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

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4 **1 Exercise interventions for ankylosing spondylitis: A protocol for a Bayesian**
5 **2 network meta-analysis**
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4 Shun-Li Kan¹, Ling-Xiao Chen², Zhi-Fang Yuan³, Wei Hu¹, Ru-Sen Zhu¹

6 ¹Department of Spine Surgery, Tianjin Union Medical Center, 190 Jieyuan Road,
7 Hongqiao District, Tianjin, China

8 ²Institute of Bone and Joint Research, The Kolling institute, Sydney Medical School,
9 The University of Sydney

10 ³Department of Respiratory and Critical Care Medicine, Tianjin Medical University
11 General Hospital, 154 Anshan Road, Heping District, Tianjin, China

12
13 S-LK, L-XC and Z-FY contributed equally to this work.

14
15 Correspondence to

16 Dr Ru-Sen Zhu;

17 rszhuspine@163.com

31 **ABSTRACT**

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

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

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

49 **Protocol registration number:** PROSPERO CRD42019123099.

50 **Strengths and limitations of this study**

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

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61 INTRODUCTION

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

72 Non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors,
73 are recommended as the first-line drug intervention for reducing pain and stiffness.
74 Biological disease modifying antirheumatic drugs have also proved effective for the
75 manage inhibitors, the anti-interleukin-17 inhibitor, and so on.⁶ However, some patients
76 suffering from AS do not react well to pharmacological interventions.⁷ Exercise is
77 recommended by several guidelines as a co-intervention in combination with
78 pharmacological interventions to treat patients with AS.^{2 8} Previous systematic
79 reviews⁹⁻¹¹ demonstrated that exercises have significant positive effects on pain, spinal
80 mobility, and physical function. However, they did not classify different types of
81 exercise, such as group exercise, individualized exercise, supervised exercise, home-
82 based exercise, and so on. Therefore, we do not know which is the best one. When no
83 studies exist that directly compare all relevant treatment choices, a network meta-
84 analysis can be performed by comparing the relative effects of treatments against a
85 common comparator or combining a variety of comparisons that are taken together
86 from one or more chains linking the treatments of interest.¹²

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

90

91 **METHODS**

92 **Design**

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

100

101 **Eligibility criteria**

102 1. Type of study

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

105 2. Participants

106 Trials enrolling adults, aged at least 18 years, with a diagnosis of AS according to the
107 Modified New York criteria¹⁵ or the Amor criteria¹⁶ or radiographic axial
108 spondyloarthritis (SpA) according to the criteria for axial SpA defined by the
109 Assessment of Spondyloarthritis International Society (ASAS)¹⁷ will be included.

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

112 3. Type of interventions

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

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

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

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4 121 elsewhere) or different delivery method (individual, group, supervision, or mixed) will
5
6 122 be included.

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8 123 Trials comparing an exercise intervention with no treatment, standard care or usual
9
10 124 physical activity will be considered.

11 125 4. Outcomes of interest

12 126 4.1 Primary outcomes

13 127 The Bath Ankylosing Spondylitis Functional Index (BASFI)¹⁹ is 10 item index that
14
15 128 evaluate the functional capacity in performing daily activities of patients with AS.
16
17 129 Higher score of the BASFI reflects greater impairment in functional capacity.

18
19 130 Pain will be measured based on a visual analogue scale (VAS) or numerical rating
20
21 131 scale (NRS). We will record data on back pain at night, total back pain, overall pain at
22
23 132 night, or overall pain. And the highest pain score on numeric value will be regarded as
24
25 133 the final pain score.

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27 134 The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)²⁰ is the gold
28
29 135 standard for measuring and evaluating disease activity in AS. Higher score of the
30
31 136 BASDAI indicates greater disease activity.

32 137 4.2 Secondary outcomes

33 138 The Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) will
34
35 139 be used to evaluate the quality of life, with higher scores indicating better quality of
36
37 140 life.

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39 141 The Bath Ankylosing Spondylitis Metrology Index (BASMI)²¹ is the most widely
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41 142 reported, validated objective axial mobility measure, which consists of five steps:
42
43 143 cervical rotation, tragus to wall distance, lumbar side flexion, modified Schober's test
44
45 144 and intermalleolar distance. High scores mean severer limitation of movement.

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48 146 **Data sources and search strategy**

49
50 147 We will systematically search PubMed, EMBASE and the Cochrane Library for
51
52 148 primary studies up to February 2019. The search strategy will combine free text words
53
54 149 and medical subject headings regarding exercise, spondyloarthritis and randomized
55
56 150 controlled trials. The detail of the search strategy for PubMed is shown in online

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4 151 supplementary file S1. This search strategy will be modified as required for other
5
6 152 databases. Furthermore, we will also retrieve the World Health Organization (WHO)
7
8 153 International Clinical Trials Registry Platform and ClinicalTrials.gov to identify
9
10 154 ongoing trial registers. We will examine bibliographies of pertinent systematic reviews
11
12 155 and meta-analyses for additional related studies. We will not limit language of
13
14 156 publication or publication period.

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17 158 **Study selection**

19 159 Two reviewers will independently check the titles and abstracts through the initial
20
21 160 retrieval. Publications not fulfilling the eligibility criteria will be eliminated. After
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23 161 excluding the irrelevant publications, we will examine the full text of the remaining
24
25 162 publications based on the same eligibility criteria. Any discrepancies will be settled by
26
27 163 discussion and consensus. Excluded publications and the reasons for exclusion will be
28
29 164 reported and confirmed by a third investigator.

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32 166 **Data extraction**

34 167 Data from included publications will be independently extracted by two reviewers using
35
36 168 a standardized data abstraction list. The following characteristic information will be
37
38 169 extracted: study characteristics (first author, publication year, study year, number of
39
40 170 centers, country and sponsor), patient characteristics (sample size, mean age, gender
41
42 171 ratio, the stage of the disease, and inclusion/exclusion criteria), intervention details for
43
44 172 each treatment group (e.g., number of intervention groups, exercise modality and the
45
46 173 detailed description, frequency and duration of the intervention, the duration of follow-
47
48 174 up, and co-interventions) and outcome measures (BASFI, BASDAI, BASMI, pain, and
49
50 175 SF-36). Numerical data will be extracted to calculate pooled estimations. If the data are
51
52 176 not reported in the texts directly, we will infer them from the associated graphs. Any
53
54 177 disagreements will be settled by discussion and consensus.

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57 179 **Risk of bias assessment**

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59 180 The Cochrane Risk of Bias Tool will be used to appraise the risk of bias for individual
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4 181 studies.²² Each study will be evaluated and scored as high, low, or unclear risk of bias
5
6 182 based on the following criteria: randomization, allocation concealment, blinding of
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8 183 participants and personnel, blinding of outcome assessors, incomplete outcome data,
9
10 184 selective reporting and other biases. A study with a high risk of bias in one or more
11
12 185 domains will be viewed as high risk of bias. A study with a low risk of bias in all
13
14 186 domains will be considered as low risk of bias. If not, a study will be treated as unclear
15
16 187 risk of bias. Any disagreements were resolved by discussion and consensus.

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19 189 **Statistical analysis**

20
21 190 A traditional pairwise meta-analysis will be done when at least two studies exist for an
22
23 191 outcome. A random-effects model with DerSimonian and Laird inverse-variance
24
25 192 method will be used to estimate pooled mean difference (MD) and 95% confidence
26
27 193 interval (CI) accounting for methodological and clinical heterogeneity across studies,
28
29 194 with Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane
30
31 195 Collaboration, Copenhagen, 2014).²³ The extent of between-trial heterogeneity will be
32
33 196 assessed with I^2 statistic, with values over 50% indicating considerable heterogeneity.²⁴

34
35 197 We will perform network meta-analyses to merge direct and indirect comparisons.
36
37 198 All network meta-analyses will be conducted using a Bayesian Markov chain Monte
38
39 199 Carlo (MCMC) framework in R version 3.2.5 software ([https://cran.r-](https://cran.r-project.org/src/base/R-3/)
40
41 200 [project.org/src/base/R-3/](https://cran.r-project.org/src/base/R-3/)) via the gemtc version 0.8-2 package. MD and 95% credible
42
43 201 interval (CrI) will be used as summary statistics to quantify the effect of different
44
45 202 exercise interventions. Random-effects and consistency models will be adopted in this
46
47 203 network meta-analysis, as they are considered to be the most conservative approach to
48
49 204 dealing with between-study heterogeneity.²⁵ To generate posterior distributions of
50
51 205 model parameters, 150 000 iterations of MCMC after 50 000 tuning iterations in three
52
53 206 chains will be run.²⁶ Convergence of iterations will be examined with the Gelman-
54
55 207 Rubin-Brooks diagnostic plots.²⁷ For any specific outcome, we will rank the probability
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57 208 of each intervention being the best (superior to all other interventions), second best,
58
59 209 third best, etc.

60 210 The posterior mean residual deviance, an absolute measure of fit, will be computed.

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4 211 The value of posterior mean residual deviance and the number of independent data
5
6 212 points will be assessed to check if the model fits the data satisfactorily.²⁸ To appraise
7
8 213 the consistency, we will use the following methods. Firstly, the model fit from the
9
10 214 consistency model will be compared with that from the inconsistency model.²⁹
11
12 215 Secondly, network meta-analysis results (indirect evidence using the node-split
13
14 216 approach) will be compared with pairwise meta-analysis results (direct evidence in a
15
16 217 frequentist framework).³⁰

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18 218 Clinical and methodological heterogeneity will be evaluated by checking the
19
20 219 characteristics and design of the included studies. Statistical heterogeneity in the
21
22 220 network will be assessed according to the heterogeneity parameter (I^2 or τ^2) derived
23
24 221 from the network meta-analysis. I^2 more than 50% indicates substantial heterogeneity.
25
26 222 Heterogeneity will be explored by fitting covariates (ie, mean age, sample size, the
27
28 223 duration of symptoms, the dose of exercise (frequency \times duration intensity), and the
29
30 224 duration of follow-up) in network meta-regression analyses.³¹ Subgroup analyses will
31
32 225 be further conducted ground on the duration of symptoms (early or long-term disease)
33
34 226 and concomitant pharmacological treatment (anti-TNF agents, NSAIDs, or other
35
36 227 pharmacological interventions), if possible. Sensitivity analyses will be executed to test
37
38 228 the robustness of outcomes by limiting analyses to studies with low risk of bias.

39
40 229 To examine the potential of small-study effects in the network, comparison-
41
42 230 adjusted funnel plots will be produced.³² For the comparison-adjusted funnel plot, the
43
44 231 horizontal axis will represent the difference between study-specific effect sizes and the
45
46 232 comparison-specific summary effect. In the absence of small-study effects, the
47
48 233 comparison-adjusted funnel plot should be symmetric around the zero line.

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50 235 **Quality of evidence**

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52 236 We will follow the Grading of Recommendations, Assessment, Development and
53
54 237 Evaluation (GRADE) four-step approach to grade the quality of treatment effect
55
56 238 estimations from network meta-analysis.³³ Firstly, present direct and indirect treatment
57
58 239 estimates for each comparison of the evidence network. Secondly, rate the quality of
59
60 240 each direct and indirect effect estimate. Then, present the network meta-analysis

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4 241 estimate for each comparison of the evidence network. At last, rate the quality of each
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6 242 network meta-analysis effect estimate. According to risk of bias, inconsistency,
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8 243 indirectness, imprecision and publication bias, the quality of evidence will be graded as
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10 244 high, moderate, low, or very low.

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13 246 **ETHICS AND DISSEMINATION**

14 15 247 **Ethical issues**

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17 248 As no primary data collection will be undertaken, no additional formal ethical
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19 249 assessment and no informed consent are required.

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22 23 251 **Publication plan**

24
25 252 This network meta-analysis will be submitted to a peer-reviewed journal. It will be
26
27 253 disseminated electronically and in print.

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31 255 **Contributors** S-LK, L-XC, Z-FY and R-SZ participated in the conception and design
32
33 256 of the study, including search strategy development. L-XC, Z-FY and WH tested the
34
35 257 feasibility of the study. S-LK wrote the manuscript. All the authors critically reviewed
36
37 258 this manuscript and approved the final version.

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40
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46
47 263 decision to publish, or preparation of the manuscript.

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51 265 **Competing interests** None declared.

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55 267 **Provenance and peer review** Not commissioned; externally peer reviewed.

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PubMed

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7 #1 "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
8
9 #2 (((placebo[Title/Abstract]) OR randomized[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR
10 groups[Title/Abstract]
11
12 #3 ("Animals"[Mesh]) NOT "Humans"[Mesh]
13
14 #4 (#1 OR #2) NOT #3
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16 #5 "Spondylarthritis"[Mesh]
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18 #6 "Spondylitis, Ankylosing"[Mesh]
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20 #7 "Sacroiliitis"[Mesh]
21
22 #8 (((Bechterew Disease[Title/Abstract]) OR Marie-Struempell Disease[Title/Abstract]) OR Ankylosing Spondylitis[Title/Abstract])
23 OR AS[Title/Abstract]) OR axSpA[Title/Abstract]) OR axial spondyloarthritis[Title/Abstract]
24
25 #9 (((axial[Title/Abstract]) OR spin*[Title/Abstract]) OR peripheral[Title/Abstract]) OR vertebral[Title/Abstract]
26
27 #10 (((joint*[Title/Abstract]) OR spondyloarthritis[Title/Abstract]) OR arthritis[Title/Abstract]) OR ankylosing[Title/Abstract]
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29 #11 #9 AND #10
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31 #12 #5 OR #6 OR #7 OR #8 OR #11
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33 #13 "Exercise"[Mesh]
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35 #14 "Exercise Therapy"[Mesh]
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- 5 #15 "Exercise Movement Techniques"[Mesh]
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7 #16 "Physical Therapy Modalities"[Mesh]
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9 #17 "Motor Activity"[Mesh]
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11 #18 "Rehabilitation"[Mesh]
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13 #19 "Proprioception"[Mesh]
14
15 #20 (((((program*[Title/Abstract]) OR therap*[Title/Abstract]) OR behavior*[Title/Abstract]) OR intervention*[Title/Abstract]) OR
16 train*[Title/Abstract]) OR activit*[Title/Abstract])
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18 #21 exercise AND #20
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20 #22 physical AND #20
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22 #23 (((AS[Title/Abstract]) OR non drug*[Title/Abstract]) OR non pharmacological*[Title/Abstract]) OR complementary[Title/Abstract]
23
24 #24 ((management[Title/Abstract]) OR intervention*[Title/Abstract]) OR treatment*[Title/Abstract]
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26 #25 #23 AND #24
27
28 #26 ((((((Train*[Title/Abstract]) OR exercise*[Title/Abstract]) OR therap*[Title/Abstract]) OR fitness[Title/Abstract]) OR
29 program*[Title/Abstract]) OR reeducation[Title/Abstract]) OR rehab*[Title/Abstract])
30
31 #27 (((home[Title/Abstract]) OR water[Title/Abstract]) OR spa[Title/Abstract]) OR group[Title/Abstract]
32
33 #28 #26 AND #27
34
35 #29 (((((((((sport*[Title/Abstract]) OR recreation*[Title/Abstract]) OR walk*[Title/Abstract]) OR swim*[Title/Abstract]) OR
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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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	49
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-260
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-260
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-260
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	145-154
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	178-185
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	188-219
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	220-226
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	227-231
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	234-242

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-029991.R1
Article Type:	Protocol
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Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Rheumatology
Keywords:	exercise, ankylosing spondylitis, network meta-analysis, Bayesian

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Manuscripts

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4 **1 Exercise interventions for ankylosing spondylitis: A protocol for a Bayesian**
5 **2 network meta-analysis**
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10 4 Shun-Li Kan¹, Ling-Xiao Chen², Zhi-Fang Yuan³, Wei Hu¹, Ru-Sen Zhu¹
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12

13 6 ¹Department of Spine Surgery, Tianjin Union Medical Center, 190 Jieyuan Road,
14 Hongqiao District, Tianjin, China
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17 8 ²Institute of Bone and Joint Research, The Kolling institute, Sydney Medical School,
18 The University of Sydney
19
20

21 10 ³Department of Respiratory and Critical Care Medicine, Tianjin Medical University
22 General Hospital, 154 Anshan Road, Heping District, Tianjin, China
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26
27 13 S-LK and L-XC contributed equally to this work.
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31 15 Correspondence to
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33 16 Dr Ru-Sen Zhu;
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35 17 rszhuspine@163.com
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31 **ABSTRACT**

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

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

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

51 **Protocol registration number:** PROSPERO CRD42019123099.

52 **Strengths and limitations of this study**

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

59
60

61 INTRODUCTION

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

72 Non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors,
73 are recommended as the first-line drug intervention for reducing pain and stiffness.
74 Biological disease modifying antirheumatic drugs have also proved effective for the
75 manage inhibitors, the anti-interleukin-17 inhibitor, and so on.⁶ However, some patients
76 suffering from AS do not react well to pharmacological interventions.⁷ Exercise is
77 recommended by several guidelines as a co-intervention in combination with
78 pharmacological interventions to treat patients with AS.^{2 8} Previous systematic
79 reviews⁹⁻¹¹ demonstrated that exercises have significant positive effects on pain, spinal
80 mobility, and physical function. However, they did not classify different types of
81 exercise, such as group exercise, individualized exercise, supervised exercise, home-
82 based exercise, and so on. Therefore, we do not know which is the best one. When no
83 studies exist that directly compare all relevant treatment choices, a network meta-
84 analysis can be performed by comparing the relative effects of treatments against a
85 common comparator or combining a variety of comparisons that are taken together
86 from one or more chains linking the treatments of interest.¹²

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

90

91 **METHODS**

92 **Design**

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

100

101 **Eligibility criteria**

102 1. Type of study

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

110 2. Participants

111 Trials enrolling adults, aged at least 18 years, with a diagnosis of AS according to the
112 Modified New York criteria¹⁵ or the Amor criteria¹⁶ or radiographic axial
113 spondyloarthritis (SpA) according to the criteria for axial SpA defined by the
114 Assessment of Spondyloarthritis International Society (ASAS)¹⁷ will be included.

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

117 3. Type of interventions

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

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3
4 121 Trials that compare an exercise intervention combined with a co-intervention
5
6 122 versus the co-intervention alone or the exercise intervention alone (e.g., an exercise
7
8 123 intervention plus anti-TNF α therapy versus anti-TNF α therapy alone, an exercise
9
10 124 intervention plus spa therapy versus the exercise intervention) will be considered.

11
12 125 Trails investigating exercise interventions with different setting (home, hospital, or
13
14 126 elsewhere) or different delivery method (individual, group, supervision, or mixed) will
15
16 127 be included.

17
18 128 Trials comparing an exercise intervention with no treatment, standard care or usual
19
20 129 physical activity will be considered.

21 130 4. Outcomes of interest

22 23 131 4.1 Primary outcomes

24
25 132 The Bath Ankylosing Spondylitis Functional Index (BASFI)¹⁹ is 10 item index that
26
27 133 evaluate the functional capacity in performing daily activities of patients with AS.
28
29 134 Higher score of the BASFI reflects greater impairment in functional capacity.

30
31 135 Pain will be measured based on a visual analogue scale (VAS) or numerical rating
32
33 136 scale (NRS). We will record data on back pain at night, total back pain, overall pain at
34
35 137 night, or overall pain. We will collect the highest pain score from the mentioned
36
37 138 alternatives. And the highest pain score on numeric value will be regarded as the final
38
39 139 pain score.

40
41 140 The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)²⁰ is the gold
42
43 141 standard for measuring and evaluating disease activity in AS. Higher score of the
44
45 142 BASDAI indicates greater disease activity.

46 47 143 4.2 Secondary outcomes

48
49 144 The Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) will
50
51 145 be used to evaluate the quality of life, with higher scores indicating better quality of
52
53 146 life.

54
55 147 The Bath Ankylosing Spondylitis Metrology Index (BASMI)²¹ is the most widely
56
57 148 reported, validated objective axial mobility measure, which consists of five steps:
58
59 149 cervical rotation, tragus to wall distance, lumbar side flexion, modified Schober's test
60
150 and intermalleolar distance. High scores mean severer limitation of movement.

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4 1515 152 **Data sources and search strategy**

6
7 153 We will systematically search PubMed, EMBASE and the Cochrane Library for
8
9 154 primary studies up to February 2019. The search strategy will combine free text words
10
11 155 and medical subject headings regarding exercise, spondyloarthritis and randomized
12
13 156 controlled trials. The detail of the search strategy for PubMed is shown in online
14
15 157 supplementary file S1. This search strategy will be modified as required for other
16
17 158 databases. Furthermore, we will also retrieve the World Health Organization (WHO)
18
19 159 International Clinical Trials Registry Platform and ClinicalTrials.gov to identify
20
21 160 ongoing trial registers. We will examine bibliographies of pertinent systematic reviews
22
23 161 and meta-analyses for additional related studies. We will not limit language of
24
25 162 publication or publication period.

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27 16328
29 164 **Study selection**

30
31 165 Two reviewers will independently check the titles and abstracts through the initial
32
33 166 retrieval. Publications not fulfilling the eligibility criteria will be eliminated. After
34
35 167 excluding the irrelevant publications, we will examine the full text of the remaining
36
37 168 publications based on the same eligibility criteria. Any discrepancies will be settled by
38
39 169 discussion and consensus. Excluded publications and the reasons for exclusion will be
40
41 170 reported and confirmed by a third investigator.

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43 17144
45 172 **Data extraction**

46
47 173 Data from included publications will be independently extracted by two reviewers using
48
49 174 a standardized data abstraction list. The following characteristic information will be
50
51 175 extracted: study characteristics (first author, publication year, study year, number of
52
53 176 centers, country and sponsor), patient characteristics (sample size, mean age, gender
54
55 177 ratio, the stage of the disease, and inclusion/exclusion criteria), intervention details for
56
57 178 each treatment group (e.g., number of intervention groups, exercise modality and the
58
59 179 detailed description, frequency and duration of the intervention, the duration of follow-
60
180 up, and co-interventions) and outcome measures (BASFI, BASDAI, BASMI, pain, and

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4 181 SF-36). We will prioritize the data at the end of the studies compared with the changes
5
6 182 from baseline in all the outcomes. Numerical data will be extracted to calculate pooled
7
8 183 estimations. If the study only reports SE, p value or CI, we will convert them into SD.²²
9
10 184 If the study reports median and IQR, we will calculate SD by dividing the IQR by 1.35
11
12 185 and considering the median equivalent to the mean.²² If the data are not reported in the
13
14 186 texts directly, we will infer them from the associated graphs. If data cannot be obtained,
15
16 187 we will contact the corresponding authors. Any disagreements will be settled by
17
18 188 discussion and consensus.

19 189

20 21 22 **Risk of bias assessment**

23 191 The Cochrane Risk of Bias Tool will be used to appraise the risk of bias for individual
24
25 192 studies.²³ Each study will be evaluated and scored as high, low, or unclear risk of bias
26
27 193 based on the following criteria: randomization, allocation concealment, blinding of
28
29 194 participants and personnel, blinding of outcome assessors, incomplete outcome data,
30
31 195 selective reporting and other biases. A study with a high risk of bias in one or more
32
33 196 domains will be viewed as high risk of bias. A study with a low risk of bias in all
34
35 197 domains will be considered as low risk of bias. If not, a study will be treated as unclear
36
37 198 risk of bias. Any disagreements were resolved by discussion and consensus.

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40 41 42 **Statistical analysis**

43 201 A traditional pairwise meta-analysis will be done when at least two studies exist for an
44
45 202 outcome. A random-effects model with the Hartung-Knapp-Sidik-Jonkstra method²⁴
46
47 203 will be used to estimate the effect size and 95% confidence interval (CI) accounting for
48
49 204 methodological and clinical heterogeneity across studies, with Stata, version 13.0 (Stata
50
51 205 Corp, College Station, TX).²⁵ We will use mean difference (MD) for a certain outcome
52
53 206 when more than 50 percent studies reporting the outcome use the same measurement.
54
55 207 Otherwise, standardized mean difference (SMD) will be used. The extent of between-
56
57 208 trial heterogeneity will be assessed with I² statistic, with values over 50% indicating
58
59 209 considerable heterogeneity.²⁶

60 210 We will perform network meta-analyses to merge direct and indirect comparisons.

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4 211 All network meta-analyses will be conducted using a Bayesian Markov chain Monte
5
6 212 Carlo (MCMC) framework in R version 3.2.5 software ([https://cran.r-](https://cran.r-project.org/src/base/R-3/)
7
8 213 [project.org/src/base/R-3/](https://cran.r-project.org/src/base/R-3/)) via the gemtc version 0.8-2 package. MD and 95% credible
9
10 214 interval (CrI) will be used as summary statistics to quantify the effect of different
11
12 215 exercise interventions. Random-effects and consistency models will be adopted in this
13
14 216 network meta-analysis, as they are considered to be the most conservative approach to
15
16 217 dealing with between-study heterogeneity.²⁷ To generate posterior distributions of
17
18 218 model parameters, 150 000 iterations of MCMC after 50 000 tuning iterations in three
19
20 219 chains will be run.²⁸ Convergence of iterations will be examined with the Gelman-
21
22 220 Rubin-Brooks diagnostic plots.²⁹ For any specific outcome, we will rank the probability
23
24 221 of each intervention being the best (superior to all other interventions), second best,
25
26 222 third best, etc.

27 223 The posterior mean residual deviance, an absolute measure of fit, will be computed.
28
29 224 The value of posterior mean residual deviance and the number of independent data
30
31 225 points will be assessed to check if the model fits the data satisfactorily.³⁰ To appraise
32
33 226 the consistency, we will use the following methods. Firstly, the model fit from the
34
35 227 consistency model will be compared with that from the inconsistency model.³¹
36
37 228 Secondly, network meta-analysis results (indirect evidence using the node-split
38
39 229 approach) will be compared with pairwise meta-analysis results (direct evidence in a
40
41 230 frequentist framework).³²

42 231 Clinical and methodological heterogeneity will be evaluated by checking the
43
44 232 characteristics and design of the included studies. Statistical heterogeneity in the
45
46 233 network will be assessed according to the heterogeneity parameter (I^2 or τ^2) derived
47
48 234 from the network meta-analysis. I^2 more than 50% indicates substantial heterogeneity.
49
50 235 Heterogeneity will be explored by fitting covariates (ie, mean age, sample size, the
51
52 236 duration of symptoms, the dose of exercise (frequency \times duration intensity), and the
53
54 237 duration of follow-up) in network meta-regression analyses.³³ Subgroup analyses will
55
56 238 be further conducted ground on the duration of symptoms (early or long-term disease)
57
58 239 and concomitant pharmacological treatment (anti-TNF agents, NSAIDs, or other
59
60 240 pharmacological interventions), if possible. Sensitivity analyses will be executed to test

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4 241 the robustness of outcomes by limiting analyses to studies with low risk of bias.

5 242 To examine the potential of small-study effects in the network, comparison-
6
7 243 adjusted funnel plots will be produced.³⁴ For the comparison-adjusted funnel plot, the
8
9 244 horizontal axis will represent the difference between study-specific effect sizes and the
10
11 245 comparison-specific summary effect. In the absence of small-study effects, the
12
13 246 comparison-adjusted funnel plot should be symmetric around the zero line.
14

15 247

17 248 **Quality of evidence**

19 249 We will follow the Grading of Recommendations, Assessment, Development and
20
21 250 Evaluation (GRADE) four-step approach to grade the quality of treatment effect
22
23 251 estimations from network meta-analysis.³⁵ Firstly, present direct and indirect treatment
24
25 252 estimates for each comparison of the evidence network. Secondly, rate the quality of
26
27 253 each direct and indirect effect estimate. Then, present the network meta-analysis
28
29 254 estimate for each comparison of the evidence network. At last, rate the quality of each
30
31 255 network meta-analysis effect estimate. According to risk of bias, inconsistency,
32
33 256 indirectness, imprecision and publication bias, the quality of evidence will be graded as
34
35 257 high, moderate, low, or very low.
36

37 258

39 259 **Patient and Public Involvement**

40 260 Patients or public will not be involved.
41

42 261

44 262 **ETHICS AND DISSEMINATION**

46 263 **Ethical issues**

48 264 As no primary data collection will be undertaken, no additional formal ethical
49
50 265 assessment and no informed consent are required.
51

52 266

54 267 **Publication plan**

56 268 This network meta-analysis will be submitted to a peer-reviewed journal. It will be
57
58 269 disseminated electronically and in print.
59

60 270

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4 271 **Contributors** S-LK, L-XC, Z-FY and R-SZ participated in the conception and design
5
6 272 of the study, including search strategy development. S-LK, L-XC, Z-FY and WH tested
7
8 273 the feasibility of the study. S-LK wrote the manuscript. All the authors critically
9
10 274 reviewed this manuscript and approved the final version.

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12 275

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14
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19 279 decision to publish, or preparation of the manuscript.

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23 281 **Competing interests** None declared.

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27 283 **Patient consent for publication** Not required.

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31 285 **Provenance and peer review** Not commissioned; externally peer reviewed.

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For peer review only

PubMed

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7 #1 "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
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10 groups[Title/Abstract]
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12 #3 ("Animals"[Mesh]) NOT "Humans"[Mesh]
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16 #5 "Spondylarthritis"[Mesh]
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23 OR AS[Title/Abstract]) OR axSpA[Title/Abstract]) OR axial spondyloarthritis[Title/Abstract]
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 - #16 "Physical Therapy Modalities"[Mesh]
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 - #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])
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 - #24 ((management[Title/Abstract]) OR intervention*[Title/Abstract]) OR treatment*[Title/Abstract]
 - #25 #23 AND #24
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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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	49
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-260
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-260
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-260
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	145-154
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	178-185
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	188-219
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	220-226
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	227-231
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	234-242

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-029991.R2
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Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Rheumatology
Keywords:	exercise, ankylosing spondylitis, network meta-analysis, Bayesian

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4 **1 Exercise interventions for ankylosing spondylitis: A protocol for a Bayesian**
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4 Shun-Li Kan¹, Ling-Xiao Chen², Zhi-Fang Yuan³, Wei Hu¹, Ru-Sen Zhu¹

6 ¹Department of Spine Surgery, Tianjin Union Medical Center, 190 Jieyuan Road,
7 Hongqiao District, Tianjin, China

8 ²Institute of Bone and Joint Research, The Kolling institute, Sydney Medical School,
9 The University of Sydney

10 ³Department of Respiratory and Critical Care Medicine, Tianjin Medical University
11 General Hospital, 154 Anshan Road, Heping District, Tianjin, China

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13 S-LK and L-XC contributed equally to this work.

14
15 Correspondence to

16 Dr Ru-Sen Zhu;

17 rszhuspine@163.com

31 **ABSTRACT**

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

40 **Methods and analysis:** We will conduct a systematic literature review of randomized
41 controlled trials that compare different types of exercise interventions for individuals
42 with AS. PubMed, EMBASE and the Cochrane Library will be searched up to February
43 2019. The primary outcomes are functional capacity, pain, and disease activity. The
44 risk of bias for individual studies will be evaluated according to the Cochrane
45 Handbook. A Bayesian network meta-analysis will be performed to compare the
46 efficacy of different types of exercise interventions. The quality of evidence will be
47 assessed by the Grading of Recommendations, Assessment, Development and
48 Evaluation (GRADE) approach.

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

52 **Protocol registration number:** PROSPERO CRD42019123099.

53 **Strengths and limitations of this study**

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

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4 61 of exercise interventions.

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6 62 **INTRODUCTION**

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8 63 Ankylosing spondylitis (AS) is a universal chronic inflammatory rheumatic disease
9
10 64 which predominantly influences the axial skeleton (e.g., spine, hips and shoulders).^{1 2}
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12 65 AS is characterized by inflammatory back pain which is caused by sacroiliitis and
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14 66 spondylitis.¹ Inflammatory back pain may happen in 70% to 80% of patients with AS.
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16 67 AS commonly starts early and about 10% to 20% of patients with AS commence to
17
18 68 develop the first symptoms before 16 years of age.^{3 4} It has reported that estimates for
19
20 69 the prevalence of AS vary from 0.01% to 1.8%.⁵ Patients with AS often experience
21
22 70 chronic back pain, stiffness, arthritis and enthesitis, which seriously affect patients'
23
24 71 health and quality of life, disturb their recreational activities, work, family life and
25
26 72 relationships, and result in considerable psychological distress and fears.

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28 73 Non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors,
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30 74 are recommended as the first-line drug intervention for reducing pain and stiffness.
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32 75 Biological disease modifying antirheumatic drugs have also proved effective for the
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34 76 manage inhibitors, the anti-interleukin-17 inhibitor, and so on.⁶ However, some patients
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36 77 suffering from AS do not react well to pharmacological interventions.⁷ Exercise is
37
38 78 recommended by several guidelines as a co-intervention in combination with
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40 79 pharmacological interventions to treat patients with AS.^{2 8} Previous systematic
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42 80 reviews⁹⁻¹¹ demonstrated that exercises have significant positive effects on pain, spinal
43
44 81 mobility, and physical function. However, they did not classify different types of
45
46 82 exercise, such as group exercise, individualized exercise, supervised exercise, home-
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48 83 based exercise, and so on. Therefore, we do not know which is the best one. When no
49
50 84 studies exist that directly compare all relevant treatment choices, a network meta-
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52 85 analysis can be performed by comparing the relative effects of treatments against a
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54 86 common comparator or combining a variety of comparisons that are taken together
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56 87 from one or more chains linking the treatments of interest.¹²

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58 88 Therefore, the purpose of this study is to comprehensively review the literature and
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60 89 determine the relative efficacy of different types of exercise interventions for
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91 90 individuals with AS using a Bayesian network meta-analysis.

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4 915 92 **METHODS**6 93 **Design**

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9 94 A network meta-analysis using a Bayesian framework will be implemented in this study.
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11 95 This protocol of network meta-analysis will be performed on the basis of the Preferred
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13 96 Reporting Items for Systematic review and Meta-Analysis Protocol (PRISMA-P),¹³ and
14
15 97 the reporting of the following network meta-analysis will obey the PRISMA extension
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17 98 statement for reporting of systematic reviews incorporating network meta-analysis of
18
19 99 health care interventions.¹⁴ This study has been registered at PROSPERO
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21 100 (<http://www.crd.york.ac.uk/PROSPERO>) with registration number CRD42019123099.
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25 102 **Eligibility criteria**26
27 103 1. Type of study

28
29 104 We will include randomized controlled trials comparing different exercise interventions,
30
31 105 and/or comparing a specific exercise intervention with no treatment, standard care or
32
33 106 usual physical activity. For cross-over studies, we only use the data before wash-out
34
35 107 period. We will not restrain the language or date of publication. We will divide the trial
36
37 108 duration into short-term follow-up (6 months) and long-term follow-up (12 months). If
38
39 109 the trial duration is closer to 6 months or 12 months, we will classify the trial duration
40
41 110 as short-term follow-up or long-term follow-up.

42
43 111 2. Participants

44
45 112 Trials enrolling adults, aged at least 18 years, with a diagnosis of AS according to the
46
47 113 Modified New York criteria¹⁵ or the Amor criteria¹⁶ or radiographic axial
48
49 114 spondyloarthritis (SpA) according to the criteria for axial SpA defined by the
50
51 115 Assessment of Spondyloarthritis International Society (ASAS)¹⁷ will be included.

52
53 116 We will exclude studies involving participants with non-radiographic axial SpA
54
55 117 according to the criteria for axial SpA defined by the ASAS.

56
57 118 3. Type of interventions

58
59 119 Any type of exercise interventions will be included. Exercise intervention is defined as
60
120 a type of physical activity that is planned, structured and repeated over a period of

1
2
3
4 121 time.¹⁸

5 122 Trials that compare an exercise intervention combined with a co-intervention
6
7 123 versus the co-intervention alone or the exercise intervention alone (e.g., an exercise
8
9 124 intervention plus anti-TNF α therapy versus anti-TNF α therapy alone, an exercise
10
11 125 intervention plus spa therapy versus the exercise intervention) will be considered.

12
13 126 Trails investigating exercise interventions with different setting (home, hospital, or
14
15 127 elsewhere) or different delivery method (individual, group, supervision, or mixed) will
16
17 128 be included.

18
19 129 Trials comparing an exercise intervention with no treatment, standard care or usual
20
21 130 physical activity will be considered.

22 23 131 4. Outcomes of interest

24 25 132 4.1 Primary outcomes

26
27 133 The Bath Ankylosing Spondylitis Functional Index (BASFI)¹⁹ is 10 item index that
28
29 134 evaluate the functional capacity in performing daily activities of patients with AS.
30
31 135 Higher score of the BASFI reflects greater impairment in functional capacity.

32
33 136 Pain will be measured based on a visual analogue scale (VAS) or numerical rating
34
35 137 scale (NRS). We will record data on back pain at night, total back pain, overall pain at
36
37 138 night, or overall pain. We will collect the highest pain score from the mentioned
38
39 139 alternatives. And the highest pain score on numeric value will be regarded as the final
40
41 140 pain score.

42
43 141 The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)²⁰ is the gold
44
45 142 standard for measuring and evaluating disease activity in AS. Higher score of the
46
47 143 BASDAI indicates greater disease activity.

48 49 144 4.2 Secondary outcomes

50
51 145 The Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) will
52
53 146 be used to evaluate the quality of life, with higher scores indicating better quality of
54
55 147 life.

56
57 148 The Bath Ankylosing Spondylitis Metrology Index (BASMI)²¹ is the most widely
58
59 149 reported, validated objective axial mobility measure, which consists of five steps:
60
150 cervical rotation, tragus to wall distance, lumbar side flexion, modified Schober's test

1
2
3
4 151 and intermalleolar distance. High scores mean severer limitation of movement.
5
6 152

7
8 153 **Data sources and search strategy**

9 154 We will systematically search PubMed, EMBASE and the Cochrane Library for
10
11 155 primary studies up to February 2019. The search strategy will combine free text words
12
13 156 and medical subject headings regarding exercise, spondyloarthritis and randomized
14
15 157 controlled trials. The detail of the search strategy for PubMed is shown in online
16
17 158 supplementary file S1. This search strategy will be modified as required for other
18
19 159 databases. Furthermore, we will also retrieve the World Health Organization (WHO)
20
21 160 International Clinical Trials Registry Platform and ClinicalTrials.gov to identify
22
23 161 ongoing trial registers. We will examine bibliographies of pertinent systematic reviews
24
25 162 and meta-analyses for additional related studies. We will not limit language of
26
27 163 publication or publication period.
28

29 164

30
31 165 **Study selection**

32
33 166 Two reviewers will independently check the titles and abstracts through the initial
34
35 167 retrieval. Publications not fulfilling the eligibility criteria will be eliminated. After
36
37 168 excluding the irrelevant publications, we will examine the full text of the remaining
38
39 169 publications based on the same eligibility criteria. Any discrepancies will be settled by
40
41 170 discussion and consensus. Excluded publications and the reasons for exclusion will be
42
43 171 reported and confirmed by a third investigator.
44

45 172

46 173 **Data extraction**

47
48 174 Data from included publications will be independently extracted by two reviewers using
49
50 175 a standardized data abstraction list. The following characteristic information will be
51
52 176 extracted: study characteristics (first author, publication year, study year, number of
53
54 177 centers, country and sponsor), patient characteristics (sample size, mean age, gender
55
56 178 ratio, the stage of the disease, and inclusion/exclusion criteria), intervention details for
57
58 179 each treatment group (e.g., number of intervention groups, exercise modality and the
59
60 180 detailed description, frequency and duration of the intervention, the duration of follow-

1
2
3
4 181 up, and co-interventions) and outcome measures (BASFI, BASDAI, BASMI, pain, and
5
6 182 SF-36). We will prioritize the data at the end of the studies compared with the changes
7
8 183 from baseline in all the outcomes. Numerical data will be extracted to calculate pooled
9
10 184 estimations. If the study only reports SE, p value or CI, we will convert them into SD.²²
11
12 185 If the study reports median and IQR, we will calculate SD by dividing the IQR by 1.35
13
14 186 and considering the median equivalent to the mean.²² If the data are not reported in the
15
16 187 texts directly, we will infer them from the associated graphs. If data cannot be obtained,
17
18 188 we will contact the corresponding authors. Any disagreements will be settled by
19
20 189 discussion and consensus.

21 190 22 23 191 **Risk of bias assessment**

24
25 192 The Cochrane Risk of Bias Tool will be used to appraise the risk of bias for individual
26
27 193 studies.²³ Each study will be evaluated and scored as high, low, or unclear risk of bias
28
29 194 based on the following criteria: randomization, allocation concealment, blinding of
30
31 195 participants and personnel, blinding of outcome assessors, incomplete outcome data,
32
33 196 selective reporting and other biases. A study with a high risk of bias in one or more
34
35 197 domains will be viewed as high risk of bias. A study with a low risk of bias in all
36
37 198 domains will be considered as low risk of bias. If not, a study will be treated as unclear
38
39 199 risk of bias. Any disagreements were resolved by discussion and consensus.

40 200 41 42 201 **Statistical analysis**

43
44 202 A traditional pairwise meta-analysis will be done when at least two studies exist for an
45
46 203 outcome. A random-effects model with the Hartung-Knapp-Sidik-Jonkstra method²⁴
47
48 204 will be used to estimate the effect size and 95% confidence interval (CI) accounting for
49
50 205 methodological and clinical heterogeneity across studies, with Stata, version 13.0 (Stata
51
52 206 Corp, College Station, TX).²⁵ We will use mean difference (MD) for a certain outcome
53
54 207 when more than 50 percent studies reporting the outcome use the same measurement.
55
56 208 Otherwise, standardized mean difference (SMD) will be used. The extent of between-
57
58 209 trial heterogeneity will be assessed with I^2 statistic, with values over 50% indicating
59
60 210 considerable heterogeneity.²⁶

1
2
3
4 211 We will perform network meta-analyses to merge direct and indirect comparisons.
5
6 212 All network meta-analyses will be conducted using a Bayesian Markov chain Monte
7
8 213 Carlo (MCMC) framework in R version 3.2.5 software ([https://cran.r-](https://cran.r-project.org/src/base/R-3/)
9
10 214 [project.org/src/base/R-3/](https://cran.r-project.org/src/base/R-3/)) via the gemtc version 0.8-2 package. MD and 95% credible
11
12 215 interval (CrI) will be used as summary statistics to quantify the effect of different
13
14 216 exercise interventions. Random-effects and consistency models will be adopted in this
15
16 217 network meta-analysis, as they are considered to be the most conservative approach to
17
18 218 dealing with between-study heterogeneity.²⁷ To generate posterior distributions of
19
20 219 model parameters, 150 000 iterations of MCMC after 50 000 tuning iterations in three
21
22 220 chains will be run.²⁸ Convergence of iterations will be examined with the Gelman-
23
24 221 Rubin-Brooks diagnostic plots.²⁹ For any specific outcome, we will rank the probability
25
26 222 of each intervention being the best (superior to all other interventions), second best,
27
28 223 third best, etc.

29 224 The posterior mean residual deviance, an absolute measure of fit, will be computed.
30
31 225 The value of posterior mean residual deviance and the number of independent data
32
33 226 points will be assessed to check if the model fits the data satisfactorily.³⁰ To appraise
34
35 227 the consistency, we will use the following methods. Firstly, the model fit from the
36
37 228 consistency model will be compared with that from the inconsistency model.³¹
38
39 229 Secondly, network meta-analysis results (indirect evidence using the node-split
40
41 230 approach) will be compared with pairwise meta-analysis results (direct evidence in a
42
43 231 frequentist framework).³²

44 232 Clinical and methodological heterogeneity will be evaluated by checking the
45
46 233 characteristics and design of the included studies. Statistical heterogeneity in the
47
48 234 network will be assessed according to the heterogeneity parameter (I^2 or τ^2) derived
49
50 235 from the network meta-analysis. I^2 more than 50% indicates substantial heterogeneity.
51
52 236 Heterogeneity will be explored by fitting covariates (ie, mean age, sample size, the
53
54 237 duration of symptoms, the dose of exercise (frequency \times duration intensity), and the
55
56 238 duration of follow-up) in network meta-regression analyses.³³ Subgroup analyses will
57
58 239 be further conducted ground on the duration of symptoms (early or long-term disease)
59
60 240 and concomitant pharmacological treatment (anti-TNF agents, NSAIDs, or other

1
2
3
4 241 pharmacological interventions), if possible. Sensitivity analyses will be executed to test
5
6 242 the robustness of outcomes by limiting analyses to studies with low risk of bias.

7
8 243 To examine the potential of small-study effects in the network, comparison-
9
10 244 adjusted funnel plots will be produced.³⁴ For the comparison-adjusted funnel plot, the
11
12 245 horizontal axis will represent the difference between study-specific effect sizes and the
13
14 246 comparison-specific summary effect. In the absence of small-study effects, the
15
16 247 comparison-adjusted funnel plot should be symmetric around the zero line.

17
18 248

19 249 **Quality of evidence**

20
21 250 We will follow the Grading of Recommendations, Assessment, Development and
22
23 251 Evaluation (GRADE) four-step approach to grade the quality of treatment effect
24
25 252 estimations from network meta-analysis.³⁵ Firstly, present direct and indirect treatment
26
27 253 estimates for each comparison of the evidence network. Secondly, rate the quality of
28
29 254 each direct and indirect effect estimate. Then, present the network meta-analysis
30
31 255 estimate for each comparison of the evidence network. At last, rate the quality of each
32
33 256 network meta-analysis effect estimate. According to risk of bias, inconsistency,
34
35 257 indirectness, imprecision and publication bias, the quality of evidence will be graded as
36
37 258 high, moderate, low, or very low.

38
39 259

40 260 **Patient and Public Involvement**

41
42 261 Patients or public will not be involved.

43
44 262

45 263 **ETHICS AND DISSEMINATION**

46 264 **Ethical issues**

47
48 265 As no primary data collection will be undertaken, no additional formal ethical
49
50 266 assessment and no informed consent are required.

51
52 267

53 268 **Publication plan**

54
55 269 This network meta-analysis will be submitted to a peer-reviewed journal. It will be
56
57 270 disseminated electronically and in print.

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4 271

5 272 **Contributors** S-LK, L-XC, Z-FY and R-SZ participated in the conception and design
6
7 273 of the study, including search strategy development. S-LK, L-XC, Z-FY and WH tested
8
9 274 the feasibility of the study. S-LK wrote the manuscript. All the authors critically
10
11 275 reviewed this manuscript and approved the final version.
12

13 276

14
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20
21 280 decision to publish, or preparation of the manuscript.
22

23 281

24
25 282 **Competing interests** None declared.
26

27 283

28
29 284 **Patient consent for publication** Not required.
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31 285

32
33 286 **Provenance and peer review** Not commissioned; externally peer reviewed.
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For peer review only

PubMed

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7 #1 "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
8
9 #2 (((((placebo[Title/Abstract]) OR randomized[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR
10 groups[Title/Abstract]
11
12 #3 ("Animals"[Mesh]) NOT "Humans"[Mesh]
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14 #4 (#1 OR #2) NOT #3
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16 #5 "Spondylarthritis"[Mesh]
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18 #6 "Spondylitis, Ankylosing"[Mesh]
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20 #7 "Sacroiliitis"[Mesh]
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22 #8 ((((((Bechterew Disease[Title/Abstract]) OR Marie-Struempell Disease[Title/Abstract]) OR Ankylosing Spondylitis[Title/Abstract])
23 OR AS[Title/Abstract]) OR axSpA[Title/Abstract]) OR axial spondyloarthritis[Title/Abstract]
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25 #9 (((axial[Title/Abstract]) OR spin*[Title/Abstract]) OR peripheral[Title/Abstract]) OR vertebral[Title/Abstract]
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27 #10 (((joint*[Title/Abstract]) OR spondyloarthritis[Title/Abstract]) OR arthritis[Title/Abstract]) OR ankylosing[Title/Abstract]
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33 #13 "Exercise"[Mesh]
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35 #14 "Exercise Therapy"[Mesh]
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15 #20 (((((program*[Title/Abstract]) OR therap*[Title/Abstract]) OR behavior*[Title/Abstract]) OR intervention*[Title/Abstract]) OR
16 train*[Title/Abstract]) OR activit*[Title/Abstract])
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24 #24 ((management[Title/Abstract]) OR intervention*[Title/Abstract]) OR treatment*[Title/Abstract]
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26 #25 #23 AND #24
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28 #26 ((((((Train*[Title/Abstract]) OR exercise*[Title/Abstract]) OR therap*[Title/Abstract]) OR fitness[Title/Abstract]) OR
29 program*[Title/Abstract]) OR reeducation[Title/Abstract]) OR rehab*[Title/Abstract])
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31 #27 (((home[Title/Abstract]) OR water[Title/Abstract]) OR spa[Title/Abstract]) OR group[Title/Abstract]
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33 #28 #26 AND #27
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35 #29 (((((((((sport*[Title/Abstract]) OR recreation*[Title/Abstract]) OR walk*[Title/Abstract]) OR swim*[Title/Abstract]) OR
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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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	49
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-260
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-260
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-260
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	145-154
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	178-185
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	188-219
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	220-226
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	227-231
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	234-242