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Does Tai Chi improve psychological well-being and quality of life in patients with cardiovascular disease and/or cardiovascular risk factors? a systematic review protocol

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Title: Does Tai Chi improve psychological well-being and quality of life in patients with cardiovascular disease and/or cardiovascular risk factors? a systematic review protocol

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ABSTRACT

Introduction Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide. Psychological risk factors such as stress, anxiety, and depression are known to play a significant and independent role in the development and progression of CVD and its risk factors. Tai Chi has been reported as potentially effective for health and well-being. It is of value to assess the effectiveness and safety of Tai Chi on psychological well-being and quality of life in people with CVD and/or cardiovascular risk factors.

Methods and analysis We will include all relevant randomised controlled trials on Tai Chi for stress, anxiety, depression, psychological well-being, and quality of life in people with CVD and cardiovascular risk factors. Literature searching will be conducted until 31st December 2016 from major English and Chinese databases. Two authors will conduct data selection and extraction independently. Quality assessment will be conducted using the risk of bias tool recommended by the Cochrane Collaboration. We will conduct data analysis using Cochrane's RevMan Software. Forest plots and summary of findings tables will illustrate the results from a meta-analysis if sufficient studies are identified.

Ethics and dissemination Ethics approval is not required as this study will not involve patients. The results of this study will be submitted to a peer-reviewed journal for publication, to inform both clinical practice and further research on Tai Chi and CVDs.

Discussion This review will summarize the evidence on Tai Chi for psychological well-being and quality of life in people with CVD and their risk factors. We anticipate that the results of this review would be useful for healthcare professionals and researchers on Tai Chi and CVDs.

Trial registration number International Prospective Register for Systematic Reviews

(PROSPERO) number CRD42016042905.

Keywords: Tai Chi, well-being, stress, depression, anxiety, cardiovascular disease

Strengths and limitations of this study:

- This systematic review will synthesise the evidence on Tai Chi for psychological well-being and quality of life in people with cardiovascular disease and risk factors for the first time.
- One limitation of this study is that significant heterogeneity may appear due to the variations in psychological measurements, durations, frequencies, styles (such as Chen, Yang, Wu, and Sun style) or forms (such as 24-form, 54-form, 83-form) of Tai Chi.
- Another limitation of this study is that the blinding of participants and personnel might not be possible in included studies which might affect the interpretation of results.

INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of morbidity and mortality worldwide, and an estimated 17.5 million people died from CVD in 2012 representing 31% of all global deaths[1]. In the UK, the total CVD mortality declined by 68% between 1980 and 2013, while the hospital admissions increased by over 46000 between 2010/2011 and 2013/2014[2]. Current statistics of premature deaths due to CVD ranges from 4% in high-income countries to astonishing estimate of 80% of the total CVD mortality occur in developing countries[3]. In addition, the disease burden on the individual and society comes not only from deaths, but also from those living with CVD. The American Heart Association estimated that the total direct and indirect cost of CVD in the US alone for 2010 was in excess of US$500 billion[4].

According to the World Health Organization (WHO)[1], the major risk factors of CVD are related to lifestyles, including tobacco smoking, unhealthy diet, physical inactivity and alcohol abuse. These factors may lead to other contributing risk factors of CVD, such as hypertension, diabetes, hyperlipidaemia, overweight and obesity. Other determinants of CVD include poverty, stress, depression, anxiety, ageing and hereditary factors.

Psychological risk factors such as stress, anxiety, and depression are known to play a significant and independent role in the development and progression of CVD and its risk factors, with many of these factors being correlated with each other[5-8]. Stress in research focuses on three major perspectives: environmental (focusing on stressors or life events), psychological (assessing subjective stress appraisal and affective reactions), and biological (assessing the activation of the physiological systems involved in the stress response) [9]. Anxiety has been defined as a stimulus, a trait, a motive and a drive, which can be differentiated into state anxiety (an emotional condition at a period of time), and trait anxiety (a personality characteristic) [10]. The prevalence of anxiety in people with coronary heart disease varies from 12.0% to 41.8% in men, and 21.5% to 63.7% in women[11]. We define depression as either elevated

depressive symptoms on a validated depression scale or a formal diagnosis of major depressive disorder. Between 31-45% of people with coronary heart disease suffer from clinically significant depressive symptoms, and 15-20% of them meet criteria of major depressive disorder which is roughly threefold higher than in the general population[12]. It is now well established that depression is related not only to the incidence of CVD but also an independent risk factor for cardiac morbidity and mortality. Therefore, psychological management is necessary for people with CVD.

Most CVDs can be prevented by addressing these risk factors mentioned above. Medical treatment is necessary for people with hypertension, diabetes, and hyperlipidaemia to reduce cardiovascular risk and prevent heart attacks and strokes[1]. For people with established CVD, it is important to prevent the occurrence of further cardiovascular events such as acute myocardial infarction. However, major treatments target only at physical conditions. There is still insufficient evidence to support the introduction of psychological management strategies for people with CVD including cardiac rehabilitation and exercise programs, general support, cognitive behavioral therapy, anti-depressant medication, and combined approaches [13]. Acceptable and effective psychological interventions for people with CVD and/or cardiovascular risk factors are warranted.

Tai Chi originated in China and purportedly developed by a famous martial artist Wang-Ting Chen towards the end of Ming Dynasty (18th Century A.D.)[14]. Tai Chi comprehensively incorporates the essence of Chinese folk and military martial arts, ancient breathing and meditative techniques, Chinese philosophy of *yin* and *yang*, and traditional Chinese medicine theory[15]. In recent years, studies on Tai Chi for CVDs and risk factors have flourished. An increasing amount of studies have demonstrated multiple physical and psychological benefits of Tai Chi, including reduction of stress, anxiety, depression, and improving quality of life.

Five systematic reviews[16-20] have reported the beneficial effects of Tai Chi on

psychological well-being, including reduction of stress, anxiety, and depression in wide population, but the findings showed methodological limitations of included trials, variations in study design or comparisons, heterogeneous outcomes or small sample size. Two out of the five systematic reviews only searched literature from English databases[16, 20]. Wang C et al.[19] summarized and analyzed 40 studies (including RCT, non-randomised trials and observational studies), in which 29 psychological measurements were identified, and concluded that Tai Chi significantly improved psychological well-being including reduced stress, anxiety, depression and mood disturbance and increased self-esteem. Recently, more clinical trials have been published in this area. However, little is known about the effect of Tai Chi for psychological well-being and quality of life measured by validated instruments specifically in people with CVD and/or cardiovascular risk factors.

The objective of this systematic review is to assess the effectiveness and safety of Tai Chi intervention for stress, anxiety, depression, other psychological well-being and quality of life in people with CVD and/or cardiovascular risk factors.

METHODS and ANALYSIS

Inclusion and Exclusion Criteria

Type of study

We will include only parallel randomised controlled trials (RCT) and only the first phase data and outcomes of randomised cross-over trials will be used in any data analysis.

Type of participants

We will include participants aged 40 years or older with a diagnosis of a cardiovascular disease (such as coronary heart disease, stroke, myocardial infarction and hypertension) or with cardiovascular risk factors (including hypertension, diabetes, and/or hyperlipidaemia). No limitation of gender will be applied.

Type of intervention

Any types of Tai Chi will be eligible, regardless of the forms (such as 24-form, 54-form, 83-form Tai Chi), styles (such as Chen, Yang, Wu and Sun style). The duration should be at least one month with a frequency at least once per week.

Type of control

No treatment, other forms of exercise, or conventional treatment will be eligible. Comparisons will also include a co-intervention if applied in all arms.

Type of outcome

The primary outcomes are psychological status of stress measured by validated instruments and adverse events. The secondary outcomes are other psychological status including anxiety, depression, mood disturbance, self-esteem and quality of life measured by validated instruments.

Search Strategies

We aim to identify all relevant RCTs regardless of language or publication status (e.g. published, unpublished, in press, or in progress). The English searching terms will include “Tai Chi”, “Tai Chi Chuan”, “Tai Chi Chih”, “ta’i chi”, “Tai Ji Quan”, “taijiquan”, “cardiovascular disease”, “hypertension”, “high blood pressure”, “diabetes”, “hyperlipidaemia”, “high cholesterol”,"randomized controlled trial", "randomised controlled trial", "controlled clinical trial", "randomly", "clinical", "trial", "random", "randomised" and "randomized". The Chinese searching terms will include Tai Chi (“*Tai_ji*”, or “*Tai_ji_chuan*”), cardiovascular disease (“Xin_xue_guan_bing”), cardiovascular risk factors (“Gao_xue_ya (hyeprtension)”, “Tang_niao_bing (diabetes)”, “Gao_xue_zhi (hyperlipidaemia)”) and randomized (“*sui_ji*”). Examples of detailed search strategies for one English database and one Chinese database are available in Table 1 (See Table 1). We will apply a similar strategy for other electronic databases.

Table 1 – Search strategies

Database	Number	Search items
PubMed	#1	[Title/Abstract] ("Tai Chi" OR "Tai ji" OR "Tai Chi Chih" OR "Ta'i chi" OR "taichi" OR "tai chi chuan" OR "taichi chuan" OR "taiji" OR "Tai Ji Quan" OR "taijiquan" OR "martial arts")
	#2	[Title/Abstract] ("cardiovascular disease" OR "hypertension" OR "high blood pressure" OR "diabetes" OR "hyperlipidaemia" OR "high cholesterol")
	#3	[All fields] ("randomized controlled trial" OR "randomised controlled trial" OR "controlled clinical trial" OR "randomly" OR "clinical" OR "trial" OR "random" OR "randomised" OR "randomized")
	#4	#1 and #2 and 3#
CNKI	#1	[Abstract] ("*Tai_ji*" (Tai Chi) OR "*Tai_ji_quan*" (Tai Chi)
	#2	[Abstract] ("*Xin_xue_guan_bing*" (cardiovascular disease) OR "*Gao_xue_ya*" (hypertension) OR "*Tang_niao_bing*" (diabetes) OR "*Gao_xue_zhi*" (hyperlipidaemia)
	#3	[All fields] ("*sui_ji*" (randomized or randomised))
	#4	#1 and #2 and 3#

Note: CNIK, China National Knowledge Infrastructure.

We will conduct electronic searches from the following databases until 31st December 2016: Cochrane Heart Review Group Specialised Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Library (2017, Issue 1), MEDLINE (from 1946), EMBASE (from 1974), PubMed (from 1966), Sino-Med database (CBM, from 1978), China National Knowledge Infrastructure (CNKI, from 1979), VIP Journal Integration Platform (VJIP, from 1989), and Wanfang Data Chinese database (from 1985).

We will also search the following trials registers to identify those completed trials and request for unpublished data until 31st December 2016: Current Controlled Trials (www.controlled-trials.com), US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov), Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), and the World Health Organization International Clinical Trials

Registry platform (www.who.int/trialsearch). Additional clinical trials will be identified by searching the reference lists of relevant trials. Authors of identified studies will be also contacted to identify other studies.

Data Selection and Extraction

Selection of studies

Two authors (GYY and WYL) will screen the titles and abstracts independently. We will retrieve full texts of all potentially relevant studies. Any disagreement about the selection of studies will be resolved by discussion, and another author will arbitrate when necessary. The selection procedure is shown in a PRISMA flow chart (See figure 1).

Data Extraction and Management

Two authors (GYY and WYL) will extract the data from the included trials independently by using Epidata 2.8 software. Any disagreements will be resolved by discussion with a third author. The extracted data will include the following information: (1) publication information: authors, country, journal name, year of publication.; (2) study designs: method of random number generation and allocation concealment, details of blinding methods; (3) participants: sample size, characteristics of participants (e.g. age, gender, duration of disorder, and severity of disorder); (4) intervention: type and/or form of Tai Chi, details of treatment and control; and (5) outcome data: outcomes measures, main data of the outcomes. In case of missing data or having unclear information, we will contact the original authors to clarify the information. A pre-defined data extraction form developed based on the recommendation of the Cochrane Collaboration[21] is available in **Table 2**.

Table 2 – Data extraction form

Review title or ID	
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	

General Information	
Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Study Methods (extract information from descriptions as stated in report/paper)	
Design *(e.g. parallel, crossover)*	
Start date	
End date	
Duration of participation *(from recruitment to last follow-up)*	
Participants (extract the description as stated in report/paper. *Include comparative information for each intervention or comparison group if available)*	
Setting *(including location and social context)*	
Inclusion criteria	
Exclusion criteria	
Total no. randomised	
Baseline imbalances	
Withdrawals and exclusions *(if not provided below by outcome)*	
Age	
Sex	
Illness and Severity	
Co-morbidities	
Other relevant socio-demographics	
Subgroups measured	
Subgroups reported	
Intervention groups (extract the description as stated in report/paper. *Copy and paste table for each intervention and comparison group)*	
Group name	
No. randomised to group	

Description *(include sufficient details, e.g. style, form, components)*	
Duration of treatment	
Timing *(e.g. frequency, duration of each practice)*	
Learning method *(e.g. DVD, instructors, one-to-one, in group)*	
Providers *(e.g. a Tai Chi instructor with 10 years of experience etc. if relevant)*	
Co-interventions	
Compliance	
Outcomes (extract the description as stated in report/paper. *Copy and paste table for each outcome.)*	
Outcome name	
Time points measured *(specify whether from start or end of intervention)*	
Time points reported	
Outcome definition *(with diagnostic criteria if relevant)*	
Person measuring/ reporting	
Scales: upper and lower limits *(indicate whether high or low score is good)*	
Is outcome/tool validated?	☐Yes ☐No ☐Unclear
Imputation of missing data *(e.g. assumptions made for ITT analysis)*	

Assumed risk estimate *(e.g. baseline or population risk noted in Background)*							
Results	*Dichotomous outcome*	**Intervention**		**Comparison**			
		No. with event	Total in group	No. with event	Total in group		
	Continuous outcome	**Intervention**			**Comparison**		
		Mean	SD	No. Participants	Mean	SD	No. Participants

Risk of Bias assessment				
Domain	Risk of bias			Support for judgement *(include direct quotes where available with explanatory comments)*
	Low	High	Unclear	
Random sequence generation *(selection bias)*	☐	☐	☐	
Allocation concealment *(selection bias)*	☐	☐	☐	
Blinding of outcome assessment *(detection bias)*	☐	☐	☐	
Incomplete outcome data *(attrition bias)*	☐	☐	☐	
Selective outcome reporting? *(reporting bias)*	☐	☐	☐	
Other bias	☐	☐	☐	
Other information (extract the description as stated in report/paper)				
Key conclusions of authors				
Notes:				

Quality Assessment

We will use the risk of bias tool provided by the Cochrane Handbook for Systematic Reviews of Interventions[22] to assess the methodical quality of included studies. We

will assess the following categories of bias for each study: selection bias (random sequence generation and allocation concealment); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data); reporting bias (selective reporting); and other bias. We will not report performance bias, considering the difficulty to blind the participants and personnel in Tai Chi study. For each item, there are three potential bias judgements: 'low risk', 'high risk', or 'unclear risk'. A clinical trial meeting all criteria will be judged as having a low risk of bias, a trial meeting none of the criteria will be judged as having a risk of bias, and a trial with insufficient information to judge will be classified as unclear risk of bias. Any disagreements will be resolved by discussion, with involvement a third author where necessary.

Data Synthesis

We will summarise data using risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes or mean difference (MD) with 95% CI for continuous outcomes. We will assess clinical heterogeneity according to the characteristics of the included studies and the participants, details of the intervention or control, and types of outcome measurements. We will assess statistical heterogeneity by using the I^2 statistic, and heterogeneity will be regarded as substantial if the I^2 statistic is greater than 50%.

We will perform statistical analyses by the Cochrane's Review Manager software (version 5.3). We will pool data if the I^2 statistic is less than 75% and the clinical heterogeneity among trials is acceptable. We will use random-effects model to conduct the meta-analysis unless the I^2 statistic is less than 25%. Forest plots will visualise the results of the meta-analysis if there are more than 10 included trials in one meta-analysis.

Subgroup analyses

To explore whether the treatment effects are different in different subgroups, we plan to conduct subgroup analyses for different psychological measurements, durations,

frequencies, styles (such as Chen, Yang, Wu and Sun style) or forms (such as 24-form, 54-form and 83-form Tai Chi) of Tai Chi, if sufficient studies are identified. We will also calculate the incidence rates of different types of adverse events.

Sensitivity analysis

To ensure the robustness of evidence, we will perform sensitivity analysis to assess the impact of studies with high risk of bias. We will compare the results to decide whether studies with lower quality should be excluded on the basis of sample size, strength of evidence and influence on pooled effect size.

Grading the quality of evidence

We will generate 'Summary of findings' (SoF) tables for the primary outcomes using GRADEPro software (version 3.2), to assist health decision-making for individual patients. The SoF tables will demonstrate the overall quality of the body of evidence for clinical outcomes only from results of meta-analysis, by using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria (study limitations, consistency of effect, imprecision, indirectness, and publication bias).

ETHICS AND DISSEMINATION

Formal ethical approval is not required because all data used in this study will be anonymous with no concerns regarding privacy. This systematic review will summarize the evidence on the effectiveness and safety of Tai Chi for psychological well-being and quality of life in people with CVD and CVD risk factors. The results of this study will be disseminated through a peer-reviewed journal for publication.

DISCUSSION

Results from this systematic review will be valuable for clinical practice and research on Tai Chi and CVD. To the best of our knowledge, this is the first systematic review that will examine Tai Chi on psychological well-being and quality of life in people

with CVD and/or CVD risk factors. The findings of this systematic review may be applied in clinical practice for the prevention, treatment and rehabilitation of CVDs. Gaps in the literature will be identified to provide implications for future research on Tai Chi for CVD.

One limitation of this study is that significant heterogeneity may appear due to the various styles (such as Chen, Yang, Wu and Sun style) and forms (such as 24-form, 54-form and 83-form Tai Chi) of Tai Chi, durations and frequencies. We plan to conduct subgroup analyses to explore the differences between different subgroups. Another limitation of this study is that performance bias of included studies might be at high risk, because blinding of participants and personnel in included studies is unlikely. We plan to report the blinding of outcome assessment, and conduct sensitivity analysis to assess the impact of studies with high risk of bias.

Authors' contributions

GYY, NK and DC designed and conceived the study. GYY drafted and revised the study protocol with contributions from WYL, HJC, NK, JPL, AB, HK and DC. GYY and WYL will conduct literature search and selection. GYY and WYL will independently perform data extraction and assessment of quality. GYY will conduct the data analysis. All authors read and approved the final manuscript of the study protocol.

Acknowledgments

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Competing interest

The authors declare no competing interests.

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Figure Legend

Figure 1 - PRISMA Flow Diagram

Note: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, which is used worldwide to improve the reporting of systematic reviews and meta-analyses.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	#2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	#15
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No
Support:			
Sources	5a	Indicate sources of financial or other support for the review	#15
Sponsor	5b	Provide name for the review funder and/or sponsor	No
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	No
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	#4-#6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	#6
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	#6-#7
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	#8
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	#7 & Table 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	#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 (that is, screening, eligibility and inclusion in meta-analysis)	#8
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	#9 & Table 2
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	#9 & Table 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	#8-#9
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	#12-#13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	#12-#14
	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 I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	#13-#14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	#14

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

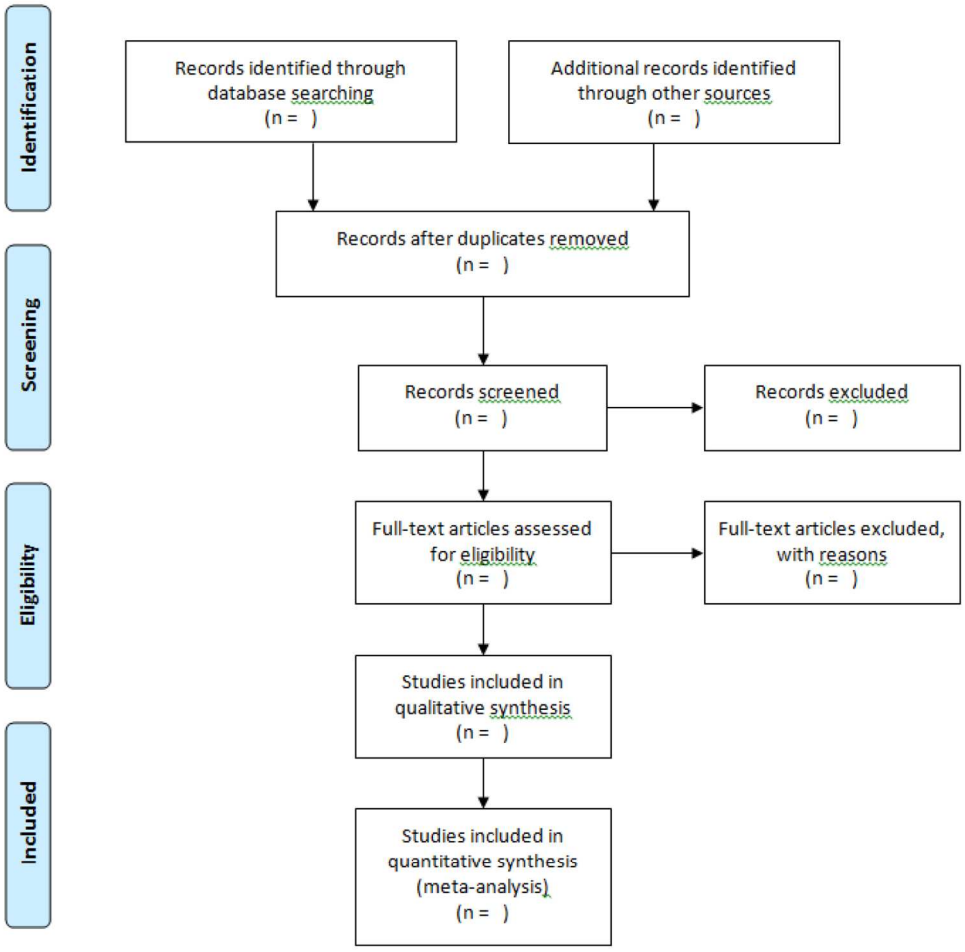

Figure 1 - PRISMA Flow Diagram

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Does Tai Chi improve psychological well-being and quality of life in patients with cardiovascular disease and/or cardiovascular risk factors? a systematic review protocol

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Keywords:	Tai Chi, well-being, stress, depression, anxiety, cardiovascular disease

Title: Does Tai Chi improve psychological well-being and quality of life in patients with cardiovascular disease and/or cardiovascular risk factors? a systematic review protocol

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ABSTRACT

Introduction Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide. Psychological risk factors such as stress, anxiety, and depression are known to play a significant and independent role in the development and progression of CVD and its risk factors. Tai Chi has been reported as potentially effective for health and well-being. It is of value to assess the effectiveness and safety of Tai Chi on psychological well-being and quality of life in people with CVD and/or cardiovascular risk factors.

Methods and analysis We will include all relevant randomised controlled trials on Tai Chi for stress, anxiety, depression, psychological well-being, and quality of life in people with CVD and cardiovascular risk factors. Literature searching will be conducted until 31st December 2016 from major English and Chinese databases. Two authors will conduct data selection and extraction independently. Quality assessment will be conducted using the risk of bias tool recommended by the Cochrane Collaboration. We will conduct data analysis using Cochrane's RevMan Software. Forest plots and summary of findings tables will illustrate the results from a meta-analysis if sufficient studies are identified.

Ethics and dissemination Ethics approval is not required as this study will not involve patients. The results of this study will be submitted to a peer-reviewed journal for publication, to inform both clinical practice and further research on Tai Chi and CVDs.

Discussion This review will summarize the evidence on Tai Chi for psychological well-being and quality of life in people with CVD and their risk factors. We anticipate that the results of this review would be useful for healthcare professionals and researchers on Tai Chi and CVDs.

Trial registration number International Prospective Register for Systematic Reviews

(PROSPERO) number CRD42016042905.

Keywords: Tai Chi, well-being, stress, depression, anxiety, cardiovascular disease

Strengths and limitations of this study:

- This systematic review will synthesise the evidence on Tai Chi for psychological well-being and quality of life in people with cardiovascular disease and risk factors for the first time.
- One limitation of this study is that significant heterogeneity may appear due to the variations in psychological measurements, durations, frequencies, styles (such as Chen, Yang, Wu, and Sun style) or forms (such as 24-form, 54-form, 83-form) of Tai Chi.
- Another limitation of this study is that the blinding of participants and personnel might not be possible in included studies which might affect the interpretation of results.

INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of morbidity and mortality worldwide, and an estimated 17.5 million people died from CVD in 2012 representing 31% of all global deaths[1]. In the UK, the total CVD mortality declined by 68% between 1980 and 2013, while the hospital admissions increased by over 46000 between 2010/2011 and 2013/2014[2]. Current statistics of premature deaths due to CVD ranges from 4% in high-income countries to astonishing estimate of 80% of the total CVD mortality occur in developing countries[3]. In addition, the disease burden on the individual and society comes not only from deaths, but also from those living with CVD. The American Heart Association estimated that the total direct and indirect cost of CVD in the US alone for 2010 was in excess of US$500 billion[4].

According to the World Health Organization (WHO)[1], the major risk factors of CVD are related to lifestyles, including tobacco smoking, unhealthy diet, physical inactivity and alcohol abuse. These factors may lead to other contributing risk factors of CVD, such as hypertension, diabetes, dyslipidaemia, overweight and obesity. Other determinants of CVD include poverty, stress, depression, anxiety, ageing and hereditary factors.

Psychological risk factors such as stress, anxiety, and depression are known to play a significant and independent role in the pathogenesis and progression of CVD and its risk factors, with many of these factors being correlated with each other[5-9]. Stress in research focuses on three major perspectives: environmental (focusing on stressors or life events), psychological (assessing subjective stress appraisal and affective reactions), and biological (assessing the activation of the physiological systems involved in the stress response) [10]. Anxiety has been defined as a stimulus, a trait, a motive and a drive, which can be differentiated into state anxiety (an emotional condition at a period of time), and trait anxiety (a personality characteristic) [11]. The prevalence of anxiety in people with coronary heart disease varies from 12.0% to 41.8% in men, and 21.5% to 63.7% in women[12]. We define depression as either elevated

depressive symptoms on a validated depression scale or a formal diagnosis of major depressive disorder. Between 31-45% of people with coronary heart disease suffer from clinically significant depressive symptoms, and 15-20% of them meet criteria of major depressive disorder which is roughly threefold higher than in the general population[13]. It is now well established that depression is related not only to the incidence of CVD but also an independent risk factor for cardiac morbidity and mortality. Therefore, psychological management is necessary for people with CVD.

Most CVDs can be prevented by addressing these risk factors mentioned above. Medical treatment is necessary for people with hypertension, diabetes, and dyslipidemia to reduce cardiovascular risk and prevent heart attacks and strokes[1]. For people with established CVD, it is important to prevent the occurrence of further cardiovascular events such as acute myocardial infarction. However, major treatments target only at physical conditions. There is still insufficient evidence to support the introduction of psychological management strategies for people with CVD including cardiac rehabilitation and exercise programs, general support, cognitive behavioral therapy, anti-depressant medication, and combined approaches [9, 14]. Acceptable and effective psychological interventions for people with CVD and/or cardiovascular risk factors are warranted.

Tai Chi originated in China and purportedly developed by a famous martial artist Wang-Ting Chen towards the end of Ming Dynasty (18th Century A.D.)[15]. Tai Chi comprehensively incorporates the essence of Chinese folk and military martial arts, ancient breathing and meditative techniques, Chinese philosophy of *yin* and *yang*, and traditional Chinese medicine theory[16]. In recent years, studies on Tai Chi for CVDs and risk factors have flourished. An increasing amount of studies have demonstrated multiple physical and psychological benefits of Tai Chi, including reduction of stress, anxiety, depression, and improving quality of life.

Five systematic reviews[17-21] have reported the beneficial effects of Tai Chi on

psychological well-being, including reduction of stress, anxiety, and depression in wide population, but the findings showed methodological limitations of included trials, variations in study design or comparisons, heterogeneous outcomes or small sample size. Two out of the five systematic reviews only searched literature from English databases [17, 21]. Wang C et al.[20] summarized and analyzed 40 studies (including RCT, non-randomised trials and observational studies), in which 29 psychological measurements were identified, and concluded that Tai Chi significantly improved psychological well-being including reduced stress, anxiety, depression and mood disturbance and increased self-esteem. Recently, more clinical trials have been published in this area. However, little is known about the effect of Tai Chi for psychological well-being and quality of life measured by validated instruments specifically in people with CVD and/or cardiovascular risk factors.

The objective of this systematic review is to assess the effectiveness and safety of Tai Chi intervention for stress, anxiety, depression, other psychological well-being and quality of life in people with CVD and/or cardiovascular risk factors.

METHODS and ANALYSIS

Inclusion and Exclusion Criteria

Type of study

We will include only parallel randomised controlled trials (RCT) and only the first phase data and outcomes of randomised cross-over trials will be used in any data analysis.

Type of participants

We will include participants aged 40 years or older with a diagnosis of a cardiovascular disease (such as coronary heart disease, stroke, heart failure, myocardial infarction and hypertension) or with cardiovascular risk factors (including hypertension, diabetes, and/or dyslipidemia). No limitation of gender will be applied.

Type of intervention

Any types of Tai Chi will be eligible, regardless of the forms (such as 24-form, 54-form, 83-form Tai Chi), styles (such as Chen, Yang, Wu and Sun style). The duration should be at least one month with a frequency at least once per week.

Type of control

No treatment, other forms of exercise, or conventional treatment will be eligible. Comparisons will also include a co-intervention if applied in all arms.

Type of outcome

The primary outcomes are psychological status of stress measured by validated instruments and adverse events. The secondary outcomes are other psychological status including anxiety, depression, mood disturbance, self-esteem and quality of life measured by validated instruments.

Search Strategies

We aim to identify all relevant RCTs regardless of language or publication status (e.g. published, unpublished, in press, or in progress). The English searching terms will include “Tai Chi”, “Tai Chi Chuan”, “Tai Chi Chih”, “ta’i chi”, “Tai Ji Quan”, “taijiquan”, “cardiovascular disease”, “coronary heart disease”, “stroke”, “heart failure”, “hypertension”, “high blood pressure”, “diabetes”, “dyslipidemia”, “high cholesterol”, "randomized controlled trial", "randomised controlled trial", "controlled clinical trial", "randomly", "clinical", "trial", "random", "randomised" and "randomized". The Chinese searching terms will include Tai Chi (“*Tai_ji*”, or “*Tai_ji_chuan*”), cardiovascular disease (“Xin_xue_guan_bing”), cardiovascular risk factors (“Gao_xue_ya (hyeprtension)”, “Tang_niao_bing (diabetes)”, “Gao_xue_zhi (dyslipidemia)”) and randomized (“*sui_ji*”). Examples of detailed search strategies for one English database and one Chinese database are available in Table 1 (See Table 1). We will apply a similar strategy for other electronic databases.

Table 1 – Search strategies

Database	Number	Search items
PubMed	#1	[Title/Abstract] ("Tai Chi" OR "Tai ji" OR "Tai Chi Chih" OR "Ta'i chi" OR "taichi" OR "tai chi chuan" OR "taichi chuan" OR "taiji" OR "Tai Ji Quan" OR "taijiquan" OR "martial arts")
	#2	[Title/Abstract] ("cardiovascular disease" OR "coronary heart disease" OR "stroke" OR "heart failure" OR "hypertension" OR "high blood pressure" OR "diabetes" OR "dyslipidaemia" OR "high cholesterol")
	#3	[All fields] ("randomized controlled trial" OR "randomised controlled trial" OR "controlled clinical trial" OR "randomly" OR "clinical" OR "trial" OR "random" OR "randomised" OR "randomized")
	#4	#1 and #2 and 3#
CNKI	#1	[Abstract] ("*Tai_ji*" (Tai Chi) OR "*Tai_ji_quan*" (Tai Chi)
	#2	[Abstract] ("*Xin_xue_guan_bing*" (cardiovascular disease) OR OR "Guan_xin_bing" (coronary heart disease) OR "Zhong_feng" (stroke) OR "Nao_zu_zhong) (stroke) OR "Xin_Shuai" (heart failure) OR "*Gao_xue_ya*" (hypertension) OR "*Tang_niao_bing*" (diabetes) OR "*Gao_xue_zhi*" (dyslipidaemia)
	#3	[All fields] ("*sui_ji*" (randomized or randomised))
	#4	#1 and #2 and 3#

Note: CNIK, China National Knowledge Infrastructure.

We will conduct electronic searches from the following databases until 31st December 2016: Cochrane Heart Review Group Specialised Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Library (2017, Issue 1), MEDLINE (from 1946), EMBASE (from 1974), PubMed (from 1966), Sino-Med database (CBM, from 1978), China National Knowledge Infrastructure (CNKI, from 1979), VIP Journal Integration Platform (VJIP, from 1989), and Wanfang Data Chinese database (from 1985).

We will also search the following trials registers to identify those completed trials and request for unpublished data until 31st December 2016: Current Controlled Trials (www.controlled-trials.com), US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov), Australian New Zealand Clinical Trials Registry

(www.anzctr.org.au), and the World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch). Additional clinical trials will be identified by searching the reference lists of relevant trials. Authors of identified studies will be also contacted to identify other studies.

Data Selection and Extraction

Selection of studies

Two authors (GYY and WYL) will screen the titles and abstracts independently. We will retrieve full texts of all potentially relevant studies. Any disagreement about the selection of studies will be resolved by discussion, and another author will arbitrate when necessary. The selection procedure is shown in a PRISMA flow chart (See figure 1).

Data Extraction and Management

Two authors (GYY and WYL) will extract the data from the included trials independently by using Epidata 2.8 software. Any disagreements will be resolved by discussion with a third author. The extracted data will include the following information: (1) publication information: authors, country, journal name, year of publication.; (2) study designs: method of random number generation and allocation concealment, details of blinding methods; (3) participants: sample size, characteristics of participants (e.g. age, gender, duration of disorder, and severity of disorder); (4) intervention: type and/or form of Tai Chi, details of treatment and control; and (5) outcome data: outcomes measures, main data of the outcomes. In case of missing data or having unclear information, we will contact the original authors to clarify the information. A pre-defined data extraction form developed based on the recommendation of the Cochrane Collaboration [22] is available in **Table 2**.

Table 2 – Data extraction form

Review title or ID	
Study ID *(surname of first author and year first full report of study was published e.g.*	

Smith 2001)	
General Information	
Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Study Methods (extract information from descriptions as stated in report/paper)	
Design *(e.g. parallel, crossover)*	
Start date	
End date	
Duration of participation *(from recruitment to last follow-up)*	
Participants (extract the description as stated in report/paper. *Include comparative information for each intervention or comparison group if available)*	
Setting *(including location and social context)*	
Inclusion criteria	
Exclusion criteria	
Total no. randomised	
Baseline imbalances	
Withdrawals and exclusions *(if not provided below by outcome)*	
Age	
Sex	
Illness and Severity	
Co-morbidities	
Other relevant socio-demographics	
Subgroups measured	
Subgroups reported	
Intervention groups (extract the description as stated in report/paper. *Copy and paste table for each intervention and comparison group)*	
Group name	
No. randomised to group	

Description *(include sufficient details, e.g. style, form, components)*	
Duration of treatment	
Timing *(e.g. frequency, duration of each practice)*	
Learning method *(e.g. DVD, instructors, one-to-one, in group)*	
Providers *(e.g. a Tai Chi instructor with 10 years of experience etc. if relevant)*	
Co-interventions	
Compliance	
Outcomes (extract the description as stated in report/paper. *Copy and paste table for each outcome.)*	
Outcome name	
Time points measured *(specify whether from start or end of intervention)*	
Time points reported	
Outcome definition *(with diagnostic criteria if relevant)*	
Person measuring/ reporting	
Scales: upper and lower limits *(indicate whether high or low score is good)*	
Is outcome/tool validated?	☐Yes ☐No ☐Unclear
Imputation of missing data *(e.g. assumptions made for ITT analysis)*	

Assumed risk estimate *(e.g. baseline or population risk noted in Background)*							
Results	*Dichotomous outcome*	**Intervention**		**Comparison**			
		No. with event	Total in group	No. with event	Total in group		
	Continuous outcome	**Intervention**			**Comparison**		
		Mean	SD	No. Participants	Mean	SD	No. Participants

Risk of Bias assessment				
Domain	Risk of bias			Support for judgement *(include direct quotes where available with explanatory comments)*
	Low	High	Unclear	
Random sequence generation *(selection bias)*	☐	☐	☐	
Allocation concealment *(selection bias)*	☐	☐	☐	
Blinding of outcome assessment *(detection bias)*	☐	☐	☐	
Incomplete outcome data *(attrition bias)*	☐	☐	☐	
Selective outcome reporting? *(reporting bias)*	☐	☐	☐	
Other bias	☐	☐	☐	

Other information (extract the description as stated in report/paper)	
Key conclusions of authors	
Notes:	

Quality Assessment

We will use the risk of bias tool provided by the Cochrane Handbook for Systematic Reviews of Interventions [23] to assess the methodical quality of included studies. We

will assess the following categories of bias for each study: selection bias (random sequence generation and allocation concealment); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data); reporting bias (selective reporting); and other bias. We will not report performance bias, considering the difficulty to blind the participants and personnel in Tai Chi study. For each item, there are three potential bias judgements: 'low risk', 'high risk', or 'unclear risk'. A clinical trial meeting all criteria will be judged as having a low risk of bias, a trial meeting none of the criteria will be judged as having a risk of bias, and a trial with insufficient information to judge will be classified as unclear risk of bias. Any disagreements will be resolved by discussion, with involvement a third author where necessary.

Data Synthesis

We will summarise data using risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes or mean difference (MD) with 95% CI for continuous outcomes. We will assess clinical heterogeneity according to the characteristics of the included studies and the participants, details of the intervention or control, and types of outcome measurements. We will assess statistical heterogeneity by using the I^2 statistic, and heterogeneity will be regarded as substantial if the I^2 statistic is greater than 50%.

We will perform statistical analyses by the Cochrane's Review Manager software (version 5.3). We will pool data if the I^2 statistic is less than 75% and the clinical heterogeneity among trials is acceptable. We will use random-effects model to conduct the meta-analysis unless the I^2 statistic is less than 25%. Forest plots will visualise the results of the meta-analysis if there are more than 10 included trials in one meta-analysis.

Subgroup analyses

To explore whether the treatment effects are different in different subgroups, we plan to conduct subgroup analyses for different psychological measurements, durations,

frequencies, styles (such as Chen, Yang, Wu and Sun style) or forms (such as 24-form, 54-form and 83-form Tai Chi) of Tai Chi, if sufficient studies are identified. We will also calculate the incidence rates of different types of adverse events.

Sensitivity analysis

To ensure the robustness of evidence, we will perform sensitivity analysis to assess the impact of studies with high risk of bias. We will compare the results to decide whether studies with lower quality should be excluded on the basis of sample size, strength of evidence and influence on pooled effect size.

Grading the quality of evidence

We will generate 'Summary of findings' (SoF) tables for the primary outcomes using GRADEPro software (version 3.2), to assist health decision-making for individual patients. The SoF tables will demonstrate the overall quality of the body of evidence for clinical outcomes only from results of meta-analysis, by using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria (study limitations, consistency of effect, imprecision, indirectness, and publication bias).

ETHICS AND DISSEMINATION

Formal ethical approval is not required because all data used in this study will be anonymous with no concerns regarding privacy. This systematic review will summarize the evidence on the effectiveness and safety of Tai Chi for psychological well-being and quality of life in people with CVD and CVD risk factors. The results of this study will be disseminated through a peer-reviewed journal for publication.

DISCUSSION

Results from this systematic review will be valuable for clinical practice and research on Tai Chi and CVD. To the best of our knowledge, this is the first systematic review that will examine Tai Chi on psychological well-being and quality of life in people

with CVD and/or CVD risk factors. The findings of this systematic review may be applied in clinical practice for the prevention, treatment and rehabilitation of CVDs. Gaps in the literature will be identified to provide implications for future research on Tai Chi for CVD.

One limitation of this study is that significant heterogeneity may appear due to the various styles (such as Chen, Yang, Wu and Sun style) and forms (such as 24-form, 54-form and 83-form Tai Chi) of Tai Chi, durations and frequencies. We plan to conduct subgroup analyses to explore the differences between different subgroups. Another limitation of this study is that performance bias of included studies might be at high risk, because blinding of participants and personnel in included studies is unlikely. We plan to report the blinding of outcome assessment, and conduct sensitivity analysis to assess the impact of studies with high risk of bias.

Authors' contributions

GYY, NK and DC designed and conceived the study. GYY drafted and revised the study protocol with contributions from WYL, HJC, NK, JPL, AB, HK and DC. GYY and WYL will conduct literature search and selection. GYY and WYL will independently perform data extraction and assessment of quality. GYY will conduct the data analysis. All authors read and approved the final manuscript of the study protocol.

Acknowledgments

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Competing interest

The authors declare no competing interests.

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Figure Legend

Figure 1 - PRISMA Flow Diagram

Note: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, which is used worldwide to improve the reporting of systematic reviews and meta-analyses.

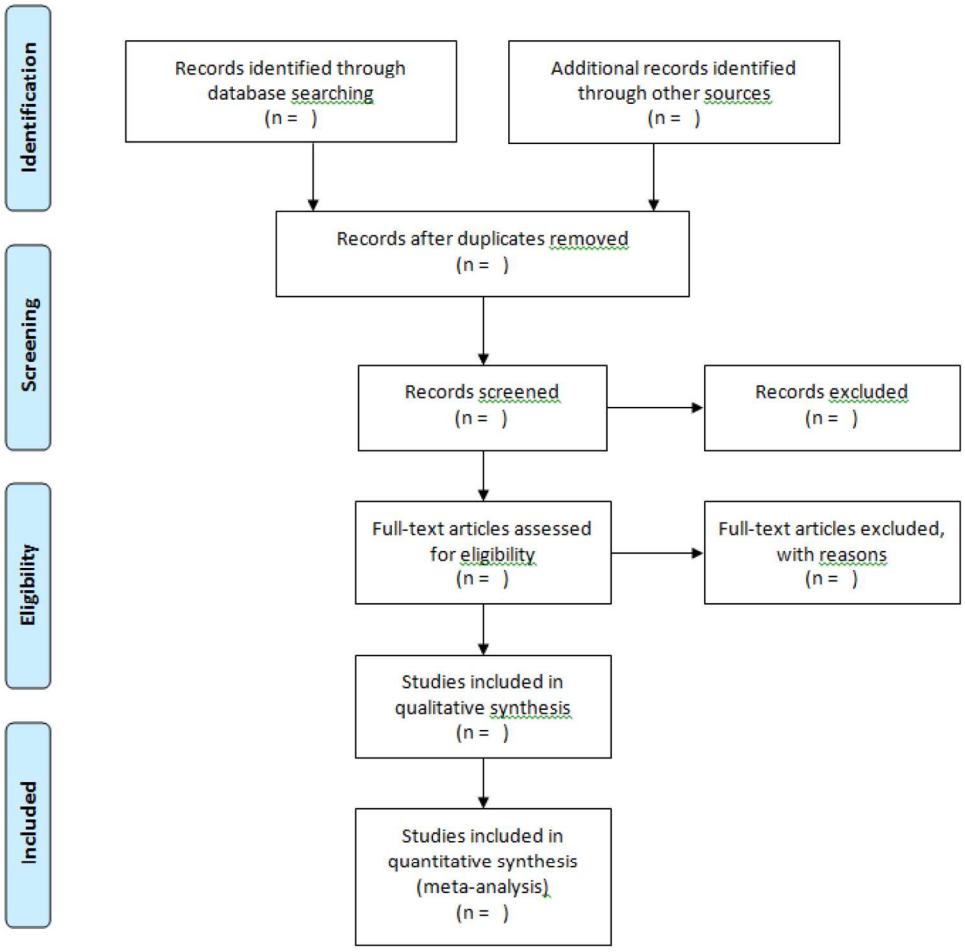

Figure 1 - PRISMA Flow Diagram

140x137mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	#2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	#15
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No
Support:			
Sources	5a	Indicate sources of financial or other support for the review	#15
Sponsor	5b	Provide name for the review funder and/or sponsor	No
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	No
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	#4-#6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	#6
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	#6-#7
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	#8
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	#7 & Table 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	#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 (that is, screening, eligibility and inclusion in meta-analysis)	#8
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	#9 & Table 2
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	#9 & Table 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	#8-#9
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	#12-#13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	#12-#14
	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 I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	#13-#14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	#14

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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