

# INPLASY PROTOCOL

To cite: Luo et al. Effect of acupuncture on cognitive function in patients with post-stroke cognitive impairment: a Systematic review and meta-analysis. Inplasy protocol 2022110115. doi: 10.37766/inplasy2022.11.0115

Received: 23 November 2022

Published: 23 November 2022

**Corresponding author:**  
Caiqin Wu

yuwuchina@aliyun.com

**Author Affiliation:**  
Shanghai University of  
Traditional Chinese Medicine.

**Support:** SHUTCM-Natural  
Science Project.

**Review Stage at time of this  
submission:** Completed but  
not published.

**Conflicts of interest:**  
None declared.

## Effect of acupuncture on cognitive function in patients with post-stroke cognitive impairment: a Systematic review and meta-analysis

Luo, ZY<sup>1</sup>; Li, WX<sup>2</sup>; Jiang, JT<sup>3</sup>; Sun, J<sup>4</sup>; Zhang, MY<sup>5</sup>; Li, KP<sup>6</sup>; Wu, CQ<sup>7</sup>.

**Review question / Objective:** To systematically review the effect of acupuncture on post-stroke cognitive impairment (PSCI)

**Condition being studied:** In this paper, we reported the effect of acupuncture on cognitive function was significant compared with different medications, and the curative effect was efficient at 4 and 8 weeks. But the differences were not significant statistically on motor function in patients with PSCI. The results inform the duration for which the acupuncture should be administered by healthcare provider to help prevent progression of PSCI. Acupuncture and other therapies may have similar efficacy in improving PSCI patients' activities of daily living, which may also be due to the high risk of bias due to fewer included studies.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 November 2022 and was last updated on 23 November 2022 (registration number INPLASY2022110115).

### INTRODUCTION

**Review question / Objective:** To systematically review the effect of acupuncture on post-stroke cognitive impairment (PSCI)

**Rationale:** Post-stroke cognitive impairment (PSCI) refers cognitive dysfunction that presented within 6 months after stroke. PSCI occurs in more than 70% survivors and may affect the quality of life and survival time of survivors. European Stroke Organization (ESO) and the

European Academy of Neurology (EAN) developed the guidance, which recommended that PSCI could be evaluated by Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) and so on. PSCI has the characteristics of preventable and treatable<sup>5, 6</sup>. However, the best clinical prevention and treatment for PSCI are still up for debate. Although there is a dearth of high-quality clinical evidence, European guidelines suggested that cognitive rehabilitation training, particularly compensatory training strategies, may be beneficial for PSCI.

In recent decades, it has received increasing attention from the public and health professionals worldwide, and has even attracted the interest of major academic medical centers, especially for chronic diseases that are difficult to control with traditional therapies. At the same time, modern medical research has also proved that acupuncture treatment can reduce the hemorheology of patients, improve microcirculation, and increase the blood flow of local tissue.

Up to the present, it is reported that there was a number of RCTs concerning acupuncture on PSCI. But there were lack of high quality RCTs, which can not provide strong evidence.

Therefore, this study conducted a systematic review and meta-analysis of randomized controlled trials, which explored the curative effect of acupuncture at different points on cognitive impairment and evaluated the scientific research design quality of such clinical studies, providing evidence for the clinical application of the efficient of acupuncture on patients with cognitive impairment. Particularly worth mentioning is that this study put forward an innovative idea by using the subgroup analysis to explore when healthcare provider should give interventions in order to prevent the progression of PSCI.

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The results inform the duration for which the acupuncture should be administered by healthcare provider to help prevent progression of PSCI. Acupuncture and other therapies may have similar efficacy in improving PSCI patients' activities of daily living, which may also be due to the high risk of bias due to fewer included studies.

## METHODS

**Search strategy:** Cochrane Library

#1 MeSH descriptor: [Stroke] explode all trees

#2 (Apoplexy):ti,ab,kw OR (Cerebral stroke):ti,ab,kw OR (Cerebrovascular disease):ti,ab,kw OR (Cerebrovascular accident):ti,ab,kw OR (Cerebrovascular disorders):ti,ab,kw (Word variations have been searched)

#3 (Cerebral hemorrhage):ti,ab,kw OR (Hemorrhagic apoplexy):ti,ab,kw OR (hemorrhagic stroke):ti,ab,kw OR (Cerebral infarction):ti,ab,kw OR (Brain infarction):ti,ab,kw (Word variations have been searched)

#4 (Ischemic stroke):ti,ab,kw OR (Cerebrovascular Stroke):ti,ab,kw OR (CVA):ti,ab,kw OR (Brain Vascular Accident):ti,ab,kw OR (Acute Stroke):ti,ab,kw (Word variations have been searched)

#5 MeSH descriptor: [Cognition] explode all trees

#6 (Cognitive Dysfunction):ti,ab,kw OR (Cognitive Impairments):ti,ab,kw OR (Mild Cognitive Impairment):ti,ab,kw OR (Mild Neurocognitive Disorder):ti,ab,kw OR (Cognitive Decline):ti,ab,kw (Word variations have been searched)

#7 (Mental Deterioration):ti,ab,kw OR (Cognitive deficit):ti,ab,kw OR (PSCI):ti,ab,kw (Word variations have been searched)

#8 #5 or #6 or #7

#9 MeSH descriptor: [Acupuncture] explode all trees

#10 (acupuncture point):ti,ab,kw OR (acupuncture therapy):ti,ab,kw OR (acupuncture analgesia):ti,ab,kw (Word variations have been searched)

#11 #9 or #10

#12 (Acute Cerebrovascular Accident):ti,ab,kw OR (Cerebrovascular Apoplexy):ti,ab,kw (Word variations have been searched)

#13 #1 or #2 or #3 or #4 or #12  
 #14 #8 AND #11 AND #13  
 PubMed (using MeSH term)  
 ("cognition"[MeSH Terms] OR "cognitive dysfunction"[MeSH Terms] OR "cognition disorders"[MeSH Terms]) AND "stroke"[MeSH Terms] AND ("acupuncture"[MeSH Terms] OR "acupuncture therapy"[MeSH Terms])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])  
 EMBASE (using Emtree term in the PICO search function)n ('cerebrovascular accident'/exp OR 'stroke':ti,ab OR 'cva':ti,ab OR 'cerebrovascular apoplexy':ti,ab OR 'brain vascular accident':ti,ab OR 'cerebrovascular stroke':ti,ab OR 'cerebrovascular strokes':ti,ab OR 'cvas':ti,ab OR 'strokes':ti,ab OR 'cerebrovascular accidents':ti,ab OR 'apoplexy, cerebrovascular':ti,ab OR 'vascular accident, brain':ti,ab OR 'brain vascular accident':ti,ab OR 'brain vascular accidents':ti,ab OR 'stroke, cerebrovascular':ti,ab OR 'strokes, cerebrovascular':ti,ab OR 'apoplexy':ti,ab OR 'cerebral stroke':ti,ab OR 'cerebral strokes':ti,ab OR 'stroke, cerebral':ti,ab OR 'strokes, cerebral':ti,ab OR 'stroke, acute':ti,ab OR 'strokes, acute':ti,ab OR 'acute strokes':ti,ab OR 'acute stroke':ti,ab OR 'cerebrovascular accident, acute':ti,ab OR 'cerebrovascular accidents, acute':ti,ab OR 'acute cerebrovascular accidents':ti,ab OR 'acute cerebrovascular accident':ti,ab) AND ('cognition'/exp OR 'cognitive dysfunction':ab,ti OR 'cognitive dysfunctions':ab,ti OR 'dysfunction, cognitive':ab,ti OR 'dysfunctions, cognitive':ab,ti OR 'cognitive impairments':ab,ti OR 'cognitive impairment':ab,ti OR 'impairment, cognitive':ab,ti OR 'impairments, cognitive':ab,ti OR 'mild cognitive impairment':ab,ti OR 'mild cognitive impairments':ab,ti OR 'cognitive impairment, mild':ab,ti OR 'cognitive impairments, mild':ab,ti OR 'impairment, mild cognitive':ab,ti OR 'impairments, mild cognitive':ab,ti OR 'mild neurocognitive disorder':ab,ti OR 'mild neurocognitive disorders':ab,ti OR 'disorders, mild neurocognitive':ab,ti OR 'disorder, mild neurocognitive':ab,ti OR 'neurocognitive disorders, mild':ab,ti OR 'neurocognitive disorder, mild':ab,ti OR 'cognitive decline':ab,ti OR 'cognitive declines':ab,ti OR 'declines, cognitive':ab,ti OR 'decline,

cognitive':ab,ti OR 'deterioration, mental':ab,ti OR 'deteriorations, mental':ab,ti OR 'mental deteriorations':ab,ti OR 'mental deterioration':ab,ti) AND ('random':ti,ab OR 'placebo':ti,ab OR 'double-blind':ti,ab) AND ('acupuncture'/exp OR 'acupuncture point':ti,ab OR 'acupuncture therapy':ti,ab OR 'acupuncture points':ti,ab OR 'acupuncture analgesia':ti,ab)  
 Scopus  
 ( TITLE-ABS-KEY ( stroke OR cva ) AND TITLE-ABS-KEY ( cognition OR cognitivedysfunction ) AND TITLE-ABS-KEY ( acupuncture ) AND TITLE-ABS-KEY ( randomizedcontrolledtrial OR randomized OR placebo )).

**Participant or population:** Participants who had post stroke cognitive impairment (PSCI).

**Intervention:** The test group took acupuncture as the main therapy (including simple acupuncture, electroacupuncture, etc.), or combined with other treatment methods, the implementation of manipulation, the length of needle retention, and the frequency of treatment was not limited; the control group was treated with other treatment methods that did not include acupuncture. The other treatment methods except acupuncture therapy should be the same in the two groups, and the course of treatment is not limited.

**Comparator:** Medication or basic treatment, including cognition training, medicine and so on.

**Study designs to be included:** Randomized controlled trial (RCT).

**Eligibility criteria:** Inclusion criteria (1) Research subjects: meet the clinical diagnostic criteria of PSCI, and there are no restrictions on age, gender, race, and disease course. (2) Type of literature: Published clinical randomized controlled trials of acupuncture treatment of PSCI, with a sample size of no less than 20 cases in each group, and the language is Chinese or English. (3) Intervention measures: a test group and a control group were set up. The test group took acupuncture as the main

therapy (including simple acupuncture, electroacupuncture, etc.), or combined with other treatment methods, the implementation of manipulation, the length of needle retention, and the frequency of treatment was not limited; the control group was treated with other treatment methods that did not include acupuncture. The other treatment methods except acupuncture therapy should be the same in the two groups, and the course of treatment is not limited. (4) Observation indicators: The main outcome indicators include the evaluation of overall cognitive function after treatment, including Mini-mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clinical Assessment of Cognition: Loewenstein Occupational Therapy Cognitive Assessment (LOTCA), for the geriatric population, etc. Exclusion criteria (1) Non-clinical research literature such as simple descriptive studies, case reports, reviews, pharmacological experiments, and animal research experiments. (2) Literatures that do not clearly state the clinical diagnostic criteria. (3) The literature on non-randomized controlled trials, or the use of semi-random allocation method, or the random method is incorrect, such as the order of visits, medical record number, odd and even of patients' birthday, clinician's will, patient's will, and the patient's use Interventions and other methods to assign groups. (4) Research literature with a repeated publication or data repetition (select the first published literature for inclusion). (5) Unable to obtain the full text or the literature with missing data. (6) Animal experiments. Data extraction Two reviewers conducted a comprehensive and independent review of these publications and cross-checked them. In cases of disagreement, a third party arbitrated. Data items extracted were title, name of the first author, baseline characteristics of the included study (sample size, patient age, treatment measures, etc.), publication year, risk-related factors of bias (randomization method, blinding, etc.), and outcome data (MMSE, MoCA and total effectiveness). If the above data were unclear, we contacted

the corresponding author of the original text.

**Information sources:** Various databases were searched including PubMed, EBSCO, Scopus, Embase, Web of Science, and Cochrane Library were searched by computer. The retrieval time was from the establishment of the database to the date of retrieval, and the references to the literature were obtained retrospectively.

**Main outcome(s):** A total of 608 RCTs were included initially. After screening by steps, 21 RCT studies were eligible finally. Among the eligible RCTs, nine of the RCTs are English versions, twelve of ones were Chinese version, meanwhile, the 21 eligible articles are all conducted in China, of them, acupuncture was adopted in trail group, medication was in the control group. Totally 21 articles were included, with 1941 participants involved.

The overall risk of bias was deemed unknown in 19 trials. There were 3 trials with incomplete outcome data and 1 trial with unknown incomplete data resulting in attrition bias. Randomization sequence was adequately generated and concealed allocation in 12 studies. There was no evidence of publication bias for the primary outcome.

The results indicated that compared with medication, acupuncture greatly improved the Montreal Cognitive Assessment (MD=1.57, 95%CI [0.88,2.25], I<sup>2</sup>=58%, p<0.00001) and the Mini-Mental State Examination (MD=2.16, 95%CI [1.11,3.22], I<sup>2</sup>=93%, p<0.0001). Compared with medication therapy, the score of Loewenstein Occupational Therapy Cognitive Assessment has reduced and improved National Institute of Health Stroke Scale after acupuncture therapy, which was also significant statistically for P300, but the differences were not significant statistically in Barthel Index and Fuel-Meyer. The result of the subgroup analysis showed that the effect of acupuncture on cognitive function was significant compared with different medications, and the curative effect was efficient between 4 and 8 weeks.

**Additional outcome(s):** A total of 3 RCT studies reported an effective rate of acupuncture therapy, with 140 cases. Using the fixed effect model of meta-analysis, the findings revealed statistical heterogeneity ( $p=0.0001$ ,  $I^2=0\%$ ) in the effective rate of acupuncture therapy in comparison to western medication, as well as superior curative effects in the acupuncture group to the control group.

Two studies reported the adverse event. Cai JIANG's reported that there were 3 adverse events in two groups (1 case in the trial group and 2 cases in the control group) that were no longer suitable for the trial, of which, the incidence of adverse events was 2% in the acupuncture group and 4% in the routine western treatment group. Moreover, the incidence of adverse events was not significant in statistics. Yi-tai SUN's study reported that there was 1 adverse event in the treatment group that had redness and itching at the needle site, and the symptoms gradually disappeared after warm compressed with a hot towel and applying peppermint ointment, of which, the incidence of adverse event was 0.3% in the acupuncture group, there was a no adverse event in the other studies. Publication bias assessments were presented as funnel plots. From the roughly symmetrical shapes of these funnel plots, no obvious publication bias was observed.

**Data management:** EndnoteX20 and Excel was used to manage studies characteristics. RevMan 5.4 (Review Manager 5.4) was used to draw network evidence relationship diagrams.

**Quality assessment / Risk of bias analysis:** Study selection, data extraction, and quality assessment will be performed by 2 reviewers independently. Two independent reviewers (Z.Y. LUO and W.X. LI) comprehensively searched and filtrated the eligible studies. The predesigned search syntax used in PubMed as an example can be found in the protocol. The equivalent search terms were applied in different databases. We decided not to include gray literatures to guarantee the quality of the further analyzed studies. Cochrane Handbook for systematic reviews of

interventions, 5.1.0 was used for risk of bias assessment. Risk of bias assessments was performed independently by 2 reviewers (Z.Y. LUO and W.X. LI), and disagreements were resolved by a third reviewer (J.T. JIANG.). If 2 of the domains were rated as high, the study was considered to be at high risk of bias. A risk-of-bias summary table was created in Review Manager, version 5.4.

**Strategy of data synthesis:** The statistical method of a meta-analysis is based on a frequency framework, and all the outcome indicators use the random effects model for data analysis. If the evaluation indicators of this study were continuous variables MMSE and MoCA, the mean difference (MD) was used as the effect size. If it was a variable binary, the odds ratio (OR) was used as the effect size, and the corresponding 95% credibility interval (CI) was calculated. RevMan 5.4 (Review Manager 5.4) was used to draw network evidence relationship diagrams, forest plots, grade probability diagrams, funnel plots, and the corresponding statistics. When testing global consistency, if the difference was not statistically significant ( $p > 0.05$ ), this indicated that there was no overall inconsistency. This study evaluated local inconsistencies by calculating the inconsistency factors (IFs) and 95% CIs of each closed loop in the network. If the lower limit of the 95% confidence interval contained or was close to 0, the direct comparison evidence was very consistent with the indirect comparison evidence. The overall quality and certainty of the evidence for therapeutic effect estimation were rated by Cochrane Handbook for systematic reviews of interventions, 5.1.0.

**Subgroup analysis:** Four trials including 430 cases using a random effect model indicated that using acupuncture therapy versus regular training has a noticeable effect ([MD=0.98, 95%CI [0.35, 1.62],  $I^2=0\%$ ,  $p=0.002$ ]). Six trials including 375 cases using a random effect model indicated that when choosing medication as a control group, it also has a prominent effect ([MD=2.07, 95%CI [0.94,3.20],  $I^2=71\%$ ,  $p=0.0003$ ]), indicating that the reason for

the difference in the articles was in the subgroup, therefore, we aimed at the results of subgroup analysis and further explored the reasons for the high heterogeneity of articles through funnel plots. One trial 29 including 120 cases using a random effect model chose sham acupuncture as the control group, however, the statistic in this subgroup was without significance ([MD=0.40, 95%CI [-1.11, 1.91],  $p=0.60$ ]).

All studies had a significant impact except for the sham acupuncture group. This study explored how long it takes for a treatment to be meaningful and divided them into different subgroups according to the duration, and found that the effect was obvious at 4 weeks and 8 weeks.

Nine trials including 639 cases using a random effect model indicated that using acupuncture therapy versus basic treatment has a significant effect ([MD=2.24, 95%CI [0.90, 3.59],  $I^2=89%$ ,  $p=0.001$ ]). Four trials including 348 cases using a random effect model indicated that using acupuncture therapy versus drugs treatment also has an obvious effect ([MD=2.45, 95%CI [0.35, 4.55],  $I^2=95%$ ,  $p=0.02$ ]). Only 1 trial including 120 cases using the random effect model, which used sham acupuncture as the control group and acupuncture as the trial group shows that the effect of acupuncture versus sham acupuncture without significance.

Meanwhile, the study showed that the intervention duration of 3 weeks and 12 weeks has an obvious effect. The possible reasons are that the sample size is small, or the duration of the intervention is too short or long, which leads to the poor effect of the study. Therefore, the specific reasons still need further study. In future studies, researchers can design trials with an intervention duration of at least 4 weeks and collect patient data at 2, 3, 4, 6, 8, and 12 weeks to further verify the effectiveness of different intervention duration and provide empirical evidence for clinical practice.

**Sensitivity analysis:** This study recovered that Jing CHEN and Er-mei CAO's articles may be the reason for high heterogeneity in the score of MoCA, on account of different

treatments in the control group compared with other trials, which in Jing CHEN's study chose drug treatment, and oxiracetam was used in Er-mei CAO's study as the control group. In addition, because of the quality of eligible articles, this study explored the reason why the score of MMSE with high heterogeneity. In Qiang LIU's study, the baseline of MMSE score was about 7, which was inferior to other trials, indicating that the participants in his study with more serious cognitive impairment. Furthermore, this study formulated a hypothesis that among the trials that could lead to heterogeneity in the meta-analysis, all trials had one thing in common the number of males is almost twice more than females of the gender of the participants; therefore, this aspect can be further explored in the future.

**Language restriction:** English or Chinese articles were included.

**Country(ies) involved:** China.

**Other relevant information:** Highlights  
-Acupuncture has a significant effect on post-stroke cognitive impairment (PSCI) at 4 and 8 weeks.

-Acupuncture and other therapies may have similar efficacy in improving motor function and daily living.

-A more extensive series of randomized controlled trials of acupuncture on stroke-related cognitive impairment ought to be carried out.

**Keywords:** Acupuncture; Post-stroke cognitive impairment; Cognitive function; Meta-analysis; Systemic review.

**Contributions of each author:**

Author 1 - Zi-yan LUO had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Email: 15117229500@163.com

Author 2 - Wenxuan Li - Investigation data curation, and formal analysis.

Email: xuanxuan20021007@163.com

Author 3 - Jieting Jiang - Formal analysis and data curation.

Email: lia0726@foxmall.com

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**Author 4 - Jie Sun - Formal analysis and data curation.**

**Email: [sunjie970815@163.com](mailto:sunjie970815@163.com)**

**Author 5 - Mingyue Zhang - Formal analysis and data curation.**

**Email: [2874737708@qq.com](mailto:2874737708@qq.com)**

**Author 6 - Kunpeng Li - Conceptualization, methodology, data curation, writing – review, and editing.**

**Email: [yfyli@163.com](mailto:yfyli@163.com)**

**Author 7 - Caiqin Wu - Conceptualization, methodology, data curation, writing – review and editing, and supervision.**

**Email: [yuwuchina@aliyun.com](mailto:yuwuchina@aliyun.com)**