

Effects of exercise interventions for specific cognitive domains in old adults with mild cognitive impairment

A meta-analysis and subgroup analysis of randomized controlled trials

Xiang-Lian Zhou, MD, RN^a, Li-Na Wang, PhD, RN^{a,*}, Jie Wang, MD, RN^a, Ling Zhou, MD^b, Xin-Hua Shen, MD^c

Abstract

Objective: To conduct a meta-analysis and subgroup analysis investigating the effects of exercise on mild cognitive impairment (MCI) patients across specific cognitive domain outcomes. We also analyzed and identified the level of influence of exercise interventions on specific cognitive domains.

Methods: MEDLINE, EMBASE, Cochrane Library, Web of Science, CNKI, the Wan Fang Database, and CBM were searched from inception to April 2018. Randomized controlled trials of exercise interventions in MCI patients older than 55 years, with an outcome measure of cognitive function were included.

Results: Eleven studies with sufficient data met the inclusion criteria for the meta-analysis. Exercise interventions significantly improved general function (g mini-mental state examination Montreal cognitive assessment = 0.32, 95% CI 0.1 to 0.54, $P = .005$ and g Alzheimer disease assessment scale-cognition = -0.45, 95% CI -0.82 to -0.08, $P = .02$); executive functions (g digit span forward test, digit span backward test, digit span forward test _B, stroop test-A, stroop test-B = 0.66, 95% CI 0.17 to 1.15, $P = .008$); memory (g Wechsler memory scale immediate recall and Wechsler memory scale delayed recall = 0.37, 95% CI 0.15 to 0.60, $P = .001$); language ability (g category verbal fluency test and letter verbal fluency test = 0.55, 95% CI 0.22 to 0.89, $P = .001$); and visuospatial ability (g block design score = 0.38, 95% CI 0.03 to 0.72, $P = .03$). However, the improvement exercise conferred on the trail-making test part B-A was not statistically significant (g trail-making test part B-A = -0.25, 95% CI -0.88 to 0.39, $P = .45$). The preliminary ranking of the effect on the overall effect was as follows: $Z_{\text{language ability}} > Z_{\text{executive functions}} > Z_{\text{memory}} > Z_{\text{visuospatial ability}}$.

Conclusion: Exercise improves performance in the 5 cognitive domains. Across cognitive domains, language ability was the domain most affected by exercise. Besides, the kind of ranking (Z value) provides a new perspective for community health care workers to prescribe targeted exercise interventions for MCI patients.

PROSPERO registration number: CRD42018093902.

Abbreviations: ADAS-cog = Alzheimer disease assessment scale-cognition, BDS = block design score, CI = the 95% confidence interval, DSB = digit span backward test, DSF = digit span forward test, MCI = mild cognitive impairment, MMSE = mini-mental state examination, MoCA = Montreal cognitive assessment, PEDro = physiotherapy evidence database, RCTs = randomized controlled trials, SMD = standardized mean difference, TMT B-A = trail-making test part B-A.

Keywords: aged, cognitive, exercise, meta-analysis, mild cognitive impairment

Editor: Peipeng Liang.

LNW author contributed equally to this work and should be considered co-first author.

All analyses were based on previous published studies in this study, so there is no ethical approval and patient consent are required.

The authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article.

^a School of Nursing, Medical College of Huzhou University, Zhejiang Province, ^b Department of Gynecology of Traditional Chinese Medicine, Changhai Hospital, Naval Medical University, Shanghai City, ^c Department of psychosomatic diseases, Huzhou Third People's Hospital, Zhejiang Province, China.

* Correspondence: Li-Na Wang, School of Nursing, Medical College of Huzhou University, Zhejiang Province, China, Postal: 313000 (e-mail: aring2000@163.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

How to cite this article: Zhou XL, Wang LN, Wang J, Zhou L, Shen XH. Effects of exercise interventions for specific cognitive domains in old adults with mild cognitive impairment: A meta-analysis and subgroup analysis of randomized controlled trials. *Medicine* 2020;99:31(e20105).

Received: 21 April 2019 / Received in final form: 24 November 2019 / Accepted: 2 April 2020

<http://dx.doi.org/10.1097/MD.00000000000020105>

1. Introduction

The 2018 World Alzheimer Report reported that 50 million people live with dementia worldwide. With the accelerating trend of population ageing, that number is expected to increase to more than 152 million by 2050. Dementia also has a huge economic impact. The total estimated worldwide cost of dementia in 2018 is US\$1 trillion, and this figure will rise to US\$ 2 trillion by 2030.^[1] Dementia is a syndrome in which there is deterioration in memory, thinking, behaviour and the ability to perform everyday activities.^[2] The quality of daily life and activities for those living with dementia are seriously affected.^[3] However, there is as yet no really satisfactory treatment to delay the progress of dementia.

At present, for the prevention and treatment strategy of dementia, the basic research and clinical research have turned to the preclinical stage—the mild cognitive impairment (MCI) domain. MCI is an intermediate stage between normal brain ageing and dementia characterised by an impairment in memory and/or other cognitive function.^[4] It has been reported that old people with MCI are at increased risk of conversion to develop dementia, with progression rates of 16% to 20% per year, which is higher than 1% to 2% in cognitively normal people at the same age.^[5] On average, about 20% to 24% of subjects with MCI will reverse to normal cognition over time.^[6,7] Hence, MCI is a progressive, high-risk and uncertain stage. It is particularly important for the prevention of dementia.

At present, treatment of MCI mainly includes pharmacological treatments and nonpharmacological therapies. The American Academy of Neurology plainly recommend against use of cholinesterase inhibitors in MCI.^[8] Evidence in the guidelines, and in systematic reviews, clearly shows that cholinesterase inhibitors have no reliable benefit on cognition and do not reduce progression to dementia.^[9–11] In addition, Patients complained about side effects, including gastrointestinal symptoms and cardiac concern.^[12] At present, nonpharmacological therapies have been validated and recommended for patients with MCI.^[13–15]

As 1 of the nonpharmacological therapeutic modalities, exercise intervention plays an increasingly important role in prevention, rehabilitation and health medicine over the past 2 decades. It has been proposed that exercise promotes brain remodelling, including increases brain volume, improves synaptic plasticity,^[16,17] triggers several molecular and cellular cascades,^[18] facilitates growth, development, function, and survival of neurons,^[19,20] upregulate of hippocampal brain derived neurotrophic factor levels, reduce accumulation of reactive oxygen species, which promote brain health over time and delay the onset of cognitive decline in aging and dementia.^[21,22] Indeed, evidence from neuroimaging works, cross-sectional and epidemiological, which consistently find exercise to be beneficial for cognitive function in the elderly.^[16,23–25] However, the effects of the particular exercise intervention methods, the exercise intensity and the duration of exercise intervention on the functioning in various cognitive domains are different. In terms of exercise intervention method, combining aerobic exercise with resistance training and flexibility training may improve performance on executive tasks, including working memory, processing speed and attention more efficiently than 1 form of exercise by itself.^[26] In terms of the intensity of the exercise intervention, compared to stretching exercises with a heart rate reserve at or below 50%, exercise with a heart rate reserve of 75% to 85% can significantly improve executive control processes such as cognitive flexibility, multitasking, selective attention, and

information processing efficiency.^[27] In terms of the duration of exercise interventions, a randomized controlled trial shown 6 months of aerobic exercise significantly improved learning performance and verbal memory.^[28] Lam et al reported that weekly engagement in physical activity for twelve months could improve global cognitive ability, delayed recall and verbal fluency with time ($P < .05$) in people with MCI.^[29]

From the studies presented above, there were conflicting results on the specific cognitive domains affected, with some studies reporting cognitive gains from exercise interventions in memory function or verbal fluency,^[28,29] and other studies reporting effects on executive function.^[26,27] The changes in the emphasis on or trends in different cognitive domains in the process of developing exercise interventions needs to be further explored. Up until now, there has been no published literature on examining a subgroup analysis of the effects of exercise interventions on different cognitive domains in the elderly with MCI. Based on the hypothesis that exercise interventions may have some regular, generalized effects on various cognitive domains of the brain, the aim of this study is to explore the influence of exercise interventions on specific cognitive domains in the elderly with MCI, and produce a preliminary ranking of the degree or magnitude of the influence of certain exercise interventions on various cognitive domains. The study contributed to revealing the different effects of exercise interventions on improving various cognitive functions.

2. Methods and analysis

2.1. Methods

The meta-analysis was performed and reported in accordance with the PRISMA guidelines and the checklist was completed.^[30] PROSPERO registration number: CRD42018093902.

2.2. Search strategy

Seven electronic databases were searched (MEDLINE, EMBASE, Cochrane Library, Web of Science (Science and Social Science Citation Index), China National Knowledge Infrastructure (CNKI), the Wan Fang Database, and CBM (China Biology Medicine) from inception to April 2018 were searched. The study given a search strategy example from Cochrane Library in Supplementary Appendix Table 1, Available at: <http://links.lww.com/MD/E233>. The search strategy was modified as necessary for other databases. There was no language restriction.

Relevant randomized controlled trials (RCTs) and reviews for additional studies were hand searched for further eligible studies. Journals containing the highest numbers of included studies were hand searched for recent potentially eligible publications (≤ 12 months). In addition, the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov was checked to identify planned, ongoing or unpublished trials.

2.3. study inclusion criteria and exclusion criteria

Inclusion criteria were:

- (1) Studies were RCTs of exercise intervention (aerobic, resistance, or multicomponent exercise);
- (2) Participants were MCI patients based on the adaptations of criteria suggested by Petersen that are commonly used to identify ‘mild cognitive impairment’^[31,32] and age 55 years or older;

- (3) Outcomes which were general cognition, executive functions, memory, language ability, and visuospatial ability were considered for inclusion;
- (4) The control interventions could be sham (such as stretching activities), placebo or no treatment or health education; and
- (5) For patients with MCI, a trial lasting for 12 weeks usually shows cognitive enhancement rather than maintenance of cognitive function.^[33]

Therefore, all trials that reported the results after randomization for at least 12 weeks or longer were included in our study. There was no minimum duration of follow up. There were no restrictions on the location of the intervention.

Participants were excluded:

- (1) They took medications for cognition, neurological conditions (eg, stroke, multiple sclerosis, Parkinson disease), chronic or acute conditions, or depressive symptoms that would preclude exercise;
- (2) They engaged in regular exercise (≥ 30 min/d, ≥ 3 d/wk);
- (3) They had medical histories that included unstable cardiac disease, significant cerebrovascular disease, musculoskeletal impairment, etc; and
- (4) They had other medical conditions with significant psychiatric or metabolic sequelae.

Article screening, data extraction and quality recorded were carried out by 2 authors independently (XLZ and JW). Discrepancies were resolved by discussion or by consulting the senior authors (LNW, LZ and XHS) (see Appendix for detail). Duplicates and manage records were omitted using EndNote software (V.X7.8).^[34] Articles that were not available were requested from the authors. The detailed information of each included study was extracted using a predetermined data form and includes the following general information, details of study, design; study subjects, intervention characteristics, outcome.

2.4. Quality assessment and data analysis

The quality of included studies was evaluated by 2 reviewers (X.L.Z and J.W.) independently using a modified assessment form: Cochrane Handbook for Systematic Reviews of Interventions^[35] and another 3 items from physiotherapy evidence database (PEDro) scale were added, including “the type of statistical analyses used (true intention-to-treat versus other)”, “eligibility criteria”, and “baseline comparability”.^[36] The ‘risks of biases’ summary were presented graphically.

All analyses were conducted with Review Manager software (RevMan 5.3.). Using a random effects model and the standardized mean difference (SMD) and the 95% confidence interval (CI) to analyze the outcomes.^[37] We set $P < .05$ as statistically significant. For results that were not presented as SMD in the original meta-analysis, RevMan5.3 was used to convert the outcomes to SMD to allow visual comparison of the results in a forest plot. If data were insufficient for conversion, data were extracted from original studies and processed as instructed by the Cochrane Collaboration.^[38]

Heterogeneity was assessed with the I^2 statistic and Q statistic for each analysis. Subgroup analysis and investigation of heterogeneity:

A subgroup analysis for specific cognitive domains played an important role in ascertaining the most sensitive cognitive domain that has noticeable improvements by exercise intervention. General cognition and 4 specific cognitive domains were

analysed, including executive functions, memory, language ability, and visuospatial ability.

Subgroup analyses was used to explore possible sources of heterogeneity. We tested the heterogeneity by considering the variability in participant factors (eg, age, sex) and trial factors (eg, follow-up period, intervention type, type of control group).

3. Results

3.1. Descriptive results

3.1.1. Qualified studies. The search process is shown in the PRISMA flow diagram in Figure 1. A total of 5676 potentially relevant records were obtained from MEDLINE (1388 records), EMBASE (1360 records), the Cochrane Library (1016 records), Web of Science (1468 records), China National Knowledge Infrastructure (113 records), the Wan Fang Database (220 records), China Biology Medicine (111 records), and 485 records were obtained from other resources. Of these, 311 records were removed as duplicates, and 5809 records were excluded following screening of titles and abstracts. In total, 41 full-text records were assessed. Of these, 9 records did not provide sufficient information regarding the diagnosis of mild cognitive impairment, 2 records did not examine an intervention of interest, 4 records outcomes did not target improving cognitive impairment or maintaining cognitive function, 5 records were non-RCTs, 8 records were protocols/short articles, and 2 records were excluded because of insufficient data. Finally, eleven studies were included.^[39–49]

3.1.2. Study characteristics. The characteristics of each eligible study are summarized in Table 1. The characteristics of invention about each eligible study are summarized in Supplementary Appendix Table 2, <http://links.lww.com/MD/E234>. The studies were from 7 countries. Participates in study meet MCI diagnostic criteria. Intervention methods of all studies is physical exercise. The control groups are health education, no-exercise treatment (recreational activities or memory enhancement training program), or usual (maintained current lifestyle or used a usual stretching and toning exercise group). Primary outcomes are general cognitive performance, executive functions, memory, language ability and visuospatial ability. The intervention durations ranged between 12 weeks and 12 months. There were 357 participants in the experimental group and 319 in the control group. The sample sizes of the eligible studies ranged from 22 to 100.

3.2. Methodological quality

Two authors independently assess the risk of bias using the approach recommended by Cochrane Handbook for Systematic Reviews and PEDro. We described what was reported to have happened in each study for each domain of risk of bias and provided the rationale for the judgement of whether this domain was at low, high or unclear risk of bias. All trials were considered to be at low risk of bias regarding the MCI diagnostic criteria and provided detailed reasons justifying use of this term. Ten records^[39–42,44,45–49] provided detailed reasons for similar baseline values, but 1 study^[43] was unclear about this term. We considered 8 trials^[39–42,46–48] to be at low risk of bias for sequence generation. We judged the remaining 3 trials^[43–45] to be at unclear risk of bias for sequence generation. Four trials^[39,41,45,48] did not describe allocation concealment. The remaining 7 trials^[40,42–44,46,47,49] described relevant methods. In

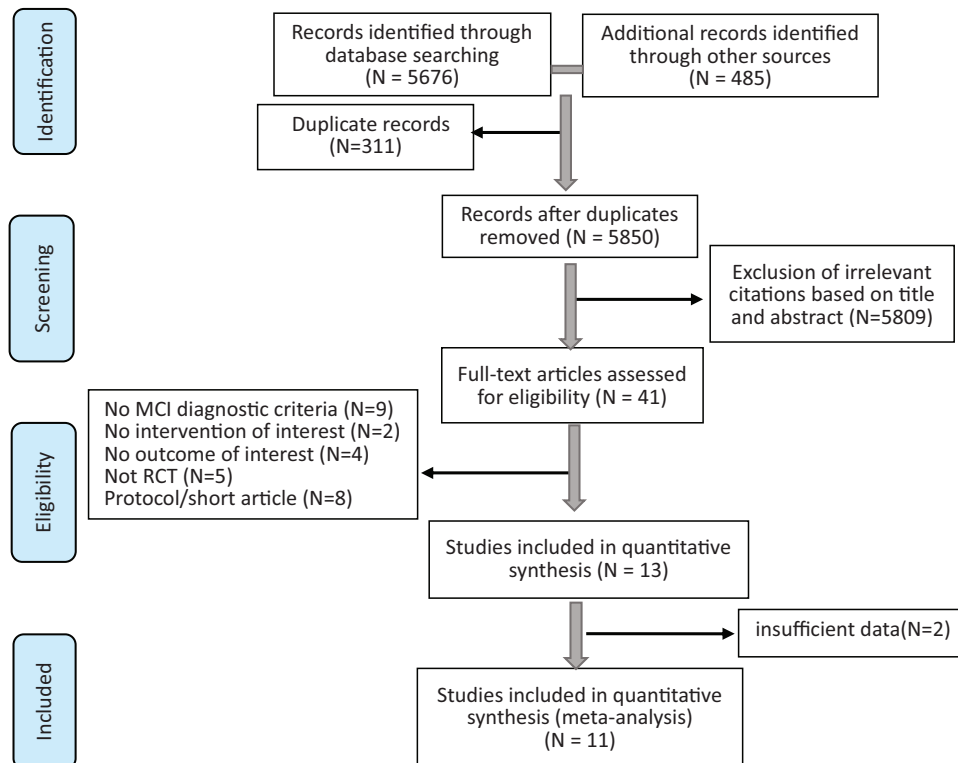


Figure 1. Flow diagram for study selection process used in this meta-analysis.

all eleven included trials, blinding of the participants and trainers was not feasible. This was unlikely to introduce bias in trainers, so we considered all eleven trials to be at low risk of bias for blinding trainers. This may have introduced bias in participants, so all eleven trials were judged to be at high risk of blinding of the participants. We judged 2 trials^[43,44] to be at high risk of bias for blinding of the assessors for the cognitive outcomes because methods regarding the assessment of cognition were not provided. The other 9 trials^[39–42,45–49] provided detailed information for this process, so we considered the studies to have a low risk of bias. Four trials^[40,42,44,49] were judged to be at high risk of bias for addressing incomplete data, based on the dropout being more than 15%, which we considered incomplete data.^[36] Another 7 trials^[39,41,43,45–48] were judged to be at low risk of bias for this item. Three trials^[42,43,45] were judged to be at unclear risk of bias for selective reporting since predetermined outcomes were not reported. All other 8 trials^[39–41,44,46–49] were judged to be at low risk of bias in this respect. Seven trials^[39,41,43,45–47,49] reported dropouts per group and analyzed using ITT (intention-to-treat) analysis principles. The other 4 trials^[40,42,44,48] were judged to be at high risk of bias for this item since they reported dropouts but either lacked information on the group assignment of these dropouts, on the ITT analysis or both. No other apparent bias was identified in each of the studies. According to the criterion in the Modified Assessment Form, 5 studies reported high-quality research, and 6 studies reported mid-quality research (see Table 2).

According to Cochrane Handbook for Systematic Reviews of Interventions: “the funnel plot asymmetry test can only be used when the meta-analysis is included in at least 10 studies, because if the inclusion of the study is too small, the test performance will

be too low, and the opportunity and true asymmetry will not be distinguished. Owing to the limited number (below 10) of studies included in each outcome analysis, the meta-analysis can’t be done.” the funnel plot asymmetry test can only be used when the meta-analysis is included in at least 10 studies, because if the inclusion of the study is too small, the test performance will be too low, and the opportunity and true asymmetry will not be distinguished. Owing to the limited number (below 10) of studies included in each outcome analysis, the meta-analysis can’t be done. so, publication bias was not assessed.

3.3. Data Extraction

3.3.1. Posttest effects of exercise interventions on cognitive function. The effects of all subgroup meta-analyses conducted are presented in Figure 2A~2G.

3.3.2. General cognition.

- (1) Mini-mental state examination (MMSE) and Montreal cognitive assessment (MoCA). Using a random effects model, the meta-analysis of 6 studies^[39,40,43,45,48,49] with 355 patients shown that exercise could have improved the MMSE and MoCA scores ($g=0.32$, 95% CI 0.1 to 0.54, $z=2.8$, $P=.005$, Fig. 2-A). There was low heterogeneity among studies ($I^2=0\%$).
- (2) Alzheimer disease assessment scale-cognition (ADAS-cog). Two studies^[41,48] were included to estimate the effect of exercise on general cognition assessed with the ADAS-cog. The exercise group outperformed the control group in terms of improving general cognition using a random effects model ($g=-0.45$, 95% CI -0.82 to -0.08, $z=2.38$, $P=.02$, Fig. 2-A). Heterogeneity was low between studies ($I^2=20\%$).

Table 1**The characteristics of eligible studies.**

Author, yr	Country	Inclusion criteria	Type (Inclusion N/ Analysis N)	Age, yr (SD)	N (% F)	Duration (Follow up)	Cognitive function outcome	Registry number
[Sungkarat 2017] ^[46]	Thailand	Petersen's criteria (a-MCI 2004), ≥60 yrs, MMSE≥24 scores, MoCA≤26 scores, comprehended instructions.	1.Taiji (33/30); 2.Health education (33/29)	68.3 (6.7); 67.5 (7.3)	31 (94); 26 (79)	15 (no) wk	1.Visuospatial ability—BDS; 2. Executive functions—DSF-B, TMT B-A.	No
[Suzuki 2013] ^[48]	Japan	≥65years, CRD=0.5 scores, neuropsychological tests, Petersen's criteria-2004.	1. Multicomponent exercise (50/47); 2. Health education (50/45)	74.8 (7.4); 75.8 (6.1)	25 (50); 24 (48)	24 (no) wk	1.General cognitive function—MMSE, ADAS-cog; 2. Memory function—WMSLM-I and II (immediate recall, delay recall).	UMIN-CTR UMIN000003662
[Takao 2012] ^[39]	Japan	≥65yr, CDR=0.5 scores, neuroimaging evidence, Petersen's criteria-2004, lower memory in WMS-LM II.	1.Multicomponent exercise (25/24); 2. Health education (25/23)	75.3 (7.5); 76.8 (6.8)	12 (48); 11 (44)	24 (48) wk	1. General cognitive function—MMSE; 2. Memory function—WMSLM-I and II (immediate recall, delay recall); 3. Language ability—LVFT, CVFT; 5. Executive functions—ST-A.	No
[Hong 2017] ^[43]	Korea	K-MoCA<24 scores, Peterson1999, No dementia (DSM-IV-TR).	1. Resistance exercises with an elastic band (10/8); 2. Maintain current lifestyle (12/11)	77.9 (3.3); 75.9 (4.7)	7 (70); 9 (75)	12 (no) wk	1. Language ability—LVFT, CVFT; 2. Executive functions-ST-A, ST-B, DSF, DSB; 4. General cognitive function—K-MoCA.	IRB No. 1309/001-009
[Chun 2017] ^[40]	Canada	MoCA<26, MMSE>20, clinically diagnosed with mild SIVCI.	1.Aerobic training (35/10); 2.Usual care and health education (35/11)	71.7 (8.8); 72.3 (8.8)	6 (60); 7 (64)	24 (no) wk	1.General cognitive function—MMSE, MoCA.	NCT01027858
[Kang; 2014] ^[44]	Korea	20≤MMSE-K<24, MoCA-K<23.	1.High-Speed Elastic Band Training (20/14); 2. Muscle-stretching exercise (19/7)	75.0 (3.5); 78.0 (2.8)	None	12 (no) wk	1. Executive functions—DSF, DSB, ST-A, ST-B.	SNUIRB No. 1305/001-009
[Teresa 2016] ^[41]	Canada	Neuroimaging evidence, neurologic signs, MoCA<26 scores, MMSE≥20scores, caregiver/family Member confirmed cognitive decline	1. Aerobic exercise training (36/33); 2. Usual care plus education (35/25)	74.8 (8.4); 73.7 (8.3)	19 (54); 17 (49)	24 (48) wk	1. General cognitive function—ADAS-Cog; 2. Executive functions—TMT B-A.	NCT01027858
[Varela 2012] ^[49]	Spain	MCI clinical diagnosis-the Spanish Society of Geriatrics and Gerontology, ≥65years, stand and walk for 30 min without shortness of breath, Resident in study area.	1. Aerobic exercise with 40%intensity levels (27/17); 2. Aerobic exercise with 60%intensity levels (26/15); 3. Recreational activities (15/15)	79.2 (10.1); 76.4 (11.4); 79.4 (6.7)	None	12 (24) wk	1. General cognitive function—MMSE	None
[Eyre 2017] ^[42]	USA	≥55years, subjective memory complaints, CDR=0.5scores, comprehended instructions.	1. Yoga training (38/26); 2. Memory enhancement training (41/28)	68.1 (8.7); 67.6 (8.0)	25 (66); 27 (66)	12 (24) wk	1.Memory function-The WMSLM-I and II (immediate recall, delay recall)	NCT01983930
[Sungkarat 2018] ^[47]	Thailand	Petersen-aMCI (2004), MMSE≥24, MoCA<26, comprehended instructions.	1. Tai Chi (33/29); 2. Health education (33/27)	68.3 (6.7); 67.5 (7.3)	31 (94); 26 (77)	24 (none) wk	1.Memory function-WMSLM-II (delayed recall); 2. Visuospatial ability-BDS; 3. Excutive functions-DSF-B, TMT B-A.	NCT02552329
[Nascimento 2014] ^[45]	Brazil	Neuropsychological screening, Petersen2004, subjects or caregivers described cognitive deficits in the participants.	1. Multimodal physical exercise (24/22); 2. Maintain current lifestyle (21/18)	67.5 (6.0); 67.5 (4.9)	17 (71); 15 (71)	16 (none) wk	1. General cognitive function-MoCA	Protocol #7143

BDS = the block design score; CVFT = category verbal fluency test; DSC = digit-symbol coding; DSF-B = the digit span forward-backward; K-MoCA = the Korean version of Montreal cognitive assessment; LVFT = letter verbal fluency test; MMSE = mini-mental state examination; MoCA = Montreal cognitive assessment; ST-A = stoop test A; ST-B = stoop test B; TMT B-A = trail-making test part B-A.

Table 2
Quality assessment of eligible studies.

Author, year	MCI diagnostic criteria	similar baseline	Sequence generation	Allocation concealment	Blinding of participants	Blinding of therapists	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	treatment as allocated or ITT	Other sources of bias	Total (scores)
[Sungkarat 2017] ^[46]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10/11
[Suzuki 2013] ^[48]	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	8/11
[Takao 2012] ^[39]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	9/11
[Hong 2017] ^[43]	Y	N	N	Y	N	Y	N	Y	N	Y	Y	6/11
[Chun 2017] ^[40]	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	8/11
[Kang 2014] ^[44]	Y	Y	N	Y	N	Y	N	N	Y	N	Y	6/11
[Teresa 2016] ^[41]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	9/11
[Varela 2012] ^[49]	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	9/11
[Eyre 2017] ^[42]	Y	Y	Y	Y	N	Y	Y	N	N	N	Y	7/11
[Sungkarat 2018] ^[47]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10/11
[Nascimento2014] ^[45]	Y	Y	N	N	N	Y	Y	Y	N	Y	Y	7/11

Modified assessment form. Y = yes (explicitly described in article and verified by communication); N = no (absent or unclear). Y scores 1, N scores 0. Three quality level: high (total scores 9–11), moderate (total scores 6–8), low (total scores 0–5).

3.3.3. Executive functions.

- (1) Digit span forward test (DSF), Digit span backward test (DSB), DSF/Backward, Stroop Test A, stroop test B. Five studies^[39,43,44,46,47] with 243 patients were included to assess the effects of exercise on executive functions. Exercise could have improved executive functions ($g=0.66$, 95% CI 0.17 to 1.15, $z=2.26$, $P=.008$, Fig. 2-B). Heterogeneity among the 5 exercise versus nonexercised control studies was significant ($I^2=77\%$).
- (2) Trail-Making Test Part B–A (TMT B-A). Three studies^[41,46,47] with 203 patients were included to assess the effect of exercise on executive function. Exercise had a nonsignificant positive effect on executive function assessed using a random effects model ($g=-0.25$, 95% CI -0.88 to 0.39, $z=0.76$, $P=.45$, Fig. 2-B). High heterogeneity between studies ($I^2=79\%$).

3.3.4. Memory. Wechsler memory scale immediate recall, Wechsler memory scale delayed recall. The meta-analysis of 4 studies^[39,43,47,48] with 295 patients who were suitable for inclusion indicated that exercise had a significant effect on memory ($g=0.37$, 95% CI 0.15 to 0.60, $z=3.21$, $P=.001$, Fig. 2-C). There was low heterogeneity between studies ($I^2=33\%$). One study^[43] used the Rey 15-Item memory test as an outcome measure; therefore, no meta-analyses could be conducted.

3.3.5. Language ability. Category Verbal Fluency Test, letter verbal fluency test. Two studies^[39,43] with 72 patients were included to assess the effect of exercise on language ability. Exercise could have improved language ability ($g=0.55$, 95% CI 0.22 to 0.89, $z=3.23$, $P=.001$, Fig. 2-D). There was no heterogeneity between studies ($I^2=0\%$).

3.3.6. Visuospatial ability. Block design score (BDS). The meta-analysis of 2 studies^[46,47] with 132 patients who were suitable for inclusion indicated that exercise had a significant effect on the visuospatial ability ($g=0.38$, 95% CI 0.03 to 0.72, $z=2.15$, $P=0.03$, Fig. 2-E). There was low heterogeneity between studies ($I^2=0\%$).

3.3.7. Overall effect results. The Z (P value) overall effect results of all meta-analyses conducted are presented in Table 3

and are summarized as follows: general cognitive (MMSE, MoCA, $Z=2.80$ [.005]; ADAS-cog, $Z=2.38$ [.02]), executive functions (DSF, DSB, DSF/Backward, stroop test-A, stroop test B, $Z=2.66$ [.008]), memory (Wechsler memory scale immediate recall, Wechsler memory scale delayed recall, $Z=3.21$ [.001]), language ability (category verbal fluency test, letter verbal fluency test, $Z=3.23$ [.001]), and visuospatial ability (BDS, $Z=2.15$ [.03]).

4. Discussion

Exercise intervention is beneficial for cognitive ability in older adults with MCI. Previous studies have examined the results of exercise versus no exercise on cognitive function in MCI patients.^[26–29] However, none have focused on conducting a subgroup analysis of the effects of exercise on different cognitive domains in the elderly with MCI. Therefore, this review integrated evidence from a large number of trials that evaluated the effect of exercise on different cognitive domains in the elderly with MCI and produced a preliminary ranking of the degree or magnitude of the influence of certain exercise interventions on various cognitive domains. This meta-analysis included 676 patients who participated in eleven RCTs. Five high-quality and 6 mid-quality research reports are included in this systematic review according to the modified assessment form of Cochrane Collaboration recommendations and PEDro.^[36] The meta-analysis revealed that exercise had a significant positive effect on general cognition, executive functions, memory, language ability and visuospatial ability in patients with MCI; however, exercise interventions have not shown benefit on executive functions measured by TMT B-A. Only 1 study described processing speed using the digit symbol-coding subset of the Wechsler adult intelligence scale III,^[39] therefore, no meta-analyses could be conducted.

We used the chi-square test and I^2 statistic to assess the heterogeneity among the studies.

The pooled estimate of the effect for the TMT B-A (Fig. 2-B) was extremely heterogeneous (I -squared 79%). It is probable that there are important clinical and methodological differences among studies. These might include differences in populations since of the 3 articles, two studies^[46,47] came from Thailand and one^[41] came from Canada, or differences in the experimental and

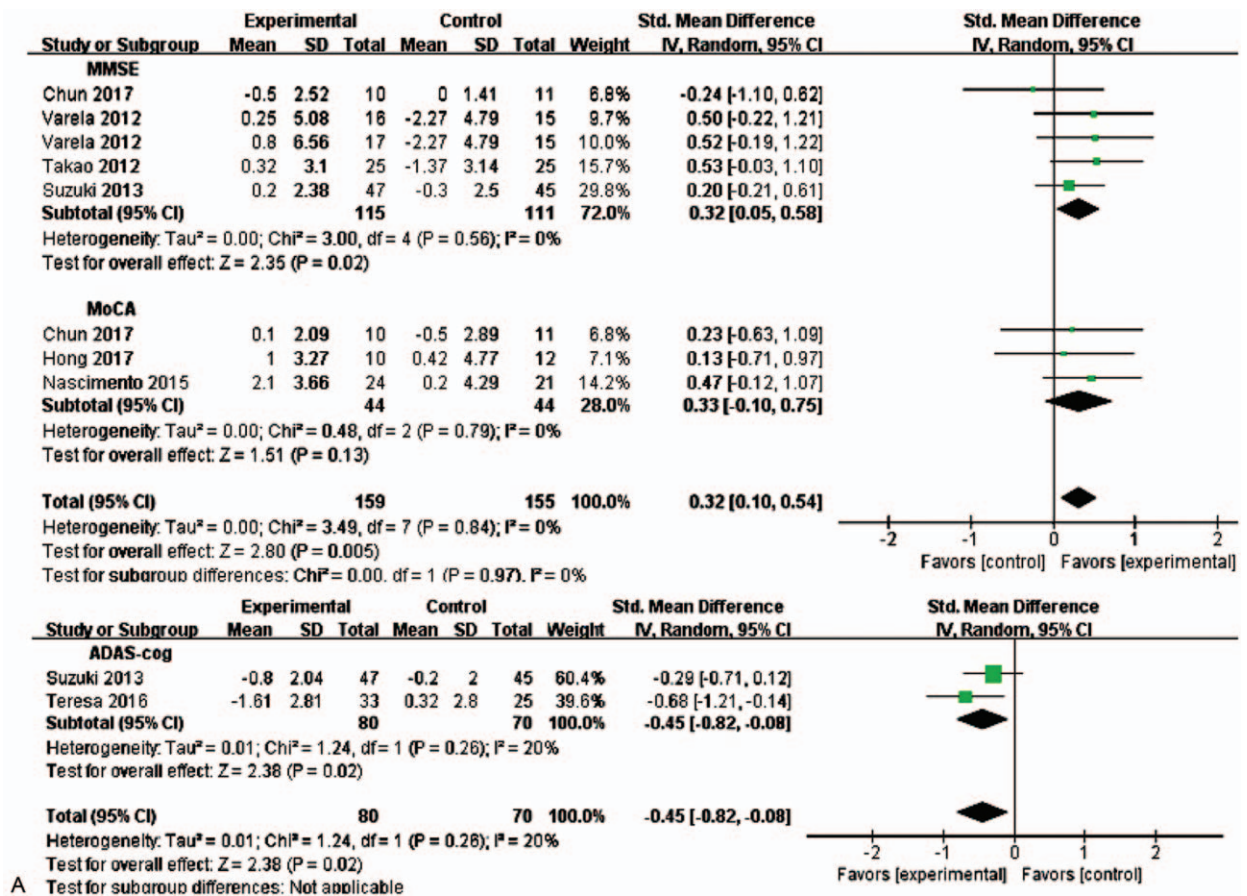


Figure 2. A. Forest plot of exercise versus no exercise on general cognition in MCI patients. Outcomes: MMSE, MoCA and ADAS-cog. MMSE, Mini-mental state examination; MoCA, montreal cognitive assessment; ADAS-cog, Alzheimer disease assessment scale-cognition. Figure 2-B. Forest plot of exercise versus no exercise on executive functions in MCI patients. Outcomes: DSF, DSB, DSF-B, ST-A, ST-B and TMT B-A. DSF, digit span forward test; DSB, digit span backward test; DSF-B, digit span forward/backward; ST-A, stroop test A; ST-B, stroop test B; TMT B-A, trail-making test Part B-A. Figure 2-C. Forest plot of exercise versus no exercise on memory in MCI patients. Outcomes: WMS-I and WMS-II. WMS-I, Wechsler memory scale immediate recall; WMS-II, Wechsler memory scale delayed recall. Figure 2-D. Forest plot of exercise versus no exercise on language ability in MCI patients. Outcomes: CVFT and LVFT. CVFT, Category verbal fluency test; LVFT, letter verbal fluency test. Figure 2-E. Forest plot of exercise versus no exercise on visuospatial ability in MCI patients. Outcome: BDS. BDS, block design score.

control groups such that the experimental and control groups of 2 studies^[46,47] were Taiji and health education, and the other study^[41] had aerobic training and no-treatment groups. At the same time, we consider TMT B-A indicators to be less specific or sensitive to the measurement of executive functions, so it is recommended to use more sensitive indicators to measure the impact of exercise on executive functions. In the future, the effect of exercise interventions on executive functions in MCI patients need to be further explored. The pooled estimate of effect for the DSF and DSB (Fig. 2-B) shown a high level of heterogeneity (I-squared 77%). Clinical and methodological differences may exist among these studies: three studies^[39,46,47] used health education, 1 study^[43] used a no-treatment control and one study^[44] used muscle-stretching exercise. There were also differences in intensity and duration that may have led to different results. Accordingly, we found that different durations of training were used for the included articles, in which 2 studies^[43,44] trained for twelve weeks, 1 study^[46] trained for fifteen weeks and 2 studies^[39,47] trained for 6 months.

The preliminary ranking of the effect of exercise interventions across domains of cognitive function based on the overall effect was $Z_{\text{language ability}} > Z_{\text{memory}} > Z_{\text{executive functions}} > Z_{\text{visuospatial ability}}$.

The effect of exercise interventions on language ability in MCI patients was most significant. Neva and his colleagues (2017) found that a session of exercise decreased intracortical and interhemispheric inhibition and then improved learning skills.^[50] Furthermore, group activities promoted interpersonal relations. Sports programs in groups have been shown to enrich old people's lives, harmonize feelings and provide more opportunities for communication among the elderly. This study demonstrated that language ability itself as a communication tool in social interactions could be the target, thereby making therapies on language ability more effective. In contrast, the strategy of focusing on the discourse itself seems less effective, at least in the current noncommunicative context of confrontation naming.^[51] Berthier and his group also found that if verbal utterances are embedded in behaviorally relevant settings (in the context of group exercise) the outcome of speech-language therapy may improve.^[52]

Among the other cognitive functions, visuospatial ability ranked last. In this study, there were only 2 studies,^[46,47] which used BDS to measure visuospatial ability. The effect of exercise on visuospatial ability was more prominent at the beginning of the exercise intervention and reached a plateau over time,^[47] which

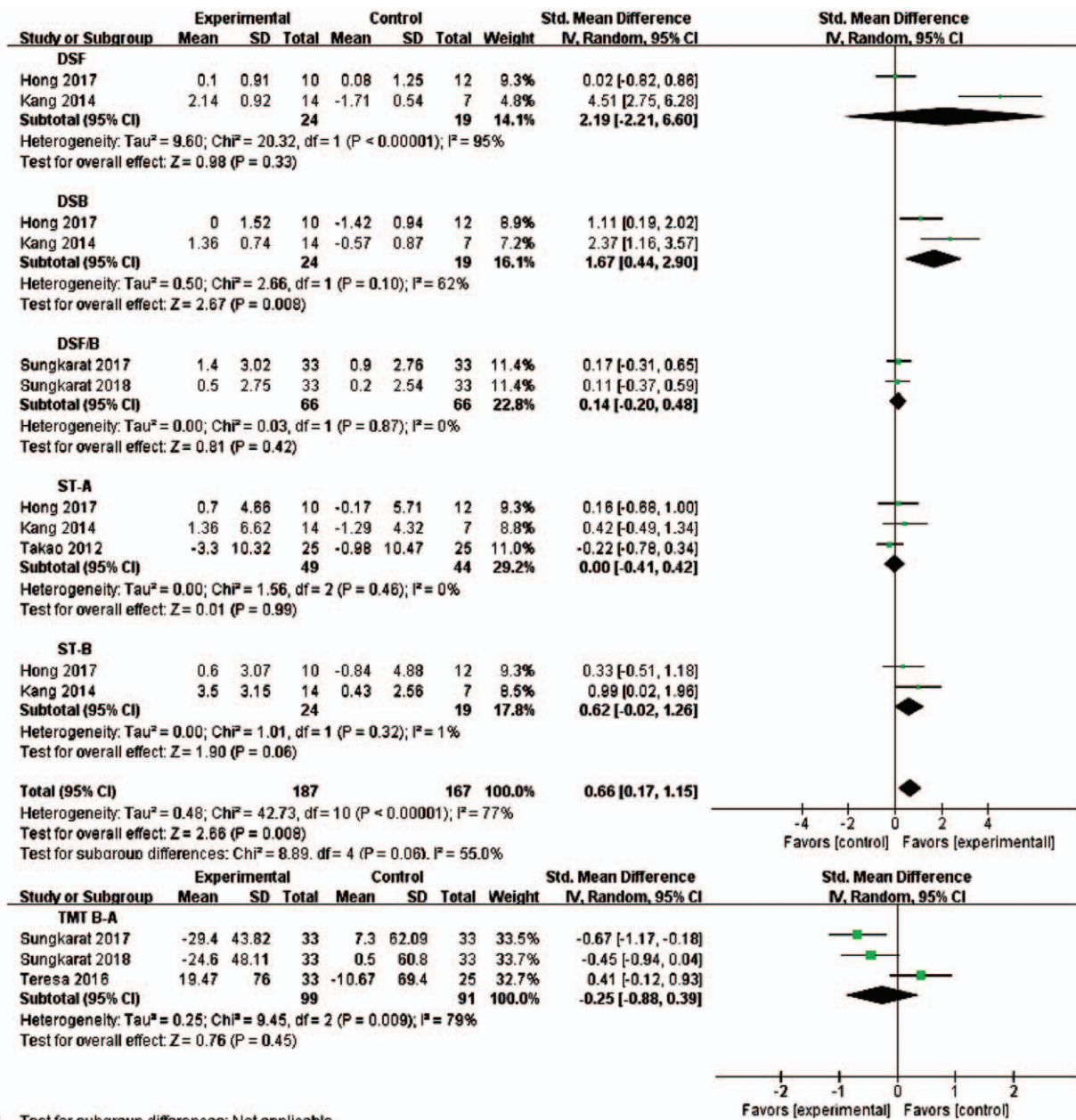


Figure 2. (Continued)

may be the reason why long-term exercise intervention has no significant effect on visual spatial ability. Therefore, the ability of exercise to improve visuospatial ability may be limited. An alternative explanation may be the limited duration of the exercise and the assessment of visuospatial ability in the maintenance phase.^[47] A study shown that solving jigsaw puzzles was highly correlated with performance in visuospatial reasoning tasks,^[53] and engagement in intellectual activities, including jigsaw puzzles, predicted a reduced risk of dementia.^[54–56]

5. Limitations

This systematic review has certain limitations. First, the outcome assessors could not be blinded for the comparisons between the exercise group and the no-exercise groups, therefore generating

potential response and performance bias. Second, there was no distinction between primary and secondary outcomes related to cognitive functions in this study, so perhaps the results are at higher risk of chance findings due to selective reporting and the multiplicity of testing. Third, different types of exercise may have led to clinical heterogeneity to some extent. Fourth, there were a limited number of the eligible studies with the sample sizes ranged from 22 to 100 which may impact the present findings. Fifth, we did not distinguish assessments during the exercise intervention and during the follow-up time (up to 6 months), and we used the data closest to the sixth month to perform the meta-analysis. The effects of some exercise interventions may have delayed effects, which may cause bias in the comparison of outcome indicators and affect the comparability of outcome indicators.

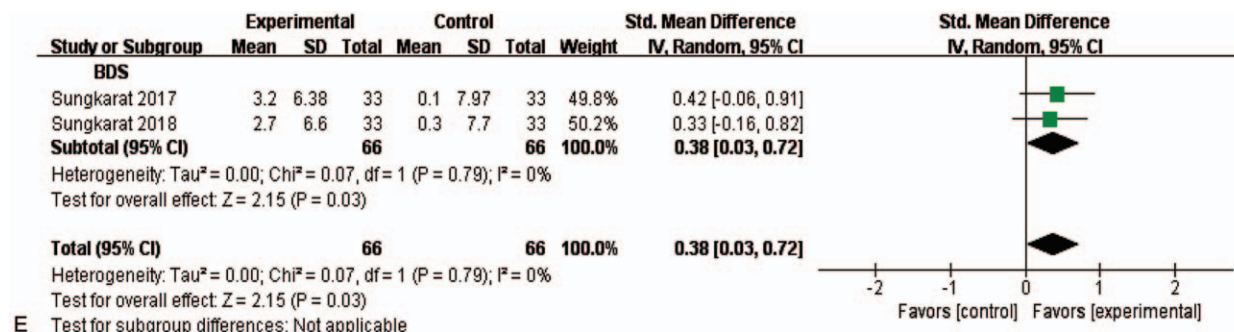
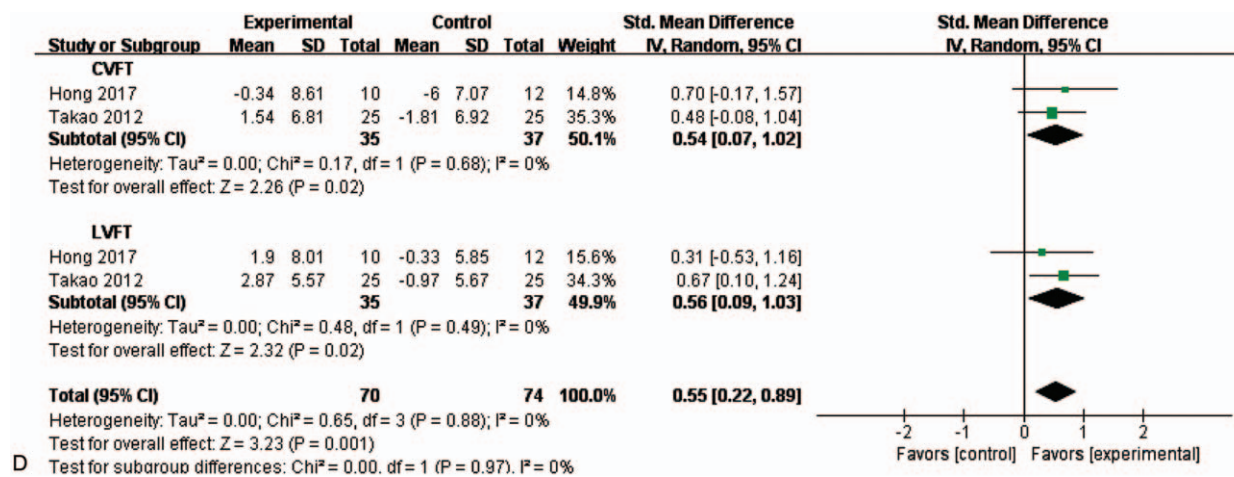
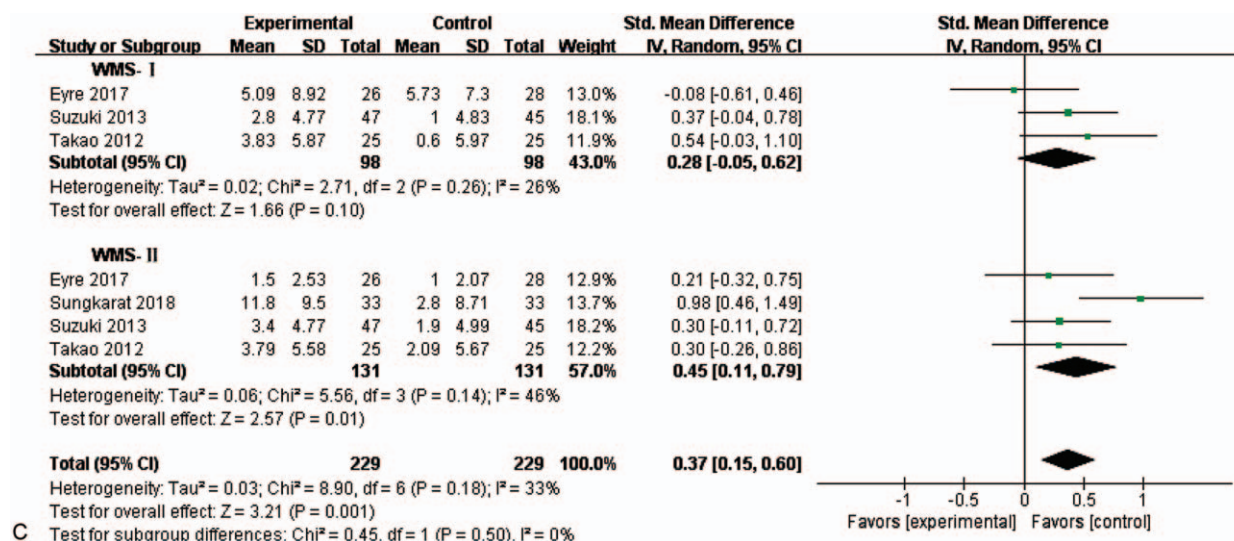


Figure 2. (Continued).

6. Implications

First, the study shown that the effect of exercise on the improvement of language ability was most significant, although previous studies seldom used the language ability to evaluate the effectiveness of an exercise intervention. Therefore, future studies of exercise interventions should pay more attention to changes in language ability.

Second, this study shown that there were differences in the overall effect of exercise interventions across various cognitive domains. However, whether the observed differences are significant remains to be verified by a rigorous research design. These differences provide a possibility for medical workers to conduct personalized exercise interventions. For MCI patients with severe memory impairment, the effects of exercise intervention may not be as good as cognitive training; however,

Table 3**The overall effect results of eligible meta-analyses.**

Outcome	Trials	Participants	Statistical method	Pooled effect size (95%)	Heterogeneity I^2 , % (P value)	Z overall effect (P value)
General cognitive						
MMSE, MoCA	40 49 39 48 43 45	355	Standard mean difference (IV, Random, 95% CI)	0.32 [0.10 to 0.54]	0.0 (.84)	2.80 (.005)
ADAS-cog	48 41	171	Standard mean difference (IV, random, 95% CI)	-0.45 [-0.82 to -0.08]	20.0 (.26)	2.38 (.02)
Executive functions						
DSF, DSB, DSF-B, ST-A, ST-B	43 44 46 47 39	243	Standard mean difference (IV, random, 95% CI)	0.66 [0.17 to 1.15]	77.0 (<.001)	2.66 (.008)
TMT B-A	46 47 41	203	Standard mean difference (IV, random, 95% CI)	-0.25 [-0.88 to 0.39]	79.0 (.009)	0.76 (.45)
Memory						
WMS-I, WMS-II	42 48 39 47	295	Standard mean difference (IV, random, 95% CI)	0.37 [0.15 to 0.60]	33.0 (.18)	3.21 (.001)
Language ability						
CVFT, LVFT	43 39	72	Standard mean difference (IV, random, 95% CI)	0.55 [0.22 to 0.89]	0.0 (.88)	3.23 (.001)
Visuospatial ability						
BDS	46 47	132	Standard mean difference (IV, random, 95% CI)	0.38 [0.03 to 0.72]	0.0 (.79)	2.15 (.03)

ADAS-cog = Alzheimer disease assessment scale-cognition; BDS = block design score; CVFT = category verbal fluency test; DSB = digit span backward test; DSF = digit span forward test; DSF-B = digit span forward/backward; LVFT = letter verbal fluency test; MMSE = mini-mental state examination; MoCA = montreal cognitive assessment; ST-A = stroop test A; ST-B = stroop test B; TMT B-A = trail-making test part B-A; WMS-I = Wechsler memory scale immediate recall; WMS-II = Wechsler memory scale delayed recall.

for MCI patients with more serious executive function impairment, exercise training will be an effective attempt to delay their cognitive impairment.

Third, this study did not explore the effect of the specific exercise intervention (aerobic exercise, resistance exercise or multicomponent exercise) on the specific cognitive domain. Therefore, to provide more accurate guidance for improving the function of the specific cognitive domains, more high-quality RCT studies are needed to reveal the relationship between the specific exercise methods and effects on specific cognitive domains.

Acknowledgments

This work was supported by the National Natural Science Foundation (NO.71704053);

China Scholarship Council (NO.201908330251); and Zhejiang Province Natural Science

Foundation (NO. LQ17G030002). Thank statistician Xue-qiang Wang for providing statistical guidance to this study.

Author contributions

LNW and XHS conceived the study. XLZ and JW independently work on study selection, quality assessment, data extraction, and synthesis. XLZ and LNW wrote the first draft of the manuscript. XHS provided substantial input into all aspects of the manuscript. All authors contributed to and approved the final manuscript.

Conceptualization: Lina Wang, Xin-Hua Shen.

Data curation: Xianglian Zhou, Jie Wang.

Formal analysis: Xianglian Zhou, Lina Wang, Jie Wang.

Funding acquisition: Lina Wang.

Methodology: Xianglian Zhou, Lina Wang, Jie Wang, Xin-Hua Shen.

Project administration: Xin-Hua Shen.

Software: Xianglian Zhou, Jie Wang.

Supervision: Lina Wang, Xin-Hua Shen.

Validation: Lina Wang, Xin-Hua Shen.

Writing – original draft: Xianglian Zhou, Lina Wang.

Writing – review and editing: Xianglian Zhou, Lina Wang.

References

- [1] World Health Organization. The state of the art of dementia research: New frontiers (Published September 2018). Available at: <https://www.alz.co.uk/research/worldreport-2018>. Accessed November 13, 2018.
- [2] World Health Organization. Dementia. Available at: <https://www.who.int/zh/news-room/fact-sheets/detail/dementia>. Published December 2017. Accessed November 13 2018.
- [3] Giebel CM, Sutcliffe C, Challis D. Activities of daily living and quality of life across different stages of dementia: a UK study. *Aging Ment Health* 2015;19:63–71.
- [4] Flak MM, Hernes SS, Skranes J, et al. The Memory Aid study: protocol for a randomized controlled clinical trial evaluating the effect of computer-based working memory training in elderly patients with mild cognitive impairment (MCI). *Trials* 2014;15:156.
- [5] Farias ST, Mungas D, Reed BR, et al. Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. *Arch Neurol* 2009;66:1151–7.
- [6] Roberts R, Knopman DS. Classification and epidemiology of MCI. *Clin Geriatr Med* 2013;29:753–72.
- [7] Wood H. Alzheimer disease: meta-analysis finds high reversion rate from MCI to normal cognition. *Nat Rev Neurol* 2016;12:189.
- [8] Valenzuela M, Sachdev P, Brodaty H. Practice guideline update summary: Mild cognitive impairment: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018;91:372.
- [9] Russ TC, Morling JR. Cholinesterase inhibitors for mild cognitive impairment. *Cochrane Database Syst Rev* 2012;9:CD009132.
- [10] Cooper C, Li R, Lyketsos C, et al. Treatment for mild cognitive impairment: systematic review. *Br J Psychiatry* 2013;203:255–64.
- [11] Fink HA, Jutkowitz E, McCarten JR, et al. Pharmacologic interventions to prevent cognitive decline, mild cognitive impairment, and clinical Alzheimer-type dementia: a systematic review. *Ann Intern Med* 2018;168:39–51.
- [12] Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: mild cognitive impairment: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018;90:126–35.
- [13] Tao J, Chen X, Egorova N, et al. Tai Chi Chuan and Baduanjin practice modulates functional connectivity of the cognitive control network in older adults. *Sci Rep* 2017;7:41581.
- [14] Tao J, Liu J, Liu W, et al. Tai Chi Chuan and Baduanjin increase grey matter volume in older adults: a brain imaging study. *J Alzheimers Dis* 2017;60:389–400.
- [15] Brasrue M, Desai P, Davila H, et al. Physical activity interventions in preventing cognitive decline and Alzheimer-type dementia: a systematic review. *Ann Intern Med* 2018;168:30–8.
- [16] Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci USA* 2011;108:3017–22.

- [17] Alkadhhi KA, Eriksen JL, Salim S, et al. Treadmill exercise prevents learning and memory impairment in Alzheimer's disease-like pathology. *Curr Alzheimer Res* 2013;10:507–15.
- [18] Vivar C, Peterson BD, Van PH. Running rewires the neuronal network of adult-born dentate granule cells. *Neuroimage* 2016;131:29–41.
- [19] Jin K, Zhu Y, Sun Y, et al. Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. *Proc Natl Acad Sci USA* 2002;99:11946–50.
- [20] Pereira AC, Huddleston DE, Brickman AM, et al. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci USA* 2007;104:5638–43.
- [21] Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci* 2002;25:295–301.
- [22] Berchtold NC, Kessler JP, Cotman CW. Hippocampal brain-derived neurotrophic factor gene regulation by exercise and the medial septum. *J Neurosci Res* 2002;68:511–21.
- [23] Middleton LE, Barnes DE, Lui LY, et al. Physical activity over the life course and its association with cognitive performance and impairment in old age. *J Am Geriatr Soc* 2010;58:1322–6.
- [24] Barnes DE, Blackwell T, Stone KL, et al. Cognition in older women: the importance of daytime movement. *J Am Geriatr Soc* 2008;56:1658–64.
- [25] Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci* 2003;14:125–30.
- [26] Snigdha S, Prieto GA. Chapter 16—Exercise enhances cognitive capacity in the aging brain. In Ronald RW, ed. *Phys Activity Aging Brain (Effects of Exercise on Neurological Function)*. 1st ed. University of Arizona, Arizona Health Sciences Center, Tucson, AZ, USA: Elsevier. 2017;161–72.
- [27] Baker LD, Frank LL, Fosterschubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol* 2010;67:71–9.
- [28] Brinke LFT, Bolandzadeh N, Nagamatsu LS, et al. Aerobic exercise increases hippocampal volume in older women with probable mild cognitive impairment: a 6-month randomized controlled trial. *Brit J Sport Med* 2014;49:248–54.
- [29] Lam LC, Chan WC, Leung T, et al. Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition?: a cluster randomized controlled trial. *PLoS One* 2015;10:e0118173.
- [30] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- [31] Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–8.
- [32] Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256:183–94.
- [33] Forbes SC, Forbes D, Forbes S, et al. Exercise interventions for preventing dementia or delaying cognitive decline in people with mild cognitive impairment. *Cochrane Database Syst Rev* 2015;5:CD011706.
- [34] Song GM, Liu XL, Bian W, et al. Systematic review with network meta-analysis: comparative efficacy of different enteral immunonutrition formulas in patients underwent gastrectomy. *Oncotarget* 2017;8:23376–88.
- [35] Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.6 [updated September 2006]. Available at: <http://www.cochrane.org/resources/handbook/hbook.htm> (accessed 6th October 2006).
- [36] Maher CG, Sherrington C, Elkins MR. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther* 2003;83:713–21.
- [37] Zhai J, Mu W, Si J, et al. Acupuncture for constipation in patients with stroke: protocol of a systematic review and meta-analysis. *BMJ Open* 2018;8:e020400.
- [38] Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* 5.1.0 (updated March, 2011). Available at: <http://www.cochrane.org/resources/handbook/hbook.htm>. Accessed May 1, 2011.
- [39] Suzuki T, Shimada H, Makizako H, et al. Effects of multicomponent exercise on cognitive function in the older adults with amnesic mild cognitive impairment: a randomized control trial. *BMC Neurol* 2012;12:128.
- [40] Hsu CL, Best JR, Davis JC, et al. Aerobic exercise promotes executive functions and impacts functional neural activity among older adults with vascular cognitive impairment. *Br J Sports Med* 2018;52:184–91.
- [41] Liuambrose T, Best JR, Davis JC, et al. Aerobic exercise and vascular cognitive impairment: a randomized controlled trial. *Neurology* 2016;87: 2082–90.
- [42] Eyre HA, Siddarth P, Acevedo B, et al. A randomized controlled trial of Kundalini yoga in mild cognitive impairment. *Int Psychogeriatr* 2017;29: 557–67.
- [43] Hong SG, Kim JH, Jun TW. Effects of 12-week resistance exercise on electroencephalogram patterns and cognitive function in the elderly with mild cognitive impairment: a randomized controlled trial. *Clin J Sport Med* 2018;28:500–8.
- [44] Kang D, Kim H, Yoon D, et al. Effects of 12 weeks high-speed elastic band training on cognitive function, physical performance and muscle strength in older women with mild cognitive impairment: a randomized controlled trial. *Korean J Health Promot* 2014;14:26–32.
- [45] Nascimento CM, Pereira JR, Larissa PDA, et al. Physical exercise improves peripheral BDNF levels and cognitive functions in elderly mild cognitive impairment individuals with different BDNF val66Met genotypes. *J Alzheimers Dis* 2014;43:81–91.
- [46] Sungkarat S, Boripuntakul S, Chattipakorn N, et al. Effects of Tai Chi on cognition and fall risk in older adults with mild cognitive impairment: a randomized controlled trial. *J Am Geriatr Soc* 2017;65:721–7.
- [47] Sungkarat S, Boripuntakul S, Kumfu S, et al. Tai Chi improves cognition and plasma BDNF in older adults with mild cognitive impairment: a randomized controlled trial. *Neurorehabil Neural Repair* 2018;32: 142–9.
- [48] Suzuki T, Shimada H, Makizako H, et al. A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. *PLoS One* 2013;8:e61483.
- [49] Varela S, Ayán C, Cancela JM, et al. Effects of two different intensities of aerobic exercise on elderly people with mild cognitive impairment: a randomized pilot study. *Clin Rehabil* 2012;26:442–50.
- [50] Neva JL, Brown KE, Mang CS, et al. An acute bout of exercise modulates both intracortical and interhemispheric excitability. *Eur J Neurosci* 2017;45:1343–55.
- [51] Stahl B, Mohr B, Dreyer FR, et al. Using language for social interaction: communication mechanisms promote recovery from chronic non-fluent aphasia. *Cortex* 2016;85:90–9.
- [52] Pulvermuller F, Berthier ML. Neuroscience insights improve neuro-rehabilitation of poststroke aphasia. *Nat Rev Neurol* 2011;7:86–97.
- [53] Dykens EM. Are jigsaw puzzle skills 'spared' in persons with Prader-Willi syndrome? *J Child Psychol Psych* 2002;43:343–52.
- [54] Lindstrom HA, Fritsch T, Petot G, et al. The relationships between television viewing in midlife and the development of Alzheimer's disease in a case-control study. *Brain Cogn* 2005;58:157–65.
- [55] Friedland RP, Fritsch T, Smyth KA, et al. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Proc Natl Acad Sci USA* 2001;98:3440–5.
- [56] Possin , Katherine L. Visual spatial cognition in neurodegenerative disease. *Neurocase* 2010;16:466–87.