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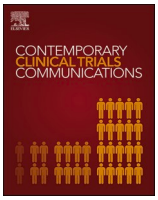

Effect of acupuncture on mild cognitive impairment in the elderly: A randomized controlled trial

Yan Cao [a,1], Qin Gao [b,1], Xia Peng [a,1], Junyi Wu [a], Baojun Liu [a], Yongning Sun [a,*], Shifen Xu [a,**]

[a] Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China
[b] Shanghai Tongji Hospital, Tongji University of Medicine, Shanghai, China

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ABSTRACT

Background and objective: Mild cognitive impairment (MCI) is a cognitive dysfunction syndrome defined mostly by memory or other cognitive impairments, and may serve as a precursor to Alzheimer's disease (AD). In recent years, acupuncture has gained recognition as a potential intervention for MCI, attracting significant attention as a promising and well-established therapy. In this study, we critically evaluate the clinical efficacy and safety of an innovative acupuncture approach, termed "Kidney Nourishment and Spirit Regulation", as a therapeutic modality for MCI in geriatric populations.

Methods: A prospective, randomized, single-blind, placebo-controlled, single-center clinical trial design where patients will be allocated in acupuncture, placebo (sham acupuncture sessions), or blank for eight weeks. The blank group will receive health education over the same eight-week period and will be offered compensatory acupuncture therapy after this period. The selected acupoints for this investigation include GV20, EX-HN1, GV24, GV29, CV6, CV4, PC6, KI3, LI4, LR3, HT7 and SP6. The primary outcome measure will be the Montreal Cognitive Assessment (MoCA), while secondary outcomes include the Mini Mental State Examination (MMSE), Activity of Daily Living (ADL), and Electroencephalogram (EEG).

Discussion: This study seeks to provide an optimum regimen for acupuncture therapy in elderly MCI patients and to provide considerable theoretical evidence for its popularization and future broad adoption. We thus postulate that the current trial data might enlighten and potentially guide future research in terms of study design refinement.

1. Introduction

Mild cognitive impairment (MCI) refers to a cognitive impairment syndrome typified by memory or cognitive deficits. This disorder typically manifests as an unstable clinical state, occurring between normal aging and dementia. MCI is unnoticeable for patients and commonly goes unnoticed in the early stages [1,2]. Furthermore, MCI is frequently seen as an early expression of a forerunner to Alzheimer's disease (AD), and people diagnosed with MCI constitute a group with a high prevalence of AD [3]. The frequency of MCI in people aged 70 years or older was 23.5 %, with 14.3 % of these people potentially acquiring dementia within a two-year period [4]. Despite these troubling figures, many people dismiss MCI as a natural part of the aging process and ignore it. Once again, this typically leads to underdiagnosis. When dementia develops in the elderly, other problems may arise, such as depressive mood and accidental falls, which significantly degrade the quality of life of elderly people and place a heavy burden on affected individuals while also imposing a significant burden on both families and society [5,6]. Currently, MCI is regarded as the best temporal window for therapeutic intervention in Alzheimer's disease, although there is no cure and effective drugs have not yet been developed [7]. To date, various drugs already have been approved for use in some clinical trials for MCI, including encompassing acetylcholine inhibitors, anti-glutamate anti--glutamate drugs, glutamate receptor antagonists, intellectual drugs nootropics, antioxidants, estrogen estrogens, anti-inflammatory drugs, brain and cerebral metabolism improvers, and so enhancers [8].

* Corresponding author.
** Corresponding author.
E-mail addresses: liyangcao@126.com (Y. Cao), wennie-12.3@hotmail.com (Q. Gao), a2010xia211@163.com (X. Peng), mify@163.com (J. Wu), liubaojun@126.com (B. Liu), yusun2002@126.com (Y. Sun), xu_teacher2006@126.com (S. Xu).
[1] Co-first authors: Yan Cao, Qin Gao, and Xia Peng are contributed equally to this article.

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However, the long-term efficacy of these drugs mentioned above pharmacological interventions in improving ameliorating cognitive function in MCI patients remains uncertain [9]. Non-pharmacologic pharmacological treatments involved include memory training, psychological resistance resilience training, sports physical exercise, electrotherapy, and hyperbaric oxygen treatment, etc. But these therapies only acted on a part therapy. Despite these concerning statistics, MCI is frequently viewed as a typical aspect of the aging process, which can result in a lack of proper diagnosis. The onset of dementia can lead to various comorbidities, including depression and unexpected falls, which can greatly diminish the quality of life for affected individuals and place significant pressure on patients [10].

Acupuncture has gained popularity as a viable therapy for MCI. In modern practice, practitioners utilize traditional acupuncture, electroacupuncture, or a combination of acupuncture, moxibustion, and medication to provide early intervention and prevent the course of Alzheimer's disease. A recent meta-analysis of 52 studies found that acupuncture was more beneficial than medicine and conventional treatment in treating moderate cognitive impairment [11].

Additionally, different researches discovered that acupuncture patients had improved resting-state functional magnetic resonance imaging connections between cognition-related brain areas [12]. The use of acupuncture for MCI has been supported by the research listed above; however, there is still disagreement on the best acupuncture sites to employ.

Based on traditional Chinese medicine's (TCM) understanding of MCI and collected clinical knowledge [13], we chose the "Kidney Nourishment and Spirit Regulation" acupuncture therapy and included GV20, GV24, GV29, and EX-HN1 as the main acupoints in the current clinical investigation. To minimize potential biases arising from patient subjective factors, we employed a sham needle device in the untreated control group. This study's main objective is to assess the clinical effectiveness and security of the acupuncture treatment "Kidney Nourishment and Spirit Regulation" for MCI in the senior population. The SPIRIT reporting checklist is followed in the presentation of this protocol.

2. Methods and design

2.1. Research overview and study design

This article reports on a single-center prospective study that was conducted in Shanghai municipal Hospital of Traditional Chinese Medicine. The study design was randomized, single-blind, and placebo-controlled. The study participants were drawn from both inpatients and outpatients. In this trial, MCI patients will be carefully assigned to one of three groups: Acupuncture group, Placebo group, and Blank group, with each group consisting of 30 subjects. The Acupuncture group will receive acupuncture therapy three times a week for eight weeks, resulting in a total of 24 sessions. The Placebo group will receive sham acupuncture therapy during the same time frame and frequency. During the eight-week period, participants in the Blank group will only receive health education. After the eight-week period, they will be provided with compensatory acupuncture therapy. The trial design and the flow of subjects through the trial is represented in Fig. 1.

2.2. Participant recruitment

To recruit participants for this study, posters will be placed in the ward and outpatient clinics. These posters will provide information about the study, allowing potential participants to learn more. Interested patients will then be briefed on the specifics of the study by researchers, who will also conduct preliminary assessments to determine if the subjects meet the inclusion criteria. The study team will inform patients of both the potential benefits and risks associated with participating in the trial. Prior to beginning the trial, eligible participants will be required to sign an informed consent form.

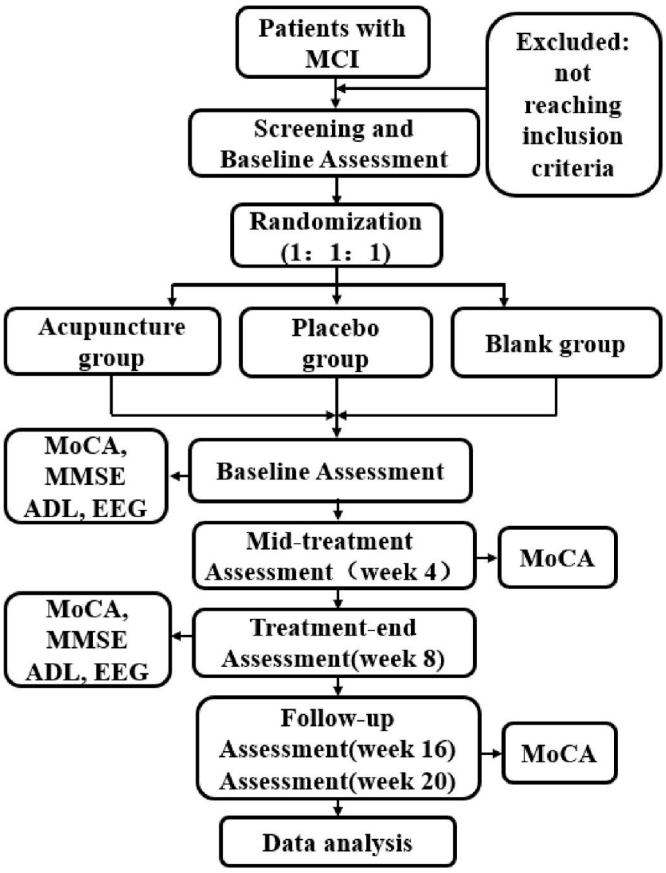

Fig. 1. Study flow chart of enrollment, allocation, intervention, and assessment.

2.3. Diagnostic criteria

The study will use diagnostic criteria outlined in the 'China Expert Consensus on Prevention and Treatment of Cognitive Dysfunction' guidelines, which include the following criteria.

1. The primary complaint is memory impairment, verified by a reliable informant.
2. Other cognitive functions are relatively preserved or only mildly impaired.
3. The individual's ability to perform daily tasks remains unaffected.
4. The patient does not meet the diagnostic criteria for dementia.
5. Other systemic diseases that could contribute to cognitive decline have been ruled out.
6. Scale Evaluation: A Global Deterioration Scale (GDS) score of 2–3, a Clinical Dementia Rating (CDR) Scale score of 0.5, a memory test score below the 1.5 standard of age and education matched control group, and a Mini Mental State Examination (MMSE) score of at least 24, or a score on the Mattis Dementia Rating Scale (DRS, Dementia Rating).

Patients satisfying all the above-mentioned criteria will be diagnosed as MCI.

2.4. Inclusion criteria

1. Aged between 65 and 80 years.
2. Fulfillment of all diagnostic criteria as outlined above.

3. Clear consciousness and the ability to understand all scale items and complete the evaluation.
4. Willingness to participate in the study and sign the written informed consent form.

2.5. Exclusion criteria

1. Normal or dementia scores on the Clinical Dementia Rating (CDR) Scale.
2. Presence of schizoaffective disorder, schizophrenia, primary adult affective disorder (including a history of adult affective disorder), severe neurological deficits, such as various types of aphasia and agnosia.
3. Presence of Alzheimer's disease, Parkinson's disease, post-traumatic dementia, central nervous system infection, metabolic encephalopathy, multiple sclerosis, Huntington's disease, mental retardation, and untreated primary endocrine diseases.
4. Presence of serious primary diseases involving the brain, liver, kidney, or hematopoietic system.
5. Recent treatment (within the past two weeks) with systematic nootropic drugs.

2.6. Attrition criteria

1. Occurrence of severe adverse events or adverse reactions.
2. Inability to comply with the treatment plan and related requirements.
3. Participants who withdraw from the study midway.

2.7. Sample size estimation

The sample size for our study was determined based on Chen et al., 2019 randomized controlled trial, which used the Montreal Cognitive Assessment (MoCA) rating scale as the primary outcome measure. Our study utilized a parallel control design with three groups to evaluate the therapeutic efficacy of 'kidney nourishment and spirit regulation' acupuncture therapy compared to placebo group and blank group. Our goal is to confirm the superiority of this therapy. The study measured the respective intervention parameters for three groups: the acupuncture group had a mean of 3.22 ± 1.3, the placebo group had a mean of 1.97 ± 1.3, and the blank group had a mean of 1.97 ± 1.3. The test level was set at $\alpha = 0.05$ and $\beta = 0.1$. Sample size calculations were performed using SPSS 26.0 software and indicated that each group required 24 participants. However, to account for a potential dropout rate of 20 %, each group would require 30 participants, resulting in a total sample size of 90 participants.

2.8. Randomization and allocation concealment

In this study, participants will be randomly assigned to one of three groups: acupuncture, placebo, or blank group. The allocation will be done in a 1:1:1 ratio using central stratification and variable block randomization. SPSS 26.0 software will be used at the Shanghai Traditional Chinese Medicine Hospital for the randomization process. An independent staff member who is not affiliated with the study will perform the allocation. The randomized list will be strictly secured and kept confidential until the study begins.

2.9. Intervention

2.9.1. Standard care

To ensure patient safety and health, we will not impose any restrictions on daily medications, unless they are specifically related to MCI. However, it is important to note that drugs like cholinesterase inhibitors and glutamate antagonists, which may have therapeutic effects on cognitive dysfunction, are not allowed.

2.9.2. Acupuncture group

The acupoint prescriptions include Baihui (GV20), Sishencong (EX-HN1), Shenting (GV24), Yintang (GV29), Qihai (CV6), Guanyuan (CV4), Neiguan (bilateral, PC6), Taixi (bilateral, KI3), Hegu (bilateral, LI4), Taichong (bilateral, LR3), Shenmen (bilateral, HT7) and Sanyinjiao (bilateral, SP6) as listed in Table 1.

Methods: During the acupuncture procedure, patients will be instructed to wear an eye mask and lie in a supine position. As a routine precaution, all acupoints will be disinfected. The needles (0.25×25 mm and 0.30×40 mm; Wuxi Jiajian Medical Material Co., Ltd., China) will be inserted using tube needles. 0.25×25 mm needles were used at GV20, EX-HN1, GV24, GV29, and PC6. 0.30×40 mm needles were used at CV6, CV4, KI3, LI4, LR3, and SP6. The depth of needle insertion varied depending on the acupoint with 10 mm at HT7, 10 mm at GV20, EX-HN1, GV24, GV29, PC6, KI3, LI4 and LR3, 15 mm at CV6, CV4 and SP6.

According to acupuncture practices, the insertion angle for GV20, EX-HN1, and GV24 points should be 30° with the scalp. The needle should be quickly inserted along the front and back midline, penetrating under the scalp to a depth of 10 mm. GV29 should be needled by pinching the local skin and pointing downwards. Other acupoints should be needled by inserting the needle vertically at a depth of 5–15 mm. The study involved using acupuncture to stimulate specific points on the body until the participant experienced the De-qi sensation. The needles were kept for 30 min before removal. The treatment was administered every other day, three times a week, for a total of eight weeks.

2.9.3. Placebo group

The placebo group will receive the same procedures as the acupuncture group, but with the use of a placebo needle that does not penetrate the skin. This needle is known as the Streitberger placebo needle and manufactured by Asiamed in Suhl, Germany. The treatment cycle, frequency and needle retention time will be consistent with those of the acupuncture group.

2.9.4. Blank group

The blank group will receive only health education for the first eight weeks, followed by compensatory acupuncture therapy upon patient

Table 1
The specific locations of selected acupoints.

Acupoints	Locations
Baihui (GV20)	On the anterior midline of the head, 5 cun superior to the anterior hairline.
Sishencong (EX-HN1)	At the vertex of the head, 1 cun anterior, posterior, and lateral to Baihui (GV20), four points in total.
Shenting (GV24)	On the anterior midline of the head, 0.5 cun superior to the anterior hairline.
Yintang (GV29)	At the midpoint between the medial ends of the eyebrows.
Qihai (CV6)	On the anterior midline of the lower abdomen, 1.5 cun below the umbilicus.
Guanyuan (CV4)	On the anterior midline of the lower abdomen, 3 cun below the umbilicus.
Neiguan (PC6)	On the anterior aspect of the forearm, between the palmaris longus and flexor carpi radialis tendons and 2 cun proximal to the palmar wrist crease.
Taixi (KI3)	On the posteromedial aspect of the ankle, in the depression between the prominence of the medial malleolus and the calcaneal tendon.
Hegu (LI4)	On the dorsum of the hand, at the midpoint of the second metacarpal bone on the radial side.
Taichong (LR3)	On the dorsum of the foot, between the first and second metatarsal bones, in the depression between the junction of the bases of the two bones and over the dorsalis pedis artery.
Shenmen (HT7)	On the anterior and medial aspect of the wrist, radial to the flexor carpiulnaris tendon at the palmar wrist crease.
Sanyinjiao (SP6)	On the tibial aspect of the leg, posterior to the medial border of the tibia and 3 cun superior to the prominence of the malleolus.

The "cun" in acupuncture is the bone-length proportion, which is divided by the body surface mark of the patient him or herself.

request. The treatment regimen and frequency for both the acupuncture group and the compensatory acupuncture therapy group will be the same.

2.10. Single-blind method implementation and researcher blinding

A single-blind method will be used in this trial to ensure blinding. Patients will be positioned supine and wear an eye mask to maintain blinding. All treatments will be administered in a concealed manner, including screen isolation. Before the trial begins, all researchers will receive extensive training on how to carry out the research protocol. Additionally, they will strictly adhere to the principle of departmental segregation.

2.10.1. Primary endpoint

2.10.1.1. Montreal Cognitive assessment (MoCA). The MoCA is a cognitive function evaluation tool used to assess various cognitive domains. It includes attention, concentration, memory, language, visuospatial abilities, abstract thinking, calculation, and orientation. The test can be completed in approximately 10 min and is scored out of 30 points. A lower score indicates a higher level of cognitive impairment, while a score above 26 indicates normal cognition.

2.10.2. Secondary endpoints

2.10.2.1. Mini Mental State Examination (MMSE). The MMSE assesses seven cognitive domains: orientation to time and place, immediate memory, attention and calculation, delayed recall, language, and visuospatial abilities. The scale scores range from 0 to 30, where scores of 27–30 represent normal cognitive function. Scores below 27 indicate cognitive dysfunction, with severity classified as mild impairment (21–26), moderate impairment (10–20), and severe impairment (0–9).

2.10.2.2. Activity of Daily Living (ADL). The ADL scale is a measurement tool used to assess the impact of cognitive decline on daily functioning. It comprises 20 items that evaluate six aspects of physical self-care and eight aspects of instrumental ADL. Each item is rated on a four-point scale, ranging from complete independence to complete dependence. A total score of 26 indicates no functional impairment, while scores above 26 indicate varying degrees of functional decline.

2.10.2.3. Electroencephalogram (EEG). EEG will be captured using Neuracle™, a mobile EEG recorder, in conjunction with an amplifier and a 64-lead EEG cap. The Neuracle EEG Recorder software will record 16/32/64channel EEG signals. In the recorded amplitude-integrated EEG (aEEG), EEG segments without artifacts will be chosen for beam spectrum analysis, Power spectral analysis technology will be used to calculate the absolute power values for each frequency band.

2.10.3. Observation schedule and follow-up period

Five evaluation points will be used: baseline, 4 weeks after treatment started, 8 weeks after treatment started (the conclusion of therapy), 8 weeks after treatment, and 12 weeks after treatment. All results will be assessed at baseline and eight weeks after the treatment. Additionally, the MoCA will be assessed at the 4-week, 8-week, and 12-week marks following therapy (Table 2).

2.11. Adverse events documentation and reporting

Dizziness, discomfort, itching, redness, and swelling are just a few of the adverse occurrences that will be properly documented. A decision on the continuation of therapy will be made based on an evaluation of the severity and its relationship to the intervention. For any negative outcomes throughout the study, an "adverse event form" must be completed, followed by follow-up inquiries. It is necessary to thoroughly document the course of treatment and its results.

2.12. Data management

2.12.1. Data entry

The Epi-Data system will be used for data administration and input. Two independent research assistants will enter data within 3 days following the gathering. After data input, the acupuncturists and therapists will archive the original data books. The data can be exported, corrected, and verified using the system. After verification, the database will be secured and sent for statistical analysis.

2.12.2. Missing data handling

In accordance with the principle of Intention-To-Treat (ITT), the Last Observation Carried Forward (LOCF) approach will be implemented for instances of missing data.

2.13. Data monitoring

An independent Data and Safety Monitoring Board (DSMB) will be established to oversee this study. The DSMB, comprises experts in acupuncture, neurology, and statistics, who will monitor the trial's progress, ensure adherence to the research design and accepted criteria, check the study's progress, and guarantee the correctness and validity of the data. Moreover, they will check for thorough documentation of subject adverse events and their causality. Any severe adverse events

Table 2
Schedule of enrollment, interventions, and assessment.

Timepoint	Enrolment	Baseline	Treatment phase		Follow-up phase	
	−1 week	0 week (Vist 1)	4 weeks (Vist 2)	8 weeks (Vist 3)	16 weeks (Vist 4)	20 weeks (Vist 5)
Enrolment						
Eligibility screen	×					
Medical history	×					
Informed consent		×				
Allocation		×				
Interventions						
Acupuncture		×	×	×		
Sham acupuncture		×	×	×		
Health education		×	×	×		
Assessments						
MoCA		×	×	×	×	×
MMSE		×		×		
ADL		×		×		
EEG		×		×		
Safety assessments		×	×	×	×	×

× = Yes; MoCA = Montreal Cognitive Assessment; MMSE = Mini Mental State Examination; ADL = Activity of Daily Living; EEG = Electroencephalogram.

must be reported to the ethics committee and the lead investigators within 24 h. Following discussions with the primary investigators, the ethical committee will forward the suggested remedies to the DSMB, which will then have the option of recommending that the principal investigators terminate the experiment.

2.14. Statistical analysis

Using the SPSS 26.0 program, a statistical specialist who is impartial and unaware of the group allocations, will analyze the data. All data, including those from participants who withdrew, will be examined in accordance with the ITT principle. The Chi-square test and Fisher's exact test will be used to compare the baseline characteristics of the three groups. The change in baseline MoCA scores after eight weeks of therapy serves as the main outcome indicator. To compare outcomes between groups, a non-parametric analysis of variance. For the secondary outcomes, repeated measures analysis of variance or the rank sum test will be used to compare measurement data within groups; non-parametric analysis of variance will be used to compare measurement data across groups. Chi-square tests will be used to examine count data, while rank data will be subjected to rank sum tests. All P-values are two-tailed, and statistical significance is defined as a P-value 0.05.

3. Discussion

The objective of this study is to evaluate the therapeutic effectiveness of "Kidney Nourishment and Spirit Regulation" acupuncture therapy for MCI in older individuals. The study incorporates various TCM theories. To demonstrate the validity of the investigation, a standardized, single-blind, randomized controlled trial will be carried out with the most appropriate sample size. The MMSE, MoCA and electroencephalogram assessments will all be used as part of a tripartite framework for evaluating the therapeutic effects of treatment. The placebo group will be subjected to sham acupuncture, and the experimenters involved in recruitment, evaluation, and data analysis will be intentionally blinded to the group assignments, which bolsters allocation concealment and effectively mitigates potential bias.

Strict adherence to the STRICTA international standard will ensure that the acupuncture therapy is controlled for quality [14]. The choice of acupoints, manipulation methods, acupuncture equipment, and therapist education will all be standardized. The application of STRICTA further enhances the reliability of the evaluation. Thus, this study aims to evaluate an optimized acupuncture therapy called "Kidney Nourishment and Spirit Regulation" for elderly individuals with MCI. The findings of this study will provide theoretical support for the future dissemination and practical application of this therapy.

Acupuncture as an ancient therapy, offers several advantages over drug-based treatments, such as avoiding drug toxicities and side effects [15]. The therapeutic mechanisms of acupuncture are diverse and include controlling central neurotransmitter release, protection against neuronal oxidative damage, eliminating free radicals, inhibiting of neuronal apoptosis, reducing inflammatory responses in brain tissue, activating hippocampal protein kinases, and suppression of tau protein expression in relation to microvessels [16]. The effectiveness of acupuncture for MCI has been examined in a number of recent Randomized Controlled Trials (RCTs) [17–19]. The unique study group design what gives our study an edge is above earlier studies. There are debatable arguments suggesting that the effectiveness of acupuncture, primarily due to the placebo effect or the possibility that sham acupuncture controls may not be completely ineffective [20]. The participants will be divided into three separate groups: acupuncture group, placebo group, and blank group. This makes it possible to compare the results of three groups side by side. The effectiveness of "Kidney Nourishment and Spirit Regulation" acupuncture therapy will be assessed, and it will be determined whether sham acupuncture is ineffective when compared to the blank group. The findings from this trial will be valuable for future research on study design. One strength of our study is the careful selection of acupoints based on TCM theory. According to TCM theory, MCI in elderly patients is often caused by a deficiency of kidney essence. Acupuncture is used to stimulate the Du meridian and regulate the mind, which promotes the smooth flow of blood and Qi in the Du meridian. This process unblocks kidney essence, allowing Qi and blood to nourish the brain marrow and maintain proper brain function.

This study protocol aims to investigate the effectiveness of 'Kidney Nourishment and Spirit Regulation' acupuncture therapy for MCI within standard medical practice conditions. The results of this study will be crucial in developing an optimal acupuncture therapy plan specifically tailored for elderly MCI patients. Moreover, the results will provide significant theoretical support for the future use and application of the acupuncture in MCI.

Ethics approval and participant consent

The study design, procedures, and informed consent protocol of this research have been approved by the Ethics Committee of Shanghai Traditional Chinese Medicine Hospital under permission number 2020SHL-KY-46-02. All participants will be requested to provide their consent to participate. ChiCTR2000037713 is the registration number for the study with the China Clinical Trial Registration Center.

Authors' contributions

Yan Cao, Qin Gao and Xia Peng designed trial and drafted the paper, and revised by Junyi Wu and Baojun Liu; Yan Cao, Qin Gao and Xia Peng independently worked on study selection, quality inspection, data mining; Yongning Sun worked on data synthesis; Shifen Xu resolved any divergences.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

References

[1] A.M. Sanford, Mild cognitive impairment, Clin. Geriatr. Med. 33 (3) (2017) 325–337.
[2] S. Jongsiriyanyong, P. Limpawattana, Mild cognitive impairment in clinical practice: a review article, Am J Alzheimers Dis Other Demen 33 (8) (2018) 500–507.
[3] A. Ward, H.M. Arrighi, S. Michels, et al., Mild cognitive impairment: disparity of incidence and prevalence estimates, Alzheimers Dement 8 (1) (2012) 14–21.
[4] H. Brodaty, M. Heffernan, N.A. Kochan, et al., Mild cognitive impairment in a community sample: the sydney memory and ageing study, Alzheimers Dement 9 (3) (2013) 310–317.
[5] N. Li, G. Chen, P. Zeng, et al., Prevalence and factors associated with mild cognitive impairment among Chinese older adults with depression, Geriatr. Gerontol. Int. 18 (2) (2018) 263–268.

[6] K. Delbaere, N.A. Kochan, J.C. Close, et al., Mild cognitive impairment as a predictor of falls in community-dwelling older people, Am. J. Geriatr. Psychiatr. 20 (10) (2012) 845–853.
[7] M.S. Albert, S.T. DeKosky, D. Dickson, et al., The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement 7 (3) (2011) 270–279.
[8] J.N. Vega, P.A. Newhouse, Mild cognitive impairment: diagnosis, longitudinal course, and emerging treatments, Curr. Psychiatr. Rep. 16 (10) (2014) 490.
[9] N.D. Anderson, State of the science on mild cognitive impairment (MCI), CNS Spectr. 24 (1) (2019) 78–87.
[10] C.W. McMonnies, Hyperbaric oxygen therapy and the possibility of ocular complications or contraindications, Clin. Exp. Optom. 98 (2) (2015) 122–125.
[11] W. He, M. Li, X. Han, W. Zhang, Acupuncture for mild cognitive impairment and dementia: an overview of systematic reviews, Front. Aging Neurosci. 13 (2021), 647629.
[12] T.T. Tan, D. Wang, J.K. Huang, et al., Modulatory effects of acupuncture on brain networks in mild cognitive impairment patients, Neural Regen Res 12 (2) (2017) 250–258.
[13] Y.Q. Chen, H.G. Wu, P. Yin, et al., Tongdu Tiaoshen acupuncture for mild cognitive impairment: a randomized controlled study, Chinese Acupuncture[J] 39 (11) (2019) 1141–1145.
[14] H. Macpherson, R. Hammerchlag, D.G. Altman, et al., Revised standards for reporting interventions in clinical trials of acupuncture (STRICTA): extending the consort statement, Alter Complement Med 16 (10) (2010) ST1–10.
[15] W. He, M. Li, X. Han, W. Zhang, Acupuncture for mild cognitive impairment and dementia: an overview of systematic reviews, Front. Aging Neurosci. 13 (2021 May 14), 647629.
[16] F. Cao, X.L. Pan, H.C. Li, B. Chen, Y. Jin, P. Huang, Systematic review and Meta-analysis of the effect of acupuncture therapy on senile dementia in Chinese population, J. Nanchang Univ. (Nat. Sci.) 54 (2014) 59–61.
[17] Y.Q. Chen, H.G. Wu, P. Yin, J. Xu, E.T. Huang, S.F. Xu, Zhongguo Zhen Jiu 39 (11) (2019) 1141–1145.
[18] Y. Chen, W. Zhang, H. Wu, L. Lao, J. Xu, S. Xu, Combination of acupuncture and Chinese herbal formula for elderly adults with mild cognitive impairment: protocol for a randomized controlled trial, Trials 20 (1) (2019) 117.
[19] Y. Shan, J.J. Wang, Z.Q. Wang, et al., Neuronal specificity of acupuncture in Alzheimer's disease and mild cognitive impairment patients: a functional MRI study, Evid Based Complement Alternat Med (2018), 7619197, 2018 Jul 17.
[20] K. Linde, K. Niemann, K. Meissner, Are sham acupuncture interventions more effective than (other) placebos? A re-analysis of data from the Cochrane review on placebo effects, Forsch Komplementmed 17 (2010) 259–264.