BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034996
Article Type:	Protocol
Date Submitted by the Author:	15-Oct-2019
Complete List of Authors:	Ho, Emma; The University of Sydney, School of Physiotherapy Ferreira, Manuela; University of Sydney Institute of Bone and Joint Research, Chen, Lingxiao; The University of Sydney Institute of Bone and Joint Research, Simic, Milena; The University of Sydney, Physiotherapy Ashton-James, Claire; The University of Sydney, Pain Management Research Institute, Faculty of Medicine and Health Comachio, Josielli ; University of Sao Paulo, Department of Speech, Physical Therapy and Occupational Therapy, School of Medicine Hayden, Jill; Dalhousie University, Community Health & Epidemiology Ferreira, Paulo; University of Sydney, Faculty of Health Science
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, PSYCHIATRY

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Psychological interventions for chronic non-specific low back pain: protocol of a systematic review with network meta-analysis.

Emma Kwan-Yee Ho[a], Manuela Loureiro Ferreira[b], Lingxiao Chen[b] Milena Simic[a], Claire Ashton-James[c], Josielli Comachio[d], Jill Alison Hayden[e], Paulo Henrique Ferreira[a]

[a] The University of Sydney, Faculty of Medicine and Health, Sydney, NSW, Australia.

[b] The University of Sydney, Institute of Bone and Joint Research, Northern Clinical School, Faculty of Medicine and Health, Sydney, NSW, Australia.

[c] The University of Sydney, Pain Management Research Institute, Faculty of Medicine and Health, Sydney, NSW, Australia.

[d] Department of Speech, Physical Therapy and Occupational Therapy, School of Medicine, University of Sao Paulo, Sao Paulo, Brazil.

[e] Department of Community Health & Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada.

Address for Correspondence:

Ms. Emma Kwan-Yee Ho, Faculty of Medicine and Health

University of Sydney, PO Box 170 Lidcombe 1825 AUSTRALIA

Tel: +61 434 596 855

E-mail: emma.ho@sydney.edu.au

Word count: 2529

Funding Sources: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. PHF is funded by an NHMRC Fellowship and a Sydney University SOAR fellowship. MLF is funded by an NHMRC Fellowship and a Sydney University SOAR fellowship. MS is funded by a Sydney University SOAR fellowship. LC is funded by Northern Clinical School Higher Degree Research Support Scholarship. EKH is funded by an Australian Government Research Training Program Scholarship.

Conflict of Interest:

None declared.

ABSTRACT

Introduction: Psychological factors such as fear avoidance beliefs, depression, anxiety, catastrophic thinking, and familial and social stress, have been associated with high disability levels in chronic low back pain (LBP). Guidelines endorse the integration of psychological interventions in the management of chronic LBP; however, uncertainty surrounds the comparative effectiveness of different psychological approaches. We will perform a systematic review with a network meta-analysis (NMA) approach to compare and rank a comprehensive range of psychological interventions for improving disability and pain intensity in adults with chronic non-specific LBP.

Methods and analysis: We will search electronic databases (MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS and CINAHL) for randomised controlled trials comparing psychological interventions to any comparison interventions in adults with chronic non-specific LBP. There will be no restriction on language or publication year. The primary outcomes will include disability and pain intensity, and secondary outcomes will include health-related quality of life and fear avoidance. Risk of bias will be assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) tool and quality of evidence will be assessed using Cochrane's Confidence in NMA (CINeMA) framework. We will conduct a random-effects NMA using a frequentist approach to estimate relative treatment rankings according to the mean rank and surface under the cumulative ranking curve values. All analyses will be performed in Stata and R.

Ethics and dissemination: No ethical approval is required. The research will be published in a peer-reviewed journal.

PROSPERO registration number: CRD4201913807

Key Words: back pain, low back pain, musculoskeletal disorders, chronic, psychological, psychiatry, network meta-analysis, systematic review.

Strengths and limitations of this study

- This is the first systematic review using an NMA design to compare different types of psychological interventions for improving disability and pain intensity in people with chronic non-specific LBP.
- The main strength is the NMA design will allow for the comprehensive comparison and ranking of multiple psychological interventions simultaneously, which was not possible with previous systematic reviews that only conducted pair-wise meta-analyses.
- An additional strength is that in comparison to previous pair-wise systematic reviews, the NMA design will allow for the inclusion and synthesis of a larger number of studies investigating a wider range of psychological interventions.
- The main limitation is that we anticipate smaller nodes for emerging types of psychological interventions (e.g. acceptance and commitment therapy, cognitive functional therapy), due to the paucity of studies investigating these interventions in chronic LBP populations.

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Low back pain (LBP) is one of largest contributors to disability worldwide [1, 2] and is associated with substantial health and economic burden relating to increased health-care utilisation costs, work absenteeism and productivity loss.[3] The challenge associated with treating chronic non-specific LBP lies in the complex multifactorial interaction between genetic, biophysical, psychosocial, health and lifestyle factors which are largely individualistic.[4, 5] Particularly, psychological factors such as fear avoidance beliefs, depression, anxiety, catastrophic thinking, and familial and social stress [4] are often poorly identified and inadequately addressed,[6] and have been shown to alter pain processing pathways, perceptions, and coping responses.[5, 7] The influence of these factors in chronic non-specific LBP have been found to increase the risk of disability,[8, 9] which commonly manifests as reduced functional capacity, avoidance of usual activities including work, and impaired societal and recreational participation.[5, 10]

Psychological interventions in chronic pain conditions aim to reduce pain-related distress and disability by changing negative beliefs, behaviours and attitudes. These interventions specifically target the environmental contingencies and maladaptive cognitive and emotional processes underpinning pain in order to promote self-efficacy and increased function.[11, 12] Numerous studies investigating the use of psychological interventions for managing chronic non-specific LBP have shown promising evidence for improved overall functioning, pain experience, depression, cognitive appraisal, health-related quality of life and decreased health care utilisation.[11-14] International clinical guidelines consistently endorse the integration of psychological interventions in the management of chronic LBP.[15-19] In fact, a recent and coordinated global call for better management of LBP, led by international LBP experts and published in the *Lancet,* recommends that psychological approaches – namely cognitive behavioural therapy or mindfulness-based stress reduction – should be delivered in isolation or incorporated into multidisciplinary rehabilitation for chronic non-specific LBP.[20]

However, it remains unclear which psychological interventions offer better benefits for managing chronic LBP, as previous systematic reviews have only investigated a small selection of the available approaches.[11-13, 21-23] These reviews have resulted in numerous separate pair-wise comparisons of common interventions such as cognitive behavioural

therapy and biofeedback,[11-13, 21-23] though vigorous attempts to synthesise these separate results and compare them with emerging, less-investigated psychological approaches (e.g. health-coaching, cognitive functional therapy, acceptance and commitment therapy) have not been made. As a result, uncertainty surrounds which approaches policy makers should recommend to clinicians for managing chronic LBP. Undoubtably, the uncertainty exacerbates clinicians' reported lack of confidence and perceived competence in addressing psychological factors in this population.[24, 25] A network meta-analysis (NMA) is a robust analytical design that synthesises direct and indirect evidence to simultaneously compare and rank numerous intervention arms across all relevant studies within a single, coherent treatment network based on their relative effectiveness.[26] Indirect evidence allows for the comparison of emerging, less-investigated interventions despite the paucity of head-to-head trials. As such, the current research aims to perform a NMA to vigorously compare and rank a comprehensive range of psychological interventions for improving disability, pain intensity, health-related quality of life and fear avoidance in chronic non-specific LBP. This will provide crucial evidence to inform clinicians, patients, and policy makers on which psychological interventions offer better benefits for managing chronic LBP.

METHODS AND ANALYSIS

Study design

This protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews.[27] The systematic review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42019138074.

Eligibility criteria

Types of studies

We will include all published parallel and cluster randomised controlled trials (RCT) comparing psychological interventions to any comparison interventions. We will also include cross-over RCTs, using data collected before the washout period. There will be no restriction on length of follow-up. Observational studies, non-randomised trials, and studies that have not been published as full-text articles in peer-reviewed scientific journals will be excluded.

Types of participants

Eligible studies will include adults experiencing chronic non-specific LBP, with or without the presence of radicular leg pain. Chronic non-specific LBP will be defined according to NICE UK guidelines as pain in the back between the bottom of the rib cage and buttocks crease with no known pathoanatomical cause, for greater than 12 weeks in duration.[15, 28] Studies including participants with serious pathologies (e.g. spinal stenosis, malignancy, trauma, vertebral fracture, infection, inflammatory disorders) will be excluded.

Types of interventions and comparators

Psychological interventions will be defined as interventions that explicitly deliver a psychological component as part of treatment,[22] including but not limited to cognitive behavioural therapeutic strategies [relaxation, graded exposure (desensitisation), imagery (distraction), goal setting], mindfulness-based stress reduction, cognitive functional therapy, health-coaching, biofeedback, pain neuroscience education, and counselling directly employing principles of psychological theory. Comparison interventions will include direct comparisons between different types of psychological interventions, waiting list control, usual care, exercise regimes (not accompanied by cognitive-behavioural strategies), or other types of conservative management.

Types of outcome measures

The primary outcomes of interest include:

1. Disability, commonly measured by the Oswestry Disability Index (ODI), Roland Morris Disability Questionnaire (RMDQ), Core Outcome Measures Index (COMI), Quebec Back Pain Disability Index (QBPDI).[29] For studies providing more than one instrument, ODI will be used as first choice, followed by RMDQ, COMI, QBPDI,[29-31] or other tools that have been proposed in peer-reviewed journals.
2. Pain intensity, commonly measured by the Numeric Rating Scale (NRS) and Visual Analogue Scale (VAS).[30] For studies providing more than one instrument, NRS will be used as the first choice.[30]

Secondary outcomes of interest include:

1. Health-related quality of life (HR-QoL), commonly measured by the 12-Item or 36-Item Short Form (SF-12, SF-36), EuroQol five-dimension (EQ-5D), Nottingham Health Profile (NHP) and 10-Item Patient-Reported Outcomes Measurement Information System Global Health Short Form (PROMIS-GH-10).[30, 31] For studies

providing more than one instrument, SF-12 will be used as first choice, followed by PROMIS-GH-10, EQ-5D, SF-36, and NHP.[30, 31]

2. Fear avoidance, commonly measured by the Fear-Avoidance Beliefs Questionnaire (FABQ), Pain Catastrophizing Scale (PCS), Tampa Scale for Kinesiophobia (TSK) and Fear of Pain Questionnaire (FPQ).[32] For studies providing more than one instrument, FABQ will be used as first choice, followed by PCS, TSK, FPQ,[32] or other tools that have been proposed in peer-reviewed journals.

Study selection

Electronic searches

The following databases will be searched for eligible studies: MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS and CINAHL. Search concepts will include language and keywords for: randomised controlled trial, low back pain, and terms relating to psychological interventions, according to the eligibility criteria defined earlier in the protocol. A full MEDLINE search strategy can be found in Appendix A of this protocol. There will be no restriction on publication year or language.

Additional search strategies

We will search reference lists and perform citation tracking of included studies and relevant systematic reviews [11-13, 21-23] and clinical guidelines [15-17] to identify additional eligible studies. We will also search clinicaltrials.gov to identify registered trials and contact authors for related publications to minimise possible omission.

Identification and selection of studies

Citations identified by our search strategy will be managed using Covidence.[33] Two reviewers will independently screen citation titles and abstracts to identify potentially eligible studies. Disagreements will be resolved by consensus or a third reviewer. A PRISMA flow-diagram will be presented to map the number of records included and excluded during the study selection process, with reasons for exclusions reported.

Data extraction

Two reviewers will independently extract data from the included studies using a pre-designed data extraction form in Covidence.[33] Disagreements will be resolved by consensus or a

third reviewer. The following data will be extracted: publication characteristics (e.g. first author, publication year, journal, funding, location); study design characteristics (e.g. number of participants randomised, durations of follow-up, percentage of dropouts); patient characteristics (e.g. age, gender, body mass index, pain intensity, socioeconomic status, comorbidities); intervention and comparator characteristics (e.g. type of psychological or comparison intervention, intervention dosage and frequency); and primary and secondary outcome measures (including outcome definitions, summary data related to treatment effects, measurement tools). Data will be classified according to short-term (<6 months), mid-term (6-12 months) or long-term follow-up (≥12 months), and NMA will be performed at each time-point separately. Authors will be contacted for additional information where necessary.

Following data collection, we will consult clinical experts from the review team to establish the appropriateness of clustering similar interventions into a single treatment node, for example: no treatment (e.g. waiting list control), passive treatment (e.g. manual therapy), pharmacological treatment (e.g. medications, supplements), and active treatment (e.g. exercise). Expert opinions will also be sought regarding the appropriateness of categorising combination interventions as additional treatment nodes (e.g. psychological interventions combined with exercise). Post-hoc classification of comparison interventions into distinct or single treatment nodes will also be made based on the available types of comparators. Any post-hoc alternative network geometrics formed using this approach will be clearly identified and justified in the final review.

Risk of bias in the included studies

Two reviewers will independently assess risk of bias in the included studies using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) in Covidence.[33, 34] Disagreements will be resolved through consensus or a third reviewer. Authors will be contacted for additional information where necessary. The RoB 2 assesses five domains: (1) bias arising from the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result. Each domain will be graded as low risk of bias, some concerns, or high risk of bias, and the results will be summarised in a table. An overall risk of bias judgement (low risk of bias, some concerns, or high risk of bias) will be made based on the five domain-level judgements.

Data Analysis

Characteristics of the publications, study designs, study populations, interventions and comparators, and outcome measures will be summarised descriptively and presented in a table. Pair-wise meta-analysis will be performed in Stata (StataCorp. 2017. Stata Statistical Software: Version 13), and NMA will be performed in both Stata and R (V.3.6.1. R Core Team. 2019. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Summary measures

Dichotomous data will be reported as odds ratio (OR) and 95% confidence intervals (95% CI). Continuous data will be reported as mean differences (MD) and 95% CI for studies using the same rating scales. Standardised MD and 95% CI will be calculated for studies measuring comparable outcomes using different rating scales.

Geometry of the network

The network diagram will be used to graphically depict the available evidence. Nodes will be used to represent the different interventions and comparators, and the width of the edges will be used to visually represent the proportional volume of studies comparing two connected nodes within the network.

Pairwise meta-analysis

We will perform traditional pairwise meta-analyses of all direct comparisons using the DerSimonian and Laird inverse-variance random-effects method.[35] Heterogeneity will be quantified using Higgins I^2 statistic, with $I^2 > 50\%$ suggesting substantial heterogeneity.[35] Forest plots will be created to graphically depict individual and pooled effect sizes. Narrative analysis will be performed when statistical analysis is not feasible or sensible due to insufficient data provided or substantial heterogeneity.

Assessment of transitivity assumption

Potential effect modifiers (age, gender, pain intensity, socioeconomic status, comorbidities, intervention dosage and frequency) will be assessed to confirm baseline similarity across treatment comparisons within the network. If intransitivity is suspected, meta-regression will be performed to explore the influence on the results.

Network meta-analysis

A NMA will be performed using a frequentist approach to simultaneously compare direct and indirect evidence whilst preserving within-study randomisation.[36] Mean rank and relative treatment rankings with their 95% CI will be estimated for each intervention node according to the surface under the cumulative ranking curve (SUCRA) values (%).[37]

Assessment of inconsistency

Local inconsistencies will be assessed using the Bucher method [38] by computation of inconsistency factors and 95% CI for each triangular and quadratic loop in the network. Global inconsistency of the entire network will be assessed using the design-by-treatment interaction model,[39] which is a goodness-of-fit test. If inconsistencies are found, a node-splitting method will be used to explore the origin of the inconsistency.[36]

Sensitivity and sub-group analysis

To examine robustness of results, we will conduct a sensitivity analysis by excluding studies with high risk of bias. We will also perform the following sub-group analyses depending on available data:

(1) Delivery format of psychological intervention (e.g. face-to-face, telephone-administered, web-based, self-help booklets), the hypothesis is that face-to-face delivery format will result in greater improvements in disability and pain intensity.

(2) Individual versus group-based intervention delivery, the hypothesis is that group-based interventions will result in greater improvements in disability and pain intensity.

(3) Back pain only versus back pain and leg pain, the hypothesis is that the back pain only group will result in greater improvements in disability and pain intensity.

Meta-regression will be performed based on: (1) age; (2) percentage of males; (3) sample size; (4) baseline disability levels; (5) baseline pain levels.

Publication bias

Publication bias will be evaluated by visual inspection of comparison-adjusted funnel plots for asymmetry. As described above, meta-regression using sample size and effect estimates will be performed to detected small study effect.[40]

Grading of evidence

Quality of the evidence will be evaluated using the Confidence in Network Meta-Analysis (CINeMA) framework,[41] a Cochrane web application of the Grading of Recommendations Assessment, Development, and Evaluation ratings approach. The framework assesses six domains: within-study bias, across-studies bias, indirectness, imprecision, heterogeneity and incoherence.

Patient and public involvement

Patients will not be involved.

CONTRIBUTIONS TO LITERATURE

To date, there is no conclusive consensus regarding the most effective psychological approach for managing chronic non-specific LBP and therefore clinicians, policy makers, and patients have limited information on which approach to adopt. Previous studies have only investigated a small portion of available psychological interventions, most commonly cognitive behavioural therapy, mindfulness-based stress reduction and biofeedback, and comparisons have been limited by conventional pair-wise meta-analysis methodologies. This systematic review with NMA will synthesise direct and indirect evidence for a comprehensive variety of psychological interventions with respect to disability, pain intensity, health-related quality of life and fear avoidance for chronic non-specific LBP. The NMA will return relative treatment rankings to compare and rank the different psychological approaches and provide pragmatic support for clinical recommendations regarding their use in adults with chronic non-specific LBP.

ETHICS AND DISSEMINATION

Ethical review will not be required as the systematic review will only involve the use of previously published data for analysis. Our intention is to publish the completed research in a peer-review journal and present our findings at national and international conferences.

CONFLICTS OF INTEREST

There are no conflicts of interest in this study.

AUTHOR CONTRIBUTIONS

All authors conceived the study. EKH drafted the manuscript. EKH, LC and JC participated in the search strategy development. PHF assisted in the protocol design and revision. JAH

and LC provided statistical expertise. CA provided expertise on psychological interventions. All authors read and approved the final manuscript as submitted.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. PHF is funded by an NHMRC Fellowship and a Sydney University SOAR fellowship. MLF is funded by an NHMRC Fellowship and a Sydney University SOAR fellowship. MS is funded by a Sydney University SOAR fellowship. LC is funded by Northern Clinical School Higher Degree Research Support Scholarship. EKH is funded by an Australian Government Research Training Program Scholarship.

APPENDIX A

Database: Ovid MEDLINE

1. exp Back Pain/ or exp Low Back Pain/ or exp Backache/
2. (back pain or low back pain or lumbar pain or lumbago or dorsalgia or spinal pain or vertebral pain or backache or lumbar spine).ti,ab.
3. 1 or 2
4. exp Behavior Therapy/ or exp Cognitive Therapy/ or *Conditioning, Operant/ or exp Reinforcement, Psychology/
5. (operant conditioning or reinforcement or psychological intervention or psychological therapy).ab,ti.
6. (cognitiv* adj1 (treatment* or therap* or intervention*)).ab,ti.
7. (behavio?r* adj1 (treatment* or therap* or intervention* or techniqu* or modif* or change*)).ab,ti.
8. (graded exposure or desensiti* or imagery or goal setting).ab,ti.
9. (acceptance and commitment therapy or CBT).ab,ti.
10. 4 or 5 or 6 or 7 or 8 or 9
11. exp Mindfulness/ or *Mind-Body Therapies/ or exp Meditation/ or exp Relaxation/ or exp Relaxation Therapy/
12. (mindfulness based stress reduction*).ab,ti.
13. (mindfulness or mind-body therapies or meditation or relaxation or relaxation therap*).ab,ti.
14. (mbsr* or mbct*).ab,ti.
15. 11 or 12 or 13 or 14
16. (cognitive functional therapy or CFT).ab,ti.
17. exp Health Education/ or exp Health Promotion/ or exp Motivation/
18. (health education or health promotion or motivation).ab,ti.
19. ((health or wellness or life-style or behav*) adj1 coach*).ab,ti.
20. ((wellness or behav*) adj1 intervention*).ab,ti.
21. or/ 17 or 18 or 19 or 20
22. exp Biofeedback, Psychology/ or exp Feedback, Psychological/
23. (electromyograph* or electromyogram* or EMG*).ab,ti.
24. (bio-feedback or feedback).ab,ti.
25. 22 or 23 or 24

26. (pain neuroscience education or pain education or neuroscience education or pain physiology education or neuro-physiology education or therapeutic education).ab,ti.
27. exp Counseling/
28. (counseling or supportive psychotherap*).ab,ti.
29. 27 or 28
30. 10 or 15 or 16 or 21 or 25 or 26 or 29
31. 3 and 30
32. exp Randomized controlled trial/ or *Clinical Trial/ or *Random allocation/ or exp Controlled clinical trial/
33. randomized controlled trial.pt.
34. (random* adj3 trial).ab,ti.
35. (clinical trial or random allocation or controlled clinical trial).ab,ti.
36. 32 or 33 or 34 or 35
37. 31 and 36
38. limit 37 to humans

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1,4
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
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.	5,7
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.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	13-14
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).	7
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.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in 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.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9,10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
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).	10,11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
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.	N/A – protocol paper
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.	N/A – protocol paper
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A – protocol paper
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A – protocol paper
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A – protocol paper
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A – protocol paper
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A – protocol paper
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).	N/A – protocol paper
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).	N/A – protocol paper
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	N/A – protocol paper

PRISMA 2009 Checklist

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.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Psychological interventions for chronic non-specific low back pain: protocol of a systematic review with network meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034996.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Feb-2020
Complete List of Authors:	Ho, Emma; The University of Sydney, Faculty of Medicine and Health Ferreira, Manuela; University of Sydney Institute of Bone and Joint Research, Chen, Lingxiao; The University of Sydney Institute of Bone and Joint Research, Simic, Milena; The University of Sydney, Faculty of Medicine and Health Ashton-James, Claire; The University of Sydney, Pain Management Research Institute, Faculty of Medicine and Health Comachio, Josielli ; University of Sao Paulo, Department of Speech, Physical Therapy and Occupational Therapy, School of Medicine Hayden, Jill; Dalhousie University, Community Health & Epidemiology Ferreira, Paulo; University of Sydney, Faculty of Medicine and Health
Primary Subject Heading:	Public health
Secondary Subject Heading:	Mental health
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, PSYCHIATRY

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Psychological interventions for chronic non-specific low back pain: protocol of a systematic review with network meta-analysis.

Emma Kwan-Yee Ho[a], Manuela Loureiro Ferreira[b], Lingxiao Chen[b] Milena Simic[a], Claire Ashton-James[c], Josielli Comachio[d], Jill Alison Hayden[e], Paulo Henrique Ferreira[a]

[a] The University of Sydney, Faculty of Medicine and Health, Sydney, NSW, Australia.

[b] The University of Sydney, Institute of Bone and Joint Research, Northern Clinical School, Faculty of Medicine and Health, Sydney, NSW, Australia.

[c] The University of Sydney, Pain Management Research Institute, Faculty of Medicine and Health, Sydney, NSW, Australia.

[d] Department of Speech, Physical Therapy and Occupational Therapy, School of Medicine, University of Sao Paulo, Sao Paulo, Brazil.

[e] Department of Community Health & Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada.

Address for Correspondence:

Ms. Emma Kwan-Yee Ho, Faculty of Medicine and Health

University of Sydney, PO Box 170 Lidcombe 1825 AUSTRALIA

Tel: +61 434 596 855

E-mail: emma.ho@sydney.edu.au

Word count: 5028

Funding Sources: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. PHF is funded by an NHMRC Fellowship and a Sydney University SOAR fellowship. MLF is funded by an NHMRC Fellowship and a Sydney University SOAR fellowship. MS is funded by a Sydney University SOAR fellowship. LC is funded by Northern Clinical School Higher Degree Research Support Scholarship. EKH is funded by an Australian Government Research Training Program Scholarship.

Conflict of Interest:

None declared.

ABSTRACT

Introduction: Psychological factors such as fear avoidance beliefs, depression, anxiety, catastrophic thinking, and familial and social stress, have been associated with high disability levels in people with chronic low back pain (LBP). Guidelines endorse the integration of psychological interventions in the management of chronic LBP. However, uncertainty surrounds the comparative effectiveness of different psychological approaches. Network meta-analysis (NMA) allows comparison and ranking of numerous competing interventions for a given outcome of interest. Therefore, we will perform a systematic review with a NMA to determine which type of psychological intervention is most effective for adults with chronic non-specific LBP.

Methods and analysis: We will search electronic databases (MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS and CINAHL) from inception until 22 August 2019 for randomised controlled trials comparing psychological interventions to any comparison interventions in adults with chronic non-specific LBP. There will be no restriction on language. The primary outcomes will include physical function and pain intensity, and secondary outcomes will include health-related quality of life, fear avoidance and intervention compliance. Risk of bias will be assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) tool and confidence in the evidence will be assessed using Cochrane's Confidence in NMA (CINeMA) framework. We will conduct a random-effects NMA using a frequentist approach to estimate relative treatment rankings according to the mean rank and surface under the cumulative ranking curve values. All analyses will be performed in Stata.

Ethics and dissemination: No ethical approval is required. The research will be published in a peer-reviewed journal.

PROSPERO registration number: CRD42019138074

Key Words: back pain, low back pain, musculoskeletal disorders, chronic, psychological, psychiatry, network meta-analysis, systematic review.

Strengths and limitations of this study

- This is the first systematic review using an NMA design to simultaneously compare different types of psychological interventions for improving physical function, pain intensity, health-related quality of life, fear avoidance and intervention compliance in people with chronic non-specific LBP.
- The main strength is the NMA design will allow for the comprehensive comparison and ranking of multiple psychological interventions simultaneously, which was not possible with previous systematic reviews that only conducted pair-wise meta-analyses.
- An additional strength is that in comparison to previous pair-wise systematic reviews, the NMA design will allow for the inclusion and synthesis of a larger number of studies investigating a wider range of psychological interventions.
- The main limitation is that we anticipate numerous studies involving different combinations of psychological approaches (e.g. cognitive behavioural therapy plus pain education, counselling-based therapies plus pain education), but small number of eligible studies per combination, hence we will lump combination interventions into one treatment node for practical reasons.

Psychological interventions for chronic non-specific low back pain: protocol of a systematic review with network meta-analysis.

Low back pain (LBP) is one of largest contributors to disability worldwide [1, 2] and is associated with substantial health and economic burden relating to increased health-care utilisation costs, work absenteeism and productivity loss.[3] The challenge associated with treating chronic non-specific LBP lies in the complex multifactorial interaction between genetic, biophysical, psychosocial, health and lifestyle factors which are largely individualistic.[4, 5] Particularly, psychological factors such as fear avoidance beliefs, depression, anxiety, catastrophic thinking, and familial and social stress [4] are often poorly identified and inadequately addressed,[6] and have been shown to alter pain processing pathways, perceptions, and coping responses.[5, 7] The influence of these factors in chronic non-specific LBP have been found to increase the risk of disability,[8, 9] which commonly manifests as reduced functional capacity, avoidance of usual activities including work, and impaired societal and recreational participation.[5, 10]

Psychological interventions in chronic pain conditions aim to reduce pain-related distress and disability by changing negative beliefs, behaviours and attitudes through a combination of principles and strategies informed by psychological theories. Psychological interventions commonly focus on targeting the specific environmental contingencies and maladaptive cognitive and emotional processes underpinning pain in order to promote self-efficacy and increased function.[11, 12] In clinical trials of psychological interventions for chronic LBP, psychological interventions are delivered either in isolation [12, 13] or as part of an integrated treatment program that may involve non-psychological co-interventions such as exercise, passive treatment or physiotherapy.[14-16] For the purposes of this review, we have defined five main categories of psychological interventions relevant to LBP: behavioural therapies, cognitive behavioural therapies, mindfulness-based therapies, counselling-based therapies, and pain education-focused therapies. These categories reflect the three “waves” of how psychological interventions have evolved over time.[17] Behavioural therapies are typically considered “first wave” approaches,[17] and include interventions focused on altering maladaptive behaviours, and dysfunctional sensations or movements.[18] Cognitive behavioural therapies are considered “second wave” approaches,[17] and include interventions that aim to modify harmful cognitions (e.g. thoughts, beliefs) which may proliferate pain and disability.[18] Mindfulness-based therapies, counselling-based therapies

and pain education-focused therapies represent different types of 'third wave" approaches.[17] Unlike behavioural and cognitive behavioural therapies which focus on targeting psychological and emotional symptoms, "third wave" therapies adopt a more holistic approach to promoting health and wellness.[17] Key characteristics and examples of the psychological intervention categories that will be included in our review are summarised below in Table 1.

Table 1. Categories of Psychological Interventions for Low Back Pain

	Category	Characteristics	Examples
First wave	Behavioural therapies	Behavioural therapies focus on the removal of positive reinforcement of pain behaviours and teach patients to overcome stressful situations through relaxation skills.[17]	Biofeedback [17, 18]
Second wave	Cognitive behavioural therapies	Cognitive behavioural therapies aim to restructure negative cognitions (e.g. thoughts, beliefs) and behaviours and promote emotion regulation and problem-solving capacity.[17]	Graded activity [17] Graded exposure [17]
Third wave	Mindfulness-based therapies	Mindfulness-based therapies focus on promoting self-awareness, attention control, and pain acceptance.[13, 19]	Mindfulness-based stress reduction [17, 19] Acceptance and commitment therapy [17]
	Counselling-based therapies	Counselling-based therapies focus on using supportive communication and active listening techniques to build interpersonal clinician-patient relationships.	Health coaching [20, 21] Motivational interviewing [20, 21]
	Pain education-focused therapies	Pain education-focused therapies target a patient's understanding and knowledge of pain to reduce fear associated with LBP. Pain education interventions move away from the traditional biomechanical explanation of pathology and pain, and instead focus on the reconceptualisation of the pain experience.	Pain neuroscience education [22]

Some pain education interventions specifically aim to desensitise the nervous system.

Previous systematic reviews have shown promising evidence that psychological interventions can improve overall functioning, pain experience, depression, cognitive appraisal, health-related quality of life and decreased health care utilisation in people with chronic LBP.[11, 12, 15] Psychological interventions can also reduce fear avoidance beliefs and behaviours (e.g. kinesiophobia),[23] which are associated with increased disability and pain in people with chronic LBP.[24, 25] Based on the evidence and LBP research experts, international clinical guidelines consistently endorse the integration of psychological interventions with exercise in the management of chronic LBP.[26-31]

However, LBP guideline recommendations remain vague regarding the specific types of psychological approaches that clinicians should consider incorporating into treatment.[26-31] This may be due to the fact that previous systematic reviews, which have informed these guidelines, have mainly focused on a small selection of available approaches – namely cognitive behavioural therapy and behavioural approaches such as biofeedback.[11, 12, 15, 18, 32, 33] Emerging psychological interventions such as cognitive functional therapy (a combination of psychological approaches involving cognitive behavioural strategies, pain education and exercise)[5] and acceptance and commitment therapy have been neglected from these reviews, despite recent evidence for their effectiveness in reducing LBP-related disability.[34, 35] Importantly, previous reviews have only conducted multiple independent pairwise meta-analyses, and to our knowledge, no attempts have been made to synthesise the separate results. Ultimately, the comparative effectiveness of the wider collection of psychological interventions available for managing chronic LBP is unknown and clinical guidelines remain unclear. This represents an important gap in the evidence. Subsequently, there is an increased reliance on a clinician's expertise to select the most appropriate psychological approach for people with chronic LBP. Given that clinicians such as physiotherapists report a perceived lack of training and confidence in addressing psychological factors,[36-38] and tend to be biased towards a biomedical approach despite increasing efforts to adopt a biopsychosocial, person-centered approach,[38, 39] the gap in evidence must be addressed. A network meta-analysis (NMA) design will allow us to determine the comparative effectiveness of psychological interventions for managing chronic LBP, whilst addressing the limitations identified from previous reviews.

A NMA is an extension of a traditional pairwise meta-analysis and involves the synthesis of direct and indirect evidence to simultaneously compare numerous competing interventions within a single, coherent treatment network.[40] Direct evidence refers to data obtained from studies directly comparing competing interventions in head-to-head trials. Direct evidence can be used to indirectly estimate the effect of interventions that have not been previously compared in head-to-head trials but have been compared to a common comparator (indirect evidence). Integrating direct and indirect evidence increases the precision of treatment effect estimates, provided that the assumptions of transitivity (balanced distribution of potential effect modifiers across all competing interventions within a network) and consistency (statistical agreement between all competing interventions within a network) are satisfied. Treatment effect estimates are used to generate relative treatment rankings to rank all the competing interventions for a particular outcome measure. As such, the current research aims to perform a NMA to investigate the comparative effectiveness of psychological interventions for chronic LBP and determine which specific type is most effective for improving physical function, pain intensity, health-related quality of life, fear avoidance and intervention compliance in chronic non-specific LBP.

METHODS AND ANALYSIS

Study design

This protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews[41] and the PRISMA extension for developing review protocols (PRISMA-P)[42] and for NMA (PRISMA-NMA).[43] The systematic review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42019138074.

Eligibility criteria

Types of studies

We will include published parallel and cluster randomised controlled trials (RCT). We will also include the first phase of cross-over RCTs. There will be no restriction on length of follow-up. Observational studies, non-randomised trials, short reports, research letters, conferences abstracts, or studies that have not been published as full-length articles in peer-reviewed scientific journals will be excluded. In accordance with the Cochrane handbook,[44] we will only include data from cluster RCTs which account for the cluster

design (e.g. data analysed at the level of allocation). If cluster-level data is not reported for a given cluster RCT study, we will attempt to use the approximate approaches described in the Cochrane handbook to adjust the results,[44] otherwise the study will be excluded.

Types of participants

Eligible studies will include adults experiencing chronic non-specific LBP, with or without the presence of leg pain. Chronic non-specific LBP will be defined according to NICE UK guidelines as pain in the back between the bottom of the rib cage and buttocks crease with no known pathoanatomical cause, for greater than 12 weeks in duration.[26, 45] Studies including participants with serious pathologies (e.g. spinal stenosis, malignancy, trauma, vertebral fracture, infection, inflammatory disorders) will be excluded. We will include studies involving a combination of acute, sub-acute or chronic LBP populations, provided that >50% of participants within a given study have chronic LBP. We will also include studies of chronic LBP participants combined with other chronic pain conditions, provided that >50% of participants have a single diagnosis of chronic LBP. If it is unclear, study eligibility will be determined by consensus amongst reviewers.

Types of interventions

We will include studies of psychological interventions. Expanding on the definition provided by Hoffman et al. (2007),[12] we will consider an intervention as "psychological" if it is conceived by the authors of the study as a psychological intervention, or if it is clearly based on any of the following approaches: cognitive behavioural therapeutic strategies [relaxation, graded exposure (desensitisation), imagery (distraction), goal setting, operant conditioning], mindfulness-based stress reduction, acceptance and commitment therapy, cognitive functional therapy, health-coaching, biofeedback (delivered with a therapeutic intent to promote muscle relaxation), pain education, and counselling directly employing principles of psychological theory. Interventions such as cognitive behavioural therapeutic strategies and biofeedback were purposely included based on their inclusion across a variety of previous relevant systematic reviews.[12, 15, 17, 18] Additional approaches such as cognitive functional therapy, health coaching, and acceptance and commitment therapy were included as they have been neglected in previous reviews. If our search identifies other psychological interventions which are not explicitly listed above but meet our definition for a psychological intervention, we will consider including them in our review. Disagreements regarding their eligibility for inclusion will be resolved by consensus.

We will include studies of combination therapies, defined as interventions that contain two or more psychological approaches delivered together, with or without additional non-psychological co-interventions. There will be no restriction on the non-psychological co-interventions or comparison interventions identified by our search strategy.

Types of outcome measures

The primary outcomes of interest are physical function and pain intensity:

1. Physical function, defined as lower back specific physical function, measured at the end of treatment. Physical function is commonly measured by continuous, self-report scales (e.g. Oswestry Disability Index (ODI), Roland Morris Disability Questionnaire (RMDQ), Core Outcome Measures Index (COMI), Quebec Back Pain Disability Index (QBPDI)) or rating scales within a composite measure (e.g. 12-Item or 36-Item Short Form (SF-12, SF-36)). We will not exclude studies that use other measurement tools.
2. Pain intensity, measured at the time point closest to the end of treatment. Pain intensity is commonly measured by continuous, self-report scales (e.g. Numeric Rating Scale (NRS), Visual Analogue Scale (VAS)) or a rating scale within a composite rating scale (e.g. McGill Pain Questionnaire). We will not exclude studies that use other measurement tools.

Secondary outcomes of interest include:

1. Health-related quality of life, measured at the end of treatment. It is commonly measured by the SF-12, SF-36, EuroQol five-dimension (EQ-5D), Nottingham Health Profile (NHP) and 10-Item Patient-Reported Outcomes Measurement Information System Global Health Short Form (PROMIS-GH-10). We will not exclude studies that use other measurement tools.
2. Fear avoidance, defined as fear of pain and consequent avoidance of movement, measured at the end of treatment. Fear avoidance is commonly measured by the Fear-Avoidance Beliefs Questionnaire (FABQ), Pain Catastrophizing Scale (PCS), Tampa Scale for Kinesiophobia (TSK) and Fear of Pain Questionnaire (FPQ). We will not exclude studies that use other measurement tools.
3. Intervention compliance, measured as the proportion of participants randomised to the intervention group who completed the intervention during the intervention period.

Study selection

Electronic searches

The following databases will be searched for eligible studies via OVID from inception until 22 August 2019: MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS and CINAHL. Search concepts will include language and keywords for: randomised controlled trial, low back pain, and terms relating to psychological interventions, according to the eligibility criteria defined earlier in the protocol. A full MEDLINE search strategy can be found in Appendix A of this protocol. There will be no restriction on language.

Additional search strategies

We will search reference lists and perform citation tracking of included studies and relevant systematic reviews[11, 12, 15, 17, 18, 32, 33] and clinical guidelines[26-28] to identify additional eligible studies.

Identification and selection of studies

Citations identified by our search strategy will be managed using Endnote X9[46] and screened using Covidence.[47] Eligibility screening will be conducted independently by two reviewers in two independent stages: (i) citation titles and abstracts; (ii) full text. Disagreements will be resolved by consensus or a third reviewer. A PRISMA flow-diagram will be presented to map the number of records included and excluded during the study selection process, with reasons for exclusions reported.

Data extraction

Two reviewers will independently extract data from the included studies using a pre-designed excel data extraction form. The form will be pilot-tested on a small number of articles. Disagreements will be resolved by consensus or a third reviewer.

Publication characteristics

We will extract data on the following publication characteristics: first author, publication year, journal, funding, location.

Study design characteristics

We will extract data related to the study design, including number of participants randomised and durations of follow-up.

Participant characteristics

We will extract data on the individual study sample, including age, male/female, body mass index, baseline pain intensity, socioeconomic status and comorbidities.

Interventions and Comparators

We will extract data on the interventions of interest and any comparation interventions. We will extract the key components of the psychological intervention (e.g. details of the specific psychological principles or approaches used, qualifications of the personnel delivering the intervention, co-interventions involved) and comparison intervention. We will extract all available data on intervention dosage and frequency, and intervention duration including duration of any washout.

Outcomes

We will extract the definitions provided for our primary and secondary outcomes of interest. We will also extract the type and dimensions of the measurement tools used to assess our primary and secondary outcomes of interest.

Results

For intervention compliance, we will extract all data on the number of participants who were randomised to the intervention group and completed the intervention. If this data is not available, we will extract the number of participants randomised to the intervention group who discontinued treatment for any reason (i.e. all-cause discontinuation) within the intervention period, to calculate the number of participants who completed treatment. We will express this data as a proportion of the total number of people randomised to the intervention group. We will extract reasons for all-cause discontinuation during the intervention period if reported. We will also extract all available data on adherence, adverse and serious adverse events, including the authors' definitions of these terms.

For all other outcome measures, we will preference extracting the mean baseline and outcome scores (at the time point closest to end of treatment) for each group, and the accompanying measures of variance or statistics to impute these values. Otherwise, we will extract the

change in outcome from baseline and the accompanying measures of variance for each group. If neither are available, we will extract between-group differences in scores and the accompanying measures of variance. For the following outcomes, we will extract all available data in the order which the measurement tools are listed, in accordance with the proposed hierarchy for analysis. If a given outcome is measured by several measurement tools not explicitly listed, the hierarchy for analysis will be decided by consensus from the reviewers.

For studies measuring physical function: ODI; RMDQ; COMI; QBPQI; rating scale for disability from a composite measure of physical function (e.g. SF-12, SF-36); other measurement tools.[48, 49] For studies measuring pain intensity: NRS; 100mm VAS; 10cm VAS; rating scale for pain intensity from a composite measure of pain intensity; other measurement tools.[48, 49] We will extract data on pain intensity at the time point closest to randomisation and end of treatment, in the order of average pain intensity (preferred); worst pain intensity, alternative measures of pain intensity. If several alternative measures of pain intensity are reported, we will calculate an average score. For studies measuring health-related quality of life: PROMIS-GH-10; EQ-5D; SF-36 or SF-12 (physical component summary sub-score); SF-36 or SF-12 (mental component summary sub-score); SF-36 (overall score); NHP;[48, 49] rating scale from a composite measure of health-related quality of life; other measurement tools. If only an overall score for the SF-36 is provided, we will contact authors for the physical and mental component summary sub-scores. For studies measuring fear avoidance: FABQ (physical activity scale); FABQ (work scale); FABQ (overall score); PCS, TSK; FPQ; rating scales of fear avoidance from a composite measure of fear avoidance; other measurement tools.[50] If only an overall score for the FABQ is provided, we will contact authors for the physical activity and work sub-scores. Authors will be contacted for additional information where necessary.

Data will be classified and assessed at the following time-points: (1) pre-intervention; (2) post-intervention (i.e. timepoint closest to end of treatment); (3) short-term treatment sustainability (≥2 months but <6 months post-intervention); (4) mid-term treatment sustainability (≥6 months but <12 months post-intervention); (5) long-term treatment sustainability (≥12 months post-intervention), and NMA will be performed at each time-point separately.

Network Treatment Nodes

Using the framework proposed by Caldwell et al. (2016),[51] we will use a splitting approach to classify the psychological interventions. A splitting approach was chosen because psychological interventions are typically complex and heterogenous in nature. For example, two separate trials involving cognitive behavioural therapy may focus on utilising different psychological principles or strategies and incorporate different additional co-interventions (e.g. exercise, passive therapies). Failing to adequately account for the variability, as best as possible, may potentially result in inaccurate estimates of treatment effects. In attempts to account for heterogeneity, we will first scrutinise intervention descriptions to classify the psychological interventions into 5 treatment nodes based on 5 key approaches (behavioural, cognitive behavioural, mindfulness-based, counselling-based and pain education). We will also form a separate treatment node using a lumping method to account for combination approaches (e.g. two or more psychological approaches delivered together). Then, we will further differentiate whether additional non-psychological co-interventions are involved, which will be sub-classified as exercise, passive treatments or physiotherapy. If present, the combination of the psychological approach with a non-psychological co-intervention will form a separate treatment node (e.g. cognitive behavioural therapy plus exercise).

The following treatment nodes will be formed for the psychological interventions:

- Behavioural therapies (e.g. relaxation-based interventions, biofeedback, operant conditioning), which we will consider as psychological approaches focused on facilitating the removal of positive reinforcement of pain behaviours and promoting health behaviours, in the absence of cognitive strategies;[17, 18]
- Cognitive behavioural therapies, which we will consider as the combination of behavioural therapies with an additional focus of changing unhelpful cognitions (i.e. thoughts, beliefs and attitudes), and/or promoting emotion regulation and problem-solving.[17]
- Mindfulness-based therapies, which we will consider as psychological approaches focused on practicing techniques such as meditation, non-judgemental attention control and awareness (e.g. mindfulness-based stress reduction, acceptance and commitment therapy);[19, 52]

- Counselling-based therapies, which we will consider as psychological approaches focused on using supportive communication and active listening techniques to facilitate healthy behaviour change (e.g. health coaching, motivational interviewing);[20, 21]
- Pain education, which we will consider as psychological approaches focused on improving understanding and knowledge about pain. These interventions may involve a biomechanical explanation of LBP, but are clearly focused on the reconceptualisation of beliefs about the pain experience;[53]
- Combinations of psychological interventions (e.g. pain education combined with behavioural therapy), which we will consider as the delivery of two or more psychological approaches together, in the absence of a non-psychological co-intervention.

Non-psychological co-interventions will be classified into the following treatment nodes:

- Exercise, which we will define as interventions that formally prescribe a structured exercise program (e.g. consisting of aerobic, strengthening, stretching, stabilisation, motor control exercises) and/or direct instructions to increase physical activity levels;
- Passive treatment, including but not limited to spinal manipulative therapy, massage, and electrotherapies;
- Physiotherapy, which we will define as interventions delivered by a physiotherapist, which may involve a combination of exercise and passive treatments.

Comparison interventions will be classified into the following treatment nodes:

- Exercise, defined above;
- Passive treatment, defined above;
- Physiotherapy, defined above;
- General practitioner care, which we will define as interventions considered as standard care provided by general practitioners;
- Advice, which we will consider as interventions providing general advice that is not psychologically-informed;
- No intervention (e.g. waitlist control, no intervention).

For comparison interventions described as “usual care” by study authors, we will scrutinise the authors’ descriptions of the intervention to classify them into the above treatment nodes.

Figure 1 represents all possible combinations of treatment nodes. Consensus will be sought regarding accurate classification of interventions prior to conducting statistical analyses.

Figure 1. Network plot of all theoretically possible network comparisons

Prior to data analysis, we will consult clinical experts from the review team to establish the appropriateness of further lumping treatment nodes together if there are inadequate number of studies are available for a given treatment node (e.g. less than two studies available). Any post-hoc alternative network geometrics formed using this approach will be clearly identified and justified in the final review.

Risk of bias in the included studies

Two reviewers will independently assess risk of bias in the included studies using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[54, 55] We will use the licensed excel tool to implement the RoB2. We will pilot-test the risk of bias assessment procedure on a small number of articles. Authors will be contacted for additional information where necessary. The RoB 2 assesses five domains: (1) bias arising from the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result. Each domain will be graded as low risk of bias, some concerns, or high risk of bias, and the results will be summarised in a table. For cluster RCTs, we will use the Cochrane cluster RCT variant of the RoB 2 tool, which assesses an additional domain: bias arising from identification or recruitment of individual participants within clusters.[56] An overall risk of bias judgement (low risk of bias, some concerns, or high risk of bias) will be made based on the five (or six) domain-level judgements, as described in Sterne et al. (2019).[54] Generally, the overall risk of bias judgement corresponds to the worst risk of bias in any of the five (or six) domains, however studies with multiple domains graded as 'some concerns' may be judged as high risk of overall bias.[54] Disagreements will be resolved through consensus or a third reviewer.

Data Analysis

Characteristics of the publications, study designs, study populations, interventions and comparators, and outcome measures will be summarised descriptively and presented in a

table. Pair-wise meta-analysis and NMA will be performed in Stata using the metan command (with Knapp–Hartung adjustment applied), and the network package and network graphs package respectively.[57]

Measures of treatment effect

For continuous outcomes that use the same rating scale across all studies, we will use mean differences (MD) and 95% confidence intervals (95% CI). If different rating scales are used for comparable outcomes, all continuous data for the given outcome will be converted to a common standardised 0-100 scale. If data is reported as dichotomous, we will use odds ratios (ORs) and 95% CI.

Dealing with missing outcome data and missing statistics

For continuous outcomes, we will impute missing data by converting standard errors, p-values or CI into standard deviations (SD).[44] If a study only reports the median or interquartile range (IRQ), SD will be calculated by dividing the IRQ by 1.35, and we will consider the median to be equivalent to the mean. If relevant information is provided in figures, we will extract data from the graphs. If data cannot be obtained, we will attempt to contact authors.

Geometry of the network

The network diagram will be used to graphically depict the available evidence. Nodes will be used to represent the different interventions and comparators, and the weight of the edges will be used to visually represent the proportional number of studies comparing two connected nodes within the network.

Pairwise meta-analysis

We will perform traditional pairwise meta-analyses of all direct comparisons for which there are at least two studies available. We will apply the khartung command to adjust for the Hartung-Knapp-Sidik-Jonkman (HKSJ) random-effects method, which has less error rates compared to the DerSimonian and Laird approach in particular across studies with greater heterogeneity and when the number of studies is small.[58] We will use the Q statistic to test for statistical heterogeneity in pairwise comparisons. We will use alpha <0.10 as we anticipate a few studies per comparison. We will calculate Higgins I^2 statistic to indicate the proportion of variability in effect estimates due to heterogeneity and interpret I^2 >50% as

suggesting substantial heterogeneity.[44] Forest plots will be created to graphically depict individual and pooled effect sizes. Narrative analysis will be performed if we are unable to impute missing data or cannot contact authors for data, inadequate number of studies are available for a given comparison (e.g. <2 studies), or there is substantial heterogeneity.

Assessment of transitivity assumption

Transitivity implies the assumption that distribution of clinical and methodological variables that could potentially act as effect modifiers across available treatment comparisons is balanced within a network.[59] Given the lack of conclusive evidence on treatment effect modifiers for LBP[60] or psychological interventions,[12, 61, 62] we will consider the following factors to be potential effect modifiers: age,[60] gender,[63] pain intensity, and fear avoidance.[64] To assess transitivity, we will use Stata to adjust the weight of the edges within the network plot, proportional to the baseline distribution of the pre-specified effect modifier, and visually inspect comparability within the network.[59] If minor intransitivity is suspected (i.e. minor or negligible dissimilarities in the distribution of a given effect modifier across studies based on clinical judgement), we will proceed with the NMA and perform a network meta-regression to explore the influence of the suspected factors on the results. If the distribution of a given effect modifier is clearly dissimilar across studies, we will exclude network nodes. If intransitivity persists, we will consider not proceeding with NMA.

Network meta-analysis

A NMA will be performed using a frequentist approach to simultaneously compare direct and indirect evidence. The heterogeneity parameter is assumed to be the same for each comparison within the network. Mean rank and relative treatment rankings will be estimated for each intervention node according to the surface under the cumulative ranking curve (SUCRA) values. SUCRA is the p-score which is the frequentist analogy to the Bayesian SUCRA.[65]

Assesment of inconsistency

Valid NMA results rely on the assumption of consistency, which describes statistical agreement between all sources of evidence within a network. Global inconsistency of the entire network will be assessed using the design-by-treatment interaction model,[66] which is a goodness-of-fit test. The presence of inconsistency will be inferred based on $p<0.10$. Local inconsistencies will be assessed using the Bucher method[67] by computation of

inconsistency factors and 95% CI for each triangular and quadratic loop in the network. The Bucher method will be implemented in Stata using the ifplot command. If inconsistencies are identified, we will first check for errors in data extraction. Then, we will examine the potential influence of pre-specified effect modifiers within inconsistent loops using network meta-regression models and conduct a sensitivity analysis excluding studies that may be the source of inconsistency (e.g. high risk of bias). Otherwise, we will use a node-splitting method to further explore the origin of the inconsistency.[68] If substantial inconsistency remains and the origin remains unexplained, we will consider not proceeding with NMA.

Sensitivity and sub-group analysis

To examine robustness of results, we will conduct a sensitivity analysis by excluding studies with high risk of bias, provided that the original network structure remains the same. We will also perform the following sub-group analyses depending on available data:

(1) Delivery format of psychological intervention (e.g. face-to-face, telephone-administered, web-based, self-help booklets), the hypothesis is that face-to-face delivery format will result in greater improvements in disability and pain intensity.

(2) Individual versus group-based intervention delivery, the hypothesis is that group-based interventions will result in greater improvements in disability and pain intensity.

(3) Back pain only versus back pain with sciatica (leg pain and nerve root compromise), the hypothesis is that the back pain only group will result in greater improvements in physical function and pain intensity.

Meta-regression will be performed based on: (1) age; (2) percentage of males; (3) sample size; (4) baseline physical function levels; (5) baseline pain levels. Further, subject to the availability of data, we will attempt to perform meta-regressions to explore the effects of intervention parameters relating to dosage and/or frequency (e.g. total length (in weeks) of the intervention, total intended hours of the intervention during the intervention period).

Publication bias

Publication bias in the NMA will be evaluated by visual inspection of comparison-adjusted funnel plots for asymmetry. As described above, meta-regression using sample size and effect estimates will be performed to detected small study effect.[69]

Confidence in cumulative evidence

Judgements of the confidence in cumulative evidence will be evaluated using the Confidence in Network Meta-Analysis (CINeMA) framework,[70] a Cochrane web application of the Grading of Recommendations Assessment, Development, and Evaluation ratings approach. The framework assesses six domains: within-study bias, across-studies bias, indirectness, imprecision, heterogeneity and incoherence.

Patient and public involvement

Patients will not be involved.

CONTRIBUTIONS TO LITERATURE

To date, there is no conclusive consensus regarding the most effective psychological approach for managing chronic non-specific LBP. Previous studies have only investigated a small portion of available psychological interventions and have only conducted multiple independent pairwise meta-analyses which have not been synthesised. As such, clinical guidelines for chronic LBP, which are based on these reviews, remain vague regarding the specific type of psychological intervention which should be incorporated into treatment for the condition. This systematic review with NMA will synthesise direct and indirect evidence for a comprehensive variety of psychological interventions with respect to improving physical function, pain intensity, health-related quality of life, and fear avoidance in people with chronic non-specific LBP. The review will also assess the proportion of compliance to different psychological interventions in this population. The NMA will compare the competing interventions within the network and produce treatment effect estimates. Effect estimates will be used to generate relative treatment rankings, allowing us to rank the different types of psychological approaches for each outcome. Findings from this review will provide pragmatic support for clinical guideline recommendations regarding the use of psychological interventions for adults with chronic non-specific LBP.

ETHICS AND DISSEMINATION

Ethical review will not be required as the systematic review will only involve the use of previously published data for analysis. Our intention is to publish the completed research in a peer-review journal and present our findings at national and international conferences.

CONFLICTS OF INTEREST

There are no conflicts of interest in this study.

AUTHOR CONTRIBUTIONS

All authors conceived the study. EKH drafted the manuscript. EKH, LC and JC participated in the search strategy development. PHF assisted in the initial protocol design, and all authors assisted in the protocol revision. LC provided statistical expertise. CA provided expertise on psychological interventions. All authors read and approved the final manuscript as submitted.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. PHF is funded by an NHMRC Fellowship and a Sydney University SOAR fellowship. MLF is funded by an NHMRC Fellowship and a Sydney University SOAR fellowship. MS is funded by a Sydney University SOAR fellowship. LC is funded by Northern Clinical School Higher Degree Research Support Scholarship. EKH is funded by an Australian Government Research Training Program Scholarship.

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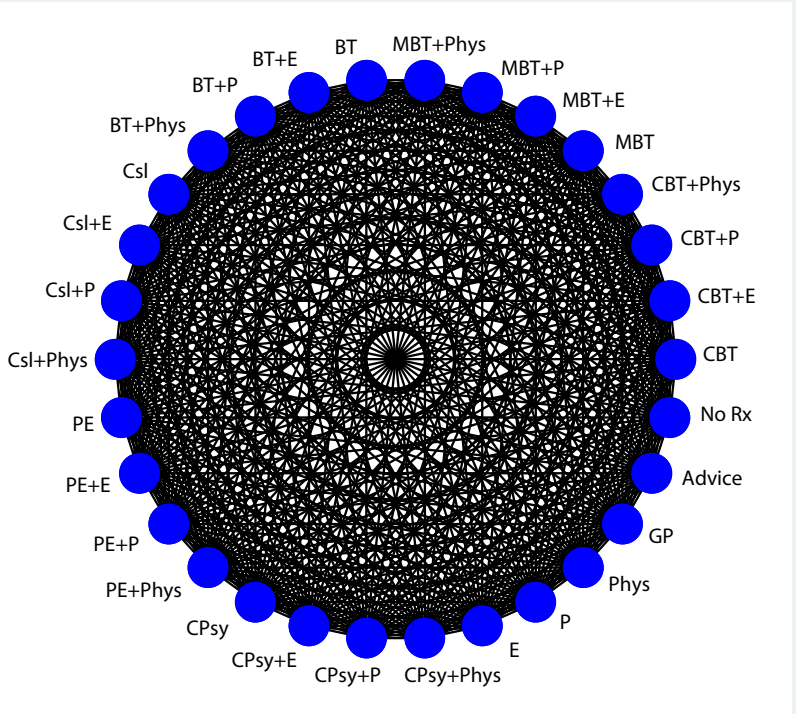


BT: behavioural therapies; CBT: cognitive behavioural therapies; MBT: mindfulness-based therapies; Csl: counselling-based therapies; PE: pain education; CPsy: combination of psychological interventions; E: exercise; P: passive treatment; Phys: physiotherapy; GP: general practioner care, No Rx: no intervention

APPENDIX A

Database: Ovid MEDLINE

1. exp Back Pain/ or exp Low Back Pain/ or exp Backache/
2. (back pain or low back pain or lumbar pain or lumbago or dorsalgia or spinal pain or vertebral pain or backache or lumbar spine).ti,ab.
3. 1 or 2
4. exp Behavior Therapy/ or exp Cognitive Therapy/ or *Conditioning, Operant/ or exp Reinforcement, Psychology/
5. (operant conditioning or reinforcement or psychological intervention or psychological therapy).ab,ti.
6. (cognitiv* adj1 (treatment* or therap* or intervention*)).ab,ti.
7. (behavio?r* adj1 (treatment* or therap* or intervention* or techniqu* or modif* or change*)).ab,ti.
8. (graded exposure or desensiti* or imagery or goal setting).ab,ti.
9. (acceptance and commitment therapy or CBT).ab,ti.
10. 4 or 5 or 6 or 7 or 8 or 9
11. exp Mindfulness/ or *Mind-Body Therapies/ or exp Meditation/ or exp Relaxation/ or exp Relaxation Therapy/
12. (mindfulness based stress reduction*).ab,ti.
13. (mindfulness or mind-body therapies or meditation or relaxation or relaxation therap*).ab,ti.
14. (mbsr* or mbct*).ab,ti.
15. 11 or 12 or 13 or 14
16. (cognitive functional therapy or CFT).ab,ti.
17. exp Health Education/ or exp Health Promotion/ or exp Motivation/
18. (health education or health promotion or motivation).ab,ti.
19. ((health or wellness or life-style or behav*) adj1 coach*).ab,ti.
20. ((wellness or behav*) adj1 intervention*).ab,ti.
21. or/ 17 or 18 or 19 or 20
22. exp Biofeedback, Psychology/ or exp Feedback, Psychological/
23. (electromyograph* or electromyogram* or EMG*).ab,ti.
24. (bio-feedback or feedback).ab,ti.
25. 22 or 23 or 24

26. (pain neuroscience education or pain education or neuroscience education or pain physiology education or neuro-physiology education or therapeutic education).ab,ti.
27. exp Counseling/
28. (counseling or supportive psychotherap*).ab,ti.
29. 27 or 28
30. 10 or 15 or 16 or 21 or 25 or 26 or 29
31. 3 and 30
32. exp Randomized controlled trial/ or *Clinical Trial/ or *Random allocation/ or exp Controlled clinical trial/
33. randomized controlled trial.pt.
34. (random* adj3 trial).ab,ti.
35. (clinical trial or random allocation or controlled clinical trial).ab,ti.
36. 32 or 33 or 34 or 35
37. 31 and 36
38. limit 37 to humans

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

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.*	***4-7***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	***7***
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.	***7***
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).*	***7-9***
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.	***10***
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	***Appendix A***
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable,	***10***

		included in the meta-analysis).	
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.	***10-12***
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	***10-12***
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.	***16***
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.	***15***
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.*	***16-17***
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.*	***16-18***
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.	***17***
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).	***18-19***
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).*	***18***

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.	***N/A – protocol paper***
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***N/A – protocol paper***
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.	***N/A – protocol paper***
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.	***N/A – protocol paper***
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	***N/A – protocol paper***
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.*	***N/A – protocol paper***
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.	***N/A – protocol paper***
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.	***N/A – protocol paper***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	***N/A – protocol paper***
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).	***N/A – protocol paper***
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).	***N/A – protocol paper***

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).*	***N/A – protocol paper***
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	***N/A – protocol paper***
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.	***20***

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.

Box. Terminology: Reviews With Networks of Multiple Treatments

Different terms have been used to identify systematic reviews that incorporate a network of multiple treatment comparisons. A brief overview of common terms follows.

Indirect treatment comparison: Comparison of 2 interventions for which studies against a common comparator, such as placebo or a standard treatment, are available (i.e., indirect information). The direct treatment effects of each intervention against the common comparator (i.e., treatment effects from a comparison of interventions made within a study) may be used to estimate an indirect treatment comparison between the 2 interventions (**Appendix Figure 1, A**). An indirect treatment comparison (ITC) may also involve multiple links. For example, in **Appendix Figure 1, B**, treatments B and D may be compared indirectly on the basis of studies encompassing comparisons of B versus C, A versus C, and A versus D.

Network meta-analysis or *mixed treatment comparison*: These terms, which are often used interchangeably, refer to situations involving the simultaneous comparison of 3 or more interventions. Any network of treatments consisting of strictly unclosed loops can be thought of as a series of ITCs (**Appendix Figure 1, A and B**). In mixed treatment comparisons, both direct and indirect information is available to inform the effect size estimates for at least some of the comparisons; visually, this is shown by closed loops in a network graph (**Appendix Figure 1, C**). Closed loops are not required to be present for every comparison under study. "Network meta-analysis" is an inclusive term that incorporates the scenarios of both indirect and mixed treatment comparisons.

Network geometry evaluation: The description of characteristics of the network of interventions, which may include use of numerical summary statistics. This does not involve quantitative synthesis to compare treatments. This evaluation describes the current evidence available for the competing interventions to identify gaps and potential bias. Network geometry is described further in **Appendix Box 4**.

Appendix Box 1. The Assumption of Transitivity for Network Meta-Analysis

Methods for indirect treatment comparisons and network meta-analysis enable learning about the relative treatment effects of, for example, treatments A and B through use of studies where these interventions are compared against a common therapy, C.

When planning a network meta-analysis, it is important to assess patient and study characteristics across the studies that compare pairs of treatments. These characteristics are commonly referred to as *effect modifiers* and include traits such as average patient age, gender distribution, disease severity, and a wide range of other plausible features.

For network meta-analysis to produce valid results, it is important that the distribution of effect modifiers is similar, for example, across studies of A versus B and A versus C. This balance increases the plausibility of reliable findings from an indirect comparison of B versus C through the common comparator A. When this balance is present, the assumption of transitivity can be judged to hold.

Authors of network meta-analyses should present systematic (and even tabulated) information regarding patient and study characteristics whenever available. This information helps readers to empirically evaluate the validity of the assumption of transitivity by reviewing the distribution of potential effect modifiers across trials.

Appendix Box 2. Differences in Approach to Fitting Network Meta-Analyses

Network meta-analysis can be performed within either a frequentist or a Bayesian framework. Frequentist and Bayesian approaches to statistics differ in their definitions of probability. Thus far, the majority of published network meta-analyses have used a Bayesian approach.

Bayesian analyses return the posterior probability distribution of all the model parameters given the data and prior beliefs (e.g., from external information) about the values of the parameters. They fully encapsulate the uncertainty in the parameter of interest and thus can make direct probability statements about these parameters (e.g., the probability that one intervention is superior to another).

Frequentist analyses calculate the probability that the observed data would have occurred under their sampling distribution for hypothesized values of the parameters. This approach to parameter estimation is more indirect than the Bayesian approach.

Bayesian methods have been criticized for their perceived complexity and the potential for subjectivity to be introduced by choice of a prior distribution that may affect study findings. Others argue that explicit use of a prior distribution makes transparent how individuals can interpret the same data differently. Despite these challenges, Bayesian methods offer considerable flexibility for statistical modeling. In-depth introductions to Bayesian methods and discussion of these and other issues can be found elsewhere.

Appendix Box 3. Network Meta-Analysis and Assessment of Consistency

Network meta-analysis often involves the combination of direct and indirect evidence. In the simplest case, we wish to compare treatments A and B and have 2 sources of information: direct evidence via studies comparing A versus B, and indirect evidence via groups of studies comparing A and B with a common intervention, C. Together, this evidence forms a closed loop, ABC.

Direct and indirect evidence for a comparison of interventions should be combined only when their findings are similar in magnitude and interpretation. For example, for a comparison of mortality rates between A and B, an odds ratio determined from studies of A versus B should be similar to the odds ratio comparing A versus B estimated indirectly based on studies of A versus C and B versus C. This assumption of comparability of direct and indirect evidence is referred to as *consistency* of treatment effects.

When a treatment network contains a closed loop of interventions, it is possible to examine statistically whether there is agreement between the direct and indirect estimates of intervention effect.

Different methods to evaluate potential differences in relative treatment effects estimated by direct and indirect comparisons are grouped as *local approaches* and *global approaches.* Local approaches (e.g., the Bucher method or the node-splitting method) assess the presence of inconsistency for a particular pairwise comparison in the network, whereas global approaches (e.g., inconsistency models, I^2 measure for inconsistency) consider the potential for inconsistency in the network as a whole.

Tests for inconsistency can have limited power to detect a true difference between direct and indirect evidence. When multiple loops are being tested for inconsistency, one or a few may show inconsistency simply by chance. Further discussions of consistency and related concepts are available elsewhere.
Inconsistency in a treatment network can indicate lack of transitivity (see **Appendix Box 1**).

Appendix Box 4. Network Geometry and Considerations for Bias

The term *network geometry* is used to refer to the architecture of the treatment comparisons that have been made for the condition under study. This includes what treatments are involved in the comparisons in a network, in what abundance they are present, the respective numbers of patients randomly assigned to each treatment, and whether particular treatments and comparisons may have been preferred or avoided.

Networks may take on different shapes. Poorly connected networks depend extensively on indirect comparisons. Meta-analyses of such networks may be less reliable than those from networks where most treatments have been compared against each other.

Qualitative description of network geometry should be provided and accompanied by a network graph. Quantitative metrics assessing features of network geometry, such as *diversity* (related to the number of treatments assessed and the balance of evidence among them), *co-occurrence* (related to whether comparisons between certain treatments are more or less common), and *homophily* (related to the extent of comparisons between treatments in the same class versus competing classes), can also be mentioned.

Although common, established steps for reviewing network geometry do not yet exist, however examples of in-depth evaluations have been described related to treatments for tropical diseases and basal cell carcinoma and may be of interest to readers. An example based on 75 trials of treatments for pulmonary arterial hypertension (**Appendix Figure 3**) suggests that head-to-head studies of active therapies may prove useful to further strengthen confidence in interpretation of summary estimates of treatment comparisons.

Appendix Box 5. Probabilities and Rankings in Network Meta-Analysis

Systematic reviews incorporating network meta-analyses can provide information about the hierarchy of competing interventions in terms of treatment rankings.

The term *treatment ranking probabilities* refers to the probabilities estimated for each treatment in a network of achieving a particular placement in an ordering of treatment effects from best to worst. A network of 10 treatments provides a total of 100 ranking probabilities—that is, for each intervention, the chance of being ranked first, second, third, fourth, fifth, and so forth).

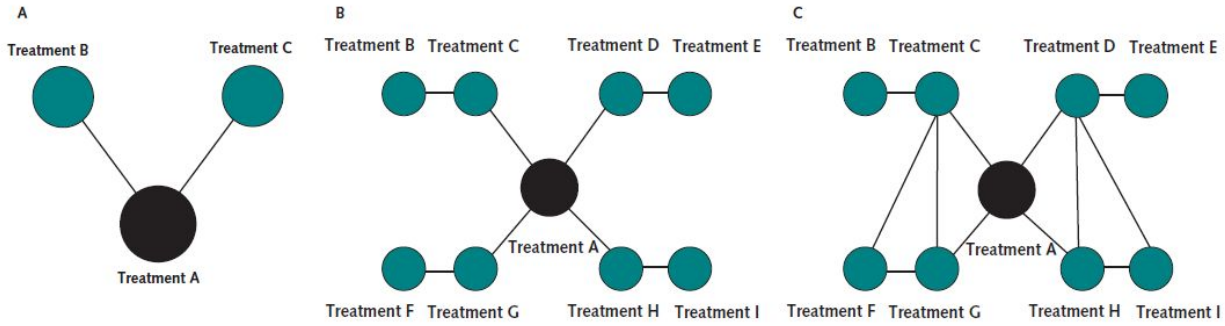
Several techniques are feasible to summarize relative rankings, and include graphical tools as well as different approaches for estimating ranking probabilities. **Appendix Figure 6** shows 2 approaches to presenting such information, on the basis of a comparison of adjuvant interventions for resected pancreatic adenocarcinoma.

Robust reporting of rankings also includes specifying median ranks with uncertainty intervals, cumulative probability curves, and the surface under the cumulative ranking (SUCRA) curve.

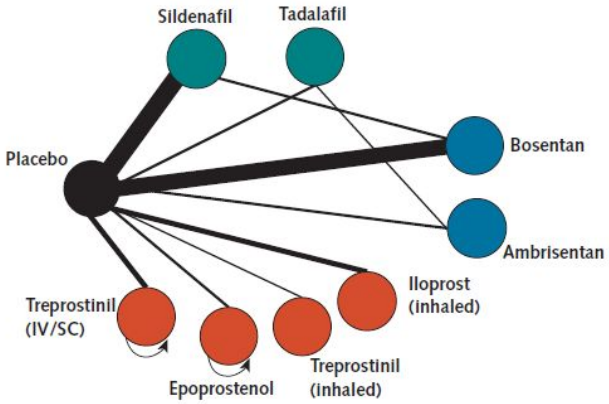
Rankings can be reported along with corresponding estimates of pairwise comparisons between interventions. Rankings should be reported with probability estimates to minimize misinterpretation from focusing too much on the most likely rank.

Rankings may exaggerate small differences in relative effects, especially if they are based on limited information. An objective assessment of the strength of information in the network and the magnitude of absolute benefits should accompany rankings to minimize potential biases.

Appendix Figure 1A-1C

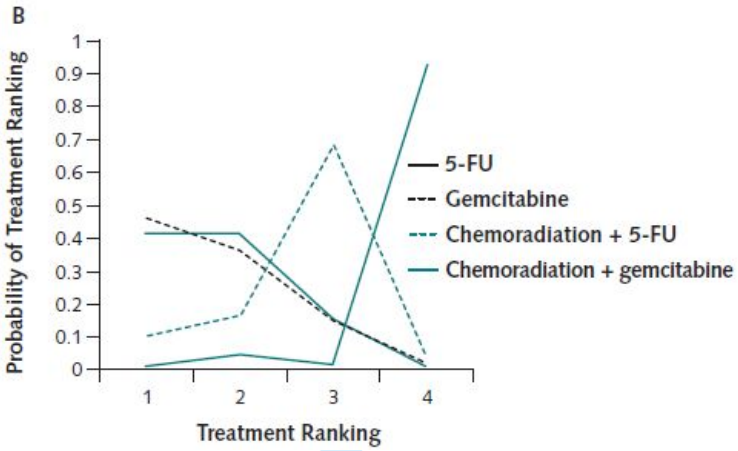


Appendix Figure 3



Appendix Figure 6

Ranking	Treatment and Cooresponding Ranking Probabilities Grade 3 or 4 Hematologic Toxicity			
	5-FU	Gemcitabine	Chemoradiation + 5-FU	Chemoradiation + gemcitabine
1	0.42	0.42	0.15	0.01
2	0.46	0.36	0.15	0.02
3	0.10	0.17	0.68	0.04
4	0.02	0.05	0.02	0.93



PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	20
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Cover letter
Support:			
Sources	5a	Indicate sources of financial or other support for the review	1, 20
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix A
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	15
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	15-16
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	18
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	17
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	18
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	18

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Psychological interventions for chronic non-specific low back pain: protocol of a systematic review with network meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034996.R2
Article Type:	Protocol
Date Submitted by the Author:	12-Jun-2020
Complete List of Authors:	Ho, Emma; The University of Sydney, Faculty of Medicine and Health Ferreira, Manuela; University of Sydney Institute of Bone and Joint Research, Chen, Lingxiao; The University of Sydney Institute of Bone and Joint Research, Simic, Milena; The University of Sydney, Faculty of Medicine and Health Ashton-James, Claire; The University of Sydney, Pain Management Research Institute, Faculty of Medicine and Health Comachio, Josielli ; University of Sao Paulo, Department of Speech, Physical Therapy and Occupational Therapy, School of Medicine Hayden, Jill; Dalhousie University, Community Health & Epidemiology Ferreira, Paulo; University of Sydney, Faculty of Medicine and Health
Primary Subject Heading:	Public health
Secondary Subject Heading:	Mental health
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, PSYCHIATRY

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Psychological interventions for chronic non-specific low back pain: protocol of a systematic review with network meta-analysis.

Emma Kwan-Yee Ho[a], Manuela Loureiro Ferreira[b], Lingxiao Chen[b], Milena Simic[a], Claire Ashton-James[c], Josielli Comachio[d], Jill Alison Hayden[e], Paulo Henrique Ferreira[a]

[a] The University of Sydney, Faculty of Medicine and Health, Sydney, NSW, Australia.

[b] The University of Sydney, Institute of Bone and Joint Research, Northern Clinical School, Faculty of Medicine and Health, Sydney, NSW, Australia.

[c] The University of Sydney, Pain Management Research Institute, Faculty of Medicine and Health, Sydney, NSW, Australia.

[d] Department of Speech, Physical Therapy and Occupational Therapy, School of Medicine, University of Sao Paulo, Sao Paulo, Brazil.

[e] Department of Community Health & Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada.

Address for Correspondence:

Ms. Emma Kwan-Yee Ho, Faculty of Medicine and Health

University of Sydney, PO Box 170 Lidcombe 1825 AUSTRALIA

Tel: +61 434 596 855

E-mail: emma.ho@sydney.edu.au

Word count: 5621

Funding Sources: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of Interest:

None declared.

ABSTRACT

Introduction: Psychological factors such as fear avoidance beliefs, depression, anxiety, catastrophic thinking, and familial and social stress, have been associated with high disability levels in people with chronic low back pain (LBP). Guidelines endorse the integration of psychological interventions in the management of chronic LBP. However, uncertainty surrounds the comparative effectiveness of different psychological approaches. Network meta-analysis (NMA) allows comparison and ranking of numerous competing interventions for a given outcome of interest. Therefore, we will perform a systematic review with a NMA to determine which type of psychological intervention is most effective for adults with chronic non-specific LBP.

Methods and analysis: We will search electronic databases (MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS and CINAHL) from inception until 22 August 2019 for randomised controlled trials comparing psychological interventions to any comparison interventions in adults with chronic non-specific LBP. There will be no restriction on language. The primary outcomes will include physical function and pain intensity, and secondary outcomes will include health-related quality of life, fear avoidance, intervention compliance and safety. Risk of bias will be assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) tool and confidence in the evidence will be assessed using the Confidence in NMA (CINeMA) framework. We will conduct a random-effects NMA using a frequentist approach to estimate relative effects for all comparisons between treatments and rank treatments according to the mean rank and surface under the cumulative ranking curve values. All analyses will be performed in Stata.

Ethics and dissemination: No ethical approval is required. The research will be published in a peer-reviewed journal.

PROSPERO registration number: CRD42019138074

Key Words: back pain, low back pain, musculoskeletal disorders, chronic, psychological, psychiatry, network meta-analysis, systematic review.

Strengths and limitations of this study

- This is the first systematic review using an NMA design to simultaneously compare different types of psychological interventions for improving physical function, pain intensity, health-related quality of life, fear avoidance and intervention compliance, and assess their safety, in people with chronic non-specific LBP.
- The main strength is the NMA design will allow for the comprehensive comparison and ranking of multiple psychological interventions simultaneously, which was not possible with previous systematic reviews that only conducted pair-wise meta-analyses.
- An additional strength is that in comparison to previous pair-wise systematic reviews, the NMA design will allow for the inclusion and synthesis of a larger number of studies investigating a wider range of psychological interventions.
- The main limitation is that we anticipate numerous studies involving different combinations of psychological approaches (e.g. cognitive behavioural therapy plus pain education, counselling-based therapies plus pain education), but small number of eligible studies per combination, hence we will lump combination interventions into one treatment node for practical reasons.

Psychological interventions for chronic non-specific low back pain: protocol of a systematic review with network meta-analysis.

Low back pain (LBP) is one of largest contributors to disability worldwide[1, 2] and is associated with substantial health and economic burden relating to increased health-care utilisation costs, work absenteeism and productivity loss.[3] The challenge associated with treating chronic non-specific LBP lies in the complex multifactorial interaction between genetic, biophysical, psychosocial, health and lifestyle factors which are largely individualistic.[4, 5] Particularly, psychological factors such as fear avoidance beliefs, depression, anxiety, catastrophic thinking, and familial and social stress[4] are often poorly identified and inadequately addressed,[6] and have been shown to alter pain processing pathways, perceptions, and coping responses.[5, 7] The influence of these factors in chronic non-specific LBP have been found to increase the risk of disability,[8, 9] which commonly manifests as reduced functional capacity, avoidance of usual activities including work, and impaired societal and recreational participation.[5, 10]

Psychological interventions in chronic pain conditions aim to reduce pain-related distress and disability by changing negative beliefs, behaviours and attitudes through a combination of principles and strategies informed by psychological theories. Psychological interventions commonly focus on targeting the specific environmental contingencies and maladaptive cognitive and emotional processes underpinning pain in order to promote self-efficacy and increased function.[11, 12] In clinical trials of psychological interventions for chronic LBP, psychological interventions are delivered either in isolation[12, 13] or as part of an integrated treatment program that may involve non-psychological co-interventions such as exercise, passive treatment or physiotherapy.[14-16] For the purposes of this review, we have defined five main categories of psychological interventions relevant to LBP: behavioural therapies, cognitive behavioural therapies, mindfulness-based therapies, counselling-based therapies, and pain education-focused therapies. These categories reflect the three “waves” of how psychological interventions have evolved over time.[17] Behavioural therapies are typically considered “first wave” approaches,[17] and include interventions focused on altering maladaptive behaviours, and dysfunctional sensations or movements.[18] Cognitive behavioural therapies are considered “second wave” approaches,[17] and include interventions that aim to modify harmful cognitions (e.g. thoughts, beliefs) which may proliferate pain and disability.[18] Mindfulness-based therapies, counselling-based therapies and pain education-

focused therapies represent different types of 'third wave" approaches.[17] Unlike behavioural and cognitive behavioural therapies which focus on targeting psychological and emotional symptoms, "third wave" therapies adopt a more holistic approach to promoting health and wellness.[17] Key characteristics and examples of the psychological intervention categories that will be included in our review are summarised below in Table 1.

Table 1. Categories of Psychological Interventions for Low Back Pain

	Category	Characteristics	Examples
First wave	Behavioural therapies	Behavioural therapies focus on the removal of positive reinforcement of pain behaviours and teach patients to overcome stressful situations through relaxation skills.[17]	Biofeedback[17, 18]
Second wave	Cognitive behavioural therapies	Cognitive behavioural therapies aim to restructure negative cognitions (e.g. thoughts, beliefs) and behaviours and promote emotion regulation and problem-solving capacity.[17]	Graded activity[17] Graded exposure[17]
Third wave	Mindfulness-based therapies	Mindfulness-based therapies focus on promoting self-awareness, attention control, and pain acceptance.[13, 19]	Mindfulness-based stress reduction[17, 19] Acceptance and commitment therapy[17]
	Counselling-based therapies	Counselling-based therapies focus on using supportive communication and active listening techniques to build interpersonal clinician-patient relationships.	Health coaching[20, 21] Motivational interviewing[20, 21]
	Pain education-focused therapies	Pain education-focused therapies target a patient's understanding and knowledge of pain to reduce fear associated with LBP. Pain education interventions move away from the traditional biomechanical explanation of pathology and pain, and instead focus on the reconceptualisation of the pain experience.	Pain neuroscience education[22]

Some pain education interventions specifically aim to desensitise the nervous system.

Previous systematic reviews have shown promising evidence that psychological interventions can improve overall functioning, pain experience, depression, cognitive appraisal, health-related quality of life and decreased health care utilisation in people with chronic LBP.[11, 12, 15] Psychological interventions can also reduce fear avoidance beliefs and behaviours (e.g. kinesiophobia),[23] which are associated with increased disability and pain in people with chronic LBP.[24, 25] Based on the evidence and LBP research experts, international clinical guidelines consistently endorse the integration of psychological interventions with exercise in the management of chronic LBP.[26-31]

However, LBP guideline recommendations remain vague regarding the specific types of psychological approaches that clinicians should consider incorporating into treatment.[26-31] This may be due to the fact that previous systematic reviews, which have informed these guidelines, have mainly focused on a small selection of available approaches – namely cognitive behavioural therapy and behavioural approaches such as biofeedback.[11, 12, 15, 18, 32, 33] Emerging psychological interventions such as cognitive functional therapy (a combination of psychological approaches involving cognitive behavioural strategies, pain education and exercise)[5] and acceptance and commitment therapy have been neglected from these reviews, despite recent evidence for their effectiveness in reducing LBP-related disability.[34, 35] Importantly, previous reviews have only conducted multiple independent pairwise meta-analyses, and to our knowledge, no attempts have been made to synthesise the separate results. Ultimately, the comparative effectiveness of the wider collection of psychological interventions available for managing chronic LBP is unknown and clinical guidelines remain unclear. This represents an important gap in the evidence. Subsequently, there is an increased reliance on a clinician's expertise to select the most appropriate psychological approach for people with chronic LBP. Given that clinicians such as physiotherapists report a perceived lack of training and confidence in addressing psychological factors,[36-38] and tend to be biased towards a biomedical approach despite increasing efforts to adopt a biopsychosocial, person-centered approach,[38, 39] the gap in evidence must be addressed. A network meta-analysis (NMA) design will allow us to determine the comparative effectiveness of psychological interventions for managing chronic LBP, whilst addressing the limitations identified from previous reviews.

A NMA is an extension of a traditional pairwise meta-analysis and involves the synthesis of direct and indirect evidence to simultaneously compare numerous competing interventions within a single, coherent treatment network.[40] Direct evidence refers to data obtained from studies directly comparing competing interventions in head-to-head trials. Direct evidence can be used to indirectly estimate the effect of interventions that have not been previously compared in head-to-head trials but have been compared to a common comparator (indirect evidence). Integrating direct and indirect evidence increases the precision of treatment effect estimates, provided that the assumptions of transitivity (balanced distribution of potential effect modifiers across all comparisons within a network)[41-43] and consistency (statistical agreement between direct and indirect evidence for each comparison)[43, 44] are satisfied. Treatment effect estimates are used to generate relative treatment rankings to rank all the competing interventions for a particular outcome measure. As such, the current research aims to perform a NMA to investigate the comparative effectiveness and safety of psychological interventions for chronic LBP and determine which specific type is most effective for improving physical function, pain intensity, health-related quality of life, fear avoidance and intervention compliance in chronic non-specific LBP.

METHODS AND ANALYSIS

Study design

This protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews[45] and the PRISMA extension for developing review protocols (PRISMA-P)[46] and for NMA (PRISMA-NMA).[47] The systematic review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42019138074.

Eligibility criteria

Types of studies

We will include published parallel and cluster randomised controlled trials (RCT). We will also include the first phase of cross-over RCTs. There will be no restriction on length of follow-up. Observational studies, non-randomised trials, short reports, research letters, conferences abstracts, or studies that have not been published as full-length articles in peer-reviewed scientific journals will be excluded. In accordance with the Cochrane handbook,[48] we will only include data from cluster RCTs which account for the cluster design (e.g. data analysed at

the level of allocation). If cluster-level data is not reported for a given cluster RCT study, we will attempt to use the approximate approaches described in the Cochrane handbook to adjust the results,[48] otherwise the study will be excluded.

Types of participants

Eligible studies will include adults experiencing chronic non-specific LBP, with or without the presence of leg pain. Chronic non-specific LBP will be defined according to NICE UK guidelines as pain in the back between the bottom of the rib cage and buttocks crease with no known pathoanatomical cause, for greater than 12 weeks in duration.[26, 49] Studies including participants with serious pathologies (e.g. spinal stenosis, malignancy, trauma, vertebral fracture, infection, inflammatory disorders) will be excluded. We will include studies involving a combination of acute, sub-acute or chronic LBP populations, provided that >50% of participants have chronic LBP and the results are reported separately for chronic LBP populations. We will also include studies of chronic LBP participants combined with other chronic pain conditions, provided that >50% of participants have a single diagnosis of chronic LBP and the results are reported separately for chronic LBP populations. If it is unclear, study eligibility will be determined by consensus amongst reviewers.

Types of interventions

We will include studies of psychological interventions. Expanding on the definition provided by Hoffman et al. (2007),[12] we will consider an intervention as "psychological" if it is conceived by the authors of the study as a psychological intervention, or if it is clearly based on any of the following approaches: cognitive behavioural therapeutic strategies [relaxation, graded exposure (desensitisation), imagery (distraction), goal setting, operant conditioning], mindfulness-based stress reduction, acceptance and commitment therapy, cognitive functional therapy, health-coaching, biofeedback (delivered with a therapeutic intent to promote muscle relaxation), pain education, and counselling directly employing principles of psychological theory. Interventions such as cognitive behavioural therapeutic strategies and biofeedback were purposely included based on their inclusion across a variety of previous relevant systematic reviews.[12, 15, 17, 18] Additional approaches such as cognitive functional therapy, health coaching, and acceptance and commitment therapy were included as they have been neglected in previous reviews. If our search identifies other psychological interventions which are not explicitly listed above but meet our definition for a psychological intervention, we will

consider including them in our review. Disagreements regarding their eligibility for inclusion will be resolved by consensus.

We will include studies of combination therapies, defined as interventions that contain two or more psychological approaches delivered together, with or without additional non-psychological co-interventions. There will be no restriction on the non-psychological co-interventions or comparison interventions identified by our search strategy.

Types of outcome measures

The primary outcomes of interest are physical function and pain intensity:

1. Physical function, defined as lower back specific physical function, measured at the end of treatment. Physical function is commonly measured by continuous, self-report scales (e.g. Oswestry Disability Index (ODI), Roland Morris Disability Questionnaire (RMDQ), Core Outcome Measures Index (COMI), Quebec Back Pain Disability Index (QBPDI)) or rating scales within a composite measure (e.g. 12-Item or 36-Item Short Form (SF-12, SF-36)). We will not exclude studies that use other measurement tools.
2. Pain intensity, measured at the time point closest to the end of treatment. Pain intensity is commonly measured by continuous, self-report scales (e.g. Numeric Rating Scale (NRS), Visual Analogue Scale (VAS)) or a rating scale within a composite rating scale (e.g. McGill Pain Questionnaire). We will not exclude studies that use other measurement tools.

Secondary outcomes of interest include:

1. Health-related quality of life, measured at the end of treatment. It is commonly measured by the SF-12, SF-36, EuroQol five-dimension (EQ-5D), Nottingham Health Profile (NHP) and 10-Item Patient-Reported Outcomes Measurement Information System Global Health Short Form (PROMIS-GH-10). We will not exclude studies that use other measurement tools.
2. Fear avoidance, defined as fear of pain and consequent avoidance of movement, measured at the end of treatment. Fear avoidance is commonly measured by the Fear-Avoidance Beliefs Questionnaire (FABQ), Pain Catastrophizing Scale (PCS), Tampa Scale for Kinesiophobia (TSK) and Fear of Pain Questionnaire (FPQ). We will not exclude studies that use other measurement tools.

3. Intervention compliance, measured as the proportion of participants who complete their assigned intervention (psychological or comparison) during the intervention period.
4. Safety, defined as the proportion of participants who experience at least one adverse effect during the intervention period. Adverse effects will be broadly defined as any 'adverse event,' 'side effect,' 'complication,' or event resulting in discontinuation of treatment, associated with the intervention (psychological or comparison) under investigation.

Study selection

Electronic searches

The following databases will be searched for eligible studies via OVID from inception until 22 August 2019: MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS and CINAHL. Search concepts will include language and keywords for: randomised controlled trial, low back pain, and terms relating to psychological interventions, according to the eligibility criteria defined earlier in the protocol. A full MEDLINE search strategy can be found in Appendix A of this protocol. There will be no restriction on language.

Additional search strategies

We will search reference lists and perform citation tracking of included studies and relevant systematic reviews[11, 12, 15, 17, 18, 32, 33] and clinical guidelines[26-28] to identify additional eligible studies.

Identification and selection of studies

Citations identified by our search strategy will be managed using Endnote X9[50] and screened using Covidence.[51] Eligibility screening will be conducted independently by two reviewers in two independent stages: (i) citation titles and abstracts; (ii) full text. Disagreements will be resolved by consensus or a third reviewer. A PRISMA flow-diagram will be presented to map the number of records included and excluded during the study selection process, with reasons for exclusions reported.

Data extraction

Two reviewers will independently extract data from the included studies using a pre-designed Microsoft Excel data extraction form. We will pilot-test the form on a small number of articles. Disagreements will be resolved by consensus or a third reviewer.

Publication characteristics

We will extract data on the following publication characteristics: first author, publication year, journal, funding, location.

Study design characteristics

We will extract data related to the study design, including number of participants randomised and durations of follow-up.

Participant characteristics

We will extract data on the individual study sample, including age, male/female, body mass index, baseline pain intensity, socioeconomic status and comorbidities.

Interventions and Comparators

We will extract data on the interventions of interest and any comparation interventions. We will extract the key components of the psychological intervention (e.g. details of the specific psychological principles or approaches used, qualifications of the personnel delivering the intervention, co-interventions involved) and comparison intervention. We will extract all available data on intervention dosage and frequency, and intervention duration including duration of any washout.

Outcomes

We will extract the definitions provided for our primary and secondary outcomes of interest. We will also extract the type and dimensions of the measurement tools used to assess our primary and secondary outcomes of interest.

Results

For intervention compliance, we will extract the number of participants randomised to each intervention group (psychological or comparison), as well as the number of participants who complete their assigned intervention (i.e. provide data at the time-point closest to the end of treatment). If this data is not available, we will extract the number of participants in each group

who discontinued treatment for any reason (i.e. all-cause discontinuation) within the intervention period, to calculate the number of participants who completed their assigned intervention. We will express this data as a proportion of the total number of participants randomised to each group respectively. For studies comparing a psychological intervention to a non-intervention comparison (i.e. waitlist control, no intervention), we will assume that the intervention compliance for the non-intervention comparison is 100%.

For safety, we will extract all available data on adverse effects, broadly encompassing adverse and serious adverse events, side effects, complications, and all-cause discontinuation. We will extract authors' definitions and reasons for any adverse effects. We will also extract all available data, including authors' definitions, on alternative measures of safety reported in the included studies. We will extract the number of participants who experience at least one adverse effect related to the psychological or comparison intervention under investigation and express this as a proportion of the total number of participants randomised to each group respectively. We will also extract data on adherence if reported.

For all other outcome measures, we will preference extracting the mean baseline and outcome scores (at the time point closest to end of treatment) for each group, and the accompanying measures of variance or statistics to impute these values. Otherwise, we will extract the change in outcome from baseline and the accompanying measures of variance for each group. If neither are available, we will extract between-group differences in scores and the accompanying measures of variance. For the following outcomes, we will extract all available data in the order which the measurement tools are listed, in accordance with the proposed hierarchy for analysis. If a given outcome is measured by several measurement tools not explicitly listed, the hierarchy for analysis will be decided by consensus from the reviewers.

For studies measuring physical function: ODI; RMDQ; COMI; QBPQI; rating scale for disability from a composite measure of physical function (e.g. SF-12, SF-36); other measurement tools.[52, 53] For studies measuring pain intensity: NRS; 100mm VAS; 10cm VAS; rating scale for pain intensity from a composite measure of pain intensity; other measurement tools.[52, 53] We will extract data on pain intensity at the time point closest to randomisation and end of treatment, in the order of average pain intensity (preferred); worst pain intensity, alternative measures of pain intensity. If several alternative measures of pain intensity are reported, we will calculate an average score. For studies measuring health-related

quality of life: PROMIS-GH-10; EQ-5D; SF-36 or SF-12 (physical component summary sub-score); SF-36 or SF-12 (mental component summary sub-score); SF-36 (overall score); NHP;[52, 53] rating scale from a composite measure of health-related quality of life; other measurement tools. If only an overall score for the SF-36 is provided, we will contact authors for the physical and mental component summary sub-scores. For studies measuring fear avoidance: FABQ (physical activity scale); FABQ (work scale); FABQ (overall score); PCS, TSK; FPQ; rating scales of fear avoidance from a composite measure of fear avoidance; other measurement tools.[54] If only an overall score for the FABQ is provided, we will contact authors for the physical activity and work sub-scores. Authors will be contacted for additional information where necessary.

Data will be classified and assessed at the following time-points: (1) pre-intervention; (2) post-intervention (i.e. timepoint closest to end of treatment); (3) short-term treatment sustainability (⩾2 months but <6 months post-intervention); (4) mid-term treatment sustainability (⩾6 months but <12 months post-intervention); (5) long-term treatment sustainability (⩾12 months post-intervention), and NMA will be performed at each time-point separately.

Network Treatment Nodes

Using the framework proposed by Caldwell et al. (2016),[55] we will use a splitting approach to classify the psychological interventions. A splitting approach was chosen because psychological interventions are typically complex and heterogeneous in nature. For example, two separate trials involving cognitive behavioural therapy may focus on utilising different psychological principles or strategies and incorporate different additional co-interventions (e.g. exercise, passive therapies). Failing to adequately account for the variability, as best as possible, may potentially result in inaccurate estimates of treatment effects. In attempts to account for heterogeneity, we will first scrutinise intervention descriptions to classify the psychological interventions into 5 treatment nodes based on 5 key approaches (behavioural, cognitive behavioural, mindfulness-based, counselling-based and pain education). We will also form a separate treatment node using a lumping method to account for combination approaches (e.g. two or more psychological approaches delivered together). Then, we will further differentiate whether additional non-psychological co-interventions are involved, which will be sub-classified as exercise, passive treatments or physiotherapy. If present, the combination of

the psychological approach with a non-psychological co-intervention will form a separate treatment node (e.g. cognitive behavioural therapy plus exercise).

The following treatment nodes will be formed for the psychological interventions:

- Behavioural therapies (e.g. relaxation-based interventions, biofeedback, operant conditioning), which we will consider as psychological approaches focused on facilitating the removal of positive reinforcement of pain behaviours and promoting health behaviours, in the absence of cognitive strategies;[17, 18]
- Cognitive behavioural therapies, which we will consider as the combination of behavioural therapies with an additional focus of changing unhelpful cognitions (i.e. thoughts, beliefs and attitudes), and/or promoting emotion regulation and problem-solving;[17]
- Mindfulness-based therapies, which we will consider as psychological approaches focused on practicing techniques such as meditation, non-judgemental attention control and awareness (e.g. mindfulness-based stress reduction, acceptance and commitment therapy);[19, 56]
- Counselling-based therapies, which we will consider as psychological approaches focused on using supportive communication and active listening techniques to facilitate healthy behaviour change (e.g. health coaching, motivational interviewing);[20, 21]
- Pain education, which we will consider as psychological approaches focused on improving understanding and knowledge about pain. These interventions may involve a biomechanical explanation of LBP, but are clearly focused on the reconceptualisation of beliefs about the pain experience;[57]
- Combinations of psychological interventions (e.g. pain education combined with behavioural therapy), which we will consider as the delivery of two or more psychological approaches together, in the absence of a non-psychological co-intervention.

Non-psychological co-interventions will be classified into the following treatment nodes:

- Exercise, which we will define as interventions that formally prescribe a structured exercise program (e.g. consisting of aerobic, strengthening, stretching, stabilisation, motor control exercises) and/or direct instructions to increase physical activity levels;

- Passive treatment, including but not limited to spinal manipulative therapy, massage, and electrotherapies;
- Physiotherapy, which we will define as interventions delivered by a physiotherapist, which may involve a combination of exercise and passive treatments.

Comparison interventions will be classified into the following treatment nodes:

- Exercise, defined above;
- Passive treatment, defined above;
- Physiotherapy, defined above;
- General practitioner care, which we will define as interventions considered as standard care provided by general practitioners;
- Advice, which we will consider as interventions providing general advice that is not psychologically-informed;
- No intervention (e.g. waitlist control, no intervention).

For comparison interventions described as "usual care" by study authors, we will scrutinise the authors' descriptions of the intervention to classify them into the above treatment nodes.

Figure 1 represents all possible combinations of treatment nodes. Consensus will be sought regarding accurate classification of interventions prior to conducting statistical analyses.

Figure 1. Network plot of all theoretically possible network comparisons

Prior to data analysis, we will consult clinical experts from the review team to establish the appropriateness of further lumping treatment nodes together if there are inadequate number of studies are available for a given treatment node (e.g. less than two studies available). Any post-hoc alternative network geometrics formed using this approach will be clearly identified and justified in the final review. A decision set and supplementary set will be formulated for the final review.

Risk of bias in the included studies

Two reviewers will independently assess risk of bias in the included studies using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[58, 59] We will use the licensed Microsoft Excel tool to implement the RoB2. We will pilot-test the risk of bias assessment

procedure on a small number of articles. Authors will be contacted for additional information where necessary. The RoB 2 assesses five domains: (1) bias arising from the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result. Each domain will be graded as low risk of bias, some concerns, or high risk of bias, and the results will be summarised in a table. For cluster RCTs, we will use the Cochrane cluster RCT variant of the RoB 2 tool, which assesses an additional domain: bias arising from identification or recruitment of individual participants within clusters.[60] An overall risk of bias judgement (low risk of bias, some concerns, or high risk of bias) will be made based on the five (or six) domain-level judgements, as described in Sterne et al. (2019).[58] Generally, the overall risk of bias judgement corresponds to the worst risk of bias in any of the five (or six) domains, however studies with multiple domains graded as 'some concerns' may be judged as high risk of overall bias.[58] Disagreements will be resolved through consensus or a third reviewer.

Data Analysis

Characteristics of the publications, study designs, study populations, interventions and comparators, and outcome measures will be summarised descriptively and presented in a table. Pair-wise meta-analysis and NMA will be performed in Stata[61] using the metan command (with Knapp–Hartung adjustment applied), and the network package[62-64] and network graphs package[65, 66] respectively.

Measures of treatment effect

For continuous outcomes that use the same rating scale across all studies, we will use mean differences (MD) and 95% confidence intervals (95% CI). If different rating scales are used for comparable outcomes, all continuous data for the given outcome will be converted to a common standardised 0-100 scale. If data is reported as dichotomous, we will use odds ratios (ORs) and 95% CI.

Dealing with missing outcome data and missing statistics

For continuous outcomes, we will impute missing data by converting standard errors, p-values or CI into standard deviations (SD).[48] If a study only reports the median or interquartile range (IRQ), SD will be calculated by dividing the IRQ by 1.35, and we will consider the

median to be equivalent to the mean. If relevant information is provided in figures, we will extract data from the graphs. If data cannot be obtained, we will attempt to contact authors.

Geometry of the network

The network diagram will be used to graphically depict the available evidence. Nodes will be used to represent the different interventions and comparators, and the weight of the edges will be used to visually represent the proportional number of studies comparing two connected nodes within the network.

Pairwise meta-analysis

We will perform traditional pairwise meta-analyses of all direct comparisons for which there are at least two studies available. We will apply the khartung command to adjust for the Hartung-Knapp-Sidik-Jonkman (HKSJ) random-effects method, which has less error rates compared to the DerSimonian and Laird approach in particular across comparisons with greater heterogeneity and when the number of studies is small.[67] We will assume the heterogeneity variance for each pairwise comparison is different. We will use the Q statistic to test for statistical heterogeneity in pairwise comparisons. We will use alpha <0.10 as we anticipate a few studies per comparison. We will calculate Higgins I^2 statistic to indicate the proportion of variability in effect estimates due to heterogeneity and interpret I^2 >50% as suggesting substantial heterogeneity.[48] Forest plots will be created to graphically depict individual and pooled effect sizes. Narrative analysis will be performed if we are unable to impute missing data or cannot contact authors for data, inadequate number of studies are available for a given comparison (e.g. <2 studies), or there is substantial heterogeneity.

Assessment of transitivity assumption

Transitivity implies the assumption that distribution of clinical and methodological variables that could potentially act as effect modifiers across available treatment comparisons is balanced within a network.[41-43, 68] Given the lack of conclusive evidence on treatment effect modifiers for LBP[69] or psychological interventions,[12, 70, 71] we will consider the following factors to be potential effect modifiers: age,[69] gender,[72] sample size,[73] baseline physical function, baseline pain intensity, baseline fear avoidance,[74] sciatica (leg pain with nerve root compromise). We anticipate that we will have difficulty assessing the distribution of effect modifiers, due to insufficient reporting the potential effect modifiers within individual studies and few studies available per pairwise comparison to make reasonable

judgments.[75] To assess transitivity, we will use Stata to adjust the weight of the edges within the network plot, proportional to the baseline distribution of the pre-specified effect modifier, and visually inspect comparability within the network.[68] If minor intransitivity is suspected (i.e. minor or negligible dissimilarities in the distribution of a given effect modifier across comparisons based on clinical judgement), we will proceed with the NMA and perform network meta-regressions or sub-group analyses (or both) to explore the influence of suspected factors on the results. If the distribution of a given effect modifier is clearly dissimilar across comparisons, we will exclude network nodes. If intransitivity persists, we will consider not proceeding with NMA.

Network meta-analysis

A NMA will be performed using a frequentist approach to simultaneously compare direct and indirect evidence. We will assume the heterogeneity variance across different comparisons within the NMA model will be the same.[76] We will use heterogeneity variances from the NMA model as an index of global network heterogeneity. Mean rank and relative treatment rankings will be estimated for each intervention node according to the surface under the cumulative ranking curve (SUCRA) values.

Assesment of inconsistency

Valid NMA results rely on the assumption of consistency, which describes statistical agreement between direct and indirect evidence for each comparison within a network.[43, 44] Global inconsistency of the entire network will be assessed using the design-by-treatment interaction model,[77] which is a goodness-of-fit test. The presence of inconsistency will be inferred based on $p<0.10$. Local inconsistencies within closed loops will be assessed with the loop specific approach (Bucher method),[78] and by fitting side-splitting models.[62] The loop specific approach (Bucher method) will be implemented in Stata using the ifplot command. We will infer the presence of local inconsistencies using a threshold of $p<0.10$ for either approach. If inconsistencies are identified, we will first check for errors in data extraction. Then, we will examine the potential influence of the pre-specified effect modifiers within inconsistent loops using network meta-regression models or sub-group analyses, and conduct sensitivity analyses excluding studies that may be the source of inconsistency (e.g. high risk of bias, studies measuring physical function using the SF-12 or SF-36). If substantial inconsistency remains and the origin remains unexplained, we will consider not proceeding with NMA.

Sensitivity and sub-group analysis

To examine robustness of results, we will conduct a sensitivity analysis by excluding studies with high risk of bias, provided that the original network structure remains the same. We will also perform a sensitivity analysis by excluding studies measuring physical function using the SF-12 or SF-36, which may be a potential source of heterogeneity, provided that sufficient data for physical function is available and the original network structure remains the same. We will also perform network meta-regressions or sub-group analyses on the following covariates, if sufficient data is available: age, gender, sample size, baseline physical function levels, baseline pain levels, baseline fear avoidance, sciatica (leg pain with nerve root compromise). We will assume that for each network meta-regression model, the regression co-efficient for each covariate will be the same across all comparisons in the network. We specify the following assumptions about the direction of effect for each covariate:

- Age (continuous): Increasing magnitudes of the covariate reduces the differences in effect sizes between the intervention and comparator (compared to trials in which the covariate is less).
- Gender (continuous): Gender will be summarised as the proportion (percentage) of males. Increasing magnitudes of the covariate reduces the differences in effect sizes between the intervention and comparator (compared to trials in which the covariate is less).
- Sample size (continuous): Increasing magnitudes of the covariate reduces the differences in effect sizes between the intervention and comparator (compared to trials in which the covariate is less).
- Baseline physical function (continuous): Increasing magnitudes of the covariate increases the differences in effect sizes between the intervention and comparator (compared to trials in which the covariate is less).
- Baseline pain intensity (continuous): Increasing magnitudes of the covariate reduces the differences in effect sizes between the intervention and comparator (compared to trials in which the covariate is less).
- Baseline fear avoidance (continuous): Increasing magnitudes of the covariate reduces the differences in effect sizes between the intervention and comparator (compared to trials in which the covariate is less).
- Sciatica (leg pain with nerve root compromise)(continuous): Presence of sciatica will be summarised as the proportion (percentage) of participants reporting sciatica at baseline.

Increasing magnitudes of the covariate reduces the differences in effect sizes between the intervention and comparator (compared to trials in which the covariate is less).

Further, subject to the availability of data, we will attempt to perform meta-regressions to explore the effects of intervention parameters relating to dosage and/or frequency (e.g. total length (in weeks) of the intervention, total intended hours of the intervention during the intervention period). We make the following assumption about the direction of effect for intervention dosage and/or frequency (continuous): Increasing magnitudes of the covariate increases the differences in effect sizes between the intervention and comparator (compared to trials in which the covariate is less).

We will also perform the following sub-group analyses, provided that sufficient data is available and the original network structure remains the same:
(1) Delivery format of psychological intervention (e.g. face-to-face, telephone-administered, web-based, self-help booklets), the hypothesis is that face-to-face delivery format will result in greater improvements in disability and pain intensity.
(2) Individual versus group-based intervention delivery, the hypothesis is that group-based interventions will result in greater improvements in disability and pain intensity.

Publication bias

Publication bias in the NMA will be evaluated by visual inspection of comparison-adjusted funnel plots for asymmetry. As described above, meta-regression using sample size and effect estimates will be performed to detected small study effect.[79]

Confidence in cumulative evidence

Judgements of the confidence in cumulative evidence will be evaluated using the Confidence in Network Meta-Analysis (CINeMA) framework,[80-82] a web application of the Grading of Recommendations Assessment, Development, and Evaluation ratings approach. The framework assesses six domains: within-study bias, across-studies bias, indirectness, imprecision, heterogeneity and incoherence.

Patient and public involvement

Patients will not be involved.

CONTRIBUTIONS TO LITERATURE

To date, there is no conclusive consensus regarding the most effective psychological approach for managing chronic non-specific LBP. Previous studies have only investigated a small portion of available psychological interventions and have only conducted multiple independent pairwise meta-analyses which have not been synthesised. As such, clinical guidelines for chronic LBP, which are based on these reviews, remain vague regarding the specific type of psychological intervention which should be incorporated into treatment for the condition. This systematic review with NMA will synthesise direct and indirect evidence for a comprehensive variety of psychological interventions with respect to improving physical function, pain intensity, health-related quality of life, and fear avoidance in people with chronic non-specific LBP. The review will also assess the proportion of compliance to different psychological interventions in this population, as well as the safety of such interventions. The NMA will compare the competing interventions within the network and produce treatment effect estimates. Effect estimates will be used to generate relative treatment rankings, allowing us to rank the different types of psychological approaches for each outcome. Findings from this review will provide pragmatic support for clinical guideline recommendations regarding the use of psychological interventions for adults with chronic non-specific LBP.

ETHICS AND DISSEMINATION

Ethical review will not be required as the systematic review will only involve the use of previously published data for analysis. Our intention is to publish the completed research in a peer-review journal and present our findings at national and international conferences.

CONFLICTS OF INTEREST

There are no conflicts of interest in this study.

AUTHOR CONTRIBUTIONS

All authors (EKH, MLF, LC, MS, CAJ, JC, JAH, PHF) conceived the study. EKH drafted the manuscript. EKH, LC and JC participated in the search strategy development. PHF assisted in the initial protocol design, and all authors (EKH, MLF, LC, MS, CAJ, JC, JAH, PHF) assisted in the protocol revision. LC provided statistical expertise. CA provided expertise on psychological interventions. All authors (EKH, MLF, LC, MS, CAJ, JC, JAH, PHF) read and approved the final manuscript as submitted.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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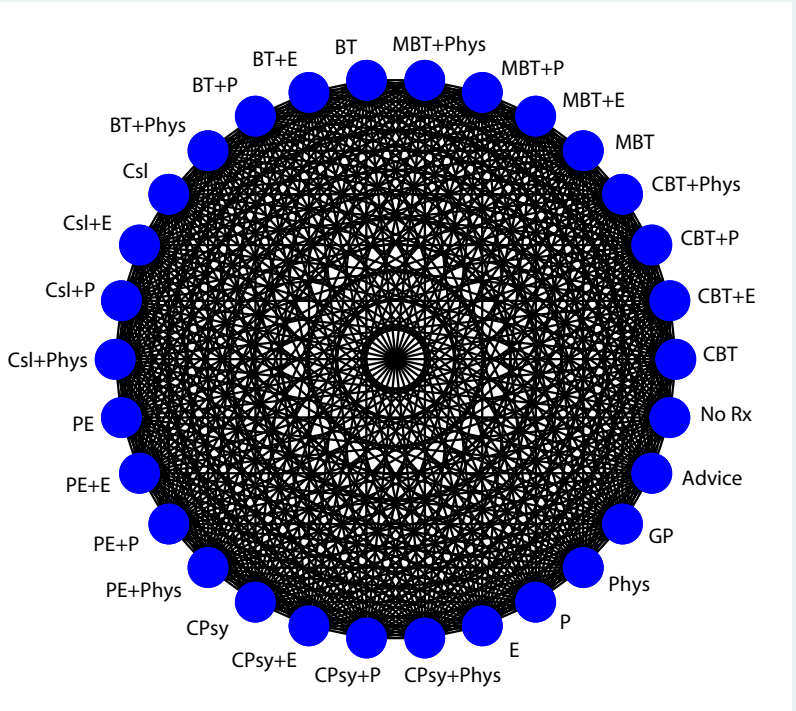


BT: behavioural therapies; CBT: cognitive behavioural therapies; MBT: mindfulness-based therapies; Csl: counselling-based therapies; PE: pain education; CPsy: combination of psychological interventions; E: exercise; P: passive treatment; Phys: physiotherapy; GP: general practioner care, No Rx: no intervention

APPENDIX A

Database: Ovid MEDLINE

1. exp Back Pain/ or exp Low Back Pain/ or exp Backache/
2. (back pain or low back pain or lumbar pain or lumbago or dorsalgia or spinal pain or vertebral pain or backache or lumbar spine).ti,ab.
3. 1 or 2
4. exp Behavior Therapy/ or exp Cognitive Therapy/ or *Conditioning, Operant/ or exp Reinforcement, Psychology/
5. (operant conditioning or reinforcement or psychological intervention or psychological therapy).ab,ti.
6. (cognitiv* adj1 (treatment* or therap* or intervention*)).ab,ti.
7. (behavio?r* adj1 (treatment* or therap* or intervention* or techniqu* or modif* or change*)).ab,ti.
8. (graded exposure or desensiti* or imagery or goal setting).ab,ti.
9. (acceptance and commitment therapy or CBT).ab,ti.
10. 4 or 5 or 6 or 7 or 8 or 9
11. exp Mindfulness/ or *Mind-Body Therapies/ or exp Meditation/ or exp Relaxation/ or exp Relaxation Therapy/
12. (mindfulness based stress reduction*).ab,ti.
13. (mindfulness or mind-body therapies or meditation or relaxation or relaxation therap*).ab,ti.
14. (mbsr* or mbct*).ab,ti.
15. 11 or 12 or 13 or 14
16. (cognitive functional therapy or CFT).ab,ti.
17. exp Health Education/ or exp Health Promotion/ or exp Motivation/
18. (health education or health promotion or motivation).ab,ti.
19. ((health or wellness or life-style or behav*) adj1 coach*).ab,ti.
20. ((wellness or behav*) adj1 intervention*).ab,ti.
21. or/ 17 or 18 or 19 or 20
22. exp Biofeedback, Psychology/ or exp Feedback, Psychological/
23. (electromyograph* or electromyogram* or EMG*).ab,ti.
24. (bio-feedback or feedback).ab,ti.
25. 22 or 23 or 24

26. (pain neuroscience education or pain education or neuroscience education or pain physiology education or neuro-physiology education or therapeutic education).ab,ti.
27. exp Counseling/
28. (counseling or supportive psychotherap*).ab,ti.
29. 27 or 28
30. 10 or 15 or 16 or 21 or 25 or 26 or 29
31. 3 and 30
32. exp Randomized controlled trial/ or *Clinical Trial/ or *Random allocation/ or exp Controlled clinical trial/
33. randomized controlled trial.pt.
34. (random* adj3 trial).ab,ti.
35. (clinical trial or random allocation or controlled clinical trial).ab,ti.
36. 32 or 33 or 34 or 35
37. 31 and 36
38. limit 37 to humans

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	20
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Cover letter and Letter of reply to editor
Support:			
Sources	5a	Indicate sources of financial or other support for the review	1, 20
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix A
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11-13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	15-16
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	16-19
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	16-19
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	16-19
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	20
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	20

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

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.*	***4-7***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	*7*
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.	*7*
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).*	***7-10***
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.	***10***
Search	8	Present full electronic search strategy for at least one	***Appendix***

		database, including any limits used, such that it could be repeated.	***A***
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).	***10***
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.	***11-13***
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	***11-13***
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.	***17***
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.	***15-16***
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.*	***16-18***
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.*	***16-18***
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.	***18***
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).	***20***
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).*	***17-20***

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.	***N/A – protocol paper***
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***N/A – protocol paper***
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.	***N/A – protocol paper***
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.	***N/A – protocol paper***
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	***N/A – protocol paper***
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.*	***N/A – protocol paper***
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.	***N/A – protocol paper***
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.	***N/A – protocol paper***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	***N/A – protocol paper***
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).	***N/A – protocol paper***
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-	***N/A – protocol paper***

		makers).	
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).*	***N/A – protocol paper***
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	***N/A – protocol paper***
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.	***22***

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.

Box. Terminology: Reviews With Networks of Multiple Treatments

Different terms have been used to identify systematic reviews that incorporate a network of multiple treatment comparisons. A brief overview of common terms follows.

Indirect treatment comparison: Comparison of 2 interventions for which studies against a common comparator, such as placebo or a standard treatment, are available (i.e., indirect information). The direct treatment effects of each intervention against the common comparator (i.e., treatment effects from a comparison of interventions made within a study) may be used to estimate an indirect treatment comparison between the 2 interventions (**Appendix Figure 1, A**). An indirect treatment comparison (ITC) may also involve multiple links. For example, in **Appendix Figure 1, B**, treatments B and D may be compared indirectly on the basis of studies encompassing comparisons of B versus C, A versus C, and A versus D.

Network meta-analysis or *mixed treatment comparison*: These terms, which are often used interchangeably, refer to situations involving the simultaneous comparison of 3 or more interventions. Any network of treatments consisting of strictly unclosed loops can be thought of as a series of ITCs (**Appendix Figure 1, A and B**). In mixed treatment comparisons, both direct and indirect information is available to inform the effect size estimates for at least some of the comparisons; visually, this is shown by closed loops in a network graph (**Appendix Figure 1, C**). Closed loops are not required to be present for every comparison under study. "Network meta-analysis" is an inclusive term that incorporates the scenarios of both indirect and mixed treatment comparisons.

Network geometry evaluation: The description of characteristics of the network of interventions, which may include use of numerical summary statistics. This does not involve quantitative synthesis to compare treatments. This evaluation describes the current evidence available for the competing interventions to identify gaps and potential bias. Network geometry is described further in **Appendix Box 4**.

Appendix Box 1. The Assumption of Transitivity for Network Meta-Analysis

Methods for indirect treatment comparisons and network meta-analysis enable learning about the relative treatment effects of, for example, treatments A and B through use of studies where these interventions are compared against a common therapy, C.

When planning a network meta-analysis, it is important to assess patient and study characteristics across the studies that compare pairs of treatments. These characteristics are commonly referred to as *effect modifiers* and include traits such as average patient age, gender distribution, disease severity, and a wide range of other plausible features.

For network meta-analysis to produce valid results, it is important that the distribution of effect modifiers is similar, for example, across studies of A versus B and A versus C. This balance increases the plausibility of reliable findings from an indirect comparison of B versus C through the common comparator A. When this balance is present, the assumption of transitivity can be judged to hold.

Authors of network meta-analyses should present systematic (and even tabulated) information regarding patient and study characteristics whenever available. This information helps readers to empirically evaluate the validity of the assumption of transitivity by reviewing the distribution of potential effect modifiers across trials.

Appendix Box 2. Differences in Approach to Fitting Network Meta-Analyses

Network meta-analysis can be performed within either a frequentist or a Bayesian framework. Frequentist and Bayesian approaches to statistics differ in their definitions of probability. Thus far, the majority of published network meta-analyses have used a Bayesian approach.

Bayesian analyses return the posterior probability distribution of all the model parameters given the data and prior beliefs (e.g., from external information) about the values of the parameters. They fully encapsulate the uncertainty in the parameter of interest and thus can make direct probability statements about these parameters (e.g., the probability that one intervention is superior to another).

Frequentist analyses calculate the probability that the observed data would have occurred under their sampling distribution for hypothesized values of the parameters. This approach to parameter estimation is more indirect than the Bayesian approach.

Bayesian methods have been criticized for their perceived complexity and the potential for subjectivity to be introduced by choice of a prior distribution that may affect study findings. Others argue that explicit use of a prior distribution makes transparent how individuals can interpret the same data differently. Despite these challenges, Bayesian methods offer considerable flexibility for statistical modeling. In-depth introductions to Bayesian methods and discussion of these and other issues can be found elsewhere.

Appendix Box 3. Network Meta-Analysis and Assessment of Consistency

Network meta-analysis often involves the combination of direct and indirect evidence. In the simplest case, we wish to compare treatments A and B and have 2 sources of information: direct evidence via studies comparing A versus B, and indirect evidence via groups of studies comparing A and B with a common intervention, C. Together, this evidence forms a closed loop, ABC.

Direct and indirect evidence for a comparison of interventions should be combined only when their findings are similar in magnitude and interpretation. For example, for a comparison of mortality rates between A and B, an odds ratio determined from studies of A versus B should be similar to the odds ratio comparing A versus B estimated indirectly based on studies of A versus C and B versus C. This assumption of comparability of direct and indirect evidence is referred to as *consistency* of treatment effects.

When a treatment network contains a closed loop of interventions, it is possible to examine statistically whether there is agreement between the direct and indirect estimates of intervention effect.

Different methods to evaluate potential differences in relative treatment effects estimated by direct and indirect comparisons are grouped as *local approaches* and *global approaches.* Local approaches (e.g., the Bucher method or the node-splitting method) assess the presence of inconsistency for a particular pairwise comparison in the network, whereas global approaches (e.g., inconsistency models, I^2 measure for inconsistency) consider the potential for inconsistency in the network as a whole.

Tests for inconsistency can have limited power to detect a true difference between direct and indirect evidence. When multiple loops are being tested for inconsistency, one or a few may show inconsistency simply by chance. Further discussions of consistency and related concepts are available elsewhere.
Inconsistency in a treatment network can indicate lack of transitivity (see **Appendix Box 1**).

Appendix Box 4. Network Geometry and Considerations for Bias

The term *network geometry* is used to refer to the architecture of the treatment comparisons that have been made for the condition under study. This includes what treatments are involved in the comparisons in a network, in what abundance they are present, the respective numbers of patients randomly assigned to each treatment, and whether particular treatments and comparisons may have been preferred or avoided.

Networks may take on different shapes. Poorly connected networks depend extensively on indirect comparisons. Meta-analyses of such networks may be less reliable than those from networks where most treatments have been compared against each other.

Qualitative description of network geometry should be provided and accompanied by a network graph. Quantitative metrics assessing features of network geometry, such as *diversity* (related to the number of treatments assessed and the balance of evidence among them), *co-occurrence* (related to whether comparisons between certain treatments are more or less common), and *homophily* (related to the extent of comparisons between treatments in the same class versus competing classes), can also be mentioned.

Although common, established steps for reviewing network geometry do not yet exist, however examples of in-depth evaluations have been described related to treatments for tropical diseases and basal cell carcinoma and may be of interest to readers. An example based on 75 trials of treatments for pulmonary arterial hypertension (**Appendix Figure 3**) suggests that head-to-head studies of active therapies may prove useful to further strengthen confidence in interpretation of summary estimates of treatment comparisons.

Appendix Box 5. Probabilities and Rankings in Network Meta-Analysis

Systematic reviews incorporating network meta-analyses can provide information about the hierarchy of competing interventions in terms of treatment rankings.

The term *treatment ranking probabilities* refers to the probabilities estimated for each treatment in a network of achieving a particular placement in an ordering of treatment effects from best to worst. A network of 10 treatments provides a total of 100 ranking probabilities—that is, for each intervention, the chance of being ranked first, second, third, fourth, fifth, and so forth).

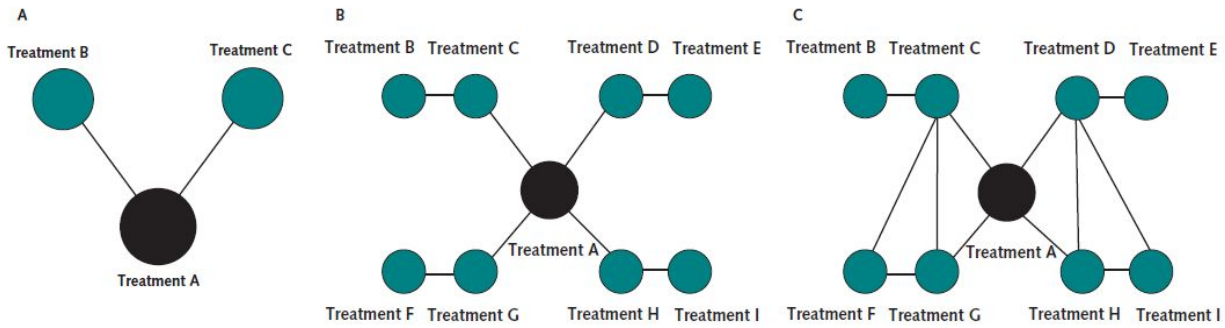
Several techniques are feasible to summarize relative rankings, and include graphical tools as well as different approaches for estimating ranking probabilities. **Appendix Figure 6** shows 2 approaches to presenting such information, on the basis of a comparison of adjuvant interventions for resected pancreatic adenocarcinoma.

Robust reporting of rankings also includes specifying median ranks with uncertainty intervals, cumulative probability curves, and the surface under the cumulative ranking (SUCRA) curve.

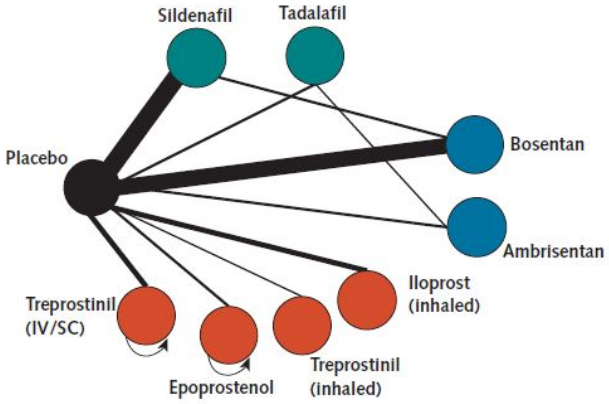
Rankings can be reported along with corresponding estimates of pairwise comparisons between interventions. Rankings should be reported with probability estimates to minimize misinterpretation from focusing too much on the most likely rank.

Rankings may exaggerate small differences in relative effects, especially if they are based on limited information. An objective assessment of the strength of information in the network and the magnitude of absolute benefits should accompany rankings to minimize potential biases.

Appendix Figure 1A-1C



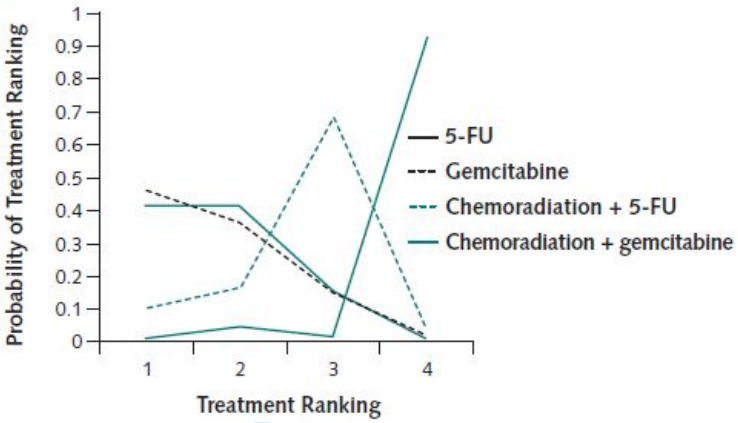
Appendix Figure 3



Appendix Figure 6

Ranking	Treatment and Cooresponding Ranking Probabilities Grade 3 or 4 Hematologic Toxicity			
	5-FU	Gemcitabine	Chemoradiation + 5-FU	Chemoradiation + gemcitabine
1	0.42	0.42	0.15	0.01
2	0.46	0.36	0.15	0.02
3	0.10	0.17	0.68	0.04
4	0.02	0.05	0.02	0.93

B



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
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.	7-10
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.	10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
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).	10
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.	11-13
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11-13
Risk of bias in 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.	15-16
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	16-18
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	16-18

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
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).	20
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	17-20
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.	N/A – protocol paper
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.	N/A – protocol paper
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A – protocol paper
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A – protocol paper
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A – protocol paper
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A – protocol paper
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A – protocol paper
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).	N/A – protocol paper
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).	N/A – protocol paper
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	N/A – protocol paper

PRISMA 2009 Checklist

FUNDING			
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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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