

# BMJ Open 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 remains 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 randomised 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 approach.

**Ethics and dissemination** Ethical approval and patient consent are not required as 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.

**PROSPERO registration number** CRD42019123099.

## INTRODUCTION

Ankylosing spondylitis (AS) is a universal chronic inflammatory rheumatic disease which predominantly influences the axial skeleton (eg, spine, hips and shoulders).<sup>1,2</sup> AS is characterised by inflammatory back pain which is caused by sacroiliitis and spondylitis.<sup>1</sup> Inflammatory back pain may happen in 70%–80% of patients with AS. AS commonly starts early and about 10%–20% of patients with AS commence to develop the first symptoms before 16 years of age.<sup>3,4</sup> It has been reported that estimates for the prevalence of AS vary from 0.01% to 1.8%.<sup>5</sup> Patients

## Strengths and limitations of this study

- This is the most comprehensive review comparing the efficacy of different types of exercise interventions for individuals with ankylosing spondylitis through a Bayesian network meta-analysis.
- The main strength is that only randomised controlled trials will be included.
- We will use the Grading of Recommendations Assessment, Development and Evaluation 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.

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 to manage inhibitors, the anti-interleukin-17 inhibitor and so on.<sup>6</sup> However, some patients suffering from AS do not react well to pharmacological interventions.<sup>7</sup> Exercise is recommended by several guidelines as a co-intervention in combination with pharmacological interventions to treat patients with AS.<sup>2,8</sup> Previous systematic reviews<sup>9–11</sup> 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, individualised 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.<sup>12</sup>

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),<sup>13</sup> 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.<sup>14</sup> This study has been registered at PROSPERO (<http://www.crd.york.ac.uk/PROSPERO>) with registration number CRD42019123099.

### Eligibility criteria

#### Type of study

We will include randomised 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 the wash-out period. We will not restrain the language or date of publication. We will divide the trial duration into a short-term follow-up (6 months) and long-term follow-up (12 months). If the trial duration is closer to 6 or 12 months, we will classify the trial duration as a short-term follow-up or long-term follow-up.

#### Participants

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

#### 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.<sup>18</sup>

Trials that compare an exercise intervention combined with a co-intervention versus the co-intervention alone or the exercise intervention alone (eg, an exercise intervention plus anti-tumour necrosis factor (TNF) $\alpha$  therapy vs anti-TNF $\alpha$  therapy alone, an exercise intervention

plus spa therapy vs the exercise intervention) will be considered.

Trials investigating exercise interventions with a 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.

### Outcomes of interest

#### Primary outcomes

The Bath Ankylosing Spondylitis Functional Index (BASFI)<sup>19</sup> is a 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.

The pain will be measured based on a visual analogue scale or numerical rating scale. 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)<sup>20</sup> is the gold standard for measuring and evaluating disease activity in AS. Higher score of the BASDAI indicates greater disease activity.

#### 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)<sup>21</sup> 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 limitations 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 randomised controlled trials. The detail of the search strategy for PubMed is shown in the online supplementary file S1. This search strategy will be modified as required for other databases. Furthermore, we will also retrieve the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov to identify ongoing trial registers. We will examine the bibliographies of pertinent systematic reviews and meta-analyses for additional related studies. We will not limit the 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 standardised data abstraction list. The following characteristic information will be extracted: study characteristics (first author, publication year, study year, number of centres, 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 (eg, 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 prioritise 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.<sup>22</sup> 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.<sup>22</sup> 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.<sup>23</sup> Each study will be evaluated and scored as high, low or unclear risk of bias based on the following criteria: randomisation, 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<sup>24</sup> will be used to estimate the effect size and 95% CI accounting for methodological and clinical heterogeneity across studies, with Stata V.13.0.<sup>25</sup> We will use mean difference (MD) for a certain outcome when >50% studies reporting the outcome use the same measurement. Otherwise, standardised MD will be used. The

extent of between-trial heterogeneity will be assessed with  $I^2$  statistic, with values over 50% indicating considerable heterogeneity.<sup>26</sup>

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 V.3.2.5 software (<https://cran.r-project.org/src/base/R-3/>) via the gemtc V.0.8–2 package. MD and 95% credible interval 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.<sup>27</sup> To generate posterior distributions of model parameters, 150 000 iterations of MCMC after 50 000 tuning iterations in three chains will be run.<sup>28</sup> The convergence of iterations will be examined with the Gelman-Rubin-Brooks diagnostic plots.<sup>29</sup> For any specific outcome, we will rank the probability of each intervention being the best (superior to all other interventions), second best, third best and so on.

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.<sup>30</sup> To appraise the consistency, we will use the following methods. First, the model fit from the consistency model will be compared with that from the inconsistency model.<sup>31</sup> Second, 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).<sup>32</sup>

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  $\tau^2$  derived from the network meta-analysis).  $I^2 > 50\%$  indicates substantial heterogeneity. Heterogeneity will be explored by fitting covariates (ie, mean age, sample size, the duration of symptoms, the dose of exercise (frequency  $\times$  duration intensity) and the duration of follow-up) in network meta-regression analyses.<sup>33</sup> 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.<sup>34</sup> 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 four-step approach to grade the quality of treatment effect estimations from network meta-analysis.<sup>35</sup> First, present direct and indirect treatment estimates for each comparison of the evidence network. Second, 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 the 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 the 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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