

Review

Comparative efficacy of various exercise interventions on cognitive function in patients with mild cognitive impairment or dementia: A systematic review and network meta-analysis

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Abstract

Background: Exercise is a promising nonpharmacological therapy for cognitive dysfunction, but it is unclear which type of exercise is most effective. The objective of this study was to compare and rank the effectiveness of various exercise interventions on cognitive function in patients with mild cognitive impairment (MCI) or dementia and to examine the effects of exercise on the symptoms relevant to cognitive impairment.

Methods: We searched PubMed, Web of Science, Embase, Cochrane Central Register of Controlled Trials, SPORTDiscus, and PsycInfo through September 2019 and included randomized controlled trials that examined the effectiveness of exercise interventions in patients with MCI or dementia. Primary outcomes included global cognition, executive cognition, and memory cognition. Secondary outcomes included activities of daily living, neuropsychiatric symptoms, and quality of life. Pairwise analyses and network meta-analyses were performed using a random effects model.

Results: A total of 73 articles from 71 trials with 5606 participants were included. All types of exercise were effective in increasing or maintaining global cognition, and resistance exercise had the highest probability of being the most effective intervention in slowing the decrease in global cognition (standard mean difference (SMD) = 1.05, 95% confidence interval (95%CI): 0.56–1.54), executive function (SMD = 0.85, 95%CI: 0.21–1.49), and memory function (SMD = 0.32, 95%CI: 0.01–0.63) in patients with cognitive dysfunction. Subgroup analyses for patients with MCI revealed different effects, and multicomponent exercise was most likely to be the optimal exercise therapy for preventing the decline of global cognition (SMD = 0.99, 95%CI: 0.44–1.54) and executive function (SMD = 0.72, 95%CI: 0.06–1.38). However, only resistance exercise showed significant effects on memory function for patients with MCI (SMD = 0.35, 95%CI: 0.01–0.69). Exercise interventions also showed various effects on the secondary outcomes.

Conclusion: Resistance exercise has the highest probability of being the optimal exercise type for slowing cognitive decline in patients with cognitive dysfunction, especially in patients with dementia. Multicomponent exercise tends to be most effective in protecting global cognition and executive function in patients with MCI.

Keywords: Cognitive function; Cognitive impairment; Exercise; Network meta-analysis

1. Introduction

With the acceleration of population aging, cognitive impairment, including dementia and mild cognitive impairment (MCI), has become an important issue in public health and has

attracted more and more attention from healthcare providers, researchers, and policymakers.^{1,2} MCI is a transitional stage between cognitive health and dementia and is commonly considered to be a key stage in the prevention of dementia.² The decline in cognitive function is usually accompanied by some neuropsychiatric symptoms and a reduced ability to perform activities of daily living (ADLs), which negatively affects the quality of life (QoL) of patients and caregivers and imposes a heavy burden on their families and society at large.³

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Exercise, as a promising nonpharmacological therapy, has played an increasingly important role in preventing the decline of cognitive function and improving the QoL of patients with cognitive impairment.⁴ Numerous randomized controlled trials (RCTs) have reported the positive effects of exercise on cognitive function, ADLs, and neuropsychiatric symptoms in patients with cognitive impairment.^{5,6} Neuroimaging studies also have shown that exercise is beneficial in enhancing functional brain plasticity.^{7,8} Exercise may exert protective effects on cognitive function by (1) raising the levels of growth factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1), (2) regulating inflammatory cytokines, (3) relieving oxidative stress, (4) increasing cerebral blood flow, (5) reducing A β concentration, and (6) inhibiting tau phosphorylation.⁹ However, these underlying mechanisms have been shown to exist only in animal models, and a number of studies that have examined these mechanisms have not yet shown that they are applicable to humans. Previous relevant studies have shown that distinctive types of exercise, such as aerobic exercise (AE) and resistance exercise (RE), might exert effects through some different molecular mechanisms and lead to various effect sizes (e.g., RE: standard mean difference (SMD) = 0.41–0.71;^{10–12} AE: SMD = 0.13–0.58^{12,13}). Therefore, the type of exercise is an important factor that should be considered when clinical professionals prescribe exercise to prevent or slow cognitive decline.¹⁴ However, the type of exercise treatment that is the most effective in preventing or slowing cognitive decline is still unclear because studies have not compared different types of exercise interventions simultaneously. Thus, healthcare professionals have had difficulty in prescribing the exercise interventions that would be most effective in treating their patients.

Network meta-analysis is a novel analytic approach that allows a comparison of the effects of more than 2 interventions simultaneously in a single analysis by combining direct and indirect evidence.¹⁵ Additionally, it allows different interventions to be ranked for a given outcome and presents the probability of each intervention's relative efficacy, which can be helpful in informing clinical decision making.¹⁵ Therefore, we used the results of previous RCTs to perform a network meta-analysis that compared the relative efficacy of different types of exercise interventions based on direct and indirect evidence. We also aimed to identify the optimal exercise treatment for protecting cognitive function in patients with MCI or dementia and to examine the effects of exercise on the symptoms relevant to cognitive impairment.

2. Methods

This systematic review was registered with PROSPERO (CRD 42020192579), and the protocol was published in a peer-reviewed journal.¹⁶ We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses—Network Meta-Analyses (PRISMA—NMA) for our study.

2.1. Search strategy

The databases for Web of Science, PubMed, Embase, Cochrane Central Register of Controlled Trials, SPORTDiscus,

and PsycInfo were searched online from inception to September 2019. To avoid missing eligible literature, we checked the reference lists of systematic reviews published over the last 3 years^{12,17–31} and performed hand searches to supplement relevant studies. We also identified eligible trials through the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov. The search strategy was first developed for the PubMed database and subsequently adapted for the other sources; the strategy was reviewed by experts from the fields of cognitive impairment and sports health to guarantee its comprehensiveness and accuracy. The detailed search strategy is presented in Supplementary Appendix 1.

2.2. Study selection

Duplications were first eliminated using the software of End-Note X8 (Clarivate Analytics, Philadelphia, PA, USA). Then 2 researchers (XH and XZ) independently screened titles and abstracts to identify all potentially relevant studies. Studies that met the inclusion criteria were identified and assessed by the same 2 reviewers independently. Disagreement was resolved by discussion or by consulting with a third expert if necessary. The detailed inclusion criteria were as follows: (1) the study design must have been an RCT, (2) the participants had to have been diagnosed with MCI or dementia, (3) the interventions could include any type of exercise training, (4) the comparator received no intervention, usual care, health education, sham exercise training, or other form of exercise, (5) the studies had to report 1 of the following outcomes, which included global cognition, executive function, memory function, ADLs, QoL, and neuropsychiatric symptoms, and (6) the studies had to be written in English. Studies were excluded for the following reasons: (1) they focused on cognitive impairment in patients with Parkinson disease, Huntington disease, epilepsy, multiple sclerosis, diabetes, or psychiatric illness (e.g., schizophrenia) (these diseases are usually accompanied by different pathological changes in addition to those directly related to cognitive dysfunction; therefore, they might have interfered with the effects of exercise on cognitive function); or (2) they examined the effects of acute exercise. If multiple articles were from the same study and reported the same or overlapping outcomes, we included only the most recently published article.

2.3. Outcomes

The primary outcome was cognitive function, including global cognition, executive function, and memory function. Global cognition is an umbrella term that refers to various domains of cognitive performance. Executive function is commonly referred to as the ability to reason and problem solve, which includes a set of processes, such as planning, strategizing, decision making, inhibiting irrelevant information, and switching flexibly between 2 tasks.³² Memory function refers to the process of holding and fetching information in the brain, which is the most complex cognitive domain.³² All of these functions were included as outcomes in our study because previous studies indicated that domain-specific cognition showed different sensitivity to exercise interventions.³³ Considering that a decrease in the ability to perform

ADLs and having a neuropsychiatric disorder are 2 common symptoms that directly affect QoL among patients with cognitive dysfunction,⁴ we took ADLs, neuropsychiatric symptoms, and QoL as our secondary outcomes. Given that depression is among the most common psychiatric symptoms in patients with dementia,³⁴ we also included depressive symptom as an independent outcome. The rating scales included for different outcomes, organized according to the frequency of use and their psychometric properties, are listed in order in Supplementary Appendix 2. If multiple tools were used to assess a certain outcome, we selected the most appropriate tool according to the prescribed hierarchy.

2.4. Data extraction

Data extraction was implemented independently by 2 researchers (XH and XZ) using a self-designed statistical form based on the Cochrane handbook.³⁵ The form included study characteristics (first author's name, publication year, title, study design, and setting), participant characteristics (types of cognitive impairment, sample size, average age, and sex ratio), interventions (types, frequency, intensity, duration per session, length of intervention, and comparator information), and outcomes (the relevant statistics at the endpoint of the intervention for estimating effect sizes, such as mean, standard deviation, and corresponding measurement tools). When the relevant statistics were incompletely reported, we estimated the mean and standard deviation based on the sample size, median, range, and *p* value according to the Cochrane handbook (Supplementary Appendix 3).³⁵

During the process of data extraction, we referred to the Chinese guidelines³⁶ for diagnosis and treatment of dementia and cognitive impairment for the classification of cognitive function, and we referred to the Physical Activity Guidelines for Americans³⁷ and previous systematic reviews for the classification of exercise interventions.^{29,31} To compare the effects of various types of exercise interventions, we classified exercise interventions into the following broad categories: (1) AE (exercise aiming to improve cardiovascular fitness, including walking, running, and cycling); (2) RE (exercise intending to increase muscular strength and power, using, for example, elastic bands and weight machines); (3) multicomponent exercise (ME, a combination of at least 2 types of exercise, such as AE, RE, and balance training); and (4) mind–body exercise (MBE, exercise aiming to improve participants' mind–body coordination and awareness by having them practice a series of controlled movements that focus on the interactions among the brain, body, mind, and behavior, such as Tai Chi, yoga, and dance).^{23,38} Others types of exercise that could not be categorized as 1 of the 4 types defined above were listed by their descriptions, such as whole-body vibration and finger exercise. In order to explore the moderators of exercise effects (Supplementary Appendix 4), the different types of exercise were further classified and encoded according to their frequency, intensity, duration per session, and the length of intervention.

2.5. Risk of bias assessment

Risk of bias was assessed by 2 pairs of authors (XH and SZ, YC and XZ) according to the Cochrane Collaboration's risk-of-bias tool.³⁵ Considering the characteristics of exercise intervention, it was impossible to blind the participants in the included studies. Thus, we assessed only the other 6 categories of risk bias, which included random sequence generation, allocation concealment, blinding of the outcome assessor, incomplete data, selective reporting, and other sources of bias. Disagreement was resolved by the third author (BL).

2.6. Data synthesis and analysis

Across all outcomes, pairwise meta-analysis was first conducted to separately explore the effects of various exercise interventions compared with the control group. Effect sizes were estimated with SMDs and 95% confidence intervals (95% CIs) using postintervention scores by the random effects model.

Network meta-analyses for the primary outcomes were conducted based on the frequentist framework using Stata software (Version 15.0; StataCorp., College Station, TX, USA).³⁹ The network analysis pooled the individual study results. It combined both direct evidence from RCTs with head-to-head comparison and indirect evidence, where each of the 2 interventions was individually compared against a common comparator.⁴⁰ Network diagrams were formed based on the network analysis, where each node represented an intervention and the connecting lines between 2 nodes represented 1 or more RCTs in which the 2 interventions had been compared directly.³⁹ The size of each node was weighted according to the number of participants who received the particular intervention, and the thickness of the lines connecting 2 nodes was weighted according to the number of studies that compared directly the interventions it connected.³⁹ Random-effects models were applied, which accounted for heterogeneity caused by clinical and other factors across studies and provided a more conservative CI for pooled point estimates.⁴¹ SMDs and 95% CIs were calculated using the endpoint data after intervention to estimate the effect sizes of continuous outcomes. For clinical interpretation, effect sizes were classified as small (SMD < 0.40), moderate (SMD = 0.40–0.70), or large (SMD > 0.70) according to the Cochrane handbook.³⁵ The exercise interventions were ranked by using the surface under the cumulative ranking curve (SUCRA) and mean rank. The SUCRA is a precise estimation of cumulative ranking probabilities for a treatment ranking top *i*. For each treatment *j* out of the *n* competing treatments, we calculated the cumulative probabilities of treatment *j* to be among the top *i* best treatments by using the following formula: $SUCRA_j = (\sum_{i=1}^{n-1} cum_{j,i}) / (n-1)$.⁴² A SUCRA value of 100% indicates that this type of exercise intervention is certain to be the most effective in the network, whereas a value of 0 indicates that it is certain to be the least effective.⁴² The larger the SUCRA value, the better the rank of an intervention in the network.

To assess the heterogeneity among studies, *I*² was calculated. The detection for global design inconsistency and local

inconsistency were implemented by using a design-by-treatment model and a loop-specific approach, respectively. The design-by-treatment interaction model was based on regression analysis, which could explain both heterogeneity and inconsistency among studies.⁴³ We performed all the analyses separately for each different outcome. We also planned to perform subgroup analyses by gender and severity of cognitive impairment, given that these 2 variables might affect the participants' responses to exercise interventions.^{33,44} However, during the process of data extraction we found that most of the studies did not report cognition outcomes separately by sex. Thus, we performed only subgroup analyses according to the severity of cognitive impairment. In order to explore the causes of heterogeneity further, we also conducted metaregression analysis (with frequency, intensity, duration, and length of exercise interventions as covariates) for the primary outcomes.

3. Results

3.1. Description of included studies

A total of 12,471 records were identified after removing duplicates. Of these records, 590 were considered potentially relevant after the initial screening of titles and abstracts. Finally, after applying the inclusion and exclusion criteria a total of 73 articles from 71 trials published between 2003 and 2019 (30 articles for MCI, 39 articles for dementia, and 2 articles for both) with 5606 participants were selected for network meta-analysis (Fig. 1). The

agreement rate for study selection and data extraction between the 2 researchers was 83.7% and 80.8%, respectively. In the included trials, 25 studies (828 participants) examined the effects of AE, 13 studies (356 participants) examined the effects of RE, 27 studies (1252 participants) examined the effects of ME, 14 studies (476 participants) examined the effects of MBE, 1 study examined the effects of whole-body vibration (27 participants), and 2 studies (31 participants) examined the effects of finger exercise. There were 11 studies that examined the effects of 2 different exercise interventions,^{5,45–55} 7 studies of which adopted 3-arm designs.^{5,45–51} Detailed study characteristics and the list of included studies are reported in Supplementary Appendix 5 and Appendix 6, respectively.

3.2. Risk of bias

The percentage of studies with high, moderate, and low risk of bias for the individual items was as follows: random-sequence generation (68.5%, 31.5%, and 0, respectively); allocation concealment (42.5%, 57.5%, and 0, respectively); blinding of outcome assessors (61.6%, 26.0%, and 12.3%, respectively); incomplete outcome (67.1%, 26.0%, and 6.8%, respectively); selective outcome reporting (78.1%, 11.0%, and 11.0%, respectively); and other risks of bias (78.1%, 15.1%, and 6.8%, respectively). Detailed information about the risks of bias for the included studies is reported in Supplementary Appendix 7.

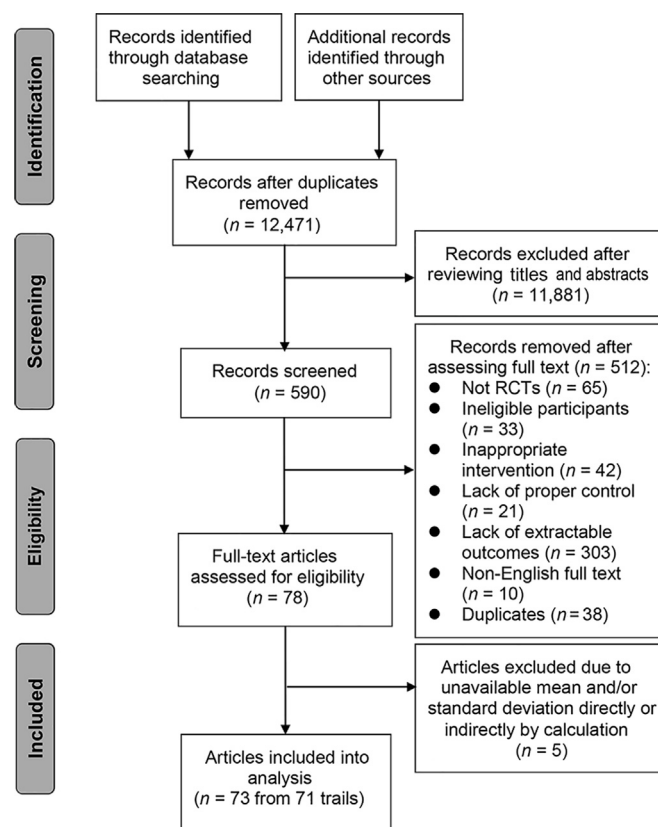


Fig. 1. Selection of studies for inclusion. RCT = randomized controlled trial.

3.3. Primary outcomes

For global cognitive function, a total of 45 studies with 3458 participants was included. Of these studies, 15 studies examined the effects of AE,^{48,51,53,56–67} 8 studies tested the effects of RE,^{5,68–74} 16 studies evaluated the effects of ME,^{5,48,52,53,75–86} and 11 studies examined the effects of MBE.^{51,52,87–95} There were 5 studies that conducted direct comparisons of various exercise interventions,^{5,48,51–53} 3 of which adopted 3-arm designs^{5,48,51} (Supplementary Appendix 8.1). Pairwise analysis indicated that exercise interventions were effective, with an overall I^2 value of 82.0% (Supplementary Appendix 8.1). An inconsistency test based on network analysis revealed no significant global inconsistency; the detailed results for inconsistency are shown in Appendix 8.1. The network plot for global cognition (Fig. 2A) shows all the available comparisons from the included trials. In Fig. 2A, all the exercise interventions are directly compared with nonexercise controls; direct comparisons between RE and AE and RE and MBE for the outcome of global cognition are lacking. The results of the network meta-analysis indicated that all types of exercise interventions were superior to nonexercise controls, with SMDs ranging from 0.60 (95%CI: 0.28–0.92) for ME to 1.05 (95%CI: 0.56–1.54) for RE. The comparative effects among various exercise interventions are presented in Fig. 3A. The ranking of the exercise interventions based on cumulative probability plots and SUCRAs are shown in Fig. 4A and Table 1. RE had the highest probability (82.4%) of being the most effective exercise type in protecting global cognition, with a SUCRA value of 93.4% (Table 1).

Our subgroup analysis of patients with MCI or dementia revealed some inconsistent results (Supplementary Appendix 8.1). For patients with dementia, RE was still the most promising exercise type, with a SUCRA value of 98.6%. But for patients with MCI, ME (with a mean rank of 1.8) had a slightly higher probability of being the most promising exercise treatment (SUCRA = 79.1%; SMD = 0.99, 95%CI = 0.44–1.54), higher than RE, which had a mean rank of 2.4 (SUCRA = 64.8%). Meta-regressions were conducted separately for different types of exercise interventions, with frequency, intensity, duration, and length of exercise intervention as covariates. The results (Supplementary Appendix 8.1)

indicated that frequency and duration per session were moderators affecting the effects of ME.

For executive function, 28 studies were selected, and they included 2055 participants. Of these studies, 11 studies examined the effects of AE,^{45,46,48,59,62,63,66,96–99} 5 studies examined the effects of RE,^{46,70–72,74} 8 studies examined the effects of ME,^{48,52,55,76,80,84,85,100} 8 studies examined the effects of MBE,^{52,55,89–91,93,95,101} and 1 study examined the effects of finger exercise.⁴⁵ There were 5 studies that conducted direct comparisons of various exercise interventions,^{45,46,48,52,55} 3 of which adopted 3-arm designs^{45,46,48} (Supplementary Appendix 8.2). Pairwise analysis indicated that exercise interventions were effective in executive function, with an overall I^2 value of 75.2%. No significant inconsistency was found (Supplementary Appendix 8.2). The network plot of intervention comparisons is shown in Fig. 2B, which indicates that all the exercise interventions were directly compared with nonexercise controls. The results of our network meta-analysis suggested that only RE (SMD = 0.85, 95%CI: 0.21–1.49) and AE (SMD = 0.47, 95%CI: 0.06–0.88) were effective (Fig. 3B). RE had the highest probability (56.7%) of being the best treatment, with a SUCRA value of 87.1% (Fig. 4B and Table 1). Our subgroup analysis results indicated that ME was significantly effective (SMD = 0.72, 95%CI: 0.06–1.38) on executive function for patients with MCI, whereas RE (1 study⁷¹) was significantly effective on executive function (SMD = 4.21, 95%CI: 2.76–5.66) for patients with dementia (Supplementary Appendix 8.2).

For memory function, 27 studies were included, with 2459 participants. Of these 27 studies, 12 studies examined the effects of AE,^{45,47–49,59,61,62,96–99,102} 5 studies examined the effects of RE,^{47,49,70,72,74} 5 studies examined the effects of ME,^{48,52,76,82,85} 9 studies examined the effects of MBE,^{52,87,89–91,93,95,101,103} and 1 study examined the effects of finger exercise.⁴⁵ The contribution plot indicated that 5 studies^{45,47–49,52} conducted direct comparisons of various exercise interventions, four^{45,47–49} of which used 3-arm designs (Supplementary Appendix 8.3). Pairwise meta-analysis indicated that exercise had an overall pooled positive effect on memory function, with an overall I^2 value of 22.5%. No evidence of significant inconsistency was found (Supplementary Appendix 8.3). The network plot is shown in Fig. 2C. All

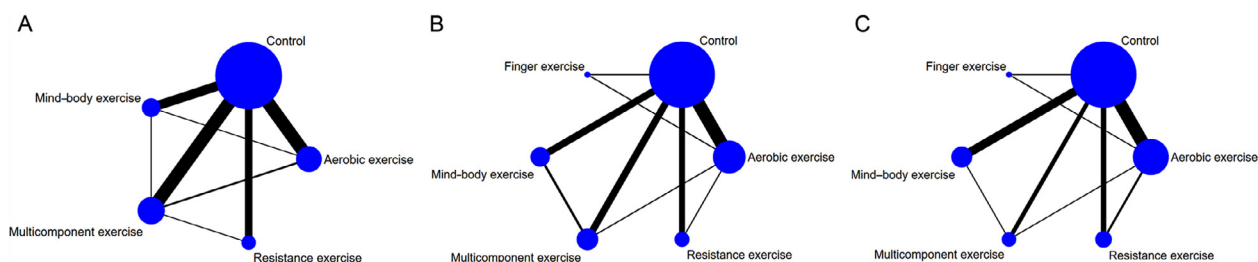


Fig. 2. Network meta-analysis of eligible comparisons for (A) global cognition, (B) executive function, and (C) memory cognition. Each node represents an intervention, and the connecting lines between 2 nodes represents 1 or more randomized clinical trials (RCTs) in which the 2 interventions have been compared directly. The size of each node is proportional to the number of randomly assigned participants, and the thickness of the lines connecting 2 nodes is weighted according to the number of RCTs that directly compared the interventions it connected.

A

Control				
0.67 (0.32 to 1.01)	AE			
1.05 (0.56 to 1.54)	0.38 (−0.22 to 0.97)	RE		
0.60 (0.28 to 0.92)	−0.07 (−0.51 to 0.38)	−0.45 (−1.01 to 0.12)	ME	
0.64 (0.25 to 1.03)	−0.03 (−0.54 to 0.47)	−0.41 (−1.04 to 0.21)	0.03 (−0.45 to 0.52)	MBE

B

Control					
0.47 (0.06 to 0.88)	AE				
0.85 (0.21 to 1.49)	0.38 (−0.33 to 1.09)	RE			
0.24 (−0.24 to 0.73)	−0.23 (−0.84 to 0.38)	−0.61 (−1.41 to 1.87)	ME		
0.26 (−0.22 to 0.74)	−0.21 (−0.84 to 0.42)	−0.59 (−1.40 to 0.21)	0.02 (−0.59 to 0.62)	MBE	
0.61 (−0.66 to 1.87)	0.13 (−1.13 to 1.40)	−0.25 (−1.65 to 1.16)	0.36 (−0.98 to 1.71)	0.35 (−1.00 to 1.70)	Finger

C

Control					
0.08 (−0.08 to 0.24)	AE				
0.32 (0.01 to 0.63)	0.24 (−0.09 to 0.56)	RE			
0.08 (−0.17 to 0.33)	0.00 (−0.28 to 0.28)	−0.24 (−0.63 to 0.15)	ME		
0.12 (−0.07 to 0.31)	0.04 (−0.21 to 0.28)	−0.20 (−0.56 to 0.16)	0.04 (−0.26 to 0.34)	MBE	
−0.15 (−0.85 to 0.56)	−0.23 (−0.94 to 0.48)	−0.47 (−1.23 to 0.30)	−0.23 (−0.98 to 0.52)	−0.27 (−1.00 to 0.46)	Finger

Fig. 3. Comparative effectiveness results for (A) global cognition, (B) executive function, and (C) memory function. Each cell shows an SMD with a 95%CI. For any cell, a negative SMD favors the upper-left intervention; a positive SMD favors the lower-right intervention. Significant results are in bold text. 95%CI = 95% confidence interval; AE = aerobic exercise; MBE = mind–body exercise; ME = multicomponent exercise; RE = resistance exercise; SMD = standardized mean difference.

the exercise interventions were directly compared with nonexercise controls. Comparisons among various exercise interventions and control groups (Fig. 3C) suggest that only RE exerted significant effect on memory function (SMD = 0.32, 95%CI: 0.01–0.63). However, all RE-related studies were implemented in patients with MCI, and none of the studies were conducted in

patients with dementia. Our subgroup analysis confirmed that RE (SMD = 0.35, 95%CI: 0.01–0.69) was effective on memory function for patients with MCI, and no other significant effects were found among patients with MCI or dementia (Supplementary Appendix 8.3).

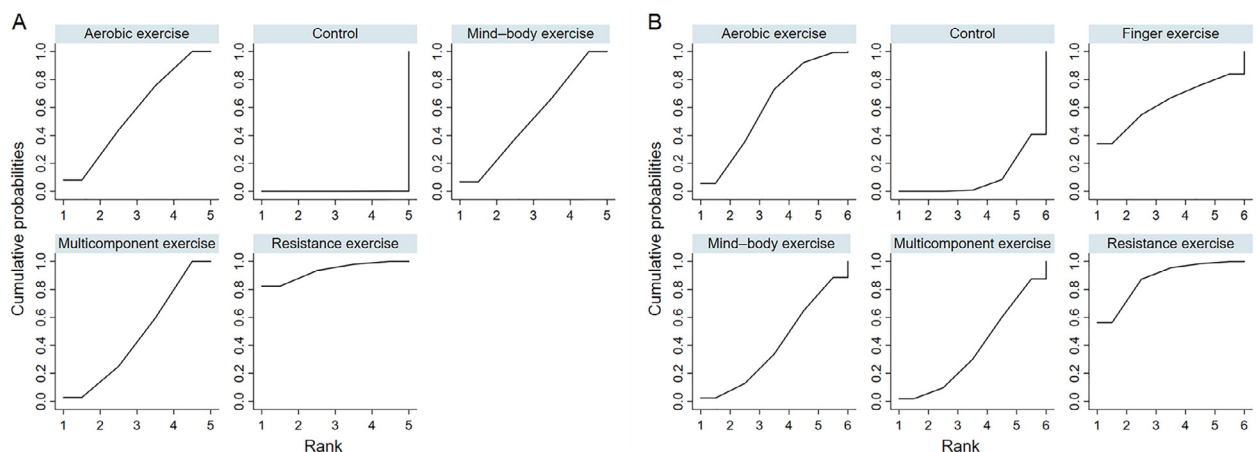


Fig. 4. Cumulative ranking probability plots for (A) global cognition and (B) executive function. The horizontal axis represents the possible rank of each treatment (from best to worst according to the outcome). The vertical axis represents the cumulative probability for each treatment to be the best option, the best of 2 options, the best of 3 options, and so on.

Table 1

The global cognition and executive function rankings for different types of exercise.

Exercise	Global cognition			Executive function		
	SUCRA (%)	Mean rank	P (%)	SUCRA (%)	Mean rank	P (%)
AE	56.9	2.7	8.0	61.5	2.9	5.3
RE	93.4	1.3	82.4	87.1	1.6	56.7
ME	46.9	3.1	2.8	37.8	4.1	1.7
MBE	52.8	2.9	6.8	40.4	4.0	2.3
Finger exercise	—	—	—	63.0	2.8	34.0
Control	0.0	5.0	0.0	10.1	5.5	0.0

Notes: Higher SUCRA and lower mean ranks indicate better-performing treatments. P indicates the probability of it being the best treatment.

Abbreviations: AE = aerobic exercise; MBE = mind–body exercise; ME = multicomponent exercise; RE = resistance exercise; SUCRA = surface under cumulative ranking curve.

3.4. Secondary outcomes

Considering the relatively small number of studies and the lack of direct comparisons among different exercise types for a certain outcome, we did pairwise meta-analysis only for secondary outcomes. For ADLs, pairwise analysis revealed positive effects for various types of exercise interventions, except for finger exercise, with pooled SMDs ranging from 0.38 (95%CI: 0.07–0.69) for AE to 1.32 (95%CI: 0.10–2.55) for RE. For neuropsychiatric symptoms measure by Neuropsychiatric Inventory, the results also showed positive effects for AE (SMD = 0.28, 95%CI: 0.11–0.45), RE (SMD = 4.49, 95%CI: 3.11–5.87), and ME (SMD = 0.17, 95%CI: 0.04–0.30). For the other outcomes, RE (1 study¹⁰⁴) showed a positive effect for depression (SMD = 0.39, 95%CI: 0.04–0.74), and AE showed a significant effect for QoL (SMD = 0.23, 95%CI: 0.05–0.40) (Supplementary Appendix 9).

4. Discussion

Our network meta-analysis compared the relative efficacy of various types of exercise interventions in global cognition, executive function, and memory function in patients with cognitive impairment of MCI or dementia. The meta-analysis was based on 73 articles from 71 studies and included 5606 participants. To our knowledge, there has been only 1 previous network meta-analysis comparing the effects of exercise on global cognition, but it omitted 1 important exercise type, ME, and focused only on the efficacy of exercise in global cognition in patients with MCI.²⁹ Therefore, our review is the first and largest network meta-analysis to explore the relative efficacy of distinct types of exercise on both global and specific domains of cognitive function. The results from our study confirmed the beneficial effects of various exercise interventions on global cognition and revealed that RE had the highest probability of being the most promising exercise treatment to slow the decline of global cognition, executive function, and memory function for patients with cognitive dysfunction, especially for patients with dementia. For patients with MCI, ME tended to be the most effective exercise therapy for preventing the decline of global cognition and executive function.

Given the increasing number of studies related to exercise intervention in patients with cognitive disorders, RE is attracting more and more attention because of its benefits to cognition. Although the potential mechanisms of these benefits are not clear, some researchers have pointed out that RE is likely to exert effects through mechanisms that are different from the mechanisms at play in other types of exercise.^{14,105} First, RE could improve cognitive function by lifting the level of IGF-1 in the hippocampus and peripheral blood, whereas AE and MBE preferentially increase BDNF.^{101,105,106} Second, RE could exert beneficial influences on both the brain and cognition by modulating inflammatory cytokines, such as interleukin-6 (IL-6), IL-1 β , and IL-15, which are usually expressed and released in response to muscle contractions.^{107,108} Furthermore, RE could exert cognitive benefits by enhancing muscle strength,¹⁰⁹ given that enhanced muscle strength or muscle mass has been associated with brain size and better cognition.^{110,111} Improving muscle strength and function through RE could further promote the release of irisin, which could elevate the levels of IGF-1 and BDNF, relieve oxidative stress, promote neurogenesis, and ameliorate insulin sensitivity.^{112,113} Overall, the results from our study showed that RE provided somewhat unexpected benefits for global cognition in patients with cognitive impairment, which is consistent with the results from previous meta-analyses.²⁹

Other types of exercise interventions also had significant facilitating effects on global cognition. Our subgroup analyses revealed that ME ranked first (followed by RE) among the MCI group but not among the dementia group. Our finding is not consistent with the results reported by Wang et al.,²⁹ who reported that RE ranked first. However, Wang et al.²⁹ did not include ME as an exercise type, which might lead to the inconsistency with our results. ME consists of various types of exercise, such as AE, RE, or others. Hence, they likely to complement each other in enhancing cognitive benefits by triggering favorable biochemical changes through multiple neurobiological mechanisms (e.g., BDNF, IGF-1, homocysteine, inflammatory cytokines).²² However, in practice, the effects of ME may be limited by several factors. First, when multiple exercise components are performed sequentially, it is hard to ensure that every component meets its optimal duration and frequency, which, in turn, may weaken its positive effects. In a study by Bossers et al.,⁴⁸ participants in an AE group implemented four 30-min walking sessions per week, whereas the ME group (AE plus RE) implemented two 30-min walking sessions and two 30-min resistance sessions per week, which meant that the duration and frequency of the aerobic component was cut by half and, thus, was far from the dose recommended by the American College of Sports Medicine.⁴⁸ Frequency and duration are the 2 moderators of effect size for ME, and higher frequency and longer duration are associated with better effects. Thus, researchers should consider these factors in future studies. Additionally, the combination of various exercise components may increase the complexity of implementing the intervention and affect intervention fidelity—the consistency between plan and execution—especially for participants with dementia. Therefore, it is not difficult to understand why, in our

study, ME tended to be the most promising exercise type in the MCI group but not in the dementia group.

For executive function, both RE and AE showed significant effects, with RE being significantly superior to AE. In previous studies, executive function has been reported as the cognitive domain most responsive to AE.¹¹⁴ The underlying mechanism may be related to the increased aerobic fitness and functional connectivity of the brain induced by AE, but this mechanism is still controversial.^{115–117} RE may share several of the mechanisms responsible for improvement in executive cognition and global cognition. The increase in serum IGF-1 and growth hormone levels induced by RE might partially explain its positive effects, which has been positively correlated with better behavioral performance, such as information-processing speed, target detection, and response speed.¹⁰⁸ Furthermore, gains in muscular strength in response to RE may also partially mediate the effects of RE on executive function.¹¹⁸ Given the relatively small number of RCTs in our meta-analysis that tested the effects of RE on executive cognition (4 RCTs^{46,70,72,74} for patients with MCI and 1 RCT⁷¹ for patients with dementia), coupled with the fact that few of them adopted biomarkers, more studies with larger samples should be conducted to verify the effects of RE on executive function and explore the potential mechanisms. Additionally, according to the results from our subgroup analysis, ME showed significant benefits for the MCI group and was the most effective exercise type for executive cognition among these patients. In addition to the complementary mechanisms of multiple exercise components, Forte et al.¹¹⁸ have pointed out that ME could directly improve executive function through cognitive stimulation inherent in multiple movement tasks characterized by perceptual motor adaptations and variable neuromuscular coordination. Future research should explore other possible mechanisms.

Consistent with previous studies, we found in our study that memory function was the cognitive domain that was least sensitive to exercise.²² Our results indicated that only RE had significant benefits on memory function for patients with MCI. In a study of seniors with probable MCI, Nagamatsu et al.¹¹⁹ found that resistance training, but not AE, could increase functional regional blood flow to the brain, which has been associated with memory performance. This partially explains the results in our study. In the absence of relevant studies, it cannot be judged whether RE is effective in patients with dementia. Thus, additional studies should be conducted to fill this gap.

In terms of the effects of exercise on cognitive-related outcomes, the benefits of exercise on ADLs were confirmed by our meta-analysis, which was consistent with previous studies.^{17,34} Because exercise interventions can improve physical fitness and mobility, they can directly facilitate the ability to perform ADLs.³⁸ The protective effects of exercise on cognition are also beneficial in performing ADLs. Moreover, we found that exercise interventions had significant effects on neuropsychiatric symptoms. This benefits caregivers by decreasing their burdens, considering that functional decline in performing ADLs and increasing neuropsychiatric symptoms are 2 of the most common causes of caregivers' distress.⁴ For the other outcomes, we found that only RE (1 study¹⁰⁴) showed significant benefits for

depressive symptoms and that AE showed favorable effects for QoL. Future studies should focus on these outcomes because there were only a small number of these types of studies included in our meta-analysis.

Our meta-analysis has some important implications for future clinical practice and scientific research. In clinical settings, RE deserves more attention and should be recommended as a complementary therapy for patients with cognitive dysfunction, given its significant benefits on cognitive function and cognitive-related outcomes (such as ADLs and neuropsychiatric symptoms). ME should also be advocated as a routine nonpharmacological therapy for patients with MCI in order to improve their global cognition and executive function. In regard to scientific research, more studies on identifying the mechanisms of exercise that affect cognitive function, including global cognition and specific cognitive domains, should be conducted. Second, although our meta-analysis showed favorable effects of RE on cognition, the number of studies about RE included in our review was very limited. Therefore, additional related studies with large sample sizes should be conducted among patients with dementia in order to test our findings. Third, the optimal combination of exercise components in ME that leads to the greatest cognitive benefits is still unclear and needs further exploration, including the optimal frequency and duration per session for each exercise component in ME. Finally, in our network meta-analysis, only 7^{5,45–49,51} of the 71 included studies adopted multiarm designs that compared the effects of different types of exercise directly; therefore, many estimates of effect sizes depended on indirect comparison. Given that evidence from direct comparisons have a higher reliability than indirect comparisons, more studies with multiarm designs should be conducted in the future.

Some limitations to our network meta-analysis should be mentioned. First, because of the large number of included studies, heterogeneity was unavoidable. Although we used subgroup analysis and meta-regression to explore some of the reasons for heterogeneity, there were nevertheless some moderators at the individual level (e.g., age, sex) and at the implementation level (e.g., exercise equipment, settings) that severely limited the available data. However, this may have increased the external validity of our results, given that heterogeneity is inherent in exercise interventions and that they tend to present some variations in real-world practice. Second, the diversity of assessment tools used to gauge cognitive function may also increase heterogeneity, although we developed a careful plan for data extraction for each outcome based on the frequency of use and psychometric properties of the different tools. Additionally, because only a few studies reported long-term follow-up data after the end of interventions, we extracted only the data at the endpoint of the intervention of those studies. Thus, our study does not provide evidence about the duration of the effects of exercise after the interventions ended. Moreover, we did not assess the effects of exercise on other domains of cognition because there was insufficient data from previous trials. Finally, we included only articles written in English, which might have led to some missing information.

5. Conclusion

This network meta-analysis synthesized the available evidence from previous studies and provided some important findings about exercise treatment for clinical professionals and researchers. Our study suggests that RE has the highest probability of being the most effective exercise type for slowing cognitive decline among patients with cognitive impairment, especially for patients with dementia. ME showed more favorable effects on global cognition and executive function for patients with MCI. However, considering limitations of our meta-analysis mentioned above and the insufficient number of studies in the existing literature, the results should be interpreted cautiously. In the future, more multiarm RCTs should be conducted to provide more direct evidence about relative efficacy of the various exercise interventions.

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Authors' contributions

XH and XZ made equal contributions to the conception and design, literature search, study selection, data extraction, risk of bias assessment, data analysis, and drafting of the manuscript; BL made substantial contributions to the conception and design of the study and the literature search; YC and SZ participated in the conception and design of the study and made substantial contributions to the risk of bias assessment; FY contributed to the conception and design of the study and revision of the manuscript for critically important intellectual content; QW, as the corresponding author, made substantial contributions to the conception and design, of the study, literature search, and revision of the manuscript for critically important intellectual content. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.jshs.2021.05.003](https://doi.org/10.1016/j.jshs.2021.05.003).

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