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Exercise interventions for ankylosing spondylitis: A protocol for a Bayesian network meta-analysis

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ABSTRACT

Introduction: Ankylosing spondylitis (AS) is a universal chronic inflammatory rheumatic disease which predominantly results in chronic back pain and stiffness. However, some patients suffering from AS do not react well to pharmacological interventions. Exercise intervention has been employed for the treatment of AS and works as a complementary part of the management of AS. However, the effect of different types of exercise interventions remain unclear. The purpose of this study is to determine the relative efficacy of different types of exercise interventions for individuals with AS using a Bayesian network meta-analysis.

Methods and analysis: We will comprehensively searched PubMed, EMBASE and the Cochrane Library, to include randomized controlled trials that compare different types of exercise interventions for individuals with AS. The risk of bias for individual studies will be evaluated according to the Cochrane Handbook. A Bayesian network meta-analysis will be performed to compare the efficacy of different types of exercise interventions. The quality of evidence will be assessed by GRADE.

Ethics and dissemination: Ethical approval and patient consent are not required since this study is a meta-analysis based on published studies. The results of this network meta-analysis will be submitted to a peer-reviewed journal for publication.

Protocol registration number: PROSPERO CRD42019123099.

Strengths and limitations of this study

- This is the most comprehensive review comparing the efficacy of different types of exercise interventions for individuals with AS through a Bayesian network meta-analysis.
- We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence.
- The results of this study will help physical therapists and patients to select appropriate exercise interventions.
- This study is based on the quantity and quality of the trials available for review.

INTRODUCTION

Ankylosing spondylitis (AS) is a universal chronic inflammatory rheumatic disease which predominantly influences the axial skeleton (e.g., spine, hips and shoulders).[1 2] AS is characterized by inflammatory back pain which is caused by sacroiliitis and spondylitis.[1] Inflammatory back pain may happen in 70% to 80% of patients with AS. AS commonly starts early and about 10% to 20% of patients with AS commence to develop the first symptoms before 16 years of age.[3 4] It has reported that estimates for the prevalence of AS vary from 0.01% to 1.8%.[5] Patients with AS often experience chronic back pain, stiffness, arthritis and enthesitis, which seriously affect patients' health and quality of life, disturb their recreational activities, work, family life and relationships, and result in considerable psychological distress and fears.

Non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, are recommended as the first-line drug intervention for reducing pain and stiffness. Biological disease modifying antirheumatic drugs have also proved effective for the manage inhibitors, the anti-interleukin-17 inhibitor, and so on.[6] However, some patients suffering from AS do not react well to pharmacological interventions.[7] Exercise is recommended by several guidelines as a co-intervention in combination with pharmacological interventions to treat patients with AS.[2 8] Previous systematic reviews[9-11] demonstrated that exercises have significant positive effects on pain, spinal mobility, and physical function. However, they did not classify different types of exercise, such as group exercise, individualized exercise, supervised exercise, home-based exercise, and so on. Therefore, we do not know which is the best one. When no studies exist that directly compare all relevant treatment choices, a network meta-analysis can be performed by comparing the relative effects of treatments against a common comparator or combining a variety of comparisons that are taken together from one or more chains linking the treatments of interest.[12]

Therefore, the purpose of this study is to comprehensively review the literature and determine the relative efficacy of different types of exercise interventions for individuals with AS using a Bayesian network meta-analysis.

METHODS

Design

A network meta-analysis using a Bayesian framework will be implemented in this study. This protocol of network meta-analysis will be performed on the basis of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocol (PRISMA-P),[13] and the reporting of the following network meta-analysis will obey the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analysis of health care interventions.[14] This study has been registered at PROSPERO (http://www.crd.york.ac.uk/PROSPERO) with registration number CRD42019123099.

Eligibility criteria

1. Type of study

We will include randomized controlled trials. For cross-over studies, we only use the data before wash-out period. We will not restrain the language or date of publication.

2. Participants

Trials enrolling adults, aged at least 18 years, with a diagnosis of AS according to the Modified New York criteria[15] or the Amor criteria[16] or radiographic axial spondyloarthritis (SpA) according to the criteria for axial SpA defined by the Assessment of Spondyloarthritis International Society (ASAS)[17] will be included.

We will exclude studies involving participants with non-radiographic axial SpA according to the criteria for axial SpA defined by the ASAS.

3. Type of interventions

Any type of exercise interventions will be included. Exercise intervention is defined as a type of physical activity that is planned, structured and repeated over a period of time.[18]

Trials that compare an exercise intervention combined with a co-intervention versus the co-intervention alone or the exercise intervention alone (e.g., an exercise intervention plus anti-TNFα therapy versus anti-TNFα therapy alone, an exercise intervention plus spa therapy versus the exercise intervention) will be considered.

Trails investigating exercise interventions with different setting (home, hospital, or

elsewhere) or different delivery method (individual, group, supervision, or mixed) will be included.

Trials comparing an exercise intervention with no treatment, standard care or usual physical activity will be considered.

4. Outcomes of interest

4.1 Primary outcomes

The Bath Ankylosing Spondylitis Functional Index (BASFI)[19] is 10 item index that evaluate the functional capacity in performing daily activities of patients with AS. Higher score of the BASFI reflects greater impairment in functional capacity.

Pain will be measured based on a visual analogue scale (VAS) or numerical rating scale (NRS). We will record data on back pain at night, total back pain, overall pain at night, or overall pain. And the highest pain score on numeric value will be regarded as the final pain score.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[20] is the gold standard for measuring and evaluating disease activity in AS. Higher score of the BASDAI indicates greater disease activity.

4.2 Secondary outcomes

The Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) will be used to evaluate the quality of life, with higher scores indicating better quality of life.

The Bath Ankylosing Spondylitis Metrology Index (BASMI)[21] is the most widely reported, validated objective axial mobility measure, which consists of five steps: cervical rotation, tragus to wall distance, lumbar side flexion, modified Schober's test and intermalleolar distance. High scores mean severer limitation of movement.

Data sources and search strategy

We will systematically search PubMed, EMBASE and the Cochrane Library for primary studies up to February 2019. The search strategy will combine free text words and medical subject headings regarding exercise, spondyloarthritis and randomized controlled trials. The detail of the search strategy for PubMed is shown in online

supplementary file S1. This search strategy will be modified as required for other databases. Furthermore, we will also retrieve the World Health Organization (WHO) International Clinical Trials Registry Platform and ClinicalTrials.gov to identify ongoing trial registers. We will examine bibliographies of pertinent systematic reviews and meta-analyses for additional related studies. We will not limit language of publication or publication period.

Study selection

Two reviewers will independently check the titles and abstracts through the initial retrieval. Publications not fulfilling the eligibility criteria will be eliminated. After excluding the irrelevant publications, we will examine the full text of the remaining publications based on the same eligibility criteria. Any discrepancies will be settled by discussion and consensus. Excluded publications and the reasons for exclusion will be reported and confirmed by a third investigator.

Data extraction

Data from included publications will be independently extracted by two reviewers using a standardized data abstraction list. The following characteristic information will be extracted: study characteristics (first author, publication year, study year, number of centers, country and sponsor), patient characteristics (sample size, mean age, gender ratio, the stage of the disease, and inclusion/exclusion criteria), intervention details for each treatment group (e.g., number of intervention groups, exercise modality and the detailed description, frequency and duration of the intervention, the duration of follow-up, and co-interventions) and outcome measures (BASFI, BASDAI, BASMI, pain, and SF-36). Numerical data will be extracted to calculate pooled estimations. If the data are not reported in the texts directly, we will infer them from the associated graphs. Any disagreements will be settled by discussion and consensus.

Risk of bias assessment

The Cochrane Risk of Bias Tool will be used to appraise the risk of bias for individual

studies.[22] Each study will be evaluated and scored as high, low, or unclear risk of bias based on the following criteria: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other biases. A study with a high risk of bias in one or more domains will be viewed as high risk of bias. A study with a low risk of bias in all domains will be considered as low risk of bias. If not, a study will be treated as unclear risk of bias. Any disagreements were resolved by discussion and consensus.

Statistical analysis

A traditional pairwise meta-analysis will be done when at least two studies exist for an outcome. A random-effects model with DerSimonian and Laird inverse-variance method will be used to estimate pooled mean difference (MD) and 95% confidence interval (CI) accounting for methodological and clinical heterogeneity across studies, with Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014).[23] The extent of between-trial heterogeneity will be assessed with I^2 statistic, with values over 50% indicating considerable heterogeneity.[24]

We will perform network meta-analyses to merge direct and indirect comparisons. All network meta-analyses will be conducted using a Bayesian Markov chain Monte Carlo (MCMC) framework in R version 3.2.5 software (https://cran.r-project.org/src/base/R-3/) via the gemtc version 0.8-2 package. MD and 95% credible interval (CrI) will be used as summary statistics to quantify the effect of different exercise interventions. Random-effects and consistency models will be adopted in this network meta-analysis, as they are considered to be the most conservative approach to dealing with between-study heterogeneity.[25] To generate posterior distributions of model parameters, 150 000 iterations of MCMC after 50 000 tuning iterations in three chains will be run.[26] Convergence of iterations will be examined with the Gelman-Rubin-Brooks diagnostic plots.[27] For any specific outcome, we will rank the probability of each intervention being the best (superior to all other interventions), second best, third best, etc.

The posterior mean residual deviance, an absolute measure of fit, will be computed.

The value of posterior mean residual deviance and the number of independent data points will be assessed to check if the model fits the data satisfactorily.[28] To appraise the consistency, we will use the following methods. Firstly, the model fit from the consistency model will be compared with that from the inconsistency model.[29] Secondly, network meta-analysis results (indirect evidence using the node-split approach) will be compared with pairwise meta-analysis results (direct evidence in a frequentist framework).[30]

Clinical and methodological heterogeneity will be evaluated by checking the characteristics and design of the included studies. Statistical heterogeneity in the network will be assessed according to the heterogeneity parameter (I^2 or τ^2) derived from the network meta-analysis. I^2 more than 50% indicates substantial heterogeneity. Heterogeneity will be explored by fitting covariates (ie, mean age, sample size, the duration of symptoms, the dose of exercise (frequency × duration intensity), and the duration of follow-up) in network meta-regression analyses.[31] Subgroup analyses will be further conducted ground on the duration of symptoms (early or long-term disease) and concomitant pharmacological treatment (anti-TNF agents, NSAIDs, or other pharmacological interventions), if possible. Sensitivity analyses will be executed to test the robustness of outcomes by limiting analyses to studies with low risk of bias.

To examine the potential of small-study effects in the network, comparison-adjusted funnel plots will be produced.[32] For the comparison-adjusted funnel plot, the horizontal axis will represent the difference between study-specific effect sizes and the comparison-specific summary effect. In the absence of small-study effects, the comparison-adjusted funnel plot should be symmetric around the zero line.

Quality of evidence

We will follow the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) four-step approach to grade the quality of treatment effect estimations from network meta-analysis.[33] Firstly, present direct and indirect treatment estimates for each comparison of the evidence network. Secondly, rate the quality of each direct and indirect effect estimate. Then, present the network meta-analysis

estimate for each comparison of the evidence network. At last, rate the quality of each network meta-analysis effect estimate. According to risk of bias, inconsistency, indirectness, imprecision and publication bias, the quality of evidence will be graded as high, moderate, low, or very low.

ETHICS AND DISSEMINATION

Ethical issues

As no primary data collection will be undertaken, no additional formal ethical assessment and no informed consent are required.

Publication plan

This network meta-analysis will be submitted to a peer-reviewed journal. It will be disseminated electronically and in print.

Contributors S-LK, L-XC, Z-FY and R-SZ participated in the conception and design of the study, including search strategy development. L-XC, Z-FY and WH tested the feasibility of the study. S-LK wrote the manuscript. All the authors critically reviewed this manuscript and approved the final version.

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Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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First: 2015/06/02]

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PubMed

#1	"Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
#2	((((placebo[Title/Abstract]) OR randomized[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR groups[Title/Abstract]
#3	("Animals"[Mesh]) NOT "Humans"[Mesh]
#4	(#1 OR #2) NOT #3
#5	"Spondylarthritis"[Mesh]
#6	"Spondylitis, Ankylosing"[Mesh]
#7	"Sacroiliitis"[Mesh]
#8	(((((Bechterew Disease[Title/Abstract]) OR Marie-Struempell Disease[Title/Abstract]) OR Ankylosing Spondylitis[Title/Abstract]) OR AS[Title/Abstract]) OR axSpA[Title/Abstract]) OR axial spondyloarthritis[Title/Abstract]
#9	(((axial[Title/Abstract]) OR spin*[Title/Abstract]) OR peripheral[Title/Abstract]) OR vertebral[Title/Abstract]
#10	(((joint*[Title/Abstract]) OR spondyloarthritis[Title/Abstract]) OR arthritis[Title/Abstract]) OR ankylosing[Title/Abstract]
#11	#9 AND #10
#12	#5 OR #6 OR #7 OR #8 OR #11
#13	"Exercise"[Mesh]
#14	"Exercise Therapy"[Mesh]

#15	"Exercise Movement Techniques"[Mesh]
#16	"Physical Therapy Modalities"[Mesh]
#17	"Motor Activity"[Mesh]
#18	"Rehabilitation"[Mesh]
#19	"Proprioception"[Mesh]
#20	(((((program*[Title/Abstract]) OR therap*[Title/Abstract]) OR behavior*[Title/Abstract]) OR intervention*[Title/Abstract]) OR train*[Title/Abstract]) OR activit*[Title/Abstract]
#21	exercise AND #20
#22	physical AND #20
#23	(((AS[Title/Abstract]) OR non drug*[Title/Abstract]) OR non pharmacological*[Title/Abstract]) OR complementary[Title/Abstract]
#24	((management[Title/Abstract]) OR intervention*[Title/Abstract]) OR treatment*[Title/Abstract]
#25	#23 AND #24
#26	((((((Train*[Title/Abstract]) OR exercise*[Title/Abstract]) OR therap*[Title/Abstract]) OR fitness[Title/Abstract]) OR program*[Title/Abstract]) OR reeducation[Title/Abstract]) OR rehab*[Title/Abstract]
#27	(((home[Title/Abstract]) OR water[Title/Abstract]) OR spa[Title/Abstract]) OR group[Title/Abstract]
#28	#26 AND #27
#29	((((((((((sport*[Title/Abstract]) OR recreation*[Title/Abstract]) OR walk*[Title/Abstract]) OR swim*[Title/Abstract]) OR

	bike*[Title/Abstract]) OR cycl*[Title/Abstract]) OR ergomet*[Title/Abstract]) OR danc*[Title/Abstract]) OR yoga[Title/Abstract]) OR tai chi [Title/Abstract]
#30	(hydrotherapy[Title/Abstract]) OR balneotherapy[Title/Abstract]
#31	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #21 OR #22 OR #25 OR #28 OR #29 OR #30
#32	#4 AND #12 AND # 31

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☑	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☑	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☑	☐	49
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☑	☐	6-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☑	☐	253-256
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	☐	☑	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☑	☐	257-260
Sponsor	5b	Provide name for the review funder and/or sponsor	☑	☐	257-260
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☑	☐	257-260
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☑	☐	62-86
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☑	☐	87-89
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☑	☐	102-124
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☑	☐	145-154
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	☑	☐	145-154
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐	☑	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☑	☐	157-162
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☑	☐	165-175
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☑	☐	165-175
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☑	☐	165-175
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	☑	☐	178-185
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☑	☐	188-207
	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 (e.g., I^2, Kendall's tau)	☑	☐	188-219
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☑	☐	220-226
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☑	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☑	☐	227-231
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☑	☐	234-242

BMJ Open

Exercise interventions for ankylosing spondylitis: A protocol for a Bayesian network meta-analysis

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Exercise interventions for ankylosing spondylitis: A protocol for a Bayesian network meta-analysis

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ABSTRACT

Introduction: Ankylosing spondylitis (AS) is a universal chronic inflammatory rheumatic disease which predominantly results in chronic back pain and stiffness. However, some patients suffering from AS do not react well to pharmacological interventions. Exercise intervention has been employed for the treatment of AS and works as a complementary part of the management of AS. However, the effect of different types of exercise interventions remain unclear. The purpose of this study is to determine the relative efficacy of different types of exercise interventions for individuals with AS using a Bayesian network meta-analysis.

Methods and analysis: We will conduct a systematic literature review of randomized controlled trials that compare different types of exercise interventions for individuals with AS. The primary outcomes are functional capacity, pain, and disease activity. The risk of bias for individual studies will be evaluated according to the Cochrane Handbook. A Bayesian network meta-analysis will be performed to compare the efficacy of different types of exercise interventions. The quality of evidence will be assessed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Ethics and dissemination: Ethical approval and patient consent are not required since this study is a meta-analysis based on published studies. The results of this network meta-analysis will be submitted to a peer-reviewed journal for publication.

Protocol registration number: PROSPERO CRD42019123099.

Strengths and limitations of this study

- This is the most comprehensive review comparing the efficacy of different types of exercise interventions for individuals with AS through a Bayesian network meta-analysis.
- The main strength is that only randomized controlled trials will be included.
- We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence.

INTRODUCTION

Ankylosing spondylitis (AS) is a universal chronic inflammatory rheumatic disease which predominantly influences the axial skeleton (e.g., spine, hips and shoulders).[1 2] AS is characterized by inflammatory back pain which is caused by sacroiliitis and spondylitis.[1] Inflammatory back pain may happen in 70% to 80% of patients with AS. AS commonly starts early and about 10% to 20% of patients with AS commence to develop the first symptoms before 16 years of age.[3 4] It has reported that estimates for the prevalence of AS vary from 0.01% to 1.8%.[5] Patients with AS often experience chronic back pain, stiffness, arthritis and enthesitis, which seriously affect patients' health and quality of life, disturb their recreational activities, work, family life and relationships, and result in considerable psychological distress and fears.

Non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, are recommended as the first-line drug intervention for reducing pain and stiffness. Biological disease modifying antirheumatic drugs have also proved effective for the manage inhibitors, the anti-interleukin-17 inhibitor, and so on.[6] However, some patients suffering from AS do not react well to pharmacological interventions.[7] Exercise is recommended by several guidelines as a co-intervention in combination with pharmacological interventions to treat patients with AS.[2 8] Previous systematic reviews[9-11] demonstrated that exercises have significant positive effects on pain, spinal mobility, and physical function. However, they did not classify different types of exercise, such as group exercise, individualized exercise, supervised exercise, home-based exercise, and so on. Therefore, we do not know which is the best one. When no studies exist that directly compare all relevant treatment choices, a network meta-analysis can be performed by comparing the relative effects of treatments against a common comparator or combining a variety of comparisons that are taken together from one or more chains linking the treatments of interest.[12]

Therefore, the purpose of this study is to comprehensively review the literature and determine the relative efficacy of different types of exercise interventions for individuals with AS using a Bayesian network meta-analysis.

METHODS

Design

A network meta-analysis using a Bayesian framework will be implemented in this study. This protocol of network meta-analysis will be performed on the basis of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocol (PRISMA-P),[13] and the reporting of the following network meta-analysis will obey the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analysis of health care interventions.[14] This study has been registered at PROSPERO (http://www.crd.york.ac.uk/PROSPERO) with registration number CRD42019123099.

Eligibility criteria

1. Type of study

We will include randomized controlled trials comparing different exercise interventions, and/or comparing a specific exercise intervention with no treatment, standard care or usual physical activity. For cross-over studies, we only use the data before wash-out period. We will not restrain the language or date of publication. We will divide the trial duration into short-term follow-up (6 months) and long-term follow-up (12 months). If the trial duration is closer to 6 months or 12 months, we will classify the trial duration as short-term follow-up or long-term follow-up.

2. Participants

Trials enrolling adults, aged at least 18 years, with a diagnosis of AS according to the Modified New York criteria[15] or the Amor criteria[16] or radiographic axial spondyloarthritis (SpA) according to the criteria for axial SpA defined by the Assessment of Spondyloarthritis International Society (ASAS)[17] will be included.

We will exclude studies involving participants with non-radiographic axial SpA according to the criteria for axial SpA defined by the ASAS.

3. Type of interventions

Any type of exercise interventions will be included. Exercise intervention is defined as a type of physical activity that is planned, structured and repeated over a period of time.[18]

Trials that compare an exercise intervention combined with a co-intervention versus the co-intervention alone or the exercise intervention alone (e.g., an exercise intervention plus anti-TNFα therapy versus anti-TNFα therapy alone, an exercise intervention plus spa therapy versus the exercise intervention) will be considered.

Trails investigating exercise interventions with different setting (home, hospital, or elsewhere) or different delivery method (individual, group, supervision, or mixed) will be included.

Trials comparing an exercise intervention with no treatment, standard care or usual physical activity will be considered.

4. Outcomes of interest

4.1 Primary outcomes

The Bath Ankylosing Spondylitis Functional Index (BASFI)[19] is 10 item index that evaluate the functional capacity in performing daily activities of patients with AS. Higher score of the BASFI reflects greater impairment in functional capacity.

Pain will be measured based on a visual analogue scale (VAS) or numerical rating scale (NRS). We will record data on back pain at night, total back pain, overall pain at night, or overall pain. We will collect the highest pain score from the mentioned alternatives. And the highest pain score on numeric value will be regarded as the final pain score.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[20] is the gold standard for measuring and evaluating disease activity in AS. Higher score of the BASDAI indicates greater disease activity.

4.2 Secondary outcomes

The Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) will be used to evaluate the quality of life, with higher scores indicating better quality of life.

The Bath Ankylosing Spondylitis Metrology Index (BASMI)[21] is the most widely reported, validated objective axial mobility measure, which consists of five steps: cervical rotation, tragus to wall distance, lumbar side flexion, modified Schober's test and intermalleolar distance. High scores mean severer limitation of movement.

Data sources and search strategy

We will systematically search PubMed, EMBASE and the Cochrane Library for primary studies up to February 2019. The search strategy will combine free text words and medical subject headings regarding exercise, spondyloarthritis and randomized controlled trials. The detail of the search strategy for PubMed is shown in online supplementary file S1. This search strategy will be modified as required for other databases. Furthermore, we will also retrieve the World Health Organization (WHO) International Clinical Trials Registry Platform and ClinicalTrials.gov to identify ongoing trial registers. We will examine bibliographies of pertinent systematic reviews and meta-analyses for additional related studies. We will not limit language of publication or publication period.

Study selection

Two reviewers will independently check the titles and abstracts through the initial retrieval. Publications not fulfilling the eligibility criteria will be eliminated. After excluding the irrelevant publications, we will examine the full text of the remaining publications based on the same eligibility criteria. Any discrepancies will be settled by discussion and consensus. Excluded publications and the reasons for exclusion will be reported and confirmed by a third investigator.

Data extraction

Data from included publications will be independently extracted by two reviewers using a standardized data abstraction list. The following characteristic information will be extracted: study characteristics (first author, publication year, study year, number of centers, country and sponsor), patient characteristics (sample size, mean age, gender ratio, the stage of the disease, and inclusion/exclusion criteria), intervention details for each treatment group (e.g., number of intervention groups, exercise modality and the detailed description, frequency and duration of the intervention, the duration of follow-up, and co-interventions) and outcome measures (BASFI, BASDAI, BASMI, pain, and

SF-36). We will prioritize the data at the end of the studies compared with the changes from baseline in all the outcomes. Numerical data will be extracted to calculate pooled estimations. If the study only reports SE, p value or CI, we will convert them into SD.[22] If the study reports median and IQR, we will calculate SD by dividing the IQR by 1.35 and considering the median equivalent to the mean.[22] If the data are not reported in the texts directly, we will infer them from the associated graphs. If data cannot be obtained, we will contact the corresponding authors. Any disagreements will be settled by discussion and consensus.

Risk of bias assessment

The Cochrane Risk of Bias Tool will be used to appraise the risk of bias for individual studies.[23] Each study will be evaluated and scored as high, low, or unclear risk of bias based on the following criteria: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other biases. A study with a high risk of bias in one or more domains will be viewed as high risk of bias. A study with a low risk of bias in all domains will be considered as low risk of bias. If not, a study will be treated as unclear risk of bias. Any disagreements were resolved by discussion and consensus.

Statistical analysis

A traditional pairwise meta-analysis will be done when at least two studies exist for an outcome. A random-effects model with the Hartung-Knapp-Sidik-Jonkstra method[24] will be used to estimate the effect size and 95% confidence interval (CI) accounting for methodological and clinical heterogeneity across studies, with Stata, version 13.0 (Stata Corp, College Station, TX).[25] We will use mean difference (MD) for a certain outcome when more than 50 percent studies reporting the outcome use the same measurement. Otherwise, standardized mean difference (SMD) will be used. The extent of between-trial heterogeneity will be assessed with I^2 statistic, with values over 50% indicating considerable heterogeneity.[26]

We will perform network meta-analyses to merge direct and indirect comparisons.

All network meta-analyses will be conducted using a Bayesian Markov chain Monte Carlo (MCMC) framework in R version 3.2.5 software (https://cran.r-project.org/src/base/R-3/) via the gemtc version 0.8-2 package. MD and 95% credible interval (CrI) will be used as summary statistics to quantify the effect of different exercise interventions. Random-effects and consistency models will be adopted in this network meta-analysis, as they are considered to be the most conservative approach to dealing with between-study heterogeneity.[27] To generate posterior distributions of model parameters, 150 000 iterations of MCMC after 50 000 tuning iterations in three chains will be run.[28] Convergence of iterations will be examined with the Gelman-Rubin-Brooks diagnostic plots.[29] For any specific outcome, we will rank the probability of each intervention being the best (superior to all other interventions), second best, third best, etc.

The posterior mean residual deviance, an absolute measure of fit, will be computed. The value of posterior mean residual deviance and the number of independent data points will be assessed to check if the model fits the data satisfactorily.[30] To appraise the consistency, we will use the following methods. Firstly, the model fit from the consistency model will be compared with that from the inconsistency model.[31] Secondly, network meta-analysis results (indirect evidence using the node-split approach) will be compared with pairwise meta-analysis results (direct evidence in a frequentist framework).[32]

Clinical and methodological heterogeneity will be evaluated by checking the characteristics and design of the included studies. Statistical heterogeneity in the network will be assessed according to the heterogeneity parameter (I^2 or τ^2) derived from the network meta-analysis. I^2 more than 50% indicates substantial heterogeneity. Heterogeneity will be explored by fitting covariates (ie, mean age, sample size, the duration of symptoms, the dose of exercise (frequency × duration intensity), and the duration of follow-up) in network meta-regression analyses.[33] Subgroup analyses will be further conducted ground on the duration of symptoms (early or long-term disease) and concomitant pharmacological treatment (anti-TNF agents, NSAIDs, or other pharmacological interventions), if possible. Sensitivity analyses will be executed to test

the robustness of outcomes by limiting analyses to studies with low risk of bias.

To examine the potential of small-study effects in the network, comparison-adjusted funnel plots will be produced.[34] For the comparison-adjusted funnel plot, the horizontal axis will represent the difference between study-specific effect sizes and the comparison-specific summary effect. In the absence of small-study effects, the comparison-adjusted funnel plot should be symmetric around the zero line.

Quality of evidence

We will follow the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) four-step approach to grade the quality of treatment effect estimations from network meta-analysis.[35] Firstly, present direct and indirect treatment estimates for each comparison of the evidence network. Secondly, rate the quality of each direct and indirect effect estimate. Then, present the network meta-analysis estimate for each comparison of the evidence network. At last, rate the quality of each network meta-analysis effect estimate. According to risk of bias, inconsistency, indirectness, imprecision and publication bias, the quality of evidence will be graded as high, moderate, low, or very low.

Patient and Public Involvement

Patients or public will not be involved.

ETHICS AND DISSEMINATION

Ethical issues

As no primary data collection will be undertaken, no additional formal ethical assessment and no informed consent are required.

Publication plan

This network meta-analysis will be submitted to a peer-reviewed journal. It will be disseminated electronically and in print.

Contributors S-LK, L-XC, Z-FY and R-SZ participated in the conception and design of the study, including search strategy development. S-LK, L-XC, Z-FY and WH tested the feasibility of the study. S-LK wrote the manuscript. All the authors critically reviewed this manuscript and approved the final version.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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quality of treatment effect estimates from network meta-analysis. *Bmj* 2014;349:g5630. doi: 10.1136/bmj.g5630 [published Online First: 2014/09/26]

PubMed

#1	"Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
#2	((((placebo[Title/Abstract]) OR randomized[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR groups[Title/Abstract]
#3	("Animals"[Mesh]) NOT "Humans"[Mesh]
#4	(#1 OR #2) NOT #3
#5	"Spondylarthritis"[Mesh]
#6	"Spondylitis, Ankylosing"[Mesh]
#7	"Sacroiliitis"[Mesh]
#8	(((((Bechterew Disease[Title/Abstract]) OR Marie-Struempell Disease[Title/Abstract]) OR Ankylosing Spondylitis[Title/Abstract]) OR AS[Title/Abstract]) OR axSpA[Title/Abstract]) OR axial spondyloarthritis[Title/Abstract]
#9	(((axial[Title/Abstract]) OR spin*[Title/Abstract]) OR peripheral[Title/Abstract]) OR vertebral[Title/Abstract]
#10	(((joint*[Title/Abstract]) OR spondyloarthritis[Title/Abstract]) OR arthritis[Title/Abstract]) OR ankylosing[Title/Abstract]
#11	#9 AND #10
#12	#5 OR #6 OR #7 OR #8 OR #11
#13	"Exercise"[Mesh]
#14	"Exercise Therapy"[Mesh]

#15	"Exercise Movement Techniques"[Mesh]
#16	"Physical Therapy Modalities"[Mesh]
#17	"Motor Activity"[Mesh]
#18	"Rehabilitation"[Mesh]
#19	"Proprioception"[Mesh]
#20	(((((program*[Title/Abstract]) OR therap*[Title/Abstract]) OR behavior*[Title/Abstract]) OR intervention*[Title/Abstract]) OR train*[Title/Abstract]) OR activit*[Title/Abstract]
#21	exercise AND #20
#22	physical AND #20
#23	(((AS[Title/Abstract]) OR non drug*[Title/Abstract]) OR non pharmacological*[Title/Abstract]) OR complementary[Title/Abstract]
#24	((management[Title/Abstract]) OR intervention*[Title/Abstract]) OR treatment*[Title/Abstract]
#25	#23 AND #24
#26	((((((Train*[Title/Abstract]) OR exercise*[Title/Abstract]) OR therap*[Title/Abstract]) OR fitness[Title/Abstract]) OR program*[Title/Abstract]) OR reeducation[Title/Abstract]) OR rehab*[Title/Abstract]
#27	(((home[Title/Abstract]) OR water[Title/Abstract]) OR spa[Title/Abstract]) OR group[Title/Abstract]
#28	#26 AND #27
#29	((((((((((sport*[Title/Abstract]) OR recreation*[Title/Abstract]) OR walk*[Title/Abstract]) OR swim*[Title/Abstract]) OR

	bike*[Title/Abstract]) OR cycl*[Title/Abstract]) OR ergomet*[Title/Abstract]) OR danc*[Title/Abstract]) OR yoga[Title/Abstract]) OR tai chi [Title/Abstract]
#30	(hydrotherapy[Title/Abstract]) OR balneotherapy[Title/Abstract]
#31	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #21 OR #22 OR #25 OR #28 OR #29 OR #30
#32	#4 AND #12 AND # 31

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☑	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☑	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☑	☐	49
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☑	☐	6-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☑	☐	253-256
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	☐	☑	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☑	☐	257-260
Sponsor	5b	Provide name for the review funder and/or sponsor	☑	☐	257-260
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☑	☐	257-260
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☑	☐	62-86
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☑	☐	87-89
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☑	☐	102-124
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☑	☐	145-154
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	☑	☐	145-154
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐	☑	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☑	☐	157-162
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☑	☐	165-175
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☑	☐	165-175
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☑	☐	165-175
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	☑	☐	178-185
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☑	☐	188-207
	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 (e.g., I^2, Kendall's tau)	☑	☐	188-219
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☑	☐	220-226
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☑	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☑	☐	227-231
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☑	☐	234-242

BMJ Open

Exercise interventions for ankylosing spondylitis: A protocol for a Bayesian network meta-analysis

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Exercise interventions for ankylosing spondylitis: A protocol for a Bayesian network meta-analysis

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ABSTRACT

Introduction: Ankylosing spondylitis (AS) is a universal chronic inflammatory rheumatic disease which predominantly results in chronic back pain and stiffness. However, some patients suffering from AS do not react well to pharmacological interventions. Exercise intervention has been employed for the treatment of AS and works as a complementary part of the management of AS. However, the effect of different types of exercise interventions remain unclear. The purpose of this study is to determine the relative efficacy of different types of exercise interventions for individuals with AS using a Bayesian network meta-analysis.

Methods and analysis: We will conduct a systematic literature review of randomized controlled trials that compare different types of exercise interventions for individuals with AS. PubMed, EMBASE and the Cochrane Library will be searched up to February 2019. The primary outcomes are functional capacity, pain, and disease activity. The risk of bias for individual studies will be evaluated according to the Cochrane Handbook. A Bayesian network meta-analysis will be performed to compare the efficacy of different types of exercise interventions. The quality of evidence will be assessed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Ethics and dissemination: Ethical approval and patient consent are not required since this study is a meta-analysis based on published studies. The results of this network meta-analysis will be submitted to a peer-reviewed journal for publication.

Protocol registration number: PROSPERO CRD42019123099.

Strengths and limitations of this study

- This is the most comprehensive review comparing the efficacy of different types of exercise interventions for individuals with AS through a Bayesian network meta-analysis.
- The main strength is that only randomized controlled trials will be included.
- We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence.
- The duration of some trials is too short to provide decisive evidence on the effects

of exercise interventions.

INTRODUCTION

Ankylosing spondylitis (AS) is a universal chronic inflammatory rheumatic disease which predominantly influences the axial skeleton (e.g., spine, hips and shoulders).[1 2] AS is characterized by inflammatory back pain which is caused by sacroiliitis and spondylitis.[1] Inflammatory back pain may happen in 70% to 80% of patients with AS. AS commonly starts early and about 10% to 20% of patients with AS commence to develop the first symptoms before 16 years of age.[3 4] It has reported that estimates for the prevalence of AS vary from 0.01% to 1.8%.[5] Patients with AS often experience chronic back pain, stiffness, arthritis and enthesitis, which seriously affect patients' health and quality of life, disturb their recreational activities, work, family life and relationships, and result in considerable psychological distress and fears.

Non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, are recommended as the first-line drug intervention for reducing pain and stiffness. Biological disease modifying antirheumatic drugs have also proved effective for the manage inhibitors, the anti-interleukin-17 inhibitor, and so on.[6] However, some patients suffering from AS do not react well to pharmacological interventions.[7] Exercise is recommended by several guidelines as a co-intervention in combination with pharmacological interventions to treat patients with AS.[2 8] Previous systematic reviews[9-11] demonstrated that exercises have significant positive effects on pain, spinal mobility, and physical function. However, they did not classify different types of exercise, such as group exercise, individualized exercise, supervised exercise, home-based exercise, and so on. Therefore, we do not know which is the best one. When no studies exist that directly compare all relevant treatment choices, a network meta-analysis can be performed by comparing the relative effects of treatments against a common comparator or combining a variety of comparisons that are taken together from one or more chains linking the treatments of interest.[12]

Therefore, the purpose of this study is to comprehensively review the literature and determine the relative efficacy of different types of exercise interventions for individuals with AS using a Bayesian network meta-analysis.

METHODS

Design

A network meta-analysis using a Bayesian framework will be implemented in this study. This protocol of network meta-analysis will be performed on the basis of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocol (PRISMA-P),[13] and the reporting of the following network meta-analysis will obey the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analysis of health care interventions.[14] This study has been registered at PROSPERO (http://www.crd.york.ac.uk/PROSPERO) with registration number CRD42019123099.

Eligibility criteria

1. Type of study

We will include randomized controlled trials comparing different exercise interventions, and/or comparing a specific exercise intervention with no treatment, standard care or usual physical activity. For cross-over studies, we only use the data before wash-out period. We will not restrain the language or date of publication. We will divide the trial duration into short-term follow-up (6 months) and long-term follow-up (12 months). If the trial duration is closer to 6 months or 12 months, we will classify the trial duration as short-term follow-up or long-term follow-up.

2. Participants

Trials enrolling adults, aged at least 18 years, with a diagnosis of AS according to the Modified New York criteria[15] or the Amor criteria[16] or radiographic axial spondyloarthritis (SpA) according to the criteria for axial SpA defined by the Assessment of Spondyloarthritis International Society (ASAS)[17] will be included.

We will exclude studies involving participants with non-radiographic axial SpA according to the criteria for axial SpA defined by the ASAS.

3. Type of interventions

Any type of exercise interventions will be included. Exercise intervention is defined as a type of physical activity that is planned, structured and repeated over a period of

time.[18]

Trials that compare an exercise intervention combined with a co-intervention versus the co-intervention alone or the exercise intervention alone (e.g., an exercise intervention plus anti-TNFα therapy versus anti-TNFα therapy alone, an exercise intervention plus spa therapy versus the exercise intervention) will be considered.

Trails investigating exercise interventions with different setting (home, hospital, or elsewhere) or different delivery method (individual, group, supervision, or mixed) will be included.

Trials comparing an exercise intervention with no treatment, standard care or usual physical activity will be considered.

4. Outcomes of interest

4.1 Primary outcomes

The Bath Ankylosing Spondylitis Functional Index (BASFI)[19] is 10 item index that evaluate the functional capacity in performing daily activities of patients with AS. Higher score of the BASFI reflects greater impairment in functional capacity.

Pain will be measured based on a visual analogue scale (VAS) or numerical rating scale (NRS). We will record data on back pain at night, total back pain, overall pain at night, or overall pain. We will collect the highest pain score from the mentioned alternatives. And the highest pain score on numeric value will be regarded as the final pain score.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[20] is the gold standard for measuring and evaluating disease activity in AS. Higher score of the BASDAI indicates greater disease activity.

4.2 Secondary outcomes

The Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) will be used to evaluate the quality of life, with higher scores indicating better quality of life.

The Bath Ankylosing Spondylitis Metrology Index (BASMI)[21] is the most widely reported, validated objective axial mobility measure, which consists of five steps: cervical rotation, tragus to wall distance, lumbar side flexion, modified Schober's test

and intermalleolar distance. High scores mean severer limitation of movement.

Data sources and search strategy

We will systematically search PubMed, EMBASE and the Cochrane Library for primary studies up to February 2019. The search strategy will combine free text words and medical subject headings regarding exercise, spondyloarthritis and randomized controlled trials. The detail of the search strategy for PubMed is shown in online supplementary file S1. This search strategy will be modified as required for other databases. Furthermore, we will also retrieve the World Health Organization (WHO) International Clinical Trials Registry Platform and ClinicalTrials.gov to identify ongoing trial registers. We will examine bibliographies of pertinent systematic reviews and meta-analyses for additional related studies. We will not limit language of publication or publication period.

Study selection

Two reviewers will independently check the titles and abstracts through the initial retrieval. Publications not fulfilling the eligibility criteria will be eliminated. After excluding the irrelevant publications, we will examine the full text of the remaining publications based on the same eligibility criteria. Any discrepancies will be settled by discussion and consensus. Excluded publications and the reasons for exclusion will be reported and confirmed by a third investigator.

Data extraction

Data from included publications will be independently extracted by two reviewers using a standardized data abstraction list. The following characteristic information will be extracted: study characteristics (first author, publication year, study year, number of centers, country and sponsor), patient characteristics (sample size, mean age, gender ratio, the stage of the disease, and inclusion/exclusion criteria), intervention details for each treatment group (e.g., number of intervention groups, exercise modality and the detailed description, frequency and duration of the intervention, the duration of follow-

up, and co-interventions) and outcome measures (BASFI, BASDAI, BASMI, pain, and SF-36). We will prioritize the data at the end of the studies compared with the changes from baseline in all the outcomes. Numerical data will be extracted to calculate pooled estimations. If the study only reports SE, p value or CI, we will convert them into SD.[22] If the study reports median and IQR, we will calculate SD by dividing the IQR by 1.35 and considering the median equivalent to the mean.[22] If the data are not reported in the texts directly, we will infer them from the associated graphs. If data cannot be obtained, we will contact the corresponding authors. Any disagreements will be settled by discussion and consensus.

Risk of bias assessment

The Cochrane Risk of Bias Tool will be used to appraise the risk of bias for individual studies.[23] Each study will be evaluated and scored as high, low, or unclear risk of bias based on the following criteria: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other biases. A study with a high risk of bias in one or more domains will be viewed as high risk of bias. A study with a low risk of bias in all domains will be considered as low risk of bias. If not, a study will be treated as unclear risk of bias. Any disagreements were resolved by discussion and consensus.

Statistical analysis

A traditional pairwise meta-analysis will be done when at least two studies exist for an outcome. A random-effects model with the Hartung-Knapp-Sidik-Jonkstra method[24] will be used to estimate the effect size and 95% confidence interval (CI) accounting for methodological and clinical heterogeneity across studies, with Stata, version 13.0 (Stata Corp, College Station, TX).[25] We will use mean difference (MD) for a certain outcome when more than 50 percent studies reporting the outcome use the same measurement. Otherwise, standardized mean difference (SMD) will be used. The extent of between-trial heterogeneity will be assessed with I^2 statistic, with values over 50% indicating considerable heterogeneity.[26]

We will perform network meta-analyses to merge direct and indirect comparisons. All network meta-analyses will be conducted using a Bayesian Markov chain Monte Carlo (MCMC) framework in R version 3.2.5 software (https://cran.r-project.org/src/base/R-3/) via the gemtc version 0.8-2 package. MD and 95% credible interval (CrI) will be used as summary statistics to quantify the effect of different exercise interventions. Random-effects and consistency models will be adopted in this network meta-analysis, as they are considered to be the most conservative approach to dealing with between-study heterogeneity.[27] To generate posterior distributions of model parameters, 150 000 iterations of MCMC after 50 000 tuning iterations in three chains will be run.[28] Convergence of iterations will be examined with the Gelman-Rubin-Brooks diagnostic plots.[29] For any specific outcome, we will rank the probability of each intervention being the best (superior to all other interventions), second best, third best, etc.

The posterior mean residual deviance, an absolute measure of fit, will be computed. The value of posterior mean residual deviance and the number of independent data points will be assessed to check if the model fits the data satisfactorily.[30] To appraise the consistency, we will use the following methods. Firstly, the model fit from the consistency model will be compared with that from the inconsistency model.[31] Secondly, network meta-analysis results (indirect evidence using the node-split approach) will be compared with pairwise meta-analysis results (direct evidence in a frequentist framework).[32]

Clinical and methodological heterogeneity will be evaluated by checking the characteristics and design of the included studies. Statistical heterogeneity in the network will be assessed according to the heterogeneity parameter (I^2 or τ^2) derived from the network meta-analysis. I^2 more than 50% indicates substantial heterogeneity. Heterogeneity will be explored by fitting covariates (ie, mean age, sample size, the duration of symptoms, the dose of exercise (frequency × duration intensity), and the duration of follow-up) in network meta-regression analyses.[33] Subgroup analyses will be further conducted ground on the duration of symptoms (early or long-term disease) and concomitant pharmacological treatment (anti-TNF agents, NSAIDs, or other

pharmacological interventions), if possible. Sensitivity analyses will be executed to test the robustness of outcomes by limiting analyses to studies with low risk of bias.

To examine the potential of small-study effects in the network, comparison-adjusted funnel plots will be produced.[34] For the comparison-adjusted funnel plot, the horizontal axis will represent the difference between study-specific effect sizes and the comparison-specific summary effect. In the absence of small-study effects, the comparison-adjusted funnel plot should be symmetric around the zero line.

Quality of evidence

We will follow the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) four-step approach to grade the quality of treatment effect estimations from network meta-analysis.[35] Firstly, present direct and indirect treatment estimates for each comparison of the evidence network. Secondly, rate the quality of each direct and indirect effect estimate. Then, present the network meta-analysis estimate for each comparison of the evidence network. At last, rate the quality of each network meta-analysis effect estimate. According to risk of bias, inconsistency, indirectness, imprecision and publication bias, the quality of evidence will be graded as high, moderate, low, or very low.

Patient and Public Involvement

Patients or public will not be involved.

ETHICS AND DISSEMINATION

Ethical issues

As no primary data collection will be undertaken, no additional formal ethical assessment and no informed consent are required.

Publication plan

This network meta-analysis will be submitted to a peer-reviewed journal. It will be disseminated electronically and in print.

Contributors S-LK, L-XC, Z-FY and R-SZ participated in the conception and design of the study, including search strategy development. S-LK, L-XC, Z-FY and WH tested the feasibility of the study. S-LK wrote the manuscript. All the authors critically reviewed this manuscript and approved the final version.

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Provenance and peer review Not commissioned; externally peer reviewed.

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PubMed

#1	"Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
#2	((((placebo[Title/Abstract]) OR randomized[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR groups[Title/Abstract]
#3	("Animals"[Mesh]) NOT "Humans"[Mesh]
#4	(#1 OR #2) NOT #3
#5	"Spondylarthritis"[Mesh]
#6	"Spondylitis, Ankylosing"[Mesh]
#7	"Sacroiliitis"[Mesh]
#8	(((((Bechterew Disease[Title/Abstract]) OR Marie-Struempell Disease[Title/Abstract]) OR Ankylosing Spondylitis[Title/Abstract]) OR AS[Title/Abstract]) OR axSpA[Title/Abstract]) OR axial spondyloarthritis[Title/Abstract]
#9	(((axial[Title/Abstract]) OR spin*[Title/Abstract]) OR peripheral[Title/Abstract]) OR vertebral[Title/Abstract]
#10	(((joint*[Title/Abstract]) OR spondyloarthritis[Title/Abstract]) OR arthritis[Title/Abstract]) OR ankylosing[Title/Abstract]
#11	#9 AND #10
#12	#5 OR #6 OR #7 OR #8 OR #11
#13	"Exercise"[Mesh]
#14	"Exercise Therapy"[Mesh]

#15	"Exercise Movement Techniques"[Mesh]
#16	"Physical Therapy Modalities"[Mesh]
#17	"Motor Activity"[Mesh]
#18	"Rehabilitation"[Mesh]
#19	"Proprioception"[Mesh]
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#22	physical AND #20
#23	(((AS[Title/Abstract]) OR non drug*[Title/Abstract]) OR non pharmacological*[Title/Abstract]) OR complementary[Title/Abstract]
#24	((management[Title/Abstract]) OR intervention*[Title/Abstract]) OR treatment*[Title/Abstract]
#25	#23 AND #24
#26	((((((Train*[Title/Abstract]) OR exercise*[Title/Abstract]) OR therap*[Title/Abstract]) OR fitness[Title/Abstract]) OR program*[Title/Abstract]) OR reeducation[Title/Abstract]) OR rehab*[Title/Abstract]
#27	(((home[Title/Abstract]) OR water[Title/Abstract]) OR spa[Title/Abstract]) OR group[Title/Abstract]
#28	#26 AND #27
#29	((((((((((sport*[Title/Abstract]) OR recreation*[Title/Abstract]) OR walk*[Title/Abstract]) OR swim*[Title/Abstract]) OR

	bike*[Title/Abstract]) OR cycl*[Title/Abstract]) OR ergomet*[Title/Abstract]) OR danc*[Title/Abstract]) OR yoga[Title/Abstract]) OR tai chi [Title/Abstract]
#30	(hydrotherapy[Title/Abstract]) OR balneotherapy[Title/Abstract]
#31	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #21 OR #22 OR #25 OR #28 OR #29 OR #30
#32	#4 AND #12 AND # 31

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☑	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☑	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☑	☐	49
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☑	☐	6-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☑	☐	253-256
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	☐	☑	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☑	☐	257-260
Sponsor	5b	Provide name for the review funder and/or sponsor	☑	☐	257-260
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☑	☐	257-260
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☑	☐	62-86
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☑	☐	87-89
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☑	☐	102-124
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☑	☐	145-154
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	☑	☐	145-154
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐	☑	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☑	☐	157-162
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☑	☐	165-175
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☑	☐	165-175
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☑	☐	165-175
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	☑	☐	178-185
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☑	☐	188-207
	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 (e.g., I^2, Kendall's tau)	☑	☐	188-219
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☑	☐	220-226
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☑	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☑	☐	227-231
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☑	☐	234-242