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Complete List of Authors:	Xu, Jianglin; Beijing University of Chinese Medicine, Dongzhimen Hospital Zhang, Zhuo; Beijing University of Chinese Medicine, Dongzhimen Hospital Li, Yan; Beijing University of Chinese Medicine, Dongfang Hospital LIU, Jing; Beijing University of Chinese Medicine, Dongfang Hospital Wan, Jie; Beijing University of Chinese Medicine, Dongfang Hospital Feng, RuLi; Beijing University of Chinese Medicine, Dongzhimen Hospital Jin, Jialin; Beijing University of Chinese Medicine, Dongzhimen Hospital Huang, Cong; China Academy of Chinese Medical Sciences, Experimental Research Centre Mao, Tianshi; Beijing University of Chinese Medicine, Dongzhimen Hospital Ji, Xiang; Beijing University of Chinese Medicine, Dongzhimen Hospital Zhou, Kun; Beijing University of Chinese Medicine, Dongfang Hospital qian, lin; Beijing University of Chinese Medicine, Dongzhimen Hospital
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Effect of traditional Asian exercise on patients with chronic heart failure: a protocol for network meta-analysis of randomised controlled trials

Jianglin Xu,[1] Zhuo Zhang,[1] Yan Li,[2] Jing Liu,[2] Jie Wan,[2] Ruli Feng,[1] Jialin Jin,[1] Cong Huang,[3] Tianshi Mao,[1] Xiang Ji,[1] Kun Zhou,[2]* Qian Lin[1]*

[1] Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China.
[2] Dongfang Hospital, Beijing University of Chinese Medicine, Beijing, China.
[3] Experimental Research Centre, China Academy of Chinese Medical Sciences, Beijing,China

Jianglin Xu, Zhuo Zhang, Yan Li and Jing Liu contributed equally to this work and should be considered joint first authors.

Corresponding Author's information: Qian Lin, e-mail: linqian62@126.com, Kun Zhou, e-mail: dfzhk@126.com

ABSTRACT

Introduction Chronic heart failure (CHF) is a common disease in the worldwide, and imposes a substantial burden to the health-care system. In CHF, limited exercise capacity and affected mental well-being leads to a reduced quality of life (QOL). How to improve the QOL and exercise endurance is critical for CHF patients. Exercise therapy, such as some traditional Asian exercises (TAEs) including Taichi, Baduanjin and Yoga, plays an important role in the rehabilitation of patients with CHF. TAE is suitable for the rehabilitation of patients with CHF because of its soft movements and can relax the body and mind. Studies have shown that TAE can regulate the overall health status of the body and tolerate exercise tolerance, improve QOL and reduce rehospitalization rate in CHF patients. However, the difference in efficacy of TAE in patients with CHF is not yet clear. The main purpose of this study is to conduct a network meta-analysis (NMA) of randomised trials to determine the impact of TAE on CHF patients of different types, different causes and different NYHA heart function classifications, and to provide references for different types of CHF patients to choose

appropriate exercise rehabilitation therapy.

Methods and analysis The literature search will be retrieved from PubMed, the Cochrane Library, EMBASE, Web of Science, Chinese National Knowledge Infrastructure(CNKI), Wan Fang Database, Chinese biomedical literature service system (SinoMed) and Chinese Scientific Journals Database (VIP) from the date of their inception until December,31,2020. All randomised controlled trials (RCTs) that evaluated the effects of three different TAE therapies (Taichi, Baduanjin and Yoga) on CHF patients will be included. The primary outcomes are exercise capacity [6-min walking distance(6MWD)], QOL tested with the Minnesota Living with Heart Failure Questionnaire (MLHF). Secondary outcomes include the levels of N-terminal pro brain natriuretic peptide(NT-proBNP), left ventricular ejection fraction, systolic blood pressure, diastolic blood pressure, and peak VO_2. For included articles, two reviewers will independently extract the data, and Cochrane Collaboration's tool will be used to assess risk of bias. We will perform the Bayesian network meta-analyses to pool all treatment effects. The ranking probabilities for the optimal intervention of various treatments (Taichi, Baduanjin or Yoga) will be estimated by the mean ranks and surface under the cumulative ranking curve. Subgroup analysis for different types, different causes and different NYHA heart function classifications of CHF will be performed. We will use the Grading of Recommendations Assessment, Development and Evaluation System to assess the quality of evidence contributing to each network estimate.

Ethics and dissemination The results will be disseminated through peer-reviewed publications. They will provide useful information to inform clinicians on the potential functions of TAE in CHF, and to provide consolidated evidence for clinical practice and further research of TAE.

PROSPERO registration number CRD42020179304

Strengths and limitations of this study

- ► As far as we know, this will be the first network meta-analysis to compare the various forms of traditional Asian exercise (TAE).
- ► This is the first study to use network meta-analysis to evaluate the effectiveness and differences of TAE (Taichi, Baduanjin and Yoga) in CHF patients.
- ► Due to well established eligible criteria, rigorous data collection and quality assessment, standardized statistical analysis, subgroup and sensitivity analyses, study strength may be increased and heterogeneity may be reduced.
- ► The drawbacks of this study may potentially reside in the changes in the frequency and duration of treatment, which may be result in methodological heterogeneity.

Background

Chronic heart failure (CHF) refers to a condition that the heart is unable to pump sufficient blood to maintain the body's needs, and is always caused by various cardiopulmonary diseases.[1] CHF is usually associated with high health expenditure and significant morbidity and mortality. Approximately 50% individuals diagnosed with HF will die within 5 years and the high cost of HF-related hospitalization is about $23 077 per patient in the United States.[2 3] In CHF, limited exercise capacity and affected mental well-being leads to a markedly reduced quality of life (QOL).[4] But progress on new drugs of CHF has been minimal. How to improve the QOL and exercise endurance is critical for CHF patients. More and more regions focus on the prevention and treatment of HF by means of exercise and mental regulation so that patients with CHF can have a longer survival time or a higher QOL.[5]

Traditional Asian exercise (TAE, including Taichi, Baduanjin and Yoga) (figure 1), plays an important role in the rehabilitation of patients with CHF and is suitable for the rehabilitation of patients with CHF because of its soft movements and mind relaxation. TAE has been widely used in China for the prevention of cardiovascular disease and gained popularity in Western countries as an alternative form of exercise. Many studies have demonstrated the safety and efficacy of exercise rehabilitation for CHF, which can reduce mortality and hospitalization rates in patients with CHF, and improve exercise tolerance and QOL in patients[6-8]. Taichi emphasizes on guiding the body movement

following people's thoughts. These movements are considered to be low risk interventions and studies have found positive effects of TAE on exercise load and QOL in CHF patients. Long-term practice of Taichi can relax the whole body and fully exercise the bones and muscles. Taichi exercise may benefit patients at all stages of HF, by enhancing QOL and exercise capacity, and reducing depressive symptoms.[9 10] Baduanjin is composed of eight different basic movements, which are soft and slow, smooth and coherent, and suitable for patients with HF. Yoga combines body movement, breathing and mind control, and proves to improve the QOL in patients with HF and increase exercise capacity (peak VO_2).[11 12] Many published systematic reviews have focused on specific forms of TAE, such as Taichi or Baduanjin[7 13].

However, the difference in efficacy of TAE in patients with CHF is not yet clear. The main purpose of this study is to conduct a network meta-analysis (NMA) of randomised controlled trials (RCTs) to determine the effect of TAE on CHF patients of different types, different causes and different New York Heart Association (NYHA) heart function classifications, and to provide references for different types of CHF patients to choose appropriate exercise rehabilitation therapy.

METHODS AND ANALYSIS

Study type:

All RCTs that evaluated the effects of three different TAE therapies (Taichi, Baduanjin and Yoga) on CHF patients will be included. For cross-over studies and cluster randomized trials, we will include only the first-phase treatment. Non-RCTs, duplicate reports, pilot studies and studies lacking primary outcome data will be excluded.

Participants:

We will include adults (age≥18 years) with stable CHF (NYHA class I-III) based on WHO's diagnosis of CHF. HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF) will be included. There are no limitations on the participant's characteristics (such as sex, comorbidity and treatment course). Patients will be excluded as follows: HF caused by congenital heart disease, unstable structural valvular diseases, dilated cardiomyopathy and chronic obstructive pulmonary disease; Patients with unstable

vital signs: resting heart rate>100beats/min and blood pressure >180/110mmHg or <90/60mmHg.

Intervention/control:

Studies reporting TAE : Taichi, Baduanjin and Yoga, any form of exercise such as "simplified 24 forms" , with or without education or usual care, understood as repeated bouts of exercise over time involving more than 1 sessions/week at least will be included. For comparisons, both active (e g, aerobic exercise, endurance training (cycling and walking)) or non-active (e g, usual care, pharmacologic therapy, dietary, exercise counseling and education sessions) controls compared with TAE will be eligible for inclused. We will also obtain informations from placebo controlled trials.

Outcomes:

Primary outcomes

1. Exercise capacity tested by 6-min walking distance(6MWD);
2. QOL tested with the Minnesota Living with Heart Failure Questionnaire (MLHF);

Secondary outcomes

1. Levels of N-terminal pro brain natriuretic peptide (NT-proBNP);
2. Left ventricular ejection fraction (LVEF);
3. Systolic blood pressure (SBP), diastolic blood pressure (DBP);
4. Peak oxygen uptake (peak VO_2).

Search strategy:

The literature search will be retrieved from PubMed, the Cochrane Library, EMBASE, Web of Science, Chinese National Knowledge Infrastructure(CNKI), Wan Fang Database, Chinese biomedical literature service system (SinoMed) and Chinese Scientific Journals Database (VIP) from the inception to December,31,2020.

The following search terms will be included in the search strategy:(tai chi OR taiji or taiqi OR tai ji quan OR tai chi chuan OR taichi qigong OR shadowboxing OR baduanjin OR Baduanjin exercise OR eight section brocades OR yoga OR yogic OR asana or pranayama OR dhyana)AND(chronic heart failure OR heart failure with reduced ejection fraction OR heart failure with mid-range ejection fraction OR heart failure with preserved ejection fraction OR cardiac failure OR heart failure OR heart decompensation OR right-sided heart failure OR myocardial failure OR congestive heart failure OR left sided heart failure OR ventricular failure). The search strategy for PubMed is shown in table 1. Previous reviews, meta-analyses and relevant references cited in the selected studies will be screened. We will conduct a search of the following trial registers for ongoing or unpublished trials: Chinese Clinical Trial Registry (ChCTR), ClinicalTrials.gov, International Clinical Trials Registry Platform(WHO-

ICTRP). For unpublished or incomplete data, we will contact the original authors to supplement data. The search strategy will be independently conducted by four reviewers (JX, JL, ZZ, KZ), and disagreements will be discussed and solved by consensus or involving a third member of the review team (QL).

Table1 Search strategy for the PubMed database

Number.	Search terms
1	tai chi
2	taiji
3	taiqi
4	tai ji quan
5	tai chi chuan
6	taichi qigong
7	shadowboxing
8	baduanjin
9	Baduanjin exercise
10	eight section brocades
11	yoga
12	yogic
13	asana
14	pranayama
15	dhyana
16	OR 1-15
17	chronic heart failure
18	heart failure with reduced ejection fraction
19	heart failure with mid-range ejection fraction
20	heart failure with preserved ejection fraction
21	cardiac failure
22	heart failure
23	heart decompensation
24	right-sided heart failure
25	myocardial failure
26	congestive heart failure
27	left sided heart failure
28	ventricular failure
29	OR 17-28
30	16 and 29

Study selection

Endnote X8 will be used to manage literatures and exclude duplicate records. Three reviewers (RF, TM, XJ) will screen the titles and abstracts of all the retrieved articles and remove those failing to meet the eligible criteria independently. They will then get the full texts for potentially eligible studies to further determine whether they fulfil the same eligible criteria. Any disagreements will be resolved by a third review author (JL) for arbitration. The selection process will be described in a PRISMA flow chart(http://www.prisma-statement.org) (figure 2).[14]

Data extraction

We will design a data extraction form from a random sample of three studies to ensure consistency and reduce bias and improve validity and reliability during reviewing. Then modify the form based on the problems in the pilot stage. Four review authors (JX, YL, CH, JJ) will independently extract study characteristics and outcome data from the included studies. Two reviewers (YL, ZZ) will re-check that the data are entered correctly into the final data set. Any disagreements will be resolved by discussion with the whole team or by involving a third review author (KZ).

The following items will be extracted:

1. Study characteristics: lead author, publication year and journal

2. Methods: study design, duration of study, details of trial design (i.e., randomization, allocation concealment, blinding)

3. Participants: sample size, number randomized, number of losing follow-up visits/withdrawing from studies, diagnostic criteria of CHF, mean age, age range, sex, design setting, country, course of treatment and severity of CHF, comorbidities, and inclusion and exclusion criteria.

4. Intervention: intervened measures and control therapy (type of exercise, length, frequency, number of sessions, and duration of each session), response event, non-response event

5. Outcomes: primary and secondary outcomes specified and collected, time points reported, mean value, and mean difference.

6. Miscellaneous: funding source, and notable conflicts of interest of trial authors, register ID.

Dealing with missing data

We will initially contact authors through email or telephone to obtain any missing data. If we are unable to obtain the data, we will analyzes the available data and assess the potential impact of missing data on the study results in the discussion section.

Risk of bias assessment

Three reviewers (JL, XJ, JW) will assess risk of bias in the included studies using the Cochrane Collaboration's tool.[15] We will resolve any disagreements by discussion or another review author. The risk of bias in the following domains will be evaluated: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias (e.g., industry-sponsored funding, lack of individual randomization). We will grade each potential source of bias as high, low, or unclear. Since double-blinding is difficult to achieve in trials, performance bias will likely be present in all trials. For objective outcomes such as NT-proBNP, performance bias and detection bias might not be so critical so that we can grade this trial low risk if bias of other remaining domains is also ranked as low. However, for highly subjective outcomes such as QOL, we may consider that both blinding of participants and outcome assessment are important, and high risk of bias for one or more key domains within a study will be judged as high risk of bias. When it comes to selective outcome reporting, we will grade with regard to the two primary outcomes in our study. Low risk of bias is rated if the number of responders or total dropouts is reported. We will rate at high risk of bias if neither is reported. It will be rated as unclear risk of bias otherwise.

Statistical synthesis of study data

Methods for direct treatment comparisons

We will use DerSimonian–Laird random effects model to perform Standard pairwise meta-analysis. Dichotomous outcomes will be calculated as odds ratio (OR) and continuous data as standardised mean difference (SMD), both with corresponding 95% confidence intervals (CIs). Study heterogeneity will be assessed by Cochran Q test and presented as the I^2-statistic. Sensitivity analysis of pairwise meta-analysis will be conducted to validate the robustness of the results.

Methods for indirect and mixed comparisons

A random-effects NMA will be conducted within a Bayesian framework.[16] We will use the Markov Chain Monte Carlo algorithm by applying WinBUGS 1.4.3. OR, SMD or weighted mean difference (WMD) will be calculated with 95% CIs. We will obtain a comprehensive ranking of all treatments. The surface under the cumulative ranking curve (SUCRA) and the mean ranks will be used for the treatment hierarchy. We will describe SUCRA with percentages.

Examination of assumptions in NMA (consistency, transitivity and heterogeneity)

We will use local method, global method and node-splitting methods to evaluate

consistency. Local method evaluates inconsistency in each closed loop using a loop-specific approach. Global method compares the difference between consistency and inconsistency models based on a $\chi 2$ test using a design-by-treatment approach.[17] The node splitting method will be used to assesses the inconsistency of the model by separating evidence of one particular comparison into direct and indirect evidence. To assess global heterogeneity in the network, we will calculate the I^2 and generate predictive interval plot.[18] Transitivity, a key underlying assumption of NMA, will be evaluated by comparing the distribution of clinical and methodological variables that can act as effect modifiers across treatment comparisons.

All analyses will be performed using R 3.5.0 (gemtc package, network meta analysis, assessment of global heterogeneity, network meta regression, and SUCRA graphs), and STATA 13.0 (pairwise meta-analysis, estimation of inconsistency, transitivity and local heterogeneity, funnel plot).

Subgroup analysis and sensitivity analysis

To assess whether the results were influenced by study characteristics (effect modifiers), subgroup analysis for primary outcome will be conducted based on age group, treatment duration, years of CHF, sample size, quality of study, comorbidity and sponsorship. Subgroup analysis for different types, different causes and different NYHA heart function classifications of CHF will also be performed. Inconsistent sources will be explored by performing univariate and multivariate meta-regressions a network meta-regression. We will conduct sensitivity analysis to exclude trials with small sample sizes (i.e., arms of less than 10 patients) and remove trails that report the generation of non-random sequences. All of these analyses were performed in STATA 13.0.

Publication bias

Publication bias will be assessed by performing Egger's regression test. Additionally, a comparison-adjusted funnel plot will be used to investigate whether results in imprecise trials differ from those in more precise ones.

Quality of evidence

Two reviewers(CH, ZZ) will use the GRADE(The Grading of Recommendations Assessment, Development, and Evaluation) framework to assess the quality of evidence contributing to each network estimate. The study limitations, imprecision, inconsistency, indirectness and publication bias will be investigated. Four levels of quality of evidence will be used: high, moderate, low or very low.

DISCUSSION

Taichi, Baduanjin and Yoga CHF is considered to be the end stage of heart disease manifested with reduced exercise ability and poor QOL. Exercise training is widely regarded as a non-drug intervention to improve patient's exercise tolerance and QOL.

Exercise-based cardiac rehabilitation is safe and effective for CHF. Previous studies have shown that Taichi, Baduanjin and Yoga are beneficial for CHF. Taichi improves body functions,[19] such as lowering blood pressure in adults with hypertension,[20 21] enhancing aerobic endurance[22 23],reducing stress, anxiety and depression, and ameliorating QOL.[24 25] Baduanjin can reduce the load of the heart, increase the body's ability to transport and utilize oxygen in blood circulation,[26 27] and thus improving HF. Yoga can improve peak VO_2 in CHF patients, which is considered as another method of exercise training for CHF patients.[11]

Therefore, Taichi, Baduanjin and Yoga are effective exercise ways to treat CHF, however, the difference in efficacy of TAE in patients with CHF is not yet clear. We attempt to conduct a NMA of a sufficient number of randomized controlled trials to determine the impact of TAE on CHF patients of different types, different causes and different NYHA heart function classifications, and to provide stronger evidence to help CHF patients choose more appropriate exercise rehabilitation therapy. To our knowledge, this review will be the first to assess the impact of TAE on patients with CHF, and we hope that the results of this study can provide help for the rehabilitation of patients with CHF.

Ethics and dissemination

This protocol is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and has been registered at the International Prospective Register of Systematic Reviews (CRD42020179304; available from https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=179304)

As no individual patient data will be used in this NMA, ethical approval is not required. We aim to publish this NMA in a peer-reviewed journal. The results of this NMA will provide a more comprehensive and more reliable information about the effect of TAE for patients with CHF.

Contributors

QL, KZ, JX, ZZ YL and JLconceived and designed the study. JX and ZZ drafted this protocol. JL YL and ZZ revised it. JW, RF, TM, CH, ZZ, JJ and XJ developed the search strategies and conducted data collection. All authors have read this manuscript and approved the publication of this protocol. Jianglin Xu, Zhuo Zhang, Yan Li and Jing Liu contributed equally to this work and should be considered joint first authors. Both Qian Lin and Kun Zhou are corresponding authors.

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ORCID iDs
Jianglin Xu https://orcid.org/0000-0002-2006-7101
Zhuo Zhang https://orcid.org/0000-0003-4435-8509
Yan Li https://orcid.org/0000-0002-7619-2809
Jing Liu https://orcid.org/0000-0002-0729-502X
Tianshi Mao https://orcid.org/0000-0003-4676-7584
Xiang Ji https://orcid.org/0000-0003-1305-713X
Kun Zhou https://orcid.org/0000-0002-4058-7497
Qian Lin https://orcid.org/0000-0001-9166-5099

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Figure legend

Figure 1 Presentation of three traditional Asian exercise (A) Taichi， (B) Baduanjin, and (C) Yoga.The pictured individual has agreed to publish his image.

Figure 2 Flowchart of the study selection process.

A B C

Figure 1 Presentation of three traditional Asian exercise (A) Taichi, (B) Baduanjin, and (C) Yoga.The pictured individual has agreed to publish his image.

169x72mm (600 x 600 DPI)

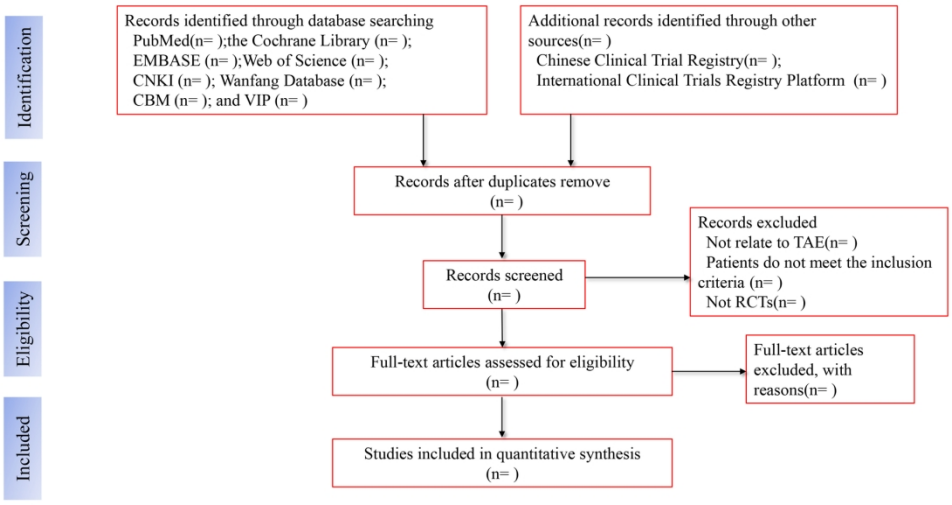

Figure 2 Flowchart of the study selection process.

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Complete List of Authors:	Xu, Jianglin; Beijing University of Chinese Medicine, Dongzhimen Hospital Zhang, Zhuo; Beijing University of Chinese Medicine, Dongzhimen Hospital Li, Yan; Beijing University of Chinese Medicine, Dongfang Hospital LIU, Jing; Beijing University of Chinese Medicine, Dongfang Hospital Wan, Jie; Beijing University of Chinese Medicine, Dongfang Hospital Feng, RuLi; Beijing University of Chinese Medicine, Dongzhimen Hospital Jin, Jialin; Beijing University of Chinese Medicine, Dongzhimen Hospital Huang, Cong; China Academy of Chinese Medical Sciences, Experimental Research Centre Mao, Tianshi; Beijing University of Chinese Medicine, Dongzhimen Hospital Ji, Xiang; Beijing University of Chinese Medicine, Dongzhimen Hospital Zhou, Kun; Beijing University of Chinese Medicine, Dongfang Hospital qian, lin; Beijing University of Chinese Medicine, Dongzhimen Hospital
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Keywords:	REHABILITATION MEDICINE, Heart failure < CARDIOLOGY, COMPLEMENTARY MEDICINE

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Effect of traditional Asian exercise on patients with chronic heart failure: a protocol for network meta-analysis of randomised controlled trials

Jianglin Xu,[1] Zhuo Zhang,[1] Yan Li,[2] Jing Liu,[2] Jie Wan,[2] Ruli Feng,[1] Jialin Jin,[1] Cong Huang,[3] Tianshi Mao,[1] Xiang Ji,[1] Kun Zhou,[2]* Qian Lin[1]*

[1] Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China.
[2] Dongfang Hospital, Beijing University of Chinese Medicine, Beijing, China.
[3] Experimental Research Centre, China Academy of Chinese Medical Sciences, Beijing,China

Jianglin Xu, Zhuo Zhang, Yan Li and Jing Liu contributed equally to this work and should be considered joint first authors.

Corresponding Author's information: Qian Lin, e-mail: linqian62@126.com, Kun Zhou, e-mail: dfzhk@126.com

ABSTRACT

Introduction Chronic heart failure (CHF) is a common disease worldwide, and imposes a substantial burden to the health-care system. In CHF, limited exercise capacity and affected mental well-being leads to a reduced quality of life (QOL). How to improve the QOL and exercise endurance is critical for CHF patients. Exercise therapy, such as some traditional Asian exercises (TAEs) including Taichi, Baduanjin and Yoga, plays an important role in the rehabilitation of patients with CHF. TAE is suitable for the rehabilitation of patients with CHF because of its soft movements and can relax the body and mind. Studies have shown that TAE can regulate the overall health status of the body and exercise tolerance, improve QOL and reduce rehospitalization rate in CHF patients. However, the difference in efficacy of TAE in patients with CHF is not yet clear. The main purpose of this study is to conduct a network meta-analysis (NMA) of randomised trials to determine the impact of TAE on CHF patients of different types, different causes and different NYHA heart function classifications, and to provide references for different types of CHF patients to choose

appropriate exercise rehabilitation therapy.

Methods and analysis The literature search will be retrieved from PubMed, the Cochrane Library, EMBASE, Web of Science, Chinese National Knowledge Infrastructure(CNKI), Wan Fang Database, Chinese biomedical literature service system (SinoMed) and Chinese Scientific Journals Database (VIP) from the date of their inception until August 1,2021. All randomised controlled trials (RCTs) that evaluated the effects of three different TAE therapies (Taichi, Baduanjin and Yoga) on CHF patients will be included. The primary outcomes are exercise capacity [6-min walking distance(6MWD)], QOL tested with the Minnesota Living with Heart Failure Questionnaire (MLHF). Secondary outcomes include the levels of N-terminal pro brain natriuretic peptide(NT-proBNP), left ventricular ejection fraction, systolic blood pressure, diastolic blood pressure, and peak VO_2. For included articles, two reviewers will independently extract the data, and Cochrane Collaboration's tool will be used to assess risk of bias. We will perform the Bayesian network meta-analyses to pool all treatment effects. The ranking probabilities for the optimal intervention of various treatments (Taichi, Baduanjin or Yoga) will be estimated by the mean ranks and surface under the cumulative ranking curve. Subgroup analysis for different types, different causes and different NYHA heart function classifications of CHF will be performed. We will use the Grading of Recommendations Assessment, Development and Evaluation System to assess the quality of evidence contributing to each network estimate.

Ethics and dissemination The results will be disseminated through peer-reviewed publications. They will provide useful information to inform clinicians on the potential functions of TAE in CHF, and to provide consolidated evidence for clinical practice and further research of TAE.

PROSPERO registration number CRD42020179304

Strengths and limitations of this study

- ► As far as we know, this will be the first network meta-analysis to compare the various forms of traditional Asian exercise (TAE).
- ► This is the first study to use network meta-analysis to evaluate the effectiveness and differences of TAE (Taichi, Baduanjin and Yoga) in CHF patients.
- ► Due to well established eligible criteria, rigorous data collection and quality assessment, standardized statistical analysis, subgroup and sensitivity analyses, study strength may be increased and heterogeneity may be reduced.
- ► The drawbacks of this study may potentially reside in the changes in the frequency and duration of treatment, which may be result in methodological heterogeneity.

Background

Chronic heart failure (CHF) refers to a condition that the heart is unable to pump sufficient blood to maintain the body's needs, and is always caused by various cardiopulmonary diseases.[1] CHF is usually associated with high cost and significant morbidity and mortality. Approximately 50% individuals diagnosed with HF will die within 5 years and the high cost of HF-related hospitalization is about $23 077 per patient in the United States.[2 3] In CHF, limited exercise capacity and affected mental well-being leads to a markedly reduced quality of life (QOL).[4] But progress on new drugs of CHF has been minimal. How to improve the QOL and exercise endurance is critical for CHF patients. More and more regions focus on the prevention and treatment of HF by means of exercise and mental regulation so that patients with CHF can have a longer survival time or a higher QOL.[5]

Traditional Asian exercise (TAE, including Taichi, Baduanjin and Yoga) (figure 1), plays an important role in the rehabilitation of patients with CHF and is suitable for the rehabilitation of patients with CHF because of its soft movements and mind relaxation. TAE has been widely used in China for the prevention of cardiovascular disease and gained popularity in Western countries as an alternative form of exercise. Many studies have demonstrated the safety and efficacy of exercise rehabilitation for CHF, which can reduce mortality and hospitalization rates in patients with CHF, and improve exercise tolerance and QOL in patients.[6-8] Taichi emphasizes on guiding the body movement following people's thoughts. These movements are considered to be low risk

interventions and studies have found positive effects of TAE on exercise load and QOL in CHF patients. [9 10] Long-term practice of Taichi can relax the whole body and fully exercise the bones and muscles. Taichi exercise may benefit patients at all stages of HF, by enhancing QOL and exercise capacity, and reducing depressive symptoms.[11 12] Baduanjin is composed of eight different basic movements, which are soft and slow, smooth and coherent, and suitable for patients with HF. Yoga combines body movement, breathing and mind control, and proves to improve the QOL in patients with HF and increase exercise capacity (peak VO_2). [9 13] Many published systematic reviews have focused on specific forms of TAE, such as Taichi or Baduanjin.[7 10]

Exercise intensity is closely related to the pumping ability of the heart, endothelial system and mitochondrial function in skeletal muscle, which is the cause for influencing peak VO_2. [14] Taichi and Baduanjin can be classified as a mild to moderate form of exercise intensity, while Yoga is as moderate form of exercise intensity. [15 16] Moreover, participants of Yoga may only perform breathing exercises or meditate at the same time. This is different from Tai Chi and Baduanjin, which emphasis on the coordination of breathing and exercise. Recently, a large cohort studies showed that a strong and dose-dependent association of physical activity with HF with preserved ejection fraction (HFpEF) but not with HF with reduced ejection fraction (HFrEF). [17] Further consider the diversity of the etiology of HFrEF and HFpEF. Therefore, TAE may have different effects on different types, different causes and different New York Heart Association (NYHA) heart function classifications of CHF.

The main purpose of this study is to conduct a network meta-analysis (NMA) of randomised controlled trials (RCTs) to determine the effect of TAE on CHF patients of different types, different causes and different New York Heart Association (NYHA) heart function classifications, and to provide references for different types of CHF patients to choose appropriate exercise rehabilitation therapy.

METHODS AND ANALYSIS

Design

This study will be reported following the Preferred Reporting Items for Systematic

Review and Meta-Analysis Protocols (PRISMA-P) guidelines (supplemental file 1).

Study type

All RCTs that evaluated the effects of three different TAE therapies (Taichi, Baduanjin and Yoga) on CHF patients will be included. For cross-over studies and cluster randomized trials, we will include only the first-phase treatment. Non-RCTs, duplicate reports, pilot studies and studies lacking primary outcome data will be excluded.

Participants

We will include adults (age≥18 years) with stable CHF (NYHA class I-III) based on WHO's diagnosis of CHF. HFrEF [left ventricular ejection fraction (LVEF)<40%), HF with mid-range ejection fraction (HFmrEF, 40%≤LVEF≤49%) and HFpEF (LVEF≥ 50%) will be included. There are no limitations on the participant's characteristics (such as sex, comorbidity and treatment course). Patients will be excluded as follows: HF caused by congenital heart disease, unstable structural valvular diseases, dilated cardiomyopathy and chronic obstructive pulmonary disease; Patients with unstable vital signs: resting heart rate>100beats/min and blood pressure >180/110mmHg or <90/60mmHg.

Intervention/control

Studies reporting TAE : Taichi, Baduanjin and Yoga, any form of exercise such as "simplified 24 forms" , with or without education or usual care, understood as repeated bouts of exercise over time involving more than 4 weeks at least will be included. For comparisons, both active (e g, aerobic exercise, endurance training (cycling and walking)) or non-active (e g, usual care, pharmacologic therapy, dietary, exercise counseling, education sessions and psychosocial interventions) controls compared with TAE will be eligible for included. We will also obtain informations from placebo controlled trials.

Outcomes

Primary outcomes

1. Peak oxygen uptake (peak VO_2);
2. Exercise capacity tested by 6-min walking distance(6MWD);
3. QOL tested with the Minnesota Living with Heart Failure Questionnaire (MLHF);

Secondary outcomes

1. Levels of N-terminal pro brain natriuretic peptide (NT-proBNP);
2. LVEF;
3. Systolic blood pressure (SBP), diastolic blood pressure (DBP);

Search strategy

The literature search will be retrieved from PubMed, the Cochrane Library, EMBASE, Web of Science, Chinese National Knowledge Infrastructure(CNKI), Wan Fang Database, Chinese biomedical literature service system (SinoMed) and Chinese Scientific Journals Database (VIP) from the inception to August 1,2021.

The following search terms will be included in the search strategy:(tai chi OR taiji or taiqi OR tai ji quan OR tai chi chuan OR taichi qigong OR shadowboxing OR baduanjin OR Baduanjin exercise OR eight section brocades OR yoga OR yogic OR asana or pranayama OR dhyana)AND(chronic heart failure OR heart failure with reduced ejection fraction OR heart failure with mid-range ejection fraction OR heart failure with preserved ejection fraction OR cardiac failure OR heart failure OR heart decompensation OR right-sided heart failure OR myocardial failure OR congestive heart failure OR left sided heart failure OR ventricular failure). The search strategy for PubMed is shown in table 1 and supplemental file 2. Previous reviews, meta-analyses and relevant references cited in the selected studies will be screened. We will conduct a search of the following trial registers for ongoing or unpublished trials: Chinese Clinical Trial Registry (ChCTR), ClinicalTrials.gov, International Clinical Trials Registry Platform(WHO-ICTRP). For unpublished or incomplete data, we will contact the original authors to supplement data. The search strategy will be independently conducted by four reviewers (JX, JL, ZZ, KZ), and disagreements will be discussed and solved by consensus or involving a third member of the review team (QL).

Table1 Search strategy for the PubMed database

Number.	Search terms
1	tai chi
2	taiji
3	taiqi
4	tai ji quan
5	tai chi chuan
6	taichi qigong
7	shadowboxing
8	baduanjin
9	Baduanjin exercise
10	eight section brocades
11	yoga
12	yogic
13	asana

14	pranayama
15	dhyana
16	OR 1-15
17	chronic heart failure
18	heart failure with reduced ejection fraction
19	heart failure with mid-range ejection fraction
20	heart failure with preserved ejection fraction
21	cardiac failure
22	heart failure
23	heart decompensation
24	right-sided heart failure
25	myocardial failure
26	congestive heart failure
27	left sided heart failure
28	ventricular failure
29	OR 17-28
30	16 and 29

Study selection

Endnote X8 will be used to manage literatures and exclude duplicate records. Three reviewers (RF, TM, XJ) will screen the titles and abstracts of all the retrieved articles and remove those failing to meet the eligible criteria independently. They will then get the full texts for potentially eligible studies to further determine whether they fulfil the same eligible criteria. Any disagreements will be resolved by a third review author (JL) for arbitration. The selection process will be described in a PRISMA flow chart(http://www.prisma-statement.org) (figure 2).[18]

Data extraction

We will design a data extraction form from a random sample of three studies to ensure consistency and reduce bias and improve validity and reliability during reviewing. Then modify the form based on the problems in the pilot stage. Four review authors (JX, YL, CH, JJ) will independently extract study characteristics and outcome data from the included studies. Two reviewers (YL, ZZ) will re-check that the data are entered correctly into the final data set. Any disagreements will be resolved by discussion with the whole team or by involving a third review author (KZ).

The following items will be extracted:

1. Study characteristics: lead author, publication year and journal
2. Methods: study design, duration of study, details of trial design (i.e.,

randomization, allocation concealment, blinding)

3. Participants: sample size, number randomized, number of losing follow-up visits/withdrawing from studies, diagnostic criteria of CHF, mean age, age range, sex, design setting, country, course of treatment and severity of CHF, comorbidities, and inclusion and exclusion criteria.

4. Intervention: intervened measures (type of exercise, length, frequency, number of sessions, and duration of each session), cointerventions, studies with education components and comparators [both active (e g, aerobic exercise, endurance training (cycling and walking)) or non-active (e g, usual care, pharmacologic therapy, dietary, exercise counseling and psychosocial interventions)].

5. Outcomes: primary and secondary outcomes specified and collected, time points reported, mean value, and mean difference.

6. Miscellaneous: funding source, and notable conflicts of interest of trial authors, register ID.

Dealing with missing data

We will initially contact authors through email or telephone to obtain any missing data. If we are unable to obtain the data, we will analyzes the available data and assess the potential impact of missing data on the study results in the discussion section.

Risk of bias assessment

Three reviewers (JL, XJ, JW) will assess risk of bias in the included studies using the Cochrane Collaboration's Risk of Bias tool (RoB2).[19] We will resolve any disagreements by discussion or another review author. The risk of bias in the following domains will be evaluated: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome selection of the reported result and overall risk.

Statistical synthesis of study data

Methods for direct treatment comparisons

We will use DerSimonian–Laird random effects model to perform Standard pairwise meta-analysis. Dichotomous outcomes will be calculated as odds ratio (OR) and continuous data as standardised mean difference (SMD), both with corresponding 95% confidence intervals (CIs). Study heterogeneity will be assessed by Cochran Q test and presented as the I^2-statistic. Sensitivity analysis of pairwise meta-analysis will be conducted to validate the robustness of the results.

Methods for indirect and mixed comparisons

A random-effects NMA will be conducted within a Bayesian framework.[20] We will use the Markov Chain Monte Carlo algorithm by applying WinBUGS 1.4.3. OR, SMD

or weighted mean difference (WMD) will be calculated with 95% CIs. We will obtain a comprehensive ranking of all treatments. The surface under the cumulative ranking curve (SUCRA) and the mean ranks will be used for the treatment hierarchy. We will describe SUCRA with percentages.

Examination of assumptions in NMA (consistency, transitivity and heterogeneity)

We will use local method, global method and node-splitting methods to evaluate consistency. Local method evaluates inconsistency in each closed loop using a loop-specific approach. Global method compares the difference between consistency and inconsistency models based on a $\chi 2$ test using a design-by-treatment approach.[21] The node splitting method will be used to assesses the inconsistency of the model by separating evidence of one particular comparison into direct and indirect evidence. To assess global heterogeneity in the network, we will calculate the I^2 and generate predictive interval plot.[22] Transitivity, a key underlying assumption of NMA, will be evaluated by comparing the distribution of clinical and methodological variables that can act as effect modifiers across treatment comparisons.

All analyses will be performed using R 3.5.0 (gemtc package, network meta analysis, assessment of global heterogeneity, network meta regression, and SUCRA graphs), and STATA 13.0 (pairwise meta-analysis, estimation of inconsistency, transitivity and local heterogeneity, funnel plot).

Subgroup analysis and sensitivity analysis

To assess whether the results were influenced by study characteristics (effect modifiers), subgroup analysis for primary outcome will be conducted based on age group, treatment duration, years of CHF, sample size, quality of study, comorbidity and sponsorship. Subgroup analysis for different types, different causes and different NYHA heart function classifications of CHF will also be performed. Inconsistent sources will be explored by performing univariate and multivariate meta-regressions a network meta-regression. We will conduct sensitivity analysis to exclude trials with small sample sizes (i.e., arms of less than 10 patients) and remove trails that report the generation of non-random sequences. All of these analyses were performed in STATA 13.0. If data extraction is insufficient, a qualitative synthesis will be created.

Publication bias

Publication bias will be assessed by performing Egger's regression test. Additionally, a comparison-adjusted funnel plot will be used to investigate whether results in imprecise trials differ from those in more precise ones.

Quality of evidence

Two reviewers(CH, ZZ) will use the GRADE(The Grading of Recommendations Assessment, Development, and Evaluation) framework to assess the certainty of evidence contributing to each network estimate. The study limitations, imprecision,

inconsistency, indirectness and publication bias will be investigated. Four levels of quality of evidence will be used: high, moderate, low or very low.

Timelines

The study will be conducted from January 1, 2021 to December 31, 2021.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

DISCUSSION

CHF is considered to be the end stage of heart disease manifested with reduced exercise ability and poor QOL. Exercise training is widely regarded as a non-drug intervention to improve patient's exercise tolerance and QOL. Exercise-based cardiac rehabilitation is safe and effective for CHF. Previous studies have shown that Taichi, Baduanjin and Yoga are beneficial for CHF. Taichi improves body functions,[23] such as lowering blood pressure in adults with hypertension,[24 25] enhancing aerobic endurance[26 27],reducing stress, anxiety and depression, and ameliorating QOL.[28 29] Baduanjin can reduce the load of the heart, increase the body's ability to transport and utilize oxygen in blood circulation,[30 31] and thus improving HF. Yoga can improve peak VO_2 in CHF patients, which is considered as another method of exercise training for CHF patients.[9]

Therefore, Taichi, Baduanjin and Yoga are effective exercise ways to treat CHF, however, the difference in efficacy of TAE in patients with CHF is not yet clear. We attempt to conduct a NMA of a sufficient number of randomized controlled trials to determine the impact of TAE on CHF patients of different types, different causes and different NYHA heart function classifications, and to provide stronger evidence to help CHF patients choose more appropriate exercise rehabilitation therapy. To our knowledge, this review will be the first to assess the impact of TAE on patients with CHF, and we hope that the results of this study can provide help for the rehabilitation of patients with CHF.

Ethics and dissemination

This protocol is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and has been registered at the International Prospective Register of Systematic Reviews (CRD42020179304; available from https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=179304)

As no individual patient data will be used in this NMA, ethical approval is not required. We aim to publish this NMA in a peer-reviewed journal. The results of this NMA will provide a more comprehensive and more reliable information about the

effect of TAE for patients with CHF.

Contributors
QL, KZ, JX, ZZ YL and JLconceived and designed the study. JX and ZZ drafted this protocol. JL YL and ZZ revised it. JW, RF, TM, CH, ZZ, JJ and XJ developed the search strategies and conducted data collection. All authors have read this manuscript and approved the publication of this protocol. Jianglin Xu, Zhuo Zhang, Yan Li and Jing Liu contributed equally to this work and should be considered joint first authors. Both Qian Lin and Kun Zhou are corresponding authors.

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ORCID iDs
Jianglin Xu https://orcid.org/0000-0002-2006-7101
Zhuo Zhang https://orcid.org/0000-0003-4435-8509
Yan Li https://orcid.org/0000-0002-7619-2809
Jing Liu https://orcid.org/0000-0002-0729-502X
Tianshi Mao https://orcid.org/0000-0003-4676-7584
Xiang Ji https://orcid.org/0000-0003-1305-713X
Kun Zhou https://orcid.org/0000-0002-4058-7497
Qian Lin https://orcid.org/0000-0001-9166-5099

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Figure legend

Figure 1 Presentation of three traditional Asian exercise (A) Taichi， (B) Baduanjin, and (C) Yoga.The pictured individual has agreed to publish his image.

Figure 2 Flowchart of the study selection process.

A B C

Figure 1 Presentation of three traditional Asian exercise (A) Taichi, (B) Baduanjin, and (C) Yoga.The pictured individual has agreed to publish his image.

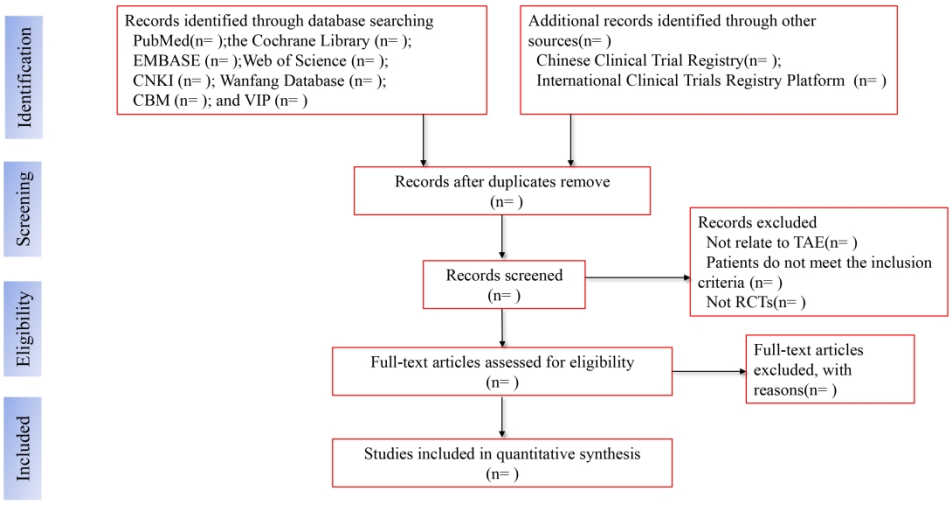

Figure 2 Flowchart of the study selection process.

Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation			
Section and topic	**Item No**	**Checklist item**	**Page/line numbers**
Section 1: Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1, Line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	None. The protocol is conducting a new systematic review.
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2, Line 26
Authors:			
Contact information	3a	Provide name, institutional affiliation, and email address of all protocol authors; provide physical mailing address of corresponding author	Page 1, Line 8-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 10, Line 33-37
Amendments	4	If the report represents an amendment of a previously completed or published protocol, identify as such and indicate what changes were made; otherwise state plan for documenting important protocol amendments	None
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 11, Line 5-6
Sponsor	5b	Provide name of the review funder and/or sponsor	Page 11, Line 5-6
Role of sponsor and/or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	None

Section 2: Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4
Section 3: Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 5-6
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	Page 5-6
Study records			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (screening, eligibility, and inclusion in meta-analysis)	Page 7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and	Page 7

		confirming data from investigators	
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources) and any pre-planned data assumptions and simplifications	Page 7
Outcomes and prioritisation	13	List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale	Page 5 and 7
Risk of bias 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	Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 8
	15b	If data are appropriate for synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 8
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	Page 9

	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 9
Confidence in cumulative estimate	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 9

Search strategy

Pubmed database

((((((((((((((((tai chi[All Fields])) OR (taiji)) OR (taiqi)) OR (tai ji quan)) OR (tai chi chuan)) OR (taichi qigong)) OR (shadowboxing)) OR (baduanjin)) OR (Baduanjin exercise)) OR (eight section brocades)) OR (yoga)) OR (yogic)) OR (asana)) OR (pranayama)) OR (dhyana)[All Fields])) AND ((((((((((((chronic heart failure[All Fields])) OR (heart failure with reduced ejection fraction)) OR (heart failure with mid-range ejection fraction)) OR (heart failure with preserved ejection fraction)) OR (cardiac failure)) OR (heart failure)) OR (heart decompensation)) OR (right-sided heart failure)) OR (myocardial failure)) OR (congestive heart failure)) OR (left sided heart failure)) OR (ventricular failure))