BMJ Open

Effect of Baduanjin Exercise on patients with Chronic heart failure: protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028771
Article Type:	Protocol
Date Submitted by the Author:	02-Jan-2019
Complete List of Authors:	Li, Jieying; Guangzhou University of Chinese Medicine, First Clinical College Yu, Feng; The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Emergency Department Huang, Na; Guangzhou University of Chinese Medicine, First Clinical College Lu, Jianhui; Guangzhou University of Chinese Medicine, First Clinical College Xu, Weixian; Guangzhou University of Chinese Medicine, First Clinical College Liu, Nan; The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Emergency Department
Keywords:	Heart failure < CARDIOLOGY, Baduanjing Exercise, systematic review, meta-analysis, protocol

Effect of Baduanjin Exercise on patients with Chronic heart failure: protocol for a systematic review and meta-analysis

Jieying Li[1], Feng Yu[2], Na Huang[1], Jianhui Lu[1], Weixian Xu[1], Nan Liu[2,*]

Author affiliations

[1]First Clinical College, Guangzhou University of Chinese Medicine, Guangzhou 510405,China

[2]The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510405,China

*Corresponding author:

Name: Nan Liu; E- mail address: liunan0954@126.com; Postal address: 510405(Guangzhou China)

Tel:+135-7047-9073;

E-mail address: JYL:609152155@qq.com; FY: doctoryufeng@126.com; NH: 1571710522@qq.com;

JHL: tomorrow-9@163.com; WXX: 958194032@qq.com; NL: liunan0954@126.com

ABSTRACT

Introduction: Chronic heart failure (CHF), the end stage of various cardiopulmonary diseases, is a serious burden for both individuals and society. Baduanjin exercise(BDJE), a form of traditinal Chinese regimen in cardiac rehabilitation, has become a promising therapy for CHF in clinical practice recently. Relevant evidence lacking, the aim of this systematic review is to evaluate the efficacy and safety of BDJE for the CHF patients.

Methods and analysis: A systematic literature search for articles up to October 2018 will be performed in following databases: Web of Science, Pubmed, Embase, Cochrane Library, Chinese Science and Technology Periodicals Database, Chinese National Knowledge Infrastructure and Wanfang database. We will asol search other resources. Inclusion criteria are randomized controlled trials(RCTs) that CHF patients were treated with BDJE. The primary outcome measures will be quality of life assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and walking distance in the 6-min Walk Test(6MWT). Stata 13.1 software will be uesd for data synthesis, sensitivity analysis, meta-regression analysis, subgroup analysis and risk of bias assessment. A funnel plot will be developed to evaluate reporting bias and Begg and Egger tests will be used to assess funnel plot symmetries. We will use the Grading of Recommendations Assessment, Development and Evaluation(GRADE) system to assess the quality of evidence.

Ethics and dissemination: This systematic review will be submitted to a peer-reviewed journal.

Trial registration number: PROSPERO CRD 42018114672.

Keywords: Baduanjin Exercise, Chronic heart failure, systematic review, meta-analysis, protocol.

Strengths and limitations of this study

- This study will be the first to assess the safety of BDJE and their effect on CHF patients.
- The Grading of Recommendations Assessment, Development and Evaluation system will be used to further evaluate study findings.
- There may be a language bias, for both English and Chinese studies will be included.
- Clinical heterogeneity can also exist, because of variations in treatment frequency and duration and the use of additional therapies (eg, herbal medicine).

INTRODUCTION

Chronic heart failure(CHF),a terminal stage of kinds of cardiovascular diseases, with high morbidity and mortality, is characterized by fatigue, chronic reduction of cardiopulmonary function and exercise tolerance[1-3].Exercise intolerance, as the most important determinant of prognosis as well as reduced life quality, is a primary symptom among CHF patients[4]. Cardiac rehabilitation exercise was considered to be

a contraindication for CHF patients before 1970s, for it was believed that exercise places an extra load on the heart. But exercise-based cardiac rehabilitation(EBCR) has become the Class I recommendation of the International Guidelines for the Treatment and Management of Heart Failure today. Many researches show that EBCR which can potentially improve exercise load of CHF patients, as well as quality of life in recent years[5].

Traditional Chinese medicine(TCM) theory holds that the asthenia of vital qi and the sthenia of evil qi leads to CHF, and heart-qi deficiency is the root of the disease which lead to blood stasis[6].Some ancient China regimens, such as Tai Chi, that emphasizes the balance of body and mind were also found to have positive effects on balance control, cardiovascular fitness, fatigue and quantity of life in CHF patients[7].So the role of TCM physical movement in cardiac rehabilitation has been accepted by experts at home and abroad gradually. However, Tai Chi is complicated and difficult to learn so that it can limit participant's adherence to the exercise. BDJE may be a perfect alternative. BDJE, combining medication with slow, gentle, and graceful qi movement, as well as deep breathing and relaxation[8],is an aerobic exercise that can regulate the vital energy of collateral channels and organs in the body. It helps to relieve the cardiac load and improve the body's ability to transport and utilize oxygen in blood circulation, so that it can reduce oxygen consumption of myocardial[9].BDJE can also improve the elasticity of blood vessels effectively, inhibit the formation of free radicals, and reduce the blood viscosity to ensure the normal flow of blood[10-12].However, no systematic review concerning BDJE for CHF patients been carried out or published yet. An examination of this therapy's effect on CHF patients is urgently needed. Consequently, we plan to conduct a systematic review and meta-analysis to evaluate current evidence of BDJE on CHF patients.

METHODS AND ANALYSIS

Inclusion and exclusion criteria for study selection

Type of studies

All RCTs that evaluated the safety and effect of BDJE on CHF patients will be included no matter how long the treatment proceeded.

Participants

The inclusion criteria for participants will be as follows:(a)≥18 years;(b)diagnosed with CHF based on World Health Organization's(WHO) definition of CHF including HF with reduced ejection fraction or preserved ejection;(c)diagnosed with stable heart failure by a physician according to New York Heart Association(NYHA)class I-III. Patients will be excluded if they had (a)impaired mobility, defined as a limitation in independent physical movement of the body;(b)history of unstable structural valvular diseases, open-heart surgery, or chronic obstructive pulmonary disease (COPD);(c) diagnosis of major depression and cognitive disorders; or (d)unstable vital signs, defined as blood pressure>180/110mmHg or <90/60mmHg and resting heart rate>100beats/min.

Interventions

Control group patients will receive standard treatment according to HF guidelines and be advised to maintain their daily routine. The intervention group will receive BDJE of various duration and frequency based on routine regimens except conventional therapy.

Outcome measures

The primary outcome measures will be quality of life assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and walking distance in the 6-min

Walk Test(6MWT).The secondary outcome measures will be peak VO2,ejection fraction, NYHA class, hsCRP, NT-proBNP and adverse events.

Search strategy

Electronic searches

The following electronic databases will be searched from inception to October 2018: Web of Science, Pubmed, Embase, CochraneLibrary, Chinese Science and Technology Periodicals Database, Chinese National Knowledge Infrastructure and Wanfang Data. Search terms are grouped into 3 blocks (Table 1).

Table 1. Search terms

Search block	Search items
Participants	Cardiac Failure OR Heart Decompensation OR Decompensation, Heart OR Heart Failure, Right-Sided OR Heart Failure, Right Sided OR Right-Sided Heart Failure OR Right Sided Heart Failure OR Myocardial Failure OR Congestive Heart Failure OR Heart Failure, Congestive OR Heart Failure, Left-Sided OR Heart Failure, Left Sided OR Left-Sided Heart Failure OR Left Sided Heart Failure
Intervention	Qigong OR Baduanjin OR Baduanjin exercise OR eight section brocades OR regimen OR Chinese regimen OR Chinese ancient regimen OR rehabilitation exercise
Study design	Randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups

Other resources

The following sources will also be searched to identify clinical trials, which are in progress or completed: Google scholar (http://scholar.google.com) and Baidu scholar (http://xueshu.baidu.com/); Clinical Trials.gov (http://www.clinical trails.gov) and Chinese Clinical Trial Registry (http://www.chictr.org/cn/);the reference lists of the retrieved articles.

Study selection and data extraction

NoteExpress 3.2 will be used to manage literatures and remove duplications. Firstly, two reviewers (NH and JL) will screen the titles and abstracts of all the retrieved studies to find potentially eligible studies independently. The potentially eligible studies for which no relevant outcomes is presented, where relevant information is unavailable or results are duplicated will be excluded. Then two reviewers (NH and JL) will independently review the full texts for the potentially eligible studies. After filtering the final eligible articles, the data from the included articles will be extracted independently from two authors (NH and JL).Disagreements will be resolved through discussion and if indispensable, discrepancies will be discussed with the third author (FY).We will use a spreadsheet to record information from eligible articles about study design, year of publication, study location, study period, and authors. We also record participant, interventions and outcomes. Lastly, all the included studies will be taken into Systematic Reviews and the studies which are selected according to the quality of included literatures will be made a meta-analysis. A Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow chart will be produced to show the number of articles identified, screened, included and excluded, reasons for exclusion and to ascertain eligible studies. The study selection process will be described in a PRISMA flow chart (http://www.prisma-statement.org) (figure 1).

Figure 1. Flow diagram of study selection process

Addressing missing data or unclear measurement scales

If necessary, we will contact authors of articles though email or telephone to request missing data or additional information about evaluation scales. If sufficient information cannot be obtained in this way, we will analyze the available data and take into account the potential impact of insufficient data on the review results in the discussion section.

Risk of bias in included studies

Risk of bias for the studies included in meta-analyses will be evaluated according to the Cocharne Handbook. This recommends the assessment of several sources of bias, including random sequence generation, allocation concealment, blinding of outcome assessments, incomplete outcome data and selective outcome reporting. Since double-blinding is impossible to achieve in clinical trials, the bias among participants and investigators will not be considered. The risks will be judged as low, high or unclear (unclear or unknown risk of bias).

Data synthesis and analysis

Statistical analysis will be conducted with Stata 13.1software.Weighted mean difference and 95%CIs will be calculated. The Q and I^2 test statistics will be used to assess the heterogeneity of included studies. For the Q statistic, $p<0.05$will be considered as indicating significant differences. For the I^2 statistic, $I^2<25\%$indicates no significant heterogeneity,$I^2=25\%$-50% is considered moderate heterogeneity and $I^2>50\%$ indicates strong heterogeneity. If there is no heterogeneity among studies, we will use fixed effects models, otherwise the random effects models will be used.

Additional analyses

Sensitivity analysis, meta-regression analysis and subgroup-stratified analysis based on various study characteristics will be performed, such as type, location, and quality of study, sample size, adjustment (or not) for confounders ,Baduanjin regimens and other relevant parameters (eg, diet and lifestyle) to explore potential sources of heterogeneity. We will create a qualitative synthesis if data extraction is insufficient.

Assessment of reporting biases

A funnel plot will be conducted to evaluate reporting bias of the included studies. Begg and Egger tests will be used to assess funnel plot symmetry and we will interpret values of $p<0.1$ as showing statistical significance (ie, publication bias).

Quality of evidence

We will evaluate the quality of evidence of the included studies through the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The limitations of the study, inconsistencies, indirect evidence, inaccuracies and publication bias will also be considered. Four levels of quality of evidence will be used: high, moderate, low or very low.

Ethics and dissemination:

We aim to publish this systematic review in a peer-reviewed journal. Our findings will provide information about the safety and effect of BDJE for patients with CHF. The study will not involve individual privacy, thus ethical approval is not required.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not involved in the design of the study.

DISCUSSION

According to TCM theory, BDJE can boost qi and blood circulation, and coordinate the internal organs by relaxing muscles and strengthening bones, nourishing qi and enhancing strength. It is mainly used to regulate heart, breath and dredge channels and vessels, relieving heart pressure, and eventually making individuals calm and modify spirits[13].

Previous studies have studied the effects of aerobic exercise such walking[14-17],cardiac rehabilitation training[18],or Tai Chi[19]on the fatigue and quantity of life on CHF patients. A meta-analysis of six studies also showed BDJE can significantly improve the quality of life of all sorts of populations[20].BDJE can systematically mobilize joints and muscles, stimulate metabolism and blood circulation, and relaxing the mind[21].

BDJE could therefore be used to relieve symptoms and improve the quality of life of CHF patients, but there is lack of evidence to prove that. We aim to ensure adequate power for the meta-analysis. On balance, this review will be the first to evaluate the impact of BDJE on CHF patients. The results of this review may help to establish a better approach to improve the quality of life of HF patients.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist[22] of this protocol is presented in online supplementary Appendix 2.

Author Contributions

JYL, FY and NL conceived and designed the study. The manuscript of this protocol was drafted by JYL, FY and NH and revised by JHL and WXX. NH and JHL designed the search strategies and will perform the search, screening and assessment of the risk of bias independently. JYL and WXX will analyze and interpret the data. FY will arbitrate any disagreements during the review. All authors approved the final version of this protocol.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

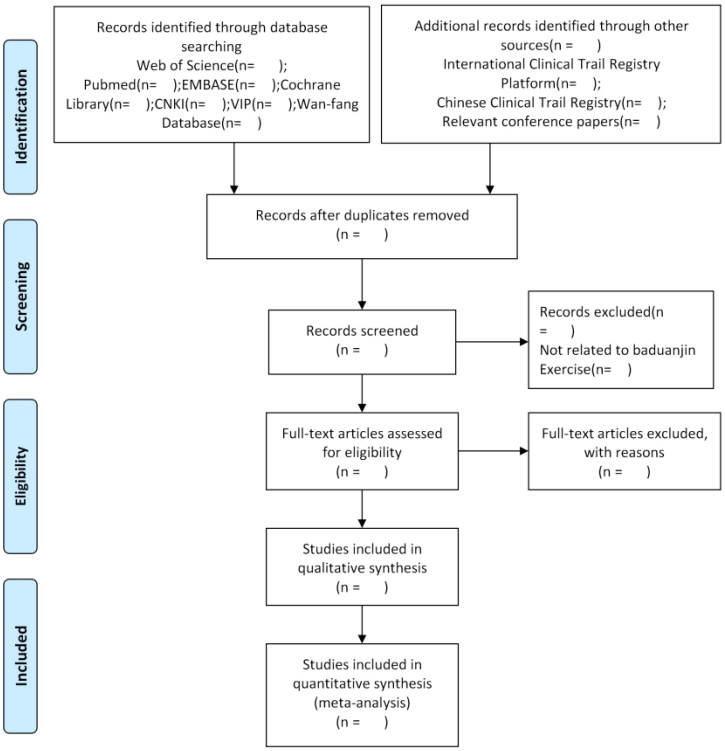
Data statement: No additional data are available.

WORD ACOUNT: 1732.

References

1. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail.* 2013;6(3):606-619.
2. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation.* 2016;133(4):e38-360.
3. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol.* 2016;13(6):368-378.
4. Fleg JL, Cooper LS, Borlaug BA, et al. Exercise training as therapy for heart failure: current status and future directions. *Circ Heart Fail.* 2015;8(1):209-220.
5. Taylor RS, Walker S, Smart NA, et al. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. *Eur J Heart Fail.* 2018;20(12):1735-1743.
6. Zhu M, li SN. The research progress of Traditional Chinese Medicine on Chronic Heart Failure. *Chinese Traditional Patent Medicine.* 2018;40(8):1804-1807.
7. Pan L, Yan J, Guo Y, Yan J. Effects of Tai Chi training on exercise capacity and quality of life in patients with chronic heart failure: a meta-analysis. *Eur J Heart Fail.* 2013;15(3):316-323.
8. Chen MC, Liu HE, Huang HY, Chiou AF. The effect of a simple traditional exercise programme (Baduanjin exercise) on sleep quality of older adults: a randomized controlled trial. *Int J Nurs Stud.* 2012;49(3):265-273.

9. Shi XM, Jiang GL, Liu WH, et al. The influence of baduanjin on cardiopulmonary function during cardiac rehabilitation for CHD patients. *Med & Pharm J Chin PLA.* 2017;29(2):24-27.
10. Xiong X, Wang P, Li S, Zhang Y, Li X. Effect of Baduanjin exercise for hypertension: a systematic review and meta-analysis of randomized controlled trials. *Maturitas.* 2015;80(4):370-378.
11. Chen BL, Guo JB, Liu MS, et al. Effect of Traditional Chinese Exercise on Gait and Balance for Stroke: A Systematic Review and Meta-Analysis. *PLoS One.* 2015;10(8):e0135932.
12. Wang XQ, Pi YL, Chen PJ, et al. Traditional Chinese Exercise for Cardiovascular Diseases: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc.* 2016;5(3):e002562.
13. Wu XY, Li L, Ding PR, Li J. The impact of baduanjin exercise on 62 coronary heart disease patients with depression. *World Chinese Medicine.* 2014;9(1):39-43.
14. Oka RK, De Marco T, W.L. H, et al. Impact of a Home-Based Walking and Resistance Training Program on Quality of Life in Patients With Heart Failure. *Am J Cardiol.* 2000;85:365-369.
15. Corvera-Tindel T, Doering LV, Woo MA, Khan S, Dracup K. Effects of a home walking exercise program on functional status and symptoms in heart failure. *Am Heart J.* 2004;147(2):339-346.
16. Gary RA, Sueta CA, Dougherty M, et al. Home-based exercise improves functional performance and quality of life in women with diastolic heart failure. *Heart Lung.* 2004;33(4):210-218.
17. Hassanpour Dehkordi A, Khaledi Far A. Effect of exercise training on the quality of life and echocardiography parameter of systolic function in patients with chronic heart failure: a randomized trial. *Asian J Sports Med.* 2015;6(1):e22643.
18. Pozehl B, Duncan K, Hertzog M. The effects of exercise training on fatigue and dyspnea in heart failure. *Eur J Cardiovasc Nurs.* 2008;7(2):127-132.
19. Yeh GY, McCarthy EP, Wayne PM, et al. Tai chi exercise in patients with chronic heart failure: a randomized clinical trial. *Arch Intern Med.* 2011;171(8):750-757.
20. Zou L, SasaKi JE, Wang H, Xiao Z, Fang Q, Zhang M. A Systematic Review and Meta-Analysis Baduanjin Qigong for Health Benefits: Randomized Controlled Trials. *Evid Based Complement Alternat Med.* 2017;2017:4548706.
21. Liao Y, Lin Y, Zhang C, et al. Intervention Effect of Baduanjin Exercise on the Fatigue State in People with Fatigue-Predominant Subhealth: A Cohort Study. *J Altern Complement Med.* 2015;21(9):554-562.
22. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ.* 2015;350:g7647.



209x297mm (288 x 288 DPI)

Reporting checklist for protocol of a systematic review.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a (This study will be the first to assess the safety of BDJE and their effect on CHF patients)
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	5
	#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	n/a (This study will be the first to assess the safety of BDJE and their effect on CHF patients)
Sources	#5a	Indicate sources of financial or other support for the review	5
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a (This research received no external funding)
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a (This research received no external funding)

Rationale	#6	Describe the rationale for the review in the context of what is already known	1
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2,3
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	2,3
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	1,3,4
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	3
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	3
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	3
Study records - 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 confirming data from investigators	3
Data items	#12	List and define all variables for which data	4

		will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	2,3
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	4
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	4
	#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 (such as I2, Kendall's τ)	4
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	4
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a (All the included studies will be taken into Systematic Reviews and the studies which are selected according to the quality of included literatures will be made a meta-analysis)
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	4
Confidence in cumulative	#17	Describe how the strength of the body of evidence will be assessed (such as	4

evidence GRADE)

BMJ Open

Effect of Baduanjin Exercise on patients with Chronic heart failure: protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028771.R1
Article Type:	Protocol
Date Submitted by the Author:	17-May-2019
Complete List of Authors:	Li, Jieying; Guangzhou University of Chinese Medicine, First Clinical College Yu, Feng; The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Emergency Department Huang, Na; Guangzhou University of Chinese Medicine, First Clinical College Lu, Jianhui; Guangzhou University of Chinese Medicine, First Clinical College Xu, Weixian; Guangzhou University of Chinese Medicine, First Clinical College Liu, Nan; The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Emergency Department
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Evidence based practice, Complementary medicine
Keywords:	Heart failure < CARDIOLOGY, Baduanjing Exercise, systematic review, meta-analysis, protocol

Effect of Baduanjin Exercise on patients with Chronic heart failure:protocol for a systematic review and meta-analysis

Jieying Li[1], Feng Yu[2], Na Huang[1], Jianhui Lu[1], Weixian Xu[1], Nan Liu[2,*]

Author affiliations

[1]First Clinical College, Guangzhou University of Chinese Medicine, Guangzhou 510405,China

[2]The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510405,China

*Corresponding author:

Name:NanLiu;E- mail address:liunan0954@126.com;Postal address:510405(Guangzhou China)

Tel:+135-7047-9073;

E-mail address: JYL:609152155@qq.com; FY: doctoryufeng@126.com; NH: 1571710522@qq.com;

JHL: tomorrow-9@163.com; WXX: 958194032@qq.com; NL: liunan0954@126.com

ABSTRACT

Introduction: Chronic Heart Failure(CHF) is defined when the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs, and it's caused by various cardiopulmonary diseases. CHF is a common, lifelong and costly condition. Baduanjin Exercise (BDJE), a form of traditional Chinese regimen, has been integrated into China's clinical practice in recent years and has shown promise in cardiac rehabilitation of CHF patients. However, the efficacy of BDJE on CHF patients has not been fully statistically evaluated. In this study, we aim to systematically examine the efficacy and safety of BDJE for CHF patients.

Methods and Analysis: A systematic literature search for articles up to October 2018 will be conducted in following databases: Web of Science, Pubmed, Embase, Cochrane Library, Chinese Science and Technology Periodicals Database, Chinese National Knowledge Infrastructure and Wanfang database. We will also search other resources. Randomized controlled trials (RCTs) that examined treatment of CHF patients with BDJE will be selected. Results will be analyzed by assessing the Quality of Life (QoL) of patients using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and measurement of distance walked over a span of 6 minutes in the 6-min Walk Test (6MWT).RevMan 5.3will be used for data synthesis, sensitivity analysis, meta-regression analysis, subgroup analysis and risk of bias assessment. A funnel plot will be developed to evaluate reporting bias and Begg and Egger tests will be used to assess funnel plot symmetries. Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be utilized to assess the quality of evidence.

Ethics and dissemination: This systematic review will be submitted to a peer-reviewed journal.

Trial registration number: PROSPEROCRD 42018114672.

Keywords: Baduanjin Exercise, Chronic heart failure, systematic review, meta-analysis, protocol.

Strengths and limitations of this study

- This study will be the first to assess the safety of BDJE and their effect on CHF patients.
- The Grading of Recommendations Assessment, Development and Evaluation system will be used to further evaluate study findings.
- Language bias should be considered due to the inclusion of both English and Chinese studies.
- Clinical heterogeneity can also exist, because of variations in treatment frequency and duration and the use of additional therapies (eg, herbal medicine).

INTRODUCTION

Chronic heart failure (CHF) is a progressive and debilitating disease that underlines the ongoing inability of the heart to perform its circulatory function with the desired efficiency due to structural and/or functional (systolic ordiastolic) alterations.[1]CHF is a long-term condition with symptoms that gradually worsens over time while the acute heart failure has a sudden onset and symptoms. Shortness of breath, fatigue, swelling of the legs and ankles, chest pain and coughing are the most common symptoms in CHF patients. A limited ability to exercise which associated with the life expectancy, frequency of hospitalization and quality of life (QoL), is a primary symptom among CHF patients.[2]

Despite advancements in the treatment of CHF, the condition still has a high morbidity and mortality. It is a rapidly growing public health issue with an estimated prevalence of more than 37.7 million individuals globally and the total medical costs for patients with HF are expected to double from US $20.9 billion in 2012 to $53.1 billion by 2030 in the United States of America.[3]It is therefore crucial to study potential treatments of CHF aimed to retard and stagnate the progression of the condition and explore methods to improve the QoL of CHF patients. Progress on new drugs has been minimal and the current effective treatment for clinically CHF patients is Ivobradine after the advent of ARB in the 1990s.[4] Furthermore, indiscriminate or prolonged uses of the referred drugs may lead to severe side effects, such as hypotension, and electrolyte, fluid depletion.[5]Traditional Chinese medicine(TCM) emphasizes on syndrome differentiation and focuses treatment based on the overall concept of the patient, while Western Medicine(WM) studies for the specific causes of the diseases and bases treatments on medical tests. Due to the fundamental differences in approaches between the two medicines, it could be speculated that TCM can complement and improve the range of treatment of Western Medicine. A number of clinical literatures indicated that a combination of treatment of TCM and Western Medicine in the treatment of CHF patients were superior to that of the group who received only Western Medicine. There were reduced recurrence rate, improved overall prognosis, and relieved symptoms in (TCM and WM) group thereby improving patients' quality of life.[6]

There has been an increased focus on cardiac rehabilitation(CR), a medically supervised program aimed at improving cardiovascular health. CR includes medical evaluation and baseline patient assessment, education concerning medication adherence, risk factor reduction including dietary recommendations, psychosocial support (which may include peer support), as well as supervised exercise training and counseling.[7]The benefits of exercise training have been recognized among patients with CHF and is widely recommended by physicians, and therefore exercise-based cardiac rehabilitation (EBCR) is an invaluable tool in the management of CHF.[8]EBCR was considered to be a contraindication for CHF patients before 1970s, for it was believed that exercise might place the heart muscle under more stress. However in modern times, EBCR is the Class I recommendation of the International Guidelines for the Treatment and Management of Chronic stable heart failure.[9] Many researches show that EBCR which can potentially improve exercise load of CHF patients, as well as quality of life (QoL) in recent years. A large number of evidence-based studies support the safety of EBCR for CHF patients. Additionally, numerous domestic studies reported no adverse effects on CHF patients when undergoing cardiopulmonary exercise test (CPET) and aerobic cardiac exercise rehabilitation(such as walking, swimming, cycling).[10]HF-ACTION study established a link between exercise therapy and alleviation of depressive symptoms of CHF patients. The study concluded that improvements in exercise ability is directly proportional to the alleviation of depressive symptoms.[9, 11]

TCM theory holds that the asthenia of vital qi and the sthenia of evil qi leads to CHF, and heart-qi deficiency is the root of the disease which lead to blood stasis.[12]Huangdi Neijingis an ancient medical text and has been the fundamentals of Chinese Medicine for more than two millennia. It states that "movement to nourish form, stillness to nourish spirit", indicating the ancient Chinese's understanding and acknowledgement of the importance of proper exercise to strengthen one's physique. It is understood that movements can exhilarate Yang Qi, adjust Qi and Blood to alleviate the symptoms of heart failure and improve the QoL of patients. Traditional Chinese Exercise (TCE) such as Taijiquan, Qigong and Baduanjin have been undertaken by many as a form of proper exercise passed down from the Chinese ancestors thus have found a surge in popularity around the world in recent years.[13]Tai Chi, Wuqinxi, Qigong and Baduanjin were found to have positive effects on balance control, cardiovascular fitness, fatigue and quality of life in CHF patients.[14-16]However, Tai Chi and Wuqinxi are complicated and difficult to master and might therefore limit patient's adherence to the exercise

regimen. On the other hand, Baduanjin exercise (BDJE)also known as the “eight section brocades”, is an aerobic exercise with simple, slow, and relaxing movements, which is composed of 8 set of actions including support heaven with both hands, dragon sprays water with force, big bird spreads its wings, lift window to look at the moon on the left, descend to earth with force, beautiful maiden twists her waist to the right, extend shoulders to bring hands together, and dragon claws to the left.[17]In accordance to TCM theory, BDJE can regulate the vital energy of collateral channels and organs in the body as well asrelieve the cardiac load and improve the body's ability to transport and utilize oxygen in blood circulation, so that it can reduce oxygen consumption of myocardial.[18]BDJE can also improve the elasticity of blood vessels effectively, inhibit the formation of free radicals, and reduce the blood viscosity to ensure the normal flow of blood.[13, 17, 19]

However, no systematic review about effect of BDJE on CHF patients has been carried out or published so far. An examination of this therapy’s effect on CHF patients is therefore urgently needed. Consequently, we plan to conduct a systematic review and meta-analysis to evaluate current evidence of BDJE on CHF patients.

METHODS AND ANALYSIS

Inclusion and exclusion criteria for study selection

Type of studies

All RCTs that evaluated the safety and effect of BDJE on CHF patients will be included regardless of the duration of the treatment.

Participants

The inclusion criteria for participants will be as follows:(a)≥18 years;(b)diagnosed with CHF based on World Health Organization’s(WHO) definition of CHF including HF with reduced ejection fraction or preserved ejection;(c)diagnosed with stable heart failure by a physician according to New York Heart Association(NYHA)class I-III. Patients will be excluded if they had(a)impaired mobility, defined as a limitation in independent physical movement of the body;(b)history of unstable structural valvular diseases, open-heart surgery, or chronic obstructive pulmonary disease (COPD);(c) diagnosis of major depression and cognitive disorders; or (d)unstable vital signs, defined as blood pressure>180/110mmHg or <90/60mmHg and resting heart rate>100beats/min.

Interventions

Control group patients will receive standard treatment according to HF guidelines and be advised to maintain their daily routine. The intervention group will receive BDJE of various duration and frequency based on routine regimens except conventional therapy.

Outcome measures

The primary outcome measures will be quality of life assessed by the Minnesota Living with Heart Failure Questionnaire(MLHFQ)and walking distance in the 6-min Walk Test(6MWT).The secondary outcome measures will be peak VO2,ejection fraction, NYHA class, hsCRP, NT-proBNP.

Search strategy

Electronic searches

The following electronic databases will be searched from inception to October 2018: Web of Science, Pubmed,Embase, Cochrane Library, Chinese Science and Technology Periodicals Database, Chinese National Knowledge Infrastructure and Wanfang Data. Search terms are grouped into 3 blocks (Table 1).

Table 1. Search terms

Search block	Search items
Participants	Cardiac Failure OR Heart Decompensation OR Heart Failure OR Right-Sided Heart Failure OR Myocardial Failure OR Congestive Heart Failure OR Left Sided Heart Failure

Intervention	Qigong OR Baduanjin OR Baduanjin exercise OR eight section brocades OR regimen OR Chinese regimen OR Chinese ancient regimen OR rehabilitation exercise
Study design	Randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups

Other resources

The following sources will also be searched to identify clinical trials, which are in progress or completed: Google scholar (http://scholar.google.com) and Baidu scholar (http://xueshu.baidu.com/); Clinical Trials.gov(http://www.clinicaltrails.gov)andChinese Clinical Trial Registry (http://www.chictr.org/cn/);the reference lists of the retrieved articles.

Study selection and data extraction

NoteExpress 3.2 will be used to manage literatures and remove duplications. Firstly, two reviewers(NH and JL)will screen the titles and abstracts of all the retrieved studies to find potentially eligible studies independently. The potentially eligible studies for which no relevant outcomes is presented, where relevant information is unavailable or results are duplicated will be excluded. Then two reviewers(NH and JL)will independently review the full texts for the potentially eligible studies. After filtering the final eligible articles, the data from the included articles will be extracted independently from two authors (NH and JL).Disagreements will be resolved through discussion and if indispensable, discrepancies will be discussed with the third author (FY).We will use a spreadsheet to record information from eligible articles about study design, year of publication, study location, study period, and authors. We also record participant, interventions and outcomes. Lastly, all the included studies will be taken into Systematic Reviews and the studies which are selected according to the quality of included literatures will be made a meta-analysis. A Preferred Reporting Items for Systematic Reviews and Meta-analysis(PRISMA)flow chart will be produced to show the number of articles identified, screened, included and excluded, reasons for exclusion and to ascertain eligible studies. The study selection process will be described in a PRISMA flow chart (http://www.prisma-statement.org) ,which is presented in online supplementary Appendix 1.

Addressing missing data or unclear measurement scales

If necessary, we will contact authors of articles though email or telephone to request missing data or additional information about evaluation scales.If sufficient information cannot be obtained in this way,we will analyze the available data and take into account the potential impact of insufficient data on the review results in the discussion section.

Risk of bias in included studies

Risk of bias for the studies included in meta-analyses will be evaluated according to the Cocharne Handbook. This recommends the assessment of several sources of bias, including random sequence generation, allocation concealment, blinding of outcome assessments, incomplete outcome data and selective outcome reporting. Since double-blinding is impossible to achieve in clinical trials, the bias among participants and investigators will not be considered. The risks will be judged as low, high or unclear (unclear or unknown risk of bias).

Data synthesis and analysis

The statistical analysis will be performed according to the recommendations of the Cochrane Handbook and using the software of Cochrane Collaboration, RevMan 5.3, available from the Cochrane website (http://tech.cochrane.org/revman). All outcomes will be continuous variables. The standardized mean difference (SMD) and its 95% CIs will be calculated. Initially, a fixed-effect model will be used to compare the outcomes expressed in the same scale. The heterogeneity of the effects of trials will be evaluated by the Q^2 test and the I^2 test. Heterogeneity will be considered as substantial if the I^2 statistic $\geq 50\%$ and $p<0.10$. If heterogeneity is considered as substantial, reasons for this heterogeneity will be searched for and a random-effect model could be used for comparison.

Additional analyses

Sensitivity analysis, meta-regression analysis and subgroup-stratified analysis based on various study characteristics will be performed, such as type, location, and quality of study, samplesize, adjustment(or not)for confounders,Baduanjin regimens and other relevant parameters(eg,diet and lifestyle)to explore potential sources of heterogeneity. We will create a qualitative synthesis if data extraction is insufficient.

Assessment of reporting biases

A funnel plot will be conducted to evaluate reporting bias of the included studies. Begg and Egger tests will be used to assess funnel plot symmetry and we will interpret values of $p<0.1$ as showing statistical significance(ie,publication bias).

Quality of evidence

We will evaluate the quality of evidence of the included studies through the Grading of Recommendations Assessment, Development and Evaluation(GRADE) approach. The limitations of the study, inconsistencies, indirect evidence, inaccuracies and publication bias will also be considered. Four levels of quality of evidence will be used: high, moderate, low or very low.

Ethics and dissemination

We aim to publish this systematic review in a peer-reviewed journal. Our findings will provide information about the safety and effect of BDJE for patients with CHF. The study will not involve individual privacy, thus ethical approval is not required.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not involved in the design of the study.

DISCUSSION

BDJE can boost qi and blood circulation, stimulate metabolism and coordinate the internal organs by nourishing qi, relaxing muscles and enhancing strength. It regulates heart, breathing and dredge channels and vessels to relieve heart pressure, keeps individuals calm and modify spirits.[20]Previous studies have certified the positive effects of aerobic exercise(such as walking[21-24]cardiac rehabilitation training,[25]or Tai Chi[26]on the fatigue and quality of life on CHF patients. In addition to Chinese ancient regimens like BDJE being beneficial to CHF, the effects of Chinese Herbal Medicine(CHM) and acupuncture have also been highlighted in numerous studies as being beneficial to CHF patients. Several prescribed formulae have been clinically proven more effective for the treatment of CHF when compared with standardized western medicine. The prescribed formulae used in the comparison includes DanshenYin, Qishenyiqi Dripping pill (QSYQ), Fufangdanshen Dripping pill, ect.[5]The coexistence of western medicine (WM) and TCM, is known as integrative medicine(IM). The introduction of WM into China in the 16th century created a healthcare model unique to China, where TCM and WM are both effectively implemented into the healthcare system of the people. China's system is therefore essential for comparisons between both medicines to be conducted with the least possible bias, as well as a global platform to introduce TCM to the world. An example of effective IM is Cardiovascular Disease (CVD), restenosis after percutaneous coronary intervention and myocardial ischemia reperfusion injury (MIRI).[27]There is evidence for several promising integrative therapies for the treatment and prevention of CVD, including meditation, yoga, acupuncture and herbal therapies.[28]Current evidence from RCTs indicates that IM might be effective in control of cardiovascular risk factors, and exert beneficial effects on CVD and CHF.[29]CHM in the treatment of CVD by activating the signaling pathway of NO, inhibiting inflammation, attenuating oxidative stress and inhibiting apoptosis[30].The long-loop pathway as the physiologic mechanism of acupuncture which can specifically improve cardiac function and quality of life measures in the management of CVD and CHF.[31]IM used among patients with CVD is common, with dietary

supplements (eg, CoQ10,garlic, vitamin D, ect) and mind-body therapies (MBTs) being the most commonly used treatment modalities.[32]

In summary, integrative medicine will play a potent role in primary and secondary prevention of chronic disease, in particular CVD in the future.[33]The safety and efficacy of BDJE on CHF patients will be examined in the review. A systematic review of other IM treatment methods for CVD and CHF should be carried out in order to provide more evidence to further guide treatment for CHF and CVD patients.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist[34]of this protocol is presented in online supplementary Appendix 2.

Author Contributions

JYL, FY and NL conceived and designed the study. The manuscript of this protocol was drafted by JYL, FY and NH and revised by JHL and WXX. NH and JHL designed the search strategies and will perform the search, screening and assessment of the risk of bias independently. JYL and WXX will analyze and interpret the data. FY will arbitrate any disagreements during the review. All authors approved the final version of this protocol.

Funding This research received no external funding.

Conflicts of Interest The authors declare no conflict of interest.

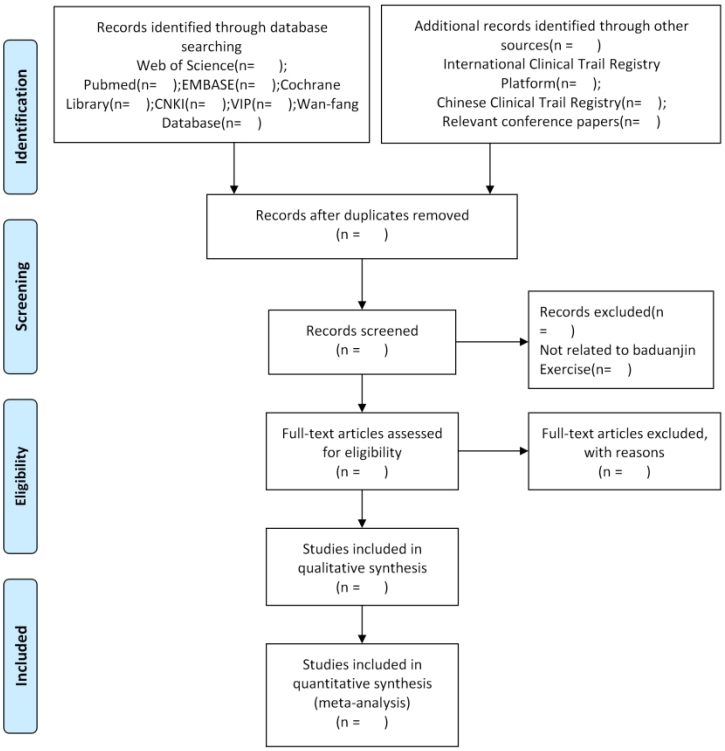
Data statement No additional data are available.

WORD ACOUNT 3872.

Reference

1. Mishra S, Mohan JC, Nair T, et al. Management protocols for chronic heart failure in India. Indian Heart J. 2018;70:105-27.
2. Fleg JL, Cooper LS, Borlaug BA, et al. Exercise training as therapy for heart failure: current status and future directions. Circ Heart Fail. 2015;8:209-20.
3. Ziaeian B, GC. F. Epidemiology and aetiology of heart failure. Nat Rev Cardiol. 2016;13:368-78.
4. Huang J. The current status and the prospect of TCM in the treatment of chronic Heart failure. Journal of Cardiovascular and Cerebrovascular Diseases combined with traditional Chinese and Western Medicine. 2015;13:1-2.
5. Wang Y, Wang Q, Li C, et al. A Review of Chinese Herbal Medicine for the Treatment of Chronic Heart Failure. Curr Pharm Des. 2017;23:5115-24.
6. Gong QH, Shi LP, Qi P, et al. Research status of TCM in the treatment of chronic Heart failure. Journal of practical traditional Chinese Medicine. 2018;34:868-70.
7. Ades PA, Keteyian SJ, Balady GJ, et al. Cardiac rehabilitation exercise and self-care for chronic heart failure. JACC Heart Fail. 2013;1:540-7.
8. McMahon SR, Ades PA, Thompson PD. The role of cardiac rehabilitation in patients with heart disease. Trends Cardiovasc Med. 2017;27:420-5.
9. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:e147-239.
10. Jiang FR, Liu DJ, Kong YM. Progress in the study of the role of cardiac rehabilitation exercise in CHF patients. Journal of Cardiovascular Rehabilitation Medicine. 2018;27:716-20.
11. Henkin Y. Participation in cardiac rehabilitation after coronary bypass surgery: good news, bad news. Harefuah. 2012;151:522- 56.
12. Zhu M, li SN. The research progress of Traditional Chinese Medicine on Chronic Heart Failure. Chinese Traditional Patent Medicine. 2018;40:1804-7.

13. Wang XQ, Pi YL, Chen PJ, et al. Traditional Chinese Exercise for Cardiovascular Diseases: Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2016;5:e002562.
14. Yao CD, Li F, YB. M. Effect of Tai chi on cardiac rehabilitation of patients with chronic heart failure. Journal of Cardiovascular Rehabilitation Medicine2010. p. 364-7.
15. Yeh GY, Wood MJ, Wayne PM, et al. Tai chi in patients with heart failure with preserved ejection fraction. Congest Heart Fail. 2013;19:77-84.
16. Yu J. Modern distance Education of traditional Chinese Medicine in China. Study on the effect of TCM Aerobics on exercise endurance in CHF patients. 2015;13:12-4.
17. Xiong X, Wang P, Li S, et al. Effect of Baduanjin exercise for hypertension: a systematic review and meta-analysis of randomized controlled trials. Maturitas. 2015;80:370-8.
18. Shi XM, Jiang GL, Liu WH, et al. The influence of baduanjin on cardiopulmonary function during cardiac rehabilitation for CHD patients. Med & Pharm J Chin PLA. 2017;29:24-7.
19. Chen BL, Guo JB, Liu MS, et al. Effect of Traditional Chinese Exercise on Gait and Balance for Stroke: A Systematic Review and Meta-Analysis. PLoS One. 2015;10:e0135932.
20. Wu XY, Li L, Ding PR, et al. The impact of baduanjin exercise on 62 coronary heart disease patients with depression. World Chinese Medicine. 2014;9:39-43.
21. Oka RK, De Marco T, Haskell WL, et al. Impact of a Home-Based Walking and Resistance Training Program on Quality of Life in Patients With Heart Failure. Am J Cardiol. 2000;85:365-9.
22. Corvera-Tindel T, Doering LV, Woo MA, et al. Effects of a home walking exercise program on functional status and symptoms in heart failure. Am Heart J. 2004;147:339-46.
23. Gary RA, Sueta CA, Dougherty M, et al. Home-based exercise improves functional performance and quality of life in women with diastolic heart failure. Heart Lung. 2004;33:210-8.
24. Hassanpour Dehkordi A, Khaledi Far A. Effect of exercise training on the quality of life and echocardiography parameter of systolic function in patients with chronic heart failure: a randomized trial. Asian J Sports Med. 2015;6:e22643.
25. Pozehl B, Duncan K, Hertzog M. The effects of exercise training on fatigue and dyspnea in heart failure. Eur J Cardiovasc Nurs. 2008;7:127-32.
26. Yeh GY, McCarthy EP, Wayne PM, et al. Tai chi exercise in patients with chronic heart failure: a randomized clinical trial. Arch Intern Med. 2011;171:750-7.
27. Wang J, Xiong X. Current situation and perspectives of clinical study in integrative medicine in china. Evid Based Complement Alternat Med. 2012;2012:268542.
28. Aggarwal M, Aggarwal B. Rao J. Integrative Medicine for Cardiovascular Disease and Prevention. Med Clin North Am. 2017;101:895-923.
29. Hao P, Jiang F, Cheng J, et al. Traditional Chinese Medicine for Cardiovascular Disease: Evidence and Potential Mechanisms. J Am Coll Cardiol. 2017;69:2952-66.
30. Liu C, Huang Y. Chinese Herbal Medicine on Cardiovascular Diseases and the Mechanisms of Action. Front Pharmacol. 2016;7:469.
31. Ni YM, Frishman WH. Acupuncture and Cardiovascular Disease: Focus on Heart Failure. Cardiol Rev. 2018;26:93-8.
32. Mehta D. Integrative Medicine and Cardiovascular Disorders. Prim Care. 2017;44:351-67.
33. Shi DZ. Integrative Medicine Intervention for Chronic Disease Management-Cardiovascular Disease. Chin J Integr Med. 2018;24:883-5.
34. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.



209x297mm (288 x 288 DPI)

Reporting checklist for protocol of a systematic review.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a (This study will be the first to assess the safety of BDJE and their effect on CHF patients)
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	6
	#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	n/a (This study will be the first to assess the safety of BDJE and their effect on CHF patients)
Sources	#5a	Indicate sources of financial or other support for the review	6
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a (This research received no external funding)
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a (This research received no external funding)

Rationale	#6	Describe the rationale for the review in the context of what is already known	1
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3,4,
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	3,4,
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	1,3,4,
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	3,4
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Study records - 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 confirming data from investigators	3
Data items	#12	List and define all variables for which data	3

		will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3
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	4,5
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	4
	#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 (such as I2, Kendall's τ)	4
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	4,5
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a (All the included studies will be taken into Systematic Reviews and the studies which are selected according to the quality of included literatures will be made a meta-analysis)
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	4,5
Confidence in cumulative	#17	Describe how the strength of the body of evidence will be assessed (such as	5

evidence GRADE)