


BMJ Open Effects of moxibustion on symptoms of mild cognitive impairment: protocol of a systematic review and meta-analysis

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ABSTRACT

Introduction Mild cognitive impairment (MCI) is considered the intermediate phase between normal age-related cognitive decline and dementia. Moxibustion has gained increased popularity for the management of MCI in China. This study aimed to evaluate the effects and safety of moxibustion on symptoms of MCI.

Methods and analysis Four English databases and six Chinese databases will be searched from their inception to October 2019: Embase, MEDLINE, Cochrane Central Register of Controlled Trials, Allied and Complementary Medicine Database, China National Knowledge Infrastructure, Chongqing VIP Chinese Science and Technology Periodical Database, Wanfang Database, SinoMed, China Doctoral Dissertations Full-text Database and the China Master's Theses Full-text Database. Only clinical randomised controlled trials and the first period in randomised cross-over trial related to moxibustion for MCI will be included. The primary outcomes include the improvement of cognitive function, as measured by validated assessment tools. The secondary outcomes include changes in the activity of daily living scale, effective rate and the incidences of adverse events. The selection of studies, data extraction and risk of bias assessment will be carried out by two independent reviewers. Review Manager V.5.3 software will be used for statistical analyses. Heterogeneity test, data synthesis and subgroup analysis will be performed if necessary. The risk of bias of included studies will be assessed by the *Cochrane Handbook* risk of bias tool. Evidence quality will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation system.

Ethics and dissemination Ethics approval is not required as no private information from individuals are collected. The results will be published in a peer-reviewed journal or disseminated in relevant conferences.

Trial registration number CRD42018112657.

INTRODUCTION

Mild cognitive impairment (MCI) is characterised by deterioration of cognitive function,¹ with minimal impairment of activities of daily living (ADLs).² It is also considered the intermediate phase between normal age-related cognitive decline and dementia.^{3 4} MCI affects about 21.5–71.3 per 1000 adults and is reported to have an incidence of

Strengths and limitations of this study

- This study will be the first systematic review and meta-analysis that investigated the effects of moxibustion on symptoms of mild cognitive impairment.
- This study will employ strict inclusion and exclusion criteria to search for randomised controlled trial in four English databases and six Chinese databases.
- Any missing or inadequate data will be obtained by contacting the first or corresponding author of included studies.
- Different types of moxibustion therapy may lead to a large degree of heterogeneity and make data synthesis more difficult.

6%–42% in the elderly worldwide each year.^{5 6} Its prevalence increases with age and is associated with lower educational levels.⁶ The severity of MCI involvement varies and the risk of MCI conversion to dementia is 10%–15% per year,^{7–9} further increasing the societal burden of this condition.

It is estimated that the prevalence of MCI is significantly increasing worldwide, and MCI increases the risk of progression to dementia.⁹ Accordingly, conceptual frameworks for new preventive strategies and effective therapies for treating MCI are urgently needed. Currently, strategies to prevent MCI include stress reduction, avoidance of toxins, and treatment for neurological, neurodegenerative and systemic disorders.^{10 11} Non-pharmacological interventions, such as physical activity programmes, cognitive rehabilitation, psychological treatments, aromatherapy and light therapy have been attempted as well.¹² However, evidence as to the efficacy and safety of these therapies is limited.

Moxibustion is a form of traditional Chinese medicine that has been widely used in East Asia for thousands of years.¹³ It involves the burning of dried mugwort leaves at one or more relevant acupoints, or on the handle of an acupuncture needle after insertion.¹⁴

Moxibustion is painless, easy to operate and associated with few adverse events.¹⁵ Additionally, patients can perform it at home. Moxibustion imparts both heat stimulation via infrared radiation and the pharmacological actions of its herbal components.^{16 17} It regulates a multidimensional network that includes the nervous, endocrine and immune systems, all of which play important roles in maintaining homeostasis, potentially exerting significant therapeutic effects.^{18–22} Various clinical trials and animal studies, mostly out of China, have been conducted to investigate the benefits and mechanisms of moxibustion for preventing and treating MCI.^{23 24}

In spite of its long history of use and clinical and experimental support, the effects of moxibustion for MCI have not been fully validated. Additionally, systematic reviews and meta-analyses have not been done. Thus, this systematic review and meta-analysis aimed to assess the effects and safety of moxibustion on symptoms of MCI.

METHODS

Criteria for including studies in the review

Types of studies

The review will include randomised controlled trials (RCTs) and the first period in randomised cross-over trials, regardless of publication status. Studies without comparable baselines and duplicate publications will be removed.

Types of participants

Participants with all types of MCI, including amnesic mild cognitive impairment (aMCI), non-aMCI and vascular MCI, who meeting the diagnostic criteria of MCI will be included. These criteria include the *Diagnostic and Statistical Manual of Mental Disorders*, International Classification of Diseases, diagnostic criteria from the International Working Group on Mild Cognitive Impairment, diagnostic criteria from the MCI Working Group of the European Consortium on Alzheimer's Disease and the Chinese Classification of Mental Disorders. There is no restriction on age, gender, ethnicity or economic status of the enrolled participants.

Types of interventions

Interventions in the treatment group will include any kind of moxibustion treatment, regardless of manipulation. These include moxa cone moxibustion, moxa stick moxibustion, moxa burner moxibustion, medicine thread moxibustion and warm needling. We also include moxibustion in combination with other conservative treatments, such as acupuncture therapy, cognitive rehabilitation and oral drugs. However, combined interventions consisting of three or more therapies or with potential safety problems will be excluded.

Control interventions will include no treatment, waiting list, oral drugs, cognitive rehabilitation and sham moxibustion.

Types of outcomes

The primary outcome of the study is the improvement of cognitive function, as measured by validated assessment tools. The assessment tools include the Mini-Mental State of Examination, Montreal Cognitive Assessment, Global Deterioration Scale, Clinical Memory Scale and Hasegawa Dementia Scale.

The secondary outcomes included changes in the ADL, clinical efficacy and the incidences of adverse events related to moxibustion (such as allergy, scalding, local infection, coughing and nausea).

Search methods for identification of studies

Electronic searches

The following databases will be searched from their inception until October 2019: Embase, MEDLINE, Cochrane Central Register of Controlled Trials, Allied and Complementary Medicine Database, China National Knowledge Infrastructure, Chongqing VIP Chinese Science and Technology Periodical Database, Wanfang Database, SinoMed, China Doctoral Dissertations Full-text Database and the China Master's Theses Full-text Database. Only RCTs that investigate the effects of moxibustion for MCI in comparison with the aforementioned comparator controls will be included. The following Medical Search Headings (MeSH) will be used: mild cognitive impairment, cognitive impairment, cognitive dysfunctions, mild neurocognitive disorder, cognitive decline, moxibustion, mugwort, artemisia, moxa, randomised controlled trial, randomised controlled, randomised, controlled, clinical trial, comparative study and prospective study. Chinese translations of these search terms will be used for the Chinese databases. The search strategy for MEDLINE is listed in [table 1](#). The search strategy for other online databases will be adjusted according to their requirements.

Searching other resources

The reference lists of all included studies or relevant reports of clinical trials or reviews will be screened for additional relevant articles. The WHO International Clinical Trials Registry Platform, Chinese Clinical Trial Registry and ClinicalTrials.gov will also be searched to identify the ongoing or unpublished trials.

Data collection and analysis

Selection of studies

Clinical studies will be identified and reviewed by two independent reviewers (G-LW and J-QS). The reviewers will read the titles, abstracts and, if necessary, full texts, and collect the studies that meet inclusion criteria. Applicable RCTs will be selected and cross-checked by the two reviewers (G-LW and J-QS). Disagreements related to study selection will be discussed after cross-checking and adjudicated by a third reviewer (L-PW). The process of study selection is presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram ([figure 1](#)).

Table 1 Search strategy in MEDLINE

Number	Search terms
#1	randomised controlled trial.pt.
#2	controlled clinical trial.pt.
#3	randomised.ab.
#4	randomised.ab.
#5	placebo.ab.
#6	randomly.ab.
#7	trial.ab.
#8	clinical trials as topic (MeSH)
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	cognitive impairment (MeSH)
#11	neurocognitive disorder (MeSH)
#12	cognitive dysfunction (MeSH)
#13	cognitive decline (MeSH)
#14	#10 OR #11 OR #12 OR #13
#15	moxibustion (MeSH)
#16	artemisia (MeSH)
#17	moxa.ab.
#18	mugwort.ab.
#19	#15 OR #16 OR #17 OR #18
#20	#9 AND #14 AND #19
#21	remove duplicates from #20

Data extraction and management

A predefined data extraction form will be developed based on *Cochrane Handbook* V.5.1.0 and independently completed by each of the two reviewers (X-WM and H-LJ).

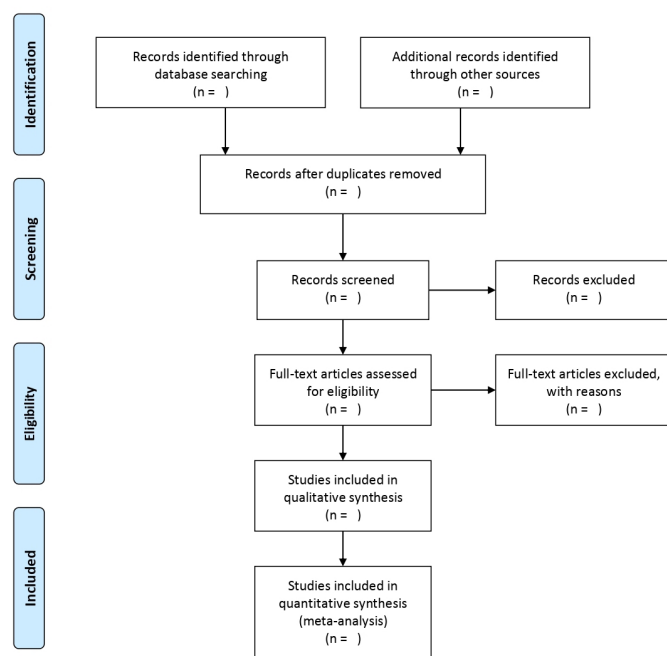


Figure 1 PRISMA flow diagram of the study process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

The data extraction form contains information about the participants, interventions, outcomes, adverse events, randomisation, allocation concealment, incomplete data, blinding, selective report, conflict of interest and self-analysis of risk of bias by the author. The data extraction results will be cross-checked, and any disagreements will be discussed and adjudicated by a third reviewer (C-ZL).

Assessment of risk of bias in included studies

According to the methods for assessing risk of bias using the *Cochrane Handbook* 'risk of bias' tool V.5.1.0, the following types of bias will be assessed: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants, investigators and care providers), detection bias (blinding of outcome assessment), attrition bias (incomplete data or differential dropout), reporting bias (selective reporting) and other biases (conflict of interest).^{25 26} These will be independently evaluated by two reviewers (TZ and BL). The result of the assessment will be cross-checked. Any disagreement will be discussed and adjudicated by a third reviewer (L-PW).

Measures of treatment effect

Review Manager statistical software (RevMan) V.5.3 will be used for data synthesis and analysis. Dichotomous data will be analysed by using a risk ratio with 95% CIs. For continuous outcomes, data will be analysed by using a mean difference with 95% CIs.

Unit of analysis issues

The units of each outcome from different studies will be converted to the International System of Units before statistical analysis.

Dealing with missing data

If required data are inadequate or not reported in the studies, reviewers will contact the first or corresponding author of those studies by phone or email. If missing data are unobtainable, those studies will be excluded.

Assessment of heterogeneity

Prior to the meta-analysis, we will assess study heterogeneity using the Mantel-Haenszel χ^2 test and I square (I^2) statistic of homogeneity by RevMan. A low p value ($p < 0.10$) and a high I^2 value indicated statistically significant heterogeneity. According to the *Cochrane Handbook*, I^2 value can be classified into four categories: a value of 0%–40% indicates little or no heterogeneity; a value of 30%–60% indicates moderate heterogeneity; a value of 50%–90% indicates substantial heterogeneity; and a value of 75%–100% indicates considerable heterogeneity.²⁵

Assessment of reporting biases

A funnel plot will be generated to observe the reporting bias when more than 10 studies are included. The plots will be assessed visually and by using Egger's test.²⁷

Data synthesis

RevMan software will be used for data synthesis. Two or more eligible studies with low heterogeneity ($p \geq 0.10$ and $I^2 < 50\%$) will be combined for the purpose of meta-analysis, and the results will be pooled using a fixed-effects model. If the p value is < 0.10 or I^2 is $\geq 50\%$, the results will be combined using a random-effects model. If the meta-analysis is not feasible due to considerable clinical and methodological heterogeneity, a qualitative summary of the results will be conducted.²⁸

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be performed to detect possible causes of heterogeneity in the previous analysis if necessary. It will be conducted according to variations in the characteristics of the participants, moxibustion treatments and controls.

Sensitivity analysis

Sensitivity analysis will be conducted to monitor the robustness of pooled treatment effects as suggested by the *Cochrane Handbook*. The meta-analysis will be repeated by excluding studies with small sample size, methodological weaknesses and missing data. If inconsistent results are identified, it will be discussed and caution will be taken in drawing conclusions.

Evidence quality evaluation

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiler, provided by the GRADE Working Group (www.gradeworkinggroup.org), will be used by two reviewers (G-LW and J-QS) to independently assess the methodological quality of included studies. Study limitations, inconsistency of results, indirectness of evidence, imprecision and publication bias will be evaluated to determine if their effects on the quality of evidence are negligible, serious or very serious, in accordance with the GRADE and *Cochrane Handbook* V.5.1.0 criteria.^{29,30} Evidence quality will be rated into one of four possible ratings: high, moderate, low and very low. The assessment results will also be cross-checked, and any disagreements will be discussed with, and adjudicated by, a third reviewer (BL).

Patient and public involvement

There was no patient or public involvement in the preparation of the study protocol. Patients will not be involved in the data collection and analysis of the systematic review and meta-analysis.

Amendments

The information of any amendment will be described in the final report.

Ethics and dissemination

Ethics approval is not required as the study will not collect private information from individuals or violate their personal rights. The results of this study will provide a general overview and evidence of the effects and safety of

moxibustion on symptoms of MCI. The findings will be published in a peer-reviewed journal or disseminated in relevant conferences.

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Contributors TZ, BL and C-ZL conceived the study. TZ and C-ZL drafted the manuscript. BL and L-PW designed the search strategy. G-LW, J-QS, X-WM and H-LJ reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript.

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Competing interests None declared.

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

Patient consent for publication Not required.

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