BMJ Open

Relative effectiveness of different forms of exercises for treatment of chronic low back pain: protocol for a systematic review incorporating Bayesian network meta-analysis

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To cite: Gao C, Chen G, Yang H, *et al*. Relative effectiveness of different forms of exercises for treatment of chronic low back pain: protocol for a systematic review incorporating Bayesian network meta-analysis. *BMJ Open* 2019;**9**:e025971. doi:10.1136/bmjopen-2018-025971

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-025971).

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Received 10 August 2018
Revised 7 January 2019
Accepted 14 February 2019

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ABSTRACT

Introduction Exercise is considered as an effective intervention in the management of patients with chronic low back pain (cLBP). However, the relative effectiveness as well as the hierarchy of exercise interventions have not been well established, although various exercise options are available. Therefore, the present protocol proposes to conduct a network meta-analysis (NMA) aiming to evaluate the effectiveness of different forms of exercise for treatment of cLBP.

Methods and analysis Medline, Embase, PsycINFO, the Cumulative Index to Nursing and Allied Health Literature, the Cochrane Central Register of Controlled Trials, and the Physiotherapy Evidence Database will be searched to identify all randomised controlled trials that evaluate the effectiveness of exercise in the treatment of cLBP. There will be no restrictions on date or language. Two authors will screen the literature and extract data independently based on predesigned rules, and evaluate the risk of bias of included studies using the Cochrane Risk of Bias Tool. Disagreements will be resolved through discussion or consultation with a senior reviewer. The primary outcomes of this study will be pain relief and improvement in function or disability for all interventions. Traditional pairwise meta-analysis and Bayesian NMA will be conducted to compare the effectiveness of different exercise interventions. The ranking probabilities for all interventions will be estimated and the hierarchy of each intervention will be summarised as surface under the cumulative ranking curve. The quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation instrument.

Ethics and dissemination Ethical approval and informed consent are not required since this is a protocol for a meta-analysis with no confidential personal data to be collected. The results of this NMA will be submitted to a peer-reviewed journal for publication.

PROSPERO registration number CRD42018090576.

Strengths and limitations of this study

- This will be the first systematic review to use network meta-analysis to investigate the relative effectiveness as well as the hierarchy of exercise interventions in the management of patients with chronic low back pain.
- This network meta-analysis will integrate direct evidence with indirect evidence from multiple treatment comparisons to estimate the interrelations across all treatments.
- The strengths of this review are its comprehensive search strategy, restriction of studies to randomised controlled trials, duplicate assessment of data abstraction and risk of bias, and use of the Grading of Recommendations Assessment, Development and Evaluation instrument to evaluate the quality of evidence.
- The findings of this study will provide practitioners and policymakers with tailored evidence to guide their decision-making.
- Heterogeneity may exist among the included studies due to the diversity in clinical or methodological characteristics, which may be a possible limitation.

INTRODUCTION

Rationale

Low back pain is an extremely common public health problem and the leading cause of disability worldwide, creating a large economic and societal burden.[1 2] It has been estimated that up to 70% of adults suffer from low back pain during their lifetime.[3] Between 30% and 40% of individuals with acute low back pain will never achieve full recovery and can develop into chronic low back pain (cLBP).[4]

The mechanism of pain is poorly understood in the majority of patients with cLBP; therefore, the notion of non-specific cLBP is often used to describe this population. It has been postulated that non-specific cLBP has a multifactorial pathogenesis with individual characteristics, psychosocial factors and social factors involved in its development.[5] For this

reason, a variety of interventions have been established and applied in clinical practice for treating cLBP, such as medication, acupuncture, spinal manipulation, psychological therapy as well as various physiotherapies.[6–10] In all of these, exercise is considered as an effective intervention to relieve pain intensity and to improve the functional status of patients with cLBP.[10 11] This is reflected in a recent clinical practice guideline from the American College of Physicians, which strongly recommends exercise therapy as an intervention for cLBP.[12]

The forms of exercise are complex and varied with exercise component, duration, intensity as well as treatment setting. The common exercise interventions for cLBP can be categorised as one of the following: aerobic exercise, strengthening/resistance exercise, flexibility exercise as well as aquatic exercise. Although each form of exercise has a different emphasis, all of them can reduce pain or improve function or disability of patients with cLBP, and were therefore recommended in recent guidelines.[13 14] In addition to the above, other forms of exercise, such as motor control exercise, yoga, pilates as well as taiji, have also been proposed to improving symptoms and functions of patients with cLBP.[15–18] Consequently, a growing number of exercise options are being advocated.

However, there are no recent systematic reviews which can provide clinicians with information regarding which forms of exercise interventions yield the largest treatment effect, as traditional pairwise meta-analyses cannot provide comparisons of multiple interventions in a cohesive analysis. Network meta-analysis (NMA) allows for simultaneous consideration of the relative effectiveness of all available treatment alternatives, by pooling evidence from direct and indirect comparisons of multiple treatments.[19] Moreover, both indirect and direct evidence can be used together in NMA, which can acquire a higher degree of precision in the estimation of effectiveness of different exercises compared with pairwise meta-analyses. This protocol describes the methodology for a systematic review and NMA that will determine the comparative effectiveness of different forms of exercise interventions for relieving pain and improving function or disability in patients with cLBP and provide supporting evidence for policymakers and practitioners who may desire to know which exercise intervention is the best and for whom.

Objective

The objective of this study is to conduct a systematic review incorporating Bayesian NMA to compare the effectiveness of different exercise interventions in the management of cLBP, and investigate which form of exercise is best to relieve pain or improve function or disability of these patients.

METHODS AND ANALYSIS

The reported items will be in accordance with the guidelines from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[20] A completed PRISMA-P checklist can be found in online supplementary file 1. This protocol has been registered on the International Prospective Register of Systematic Reviews (PROSPERO). Any modification to this protocol will be described in the final review.

Eligibility criteria

Eligibility criteria will be designed according to the PICOS (Participant-Intervention-Comparator-Outcome-Study design) framework.

Participants

All participants should meet the diagnostic criteria for cLBP.[21] Studies that enrolled participants with cLBP caused by specific conditions or pathologies, such as infection, neoplasm, rheumatoid arthritis or other inflammatory articular conditions and so on, will be excluded.

Interventions

According to the 2008 Physical Activity Guidelines for Americans, exercise intervention is defined as a planned, structured and repetitive activity that results in bodily movement and energy expenditure by activation of skeletal muscles.[22] Any therapeutic exercise intervention, regardless of exercise form, duration, frequency, intensity or treatment setting, will be eligible for inclusion. Studies with manipulation, mobilisation or other passive movement exercises, as well as any combination of interventions, will be excluded. Table 1 shows the classification and description of exercise interventions which will be included in the current study.

Comparators

Other forms of exercise interventions, control conditions including general exercise (defined as exercise traditionally used by physiotherapists for the management of cLBP, such as general trunk stretching exercises) or no exercise control (defined as participants who did not participate in any form of organised exercise or physical activities, except their activities of daily living, such as self-care book, wait-list control) will be included.

Outcomes

The types of outcomes may include, but will not be limited to, the following: (1) pain evaluated with Numeric Rating Scale, Visual Analogue Scale, McGill Pain Questionnaire or any other instrument; and (2) function or disability evaluated with the Roland-Morris Disability Questionnaire, Quebec Back Pain Disability, Oswestry Disability Questionnaire or any other instrument.

Study design

Only randomised controlled trials will be included. Studies will be excluded if the experimental group and control group performed identical exercise interventions.

Database and search strategy

Eligible studies will be identified through a systematic search of Medline, Embase, PsycINFO, the Cumulative

Table 1 Classification and description of exercise interventions

Exercise interventions	Description
Aerobic exercise	Exercise that involves repetitive movement of large muscle groups to improve cardiorespiratory endurance, usually performed at moderate to vigorous intensity for prolonged periods of time.[40]
Strengthening/resistance exercise	Exercise that uses the external resistance load (eg, body weight, resistance bands) to improve the ability of skeletal muscles to exert force.[41]
Flexibility exercise	Exercise that intends to increase the range of lumbar motion for patients with chronic low back pain, which usually includes three movements: lumbar flexion, lumbar extension and spinal rotation. The first two focus on an increase of lumbar movement in physiological directions (flexion and extension), while spinal rotation is an accessory movement and aims to help increase movement in the flexed direction.[42]
Aquatic exercise	Aquatic exercise, also called hydrotherapy or aquatic physiotherapy, is a broad range of approaches and therapeutic methods completed in water or a hydrotherapy pool. The aim of aquatic exercise is to decrease pain, increase range of movement and flexibility, as well as develop muscle strength and general fitness.[43]
Motor control exercise	Exercise that applies a motor learning approach to retrain the optimal control and coordination of the spine. The intervention involves the training of preactivation of the deep trunk muscles, with progression towards more complex static, dynamic and functional tasks integrating the activation of deep and global trunk muscles.[44]
Taiji	Taiji is a low-impact, moderate-intensity physical exercise characterised by slow circular movements, breath regulation, and concentration or mindfulness. It is a set of mindful movements with a primary purpose of relaxation.[45]
Pilates	Exercise which is designed with the intent to improve posture and control of movement via neuromuscular control techniques believed to improve lumbar spine stability through targeting the local stabiliser muscles of the lumbar-pelvic region or 'core muscles'.[46]
Yoga	Exercise that consists of a complex system of moral, spiritual and physical practices with the aim of attaining 'self-awareness'. These basic themes run through modern Western yoga with a focus on postures, muscle stretching, breathing exercises and meditation.[47]

Index to Nursing and Allied Health Literature, the Cochrane Central Register of Controlled Trials, and the Physiotherapy Evidence Database with no language and date restrictions. An experienced specialist in medical information will help to design search strategies for each database. The search strategy will be conducted using Medical Subject Headings (MeSH)/Emtree headings, combined with free text words. The following MeSH/Emtree/free-text terms will be included: 'randomized controlled trial', 'low back pain', 'physical therapy' and 'exercise therapy'. The preliminary search strategies for Medline and Embase are presented in online supplementary file 2. The search strategies for other databases will be adapted accordingly. The reference lists of included studies and relevant review articles or meta-analyses will be hand-searched to identify all potential eligible studies.

Study selection

Literature search records will be imported into EndNote software (V.X7.7, Thomson Reuters, USA) for management. Study selection will be performed in two stages. After removing the duplicate records, two authors will screen the titles and abstracts independently to remove irrelevant studies according to eligibility criteria. Studies passing through this initial screening stage will then be subject to full-text examination. The two authors will independently confirm the eligibility of these potentially relevant articles after reviewing the full texts. The level of agreement between the two authors on both initial screening and full-text examination will be assessed using Cohen's kappa (κ) statistic.[23] Disagreements between two authors will be resolved through consensus or adjudication by a third author. Exclusion reasons for ineligible studies will be documented and reported. The study selection process will be documented in a PRISMA-compliant flow diagram.[24]

Data extraction

The following information will be extracted by two independent authors using a pilot-tested data extraction form implemented in Microsoft Excel 2013 (Microsoft, Redmond, Washington, USA): study characteristics, including first author, publication year, study design, sample size, follow-up intervals and dropout rate; participant characteristics, including age, gender, race and other relevant baseline data; characteristics of intervention and comparator, including intervention description, duration, intensity and frequency; and outcome data of interest, including baseline and postintervention data, scales or questionnaires used to evaluate outcomes, and follow-up information. Any disagreement will be resolved through discussion or consultation with a senior author. Inter-rater agreement will be evaluated with Cohen's κ statistic.[23]

The primary outcomes of this study are pain relief and improvement in function or disability for all interventions.

Exercise interventions are usually considered to be the most effective during the application period. Therefore, data at the first time point after the end of the intervention will be used to calculate the effect sizes for pain and function or disability. Change values from baseline will be extracted when change values and SD of the changes are available. In case change values cannot be obtained or calculated, the mean values and SDs postintervention will be extracted. If SDs are missing and cannot be obtained from the authors, other available statistics will be adopted to estimate the SDs, such as SE, IQR, p values or CI, based on the approaches recorded in the Cochrane Handbook for Systematic Reviews of Interventions.[25] For multiarm studies, data from any arm that meets the inclusion criteria will be extracted. Multiarm studies will be treated as multiple independent two-arm studies in pairwise meta-analyses. In the NMA, the correlations between effect sizes induced by multiarm studies will be accounted for using a multivariate approach.[19]

Assessment of risk of bias

The Cochrane Risk of Bias Tool for randomised controlled trials will be applied to assess the quality of included studies.[26] Assessments will be performed by two authors independently, and disagreements will be recorded and resolved through consensus or adjudication by a senior a. The following aspects will be assessed: allocation sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias. Each aspect will be categorised as 'low risk of bias', 'high risk of bias' or 'unclear risk of bias'. After that, studies will be classified according to the following categories: studies with 'low risk of bias' in all of the above aspects will be considered as 'studies with low risk of bias', and studies with 'uncertain risk of bias' or 'high risk of bias' in one or more of the above aspects will be considered as 'studies with high risk of bias'. Results from these appraisals will be considered as criteria for the subsequent meta-regression and subgroup analysis.

Statistical analysis

Because pain and function or disability are generally assessed with different scales or questionnaires, standardised mean difference (SMD) will be used as a measure of effect size. The SMD is calculated as the difference in means between two groups, divided by the pooled SD of the measurements. For the purpose of this study, the effect size will be categorised as the following: small=SMD ranging from 0 to 0.2; moderate=SMD ranging from 0.2 to 0.5; and large=SMD ranging from 0.5 to 0.8.[27]

Prior to conducting NMA, a traditional pairwise meta-analysis will be performed. The degree of heterogeneity of each pairwise meta-analysis will be quantified by the I^2 statistic. An I^2 ≤50% indicates there is negligible statistical heterogeneity, and the fixed-effects model (Mantel-Haenszel method) will be employed for meta-analysis.[28] While an I^2 >50% will be considered to represent significant heterogeneity, the random-effects model (DerSimonian and Laird method) will be used for pooling the results.[29] The source of heterogeneity will be explored using meta-regression and sensitivity analyses.

A Bayesian framework using the Markov chains Monte Carlo method will be conducted to compare the relative effectiveness of different exercise interventions simultaneously.[30] The selection between fixed-effects and random-effects models will be based on the deviance information criterion (DIC) of each model. The model with the lower DIC will be selected (with difference >5 indicating a significant difference in fit).[31] As previous knowledge about exercise efficacy on cLBP is inconclusive, a non-informative prior will be used in Bayesian analysis. Posterior distributions of the model parameters will be used to present the results of the NMA. Four Markov chains will be run simultaneously with different arbitrarily chosen initial values. The first 5000 simulations will be discarded, and the posterior summaries will be based on 50 000 simulations. Convergence of the simulation will be checked with the Gelman-Rubin-Brooks method.[32] Model fitness will be assessed by comparing the posterior mean of the residual deviance with the number of unconstrained data points.[13] The inconsistency between the direct and indirect evidence will be assessed locally by using the node-splitting method[13] and globally by running the design-by-treatment interaction model.[33]

Geometry of the network will be drawn to present the structure of comparisons across studies to ensure the feasibility of the NMA. Studies will be excluded if they are not connected by interventions. Nodes in network geometry will represent different forms of exercises, and the lines between nodes will indicate the direct comparisons between different exercises. The size of nodes and the thickness of the lines will be determined by the sample size of the interventions and the numbers of included studies, respectively. Qualitative description of network geometry will be provided by evaluating the diversity (number of treatments and how often they are tested) and co-occurrence (whether particular treatments and comparisons are preferred or avoided) of the treatment network.[34]

The probability of each intervention being the best for each outcome will be calculated and reported in the form of rankograms.[35] The hierarchy of interventions will be presented as surface under the cumulative ranking curve (SUCRA), which can be interpreted as the percentage of an intervention that can be ranked first without uncertainty (with higher values indicating better efficacy).[36]

To evaluate the impact of covariates on the result of NMA, meta-regression analysis will be conducted.[37] Potential effect moderators could be (but will not be limited to) the mean age of participants, gender distribution, baseline pain intensity, study duration and risk of bias. If a significant moderator is found, further subgroup analyses will then be conducted to assess the effect of this moderator.

If sufficient studies are available, sensitivity analyses will be explored by excluding studies with imputed data from the analyses to assess the robustness of the pooled results.

To explore the presence of publication bias in each NMA, comparison-adjusted funnel plots will be drawn, if the number of studies analysed is more than 10.[35]

The pairwise meta-analyses will be conducted with Stata software (V.14.1 Stata/SE). The Bayesian meta-analyses will be performed using JAGS V.4.2.0, through the '*gemtc*' package in R software (V.3.4.0). The 'Network Graphs' package will also be used to produce some of the figures, such as the geometry (network) plots, rankograms, SUCRA plots and comparison-adjusted funnel plots.[38] If there are insufficient data for synthesis, the findings of this review will be reported in a narrative form.

Assessment of quality of evidence

Two authors will independently assess the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation instrument for NMA.[39] The overall strength of evidence for each outcome will be rated as very low, low, moderate and high quality. If agreement cannot be reached, the third author will be consulted.

DISCUSSION

Validity of the assumptions

The assumption of transitivity is the principle for NMA. In the case that transitivity is violated, the validity of indirect and mixed treatment effect estimates is compromised.[19] The distribution of clinical and methodological variables that could act as effect modifiers across treatment comparisons will be evaluated to assure the similarity between the included studies is sufficiently comparable to allow for reliable data synthesis. Consistency is the extension of transitivity across a closed 'loop of evidence', where both direct and indirect evidence are available for a given treatment comparison. To check the assumption of consistency in the entire work, local and global assessments will be applied. Heterogeneity is likely to exist among the included studies due to the diversity in clinical or methodological characteristics, which may limit the interpretation of the results. To address this potential limitation, meta-regression analyses and sensitivity analyses will be conducted to identify the sources of heterogeneity. Studies with sufficient homogeneity will be grouped together to synthesise a more precise estimate effect.

Network geometry and considerations for bias

The geometry of a network can provide the wider clinical context of the evidence, which can help to identify gaps of evidence in the treatment network, while the network structure may be shaped by various preference biases other than rational choices for treatment comparators. These biases may have important implications for the strength of interpretation of the evidence.[34] Evaluation of network geometry will be performed in this study to seek out such biases.

Probabilities and rankings

One strength of NMA is that it can provide ranking information about all evaluated interventions for studied outcomes. However, it should avoid ranking treatments solely on the basis of the probability for each treatment of being the best, because the probability of being the best does not account for the uncertainty in the relative treatment effects and can spuriously give higher ranks to treatment for which sparse data are available.[36] To minimise potential biases, ranking information will be reported accompanied with effect sizes of pairwise comparison (such as means and 95% credible intervals) in this study.

Bayesian method

Thus far, quite a few published NMAs have applied a Bayesian method, which offered more flexibility for statistical modelling than traditional methods. However, Bayesian method has been criticised for its subjectivity introduced by the choice of a prior distribution. Different prior distributions can be used which can generate different results, and therefore a sensitivity analysis is always required. There are also practical difficulties in the implementation of Bayesian methodology due to its mathematical complexity. Further work is needed to resolve this difficulty, particularly when computing large hierarchical models with extremely large number of parameters.

In conclusion, although various exercises have been shown to be effective in cLBP, there is a lack of comparison between different forms of exercises. The results of this study will provide evidence on the relative effectiveness of different forms of exercise in cLBP, and on which patient subgroup responds better to what form of exercise. These findings will provide practitioners and policymakers with tailored evidence to guide their decision-making.

Patient and public involvement

As the current study is a systematic review based on published data, patients and the public are not involved in the study design, recruitment and conduct. The results will be disseminated through open-access publication and websites to the patients with cLBP.

Ethics and dissemination

Ethical approval and informed consent are not required since this is a protocol for a meta-analysis with no confidential personal data to be collected. The results of this NMA will be submitted to a peer-reviewed journal for publication.

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Contributors CG and GC conceived the study design. The first version of the protocol was drafted by CG, GC and HY, and was revised by CH, MW, PX and ZH. The search strategy was developed by CG and GC and will be performed by HY. CG, GC, HY, ZH and PX will screen references for study selection and collect data from the included studies. CG and GC will perform the data synthesis and analysis. All authors drafted and critically reviewed this manuscript and approved the final version.

Funding This work is supported by the National Natural Science Foundation of China (Grant Number 8157223) and the Chengdu Municipal Bureau of Science and Technology (Grant Number 2015-HM02-00042-SF). The funders had no role in any part of the study or in any decision about publication.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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