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# BMJ Open

## The effectiveness and safety of manual acupuncture therapy in patients with post-stroke depression: protocol for a systematic review and meta-analysis

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Complete List of Authors:	Liu, Wei; First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Rao, Chang; First Teaching Hospital of Tianjin University of Traditional Chinese Medicine Du, Yuzheng; First Teaching Hospital of Tianjin University of Traditional Chinese Medicine; National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion Nan, Xi; First Teaching Hospital of Tianjin University of Traditional Chinese Medicine Li, Zefang; First Teaching Hospital of Tianjin University of Traditional Chinese Medicine Yin, Chunsheng; First Teaching Hospital of Tianjin University of Traditional Chinese Medicine
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4 **1 The effectiveness and safety of manual acupuncture therapy in**  
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6 **2 patients with post-stroke depression: protocol for a systematic review**  
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8  
9 **3 and meta-analysis**

10  
11 4 Wei Liu<sup>1,2,3,†</sup>, Chang Rao<sup>1,2,3,†</sup>, Yuzheng Du<sup>1,2,\*</sup>, Xi Nan<sup>1,2,3</sup>, Zefang Li<sup>1,2,3</sup>, Chunsheng  
12  
13 Yin<sup>1,2,3</sup>

14  
15 6 1. First Teaching Hospital of Tianjin University of Traditional Chinese Medicine,  
16  
17 Tianjin, China;

18  
19 8 2. National Clinical Research Center for Chinese Medicine Acupuncture and  
20  
21 Moxibustion, Tianjin, China;

22  
23 10 3. Tianjin University of Traditional Chinese Medicine Tianjin, China.

24  
25 11 † These authors contribute equally.

26  
27 12 \* Corresponding author: Yuzheng Du.

28  
29 13 Corresponding author physical mailing address: Xiqing District Changling Road No.88,  
30  
31 Tianjin,China

32  
33 15 Corresponding author E-mail address: drduyuzheng@163.com  
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## 16 Abstract

17 **Introduction:** Acupuncture is widely used on the rehabilitation of stroke survivors,  
18 including hemiplegia, constipation, emotional disorders and so on. Although the  
19 effectiveness of manual acupuncture therapy on post-stroke depression (PSD) has been  
20 confirmed by multiple randomized controlled trials, there were few meta-analysis  
21 focused on the connection between different techniques, durations or other detailed  
22 operations of manual acupuncture and their effectiveness of improving the depression  
23 severity and quality of life for PSD patients.

24 **Methods and analysis:** A systematic search will be performed on English databases  
25 (PubMed, The Cochrane Library, Medline, Embase), Chinese databases (CNKI,  
26 WanFang Data, VIP and Chinese biomedical databases) and Japanese databases(J-  
27 STAGE, CiNii). The retrieval time limit will be from the establishment of the database  
28 to November 2020. Two researchers will independently screen the literatures, extract  
29 data, and evaluate the quality of the included studies. Meta-analysis will be conducted  
30 by using STATA V. 14.0 and Review Manager V.5.3.

31 **PROSPERO registration number:** CRD42020222825.

32 **Keywords:** acupuncture; meta-analysis; post-stroke depression

## 33 Strengths and limitations of this study Introduction

- 34 1. To our knowledge, this study is the first meta-analysis especially focused on the  
35 effectiveness of manual acupuncture therapy for PSD patients.
- 36 2. Compared with previous studies, we have extracted more detailed information on the  
37 treatment schedule of acupuncture (acupoints selection, twist technique, retention time,  
38 frequency, etc) in order to study the effectiveness of manual acupuncture therapy from  
39 multiple angles.
- 40 3. The electronic search will only include randomized controlled trials published in  
41 English, Chinese and Japanese that could limit the inclusion of studies.

## 42 Introduction

43 Stroke is currently the second leading cause of death worldwide, the burden of

1  
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4 44 which has increased substantially over the past few decades due to expanding  
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6 45 population numbers and aging as well as the increased prevalence of modifiable stroke  
7  
8 46 risk factors [1,2]. Depression is a common and recurrent psychiatric disorder that starts  
9  
10 47 shortly after stroke and affects patients in the long term. A meta-analysis of the  
11  
12 48 frequency of depression after stroke shows that approximately one-third of stroke  
13  
14 49 survivors experience depression at any time-point in the first year<sup>[3]</sup>. Depression after  
15  
16 50 stroke is independently associated with poor health outcomes, including increasing  
17  
18 51 mortality, disability, anxiety and lowering quality of life (QoL)<sup>[4]</sup>. In addition, there is a  
19  
20 52 two-way relationship between depression and stroke: stroke could increase the risk of  
21  
22 53 PSD, meanwhile, depression is an independent risk factor for stroke and stroke  
23  
24 54 mortality<sup>[5,6]</sup>.

25  
26 55 This bidirectional relationship makes it more difficult to develop the treatment of  
27  
28 56 PSD, currently, few guidelines mentioned the assessment, treatment or prevention for  
29  
30 57 it<sup>[7]</sup>. For depressive disorder, Canadian network for mood and anxiety  
31  
32 58 treatments (CANMAT), the American psychiatric association (APA) and the World  
33  
34 59 federation of societies of biological psychiatry (WFSBP) guidelines supported that  
35  
36 60 selective serotonin uptake inhibitors (SSRIs) could be used as first-line treatment<sup>[8,9,10]</sup>.  
37  
38 61 But the pharmacotherapy of PSD needs to be more cautious, as some  
39  
40 62 studies<sup>[11,12,13]</sup> **Error! Reference source not found.** showed that the use of SSRI may  
41  
42 63 relate to the potential risk of hemorrhagic stroke.

43  
44 64 Acupuncture, a historic complementary therapy from China, has potential  
45  
46 65 beneficial effects on improving dependency, global neurological deficiency, and some  
47  
48 66 specific neurological impairments for people with stroke in the convalescent stage<sup>[14]</sup>.  
49  
50 67 In the treatment of depression, a recent meta-analysis<sup>[15]</sup> suggests that acupuncture  
51  
52 68 combined with antidepressant medication is effective for the treatment of depression  
53  
54 69 and has an early onset of action, safe and well-tolerated over the first 6-week treatment  
55  
56 70 period. However, few systematic reviews or meta-analysis focused on the effectiveness  
57  
58 71 of acupuncture in treating PSD, although the number of papers related to this area has  
59  
60 72 an upward trend recently<sup>[16,17]</sup>.

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4 73 Besides, there are no meta-analysis focusing on the effectiveness of manual  
5  
6 74 acupuncture on improving the depression severity and QoL of post stroke patients, so  
7  
8 75 far. What's more, there is a general problem of high heterogeneity in existing meta-  
9  
10 76 analysis. One recent meta-analysis<sup>[18]</sup>**Error! Reference source not found.** showed that  
11  
12 77 the curative effect of acupuncture for post stroke cognitive impairment may be related  
13  
14 78 to manipulation and retention time, however, most of the existing meta-analysis on PSD  
15  
16 79 didn't conduct subgroup analysis for such content due to the lack of attention to the  
17  
18 80 details of acupuncture treatment. Therefore, we considered that the higher  
19  
20 81 heterogeneity may be relevant with the difference in the type of acupuncture (manual  
21  
22 82 acupuncture, electroacupuncture, dry needle, etc) and the treatment schedule (acupoints  
23  
24 83 selection, twist technique, retention time, frequency, etc). Hence, we would like to  
25  
26 84 extract the detailed description of manual acupuncture treatment in the included articles  
27  
28 85 and conduct subgroup analysis according to them.

## 29 86 **Objectives**

30  
31 87 The primary purpose of this meta-analysis is to examine the efficacy of manual  
32  
33 88 acupuncture in improving depression severity in individuals with post-stroke  
34  
35 89 depression. Secondary aims are to evaluate its role in enhancing QoL and assess the  
36  
37 90 safety of this treatment.

## 39 91 **Methods and analysis**

40  
41 92 This systematic review protocol has registered in Prospero (registration number:  
42  
43 93 CRD42020222825). It will follow the new edition of the Cochrane handbook for  
44  
45 94 systematic reviews of interventions<sup>[19]</sup> and be reported according to the Preferred  
46  
47 95 Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-  
48  
49 96 P)<sup>[20]</sup>**Error! Reference source not found.**

## 51 97 **Criteria for considering studies for this review**

### 53 98 **Types of studies**

54  
55 99 Randomized controlled trials (RCTs) in English, Chinese and Japanese will be included.  
56  
57 100 Animal studies or studies with incomplete data will be excluded.

### 59 101 **Participants**

1  
2  
3  
4 102 We will include patients who suffered post stroke depression. The diagnosis of stroke  
5  
6 103 should base on computer tomography (CT), magnetic resonance imaging (MRI), or  
7  
8 104 clinical criteria. Meanwhile, depression should be diagnosed according to the  
9  
10 105 International Classification of Diseases Tenth Edition (ICD-10), the Diagnosis and  
11  
12 106 Statistical Manual of Mental Disorders (DSM), Chinese Classification of Mental  
13  
14 107 Disorders (CCMD) or Hamilton Rating Scale for Depression (HAMD)<sup>[21,22,23]</sup>.

15  
16 108 **Types of interventions:**

17  
18 109 The relevant RCTs will be included if the following criteria were met: (1) using manual  
19  
20 110 acupuncture alone, or in combination with another rehabilitation therapy, or in  
21  
22 111 combination with pharmacotherapy in experiment group (EG) (2) using rehabilitation  
23  
24 112 therapy other than manual acupuncture, pharmacotherapy, sham acupuncture or no  
25  
26 113 treatment in control group (CG). In addition, other kinds of acupuncture therapies, such  
27  
28 114 as electroacupuncture, dry needle, laser needle or acupoint-injection, couldn't be used  
29  
30 115 as interventions in EG or CG.

31  
32 116 **Types of outcomes measures:**

33  
34 117 **Primary outcomes:**

35  
36 118 **Depression severity:** evaluated mainly by Hamilton Depression Rating Scale  
37  
38 119 (HAMD), Montgomery-Asberg Depression Rating Scale(MADRS), Beck  
39  
40 120 Depression Inventory (BDI) and Zung Self-Rating Depression Scale(SDS).

41  
42 121 **Secondary outcomes:**

- 43  
44 122 i. **QoL:** evaluated mainly by the Medical Outcomes Study Short Form 36 (SF-  
45  
46 123 36), the Stroke Specific Quality of Life Scale (SS-QOL) or the World Health  
47  
48 124 Organization Quality of Life (WHOQOL).  
49  
50 125 ii. **Safety:** evaluated mainly by the total numbers and severity of adverse events.

51  
52 126

53  
54 127 **Search methods for identification of studies**

55  
56 128 The following ten databases will be searched from establishment to November 2020:  
57  
58 129 PubMed, The Cochrane Library, Medline, Embase, Japan science and technology  
59  
60 130 agency (J-STAGE), CiNii(National Institute of Informatics),China National



1  
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4 131 Knowledge Infrastructure (CNKI), WanFang Data, VIP and Chinese Biomedical  
5  
6 132 Databases. The combination of free words and medical subject headings, including  
7  
8 133 “depression, depressive disorder, acupuncture therapy, acupuncture, needle, needling,  
9  
10 134 stroke, etc”, will be used as the retrieval mode. The search strategy for Cochrane  
11  
12 135 Library is shown in Table 1.

### 136 **Study selection and data extraction**

137 EndNote X8.2 will be used to manage studies. First, duplicate literature will be  
138 excluded by electronic & manual based steps in EndNote. Second, two reviewers will  
139 independently screen the titles and abstracts and select the studies which meet the  
140 eligibility criteria. If there are disagreements, the third reviewer will be consulted. The  
141 evaluators will read the full text of the included literature, and then preliminarily  
142 extracted relevant data, mainly including the following information: (1)Inclusion and  
143 exclusion criteria; (2) The number of included samples (total number of cases, number  
144 of cases in the treatment group, number of cases in the control group); (3)Grouping  
145 method and process; (4) Basic data of the included research samples (mainly including  
146 gender, age and disease); (5)The intervention of the treatment group and the control  
147 group :① the treatment method, drug dose, treatment frequency, course of treatment,  
148 etc. ② a detailed description of manual acupuncture treatment including acupoints  
149 selection, twist technique, retention time, frequency, etc.(6) Evaluation of the final  
150 research results (including the treatment efficiency of different treatment measures, the  
151 scale score at the beginning and end point, etc).

### 152 **Quality assessment**

153 The quality of evidence for main outcomes will be assessed by The Grades of  
154 Recommendation, Assessment, Development, and Evaluation (GRADE) approach.  
155 Two reviewers will do this independently through GRADEpro  
156 Guideline Development Tool (GDT). GRADE approach provides guidance for rating  
157 quality of evidence and grading strength of recommendations for health care. It has  
158 important implications for those summarizing evidence for systematic reviews<sup>[24]</sup>.It  
159 assessed a body of evidence by referring to the concepts of the GRADE system , and

1  
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4 160 determined and recorded the quality of a body of evidence for each clinical question,  
5 161 there are four quality levels: high, moderate, low and very low<sup>[25]</sup>.

#### 162 **Assessment of heterogeneity, Sensitivity analysis and subgroup analysis**

163 We'll use the  $I^2$  statistic to assess the heterogeneity. If the  $I^2$  value is below 50%, the  
164 fixed effect model will be used. Otherwise, sensitivity analysis and subgroup analysis  
165 will be conducted to explore the main sources of heterogeneity, after which, the random  
166 effect model will be used if the  $I^2$  is still equal or greater than 50%. Both types of effect  
167 sizes will be presented with 95% CIs, and values of  $p < 0.05$  will be regarded as  
168 statistically significant. Continuous outcomes will be calculated as mean differences  
169 (MDs) or standardized mean differences (SMDs), meanwhile, binary outcomes will be  
170 calculated as odds ratios (ORs).

#### 171 **Assessment of the risk of bias in individual studies**

172 According to Cochrane Handbook for Systematic Reviews of Interventions version 6  
173 (<https://training.cochrane.org/handbook/current/chapter-08>), the risk of bias 2.0 (ROB  
174 2.0) tool will be used to mean the methodological quality and the risk of bias of the  
175 included studies. One researcher assessed the risk of bias of included studies by using  
176 ROB 2.0 and another researcher confirmed the judgment. If there are any differences,  
177 the third researcher will be asked to solve the problem.

#### 178 **Publication bias**

179 STATA V.14.0 will be used to evaluate publication bias. Begg's test and Egger's test  
180 will be used to assess the publication bias of the included trials and form the publication  
181 bias plot.

#### 182 **Discussion**

183 This meta-analysis will focus on the different techniques, durations or other detailed  
184 operations of manual acupuncture applied in PSD patients to explore their influence on  
185 depression severity and QoL. PSD are generally more disabled<sup>[26]</sup>. As an important part  
186 of traditional Chinese medicine, acupuncture plays an important role in clinical  
187 treatment <sup>[27]</sup>. In terms of clinical efficacy, acupuncture can assist in eliminating  
188 negative emotions by significantly improving the functional communication and

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4 189 language function [28], cognitive [29] and limb movement function [30] of stroke patients.  
5  
6 190 At the mechanism level, acupuncture can modulate glutamate receptor and excitatory  
7  
8 191 Amino Acid Transporter(EAAT) expression [31], down-regulated the levels of unclear  
9  
10 192 factor kappa light chain enhancer of activated B cells(NF-κB) protein, Inducible Nitric-  
11  
12 193 Oxide Synthase(iNOS) and Nitric Oxide(NO) [32], so as to achieve the purpose of  
13  
14 194 relieving PSD.

### 15 195 **Ethics and dissemination**

16  
17  
18 196 Non -applicable.

### 19 20 21 197 **Authors' contributions:**

22 198 Wei Liu and Chang Rao conceived, designed and wrote this protocol. Wei Liu  
23  
24 199 provided a clinical perspective, especially to the manual acupuncture. Yuzheng Du is  
25  
26 200 the guarantor of this review, and approved the final manuscript of it. Xi Nan, Zefang Li  
27  
28 201 and Chunsheng Yin provided a preliminary data retrieval.

29  
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31  
32 203 Development Project (grant number: 2019YFC0840709).

### 33 204 **Competing interests statement**

34  
35  
36 205 None declared.

### 37 206 **Patient and Public Involvement**

38  
39  
40 207 It was not appropriate or possible to involve patients or the public in the design, or  
41  
42 208 conduct, or reporting, or dissemination plans of our research

### 43 209 **Abbreviation**

44  
45  
46 210 PSD: post-stroke depression

47  
48 211 QOL: quality of life

49  
50 212 CANMAT: Canadian network for mood and anxiety treatments

51  
52 213 APA: the American psychiatric association

53  
54 214 WFSBP: the World federation of societies of biological psychiatry

55  
56 215 SSRIs: selective serotonin uptake inhibitors

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4 216 PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis  
5  
6 217 Protocols  
7  
8 218 RCTs: Randomized controlled trials  
9  
10 219 CT: computer tomography  
11  
12 220 MRI: magnetic resonance imaging  
13  
14 221 ICD-10: International Classification of Diseases Tenth Edition  
15  
16 222 DSM: the Diagnosis and Statistical Manual of Mental Disorders  
17  
18 223 CCMD: Chinese Classification of Mental Disorders  
19  
20 224 HAMD: Hamilton Rating Scale for Depression  
21  
22 225 EG: experiment group  
23  
24 226 CG: control group  
25  
26 227 HAMD:Hamilton Depression Rating Scale  
27  
28 228 MADRS: Montgomery-Asberg Depression Rating Scale  
29  
30 229 BDI: Beck Depression Inventory  
31  
32 230 SDS: Zung Self-Rating Depression Scale  
33  
34 231 SF-36: the Medical Outcomes Study Short Form 36  
35  
36 232 SS-QOL: Stroke Specific Quality of Life Scale  
37  
38 233 WHOQOL: the World Health Organization Quality of Life  
39  
40 234 J-STAGE: Japan science and technology agency  
41  
42 235 CiNii: National Institute of Informatics  
43  
44 236 CNKI: China National Knowledge Infrastructure  
45  
46 237 GRADE: Grades of Recommendation, Assessment, Development, and Evaluation  
47  
48 238 GDT: Guideline Development Tool  
49  
50 239 MDs: mean differences  
51  
52 240 SMDs: mean differences  
53  
54 241 ORs: odds ratios  
55  
56 242 ROB 2.0: the risk of bias 2.0  
57  
58 243 EAAT: excitatory Amino Acid Transporter  
59  
60 244 NF- $\kappa$ B: unclear factor kappa light chain enhancer of activated B cells

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4 245 iNOS: Inducible Nitric-Oxide Synthase

5  
6 246 NO: Nitric Oxide

7  
8 247 **Word Count:** 1,662 words excludes the title page, abstract, tables,

9  
10 248 acknowledgements, contributions and references.  
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ID	Search
#1	MeSH descriptor: [Stroke] explode all trees
#2	poststroke or post-stroke. ti,ab,kw
#3	MeSH descriptor: [Cerebral Infarction] explode all trees
#4	MeSH descriptor: [Cerebral Hemorrhage] explode all trees
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Depression] explode all trees
#7	depress* or affective disorder or affective symptoms. ti,ab,kw
#8	#6 or #7
#9	MeSH descriptor: [Acupuncture] explode all trees
#10	acupunctur* or acupoint* or needl*. ti,ab,kw
#11	#9 or #10
#12	#5 and #8 and #11

Table 1 Search strategy for Cochrane Library



**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 #
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P8
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	P8
Sponsor	5b	Provide name for the review funder and/or sponsor	P8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	P8
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	P2-P4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P4-P5
<b>METHODS</b>			
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	P4-P6
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	P5-P6
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	P5-P6 and Table 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P6
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)	P5-P6
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	P6
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	P7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P5 and P7
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	P7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P7
	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 $\tau$ )	P7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P6

**\* 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.*

# BMJ Open

## The effectiveness and safety of manual acupuncture therapy in patients with post-stroke depression: protocol for a systematic review and meta-analysis

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<b>Primary Subject Heading</b>:	Complementary medicine
Secondary Subject Heading:	Mental health
Keywords:	Neurology < INTERNAL MEDICINE, Depression & mood disorders < PSYCHIATRY, Stroke medicine < INTERNAL MEDICINE, COMPLEMENTARY MEDICINE

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4 **1 The effectiveness and safety of manual acupuncture therapy in**  
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6 **2 patients with post-stroke depression: protocol for a systematic review**  
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9 **3 and meta-analysis**  
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11 4 Wei Liu<sup>1,2,3,†</sup>, Chang Rao<sup>1,2,3,†</sup>, Qi Zhao<sup>1,2,†</sup>, Yuzheng Du<sup>1,2,\*</sup>, Xi Nan<sup>1,2,3</sup>, Zefang Li<sup>1,2,3</sup>,  
12  
13 5 Chunsheng Yin<sup>1,2,3</sup>  
14

15 6 1. First Teaching Hospital of Tianjin University of Traditional Chinese Medicine,  
16  
17 7 Tianjin, China;  
18

19 8 2. National Clinical Research Center for Chinese Medicine Acupuncture and  
20  
21 9 Moxibustion, Tianjin, China;  
22

23 10 3. Tianjin University of Traditional Chinese Medicine Tianjin, China.  
24

25 11 † These authors contribute equally.  
26

27 12 \* Corresponding author: Yuzheng Du.  
28

29 13 Corresponding author physical mailing address: Xiqing District Changling Road No.88,  
30  
31 14 Tianjin, China  
32

33 15 Corresponding author E-mail address: drduyuzheng@163.com  
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## 16 **Abstract**

17 **Introduction:** Acupuncture is widely used on the rehabilitation of stroke survivors,  
18 including hemiplegia, constipation, emotional disorders and so on. Although the  
19 effectiveness of manual acupuncture therapy on post-stroke depression (PSD) has been  
20 confirmed by multiple randomized controlled trials, there were few meta-analysis  
21 focused on the connection between different techniques, durations or other detailed  
22 operations of manual acupuncture and their effectiveness of improving the depression  
23 severity and quality of life for PSD patients.

24 **Methods and analysis:** A systematic search will be performed on English databases  
25 (PubMed, The Cochrane Library, Medline, Embase), Chinese databases (CNKI,  
26 WanFang Data, VIP and Chinese biomedical databases) and Japanese databases(J-  
27 STAGE, CiNii). The retrieval time limit will be from the establishment of the database  
28 to November 2020. Two researchers will independently screen the literatures, extract  
29 data, and evaluate the quality of the included studies. Meta-analysis will be conducted  
30 by using STATA V. 14.0 and Review Manager V.5.3.

31 **Ethics and dissemination:** The results of this meta-analysis will be disseminated  
32 through publication in peer-reviewed journals or conference presentations. The data  
33 used in this meta-analysis will not contain individual patient data, therefore, ethical  
34 approval is not required.

35 **PROSPERO registration number:** CRD42020222825.

36 **Keywords:** acupuncture; meta-analysis; post-stroke depression

## 37 **Strengths and limitations of this study**

38 1. To our knowledge, this study is the first meta-analysis especially focused on the  
39 effectiveness of manual acupuncture therapy for PSD patients.

40 2. Compared with previous studies, we will extract more detailed information on  
41 the treatment schedule of acupuncture (acupoints selection, twist technique, retention  
42 time, frequency, etc) in order to provides more analytical basis for subgroup analysis  
43 and sensitivity analysis.

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4 44 3. The electronic search will only include randomized controlled trials published  
5 45 in English, Chinese and Japanese that could limit the inclusion of studies.  
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## 8 46 **Introduction**

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10 47 Stroke is currently the second leading cause of death worldwide, the burden of  
11 48 which has increased substantially over the past few decades due to expanding  
12 49 population numbers and aging as well as the increased prevalence of modifiable stroke  
13 50 risk factors<sup>[1,2]</sup>. Depression is a common and recurrent psychiatric disorder that starts  
14 51 shortly after stroke and affects patients in the long term. A meta-analysis of the  
15 52 frequency of depression after stroke shows that approximately one-third of stroke  
16 53 survivors experience depression at any time-point in the first year<sup>[3]</sup>. Depression after  
17 54 stroke is independently associated with poor health outcomes, including increasing  
18 55 mortality, disability, anxiety and lowering quality of life (QoL)<sup>[4]</sup>. In addition, there is a  
19 56 two-way relationship between depression and stroke: stroke could increase the risk of  
20 57 PSD, meanwhile, depression is an independent risk factor for stroke and stroke  
21 58 mortality<sup>[5,6]</sup>.  
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33 59 This bidirectional relationship makes it more difficult to develop the treatment of  
34 60 PSD, currently, few guidelines mentioned the assessment, treatment or prevention for  
35 61 it<sup>[7]</sup>. For depressive disorder, Canadian network for mood and anxiety  
36 62 treatments (CANMAT), the American psychiatric association (APA) and the World  
37 63 federation of societies of biological psychiatry (WFSBP) guidelines supported that  
38 64 selective serotonin uptake inhibitors (SSRIs) could be used as first-line treatment<sup>[8,9,10]</sup>.  
39 65 But the pharmacotherapy of PSD needs to be more cautious, as some studies<sup>[11,12,13]</sup>  
40 66 showed that the use of SSRI may relate to the potential risk of hemorrhagic stroke.  
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49 67 Acupuncture, a historic complementary therapy from China, has potential  
50 68 beneficial effects on improving dependency, global neurological deficiency, and some  
51 69 specific neurological impairments for people with stroke in the convalescent stage<sup>[14]</sup>.  
52 70 In the treatment of depression, a recent meta-analysis<sup>[15]</sup> suggests that acupuncture  
53 71 combined with antidepressant medication is effective for the treatment of depression  
54 72 and has an early onset of action, safe and well-tolerated over the first 6-week treatment  
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73 period. However, few systematic reviews or meta-analysis focused on the effectiveness  
74 of acupuncture in treating PSD, although the number of papers related to this area has  
75 an upward trend recently [16,17].

76 Besides, there are no meta-analysis focusing on the effectiveness of manual  
77 acupuncture on improving the depression severity and QoL of post stroke patients, so  
78 far. What's more, there is a general problem of high heterogeneity in existing meta-  
79 analysis. One recent meta-analysis [18] showed that the curative effect of acupuncture  
80 for post stroke cognitive impairment may be related to manipulation and retention time,  
81 however, most of the existing meta-analysis on PSD didn't conduct subgroup analysis  
82 for such content due to the lack of attention to the details of acupuncture treatment.  
83 Therefore, we considered that the higher heterogeneity may be relevant with the  
84 difference in the type of acupuncture (manual acupuncture, electroacupuncture, dry  
85 needle, etc) and the treatment schedule (acupoints selection, twist technique, retention  
86 time, frequency, etc). Hence, we would like to extract the detailed description of manual  
87 acupuncture treatment in the included articles and conduct subgroup analysis according  
88 to them.

### 89 **Objectives**

90 The primary purpose of this meta-analysis is to examine the efficacy of manual  
91 acupuncture in improving depression severity in individuals with post-stroke  
92 depression. Secondary aims are to evaluate its role in enhancing QoL and assess the  
93 safety of this treatment.

### 94 **Methods and analysis**

95 This systematic review protocol has registered in Prospero (registration number:  
96 CRD42020222825). It will follow the new edition of the Cochrane handbook for  
97 systematic reviews of interventions[19] and be reported according to the Preferred  
98 Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [20].

### 99 **Criteria for considering studies for this review**

#### 100 **Types of studies**

101 Randomized controlled trials (RCTs) in English, Chinese and Japanese will be



102 included. Animal studies or studies with incomplete data will be excluded.

### 103 **Participants**

104 We will include patients who suffered post stroke depression. The diagnosis of  
105 stroke should base on computer tomography (CT), magnetic resonance imaging (MRI),  
106 or clinical criteria. Meanwhile, depression should be diagnosed according to the  
107 International Classification of Diseases Tenth Edition (ICD-10), the Diagnosis and  
108 Statistical Manual of Mental Disorders (DSM), Chinese Classification of Mental  
109 Disorders (CCMD) or Hamilton Rating Scale for Depression (HAMD)<sup>[21,22,23]</sup>.

### 110 **Types of interventions:**

111 The relevant RCTs will be included if the following criteria were met: (1) using  
112 manual acupuncture alone, or in combination with another rehabilitation therapy, or in  
113 combination with pharmacotherapy in experiment group (EG) (2) using rehabilitation  
114 therapy other than manual acupuncture, pharmacotherapy, sham acupuncture or no  
115 treatment in control group (CG). In addition, other kinds of acupuncture therapies, such  
116 as electroacupuncture, dry needle, laser needle or acupoint-injection, couldn't be used  
117 as interventions in EG or CG.

### 118 **Types of outcomes measures:**

#### 119 **Primary outcomes:**

120 **Depression severity:** evaluated mainly by Hamilton Depression Rating Scale (HAMD),  
121 Montgomery-Asberg Depression Rating Scale(MADRS), Beck Depression Inventory  
122 (BDI) , Zung Self-Rating Depression Scale(SDS), etc.

123 If the included studies used two or more of above scales, we will give preference  
124 to clinician-rated scales. Following hierarchy will be applied: (1) HAMD; (2) MADRS;  
125 (3) BDI; (4) SDS and (5) all other depression scales.

#### 126 **Secondary outcomes:**

- 127 i. **QoL:** evaluated mainly by the Medical Outcomes Study Short Form 36 (SF-  
128 36), the Stroke Specific Quality of Life Scale (SS-QOL) or the World Health  
129 Organization Quality of Life (WHOQOL).
- 130 ii. **Safety:** evaluated mainly by the total numbers and severity of adverse events.

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132 **Search methods for identification of studies**

133 The following ten databases will be searched from establishment to November 2020:

134 PubMed, The Cochrane Library, Medline, Embase, Japan science and technology

135 agency (J-STAGE), CiNii(National Institute of Informatics),China National

136 Knowledge Infrastructure (CNKI), WanFang Data, VIP and Chinese Biomedical

137 Databases. The combination of free words and medical subject headings, including

138 “depression, depressive disorder, acupuncture therapy, acupuncture, needle, needling,

139 stroke, etc”, will be used as the retrieval mode. The search strategy for Cochrane

140 Library is shown in Table 1.

ID	Search
#1	MeSH descriptor: [Stroke] explode all trees
#2	poststroke or post-stroke. ti,ab,kw
#3	MeSH descriptor: [Cerebral Infarction] explode all trees
#4	MeSH descriptor: [Cerebral Hemorrhage] explode all trees
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Depression] explode all trees
#7	depress* or affective disorder or affective symptoms. ti,ab,kw
#8	#6 or #7
#9	MeSH descriptor: [Acupuncture] explode all trees
#10	acupunctur* or acupoint* or needl*. ti,ab,kw
#11	#9 or #10
#12	#5 and #8 and #11

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142 Table 1 Search strategy for Cochrane Library

143 **Study selection and data extraction**

144 EndNote X8.2 will be used to manage studies. First, duplicate literature will be

145 excluded by electronic &amp; manual based steps in EndNote. Second, two reviewers will

146 independently screen the titles and abstracts and select the studies which meet the

147 eligibility criteria. If there are disagreements, the third reviewer will be consulted. The

148 evaluators will read the full text of the included literature, and then preliminarily

149 extracted relevant data, mainly including the following information: (1)Inclusion and

150 exclusion criteria; (2) The number of included samples (total number of cases, number

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4 151 of cases in the treatment group, number of cases in the control group); (3) Grouping  
5 152 method and process; (4) Basic data of the included research samples (mainly including  
6 153 gender, age and disease); (5) The intervention of the treatment group and the control  
7 154 group : ① the treatment method, drug dose, treatment frequency, course of treatment,  
8 155 etc. ② a detailed description of manual acupuncture treatment including acupoints  
9 156 selection, twist technique, retention time, frequency, etc. (6) Evaluation of the final  
10 157 research results (including the treatment efficiency of different treatment measures, the  
11 158 scale score at the beginning and end point, etc).

### 159 **Quality assessment**

160 The quality of evidence for main outcomes will be assessed by The Grades of  
161 Recommendation, Assessment, Development, and Evaluation (GRADE) approach.  
162 Two reviewers will do this independently through GRADEpro  
163 Guideline Development Tool (GDT). GRADE approach provides guidance for rating  
164 quality of evidence and grading strength of recommendations for health care. It has  
165 important implications for those summarizing evidence for systematic reviews<sup>[24]</sup>. It  
166 assessed a body of evidence by referring to the concepts of the GRADE system, and  
167 determined and recorded the quality of a body of evidence for each clinical question,  
168 there are four quality levels: high, moderate, low and very low<sup>[25]</sup>.

### 169 **Assessment of heterogeneity, Sensitivity analysis and subgroup analysis**

170 We'll use the  $I^2$  statistic to assess the heterogeneity. If the  $I^2$  value is below 50%,  
171 the fixed effect model will be used. Otherwise, sensitivity analysis will be conducted to  
172 explore the main sources of heterogeneity, after which, the random effect model will  
173 be used if the  $I^2$  is still equal or greater than 50%. Both types of effect sizes will be  
174 presented with 95% CIs, and values of  $p < 0.05$  will be regarded as statistically  
175 significant.

176 Meanwhile, subgroup analysis will also be conducted to explore the main sources  
177 of heterogeneity. Compared with previous studies, we will extract more detailed  
178 information on the treatment schedule of acupuncture which could provide us more  
179 analytical basis for subgroup analysis. If the necessary information is available,

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4 180 subgroup analyses will be carried out according to certain factors (acupoints selection,  
5 181 twist technique, retention time, frequency, period of treatment and different types of  
6 182 control group). After grouping, two or more groups of studies will be analyzed and  
7 183 compared in order to explore the causes of high heterogeneity.

#### 11 184 **Data synthesis**

13 185 Continuous outcomes will be calculated as mean differences (MDs) or  
14 186 standardized mean differences (SMDs). If different scales are used to measure  
15 187 continuous outcomes, like depression severity and QOL, SMD will be used as a  
16 188 measure of effect size in efficacy outcome. It's calculated as the difference in mean  
17 189 outcome between groups divided by the standard deviation of outcome among  
18 190 participants. If the same scale is used in the included literature, mean difference (MD)  
19 191 will be used. In addition, safety outcome will be the number of participants who  
20 192 dropped out due to adverse effects and the number of participants who reported at least  
21 193 one adverse event or effect. For these dichotomous outcomes, the odds ratio (OR) will  
22 194 be calculated as the effect estimate.

#### 23 195 **Assessment of the risk of bias in individual studies**

25 196 According to Cochrane Handbook for Systematic Reviews of Interventions  
26 197 version 6 (<https://training.cochrane.org/handbook/current/chapter-08>), the risk of bias  
27 198 2.0 (ROB 2.0) tool will be used to mean the methodological quality and the risk of bias  
28 199 of the included studies. One researcher assessed the risk of bias of included studies by  
29 200 using ROB 2.0 and another researcher confirmed the judgment. If there are any  
30 201 differences, the third researcher will be asked to solve the problem.

#### 31 202 **Publication bias**

32 203 STATA V.14.0 will be used to evaluate publication bias. Begg's test and Egger's  
33 204 test will be used to assess the publication bias of the included trials and form the  
34 205 publication bias plot.

#### 35 206 **Patient and Public Involvement**

36 207 It was not appropriate or possible to involve patients or the public in the design,  
37 208 or conduct, or reporting, or dissemination plans of our research.

## 209 **Discussion**

210 This meta-analysis will focus on the different techniques, durations or other  
211 detailed operations of manual acupuncture applied in PSD patients to explore their  
212 influence on depression severity and QoL. PSD are generally more disabled<sup>[26]</sup>. As an  
213 important part of traditional Chinese medicine, acupuncture plays an important role in  
214 clinical treatment<sup>[27]</sup>. In terms of clinical efficacy, acupuncture can assist in eliminating  
215 negative emotions by significantly improving the functional communication and  
216 language function<sup>[28]</sup>, cognitive<sup>[29]</sup> and limb movement function<sup>[30]</sup> of stroke patients.  
217 At the mechanism level, acupuncture can modulate glutamate receptor and excitatory  
218 Amino Acid Transporter(EAAT) expression<sup>[31]</sup>, down-regulated the levels of unclear  
219 factor kappa light chain enhancer of activated B cells(NF-κB) protein, Inducible Nitric-  
220 Oxide Synthase(iNOS) and Nitric Oxide(NO)<sup>[32]</sup>, so as to achieve the purpose of  
221 relieving PSD.

## 222 **Ethics and dissemination**

223 The results of this meta-analysis will be disseminated through publication in peer-  
224 reviewed journals or conference presentations. The data used in this meta-analysis will  
225 not contain individual patient data, therefore, ethical approval is not required.

## 226 **Authors' contributions**

227 Wei Liu and Chang Rao conceived, designed and wrote this protocol. Wei Liu  
228 provided a clinical perspective, especially to the manual acupuncture. Qi zhao provided  
229 the writing and modification of part of the article. Yuzheng Du is the guarantor of this  
230 review, and approved the final manuscript of it. Xi Nan, Zefang Li and Chunsheng Yin  
231 provided a preliminary data retrieval.

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233 This work was supported by National Key Research and Development Project  
234 (grant number: 2019YFC0840709).

## 235 **Competing interests statement**

236 None declared.

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4     237    **Abbreviation**

5  
6     238    PSD: post-stroke depression

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8     239    QOL: quality of life

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10    240    CANMAT: Canadian network for mood and anxiety treatments

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12    241    APA: the American psychiatric association

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14    242    WFSBP: the World federation of societies of biological psychiatry

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16    243    SSRIs: selective serotonin uptake inhibitors

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18    244    PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis

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20    245    Protocols

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22    246    RCTs: Randomized controlled trials

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24    247    CT: computer tomography

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26    248    MRI: magnetic resonance imaging

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28    249    ICD-10: International Classification of Diseases Tenth Edition

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30    250    DSM: the Diagnosis and Statistical Manual of Mental Disorders

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32    251    CCMD: Chinese Classification of Mental Disorders

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34    252    HAMD: Hamilton Rating Scale for Depression

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36    253    EG: experiment group

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38    254    CG: control group

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40    255    HAMD: Hamilton Depression Rating Scale

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42    256    MADRS: Montgomery-Asberg Depression Rating Scale

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44    257    BDI: Beck Depression Inventory

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46    258    SDS: Zung Self-Rating Depression Scale

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48    259    SF-36: the Medical Outcomes Study Short Form 36

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50    260    SS-QOL: Stroke Specific Quality of Life Scale

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52    261    WHOQOL: the World Health Organization Quality of Life

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54    262    J-STAGE: Japan science and technology agency

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56    263    CiNii: National Institute of Informatics

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58    264    CNKI: China National Knowledge Infrastructure

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60    265    GRADE: Grades of Recommendation, Assessment, Development, and Evaluation

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4 266 GDT: Guideline Development Tool  
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6 267 MDs: mean differences  
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8 268 SMDs: mean differences  
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10 269 ORs: odds ratios  
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12 270 ROB 2.0: the risk of bias 2.0  
13  
14 271 EAAT: excitatory Amino Acid Transporter  
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16 272 NF- $\kappa$ B: nuclear factor kappa light chain enhancer of activated B cells  
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18 273 iNOS: Inducible Nitric-Oxide Synthase  
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20 274 NO: Nitric Oxide  
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22 275 **Word Count:** 1,967 words excludes the title page, abstract, tables,  
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24 276 acknowledgements, contributions and references.

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**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 #
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P9
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	P9
Sponsor	5b	Provide name for the review funder and/or sponsor	P9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	P9
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	P3-P4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P4
<b>METHODS</b>			
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	P4-P6
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	P6
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	P6

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P6
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)	P6-P7
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	P6-P7
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	P6-P7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P5 and P7
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	P8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P7-P8
	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 $\tau$ )	P7-P8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P7-P8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P7

**\* 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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