



Cognitive interventions for mild cognitive impairment and dementia: An overview of systematic reviews



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ABSTRACT

Purpose: Conducting an overview of systematic reviews (SRs)/Meta analyses (MAs) to assess the effectiveness of cognitive interventions on participants with mild cognitive impairment (MCI) or dementia and evaluate the methodological quality of SRs/MAs.

Methods: PubMed, EMBASE, Cochrane library, Web of science, China National Knowledge Infrastructure (CNKI) and Chinese Biomedical Databases (CBM) were systematically searched from inception to January 1, 2019 to identify SRs/MAs. Three reviewers independently screened the articles, extracted data and assessed the quality of the included studies according to the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2), the Grading of Recommendations Assessment Development and Evaluation (GRADE) was used to evaluate the quality of evidence.

Results: A total of 22 reviews were included. New meta-analyses (36 RCTs) showed that cognitive interventions were more effective than routine therapies for the alleviation of MCI and dementia symptoms (SMD: 0.62; 95%CI: 0.47, 0.78; $I^2 = 53.9\%$). The results of AMSTAR-2 showed that the methodological quality of most included studies was critically low, and two reviews were low quality. The lowest score was item 10, none of reviews reported on the sources of funding for the included studies. Followed by the “provide a list of excluded studies and justify the exclusions” item with only one (4.5%) reviews conforming to this item. Results of GRADE manifested that moderate quality evidence was provided in 11 reviews (39.3%), 12 (42.9%) were low quality and 5 (17.8%) were very low.

Conclusion: The present SRs/MAs indicated that persons with MCI or dementia could benefit from cognitive interventions. Future trial designs should focus on measuring changes in individual specific cognitive functions. More high-quality evidence is needed to further determine the effectiveness of cognitive interventions.

1. Introduction

Dementia is classified as a major neurocognitive disorder because it interferes with both cognitive function and daily activities.¹ Common causes of dementia are depression, drug side effects, thyroid problems, certain vitamin deficiencies and excessive use of alcohol. According to the latest statistics of WHO in 2016, there are 47 million senile dementia patients worldwide, accounting for 5% of the world's elderly population, which has become a global public health problem.²

Cognitive function refers to memory, computational, speech, language, judgment, orientation, visual space, attention and other thinking abilities.³ Mild cognitive impairment (MCI) is the transitional phase between normal cognitive functioning and dementia,⁴ generally refers to impairment in cognition above that which is seen with normal age-

related cognitive decline.⁵ Participants with MCI had a higher risk of Alzheimer's disease or other types of dementia, with an annual conversion rate of approximately 10–15%, however, the annual conversion rate in healthy controls was 1–2%.^{6,7} There are about 10 million new cases of dementia each year, and the number will rise approximately to 131.5 million by 2050.⁴ Correct and timely diagnosis and treatment can minimize the impairment of cognitive function.⁸

In general, there are two types of treatment for MCI and dementia, drug and non-drug therapy. However, some studies have shown that until now, pharmacological therapies solely relieve symptoms of dementia, but fail to alter the progression of the disease,^{9,10} therefore, non-pharmacological cognitive interventions have attracted extensive attention.⁶ Cognitive interventions refers to non-pharmacological interventions aimed at improving cognitive function, which are mainly

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divided into three categories: (1) cognitive training (CT) consists of exercises conducted under the guidance of a series of standard tasks aimed at improving memory, attention or executive function, as well as computer cognitive training (CCT), with computers as aids. (2) cognitive rehabilitation (CR) describes the development of strategies or external aids to compensate for functional difficulties. (3) cognitive stimulation (CS) employs a series of activities and discussions aimed at the general enhancement of improving cognitive function.¹¹ Cognitive interventions are important methods to delay the decline of cognitive function and prevent dementia in the elderly in recent years. So far, a lot of reviews had systematically described the effects of cognitive interventions in persons with MCI and dementia. Most of reviews had shown that, cognitive interventions had a positive result in improving cognitive function, and might be potentially effective method to postpone cognitive decline in MCI or dementia participants.^{12,13} However, some reviews pointed that cognitive trainings had no effect on cognitive outcomes.^{11,14,15} For example, the study of Tammy Hoffmann et al. included 4 randomized controlled trials (RCTs) (376 participants), found that there was no statistically significant difference between the experimental group and the control group in the 4 studies. Therefore, it is crucial to re-evaluate the issue.^{14,15}

The current study aimed to comprehensively evaluate the published systematic reviews (SRs) and meta-analyses (MAs) on cognitive interventions for MCI and dementia, to fill the gap in current research. We performed an overview to reanalyze all of the included SRs/MAs, evaluate the methodological quality of these SRs/MAs, and rate the quality of evidence of important outcomes from them.

2. Material and methods

2.1. Search strategy

The overview was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Cochrane handbook.^{16,17} PubMed, EMBASE, Cochrane library, Web of science, China National Knowledge Infrastructure (CNKI) and Chinese Biomedical Databases (CBM) were searched from inception to January 1, 2019, and there were no language restrictions.

Search terms used to find potential articles were as follows: (“Cognitive Dysfunction” OR “Cognitive Impairment” OR “Age-Related Memory Disorders” OR “Mild Cognitive Impairment” OR “MCI” OR “Mild Neurocognitive Disorder” OR “Cognitive Decline” OR “Mental Deterioration” OR “Dementia” OR “Senile Paranoid Dementia” OR “Amentia” OR “Alzheimer Disease” OR “Alzheimer’s Disease” OR “Senile Dementia” OR “Alzheimer Type Dementia” OR “ATD” OR “Alzheimer Type Senile Dementia” OR “Primary Senile Degenerative Dementia” OR “Alzheimer Syndrome” OR “Alzheimer Dementia”) AND (“Cognitive training” OR “Cognitive intervention” OR “Cognitive function training”) AND (“Systematic” OR “Review” OR “Meta-analysis”) (full search strategy, Appendix A). References of the included studies were also retrieved manually to identify the possible missing articles in the database search.

2.2. Inclusion criteria

- (1) The SRs/MAs of RCTs about the effectiveness of cognitive training on participants with MCI or dementia were included;
- (2) Subjects included should be diagnosed with MCI or dementia, no restrictions on age, gender, and race;
- (3) Treatment group intervention: cognitive interventions therapy (CT, CCT, CS, CR);
- (4) Control group intervention: standard care, routine treatment, placebo medication, usual care, or no intervention.

2.3. Exclusion criteria

The studies were excluded if:

- (1) The main intervention in the treatment group was not cognitive intervention, or cognitive intervention was used as an intervention in the control group;
- (2) The study did not provide sufficient information for evaluation;
- (3) This study was repeated publication, comment, or meeting abstract.

2.4. Literature screening and data extraction

All retrieved articles were imported into EndNote X7 software and the duplicate publications were excluded. Three investigators (WBH, MXL and MW) independently screened titles and abstracts to identify eligible studies. Any conflicts were adjudicated through discussing or consulting a fourth member (XMH) of the review team.

Three reviewers (WBH, MXL and LLJ) independently extracted data from the included SRs/MAs. According to the characteristics of the included reviews, we extracted the following basic information: publication year, the first author, country, quality assessment methods, number of included studies, sample size, treatment interventions, control interventions, outcomes and main conclusions of each included study.

2.5. Quality assessment

Three reviewers (WBH, MXL and MW) independently assessed the quality of included SRs/MAs using the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2) checklist. AMSTAR-2 contains 16 items, among which seven are critical domains.¹⁸ Moreover, AMSTAR-2 proposes a four-level scheme (high, moderate, low, and critically low) for appraisers to rate the overall confidence in the results of a systematic review, and the evaluation option are reduced to three options, “Yes”, “Partial Yes” and “No”. We assign “yes” to 1, “No” to 0, and “Partial Yes” to 0.5 in this overview.

The Grading of Recommendations Assessment Development and Evaluation (GRADE) system was used to assess the quality of evidence associated with specific outcomes from five aspects: limitations, inconsistencies, indirectness, inaccuracy, and publication bias.¹⁹ There are five specific reasons for downgrade: (1) The design of the experiment with a large bias in random, distributive hiding or blind; (2) The confidence interval overlaps less, the heterogeneity test P is very small, and the I^2 is large; (3) Confidence interval is not narrow enough; (4) Funnel graph asymmetry; (5) Fewer studies are included and there may be greater publication bias.

2.6. Data synthesis

The meta-analysis was conducted by following the Cochrane Handbook's effect measures for the continuous outcomes.¹⁶ Pooled effect estimation, weighted mean difference (WMD) or standard mean difference (SMD) for continuous outcomes, accompanied by their respective 95% confidence intervals (CIs) were extracted from each meta-analysis. I^2 values were also extracted for appraising heterogeneity among RCTs. Meta-analysis was performed using the Stata 12.0 (StataCorp, College station, TX). Statistical significance was defined as two-sided P value less than 0.05.

3. Results

3.1. Study identification

There were a total of 1 395 reviews retrieved from the database searches. 605 remained after elimination of duplicates. Among them, 65 full-text review articles were selected for further evaluation. 43

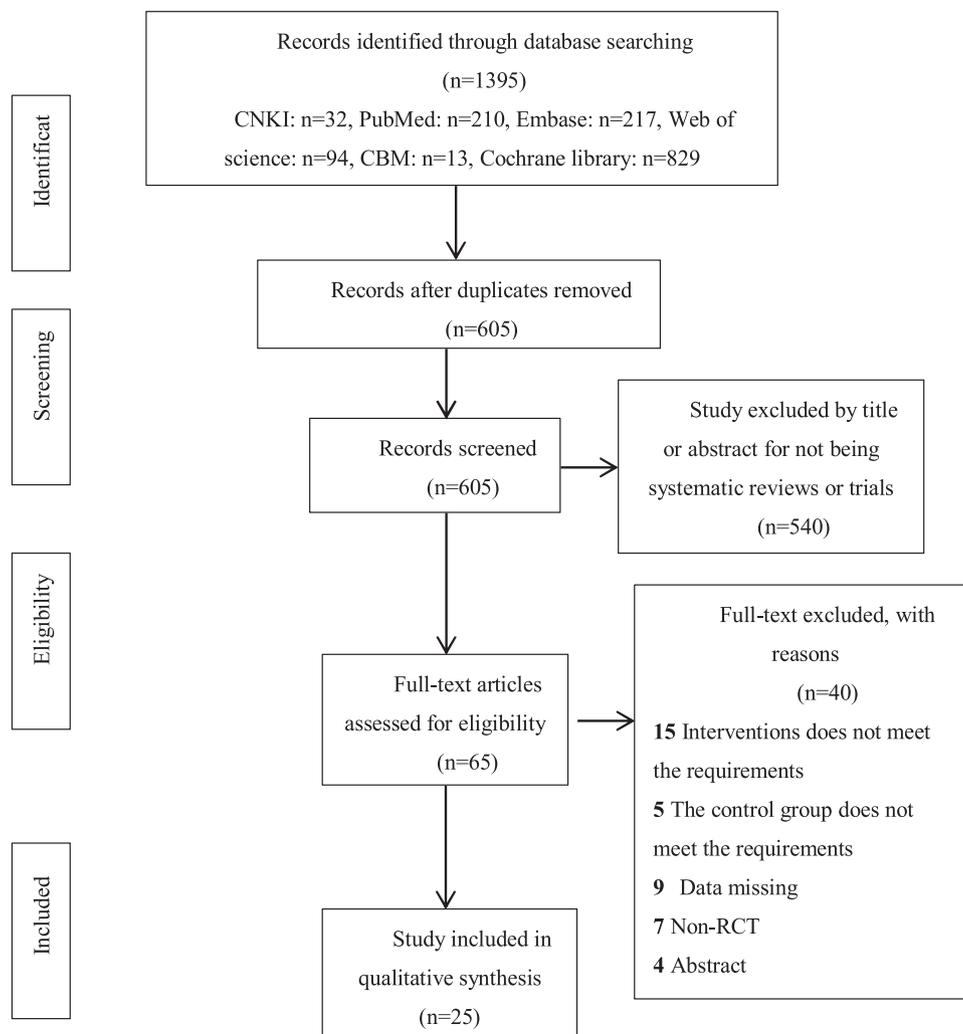


Fig. 1. Flow chart of the literature search and study selection process.

studies were excluded after full-text screening (Appendix B), 22 reviews met all inclusion criteria and were included in this review. Details of selection process can be found in Fig. 1.

3.2. Characteristics of included reviews

The 22 SRs/MAs were published between 2010 and 2019. Characteristics of these SRs/MAs can be found in Table 1. Five SRs/MAs were conducted in China,^{20–24} three SRs/MAs were in Australia,^{12,15,25} three SRs/MAs were conducted in USA,^{26–28} three SRs/MAs were conducted in Spain,^{14,29,30} two SRs/MAs were in UK,^{11,31} another six SRs/MAs were conducted in Korea, Germany, Finland, the Netherlands, Singapore and Canada respectively.^{4,32–36} 19 SRs/MAs (76%) in English and the remaining three (13.6%) were published in Chinese. Among them, 13 reviews performed meta-analysis.

3.3. Effect of the cognitive interventions in persons with MCI and dementia

All the included SRs/MAs, with a total of 36 primary comparisons, summarized evidence of cognitive interventions on MCI or dementia was presented in Table 2. For the intervention arms, there are CT (22 comparisons), CR (4 comparisons), CS (8 comparisons), CCT (2 comparisons). For the control arms, there are routine therapies (16 comparisons), active control therapy (4 comparisons), passive control therapy (6 comparisons), and blank intervention (10 comparisons).

3.3.1. Global cognitive function

In total, there were 8 pooled results on the comparison of CT compared with control condition (routine treatment, passive intervention, active intervention, non-trained, sham intervention and before CT) on the effectiveness on MCI or dementia, and the results demonstrated that CT was generally superior to control therapies in improving MCI or dementia, however, Garcia-Casal et al. found that there was no significant difference between the two interventions based on the result of only one RCT (SMD = 0.56[−0.52, 1.64]).

There were 7 pooled results on the comparison of CS compared with control condition (routine treatment, active intervention, passive intervention and before CS), and we found that CS was more effective than the control group. However, there were two pooled results showed no significant difference between them. Huntley et al. had a relatively better performance, with pooled (Hedges' $g = 0.35[0.06, 0.64]$, $I^2 = 0\%$, 3 RCTs).

A total of two SRs/MAs reported pooled results of the comparison that CR compared with control condition (routine treatment and before CR). Both showed that CR was more effective than control group, as both of the summarized evidence favored the treatment group, with pooled (SMD = 0.54[0.14, 0.94], $I^2 = 0\%$, 4 RCTs) and (MD = 2.00[0.73, 3.40], $I^2 = 11\%$, 6 RCTs)

There was one pooled result summarized from 10 RCTs comparing CCT with routine treatment. Wang et al. has a relatively better performance, with pooled (SMD = 0.36[0.13, 0.58], $I^2 = 0\%$, 10 RCTs).

The original 36 RCTs from the included SRs/MAs were extracted

Table 1
Characteristics of the included SRS/MAS.

First author (year)	Country	Quality assessment	Study design n; participants n	Intervention	Contrast	Conclusions(quote)
Tammy Hoffmann (2010)	Australia	PEDro scale	RCT's = 4; n = 376	CT	Standard care	... There was no statistically significant difference between groups on basic ADL performance in any of the four studies...
Aimee Spector (2012)	UK	Jadad scale	RCT's = 18; n = 460	CT; CCT	Routine treatment; Placebo medication; Waiting list	...For Cognitive Training, it was not possible to conclude which (if any) domains are most amenable to change...
Alex Bahar-Fuchs (2013)	Australia	NR	RCT's = 12; n = 555	CT; CCT	No treatment; Placebo medication; Waiting list	... The single RCT of cognitive rehabilitation found promising results in relation to some patient and caregiver outcomes...
Carme Carrion (2013)	Spain	SIGN checklists	RCT's = 8; n = 571	CT	No treatment; Usual care	... Stimulation of cognitive functions, improves overall cognitive function in patients suffering from dementia...
Chong Wang (2014)	China	Jadad scale	RCT's = 18; n = 330	CT; CCT	physical exercise	... Both of cognition-based intervention and physical exercise had the potential to improve global cognitive function...
Huntley (2015)	UK	Cochrane criteria	RCT's = 33; n=(NR)	CT ; CS; CR	Active/Passive control	... CS improves scores on mini-mental state examination (MMSE) and ADAS-Cog in dementia...
Chandler (2016)	USA	NR	RCT's = 30; n=(NR)	CCT	No contract control; Alternative treatment	... The results are encouraging that cognitive interventions in Mild Cognitive Impairment (MCI) may impact everyday life...
Song (2016)	Korea	Jadad scale	RCT's = 13; n = 475	CT; CCT	No treatment	... It was found that the effect on dementia patients was in the order of memory training intervention, computer-based intervention...
Jennifer L. Scott (2016)	Australia	NR	RCT's = 4; n = 505	CT	no intervention	... Pure TB-CBT interventions may offer a convenient, economical method for delivering psychological interventions to DCs...
Garcia-Casal (2017)	Spain	Downs and Black's checklist	RCT's = 12; n = 700	CCT	Active/Passive control	... Computer-based cognitive interventions have moderate effects in cognition, depression and anxiety in PWD...
Folkerts (2017)	Germany	Cochrane criteria	RCT's = 27; n=(NR)	CT; CS	No treatment	... Cognitive interventions are safe and effective for residents with dementia in long-term care facilities...
Kallio (2017)	Finland	Cochrane criteria	RCT's = 31; n = 2132	CT	Routine;	... CT may lead to observable improvements in the global cognitive status of individuals with AD...
Karsmeijer (2017)	Holland	Cochrane criteria	RCT's = 10; n = 742	CT; CCT	Educational programmes; Sham cognitive;	... These functional benefits emphasize the clinical relevance of combined cognitive and physical training strategies...
Sherman (2017)	USA	NIH Quality	RCT's = 26; n = 1938	CCT; CT	Non-trained	... Demonstrated small to moderate improvements in cognition post-intervention...
Wang (2017)	China	Cochrane criteria	RCT's = 9; n = 354	CCT	Routine	... CCT can improve the overall cognitive and memory function in patients with Alzheimer's disease...
Chen (2017)	China	Cochrane criteria	RCT's = 6; n = 390	CT	Treatment as usual	... Cognitive training interventions positively influence ADL and MMSE in patients with dementia...
Ge (2018)	USA	Joanna Briggs Institute critical appraisal checklist	RCT's = 26; n = 411	CT; CCT;	No intervention; Sham cognitive training	... Technology-based cognitive training and rehabilitation interventions show promise...
Couture (2018)	Canada	MQ score	RCT's = 13; n = 639	CT ; CS; CR	Active or passive control	... But still suggests possible benefits of these interventions in some cognitive domains...
Zhao (2018)	China	NR	RCT's = 11; n = 1059	CT	Community routine health education	... Cognitive training helps to improve the cognitive function of elderly patients with cognitive impairment...
Ultra-Curarella (2018)	Spain	Cochrane criteria	RCT's = 33; n = 1225	CT ; CS; CR	Non treatment	... Cognition-Focused Interventions proved to be no more effective than NCFI to improve performance on standardized measures of general cognitive functioning...
Kua (2019)	Singapore	Cochrane criteria	RCT's = 4; n = 138	CT; CCT	Wait-listed; Active/passive control	... Computerized cognitive trainings show promise in enhancing the cognition of patients with Heart Failure...
Liang (2019)	China	NR	RCT's = 4; n = 1368	CT ; CS; CR	Not report	... The study indicated that the CT might be the best method for improving the cognitive function of Alzheimer's Disease patients...

Notes: NR = Not report. RCT = Randomized controlled trials. CT = Cognitive training. CCT = Computer cognitive training. CS = Cognitive stimulation. CR = Cognitive rehabilitation. MT = Memory training.

Table 2
The effectiveness of cognitive interventions on participants with MCI or dementia: SR/MA results.

Author(s)	Studies, n (patients, n)	Comparison	Pooled results (95% CI)	Heterogeneity I ² (%)
Global cognitive function				
Chong Wang et al.	6(196)	CT versus Routine	SMD: 0.37(0.07, 0.68)	4
Huntley et al.	17(1010)	CS versus Passive intervention (MMSE)	Hedges' g: 0.51(0.35, 0.66)	25
Huntley et al.	3(191)	CS versus Active intervention (MMSE)	Hedges' g: 0.35(0.06, 0.64)	0
Huntley et al.	9(660)	CS versus Passive intervention (ADAS-Cog)	Hedges' g: -0.26(-0.44, -0.08)	18
Garcia-Casal et al.	4(100)	Before and after the CR	SMD: 0.54(0.14, 0.94)	0
Garcia-Casal et al.	1(30)	Before and after the CS	SMD: 0.80(0.05, 1.55)	NA
Garcia-Casal et al.	1(14)	Before and after the CT	SMD: 0.56(-0.52, 1.64)	NA
Folkerts et al.	2(47)	CT versus Passive intervention	SMD: 1.16(0.52, 1.79)	0
Folkerts et al.	3(138)	CS versus Passive intervention	SMD: 0.43(0.09, 0.78)	58
Folkerts et al.	1(15)	CT versus Active intervention	SMD: 1.19(0.01, 2.37)	NA
Folkerts et al.	2(41)	CS versus Active intervention	SMD: 0.11(-0.50, 0.73)	0
Karssemeijer et al.	10(742)	CT versus Sham intervention	MD: 0.32(0.17, 0.47)	NR
Sherman et al.	16(NR)	CT versus Non-trained	Hedges' g: 0.22(0.08, 0.36)	23
Wang et al.	10(306)	CCT versus Routine	SMD: 0.36(0.13, 0.58)	0
Liang et al.	8(462)	CT versus Routine	MD: 2.10(1.00, 3.20)	33
Liang et al.	6(654)	CS versus Routine	MD: 0.92(-0.20, 2.00)	30
Liang et al.	6(252)	CR versus Routine	MD: 2.00(0.73, 3.40)	11
Zhao et al.	11(1059)	CT versus Routine	MD: 2.52(1.76, 3.27)	77
Depression				
Garcia-Casal et al.	3(98)	Before and after the CR	SMD: 0.77(0.00, 1.53)	67
Garcia-Casal et al.	1(14)	Before and after the CT	SMD: 1.55(0.30, 2.80)	NA
Folkerts et al.	1(15)	CT versus Passive intervention	SMD: 0.65(-0.46, 1.75)	NA
Folkerts et al.	1(27)	CS versus Passive intervention	SMD: -0.38(-1.15, 0.38)	NA
Folkerts et al.	2(102)	CT versus Active intervention	SMD: 0.64(0.21, 1.07)	91
Executive function				
Chong Wang et al.	4(144)	CT versus Routine(Verbal Fluency)	SMD: 0.27(-0.18, 0.72)	38
Chong Wang et al.	2(46)	CT versus Routine(TMT-B)	SMD: 0.80(0.09, 1.50)	24
Chong Wang et al.	6(190)	CT versus Routine(Verbal Fluency& TMT-B)	SMD: 0.42(0.02, 0.83)	41
Sherman et al.	5(NR)	CT versus Non-trained	Hedges' g: 0.57(0.16, 0.98)	90
Zhao et al.	5(531)	CT versus Routine	MD: 0.20(-0.14, 0.54)	79
Working memory				
Chong Wang et al.	3(79)	CT versus Routine(Digit Span)	SMD: 0.28(-0.39, 0.95)	56
Sherman et al.	12(NR)	CT versus Non-trained	Hedges' g: 0.61(0.29, 0.94)	74
Wang et al.	8(286)	CCT versus Routine	SMD: 0.37(0.13, 0.61)	0
Zhao et al.	5(557)	CT versus Routine	MD: 0.65(0.52, 0.78)	0
Episodic memory				
Chong Wang et al.	5(155)	CT versus Routine(immediate memory)	SMD: 0.32(-0.01, 0.66)	0
Chong Wang et al.	6(185)	CT versus Routine(delayed memory)	SMD: 0.31(0.01, 0.61)	0
Anxiety				
Garcia-Casal et al.	2(68)	Before and after the CR	SMD: 0.55(0.07, 1.04)	42
Attention				
Zhao et al.	4(498)	CT versus Routine	MD: 0.86(0.67, 1.05)	50

CI = confidence interval. MMSE = mini-mental state examination. TMT-B = Trail Making Test B. ADAS-Cog = Alzheimer's disease Assessment Scale-cognitive subscale. NA = not applicable. MD = mean difference. SMD = standard mean difference. Hedges' g = Effect sizes were calculated by computing the mean change scores ($M_{\text{post}} - M_{\text{pre}}$ or $M_{\text{follow-up}} - M_{\text{pre}}$) between the intervention and comparator conditions (control or other treatment groups).

and conducted a reanalysis. We divided them into subgroups according to different intervention (CT, CS, CR, and CCT), control methods (Routine treatment, Passive control and Active control) and different diagnose (MCI or dementia). The SMD was 0.62 (95%CI: 0.47, 0.78; I² = 53.9%) using the random model. Overall, there was a statistically significant difference between cognitive interventions and control group. However, subgroup analyses showed no statistically significant differences between the CS versus Active control and CS versus Passive control group (Fig. 2 and Appendix C).

3.3.2. Other outcomes

There were five pooled results (8 RCTs) on depression, five pooled results (22 RCTs) on executive function, four SRs/MAs (28 RCTs) on working memory, two pooled results (11 RCTs) on episodic memory, one pooled result (2 RCTs) on anxiety, and one meta-analysis from 4 RCTs on attention (Table 2). We found that the conclusions on the statistical significance of the treatment effect vary from study to study, and this may be due to the small sample size and the lower quality of the part of the research.

3.4. Methodological quality of included reviews (AMSTAR-2)

AMSTAR-2 recommends that users adopt the rating process based on identification of critical domains, and the critical domains of the AMSTAR-2 scale include items 2, 4, 7, 9, 11, 13 and 15.¹⁸ The results of AMSTAR-2 assessment are given in Table 3. Based on the proposed rating scheme of AMSTAR-2, we have low confidence in the results of two reviews,^{15,25} and the critically low with the rest of 20 reviews. The key factors affecting the quality of the literature included were item 2 (just 2 reviews^{4,25} contained an explicit statement that the review methods were established prior to the conduction of the review and justified any significant deviations from the protocol), item 3 (only 4 studies^{4,12,15,20} explained their selection of the study designs for inclusion in the review), item 7 (just 1¹⁵ review authors provided a list of excluded studies and justified the exclusions) and item 10 (none of the studies reported on the sources of funding for the studies included in the review).

3.5. Quality of evidence in included reviews (GRADE)

The 22 SRs/MAs included 28 outcomes related to the effectiveness of cognitive training on participants with MCI or dementia. The results

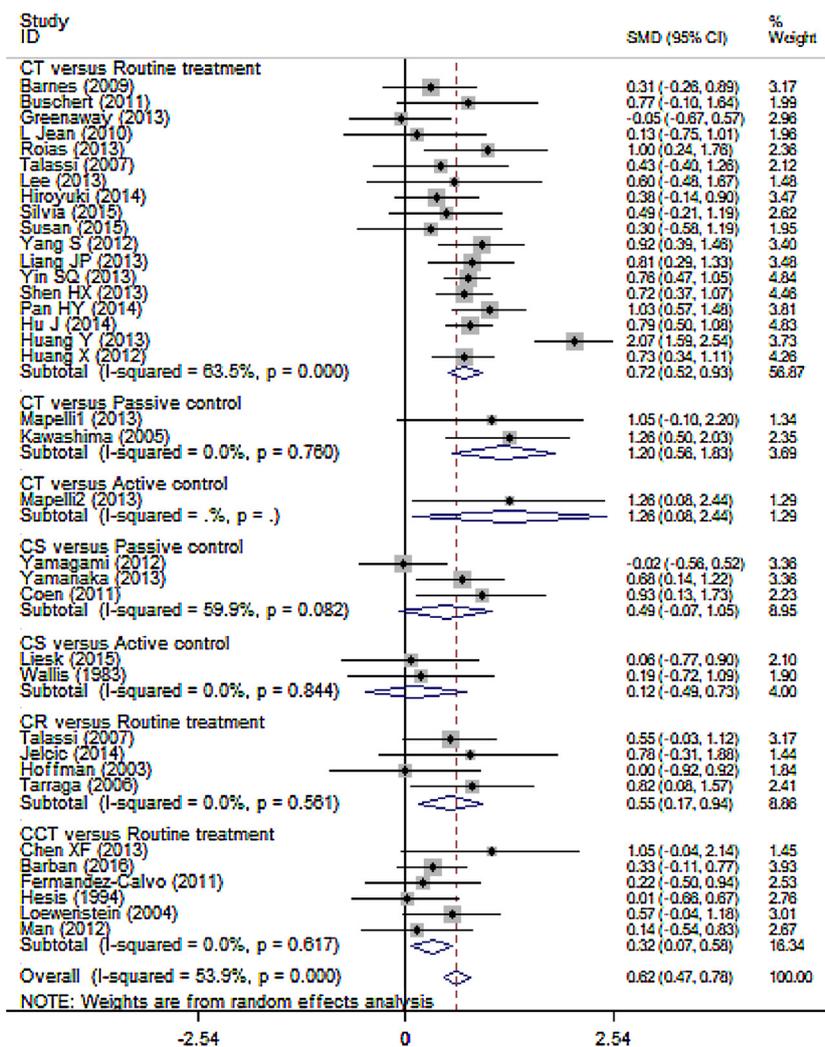


Fig. 2. Effects of cognitive intervention on overall cognitive function.

of GRADE evaluation showed that 11 (39.3%) outcomes were of moderate quality, 12 (42.9%) were low quality and 5 (17.8%) were very low (Table 4). Limitations were the most common of the downgrading items in the included reviews, all the outcomes were biased in randomness, allocation, concealment and blindness. Followed by publication bias (n = 11, 39.3%), inconsistency (n = 6, 21.4%), imprecision (n = 4, 14.3%) and indirectness (n = 0, 0.0%).

4. Discussion

SR/MA is a comprehensive research method used to evaluate the factors related to the treatment, etiology, diagnosis and prognosis of the same health problem. To the best of our knowledge, this was the first overview that systematically analyzed the efficacy of cognitive interventions on global cognitive function of participants with MCI or dementia. We evaluated the methodological quality and quality of evidence from included SRs/MAs and provided an evidence-based assessment and an objective summary on the effectiveness of cognitive interventions for MCI or dementia.

22 SRs/MAs were included of which 19 reviews showed significant improvements in global cognitive functions. The reason why cognitive interventions can improve the patients' cognitive function and delay the development of the disease is mainly based on its theoretical basis: the plasticity of the brain.²¹ Some studies have shown that cognitive interventions will improve the working memory, plot memory and other functions of participants with MCI or dementia. In addition, the activity

of the dorsolateral frontal cortex and bilateral parietal cortex of the cerebral cortex will be enhanced, forming a new neural pathway, and promoting the improvement of brain function.³⁷ However, in the included SRs/MAs, 3 reviews did not find significant advantages of cognitive interventions. It was worth noting that, all these three reviews pointed out that the small sample size and language limitations of the studies might bias the findings of their review, which reminds us to draw careful conclusions. For example, Oltra-Cucarella et al. found that CR showed a significantly higher effect in outcomes measuring functioning in targeted domains with no differences in standard cognitive tests.¹⁴ After a comprehensive analysis of published reviews, the current results suggest that cognitive interventions may be potential efficient way to improve the cognitive functions in MCI or dementia patients,^{4,35} but these results need to be further verified in the future.

Considering safety, it is obvious that cognitive interventions are safer than medication and can avoid the side effects of medication. Therefore, cognitive interventions could be an alternative, or used as an add-on treatment for pharmacotherapy. Yet, methodological shortcomings of existing trials should be addressed in the future trials.³⁸ Future RCTs should comply with the CONSORT statement, which can guide the author to improve the quality of the report, so that we can strictly evaluate the RCTs and interpret the results.³⁹

High-quality SRs/MAs can provide valuable references to patients, doctors and stakeholders. This review showed that the overall quality of the SRs/MAs was on the low side, of which 2 were of low quality and the other 20 were of critically low. All of the included studies met items

Table 3
Critical appraisal of included studies, through using the AMSTAR tool.

Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall quality
Tammy Hoffmann (2010)	1	0	1	1	1	1	1	1	1	0	1	1	1	0	1	0	L
Aimee Spector (2012)	1	0	0	1	0	0	0	1	0	0	1	1	1	0	1	0	CL
Alex Bahar-Fuchs (2013)	1	0	1	0	1	1	0	1	0	0	1	1	1	0	1	1	CL
Carne Carrion (2013)	1	0	0	1	1	1	0	1	0	0	1	1	1	0	1	1	CL
Chong Wang (2014)	1	0	0	1	1	1	0	1	1	0	1	1	1	1	1	1	CL
Huntley (2015)	1	0	0	0	1	1	0	1	1	0	1	0	0	1	0	1	CL
Chandler (2016)	1	0	0	0	1	1	0	1	0	0	1	0	0	1	1	1	CL
Song (2016)	1	0	0	0	1	1	0	1	1	0	1	1	1	0	1	1	CL
Jennifer L. Scott (2016)	1	1	0	1	1	1	0	1	1	0	1	1	1	1	1	1	L
García-Casal (2017)	1	0	0	0	1	1	0	1	1	0	1	0	1	0	0	1	CL
Folkerts (2017)	1	0	0	0	1	1	0	1	1	0	1	1	1	1	1	1	CL
Kallio (2017)	1	0	0	0	1	1	0	1	1	0	1	1	1	1	1	1	CL
Karssemeijer (2017)	1	1	1	0	1	1	0	1	1	0	1	1	1	1	1	1	CL
Sherman (2017)	1	0	0	0	1	1	0	1	1	0	1	1	0	1	0	1	CL
Wang (2017)	1	0	0	1	1	1	0	1	1	0	1	1	1	1	1	1	CL
Chen (2017)	1	0	0	0.5	1	1	0	1	1	0	1	1	0	1	0	0	CL
Ge (2018)	1	0	0	0	1	1	0	1	1	0	1	0	0	1	0	1	CL
Couture (2018)	1	0	0	1	1	1	0	1	1	0	1	1	0	0	0	1	CL
Zhao (2018)	1	0	0	1	1	1	0	1	1	0	1	1	1	1	1	1	CL
Oltra-Cucarella (2018)	1	0	0	0	1	1	0	1	1	0	1	1	1	0	0	0	CL
Kua (2019)	1	0	0	0	1	1	0	1	1	0	1	1	1	1	0	0	CL
Liang (2019)	1	0	1	1	1	1	0	0	1	0	1	0	0	0	0	0	CL
Number of 1(%)	22(100)	2(9)	4(18)	9(41)	21(95)	21(95)	1(5)	21(95)	18(82)	0(0)	22(100)	17(77)	15(68)	13(59)	13(59)	16(73)	

CL = critically low. L = low. H = high. Q1 ~Q16: See appendix D.

Table 4
Quality of evidence in included SRs/MAs with GRADE.

Author(year)	Outcomes (n)	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
Chong Wang(2014)	CT VS Routine	Effectiveness-General(6)	-1 [ⓐ]	0	0	0	Moderate
Huntley(2015)	CS VS Non-active controls	Effectiveness- General(17)	-1 [ⓐ]	0	0	0	Moderate
	CS VS Active controls	Effectiveness-General(3)	-1 [ⓐ]	0	0	-1 [ⓑ]	Low
	CS VS Non-active controls	Effectiveness-General(9)	-1 [ⓐ]	0	0	0	Moderate
Chandler(2016)	CT VS Routine	Effectiveness-General(15)	-1 [ⓐ]	0	0	-1 [ⓑ]	Low
	Therapist-based VS Routine	Effectiveness-General(56)	-1 [ⓐ]	0	0	0	Moderate
	Multiple VS Routine	Effectiveness-General(19)	-1 [ⓐ]	0	0	0	Moderate
Song(2016)	CCT VS No intervention	Effectiveness-General(4)	-1 [ⓐ]	0	0	-1 [ⓑ]	Low
	Multiple VS No intervention	Effectiveness-General(6)	-1 [ⓐ]	0	0	-1 [ⓑ]	Low
	MT VS No intervention	Effectiveness-General(3)	-1 [ⓐ]	0	0	-1 [ⓑ]	Very low
Jennifer L. Scott (2016)	CT VS Routine	Effectiveness-Depression(4)	-1 [ⓐ]	0	0	-1 [ⓑ]	Low
García-Casal(2017)	CCT VS No intervention	Effectiveness-General(5)	-1 [ⓐ]	0	0	-1 [ⓑ]	Very low
	CCT VS No intervention	Effectiveness-Depression(3)	-1 [ⓐ]	-1 [ⓑ]	0	-1 [ⓑ]	Very low
Folkerts(2017)	CT VS Passive control group	Effectiveness-General(7)	-1 [ⓐ]	0	0	-1 [ⓑ]	Low
		Effectiveness-Memory(2)	-1 [ⓐ]	0	0	-1 [ⓑ]	Low
		Effectiveness-Depression(5)	-1 [ⓐ]	0	0	0	Moderate
	CT VS Active control group	Effectiveness-General(5)	-1 [ⓐ]	-1 [ⓑ]	0	0	Low
		Effectiveness-Depression(2)	-1 [ⓐ]	-1 [ⓑ]	0	-1 [ⓑ]	Very low
Karssemeijer(2017)	CT VS Active control group	Effectiveness-General(10)	-1 [ⓐ]	0	0	0	Moderate
		Effectiveness-Memory(3)	-1 [ⓐ]	-1 [ⓑ]	0	-1 [ⓑ]	Very low
Sherman(2017)	CCT/CT VS Non-trained	Effectiveness-General(16)	-1 [ⓐ]	0	0	-1 [ⓑ]	Low
		Effectiveness-Memory(20)	-1 [ⓐ]	-1 [ⓑ]	0	0	Low
Wang(2017)	CT VS Routine	Effectiveness-General(10)	-1 [ⓐ]	0	0	0	Moderate
		Effectiveness-Memory(8)	-1 [ⓐ]	0	0	0	Moderate
Chen(2017)	CT VS Routine	Effectiveness-(MMSE)General (4)	-1 [ⓐ]	0	0	0	Moderate
		Effectiveness-(ADL)General (4)	-1 [ⓐ]	0	0	0	Moderate
Zhao(2018)	CT VS Routine	Effectiveness-General(11)	-1 [ⓐ]	-1 [ⓑ]	0	0	Low
Liang(2019)	CT VS Routine	Effectiveness-General(8)	-1 [ⓐ]	0	0	-1 [ⓑ]	Low

BPSD = behavioral and psychological symptoms. QoL = quality of life. ⓐ=The design of the experiment with a large bias in random, distributive hiding or blind. ⓑ= The confidence interval overlaps less, the heterogeneity test P is very small, and the I² is larger. ⓓ= Confidence interval is not narrow enough. ⓔ=Funnel graph asymmetry. ⓕ=Fewer studies are included and there may be greater publication bias.

1 and 11, in other words, (1) All of the research questions and criteria were based on PICO; (2) All of included reviews used appropriate methods for statistical combination of results. However, none of the included reviews reported on the sources of funding for the studies included in the review. 95% of them did not provide a list of excluded studies and justify the exclusions. Moreover, 91% reviews did not contain an explicit statement that the review methods were established prior to the conduct of the review and not report any significant deviations from the protocol, which seriously affected the integrity of the entire article. 59% SRs/MAs did not use a comprehensive literature search strategy, which might lead to bias to the final results. Altogether, the current methodological quality of SRs/MAs about the effectiveness of cognitive training on participants with mild cognitive impairment or dementia needs to be improved, and all review authors should strictly comply with the item requirements of AMSTAR-2 in order to make the results more scientific.

According to the result of the GRADE system, we found that Low or very low quality outcome indicators accounted for about 1/3 (60.7%). All of them were demoted due to the limitations caused by bias in random, distributive hiding or blind. As a matter of fact, cognitive intervention needs active cooperation of participants; therefore, it is very difficult to implement blind method in this process. At the same time, we found that smaller sample size led to greater heterogeneity among studies, and smaller number of included studies resulted in a greater publication bias. Therefore, more large samples and high-quality researches are needed in the future to further corroborate the current conclusions.

Some limitations of this overview should be noted. Firstly, the

Appendix A

Search strategies of PubMed database.

Strategies

-
- #1 Cognitive training [ti, ab] OR Cognitive intervention [ti, ab] OR Cognitive function training [ti, ab]
 - #2 Cognitive Dysfunction [Mesh]
 - #3 Cognitive Dysfunction [ti, ab] OR Cognitive Impairment [ti, ab] OR Age-Related Memory Disorders [ti, ab] OR Mild Cognitive Impairment [ti, ab] OR MCI [ti, ab] OR Mild Neurocognitive Disorder [ti, ab] OR Cognitive Decline [ti, ab] OR Mental Deterioration [ti, ab]
 - #4 (#2 OR #3)
 - #5 Dementia [Mesh]
 - #6 Dementia [ti, ab] OR Senile Paranoid Dementia [ti, ab] OR Amentia [ti, ab]
 - #7 (#5 OR #6)
 - #8 Alzheimer Disease [Mesh]
 - #9 Alzheimer Disease [ti, ab] OR Alzheimer's Disease [ti, ab] OR Senile Dementia [ti, ab] OR Alzheimer Type Dementia [ti, ab] OR ATD [ti, ab] OR Alzheimer Type Senile Dementia [ti, ab] OR Primary Senile Degenerative Dementia [ti, ab] OR Alzheimer Syndrome [ti, ab] OR Alzheimer Dementia [ti, ab]
 - #10 (#8 OR #9)
 - #11 Meta-analysis[Mesh]
 - #12 Systematic [ti, ab] OR Review [ti, ab] OR Meta-analysis [ti, ab]
 - #13 (#11 OR #12)
 - #14 (#4 OR #7 OR #10)
 - #15 (#1 AND #13 AND #14)
-

Appendix B

Full text articles excluded with reasons.

Full text articles excluded	Reasons
Patricia Heyn (2004)	The intervention does not meet the criteria
Sitzer (2006)	Not providing sufficient information
Linda Clare (2007)	Non-systematic review
Le'onie Jean (2010)	Non-RCT
Nicola J Gates (2011)	Non-RCT
Joshua Stott (2011)	Non-RCT
Huijie Li (2011)	Not providing sufficient information
Sharon Sanz Simon (2012)	Non-RCT
Drennan (2012)	The intervention does not meet the criteria
Nicole Amoyal (2012)	The intervention does not meet the criteria

evaluation of methodological and evidentiary quality is a subjective process, and the results of the evaluation may be affected by the subjective thinking of the authors. Secondly, we did not re-extract data from the original study due to the slight differences in the exclusion criteria that were included among the individual SRs/MAs. Finally, we regret that we have not retrieved any high-quality reviews this time, and expect a larger sample, a higher-quality article in the future.

5. Conclusion

The present overview of SRs/MAs indicates that persons with MCI or dementia can benefit from cognitive interventions. Future review can focus on improving specific areas of cognitive function, such as depression, working memory, executive function, episodic memory etc. to provide a more comprehensive and detailed analysis. In addition, we found that the current meta-analysis has hardly been analyzed in accordance with the normative steps strictly, resulting in low literature quality. More high-quality reviews are needed in the future to further systematically verify this conclusion.

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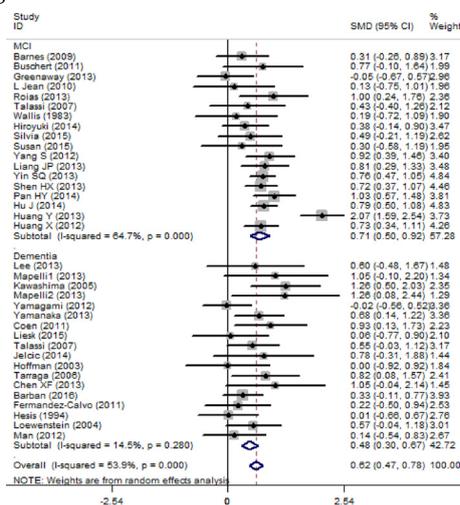
Declaration of Competing Interest

The authors have no conflict of interest to declare.

Yu Song (2012)	The intervention does not meet the criteria
Tammy Hopper (2013)	Non-RCT
Jennifer Reijnders (2013)	The object of study does not meet the criteria
Nicola Gates (2013)	The intervention does not meet the criteria
Yu Song (2013)	Data duplication
Sheldon Benjamin (2013)	Summary of the meeting
Sonia Hines (2014)	Non-RCT
Phuong Leung (2014)	The intervention does not meet the criteria
Nicolas Farina (2014)	The intervention does not meet the criteria
Lan Tan (2014)	Summary of the meeting
Michelle E (2014)	The object of study does not meet the criteria
Hannah Coyle (2014)	The intervention does not meet the criteria
Yun Jeong Hong (2015)	Non-RCT
T. HERR (2015)	The intervention does not meet the criteria
Javier (2016)	The control group not meet the criteria
H. K. Nedergaard (2016)	The intervention does not meet the criteria
C. Groot (2016)	The intervention does not meet the criteria
Philipe (2017)	The intervention does not meet the criteria
Guilan Huang (2017)	Not providing sufficient information
McGrattan (2017)	Summary of the meeting
Rigney N (2017)	Summary of the meeting
Nicole (2017)	The intervention does not meet the criteria
Franciele Cascaes (2018)	The intervention does not meet the criteria
Rohan Bhome (2018)	The intervention does not meet the criteria
Yanxia Chen (2018)	Summary of the meeting
Mary Butler (2018)	Not providing sufficient information
Michelle Brasure (2018)	Not providing sufficient information
Elizabeth S (2018)	The object of study does not meet the criteria
Shannon L (2018)	The object of study does not meet the criteria
Alex Bahar-Fuchs (2018)	Summary of the meeting

Appendix C

Effects of cognitive intervention on overall cognitive function



Appendix D

- Q1: Did the research questions and inclusion criteria for the review include the components of PICO?
- Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
- Q3: Did the review authors explain their selection of the study designs for inclusion in the review?
- Q4: Did the review authors use a comprehensive literature search strategy?
- Q5: Did the review authors perform study selection in duplicate?
- Q6: Did the review authors perform data extraction in duplicate?
- Q7: Did the review authors provide a list of excluded studies and justify the exclusions?
- Q8: Did the review authors describe the included studies in adequate detail?
- Q9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
- Q10: Did the review authors report on the sources of funding for the studies included in the review?
- Q11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
- Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

Q13: Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?

Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

Q15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

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