ORIGINAL RESEARCH

# Efficacy and Safety of Acupuncture Combined with Yishen Granule in Elderly Adults with Mild Cognitive Impairment: A Multicenter, Randomized Controlled Trial

Nana Li, MM; Ou Li, MM; Zhongwei Sha, MM; Yuxia Wang, MM; Zhimin Li, MM; Yixia Li, MM; Jie Zhang, MM; Zhenghao Zhao, MM; Shifen Xu, MD; Jian Xu, MD

## ABSTRACT

**Objective •** Mild cognitive impairment (MCI) is a clinical disease that is prevalent in the elderly. Traditional Chinese herbs (TCHs) and acupuncture are valuable therapeutic options for MCI. This study aimed to assess the efficacy and safety of acupuncture and Yishen Granule (YSG) in restoring cognitive function in elderly patients with MCI.

**Methods •** A multicenter, randomized, double-blind, parallel-group, controlled trial (8-week intervention) was conducted at two tertiary hospitals in Shanghai, China. A total of 120 participants were randomly divided into four groups (n = 30 per group): A, acupuncture with YSG; B, acupuncture with placebo herbal medicine; C, sham acupuncture with YSG; D, sham acupuncture with placebo herbal medicine. The primary outcome was a change in Montreal Cognitive Assessment (MoCA), while the secondary outcome was to evaluate improvement in the Mini-Mental State Examination (MMSE). Assessments were conducted at baseline and weeks 4 and 8.

**Results •** Of the 120 patients (69.17 ± 6.57 years; 71 women [59.17%] and 49 men [40.83%]) included in the study, 106 (88.33%) completed the study. Two-way repeated measures ANOVA showed that the MoCA and MMSE scores in group A were significantly different from those in group D at week 4 ($P < .05$). At week 8, the MoCA and MMSE scores in groups A, B, and C were significantly improved compared with those in group D ($P < .001$ for all), and the delayed recall score in group A was significantly greater than those in groups B and C ($P < .05$). Acupuncture and YSG were well tolerated and safe, and no serious adverse events were reported.

**Conclusions •** Acupuncture, YSG, and the combination of both improved cognitive function, with the combined therapy being the most effective, which can be beneficial in preventing dementia and improving the quality of life of the elderly. (*Altern Ther Health Med.* 2023;29(6):340-349).

**Nana Li, MM,** Resident Doctor**; Ou Li, MM,** Resident Doctor; **Zhongwei Sha, MM,** Attending Doctor; **Yuxia Wang, MM,** Resident Doctor; **Zhimin Li, MM,** Attending Doctor; **Zhenghao Zhao, MM,** Resident Doctor; **Jian Xu, MD,** Chief Physician; Department of Mental Diseases, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China. **Yixia Li, MM,** Resident Doctor, Department of Encephalopathy, Jing'an District Traditional Chinese Medicine Hospital, Shanghai, China. **Jie Zhang, MM,** Resident Doctor, Standardized Resident Training Staff, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China. **Shifen Xu, MD,** Chief Physician, Department of Acupuncture, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China.

*Corresponding author: Jian Xu, MD*
*E-mail: xujian0296@163.com*
*Corresponding author: Zhongwei Sha, MM*
*E-mail: shazhongwei1989@163.com*

## INTRODUCTION

Mild cognitive impairment (MCI) is characterized by objective impairment of cognition, predominantly in the form of memory impairment or other cognitive impairment with greater cognitive changes than would be expected for the individual's age and education level, but without interference in daily living activities.[1] MCI is a heterogeneous syndrome that includes two clinical subtypes—amnestic and non-amnestic,[2] and it is a multifactorial disease, with heterogeneity in etiology among individuals. Genetics, aging, education level, cerebrovascular disease, and metabolic disease are all associated with the development of MCI.

Imaging analysis can further classify MCI into forms attributed to different causes, including Alzheimer's disease (AD), cerebrovascular disease, vascular risk factors, and other diseases, with the most common form being vascular-related MCI.[3] In addition, MCI can be a risk factor for AD or other dementias;[4] approximately 5% – 15% of patients with MCI progress to dementia each year.[5] MCI is common in older populations and its prevalence increases with age. The estimated prevalence of MCI in individuals aged 60–84 years ranges from 6.7% to 25.2%.[6] As global populations age, the prevalence of MCI is expected to increase substantially. According to recent studies, the prevalence of MCI among elderly people in China is 15.5%.[7] MCI has an insidious onset. A survey reported low awareness of MCI among individuals, and without timely diagnosis and intervention, it is difficult to reverse the progression to dementia, which places a heavy burden of care and financial pressure on families and public health resources.[8] As a transitional stage between normal aging and dementia, MCI is a critical treatment stage to prevent the progression to dementia. Thus, it is vital to improve MCI awareness and diagnosis, and more people should be encouraged to participate in MCI-related clinical trials to facilitate the development of new treatments and intervention strategies.[9] Currently, there is a lack of pharmacologic agents with proven benefits for the treatment of MCI. The effects of cholinesterase inhibitors in MCI were null and failed to delay the onset of dementia.[10] Aducanumab was approved by the Food and Drug Administration (FDA) in June 2021 for the treatment of MCI and mild AD. However, studies on Aducanumab are progressing slowly; the drug is expensive and it is currently under regulatory review.[11]

Traditional Chinese medicine (TCM) has a long history in the treatment of MCI in China and is considered a potential treatment to improve MCI symptoms. TCM has numerous advantages in the treatment of MCI. TCM treatment has fewer side effects, is easy to be accepted by patients, and its efficacy has been confirmed by many studies. Herbs are usually used in combination for their anti-inflammatory, antioxidant, and neuroprotective properties to enhance cognitive function.[12] Herbs such as the Acorus calamus have been proven to be neuroprotective against MCI.[13] Clinical research has demonstrated that Chinese herbal medicines (CHMs) can improve the neuropsychological scale scores and quality of life of patients.[14] A meta-analysis showed that herbal medicine alone or in combination with other cognitive improvement drugs significantly improved Mini-Mental State Examination (MMSE) scores.[15] Interestingly, a systematic review found that acupuncture was more effective than Western medicine or conventional therapy for MCI.[16] Thus, acupuncture and CHMs are critical in preventing and reversing the progression of MCI to dementia, and can markedly reduce the prevalence and costs of dementia.

Currently, there is a lack of research on acupuncture combined with CHMs as a therapeutic option for MCI. Consequently, this clinical study was designed to compare the efficacy and safety of acupuncture, Yishen Granule (YSG), and their combination in elderly patients with MCI by evaluating scores for Montreal Cognitive Assessment (MoCA) and MMSE. The hypothesis was that both acupuncture and YSG would attenuate the progression of cognitive decline in MCI and that the combination of both treatments would be more effective compared to the individual treatments.

## MATERIALS AND METHODS

### Study Design

This multicenter, randomized, double-blind, parallel-group, and controlled trial was conducted from July 1, 2018, to December 30, 2019, at Shanghai Municipal Hospital of Traditional Chinese Medicine and Shanghai East Hospital affiliated with Tong Ji University in Shanghai, China. The protocol of the study was approved by the ethics committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (ethics no. 2017SHL-KY-05) and has been registered in the Chinese Clinical Trial Registry (registration no. ChiCTR-INR-17011569).

### Participants

The study participants included patients with MCI who fulfilled the following criteria: men or women aged 50–90 years with a MoCA score < 26 (range, 0–30, with lower scores indicating worse cognitive functioning), who met the diagnostic criteria for MCI,[17] had a Clinical Dementia Rating (CDR) scale score of 0–0.5, were able to perform basic normal activities of daily living, were able to understand and complete the cognitive assessment, agreed to sign the written informed consent form, and did not use cognitive improvement drugs for 4 weeks before the study. The key exclusion criteria were: dementia diagnosis, severe physical illnesses, psychiatric diseases, severe digestive disorders that affected the absorption of medication, severe diseases of cardiovascular or hematopoietic systems, and severe liver and kidney dysfunction; Hamilton Depression Scale (HAMD) score > 8, allergy to the study granule or suffered from needle sickness; had received herbal or acupuncture treatment in the past 4 weeks.

### Sample Size

The sample size was calculated by non-inferiority test using Power Sample Size Calculators (https://www.powerandsamplesize.com/Calculators/). Based on a clinical study of acupuncture combined with nimodipine in the treatment of MCI after cerebral infarction,[18] the effective rate of the acupuncture-combined-with-nimodipine group was 77.5%, and that of the nimodipine-alone group was 46.2%. Referring to our previous research, we hypothesized an 80% effective rate for the combination of the two treatments and a 52% effective rate for one treatment alone, taking $\alpha = 0.025$, $\beta = 0.2$, $\delta = -0.05$. The above values are the most commonly used values for testing level and effectiveness in statistical

analysis. Considering an expected dropout rate of 20% of participants, a sample size of 30 for each group was needed. Therefore, a total of 120 participants were required for the study.

### Randomization and Blinding

The task of random coding and subject grouping was undertaken by two professors from the Department of Statistics at Shanghai University of Traditional Chinese Medicine to ensure randomness and double-blindness of the study. According to the double-blind method, statistical experts and assistants divided the drugs into four groups and attached the coding label to the outside of each drug package. The 120 eligible participants were randomly divided into four equal groups. Each center distributed the drugs according to the drug number and the order of the subjects. Researchers and patients were blinded to the group assignments. The acupuncturists were not blinded to the group assignments but were not involved in the outcome assessment or data analysis. The random numbers and drug codes were placed in an opaque sealed envelope and kept in the Shanghai Municipal Hospital of Traditional Chinese Medicine throughout the trial. All researchers received standardized training.

### Research Grouping

The 120 elderly patients with MCI were randomized to groups A, B, C, or D. Patients in group A received acupuncture with YSG treatment. Patients in group B received acupuncture with a placebo herbal medicine treatment. Patients in group C received sham acupuncture with YSG treatment. Patients in group D received sham acupuncture with placebo herbal medicine treatment.

### Interventions

**Basic Treatment.** To ensure the health and safety of patients, drugs unrelated to the treatment of MCI but related to the control of the patient's original disease were not restricted.

**Acupuncture.** 0.30×25-mm and 0.30×40-mm real tube-needles and blunt stainless-steel tube-needles were provided by Wuxi Jiajian Medical Instruments Co., Ltd., China. Acupuncture was administered for 30 min, twice a week, for 8 weeks. All treatments were performed by acupuncturists with consistent training and clinical experience. The regular acupuncture method was applied to all acupoints. 0.30 × 25-mm needles were applied at the *Yintang* (GV29), *Sishencong* (EX-HN1), *Baihui* (GV20), and *Shenting* (GV24) acupoints, while 0.30 × 40-mm needles were applied at the bilateral *Anmian* (EX-HN22), bilateral *Shenmen* (HT7), bilateral *Hegu* (LI4), bilateral *Sanyinjiao* (SP6), and bilateral *Taichong* (LR3) acupoints. Participants wore an eye mask and lay in the supine position during treatment. After routine disinfection, the needle was inserted through a tube-needle, with lifting-thrusting manipulation or rotating manipulation applied to achieve a *De-Qi* sensation (a needling sensation of soreness, numbness, heaviness, and/or distention).

Sham acupuncture had the same treatment frequency, time, and acupoints as acupuncture. Non-penetrating sham acupuncture used blunt stainless-steel needles to simulate the acupuncture process without penetrating the skin.[19] When the tip of the blunt needle touched the skin, the needles retracted inside the needle tubing and appeared to be shortened; meanwhile, the participants felt a pricking sensation without *De-Qi* sensation.[20]

**Medications.** YSG (herbal medicine content 3.3 g/bag) and placebo herbal medicine were provided by Beijing Kangrentang Pharmaceutical Co., Ltd., China. The placebo herbal medicine was composed of starch, caramel, coloring, bitter, and 10% YSG ingredients to ensure the same appearance and taste as YSG. YSG or placebo herbal medicine was administered orally, twice a day, for 8 weeks. Researchers provided participants with 28 doses of packaged granules at a time (two times in total), and they were requested to return unused granules to the researchers. The granules were dissolved in warm water and administered orally every morning and evening after meals. The granules were stored at room temperature in a dry and dark location, out of the reach of children.

### Measures

**Primary Outcome.** MoCA was specifically developed as a screening tool for MCI and covers eight cognitive domains (visuospatial/executive function, naming, memory, attention, abstraction, language, delayed recall, and orientation). Higher scores indicate better cognitive function, with total scores ranging from 0 to 30. The cognitive function of the study subjects was assessed subjectively by the Beijing version of the MoCA.[21] The Chinese version and instructions of the MoCA test are available from the official website (http://www.mocatest.org/). Receiver operating characteristic (ROC) curve analysis for MoCA demonstrated that the optimal cutoff point for MCI detection was 24/25.[22] The optimal cutoff point for MCI considering significant influential factors was 13/14 for illiteracy, 19/20 for individuals with 1–6 years of education, and 24/25 for those with more than 6 years of education.[23]

**Secondary Outcome.** Based on the literature,[24] cognitive function was assessed using the Chinese version of the MMSE. The validity and reliability of the Chinese MMSE have been verified.[25,26] The MMSE provides assessments in five cognitive domains, namely, orientation, registration, attention and calculation, recall, and language. For MMSE, the total score ranges from 0 to 30, and the optimal cutoff points are 27/28.[22]

**Total Effective Rate.** Efficacy was evaluated according to the evaluation criteria of clinical efficacy formulated by the Anti-aging Committee of the Internal Medicine Branch of China Association of Chinese Medicine. The effective rate was determined according to the change in MoCA score: markedly effective (efficacy index ≥ 20%), effective (12% ≤ efficacy index < 20%), and ineffective (efficacy index < 12%).

Efficacy index = [(post-treatment MoCA score − pre-treatment MoCA score)/pre-treatment MoCA score] × 100%

Total effective rate = [(the number of people in markedly effective + the number of people in effective)/total number of people] × 100%

### Safety Assessment

Safety was assessed in participants from baseline through week 8. Safety was evaluated through vital signs, physical examinations, electrocardiograms, routine laboratory safety tests, and adverse events (AEs). Routine laboratory safety tests included routine tests of blood, urine, liver function, and kidney function. AEs during the study were recorded and assessed with symptoms, diseases, dates, severity, and outcome.

### Statistical Analyses

Statistical analyses of the basic demographic characteristics of all randomly assigned patients were based on the intention-to-treat (ITT) principle. All outcome measures in this study were analyzed using the per protocol set (PPS).[27] Safety data were analyzed using the safety set (SS). All data were analyzed using IBM SPSS Statistics version 26.0. The baseline characteristics of each group were analyzed descriptively, the counting data were expressed by frequency and composition ratio, and the quantitative data were described by mean, standard deviation, or interquartile interval $M$ ($P_{25}$, $P_{75}$). Chi-square tests or Fisher's exact tests were used for categorical data. One-way analysis of variance (ANOVA) and two-way repeated measures ANOVA were performed for continuous variables conforming to normal distribution. A Kruskal-Wallis H test was used to grade data.

The within-subject factor was the time (baseline and 4 and 8 weeks after the intervention), and the between-subject factor was the group (four interventions). When significant interaction effects were observed, simple effects analyses and pairwise comparisons were performed. The results of unitary analysis of variance were referenced when conforming to Mauchly's sphericity test; when Mauchly's sphericity test was violated, the results were based on the multivariate tests or referred to the greenhouse-Geisser correction results. The significance level was set at .05.

## RESULTS

### Patient Characteristics

A total of 120 patients with MCI were enrolled between July 1, 2018, and December 30, 2019, in two hospitals in Shanghai. Of these enrolled patients, 106 (88.33%) completed all outcome measurements at week 8 and were included in the PPS (28 in group A, 27 in group B, 25 in group C, and 26 in group D). The remaining 14 patients (11.67%) withdrew from the study owing to personal problems or unsatisfactory outcomes (2 in group A, 3 in group B, 5 in group C, and 4 in group D) (Figure 1).

Patient characteristics in the four groups were similar at baseline (Table 1). There were no significant differences in age, gender, disease duration, or education level among the four groups ($P > .05$).

### Clinical Efficacy

**MoCA Score.** The MoCA scores of the four groups are shown in Table 2. The data were analyzed to reveal changes from baseline to week 8. After four and eight weeks of intervention, the total MoCA score of group A increased from 20.93 ± 2.43 points to 24.18 ± 3.07 and 26.04 ± 2.40 points, respectively; the total MoCA score of group B increased from 20.96 ± 3.38 points to 23.67 ± 2.60 and 24.41 ± 3.09 points, respectively; the total MoCA score of group C increased from 21.24 ± 2.76 points to 23.68 ± 3.69 and 24.60 ± 3.23 points, respectively; and the score of group D increased from 20.12 ± 4.37 points to 21.85 ± 4.74 and 21.92 ± 4.30 points, respectively. Trends in the total MoCA score in the four groups are shown in Figure 2.

Time was used as a within-subject factor, and group was used as a between-subject factor. The results of two-way repeated measures ANOVA are shown in Table 3. All MoCA subdomains showed significant time effects except for orientation ($P < .001$). The total MoCA score ($P = .024$) and the MoCA score for delayed recall ($P = .040$) showed significant group effects. The total MoCA score ($P = .010$) and the MoCA score for delayed recall ($P = .024$) showed a significant interaction effect. The effect of interactions

**Figure 1.** Study Flowchart

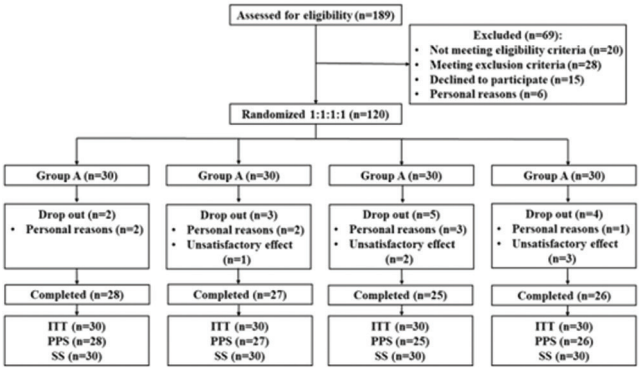



**Table 1.** Baseline Characteristics of the Intention-To-Treat Population

| Demographics | Group A (n = 30) | Group B (n = 30) | Group C (n = 30) | Group D (n = 30) | $F/\chi^2$ value | *P* value |
|---|---|---|---|---|---|---|
| Sex, *n* (%) | | | | | 6.174 | .113 |
| Male | 16 (53.33) | 7 (23.33) | 14 (46.67) | 12 (40.00) | | |
| Female | 14 (46.67) | 23 (76.67) | 16 (53.33) | 18 (60.00) | | |
| Age in years, mean (SD) | 68.30 (8.09) | 70.17 (6.74) | 70.53 (6.07) | 67.67 (4.86) | 1.371 | .255 |
| Educational level, *n* (%) | | | | | 5.900 | .385 |
| Undergraduate and above | 13 (43.33) | 12 (40.00) | 10 (33.33) | 13 (43.33) | | |
| High school and middle school | 16 (53.33) | 18 (60.00) | 20 (66.67) | 14 (46.67) | | |
| Primary school and below | 1 (0.03) | 0 (0) | 0 (0) | 3 (10.00) | | |
| Duration of MCI in months, M ($P_{25}$, $P_{75}$) | 27 (21,36) | 27 (21,48) | 33(24,52.5) | 27(24,43.5) | 1.025 | .795 |

**Table 2.** MoCA Scores Among the Study Participants

| Cognitive Function | Group | MoCA score, mean (SD) | | |
|---|---|---|---|---|
| | | Baseline | Week 4 | Week 8 |
| Total MoCA score | A | 20.93 (2.43) | 24.18 (3.07) | 26.04 (2.40) |
| | B | 20.96 (3.38) | 23.67 (2.60) | 24.41 (3.09) |
| | C | 21.24 (2.76) | 23.68 (3.69) | 24.60 (3.23) |
| | D | 20.12 (4.37) | 21.85 (4.74) | 21.92 (4.30) |
| Visuospatial/ executive function | A | 3.04 (1.11) | 3.68 (0.98) | 4.11 (0.83) |
| | B | 3.15 (1.35) | 3.56 (1.05) | 3.59 (1.15) |
| | C | 3.40 (1.19) | 3.68 (1.35) | 3.60 (1.61) |
| | D | 2.81 (1.50) | 3.27 (1.37) | 3.23 (1.24) |
| Naming | A | 2.36 (0.83) | 2.71 (0.54) | 2.86 (0.36) |
| | B | 2.30 (0.82) | 2.41 (0.80) | 2.52 (0.70) |
| | C | 2.48 (0.59) | 2.56 (0.51) | 2.68 (0.48) |
| | D | 2.35 (0.80) | 2.38 (0.70) | 2.50 (0.76) |
| Attention | A | 5.07 (0.98) | 5.36 (0.91) | 5.54 (0.84) |
| | B | 5.19 (1.18) | 5.52 (0.89) | 5.67 (0.83) |
| | C | 5.20 (1.00) | 5.44 (0.77) | 5.68 (0.69) |
| | D | 5.08 (1.09) | 5.15 (1.01) | 5.27 (1.00) |
| Abstraction | A | 1.18 (0.55) | 1.57 (0.57) | 1.68 (0.55) |
| | B | 1.30 (0.72) | 1.44 (0.51) | 1.56 (0.58) |
| | C | 1.48 (0.59) | 1.52 (0.51) | 1.64 (0.49) |
| | D | 1.04 (0.82) | 1.35 (0.63) | 1.35 (0.63) |
| Language | A | 1.71 (0.76) | 2.00 (0.90) | 2.07 (0.94) |
| | B | 2.00 (0.92) | 2.33 (0.73) | 2.26 (0.76) |
| | C | 1.60 (0.50) | 2.04 (0.79) | 2.08 (0.70) |
| | D | 1.69 (0.93) | 1.92 (1.02) | 1.88 (0.91) |
| Delayed recall | A | 1.86 (1.30) | 2.93 (1.56) | 3.82 (1.16) |
| | B | 1.41 (1.53) | 2.59 (1.55) | 3.00 (1.41) |
| | C | 1.32 (1.18) | 2.64 (1.60) | 3.04 (1.62) |
| | D | 1.54 (1.68) | 2.15 (1.59) | 2.08 (1.35) |
| Orientation | A | 5.71 (0.60) | 5.93 (0.26) | 5.96 (0.19) |
| | B | 5.63 (0.74) | 5.81 (0.48) | 5.81 (0.79) |
| | C | 5.76 (0.60) | 5.80 (0.58) | 5.88 (0.44) |
| | D | 5.62 (0.80) | 5.6 (0.85) | 5.62 (0.80) |

showed that the changes in the total MoCA score and the MoCA score for delayed recall were significantly different with the different treatment time and intervention methods.

The simple effects of group and time were further analyzed. The simple effect of time showed that the total score and the delayed recall score of groups A, B, and C changed significantly with the extension of treatment time ($P < .001$ for all), while the delayed recall score of group D showed no significant difference with the extension of treatment time ($P = .135$) (Table 4).

At baseline and week 4, the simple effect of group on the total MoCA score ($P = .646$ at baseline, and $P = .091$ after 4 weeks) and delayed recall score ($P = .537$ at baseline, and $P = .352$ after 4 weeks) was not significant, but the difference was significant after 8 weeks ($P < .001$) (Table 5).

Pairwise comparison showed that the total MoCA score and delayed recall score of group A increased sequentially at baseline, 4 weeks, and 8 weeks, and all reached the significance level ($P < .001$). The total MoCA score of group A was significantly different from that of group D at week 4 ($P < .05$). Compared with groups B and C, patients in group A had a significantly greater improvement in the MoCA score for delayed recall at week 8 ($P < .001$ for all). Compared with group D, patients in groups A, B, and C exhibited

**Figure 2.** Changes in the Total MoCA Score Among Groups Over Time

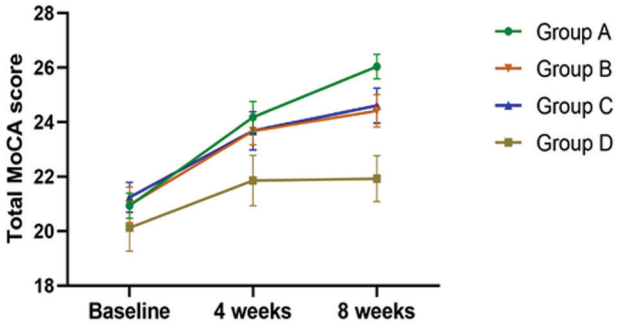



**Table 3.** Results of the Two-Way Repeated Measures ANOVA of the MoCA Scores of the Four Groups After 4 and 8 Weeks of Intervention

| Cognitive Function | Source | *F* value | *P* value | Partial eta-squared ($\eta p^2$) |
|---|---|---|---|---|
| Total MoCA score | Group | 3.284 | .024 | 0.088 |
| | Time | 84.027 | .000 | 0.452 |
| | Time.group | 3.114 | .010 | 0.084 |
| Visuospatial/ executive function | Group | 1.258 | .293 | 0.036 |
| | Time | 12.884 | .000 | 0.112 |
| | Time.group | 1.449 | .204 | 0.041 |
| Naming | Group | 1.152 | .332 | 0.033 |
| | Time | 10.275 | .000 | 0.092 |
| | Time.group | 1.106 | .359 | 0.032 |
| Attention | Group | 0.775 | .511 | 0.022 |
| | Time | 10.240 | .000 | 0.091 |
| | Time.group | 0.361 | .903 | 0.011 |
| Abstraction | Group | 1.750 | .161 | 0.049 |
| | Time | 15.384 | .000 | 0.131 |
| | Time.group | 1.247 | .290 | 0.035 |
| Language | Group | 1.349 | .263 | 0.038 |
| | Time | 12.457 | .000 | 0.109 |
| | Time.group | 0.411 | .871 | 0.012 |
| Delayed recall | Group | 2.873 | .040 | 0.078 |
| | Time | 53.787 | .000 | 0.345 |
| | Time.group | 2.574 | .024 | 0.070 |
| Orientation | Group | 1.483 | .224 | 0.042 |
| | Time | 2.085 | .138 | 0.020 |
| | Time.group | 0.391 | .847 | 0.011 |

**Table 4.** Simple Effect of Time on Total MoCA Score and MoCA Score for Delayed Recall

| Cognitive Function | Group | *F* value | *P* value | Partial eta-squared ($\eta p^2$) |
|---|---|---|---|---|
| Total MoCA score | A | 36.716 | .000 | 0.421 |
| | B | 15.704 | .000 | 0.237 |
| | C | 13.779 | .000 | 0.214 |
| | D | 4.665 | .012 | 0.085 |
| Delayed recall | A | 21.959 | .000 | 0.303 |
| | B | 13.418 | .000 | 0.210 |
| | C | 14.571 | .000 | 0.224 |
| | D | 2.039 | .135 | 0.039 |

**Table 5.** Simple Effect of Group on Total MoCA Score and MoCA Score for Delayed Recall

| Cognitive Function | Time | *F* value | *P* value | Partial eta-squared ($\eta p^2$) |
|---|---|---|---|---|
| Total MoCA score | Baseline | 0.554 | .646 | 0.016 |
| | Week 4 | 2.211 | .091 | 0.061 |
| | Week 8 | 7.125 | .000 | 0.173 |
| Delayed recall | Baseline | 0.729 | .537 | 0.021 |
| | Week 4 | 1.102 | .352 | 0.031 |
| | Week 8 | 7.094 | .000 | 0.173 |

**Table 6.** Total MMSE Score Among the Study Participants

| Group | Total MMSE score, mean (SD) | | |
|---|---|---|---|
| | Baseline | Week 4 | Week 8 |
| A | 26.04 (1.77) | 27.71 (1.74) | 28.71 (1.05) |
| B | 26.48 (1.42) | 27.59 (1.78) | 27.78 (1.50) |
| C | 26.00 (2.27) | 27.04 (1.43) | 27.64 (1.44) |
| D | 25.85 (2.85) | 26.23 (3.04) | 26.50 (3.13) |

**Table 7.** Results of the Two-Way Repeated Measures ANOVA of the Total MMSE Score of the Four Groups After 4 and 8 Weeks of Intervention

| Cognitive Function | Source | *F* value | *P* value | Partial eta-squared ($\eta p^2$) |
|---|---|---|---|---|
| Total MMSE score | Group | 2.755 | .046 | 0.075 |
| | Time | 42.073 | .000 | 0.292 |
| | Time.group | 3.193 | .007 | 0.086 |

**Table 8.** Simple Effect of Time on Total MMSE Score

| Cognitive Function | Group | *F* value | *P* value | Partial eta-squared ($\eta p^2$) |
|---|---|---|---|---|
| Total MMSE score | A | 26.593 | .000 | 0.345 |
| | B | 6.109 | .003 | 0.108 |
| | C | 8.874 | .000 | 0.149 |
| | D | 1.499 | .228 | 0.029 |

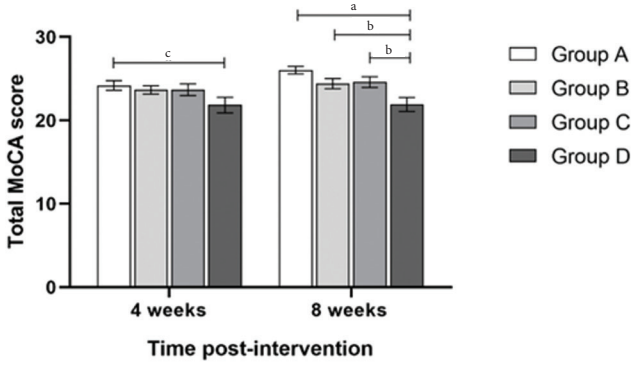
**Table 9.** Simple Effect of Group on Total MMSE Score

| Cognitive Function | Time | *F* value | *P* value | Partial eta-squared ($\eta p^2$) |
|---|---|---|---|---|
| Total MMSE score | Baseline | 0.436 | .728 | 0.013 |
| | Week 4 | 2.794 | .044 | 0.076 |
| | Week 8 | 5.905 | .001 | 0.148 |

**Table 10.** Comparison of Total Effective Rate Among the Four Groups [n (%)]

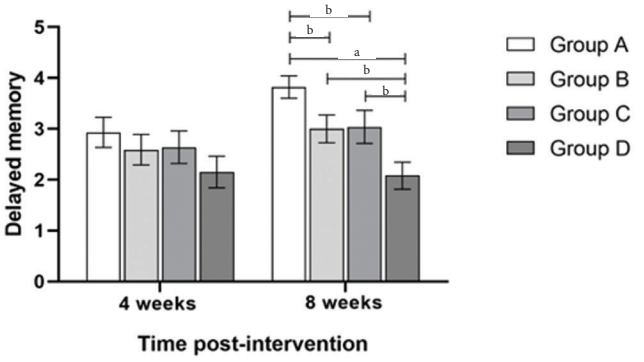
| Group | Markedly effective (n1) | Effective (n2) | Ineffective (n3) | Total effective rate (%) | *H* value | *P* value |
|---|---|---|---|---|---|---|
| A | 19 | 6 | 3 | 89.29% | 12.603 | .006 |
| B | 12 | 4 | 11 | 59.26% | | |
| C | 11 | 7 | 7 | 72.00% | | |
| D | 8 | 2 | 16 | 38.46% | | |

**Figure 3.** Differences in Total MoCA Score Among the Four Groups After Intervention




[a]$P \leq .001$
[b]$P \leq .01$
[c]$P \leq .05$)

**Figure 4.** Differences in MoCA Score for Delayed Recall Among the Four Groups After Intervention




[a]$P \leq .001$
[b]$P \leq .05$

**Figure 5.** Changes in the Total MMSE Score Among the Four Groups Over Time

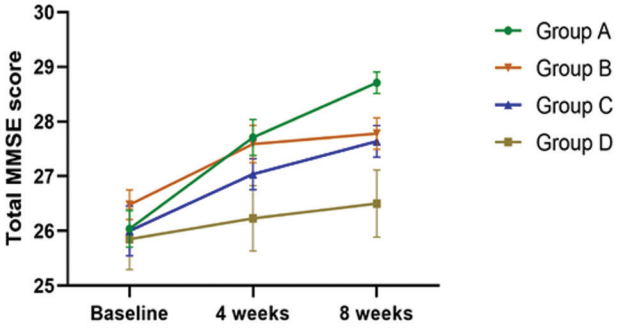
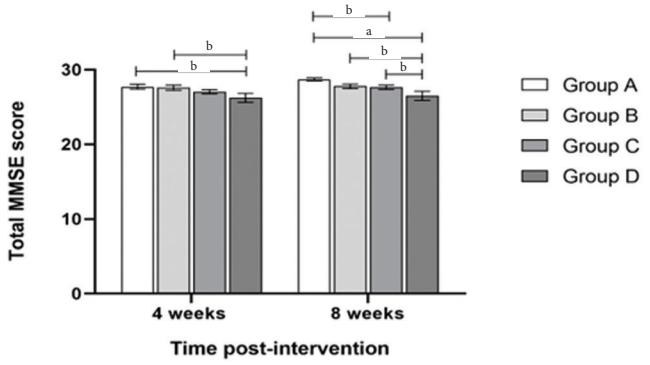


**Figure 6.** Differences in Total MMSE Score Among the Four Groups After Intervention




[a]$P \leq .001$
[b]$P \leq .05$

**Table 11.** Comparison of Adverse Events Among the Four Groups [n (%)]

| AEs | Group A (n = 30) | Group B (n = 30) | Group C (n = 30) | Group D (n = 30) | *P* value |
|---|---|---|---|---|---|
| Total, n (%) | 3 (10.00%) | 2 (6.67%) | 1 (3.33%) | 1 (3.33%) | .941 |
| Possibly related to treatment, n (%) | 2 (6.67%) | 2 (6.67%) | 1 (3.33%) | 1 (3.33%) | 1.000 |

significant improvement in the total MoCA score and MoCA score for delayed recall at week 8 ($P < .001$ for all). Figure 3 shows the differences in the total MoCA scores among the four groups, while Figure 4 shows the differences in the MoCA scores for delayed recall among the four groups.

**MMSE Score.** Table 6 and Figure 5 show the changes and trends in the total MMSE score of all four groups from baseline to week 8. The two-way repeated measures ANOVA revealed that the interactions between time and group had very significant effects on the total MMSE score ($P = .007$) (Table 7).

The simple effect of time showed that the total MMSE score of groups A, B, and C increased significantly with the treatment time ($P < .01$ for all), while no significant difference was found in group D ($P = .228$) (Table 8). The simple effect of group showed that there were no significant differences in the total MMSE score at baseline among the four groups ($P = .728$), indicating that the cognitive function was comparable between patients in different groups. The simple effect of group on MMSE total score was significant at week 4 ($P = .044$) and week 8 ($P = .001$) (Table 9).

Pairwise comparison showed that the total MMSE scores of groups A and B were significantly higher compared with that of group D at week 4 ($P < .05$ for all). After 8 weeks of treatment, the total MMSE score of group D was significantly lower compared to those of groups A, B, and C ($P < .05$ for all), and the total MMSE score of group A was significantly different from that of group C ($P = .046$, i.e., $P < .05$). Figure 6 shows the differences in the total MMSE scores among the four groups after intervention.

**Total Effective Rate.** The total effective rate was 89.29% in group A, 59.26% in group B, 72.00% in group C, and 38.46% in group D, and the differences among the four groups were significant ($P = .006$) (Table 10).

**Safety Evaluation.** Throughout the study, vital signs, physical examinations, and AEs were recorded at baseline, week 4, and week 8 visits. Laboratory tests and electrocardiograms were conducted at baseline and the final visit. Vital signs, physical examinations, laboratory tests, and electrocardiograms of the four groups were normal before and after treatment, and there were no clinically significant differences among the four groups.

No patients in the study experienced severe AEs; all AEs that were potentially related to treatment were mild. The most common AEs related to acupuncture were bruising and local pain, which occurred in one patient in group A and two patients in group B. One patient in group A had a toothache, which was unlikely to be related to interventions. Herb-related AEs occurred in groups A, C, and D after intervention; one patient from group C had mild nausea, and one patient from each groups A and D had mild diarrhea. There was no significant difference in the incidence of AEs among the four groups ($P > .05$) (Table 11). All participants recovered naturally from the AEs and continued to participate in the trial.

## DISCUSSION

MMSE and MoCA are the most commonly used scales to assess multiple cognitive domains and have good correlation and moderate agreement for detecting MCI.[28] MMSE is frequently used to assess general cognitive function, while MoCA is a comprehensive neuropsychological screening instrument.[29] Therefore, we selected both MoCA and MMSE as cognitive assessment tools in this trial.

The MoCA score was a measure of the study's primary outcome, and the results were analyzed for overall cognitive and specific cognitive domains. Acupuncture, YSG, and the combination of acupuncture and YSG all showed beneficial effects on cognitive function compared with sham acupuncture and placebo herbal treatment. Treatment with acupuncture or YSG alone improved cognitive function after 8 weeks and showed similar effects. In contrast, the combination of acupuncture and YSG had a more rapid effect, exhibiting cognitive improvement as early as week 4 of treatment, and the cognitive function of the patients improved to a greater extent at week 8 compared to that of the individual treatments. Furthermore, the combination of YSG and acupuncture was superior to acupuncture or YSG alone in improving overall cognition and delayed recall. The results

of the secondary index MMSE were consistent with the above results. In addition, the effective rate analysis also showed that acupuncture combined with YSG had the highest effective rate among the tested treatments. Taken together, when acupuncture and YSG were applied together, the individual components exhibited their respective advantages and played a synergistic role. Thus, multi-component, multi-target, and multi-link integrated therapy can restore cognitive function more quickly and effectively.

Pharmacological studies and clinical trials have confirmed that single herbs and compound TCM preparations can improve cognitive impairment and enhance memory function.[14,30,31] YSG improved the cognitive function of patients by exerting the effects of soothing the liver, regulating qi, nourishing the mind, and enlightening the brain. The herbs of YSG have a wide application prospect in the prevention and treatment of MCI, for example, Rhizoma Acori Graminei and Fructus Amomi are aromatic drugs with the effects of awakening the mind and intelligence and resolving dampness to move qi. Rhizoma Acori Graminei extract and its component α-asarone have anti-inflammatory and antioxidant effects, which can reduce murine hippocampal cell apoptosis.[32] Radix Salviae Miltiorrhiza, Rhizoma Cyperi, and Radix Curcumae are used together to regulate qi and relieve stagnation, promote blood circulation, and remove blood stasis. Rhizoma Cyperi extract increases neurogenesis, mitochondrial quality, and memory in a beta-amyloid rat model of Alzheimer's disease.[33] Rhizoma Cyperi extract has also been shown to increase the expression of brain-derived nerve growth factor (BDNF) and protect nerve cells through antioxidant and anti-apoptotic mechanisms.[34] Radix Salviae Miltiorrhiza extract Tanshinone IIA can reduce the neuroinflammatory response, Aβ deposition, and cognitive impairment.[35] Cortex Cinnamomi is a natural flavor and FDA-approved drug, and along with its metabolite sodium benzoate, Cortex Cinnamomi was shown to improve memory and learning ability in poor-learning mice by enhancing synaptic plasticity.[36] Flavonoids extracted from Radix Scutellariae have been reported to attenuate memory impairment and neuronal damage by regulating oxidative stress.[37] Stilbene glucoside, the active component of Caulis Polygoni Multiflori, was reported to promote the self-renewal and neuron-like differentiation of neural stem cells in AD mouse embryos.[38] Another study found that (-)-Syringaresinol extracted from Cortex Albizziae plays an anti-neuroinflammatory role by inhibiting NF-κB activation, regulating microglial polarization, and interacting with Erβ.[39] Extracts of Radix Aucklandiae exhibited liver protective and anti-inflammatory effects.[40] In addition, Radix Glycyrrhizae was used to harmonize various herbs.

Acupuncture is a representative non-drug therapy in traditional Chinese medicine, which is easy to operate, widely applicable, and safe. A meta-analysis showed that acupuncture improved cognitive function in older adults with MCI, suggesting that acupuncture is an effective alternative and complementary method.[41] Many studies have proved that acupuncture therapy can improve cognitive function through anti-neuroinflammation activity, inhibition of oxidative stress, regulation of brain function and neuroplasticity, and promotion of the autophagy-lysosomal pathway.[35,42-47] Data mining analysis revealed that GV20, EX-HN1, HT7, ST36, PC6, GB20, KI3, GV14, BL23, SP6, GV24, and LR3 are commonly used acupoints for AD treatment.[48] One study indicated that acupuncture at Tiaoshen Yizhi acupoints (EX-HN1, EX-HN3, PC6, KI3, ST40, LR3) can regulate brain networks by increasing connectivity between cognition-related regions, thereby improving cognitive function in patients with MCI.[49] Study reports that electroacupuncture stimulation at GV20 and ST36 points has a neuroprotective effect on rats with cerebral ischemia-reperfusion injury.[50] Furthermore, electroacupuncture stimulation of GV24 and GV20 acupoints may improve the learning and memory ability of rats by activating the PI3K/Akt signaling pathway.[51] Studies have also shown that acupuncture at LR3 activates brain functional networks involved in cognition.[52] In our study, most of the acupoints were selected from Governor Vessel and cooperated with the acupoints of the head, face, and distal limbs to achieve the effect of improving cognition.

The combination of acupuncture and YSG may show better efficacy by superimposing their mechanisms of action.

In terms of safety evaluation, no serious AEs were reported during the trial. The AEs related to the interventions were mild and patients recovered naturally, indicating that acupuncture and YSG are safe treatment methods.

There is currently no treatment for MCI, but TCM seems to be a promising option. The application of TCM therapies in elderly patients with MCI is urgently needed to prevent the conversion to dementia and actively cope with the MCI burden in the ageing population.[53] Well-designed, randomized controlled trials of acupuncture combined with Traditional Chinese medicine herb (TCMH) for MCI are currently lacking. This study evaluated the efficacy of acupuncture and YSG in the treatment of older adults with MCI and may further guide the treatment of MCI. However, the study has several limitations. First, it is difficult for the relatively small sample size to accurately represent the overall situation of the study object, which may affect the efficacy of the test results. Second, acupuncture treatment twice a week might not have been sufficient to be effective in improving cognitive functions. In addition, the 8-week treatment period is relatively short and there is a lack of follow-up evaluation after treatment, thus the durability of the effect is not established. Third, the main evaluation index of this study is subjective and susceptible to reporting bias. Future research should focus on these limitations and formulate an appropriate research protocol.

## CONCLUSIONS

The results of this multicenter, randomized controlled trial confirmed that acupuncture and YSG can separately and effectively improve cognitive function with good tolerance and safety. Moreover, the synergistic effect of acupuncture

and YSG enhances the curative effect and the effect starts earlier. The study suggests that both acupuncture and YSG are effective and safe clinical treatments for MCI, but the combination of acupuncture and YSG is a better treatment option based on more rapid and effective cognitive improvement. Findings from the study provide useful information for evaluating the role of TCM therapy in MCI treatment. Further studies should increase the evaluation of objective outcomes, increase the treatment period and follow-up period, and confirm efficacy and safety through large-scale clinical trials.

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## DATA AVAILABILITY

The data used to support the findings of this study are included in the article. The data presented in the current study are available from the corresponding author upon reasonable request.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This trial was reviewed and approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (2017SHL-KY-05). Participants were briefed on the study's purpose, procedures, possible risks, and informed consent. All participants provided written informed consent to participate in this study.

## TRIAL REGISTRATION

This trial was registered with ChiCTR-INR-17011569 on 5 June 2017.

## AUTHOR DISCLOSURE STATEMENT

Nana Li and Ou Li are co-first authors. The funders only provided financial support and had no role in the study design, patient recruitment, data collection, statistical analysis, or manuscript preparation. The authors declare that there are no conflicts of interest regarding the publication of this article.

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Nana Li, Ou Li, Zhongwei Sha, and Jian Xu were responsible for the design of this trial and coordinated personnel and facilities from all aspects. Jian Xu participated and supervised the whole trial and was responsible for the integrity of the data and the accuracy of the data analysis. Nana Li, Ou Li, and Zhongwei Sha drafted and revised the manuscript. Zhimin Li, Yixia Li, and Jie Zhang were responsible for recruiting patients. Data were collected by Yuxia Wang and Zhenghao Zhao. Zhimin Li provided funding and ethical approval. Statistical analysis was conducted by Nana Li and Yuxia Wang. Critical revision of the manuscript was performed by Jian Xu and Shifen Xu. All authors contributed to the revision of the study protocol and approved the final manuscript. The authors are very grateful to all participants for their cooperation in the study. The authors also appreciate the contributions of the acupuncturists and researchers at each center and thank all the funders for their support.

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