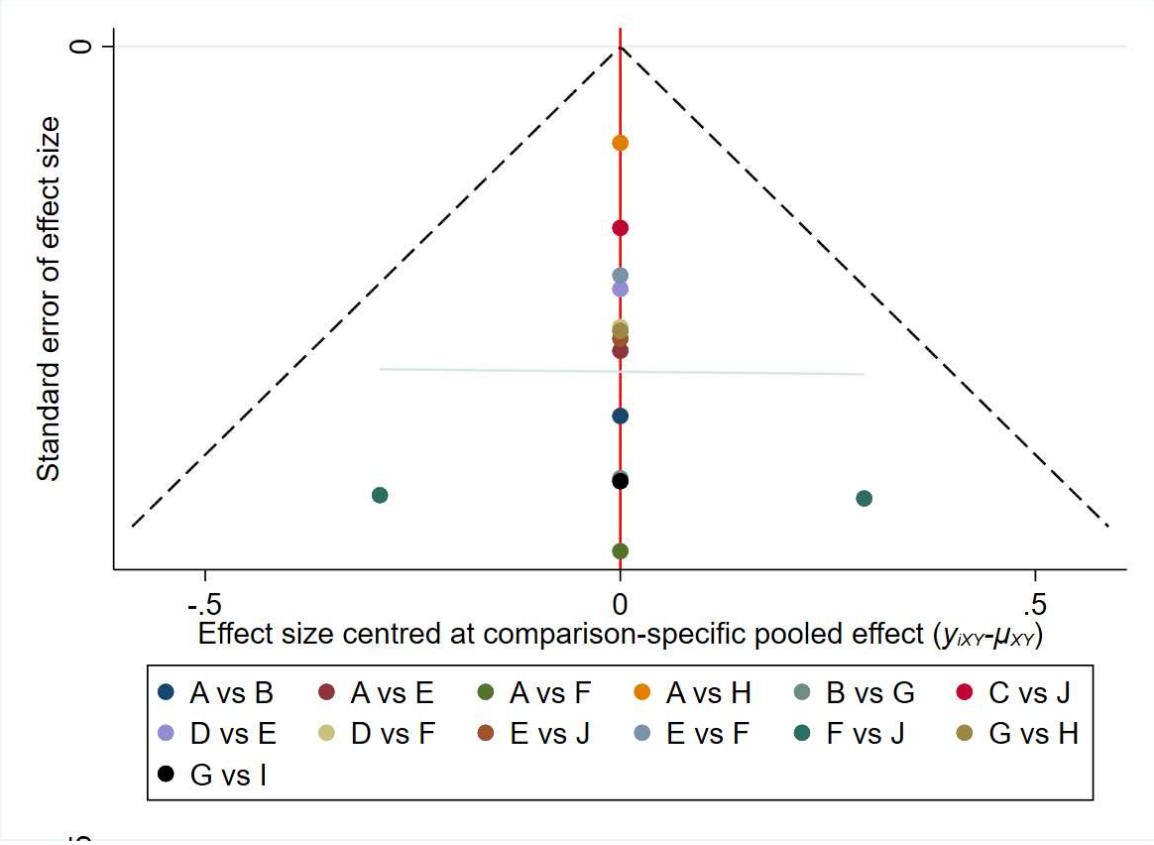
The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The green line is the regression line.

Figure 2a. Disability Outcome 1 week

Legend:

Treatments used

A (reference):	Inert treatment
B:	Acupuncture
C:	Education
D:	Exercise
E:	Heat wrap
F:	Manual therapy
G:	Muscle relaxant
H:	NSAIDs
I:	Paracetamol



The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The gray line is the regression line.

Figure 2b. Disability Outcome 1 month

Legend: Treatments used

A (reference):	Inert treatment
B:	Acupuncture
C:	Cognitive CBT
D:	Education
E:	Exercise
F:	Manual therapy
G:	NSAIDs
H:	Paracetamol
I:	Steroids
J:	Usual care

Supplement O. Contribution matrix for the network on interventions

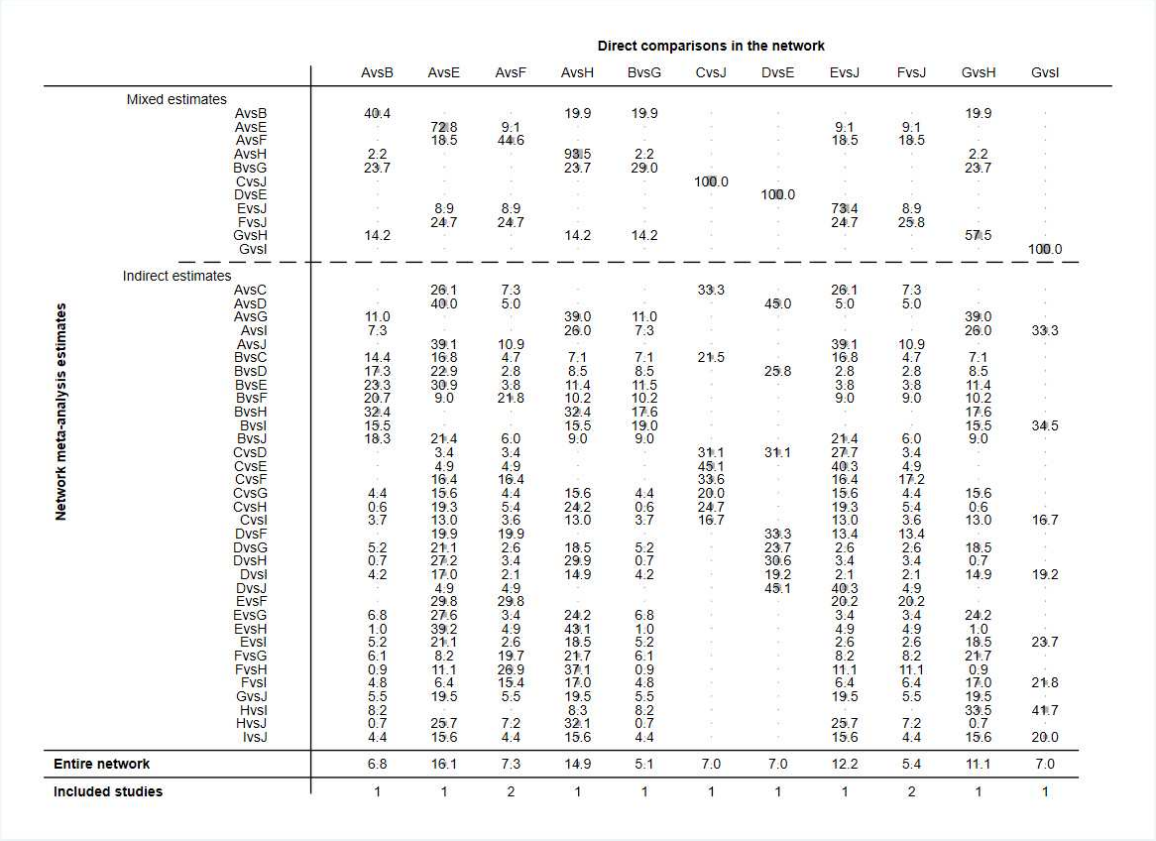
Figure 1. Contribution matrix for the network on interventions - Pain

Direct comparisons in the network

Network meta-analysis estimates	AvsB	AvsC	AvsE	AvsF	AvsG	AvsH	AvsJ	AvsK	BvsH	CvsD	CvsE	DvsE	DvsF	FvsH	HvsI	HvsJ	IvsJ
Mixed estimates																	
AvsB	38.0	0.7	0.1	0.4		11.7	9.7		22.6	0.5	0.2	0.3	0.8	1.3	3.9	5.8	3.9
AvsC	0.4	72.4	4.4	0.5		1.8	1.5		0.4	4.3	4.3	0.1	4.2	3.7	0.6	0.9	0.6
AvsE	0.4	29.5	10.0	0.6		2.2	1.8		0.4	8.5	21.0	13.6	5.0	4.4	0.7	1.1	0.7
AvsF	2.7	6.0	1.1	3.8		13.5	11.2		2.7	4.3	1.7	2.8	7.1	27.4	4.5	6.7	4.5
AvsG					100.0												
AvsH	5.4	1.6	0.3	1.0		26.5	22.0		5.4	1.1	0.4	0.7	1.9	2.9	8.8	13.2	8.8
AvsJ	1.0	0.3	0.1	0.2		5.0	81.9		1.0	0.2	0.1	0.1	0.4	0.5	2.6	3.9	2.6
AvsK								100.0									
BvsH	27.7	0.8	0.2	0.5		14.3	11.9		24.3	0.6	0.2	0.4	1.0	1.5	4.7	7.1	4.7
CvsD	0.7	11.7	3.5	1.0		3.6	3.0		0.7	27.9	12.4	16.0	8.2	7.2	1.2	1.8	1.2
CvsE	0.3	13.7	10.0	0.4		1.6	1.3		0.3	14.4	31.0	18.1	3.7	3.2	0.5	0.8	0.5
DvsE	0.5	0.4	6.3	0.7		2.5	2.1		0.5	17.9	17.5	37.6	5.9	5.2	0.8	1.3	0.8
DvsF	1.6	15.8	2.9	2.2		8.1	6.7		1.6	11.4	4.4	7.3	12.2	16.4	2.7	4.0	2.7
FvsH	1.3	7.4	1.4	4.7		6.6	5.5		1.3	5.4	2.1	3.4	8.8	44.3	2.2	3.3	2.2
HvsI	1.8	0.5	0.1	0.3		8.9	11.7		1.8	0.4	0.1	0.2	0.6	1.0	48.8	6.0	17.7
HvsJ	4.3	1.3	0.2	0.8		21.4	28.1		4.3	0.9	0.4	0.6	1.5	2.3	9.7	14.5	9.7
IvsJ	2.7	0.8	0.1	0.5		13.5	17.7		2.7	0.6	0.2	0.4	1.0	1.5	26.9	9.2	22.1
Indirect estimates																	
AvsD	0.7	26.8	4.9	1.0		3.6	3.0		0.7	19.4	7.5	12.4	8.4	7.4	1.2	1.8	1.2
AvsI	2.9	0.9	0.2	0.5		14.5	24.5		2.9	0.6	0.2	0.4	1.0	1.6	25.2	6.2	18.3
BvsC	23.1	32.7	2.0			6.3	5.2		14.0	2.3	2.1	0.1	2.4	2.4	2.1	3.1	2.1
BvsD	17.4	18.8	3.4	0.5		2.9	2.4		11.2	13.6	5.2	8.7	6.4	5.9	1.0	1.5	1.0
BvsE	17.5	18.5	6.3	0.2		4.1	3.4		10.9	5.2	13.3	8.8	3.6	3.4	1.4	2.0	1.4
BvsF	19.4	5.1	0.9	3.2		5.6	4.6		15.5	3.7	1.4	2.3	6.0	25.8	1.9	2.8	1.9
BvsG	23.7	0.4	0.1	0.3	37.8	7.3	6.0		14.1	0.3	0.1	0.2	0.5	0.8	2.4	3.6	2.4
BvsI	21.2	0.3	0.1	0.2		5.3	15.3		19.7	0.2	0.1	0.1	0.4	0.6	24.3	1.7	13.5
BvsJ	27.0	0.4	0.1	0.2		6.0	33.6		16.9	0.3	0.1	0.2	0.4	0.6	4.1	6.2	4.1
BvsK	23.7	0.4	0.1	0.3		7.3	6.0	37.8	14.1	0.3	0.1	0.2	0.5	0.8	2.4	3.6	2.4
CvsF	2.1	22.9	0.8	2.9		10.3	8.5		2.1	5.2	3.0	2.2	7.4	20.9	3.4	5.1	3.4
CvsG	0.2	40.0	2.5	0.3	44.7	1.0	0.8		0.2	2.4	2.4	0.1	2.3	2.0	0.3	0.5	0.3
CvsH	3.2	31.3	1.8	0.4		16.1	13.4		3.2	2.6	2.2	0.4	3.0	3.5	5.4	8.0	5.4
CvsI	1.9	26.2	1.5	0.2		9.3	16.4		1.9	2.0	1.8	0.2	2.2	2.4	17.6	3.9	12.4
CvsJ	0.3	39.6	2.4	0.2		1.5	40.3		0.3	2.5	2.4		2.5	2.3	1.7	2.5	1.7
CvsK	0.2	40.0	2.5	0.3		1.0	0.8	44.7	0.2	2.4	2.4	0.1	2.3	2.0	0.3	0.5	0.3
DvsG	0.5	19.1	3.5	0.7	28.6	2.6	2.2		0.5	13.8	5.3	8.8	6.0	5.3	0.9	1.3	0.9
DvsH	2.2	18.5	3.4	0.2		10.9	9.1		2.2	13.4	5.2	8.5	7.0	6.8	3.6	5.4	3.6
DvsI	1.2	15.8	2.9	0.3		5.9	11.9		1.2	11.4	4.4	7.3	5.7	5.4	14.8	5.4	9.5
DvsJ	0.2	20.2	3.7	0.7		1.0	25.8		0.2	14.6	5.6	9.3	6.5	5.8	1.8	2.7	1.8
DvsK	0.5	19.1	3.5	0.7		2.6	2.2	28.6	0.5	13.8	5.3	8.8	6.0	5.3	0.9	1.3	0.9
EvsF	1.7	14.0	5.4	2.3		8.4	7.0		1.7	2.2	11.8	10.4	8.3	17.1	2.8	4.2	2.8
EvsG	0.3	20.4	6.9	0.4	30.8	1.5	1.3		0.3	5.9	14.5	9.4	3.5	3.1	0.5	0.8	0.5
EvsH	2.4	18.0	6.2	0.1		11.9	9.9		2.4	4.9	13.1	9.0	4.1	4.3	3.9	5.9	3.9
EvsI	1.4	15.5	5.3			6.9	12.7		1.4	4.3	11.3	7.6	3.3	3.3	14.4	2.8	9.8
EvsJ		21.0	7.1	0.4		0.2	28.2		0.1	6.0	15.0	9.8	3.7	3.4	1.5	2.2	1.5
EvsK	0.3	20.4	6.9	0.4		1.5	1.3	30.8	0.3	5.9	14.5	9.4	3.5	3.1	0.5	0.8	0.5
FvsG	2.0	4.3	0.8	2.7	27.7	9.8	8.1		2.0	3.1	1.2	2.0	5.1	19.8	3.2	4.9	3.2
FvsI	0.1	5.1	0.9	3.2		0.7	10.1		0.1	3.7	1.4	2.3	6.0	27.9	25.8	1.2	11.3
FvsJ	2.0	5.2	0.9	3.2		10.0	21.3		2.0	3.7	1.4	2.3	6.1	24.4	5.0	7.4	5.0
FvsK	2.0	4.3	0.8	2.7		9.8	8.1	27.7	2.0	3.1	1.2	2.0	5.1	19.8	3.2	4.9	3.2
GvsH	3.4	1.0	0.2	0.6	36.2	16.9	14.1		3.4	0.7	0.3	0.5	1.2	1.8	5.6	8.4	5.6
GvsI	2.0	0.6	0.1	0.4	30.3	10.1	17.1		2.0	0.4	0.2	0.3	0.7	1.1	17.5	4.3	12.8
GvsJ	0.5	0.2		0.1	46.9	2.7	43.4		0.5	0.1		0.1	0.2	0.3	1.4	2.1	1.4
GvsK					50.0			50.0									
HvsK	3.4	1.0	0.2	0.6		16.9	14.1	36.2	3.4	0.7	0.3	0.5	1.2	1.8	5.6	8.4	5.6
IvsK	2.0	0.6	0.1	0.4		10.1	17.1	30.3	2.0	0.4	0.2	0.3	0.7	1.1	17.5	4.3	12.8
JvsK	0.5	0.2		0.1		2.7	43.4	46.9	0.5	0.1		0.1	0.2	0.3	1.4	2.1	1.4
Entire network	5.4	13.1	2.5	0.9	7.0	7.1	12.1	7.0	4.0	5.3	4.9	4.7	3.9	7.2	6.3	3.8	4.7
Included studies	1	1	1	2	4	3	1	1	1	1	1	1	1	1	2	2	1

Figure 1a. Contribution matrix for the network on interventions Pain Outcome 1 week

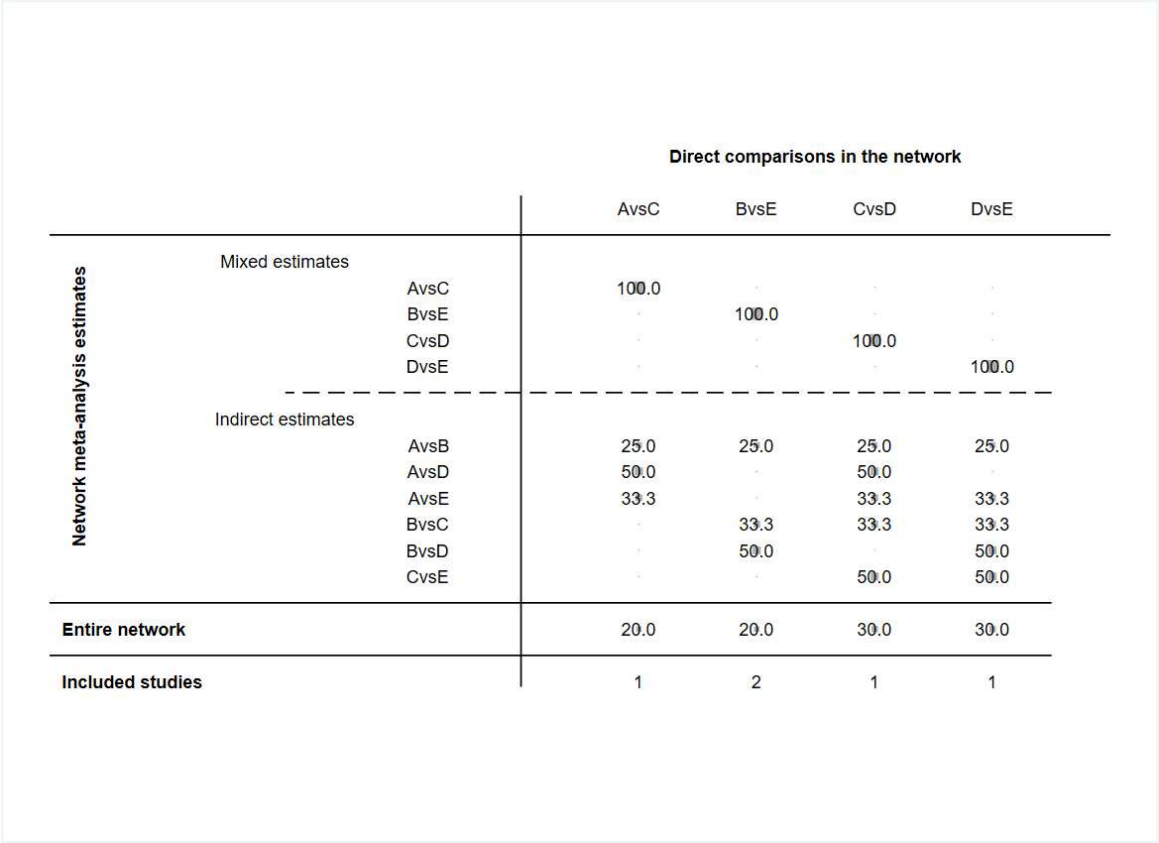
Label: direct comparisons in the network are presented in the columns, and their contributions to the combined treatment effect are presented in the rows. The entries of the matrix are the percentage weights attributed to each direct comparison. The intervention labels are: A (reference): Inert treatment; B:Acupuncture; C: Education; D: Exercise; E: Heat wrap; F: Manual therapy; G: Muscle relaxant; H: NSAIDs; I: Opioid; J: Paracetamol; K: Physical therapy



		Direct comparisons in the network										
		AvsB	AvsE	AvsF	AvsH	BvsG	CvsJ	DvsE	EvsJ	FvsJ	GvsH	GvsI
Network meta-analysis estimates	Mixed estimates											
	AvsB	40.4	.	.	19.9	19.9	.	.	.	.	19.9	.
	AvsE	.	72.8	9.1	.	.	.	.	9.1	9.1	.	.
	AvsF	.	18.5	44.6	.	.	.	.	18.5	18.5	.	.
	AvsH	2.2	.	.	98.5	2.2	.	.	.	.	2.2	.
	BvsG	23.7	.	.	23.7	29.0	.	.	.	.	23.7	.
	CvsJ	.	.	.	.	.	100.0	.	.	.	.	.
	DvsE	.	.	.	.	.	.	100.0	.	.	.	.
	EvsJ	.	8.9	8.9	.	.	.	.	73.4	8.9	.	.
	FvsJ	.	24.7	24.7	.	.	.	.	24.7	25.8	.	.
	GvsH	14.2	.	.	14.2	14.2	.	.	.	.	57.5	.
	GvsI	.	.	.	.	.	.	.	.	.	.	100.0
	Indirect estimates											
	AvsC	.	26.1	7.3	.	.	33.3	.	26.1	7.3	.	.
	AvsD	.	40.0	5.0	.	.	.	45.0	5.0	5.0	.	.
	AvsG	11.0	.	.	39.0	11.0	.	.	.	.	39.0	.
	AvsI	7.3	.	.	26.0	7.3	.	.	.	.	26.0	33.3
	AvsJ	.	39.1	10.9	.	.	.	.	39.1	10.9	.	.
	BvsC	14.4	16.8	4.7	7.1	7.1	21.5	.	16.8	4.7	7.1	.
	BvsD	17.3	22.9	2.8	8.5	8.5	.	25.8	2.8	2.8	8.5	.
	BvsE	23.3	30.9	3.8	11.4	11.5	.	.	3.8	3.8	11.4	.
	BvsF	20.7	9.0	21.8	10.2	10.2	.	.	9.0	9.0	10.2	.
	BvsH	32.4	.	.	32.4	17.6	.	.	.	.	17.6	.
	BvsI	15.5	.	.	15.5	19.0	.	.	.	.	15.5	34.5
	BvsJ	18.3	21.4	6.0	9.0	9.0	.	.	21.4	6.0	9.0	.
	CvsD	.	3.4	3.4	.	.	31.1	31.1	27.7	3.4	.	.
	CvsE	.	4.9	4.9	.	.	45.1	.	40.3	4.9	.	.
	CvsF	.	16.4	16.4	.	.	33.6	.	16.4	17.2	.	.
	CvsG	4.4	15.6	4.4	15.6	4.4	20.0	.	15.6	4.4	15.6	.
	CvsH	0.6	19.3	5.4	24.2	0.6	24.7	.	19.3	5.4	0.6	.
	CvsI	3.7	13.0	3.6	13.0	3.7	16.7	.	13.0	3.6	13.0	16.7
	DvsF	.	19.9	19.9	.	.	.	33.3	13.4	13.4	.	.
	DvsG	5.2	21.1	2.6	18.5	5.2	.	23.7	2.6	2.6	18.5	.
	DvsH	0.7	27.2	3.4	29.9	0.7	.	30.6	3.4	3.4	0.7	.
	DvsI	4.2	17.0	2.1	14.9	4.2	.	19.2	2.1	2.1	14.9	19.2
	DvsJ	.	4.9	4.9	.	.	.	45.1	40.3	4.9	.	.
	EvsF	.	29.8	29.8	.	.	.	.	20.2	20.2	.	.
	EvsG	6.8	27.6	3.4	24.2	6.8	.	.	3.4	3.4	24.2	.
	EvsH	1.0	39.2	4.9	43.1	1.0	.	.	4.9	4.9	1.0	.
	EvsI	5.2	21.1	2.6	18.5	5.2	.	.	2.6	2.6	18.5	23.7
	FvsG	6.1	8.2	19.7	21.7	6.1	.	.	8.2	8.2	21.7	.
	FvsH	0.9	11.1	26.9	37.1	0.9	.	.	11.1	11.1	0.9	.
	FvsI	4.8	6.4	15.4	17.0	4.8	.	.	6.4	6.4	17.0	21.8
	GvsJ	5.5	19.5	5.5	19.5	5.5	.	.	19.5	5.5	19.5	.
	HvsI	8.2	.	.	8.3	8.2	.	.	.	.	33.5	41.7
	HvsJ	0.7	25.7	7.2	32.1	0.7	.	.	25.7	7.2	0.7	.
	IvsJ	4.4	15.6	4.4	15.6	4.4	.	.	15.6	4.4	15.6	20.0
Entire network		6.8	16.1	7.3	14.9	5.1	7.0	7.0	12.2	5.4	11.1	7.0
Included studies		1	1	2	1	1	1	1	1	2	1	1

Figure 1b. Contribution matrix for the network on interventions Pain Outcome 1 month

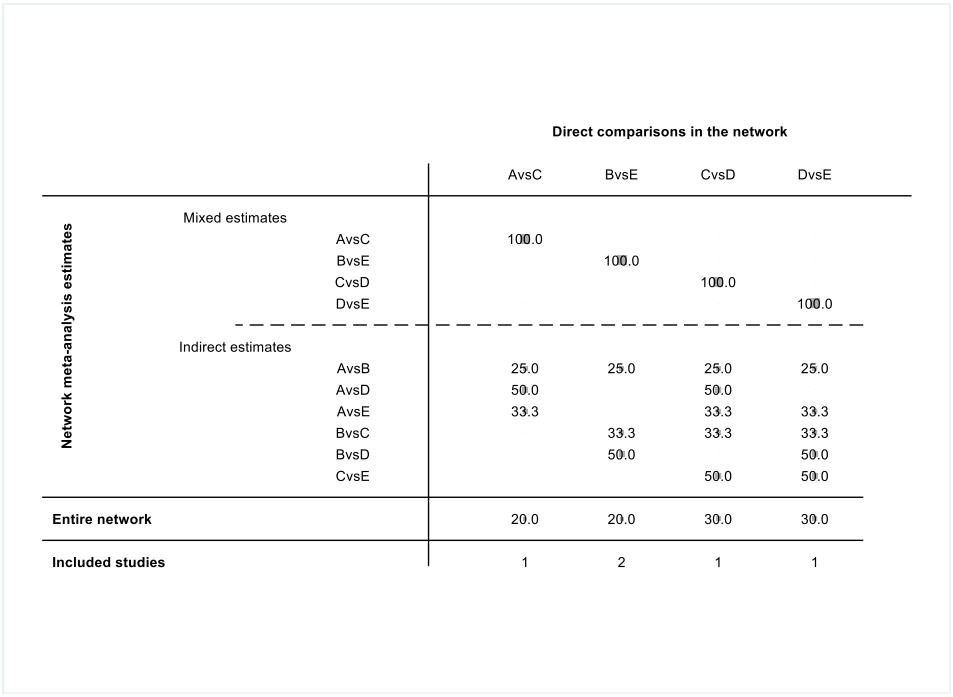
Label: direct comparisons in the network are presented in the columns, and their contributions to the combined treatment effect are presented in the rows. The entries of the matrix are the percentage weights attributed to each direct comparison. The intervention labels are: A (reference): Inert treatment; B: Acupuncture; C: Cognitive CBT; D: Education; E: Exercise; F: Manual therapy; G: NSAIDs; H: Paracetamol; I: Steroids; J:Usual care



			Direct comparisons in the network			
			AvsC	BvsE	CvsD	DvsE
Network meta-analysis estimates	Mixed estimates	AvsC	100.0			
		BvsE		100.0		
		CvsD			100.0	
		DvsE				100.0
	Indirect estimates	AvsB	25.0	25.0	25.0	25.0
		AvsD	50.0		50.0	
		AvsE	33.3		33.3	33.3
		BvsC		33.3	33.3	33.3
		BvsD		50.0		50.0
		CvsE			50.0	50.0
Entire network			20.0	20.0	30.0	30.0
Included studies			1	2	1	1

Figure 1c. Contribution matrix for the network on interventions Pain Outcome 12 months

Label: direct comparisons in the network are presented in the columns, and their contributions to the combined treatment effect are presented in the rows. The entries of the matrix are the percentage weights attributed to each direct comparison. The intervention labels are: A (reference): Inert treatment; B: Cognitive CBT; C: Education; D: Exercise; E: Usual care

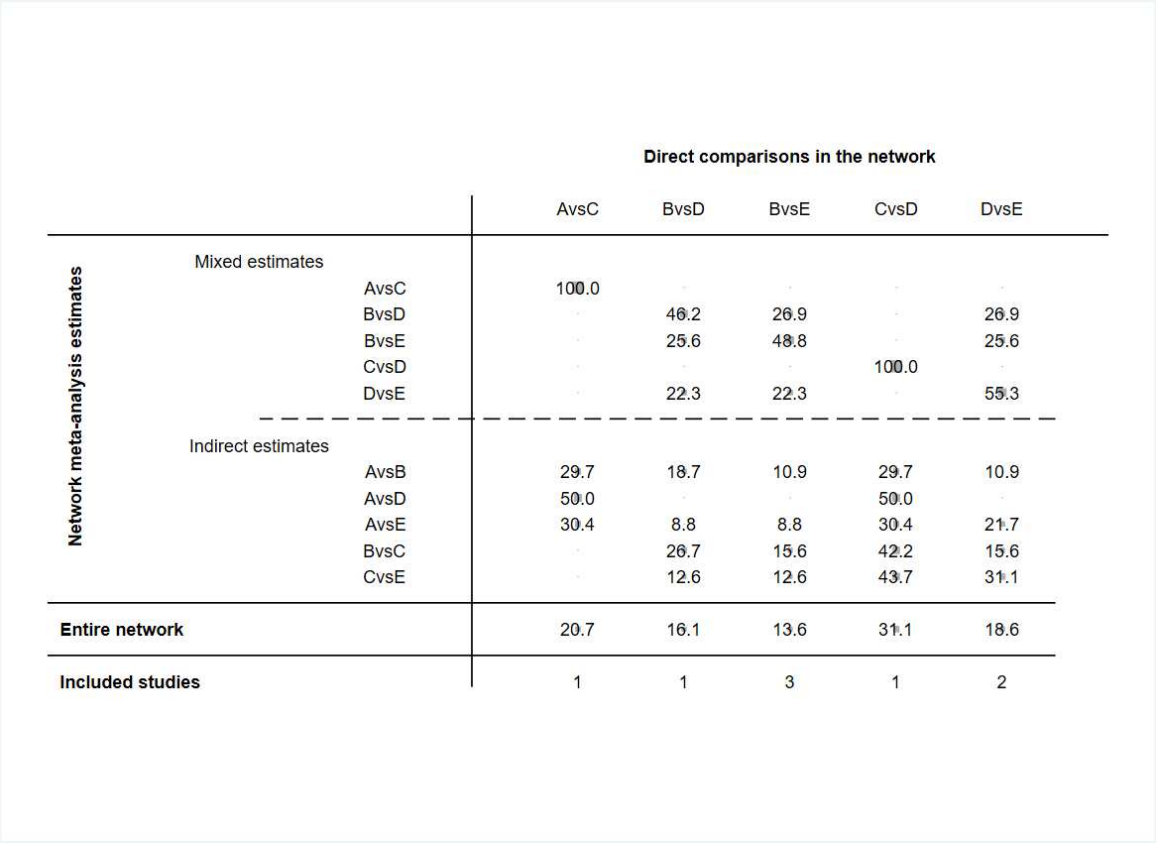


			Direct comparisons in the network			
			AvsC	BvsE	CvsD	DvsE
Network meta-analysis estimates	Mixed estimates					
		AvsC	100.0			
		BvsE		100.0		
		CvsD			100.0	
		DvsE				100.0
	Indirect estimates					
		AvsB	25.0	25.0	25.0	25.0
		AvsD	50.0		50.0	
		AvsE	33.3		33.3	33.3
		BvsC		33.3	33.3	33.3
		BvsD		50.0		50.0
		CvsE			50.0	50.0
Entire network			20.0	20.0	30.0	30.0
Included studies			1	2	1	1

Figure 2. Contribution matrix for the network on interventions - Disability

Figure 2a. Contribution matrix for the network on interventions Disability Outcome 12 months

Label: direct comparisons in the network are presented in the columns, and their contributions to the combined treatment effect are presented in the rows. The entries of the matrix are the percentage weights attributed to each direct comparison. The intervention labels are: The intervention labels are: A (reference): B: Cognitive CBT; C: Education; D: Exercise; E: Usual care



			Direct comparisons in the network				
			AvsC	BvsD	BvsE	CvsD	DvsE
Network meta-analysis estimates	Mixed estimates	AvsC	100.0				
		BvsD		46.2	26.9		26.9
		BvsE		25.6	48.8		25.6
		CvsD				100.0	
		DvsE		22.3	22.3		55.3
	Indirect estimates	AvsB	29.7	18.7	10.9	29.7	10.9
		AvsD	50.0			50.0	
		AvsE	30.4	8.8	8.8	30.4	21.7
		BvsC		26.7	15.6	42.2	15.6
		CvsE		12.6	12.6	43.7	31.1
Entire network			20.7	16.1	13.6	31.1	18.6
Included studies			1	1	3	1	2

Supplement P. GRADE for Pain Outcome

Introduction

CINeMA[26] considers 6 domains: (i) within-study bias, (ii) reporting bias, (iii) indirectness, (iv) imprecision, (v) heterogeneity, and (vi) incoherence. Features include the percentage contribution matrix, relative treatment effects for each comparison, estimation of the heterogeneity variance, prediction intervals, and tests for the evaluation of the assumption of coherence. In evaluating imprecision, heterogeneity, and incoherence, we consider the impact of these components of variability in forming clinical decisions.

Table of reasons for downgrading

We use the CINeMA software for GRADE assessment.[26 27] We downgrade network estimate according to the following criteria.

(1) Study limitations: We downgraded by one level when the contributions from low RoB comparisons were less than 25% and contributions from moderate or high RoB comparisons were 75% or greater.

(2) Imprecision: We considered a clinically meaningful threshold for SMD to be 0.5 [28] and downgraded the estimate if the SMD point estimate is 0 or more and the lower limit of its CrI is below 0.5; or if the SMD point estimate is less than 0 and the upper limit of its CrI is above 0.5.

(3) Inconsistency: We rated two concepts, heterogeneity and incoherence (inconsistency), in this domain.

For heterogeneity, we looked at the common tau and found that it is low compared to the expected value as reported in the literature,[29] so we did not downgrade any network estimate for heterogeneity. For inconsistency, we looked at the results of side splitting and we downgraded the comparisons with important inconsistency ($p<0.10$), where we have not downgraded for imprecision (we did not downgrade the same network estimate for both imprecision and inconsistency).

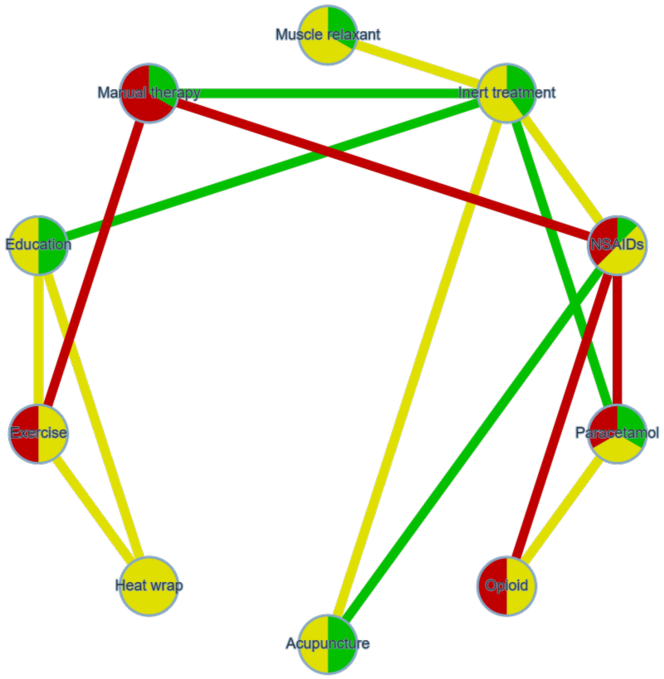
(4) Indirectness: We have assured transitivity in our network by limiting the included studies to acute and subacute population and to non-mixed treatments for NS-LBP. Thus, we did not downgrade for indirectness.

(5) Reporting bias: We cannot completely rule out the possibility that some studies are still missing. However, we assumed that publication bias was undetected.

1) Pain at 1 week

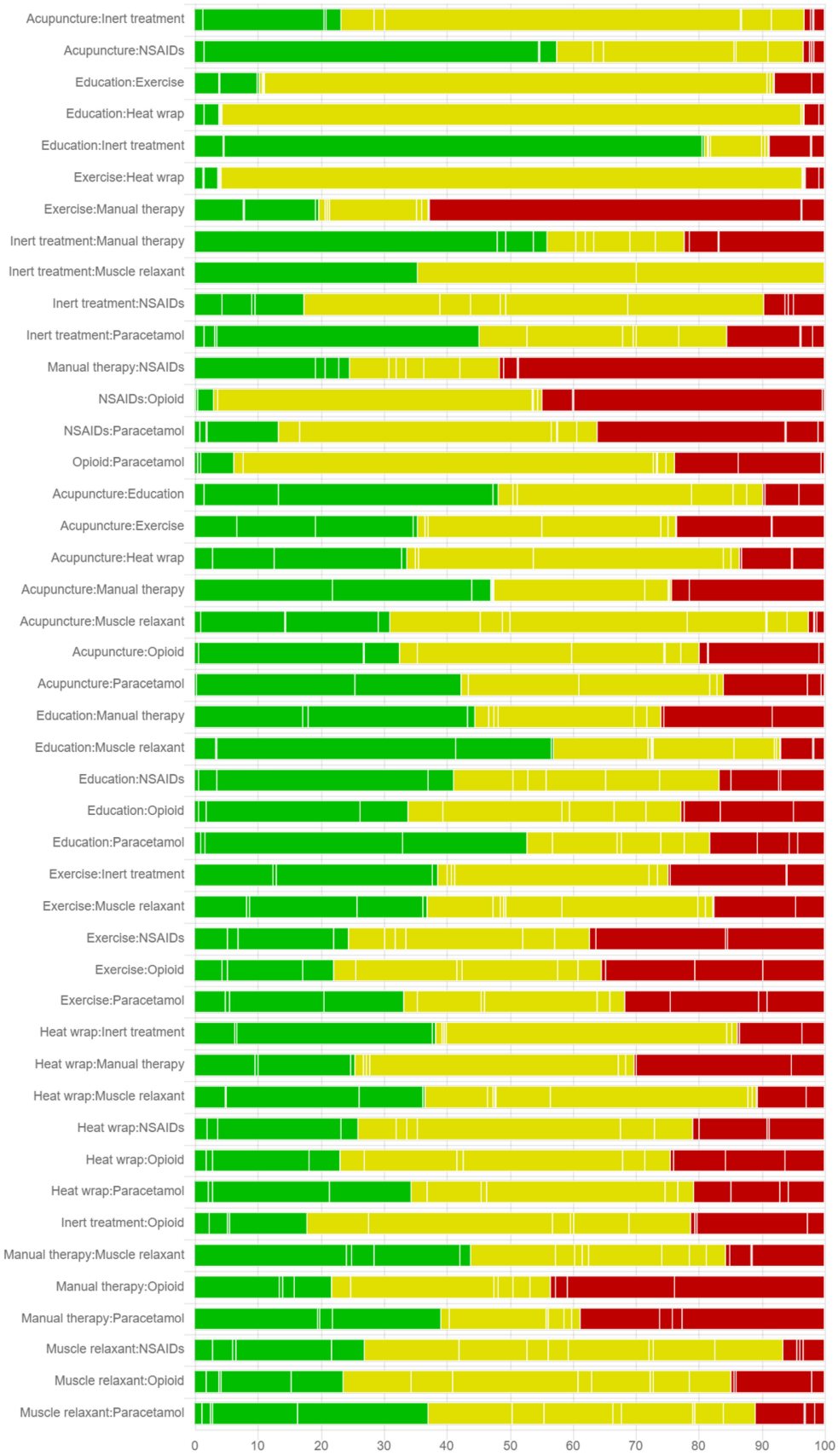
1) Summary of study limitations of the included studies

The colours in the circles indicate the percentage of low RoB studies [green], moderate RoB studies [yellow] and high RoB studies [red] involving each intervention. The colours of the line then indicate the average RoB assessment of each comparison based on the above information – low RoB comparison [green], moderate RoB comparison [yellow] and high RoB comparison [red].



2) Contribution of low or moderate RoB comparisons to each network estimate

Based on the above assessment of RoB for each comparison and the contribution matrix detailing contribution of each direct comparison to all network estimates, the following bar graphs show the percentage of low or moderate RoB contributions for each network estimate. The judgements about study limitations in each direct comparison is shown at the beginning of the graph. Each bar corresponds to a NMA relative treatment effect and shows how much information comes from comparisons at moderate risk of bias [yellow].


Acupuncture:Inert treatment
Acupuncture:NSAIDs
Education:Exercise
Education:Heat wrap
Education:Inert treatment
Exercise:Heat wrap
Exercise:Manual therapy
Inert treatment:Manual therapy
Inert treatment:Muscle relaxant
Inert treatment:NSAIDs
Inert treatment:Paracetamol
Manual therapy:NSAIDs
NSAIDs:Opioid
NSAIDs:Paracetamol
Opioid:Paracetamol
Acupuncture:Education
Acupuncture:Exercise
Acupuncture:Heat wrap
Acupuncture:Manual therapy
Acupuncture:Muscle relaxant
Acupuncture:Opioid
Acupuncture:Paracetamol
Education:Manual therapy
Education:Muscle relaxant
Education:NSAIDs
Education:Opioid
Education:Paracetamol
Exercise:Inert treatment
Exercise:Muscle relaxant
Exercise:NSAIDs
Exercise:Opioid
Exercise:Paracetamol
Heat wrap:Inert treatment
Heat wrap:Manual therapy
Heat wrap:Muscle relaxant
Heat wrap:NSAIDs
Heat wrap:Opioid
Heat wrap:Paracetamol
Inert treatment:Opioid
Manual therapy:Muscle relaxant
Manual therapy:Opioid
Manual therapy:Paracetamol
Muscle relaxant:NSAIDs
Muscle relaxant:Opioid
Muscle relaxant:Paracetamol
0
10
20
30
40
50
60
70
80
90
100

3) Summary grading of Evidence

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Mixed evidence								
Acupuncture:Inert treatment	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:NSAIDs	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Education:Exercise	1	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Education:Heat wrap	1	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Education:Inert treatment	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Exercise:Heat wrap	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Manual therapy	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Inert treatment:Manual therapy	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Inert treatment:Muscle relaxant	3	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Inert treatment:NSAIDs	3	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Inert treatment:Paracetamol	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Manual therapy:NSAIDs	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
NSAIDs:Opioid	2	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
NSAIDs:Paracetamol	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low

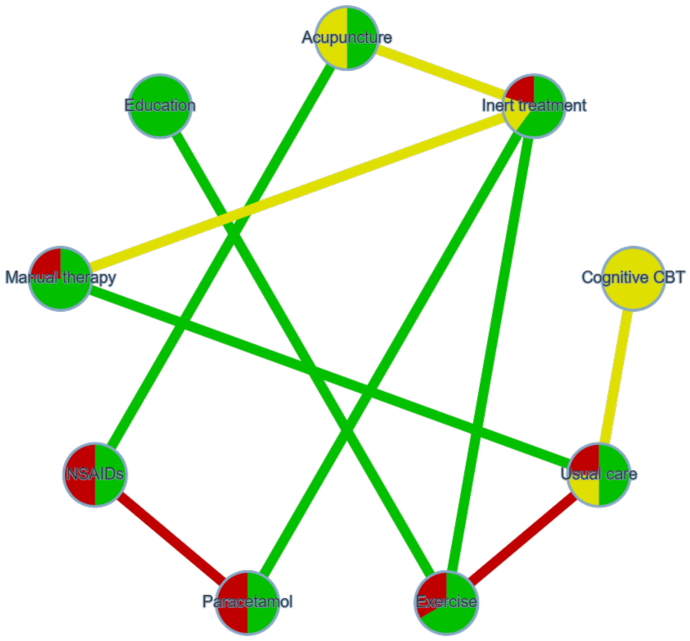
Opioid:Paracetamol	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Indirect evidence								
Acupuncture:Education	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Exercise	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Acupuncture:Heat wrap	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Acupuncture:Manual therapy	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Acupuncture:Muscle relaxant	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Acupuncture:Opioid	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Acupuncture:Paracetamol	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Manual therapy	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Education:Muscle relaxant	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Education:NSAIDs	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Opioid	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Paracetamol	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Inert treatment	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Exercise:Muscle relaxant	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:NSAIDs	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Exercise:Opioid	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low

Exercise:Paracetamol	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Heat wrap:Inert treatment	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Heat wrap:Manual therapy	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Heat wrap:Muscle relaxant	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Heat wrap:NSAIDs	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Heat wrap:Opioid	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Heat wrap:Paracetamol	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Inert treatment:Opioid	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Manual therapy:Muscle relaxant	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Manual therapy:Opioid	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Manual therapy:Paracetamol	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Muscle relaxant:NSAIDs	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Muscle relaxant:Opioid	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Muscle relaxant:Paracetamol	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low

2) Pain at 1 month

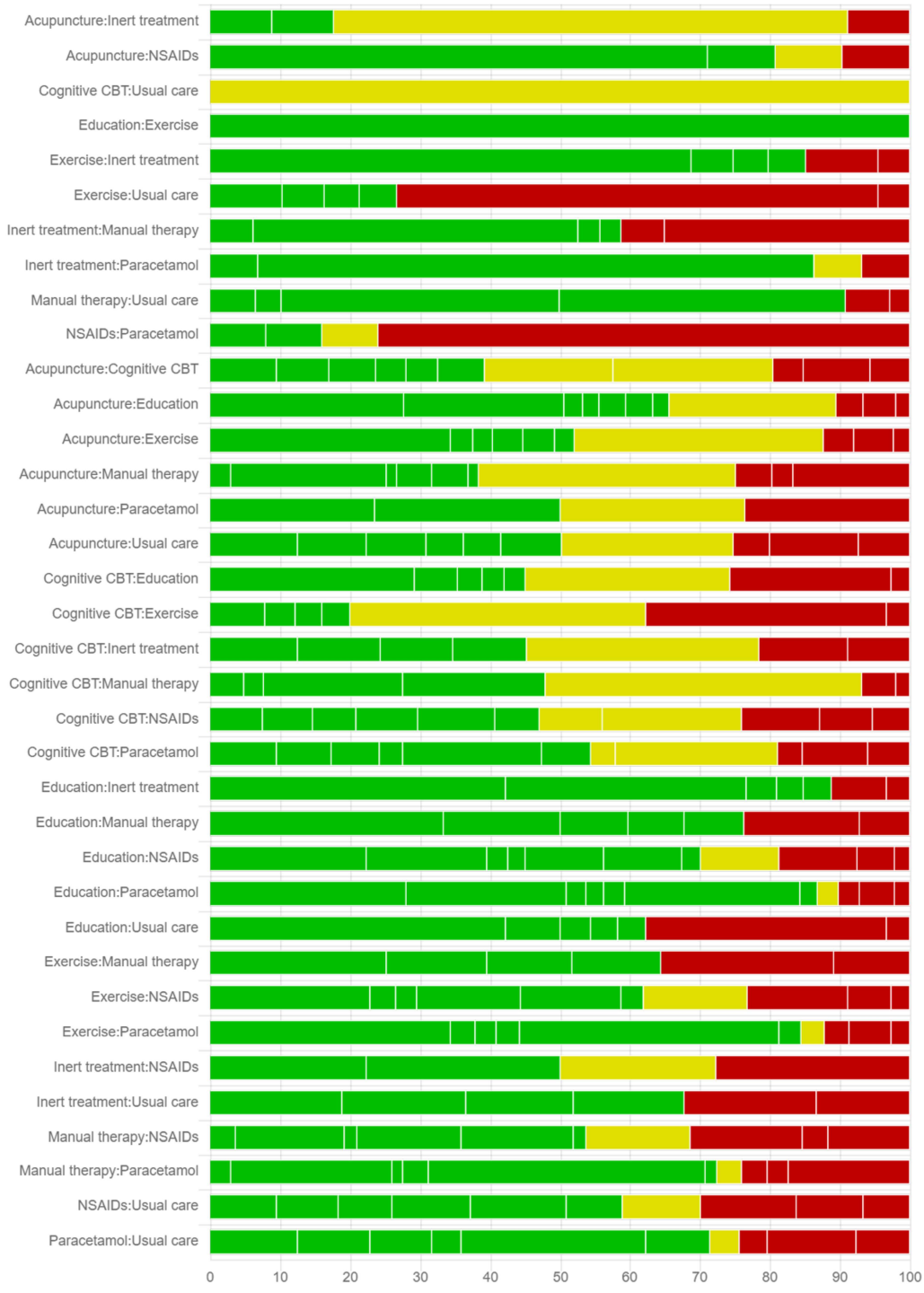
1) Summary of study limitations of the included studies

The colours in the circles indicate the percentage of low RoB studies [green], moderate RoB studies [yellow] and high RoB studies [red] involving each intervention. The colours of the line then indicate the average RoB assessment of each comparison based on the above information – low RoB comparison [green], moderate RoB comparison [yellow] and high RoB comparison [red].



2) Contribution of low or moderate RoB comparisons to each network estimate

Based on the above assessment of RoB for each comparison and the contribution matrix detailing contribution of each direct comparison to all network estimates, the following bar graphs show the percentage of low or moderate RoB contributions for each network estimate. The judgements about study limitations in each direct comparison is shown at the beginning of the graph. Each bar corresponds to a NMA relative treatment effect and shows how much information comes from comparisons at moderate risk of bias [yellow].


Acupuncture:Inert treatment
Acupuncture:NSAIDs
Cognitive CBT:Usual care
Education:Exercise
Exercise:Inert treatment
Exercise:Usual care
Inert treatment:Manual therapy
Inert treatment:Paracetamol
Manual therapy:Usual care
NSAIDs:Paracetamol
Acupuncture:Cognitive CBT
Acupuncture:Education
Acupuncture:Exercise
Acupuncture:Manual therapy
Acupuncture:Paracetamol
Acupuncture:Usual care
Cognitive CBT:Education
Cognitive CBT:Exercise
Cognitive CBT:Inert treatment
Cognitive CBT:Manual therapy
Cognitive CBT:NSAIDs
Cognitive CBT:Paracetamol
Education:Inert treatment
Education:Manual therapy
Education:NSAIDs
Education:Paracetamol
Education:Usual care
Exercise:Manual therapy
Exercise:NSAIDs
Exercise:Paracetamol
Inert treatment:NSAIDs
Inert treatment:Usual care
Manual therapy:NSAIDs
Manual therapy:Paracetamol
NSAIDs:Usual care
Paracetamol:Usual care
0
10
20
30
40
50
60
70
80
90
100

3) Summary grading of Evidence

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Mixed evidence								
Acupuncture:Inert treatment	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Acupuncture:NSAIDs	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Cognitive CBT:Usual care	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Exercise	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Exercise:Inert treatment	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Exercise:Usual care	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Inert treatment:Manual therapy	2	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Inert treatment:Paracetamol	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Manual therapy:Usual care	2	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
NSAIDs:Paracetamol	1	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Indirect evidence								
Acupuncture:Cognitive CBT		Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Education		No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Acupuncture:Exercise		Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low

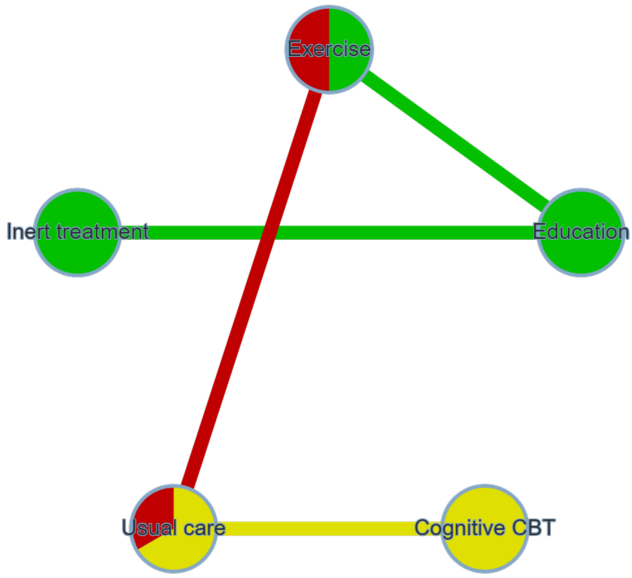
Acupuncture:Manual therapy	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Acupuncture:Paracetamol	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Acupuncture:Usual care	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Cognitive CBT:Education	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Cognitive CBT:Exercise	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Cognitive CBT:Inert treatment	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Cognitive CBT:Manual therapy	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Cognitive CBT:NSAIDs	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Cognitive CBT:Paracetamol	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Inert treatment	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Education:Manual therapy	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Education:NSAIDs	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Education:Paracetamol	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Education:Usual care	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Exercise:Manual therapy	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Exercise:NSAIDs	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Paracetamol	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

Inert treatment:NSAIDs	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Inert treatment:Usual care	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Manual therapy:NSAIDs	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Manual therapy:Paracetamol	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
NSAIDs:Usual care	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Paracetamol:Usual care	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low

3) Pain at 12 months

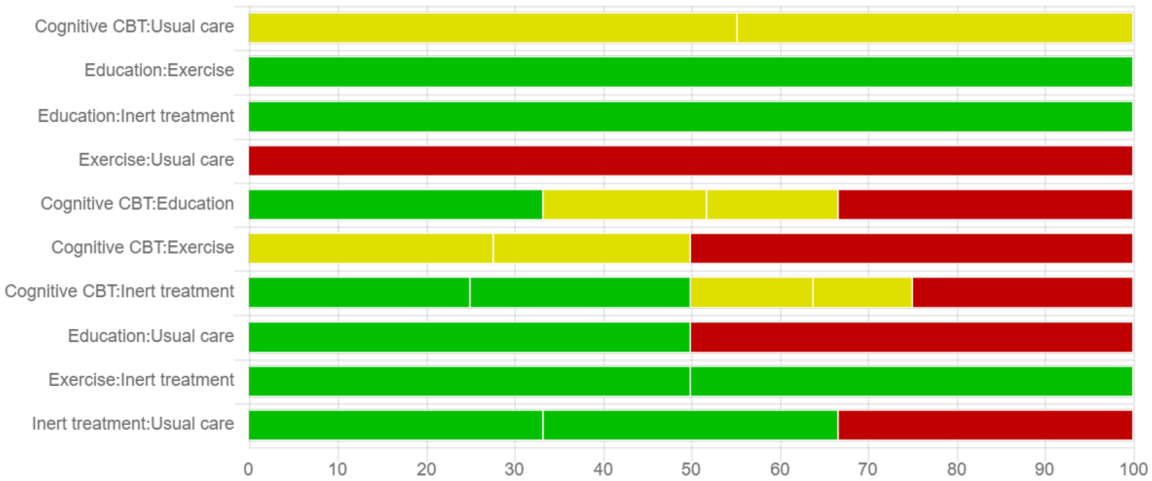
1) Summary of study limitations of the included studies

The colours in the circles indicate the percentage of low RoB studies [green], moderate RoB studies [yellow] and high RoB studies [red] involving each intervention. The colours of the line then indicate the average RoB assessment of each comparison based on the above information – low RoB comparison [green], moderate RoB comparison [yellow] and high RoB comparison [red].



2) Contribution of low or moderate RoB comparisons to each network estimate

Based on the above assessment of RoB for each comparison and the contribution matrix detailing contribution of each direct comparison to all network estimates, the following bar graphs show the percentage of low or moderate RoB contributions for each network estimate. The judgements about study limitations in each direct comparison is shown at the beginning of the graph. Each bar corresponds to a NMA relative treatment effect and shows how much information comes from comparisons at moderate risk of bias [yellow].



3) Summary grading of Evidence

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Mixed treatment								
Cognitive CBT:Usual care	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
Education:Exercise	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Education:Inert treatment	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Exercise:Usual care	1	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Indirect evidence								
Cognitive CBT:Education	-	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low

Cognitive CBT:Exercise	-	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Cognitive CBT:Inert treatment	-	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Education:Usual care	-	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Inert treatment	-	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Inert treatment:Usual care	-	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low

Supplement Q. GRADE for Disability Outcome

Introduction

CINeMA considers 6 domains: (i) within-study bias, (ii) reporting bias, (iii) indirectness, (iv) imprecision, (v) heterogeneity, and (vi) incoherence. Features include the percentage contribution matrix, relative treatment effects for each comparison, estimation of the heterogeneity variance, prediction intervals, and tests for the evaluation of the assumption of coherence. In evaluating imprecision, heterogeneity, and incoherence, we consider the impact of these components of variability in forming clinical decisions.

Table of reasons for downgrading

We use the CINeMA software for GRADE assessment.[26 27] We downgrade network estimate according to the following criteria.

(1) Study limitations: We downgraded by one level when the contributions from low RoB comparisons were less than 25% and contributions from moderate or high RoB comparisons were 75% or greater.

(2) Imprecision: We considered a clinically meaningful threshold for SMD to be 0.5 [28] and downgraded the estimate if the SMD point estimate is 0 or more and the lower limit of its CrI is below 0.5; or if the SMD point estimate is less than 0 and the upper limit of its CrI is above 0.5.

(3) Inconsistency: We rated two concepts, heterogeneity and incoherence (inconsistency), in this domain.

For heterogeneity, we looked at the common tau and found that it is low compared to the expected value as reported in the literature,[29] so we did not downgrade any network estimate for heterogeneity. For inconsistency, we looked at the results of side splitting and we downgraded the comparisons with important inconsistency ($p<0.10$), where we have not downgraded for imprecision (we did not downgrade the same network estimate for both imprecision and inconsistency).

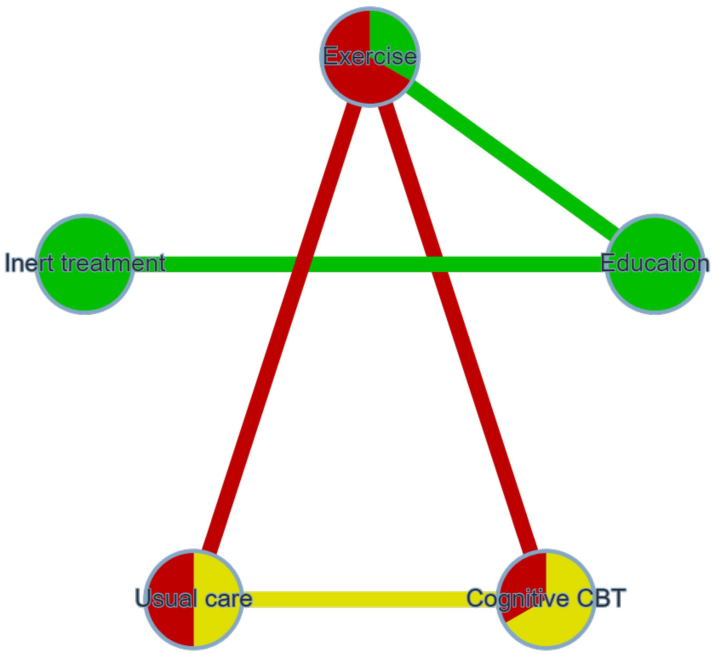
(4) Indirectness: We have assured transitivity in our network by limiting the included studies to acute and subacute population and to non-mixed treatments for LBP. Thus, we did not downgrade for indirectness.

(5) Reporting bias: We cannot completely rule out the possibility that some studies are still missing. However, we assumed that publication bias was undetected.

1) Disability at 12 months

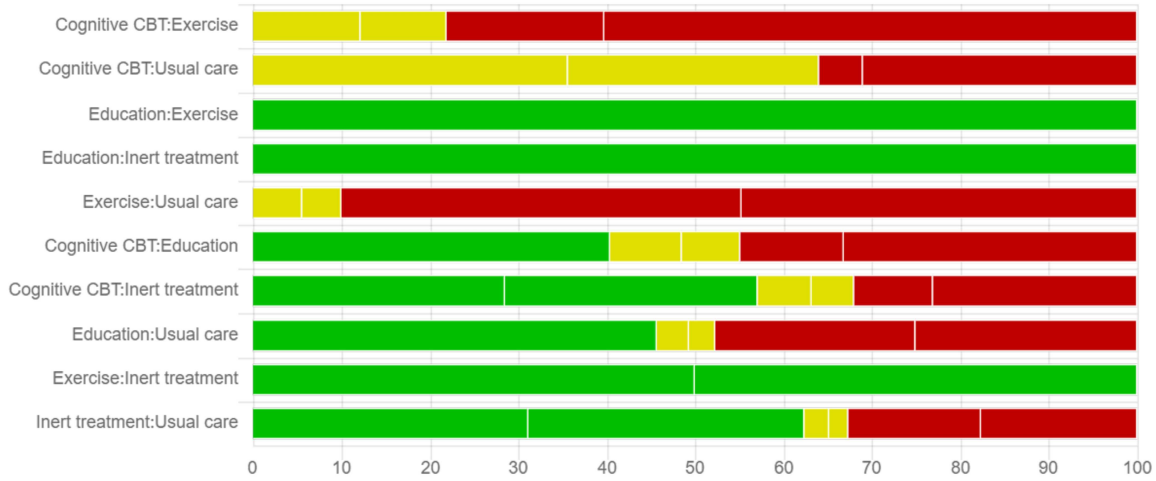
1- Summary of study limitations of the included studies

The colours in the circles indicate the percentage of low RoB studies [green], moderate RoB studies [yellow] and high RoB studies [red] involving each intervention. The colours of the line then indicate the average RoB assessment of each comparison based on the above information – low RoB comparison [green], moderate RoB comparison [yellow] and high RoB comparison [red].



2-Contribution of low or moderate RoB comparisons to each network estimate

Based on the above assessment of RoB for each comparison and the contribution matrix detailing contribution of each direct comparison to all network estimates, the following bar graphs show the percentage of low or moderate RoB contributions for each network estimate. The judgements about study limitations in each direct comparison is shown at the beginning of the graph. Each bar corresponds to a NMA relative treatment effect and shows how much information comes from comparisons at low [green] and high risk of bias [high].



3-Summary grading of Evidence

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Mixed evidence								
Cognitive CBT:Exercise	1	Major concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Very low
Cognitive CBT:Usual care	3	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Education:Exercise	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Education:Inert treatment	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Exercise:Usual care	2	Major concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Very low
Indirect evidence								
Cognitive CBT:Education	-	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Cognitive CBT:Inert treatment	-	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Education:Usual care	-	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Exercise:Inert treatment	-	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Inert treatment:Usual care	-	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low

Supplement R. Data check

We checked the dataset for data extraction errors or "outlier effect sizes" having an influence on overall effects. We defined an "outlier effect sizes" of a study, visually inspecting forest plots of pairwise meta-analyses[30], when SMDs are greater than 1.5 [31 32] assuming 2 points of between population standard deviations across comparisons (resulting from the mean estimate of all final SD values in the control groups [33 34], see row dataset in OSF repository https://osf.io/sjr4y for 0-10 NRS scale). This calculation is coherent with literature where the MID between group difference is commonly set at 1 point (2 SD) on a NRS scale of 0-10 [35]. Coherently, in the Nice Guideline for Low Back Pain and Sciatica[36] the panel considered clinical important an improvement of 10% as a measure of clinical benefit e.g. 1 point decrease on a 0-10 scale for pain intensity [35].

Supplement S. References

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Multiple choice questions (MCQs)

1. Balancing benefits and harms, which is best strategy for the management of acute and subacute NS-LBP:

    A. pharmacological interventions
    B. non-pharmacological interventions
    C. bed rest
    D. surgery

2. Paracetamol can be recommended as a treatment choice for acute and subacute NS-LBP?

    A. yes, prescription of low dosage (500 mg/die)
    B. yes, prescription of higher dosage (4000 mg/die)
    C. yes, any dosage
    D. no, it is not superior to inert treatment

3. Among pharmacological interventions, which is best efficacious?

    A. Muscle relaxants
    B. NSAIDS
    C. opioids
    D. paracetamol

4. In which treatments mild and moderate adverse events are often present?
    A. manual therapy, heat wrap
    B. opioids, NSAIDS, steroids
    C. paracetamol
    D. muscle relaxant drugs

5. How was the overall certainty of the evidence for pain and disability outcomes in management of acute and subacute NS-LBP?

    A. the range of overall certainty of the evidence was high
    B. the range of overall certainty of the evidence was moderate
    C. the range of overall certainty of the evidence varied
    D. the overall certainty of the evidence was not assessed