Neuropsychology Review (2022) 32:247–273
https://doi.org/10.1007/s11065-021-09486-4

REVIEW

The Effect of Cognitive Intervention on Cognitive Function in Older Adults With Alzheimer's Disease: A Systematic Review and Meta-Analysis

Yun-Yun Wang[1,2] · Liang Yang[1,3] · Jing Zhang[1,4] · Xian-Tao Zeng[1,2] · Yang Wang[5,6] · Ying-Hui Jin[1,2]

Received: 18 June 2019 / Accepted: 11 February 2021 / Published online: 24 April 2021

Abstract

Cognitive intervention includes cognitive stimulation, cognitive training, and cognitive rehabilitation. This systematic review was performed to re-assess the efficacy of cognitive intervention for the patients with Alzheimer's disease (AD). Twenty studies (2012 participants) were eventually included. For global cognitive function, the combined mean difference (MD) in eight studies was 1.67 (95% Confidence Interval: 0.45, 2.89, $p=0.007$; $Q=33.28$, df = 8, $p<0.0001$, $\tau^2=2.17$, $I^2=76\%$) for the short term. The pooled standardized mean difference (SMD) of six RCTs was 1.61 (95% Confidence Interval: 0.65, 2.56, $p=0.0009$; $Q=127.66$, df = 6, $p<0.00001$, $\tau^2=1.56$, $I^2=95\%$) for the medium term. The pooled SMD of seven studies was 0.79 (95% Confidence Interval: 0.33, 1.25, $p=0.0008$; $Q=35.10$, df = 7, $p<0.0001$, $\tau^2=0.33$, $I^2=80\%$) for the long term. For depression, the pooled SMD of two trials was -0.48 (95% Confidence Interval: -0.71, -0.24; $p<0.0001$, $I^2=4\%$) for the short term. Cognitive training may show obvious improvements in global cognitive function whether after short, medium, or long-term interventions and in depression after short term intervention. However, the positive effect of the intervention on general cognitive function or depression did not seem to persist after intervention ended. There is still a lack of reliable and consistent conclusions relevant to the effect of cognitive stimulation and cognitive rehabilitation on observed outcomes, cognitive training for memory or other non-cognitive outcomes. PROSPERO registration number: CRD42019121768.

Keywords Alzheimer's disease · Cognitive stimulation · Cognitive training · Cognitive rehabilitation · Meta-analysis

Introduction

Alzheimer's disease (AD) is a degenerative neurological disorder that progressively affects memory, executive function, visuospatial ability, attention, and other cognitive functions (Herrup, 2011). It is the most common form of dementia in older people, accounting for at least 60% of dementia cases (Thies & Bleiler, 2011). The number of people with dementia has been estimated to be 35.6 million worldwide. The incidence has been predicted to double every 20 years and to reach 115.4 million by 2050 (World Health Organization, 2012). An estimated 700,000 Americans aged 65 years in 2017 will have AD when they die, and their deaths will be mainly due to its complications (Alzheimer's Association, 2017). In addition, the global estimates of costs for dementia will gradually increase in the US, from $957.56 billion in 2015 to $2.54 trillion in 2030 and $9.12 trillion in 2050 (Jia et al., 2018). The total costs of AD relative to the gross domestic product were 1.31 in Asian Pacific high-income regions, 1.30 in North American high-income regions, 0.97 in Australia, and 0.90–1.29 in Europe (Jia et al., 2018).

Pharmacological therapies for AD have attracted the attention of researchers and governments. The U.S. Food and Drug Administration has approved six drugs (tacrine that was discontinued in the United States due to potentially severe side effects, galantamine, rivastigmine, donepezil,

✉ Ying-Hui Jin
jinyinghui0301@163.com

1 Center for Evidence-Based and Translational Medicine, Zhongnan Hospital of Wuhan University, Wuhan, China

2 Center for Evidence-Based and Translational Medicine, Wuhan University, Wuhan, China

3 Medical Department of Wuhan University, Wuhan, China

4 First Clinical College of Wuhan University, Wuhan, China

5 Department of General Surgery, Huaihe Hospital of Henan University, Kaifeng, China

6 Center for Evidence-Based Medicine and Clinical Research, Huaihe Hospital of Henan University, Kaifeng, China

memantine, and a drug that combined memantine and donepezil) for the treatment of AD that temporarily improved symptoms by increasing the level of neurotransmitters in the brain. However, none of these drugs stops the progression of AD, and their effectiveness varies from person to person and is limited in duration (Alzheimer's Association, 2017). Furthermore, the safety of these drugs is still unclear, for example cholinesterase inhibitors (e.g., galantamine, donepezil) may increase the risk of adverse events in AD patients. In addition, the high cost of drug development, the relatively long time needed to determine whether an investigational treatment is effective and the ability of any drug to cross the blood–brain barrier to affect disease progression also hinder the development of effective treatments for Alzheimer's (Alzheimer's Association, 2017).

Under these circumstances, nonpharmacological interventions that aim to improve or maintain cognitive function, the ability to perform activities of daily living or overall quality of life may be considered a complementary intervention option. Cognitive interventions are an important type of nonpharmacological intervention that can improve the cognitive function of older adults who are cognitively healthy or have mild impairment or dementia (Chiu et al., 2017; Hopper et al., 2013; Mewborn et al., 2017; Sherman et al., 2017; Smart et al., 2017). It includes cognitive training, cognitive stimulation, and cognitive rehabilitation (Clare et al., 2003). Cognitive training mainly consists of different tasks based on individual performance to improve specific cognitive functions (such as memory, visuospatial ability, attention, or language) and is often delivered at-home or combines home-based and supervised training (Brueggen et al., 2017; Farina et al., 2002; Zanetti et al., 1997, 2011), for example, in order to improve temporal orientation, the participants may be asked to recognize and recall the date (year, season, month, day of the week, date and time) regularly by means of some environmental aids such as calendars, clocks and pictures showing landscapes that could easily be related to a specific season. Cognitive stimulation is provided through social activities and group discussions for the purpose of improving or at least maintaining cognitive or social function in a given domain (Sherman et al., 2017). Cognitive rehabilitation focuses on improving patients' functioning in daily life, such as learning or relearning important information, and maintaining this learning over time under the guidance of family members and (or) health care professionals; such efforts help older adults to obtain or maintain optimal functioning using an individualized approach (Clare et al., 2003; Wilson, 1997).

Recent systematic reviews have concentrated on the effects of cognitive interventions for people with dementia. However, there have been some contradictory findings between these reviews. For instance, Bahar-Fuchs et al. found that cognitive training is probably connected with small to moderate positive effects on global cognition and verbal semantic fluency at the end of interventions, and these benefits appear to be maintained in the 3 to 12 months post treatment (Bahar-Fuchs et al., 2019). However, Huntley et al. found that cognitive training or combined mixed cognitive training and stimulation interventions do not improve general cognition in patients with dementia (Huntley et al., 2015). In addition, Kim et al. found that cognitive stimulation can have small to moderate effects on improving cognition and quality of life for patients with dementia (Kim et al., 2017), and there is evidence that cognitive stimulation can improve MMSE and ADAS-Cog scores, however, heterogeneity means that cognitive stimulation may not show benefits on the ADAS-Cog in all settings, and improvements on the ADAS-Cog are not generally clinically significant (Huntley et al., 2015). Liang et al. used the data from 22 studies (1368 participants) and performed a bayesian network meta-analysis to rank the included intervention, and further showed that cognitive training might be the best method for improving the cognitive function of AD patients compared with cognitive stimulation and cognitive rehabilitation (Liang et al., 2019). However, the relationship between the effects of cognitive interventions and their duration, as well as the duration of the after intervention effects to improve our understanding of the extent to which observed gains are retained, are unclear (Li et al., 2017).

Thus, this systematic review was performed to update and expand previous works on the effect of cognitive intervention for AD patients and to further explore the effect of cognitive intervention on AD patients' global cognitive function, memory, and skill level for instrumental activities of daily livings, skill level for activities of daily living, neuropsychiatric symptoms, depression and quality of life after different intervention durations as well as the duration of the effect after the intervention ends based on a comprehensive literature search and a rigorous methodological quality appraisal. We hope to provide a relatively more reliable conclusion regarding these interventions to satisfy the needs of decision makers and guideline development groups when making decisions or recommendations for people with AD.

Methods

The systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (Moher et al., 2009). The protocol for this review was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO/); Resgistration number CRD42019121768.

Eligibility Criteria

Included trials met the following criteria: (1) randomized controlled trials (RCTs) were published in English or Chinese; (2) patients were clinically diagnosed with AD or probable AD based on widely accepted, definite diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders-IV criteria (Daniel, 1994) and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984), which is mainly characterized by memory impairment, changes in ability of daily life or behavior, and progressive deterioration of the condition; (3) participants in the experimental group received cognitive intervention, as defined, and participants in the control group received either the same drug treatment or routine care as the experimental group, a placebo, or no intervention; (4) primary outcomes included memory, global cognitive function, severity of dementia, the participants' skill level for instrumental activities of daily living (IADLs), and the participants' skill level for activities of daily living (ADLs); secondary outcomes included neuropsychiatric symptoms, depression and quality of life. All outcomes were evaluated by validated instruments, such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), the Milan Overall Dementia Assessment (MODA), and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) to measure global cognitive function. Two types of outcomes were classified: cognitive outcomes (e.g., general cognitive function, memory) and non-cognitive outcomes (e.g., IADLs, ADLs, neuropsychiatric symptoms, depression, quality of life); (5) pre- and post intervention or follow-up data were available. Trials were excluded if (1) the literature was the protocol for an RCT; (2) the experimental group received cognitive interventions combined with any other intervention, such as diet interventions or physical exercise; (3) the full text of some original articles such as abstracts of conference presentations were unavailable, and efforts to contact the authors were unsuccessful, the article would have to be excluded. To reduce selection bias, two reviewers (LY and JZ) independently screened the characteristics of all RCTs and identified the included studies according to the criteria. Disagreements were resolved by discussion or by consultation with the third researcher (YW) by means of reviewing the RCTs' full text until final agreement was reached.

Search Strategy

The Embase, PubMed, Web of Science, the Cochrane Library, CNKI (China National Knowledge Infrastructure), CBM (Chinese Biomedical Literature database VIP (information/Chinese Scientific Journals database), and Wanfang databases were systematically searched to identify relevant literature from the databases' inception to December 31, 2018. The search strategy consisted of medical subject headings (MeSH) and free words (title/abstract). Search terms included: (1) "Alzheimer disease", "Alzheimer's disease", "dementia" and "AD"; (2) "cognitive intervention", "cognitive training", "cognitive stimulation", "cognitive rehabilitation", "CT", "computerized cognitive training", "CCT", "computer-based cognitive training", "cognitive enrichment", "cognitive therapy", "cognitive remediation", "brain training", "cognitive support", "cognition-focused intervention", "cognition-based intervention", "activity of daily living training", " ADL training", "memory training", "attention training", "attentional training", "thinking function training", "thinking training", "orientation training", "language training", "visual spatial training", "visual space training", "visuospatial training", "executive training"; (3) clinical trial or random. An example of the search strategy using PubMed is shown in Fig. 1.

Data Extraction and Quality Appraisal

Data collection was performed independently by two authors (YW and LY). The authors regularly discussed the data retrieval process to ensure consistency. A standardized form was used to record extracted information including author, year of publication, sample size, descriptions of the interventions, intervention duration, follow-up period after the intervention ended, and outcomes. Where opinions differed regarding the type of cognitive intervention in the experimental group, we invited a third reviewer (YJ) to be involved in the discussion, and ultimately reached an agreement.

The methodology quality of the included studies was independently evaluated by two assessors (YW and LY) using the Cochrane Collaboration's risk of bias tool (Higgins et al., 2011). The key domains of assessment included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data and selective reporting. Firstly, the assessors discussed each domain and tried to reach an agreement. Secondly, in order to deepen the understanding of domains, the assessors conducted a pre evaluation based on 6 RCTs randomly chosen from the included studies. Thirdly, we started a formal evaluation: when opinions differed; discrepancies were resolved by discussion with the third assessor (XZ). Finally, all assessors were able to reach an agreement.

Subgroup Analyses

In order to achieve our research objectives, we conducted subgroup analyses according to modes of cognitive

#1 Alzheimer Disease [Title/Abstract] OR AD [Title/Abstract] OR dementia [Title/Abstract]

#2 cognitive intervention [Title/Abstract] OR cognitive training [Title/Abstract] OR cognitive stimulation [Title/Abstract] OR cognitive rehabilitation [Title/Abstract] OR CT [Title/Abstract] OR computerized cognitive training [Title/Abstract] OR CCT [Title/Abstract] OR computer-based cognitive training [Title/Abstract] OR cognitive enrichment [Title/Abstract] OR cognitive therapy [Title/Abstract] OR cognitive remediation [Title/Abstract] OR brain training [Title/Abstract] OR cognitive support [Title/Abstract] OR cognition-focused intervention [Title/Abstract] OR cognition-based intervention [Title/Abstract] OR activity of daily living training [Title/Abstract] OR ADL training [Title/Abstract] OR memory training [Title/Abstract] OR attention training [Title/Abstract] OR attentional training [Title/Abstract] OR thinking function training [Title/Abstract] OR thinking training [Title/Abstract] OR orientation training [Title/Abstract] OR language training [Title/Abstract] OR visual spatial training [Title/Abstract] OR visual space training[Title/Abstract] OR visuospatial training [Title/Abstract] OR executive Training[Title/Abstract]

#3 "Clinical Trial" [Publication Type] NOT ("Clinical Trial, Phase I" [Publication Type] OR "Observational study" [Publication Type])

#4 "Clinical Trials as Topic" [Mesh] NOT ("Clinical Trials, Phase I as Topic" [Mesh] OR "Observational study" [Mesh])

#5 random* [Title/Abstract]

#6 #3 OR #4 OR #5

#7 #1 AND #2 AND AND #6

Fig. 1 Search strategy on Pubmed

intervention (cognitive stimulation, cognitive training and cognitive rehabilitation), the duration of intervention (short term, ≤ 10 weeks; medium term, 10 ~ 20 weeks; long term, > 20 weeks), and the time-points of follow up after the intervention ended (where data were available).

Statistical Analysis

For each reported outcome, the mean difference and standard deviation were extracted, when the data were not directly available, we obtained the standard deviation of this mean change score based on the existing data such as the mean pre-intervention and the mean post-intervention score for both groups, as well as the standard deviation, under this assumption that the pre-post correlation was 0.50 (Higgins et al., 2019). Continuous data were presented as the mean difference (MD) with 95% confidence interval (CI), and standardized mean difference (SMD) have been used when different scales were used to measure the same outcome. The meta analyses were performed using a random-effects model based on the assumption that the true effect size may vary from study to study (Borenstein et al., 2010). *P* values of < 0.05 were considered to infer statistical significance. However, where studies did not report usable data for pooling of results, these studies were included in this systematic review, but were discarded for the meta-analyses. We also conducted a qualitative analysis.

Heterogeneity in effect sizes was evaluated using the Cochrane' s Q statistic and I^2 statistic. The calculation of effect size for each outcome, pooling of effect sizes and tests of heterogeneity were performed using RevMan 5.3 software (Cochrane Collaboration). Funnel plots, Egger's tests were used to explore publication bias for each outcome that had > 10 studies (Egger et al., 1997; Sterne et al., 2000). The Duval and Tweedie trim and fill method was used to provide an estimate of potential missing effects and yield an effect size estimate if the bias was taken into consideration (Duval et al., 2000). Publication bias were performed using R version 3.6.0 software (The R Foundation for Statistical Computing, Vienna, Austria) with metabias, trimfill and funnel functions in meta packages for plotting funnel plot and Egger test (Balduzzi et al., 2019).

Results

Study Identification Process

The process of literature selection is shown in Fig. 2. After duplicates were excluded, 8732 studies from 10,613 records were chosen for further screening. Through the reading of titles and abstracts, 8653 studies were discarded, and 80 articles were reviewed for potential eligibility by reading the full text. Twenty-five studies (26 articles) were eventually included for further analysis (see Table 1).

The Characteristics and Quality of the Included Studies

The 25 studies included participants from thirteen countries, including the US, UK and China. Among the participants, 1169 AD patients received cognitive interventions, and 843 AD patients received either the same drug treatment or routine care as the experimental group, a placebo, or no intervention. The duration of the interventions ranged from 4 to 48 weeks. Detailed information is presented in Table 1. Overall, the quality of the included RCTs was not high. Most of the studies did not provide detailed information on the methods of random sequence generation, allocation concealment and the blinding of participants and personnel (Figs. 3 and 4).

Synthesis of Results

Global Cognitive Function

Cognitive Stimulation

No data was reported on the effect of cognitive stimulation on global cognitive function after short, medium or long term intervention.

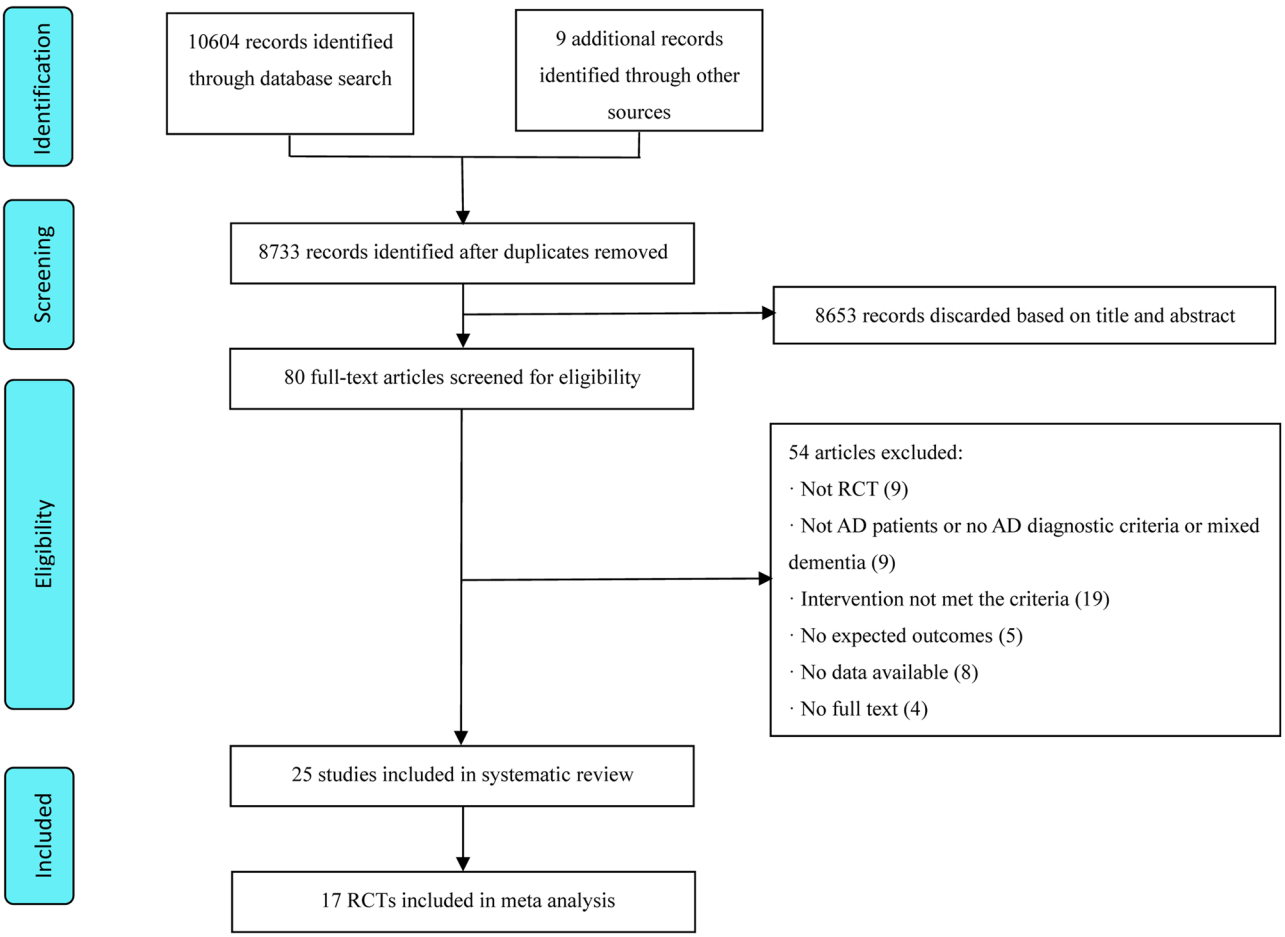

Fig. 2 Flow diagram of literature review

Table 1 Characteristic of included studies

Study	Country	Dignosis criteria	AD categories	Sample size (E/C)	Age, Mean (SD) /Range (E/C)	Intervention content		Follow-up period (week)	Number of loss (E/C)	Outcomes (measurement tools)
						Experimental group	Control group			
Davis et al., 2001	The United States of America	NINCDS-ADRDA	_____	19/18	68.67 (3.86) /72.56 (7.62)	Cognitive training Home attention exercises (30 minutes each day for 6 days per week), face-name training task and spaced- retrieval exercises individual, weekly 1-hour clinic visits for 5 weeks	Placebo condition	_____	_____	Global cognitive function (MMSE), depresssion (GDS), quality of life (QLA-P), verbal memory(WMS-R), logical memory(WMS-R)
Chapman et al., 2004	The United States of America	NINCDS-ADRDA	_____	26/28	54~91	` Cognitive stimulaition Cognitive-communication stimulation program in subgroups of 6 or 7 participants each during 8 weeks, which mainly consisted of discussion topics and verbal retelling of important life events, highlighting involvement in hobbies and activities at home Donepezil	Donepezil	40	All number of loss: 6/7	Global cognitive function (MMSE ADAS-Cog), neuropsychiatric symptoms (NPI), quality of life (QOL-AD)
Bottino et al., 2005	Brazil	NINCDS-ADRDA, ICD-10	Mild	6/7	73.7 (6.4)	Cognitive rehabilitation Temporal and spatial orientation training, using external memory aids, sharing remote life experiences or new experiences, and ADL training, 90-min group sessions, once a week for 20 weeks AChE-I	AChE-I	_____	_____	Global cognitive funciton (MMSE, ADAS-Cog), object memory (FOME), working memory (WMS-R-forward and backward digit span subset), participant's skill level on instrumental activities of daily living (IADL scale)

Table 1 (continued)

Study	Country	Dignosis criteria	AD categories	Sample size (E/C)	Age, Mean (SD) /Range (E/C)	Intervention content		Follow-up period (week)	Number of loss (E/C)	Outcomes (measurement tools)
						Experimental group	Control group			
Onder et al., 2005	Italy	NINCDS-ADRDA	Mild to moderate	79/77	75.7(7.8) /75.8 (6.3)	Cognitive training Three reality orientation session consisting of an organised, intensive cognitive training per week, 30 min every session for 25 weeks Cholinesterase inhibitor	Cholinesterase inhibitor	_____	After intervention: 9/10	Global cognitive function (MMSE, ADAS-Cog), neuropsychiatric symptoms (NPI), participant's skill level on instrumental activities of daily living (IADL scale)
Ta´rraga et al., 2006	Spain	NINCDS-ADRDA	_____	15/16	75.8 (5.9) / 77.4 (4.7	Cognitive training An interactive multimedia internet-based system focusing on cognitive function at different levels of difficulty and at various times during the day, 3 weekly, 20-min sessions of during 24 weeks 8 h/day of an integrated psychostimulation program Cholinesterase inhibitors	8 h/day of an integrated psychostimulation program Cholinesterase inhibitors	_____	_____	Global cognitive function (MMSE ADAS-cog), story recall memory (RBMT- the story recall subset)
Tadaka et al., 2007	Japan	DSM-IV	Mild to moderate	12/12	82.5(6.6) /81.2 (± 6.2)	Cognitive training Reminiscence therapy group sessions using themes and prompts suitable to the subjects' characteristics and life histories, 60-90 min per session, once a week for 8 weeks Routine day-care service	Routine day-care service	24	After intervention: 1/2 After follow up: 0/1	Global cognitive function (MMSE) depression (MOSES-depression)
Liu et al., 2008	China	DSM-IV, NINCDS-ADRDA	Mild	20/20	59~86	Cognitive training Professional training on certain cognitive function, such as memory, attention, language visual space skills training, executive function and problem solving training from Monday to Friday, 2 hours every day for 8 weeks Drug treatment: the name of drug was unclear Home care	Drug treatment The name of drug was unclear Home care	_____	_____	Global cognitive function (MMSE)

Table 1 (continued)

Study	Country	Dignosis criteria	AD categories	Sample size (E/C)	Age, Mean (SD) /Range (E/C)	Intervention content		Follow-up period (week)	Number of loss (E/C)	Outcomes (measurement tools)
						Experimental group	Control group			
Niu et al., 2010	China	NINCDS-ADRDA	Mild	16/16	80.56 (4.23)/ 79.13 (4.38)	Cognitive training Individuall training focusing on a set of tasks requiring executive functions and working memory for 10 weeks. An appropriate level of difficulty was selected for each patient on each set of tasks	Placebo condition	_____	2/1	Global cognitive function (MMSE), neuropsychiatric symptoms (NPI)
Li et al., 2011	China	DSM-IV	Mild to moderate	60/60	52~76	Cognitive training Specialized training on cognitive function by cognitive rehabilitation physicians such as improving patient's memory by retelling, semantics processing and first word memorization based on cards, objects for 12 weeks Piracetam, nimodipine	Piracetam, nimodipine	_____	_____	Global cognitive function (MMSE, MOCA), participant's skill level on activities of daily living (ADL scale)
Zong et al., 2012	China	CCMD-3	_____	30/30	70.3 (2.2)/ 71.5 (2.7)	Cognitive training Specialized training on cognitive function, such as reality orientation, memory training, 45min every time, twice one day, for 24 weeks AChE-I Routine care	AChE-I Routine care	_____	_____	Global cognitive function (MMSE), participant's skill level on activities of daily living (ADL scale)

Table 1 (continued)

Study	Country	Dignosis criteria	AD categories	Sample size (E/C)	Age, Mean (SD) /Range (E/C)	Intervention content		Follow-up period (week)	Number of loss (E/C)	Outcomes (measurement tools)
						Experimental group	Control group			
Bergamasch et al., 2013	Italy	DSM-IV, NINCDS-ADRDA	mild to moderate	16/16	78.19 (5.50) /77.72 (5.06)	Cognitive training Cognitive training consisting of time orientation exercises, spatial orientation, logical reasoning exercises in five 1 month cycles of (one cycle: 20 sessions, 2 h per day, 5 days a week) with a break of 4 weeks in between each cycle) for 48 weeks cholinesterase inhibitors	Non-specific cognitive activity at a Day Centre Cholinesterase inhibitors	_____	_____	Global cognitive function (MMSE MODA), memory (MTI), story recall-immediate memory (Story Recall-Immediate), participant's skill level on activities of daily living (ADL scale), participant's skill level on instrumental activities of daily living (IADL scale), depression (CSDD)
Lee et al., 2013	China	ICD-10, DSM-IV	_____	7/6/6	68~91	Cognitive training (a) Computer-assisted errorless memory programs with 12 30-minute training sessions for 6 weeks. Cognitive training (b) Therapy-led training program on an individual basis with 12 30-minute training sessions for 6 weeks	Placebo condition	3	_____	Global cognitive function (MMSE) prospective memory (Brief Assessment of Prospective Memory-Short form) depression (GDS) participant's skill level on instrumental activities of daily living (HKLIADL scale)

Table 1 (continued)

Study	Country	Dignosis criteria	AD categories	Sample size (E/C)	Age, Mean (SD) /Range (E/C)	Intervention content		Follow-up period (week)	Number of loss (E/C)	Outcomes (measurement tools)
						Experimental group	Control group			
Li et al., 2013	China	DSM-IV	_____	28/25	60~89	Cognitive training and cognitive rehabilitation Professional training for certain cognitive funcation, such as memory, thinking, visual spatial disorder, and training for life skills and sleep mistakes for 24 weeks Routine drug treatment	Routine drug treatment	_____	0/0	Global cognitive function (MMSE), participant's skill level on activities of daily living (ADL scale)
Van Bogaert et al., 2013	Belgium	NINCDS-ADRDA	Mild to moderate	41/41	65~101	Cognitive training 6-8 individual reminscence sessions based on the SolCos model comprising two 45-minute sessions (1 of 4 standardized topics, such as family, profession, holiday, and games) over a period of 4 weeks	Placebo condition	_____	_____	Global cognitive function (MMSE), neuropsychiatric symptoms (NPI), depression (GDS, CSDD)
Brunelle-Hamann et al. 2015 Thivierge et al., 2014	Canada	NINCDS-ADRDA, NIAAA	Mild to Moderate	9/8	80.00(6.14)/ 80.00(4.90)	Cognitive rehabilitation Home-based cognitive rehabilitation programme to learn/relearn an instrumental activity of daily living, twice a week during 4 weeks	Waiting list control	4, 8	Unclear	Everyday memory function (the Rivermead neuropsychiatric symptomsnal memory test), neuropsychiatric symptoms (NPI), participant's skill level on instrumental activities of daily living (DMT), quality of life (DQol)

Table 1 (continued)

Study	Country	Dignosis criteria	AD categories	Sample size (E/C)	Age, Mean (SD) /Range (E/C)	Intervention content		Follow-up period (week)	Number of loss (E/C)	Outcomes (measurement tools)
						Experimental group	Control group			
Barban et al., 2016	Italy	NINCDS-ADRDA	Mild	42/39	76.7(5.7)/ 76.9 (5.7)	Cognitive training 30 min of multi-component process-based cognitive training (10min for memory, 10min for executive functions, and 10min for other cognitive domains) and 30 min of reminiscence therapy, 24 one-hour treatment sessions twice weekly for a total of about 12 weeks	Waiting list control	_____	Unclear	Global cognitive function (MMSE), delayed memory (the Rey Auditory Verbal Learning Test and the Rey-Osterrieth Complex Figure Test), participant's skill level on instrumental activities of daily living (IADL scale)
Camargo et al., 2015	Brazil	DSM-IV	mild to moderate	7/7	80.86 (5.24)/ 79.43 (7.11)	Cognitive training Reality orientation sessions individually consisting of continuous exposure to memory- and orientation-related information using several approaches in weekly 30- to 60-minute during 24 weeks Conventional therapy (essentially pharmacological)	Conventional therapy (essentially pharmacological)	_____	_____	Global cognitive function (MMSE)

Table 1 (continued)

Study	Country	Dignosis criteria	AD categories	Sample size (E/C)	Age, Mean (SD) /Range (E/C)	Intervention content		Follow-up period (week)	Number of loss (E/C)	Outcomes (measurement tools)
						Experimental group	Control group			
Amieva et al., 2016	France	NINCDS-ADRDA	Mild to moderate	170/172/157/154	≥ 50	Cognitive training (a) A structured program of a set of standard tasks designed to involve various cognitive functions such as memory, attention, language, and executive function. Each task involved two levels of difficulty to suit the patients' level of ability Cognitive training (b) Reminiscence therapy focusing on a different personal theme (e.g. schooldays, birthday, wedding, working life, holidays.) in groups involved five to eight patients Cognitive rehabilitation A made-to-measure program consisting of meaningful activities with the person suffering from dementia and his/her caregiver through individual sessions. The activities to be trained had to be selected according to personally relevant goals for the patients and if appropriate could change the trained activity at any time during the program Each intervention program consisted of weekingly sessions (duration: 1h 30min) during the first months and maintenance sessions held every six weeks for the next 21 months	Usual medical care excluding non-drug therapy	_____	After the last measurement: unclear	Global cognitive function (ADAS-Cog), neuropsychiatric symptoms (NPI), depression (MADRS), quality of life (Qol-AD)

Table 1 (continued)

Study	Country	Dignosis criteria	AD categories	Sample size (E/C)	Age, Mean (SD) /Range (E/C)	Intervention content		Follow-up period (week)	Number of loss (E/C)	Outcomes (measurement tools)
						Experimental group	Control group			
Zhang et al., 2016	China	DSM-IV	Mild	60/60	≥65	Cognitive training Specialised training consisting of identifying pictures, telling stories, untying ropes to improve cognitive function for 12 weeks Donepezil hydrochloride and sodium valproate	Donepezil hydrochloride and sodium valproate	_____	_____	Global cognitive function (MMSE), participant's skill level on activities of daily living (ADL scale)
Huntley et al. 2017	UK	NINCDS-ADRDA	Mild	15/15	>60	Cognitive training 18 sessions of training over approximately 8 weeks, each session consisted of 30 trials of adaptive structured digit span task	Placebo condition	_____	_____	Global cognitive function (MMSE, ADAS-Cog) episodic memory (the Logical Memory II task and Paired Associates Learning task), working memory (digit span trial and spatial span trial)
Yang et al., 2017	Korea	NINCDS-ADRDA	Mild	10/10	71.1 (6.9)/69.9 (8.7)	Cognitive training Computer-based cognitive training, such as attention and concentration ability, spatio-temporal ability, memory, twice a week (60 minutes per session), for a total of 12 weeks	No treatment control	_____	_____	Global cognitive function (K-MMSE), verbal memory and visual memory (the Seoul Neuropsychological Screening Battery-Seoul Verbal Learning Test and the Rey Complex Figure test), depression (GDS)
Tao et al., 2017	China	NINCDS-ADRDA	_____	37/37	71.2 (5.3)/ 70.8 (5.1)	Cognitive training Reminiscence therapy mainly consisting of arousing recall, presenting and sharing life experience once a week for 12 weeks Routine drug treatment and care	Routine drug treatment and care	_____	0/0	Global cognitive function (MMSE), quality of life (QOL-AD)

Table 1 (continued)

Study	Country	Dignosis criteria	AD categories	Sample size (E/C)	Age, Mean (SD) /Range (E/C)	Intervention content		Follow-up period (week)	Number of loss (E/C)	Outcomes (measurement tools)
						Experimental group	Control group			
Trebbastoni et al., 2018	Italy	NINCDS-ADRDA	Mild to moderate	54/86	50~85	Cognitive training Cognitive training in group sessions fousing on memory, attention, language, visuo-spatial functions and executive functions. Each session was held twice a week for 24 weeks and lasted 75 minutes	Usual care	24	After intervention: 6/0 After follow-up: 3/1	Global cognitive function (MMSE), immediate and delayed memory (Rey Auditory Verbal Learning Test and Babcock Story Recall Test), spatial memory (Coris Block-Tapping), working memory (WAIS)
Bademli et al., 2018	Turkey	IWG-2	Mild to moderate	30/30	_____	Cognitive training Reminiscence therapy sessions supported by materials triggering the memory, such as photographs, household goods, 30 min every seesion, once a week and lasted for 8 weeks	No treatment control	_____	_____	Global cognitive function (SMMSE), depression (CSDD), quality of life (QOL-AD)
Niu et al., 2018	China	NINCDS-ADRDA	Mild to moderate	25/25	76.96 (6.09) /76.12 (6.36)	Cognitive training Individualized cognitive training focusing on real orientation exercise, fluency task exercise, overlapping figure recognition exercise and picture-story learning exercise, twice a week, 40 minutes per time, during 24 weeks	No treatment control	_____	1/0	Global cognitive function (MMSE), neuropsychiatric symptoms (NPI), participant's skill level on activities of daily living (ADL scale)

E Experimental group, *C* control group *NINCDS-ADRDA* the National Institute of Neurological and the Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders, *MMSE* Mini-Mental State Examination, *GDS* Geriatric Depression Scale *QLA-P* Quality of Life-Patient the *WMS-R* Wechsler Memory Scale-Revised Cognitive subscale of the *ADAS-Cog* Alzheimer' s Disease Assessment Scale, *NPI* the Neuropsychiatric Inventory, *QOL-AD* the Quality of Life in Alzheimer's Disease Scale, *ICD-10* the International Classification of Diseases, *AChE-I* Acetylcholinesterase inhibitor, *FOME* Fuld Object Memory Evaluation, *IADL* Instrumental Activities of Daily Living Scale, *MADRS* Montgomery-Asberg Depression Rating Scale, *RBMT* the Rivermead Behavioral Memory Test, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders fourth edition, *MOSES* Multi-dimensional Observation Scales for Elderly Subjects MOCA Montreal cognitive assessment, *ADL* Activities of Daily Living, *CCMD-3* Chinese Classification and Diagnostic Criteria of Mental Disorders, *MODA* the Milan Overall Dementia Assessment, *MTI* Memory Test with Interference, *CSDD* Cornell Scale for Depression in Dementia, *CDRS* Chinese version of the Mattis Dementia Rating Scale, *GDS* the Geriatric Depression Scale, *HKLIADL* Hong Kong Lawton Instrumental Activities of Daily Living Scale, *NIAAA* National Institute on Aging-Alzheimer's Association workgroups, *DMT* Direct Measure of Training, *DQoL* Dementia Quality of Life Questionnaire, *K-MMSE* Korean version of the Mini-Mental State Examination, *WAIS* the Wechsler Adult Intelligence Scale, *IWG-2* International Working Group-2 diagnostic criteria, *SMMSE* Standardized Mini-Mental State Examination (SMMSE)

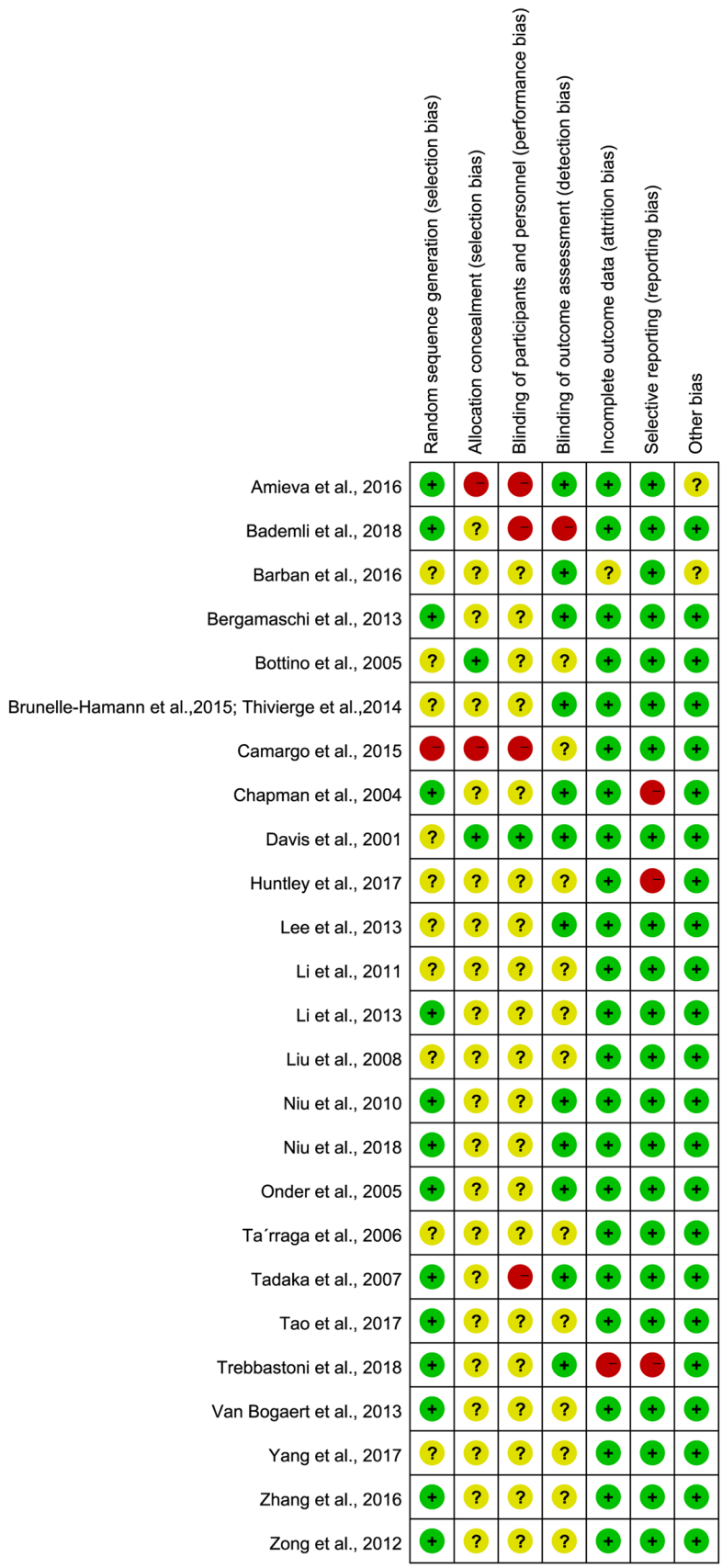

Fig. 3 The risk of bias for each included randomized controlled trial

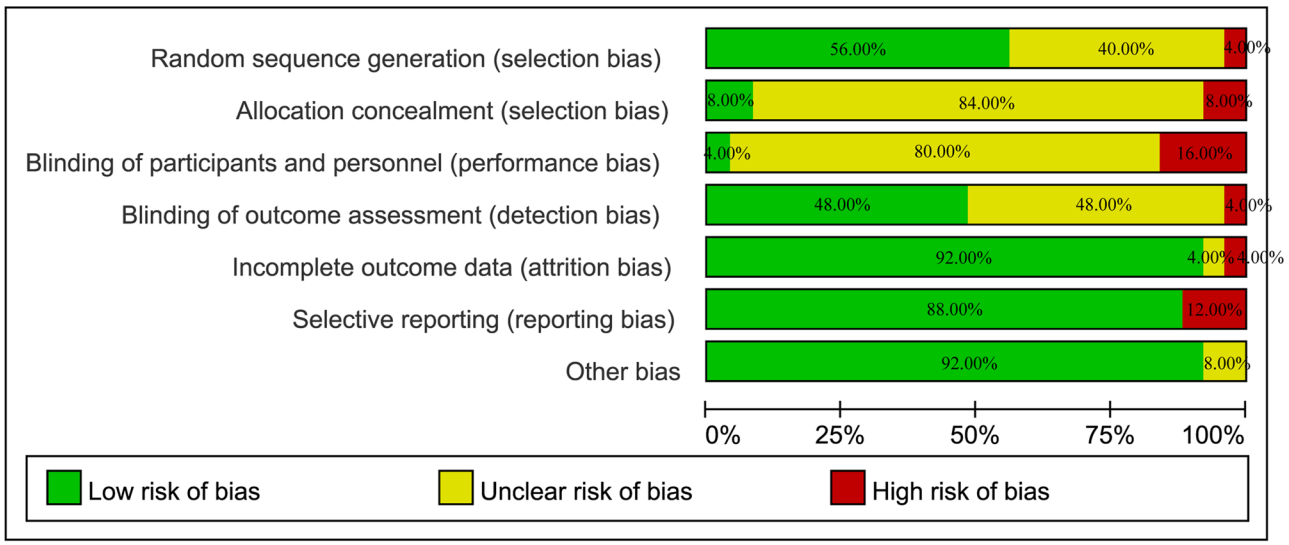

Fig. 4 The graph of risk of bias for all included randomized controlled

Cognitive Training

Twenty studies were included in the analysis of the efficacy of cognitive training for AD patients using MMSE, MOCA or MODA. The combined SMD of eight studies was 1.67 (95% CI: 0.45, 2.89, $p=0.007$; $Q=33.28$, df = 8, $p<0.0001$, $\tau^2=2.17$, $I^2=76\%$) for the short term (Fig. 5). The pooled SMD of six RCTs was 1.61 (95% CI: 0.65, 2.56, $p=0.0009$; $Q=127.66$, df = 6, $p<0.00001$, $\tau^2=1.56$, $I^2=95\%$) for the medium term (Fig. 6). The pooled SMD of seven studies was 0.79 (95% CI: 0.33, 1.25, $p=0.0008$; $Q=35.10$, df = 7, $p<0.0001$, $\tau^2=0.33$, $I^2=80\%$) for the long term (Fig. 7).

Four RCTs reported data on the efficacy of cognitive training for AD patients using ADAS-Cog. One RCT (Huntley et al., 2017) found that there was a significant difference between the groups ($p=0.001$), the control group demonstrated a non-significant increase in ADAS-Cog score ($p=0.158$), reflecting a deterioration in cognitive function, while the training group showed a significant decrease in score ($p=0.008$), representing an improvement in cognitive function following the short term training. Two trials showed contradictory findings, one, (Ta´rraga et al., 2006), showed that patients treated with cognitive training had improved outcome scores on the ADAS-Cog ($p<0.05$) after a medium term intervention, while another, (Amieva et al., 2016), found no significant difference between the experimental group and control group ($p>0.05$) (Amieva et al., 2016). As Fig. 8 shows, the combined MD of the two studies was 0.69 (95% CI: -4.26, 5.63, $p=0.79$; $Q=4.37$, df = 1, $p=0.04$, $\tau^2=9.99$, $I^2=77\%$) for the long term. The data from Amieva et al. 2016 was not included in the quantitative synthesis

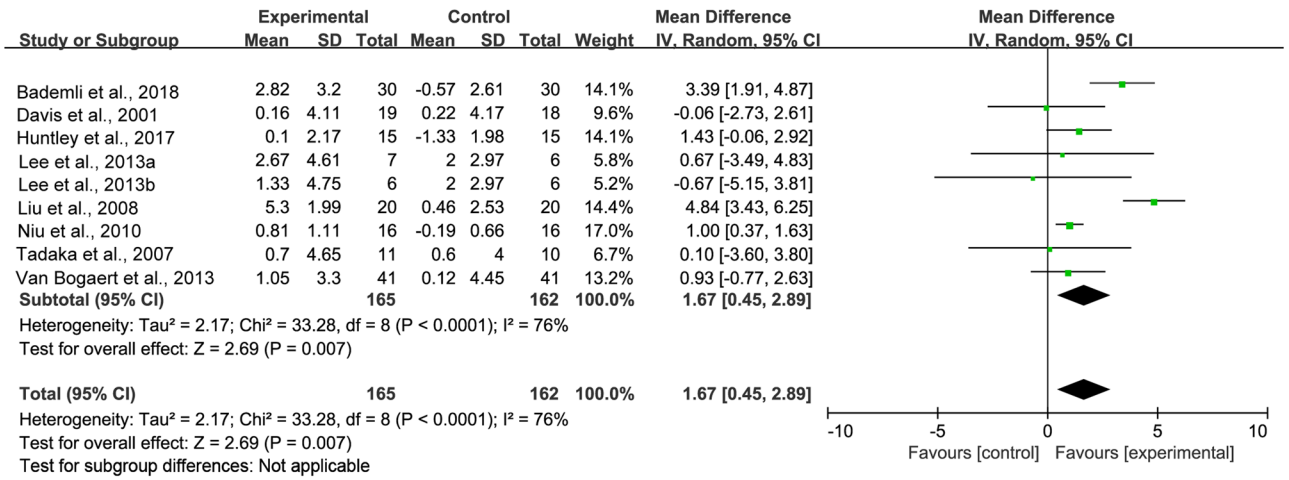

Fig. 5 Effect of cognitive training on global cognitive functions for the short term using MMSE

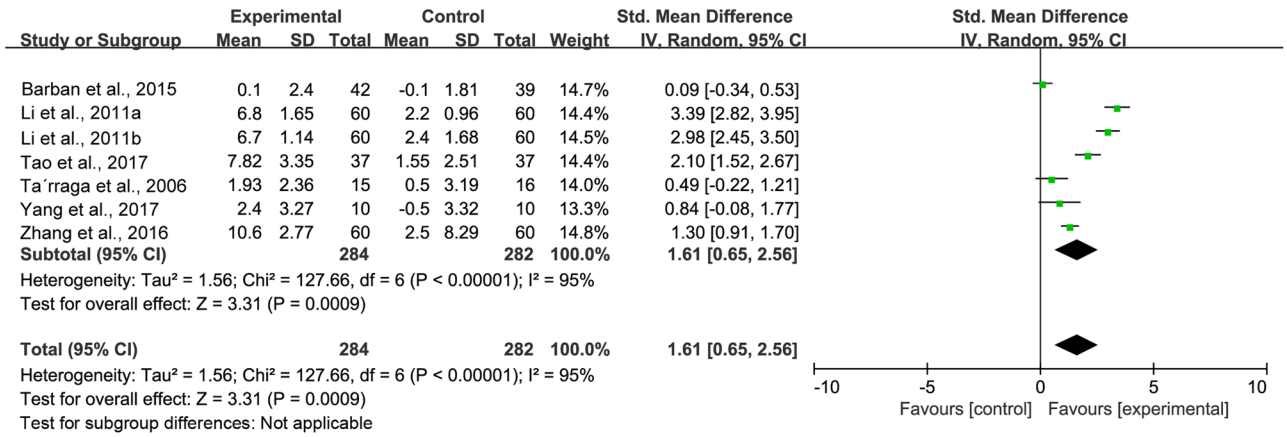

Fig.6 Effect of cognitive training on global cognitive functions for the medium term using MMSE or MOCA, MMSE, Mini-Mental State Examination. MOCA, Montreal cognitive assessment. Li et al., 2011: global cognitive function measured using MMSE. Li et al., 2011: global cognitive function measured using MOCA

due to lack of the baseline score and the mean changes of the ADAS-Cog score, it also demonstrated the same finding for effect for long term intervention.

Cognitive Rehabilitation

Three study explored the intervention effect of cognitive rehabilitation on AD patients using MMSE or ADAS-Cog. Due to lack of the baseline score and the mean changes of ADAS-Cog in the Amieva et al. (2016) trial, we could only do qualitative analysis of the two RCTs and found that there were contradictory results, one, (Bottino et al., 2005), showed that cognitive rehabilitation improved global cognitive function compared with the control group after long-term intervention ($p < 0.05$), while the other, (Amieva et al., 2016), found there was no significant difference between the two groups ($p > 0.05$). In addition, one study (Li et al., 2013) also revealed that compared with the control group, the intervention combining cognitive training and cognitive rehabilitation was beneficial for the patients' global cognitive function improvement in the experimental group after long term intervention ($p < 0.05$). Unfortunately, there were no data on the effect of cognitive rehabilitation after short or medium term intervention.

Follow Up

The donepezil-plus-cognitive stimulation group maintained their level of performance on MMSE over 1 year ($p > 0.05$). In contrast, the donepezil-only group showed a significant decline from baseline ($p < 0.05$: Chapman et al., 2004).

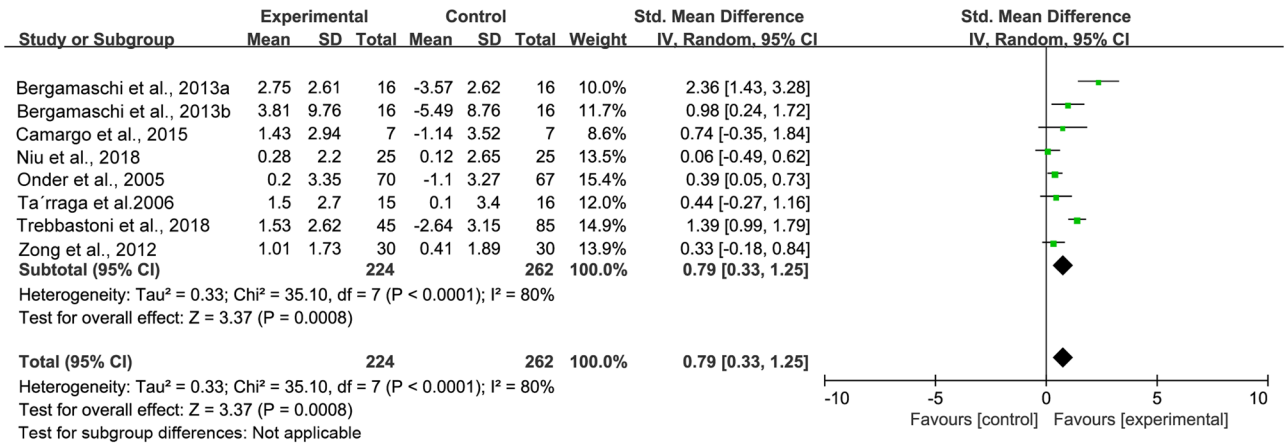

Fig. 7 Effect of cognitive training on global cognitive functions for the long term using MMSE or MODA, MMSE, Mini-Mental State Examination. MODA, The Milan Overall Dementia Assessment. Bergamaschi et al., 2013: global cognitive function measured using MMSE. Bergamaschi et al., 2013: global cognitive function measured using MODA

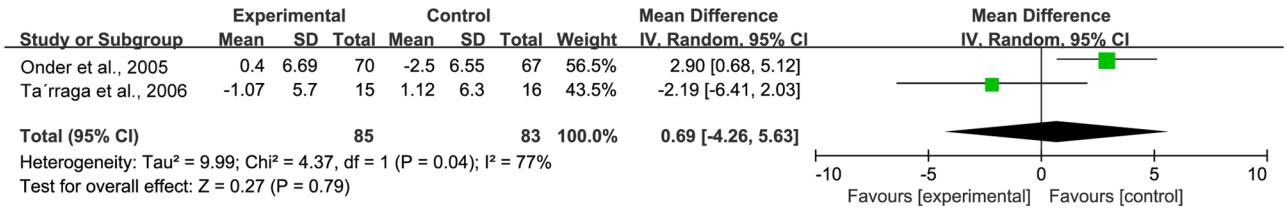

Fig. 8 Effect of cognitive training on global cognitive function for the long term using ADAS-Cog ADAS-Cog, Cognitive subscale of the Alzheimer's Disease Assessment Scale

There were similar finding in the data of ADAS-Cog, indicating that cognitive stimulation may be beneficial for global cognitive function over 1 year (Chapman et al., 2004). The pooled data from the two studies using MMSE demonstrated that cognitive training did not positively affect global cognitive function after 24 weeks of follow-up (MD = -0.09, 95% CI: -1.12, 0.94, $p = 0.86$; $Q = 0.02$, df = 1, $p = 0.88$, $\tau^2 < 0.01$, $I^2 < 0.01$) (see Fig. 9), suggesting that there was no significant difference between the two groups. In addition, no significant differences were detected between the three groups (computer-assisted errorless learning program group, computer-assisted errorless learning program group, control group) after 6 weeks' follow up using MMSE ($p > 0.05$) (Lee et al., 2013). However, there were no data on the effect of only cognitive rehabilitation alone after follow up ended.

Participants' IADL Skill Level

Cognitive Stimulation

There were no data on the effect of cognitive stimulation on AD patients' IADL skill after short, medium or long term interventions.

Cognitive Training

Four RCTs were included in the analysis of the effect of cognitive training on the participants' skill level for instrumental activities of daily living. The combined MD were 4.47 (95% CI: -0.36, 9.29, $p = 0.07$; $Q < 0.01$, df = 1, $p = 0.94$, $\tau^2 < 0.01$, $I^2 < 0.01$) for the short term (Fig. 10) and 0.28 (95% CI: -0.24, 0.80, $p = 0.29$; $Q = 0.74$, df = 1, $p = 0.39$, $\tau^2 < 0.01$, $I^2 < 0.01$) for the long term (Fig. 11). The results indicated that there was no significant difference between the experimental and control groups after short-term and long-term cognitive training. One study (Barban et al., 2016) found a difference approaching significance between the training and the nontraining period in the ratio between the number of participants who showed increased/stable IADL and the number who showed decreased IADL ($p < 0.07$). Specifically, during the medium term training, 68% of the participants showed increased/stable IADL versus 32% who showed decreased IADL, and during the nontraining period, 46% of the participants showed increasedstable IADL versus 54% who showed decreased IADL.

Cognitive Rehabilitation

There were contradictory results regarding the effects of cognitive rehabilitation on IADLs. Brunelle-Hamann suggested that short-term cognitive rehabilitation was beneficial for participant's IADL skill levels after assessment using Direct Measure of Training (DMT) ($p < 0.05$) (Brunelle-Hamann et al., 2015; Thivierge et al., 2014), but Bottino indicated that long-term cognitive rehabilitation was not beneficial using IADL scale ($p > 0.05$) (Bottino et al., 2005). There were no data reporting the effects of cognitive rehabilitation on IADLs in the medium term.

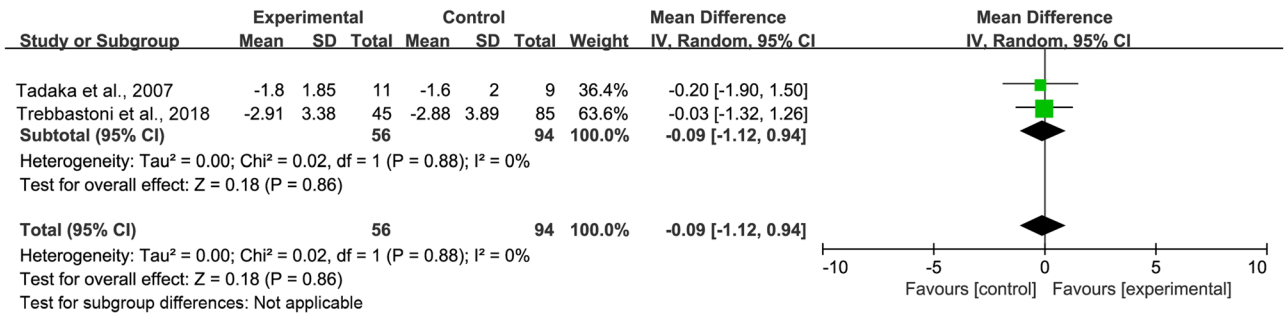

Fig.9 Effect of the cognitive training on global function after 24 weeks of follow-up using MMSE, Mini-Mental State Examination

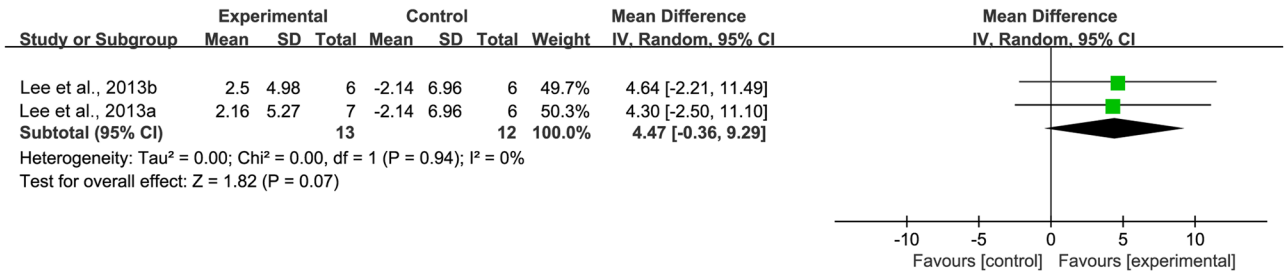

Fig.10 Effect of cognitive training on participant's IADL skill level for the short term using HKLIADL scale IADL, Intrumental Activities of Daily Living. HKLIADL, Hong Kong Lawton Intrumental Activities of Daily Living Scale. Lee et al., 2013: participants received cognitive training **a** as shown in Table 1. Lee et al., 2013: participants received cognitive training **b** as shown in Table 1

Follow Up

Only one study examined the effects of the duration of cognitive training after the intervention ended finding that cognitive training was not significantly more effective than the control condition at a 6-week follow-up (MD = -1.75, 95% CI: -6.59, 3.08; $p = 0.48$; $Q = 0.60$, df = 1, $p = 0.44$, $\tau^2 < 0.01$, $I^2 < 0.01$) (Fig.12). One RCT (Brunelle-Hamann et al., 2015; Thivierge et al., 2014) found that after assessment using DMT, improvements in the trained group were maintained for a 4-week, 8-week follow up. However, there were no data on the effect of cognitive stimulation on AD patients' IADL skill after follow up ended.

Participants' ADL Skill Level

Cognitive Stimulation

There were no data on the effect of cognitive stimulation on AD patients'ADL skill after short, medium or long term interventions.

Cognitive Training

Five eligible studies were included in the analysis of the effects of cognitive training on the participants' activities of daily living skill levels using the ADL scale.

The intervention effect of short-term cognitive training on ADLs was unclear because of a lack of data. Two individual studies (Li et al., 2011; Zhang et al., 2016) focused on the effects of medium-term cognitive training on ADLs using ADL scale. Due to lack of available data on the score of AD patients' on activities of daily living skills, we did not pool the data from the two articles. But their qualitative analysis demonstrated that cognitive training was more beneficial than the control condition for improving the participants' ADL skills ($p < 0.05$) (Li et al., 2011; Zhang et al., 2016). Figure 13 also shows that the results revealed that long-term cognitive training may not significantly affect the participants' activities of daily living skills (MD = 0.82, 95%CI: -0.01, 1.65, $p = 0.05$; $Q = 1.92$, df = 2, $p = 0.38$, $\tau^2 < 0.01$, $I^2 < 0.01$).

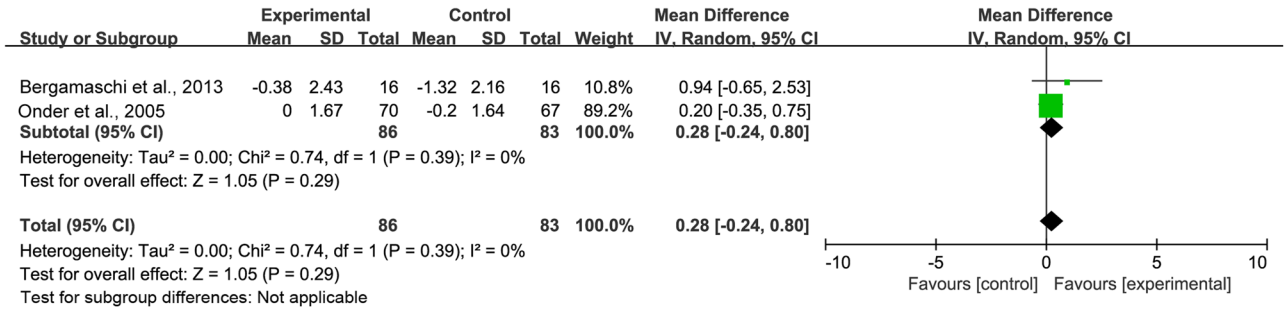

Fig. 11 Effect of cognitive training on participant's IADL skill level for the long term using IADL scale IADL, Instrumental Activities of Daily Living

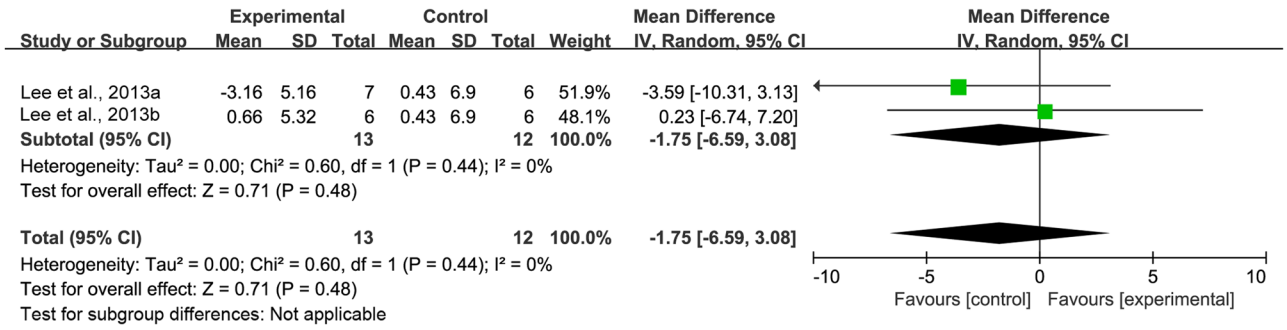

Fig. 12 Effect of cognitive training on participant's IADL skill level after 6 weeks of follow-up using HKLIADL scale IADL, Instrumental Activities of Daily Living Scale. Lee et al., 2013: participants received cognitive training **a** as shown in Table 1. Lee et al., 2013: participants received cognitive training **b** as shown in Table 1

Cognitive Rehabilitation

There were no studies exploring the intervention effect of cognitive rehabilitation alone on ADL. However, Li found that an intervention consisting of cognitive training and cognitive rehabilitation resulted in greater improvements than the control for this outcome after 24 weeks of intervention ($p < 0.05$) (Li et al., 2013).

Follow Up

There were no data on the effect of cognitive stimulation, cognitive training, or cognitive rehabilitation on AD patients' ADL skill after follow up ended.

Memory

Cognitive Stimulation

There were no data on the effect of cognitive stimulation on AD patients' memory skill after short, medium or long term interventions.

Cognitive Training

Eight RCTs analyzed the effect of cognitive training on memory, but they focused on different subdomains of memory and used different tools to measure the change in these outcomes.

Three studies showed contradictory results regarding the effects of short-term cognitive training on memory (Davis et al., 2001; Huntley et al., 2017; Lee et al., 2013). One study, (Huntley et al., 2017), demonstrated that cognitive training was beneficial for verbal episodic memory and verbal working memory ($p < 0.05$). However, two RCTs, (Davis et al., 2001; Lee et al., 2013), showed that cognitive training did not improve verbal memory, logical memory or prospective memory ($p > 0.05$). The effects of medium-term cognitive training on memory appeared to be inconclusive. One trial, (Tárraga et al., 2006), showed that cognitive training did not have a significant effect on story recall memory ($p > 0.05$), but Barban et al. found that cognitive training could increase delayed memory scores compared with the control condition ($p < 0.05$) (Barban et al., 2016). Yang et al. found similar results for verbal memory and visual memory ($p < 0.05$) (Yang et al., 2017). Regarding

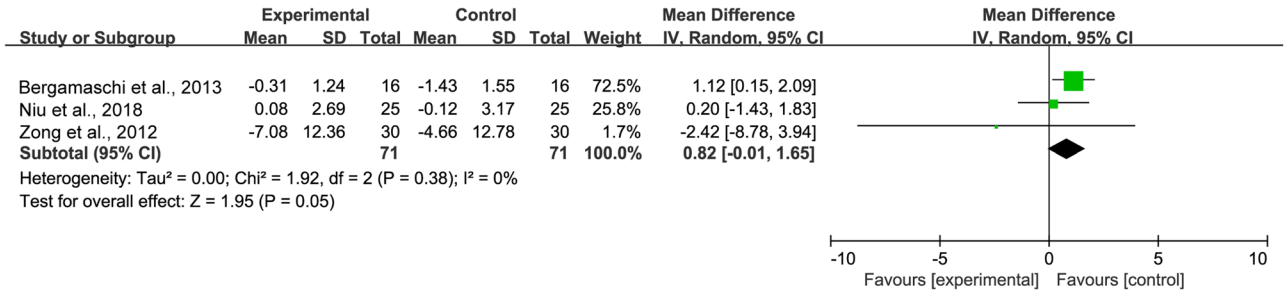

Fig.13 Effect of cognitive training on participant's ADL skill level for the long term using ADL scale ADL, Activities of Daily Living

the effects of long-term cognitive training on memory, two studies, (Tárraga et al., 2006; Trebbastoni et al., 2018), found that no significant difference between the experimental group and control group on story recall memory, spatial memory and working memory ($p > 0.05$). In contrast, two trials, (Bergamaschi et al., 2013; Trebbastoni et al., 2018), showed that cognitive training was beneficial for immediate and delayed memory and story recall-immediate memory.

Cognitive Rehabilitation

Two studies examined the effect of cognitive rehabilitation on memory. Cognitive rehabilitation did not significantly affect everyday memory function in the short term ($p > 0.05$) (Brunelle-Hamann et al., 2015; Thivierge et al., 2014). In addition, Bottino found that backward digit span scores were significantly different between the intervention and control groups after intervention ($p = 0.018$), and indicated that cognitive rehabilitation may be beneficial for memory on backward digit span (Bottino et al., 2005). No data showed the medium-term intervention effect of cognitive rehabilitation on memory.

Follow-up

Two studies explored the duration of the effects of cognitive training after the intervention ended; they found that cognitive training was not beneficial for prospective memory and spatial memory ($p > 0.05$) (Lee et al., 2013; Trebbastoni et al., 2018) but was beneficial for immediate and delayed memory and working memory ($p < 0.05$) (Trebbastoni et al., 2018). One trial, (Brunelle-Hamann et al., 2015; Thivierge et al., 2014), found that there was no significant difference in everyday memory function between the cognitive rehabilitation group and the control group ($p > 0.05$). There were no data on the effect of cognitive stimulation on memory skill after follow up ended.

Neuropsychiatric Symptoms

Cognitive Stimulation

There were no data on the effect of cognitive stimulation on AD patients' neuropsychiatric symptoms after short, medium or long term interventions.

Cognitive Training

Five studies were included in the analysis of the effects of cognitive training on neuropsychiatric symptoms using NPI (the Neuropsychiatric Inventory). The combined MD was -2.01 (95% CI: -2.84, -1.18, $p < 0.00001$; $Q = 0.31$, df = 1, $p = 0.58$, $\tau^2 < 0.01$, $I^2 < 0.01$) for the short term, 4.30 (95% CI: 0.41, 8.19, $p = 0.03$; $Q = 0.30$, df = 1, $p = 0.58$, $\tau^2 < 0.01$, $I^2 < 0.01$) for the medium term, and 1.78 (95% CI: -0.80, 4.36, $p = 0.18$; $Q = 4.47$, df = 3, $p = 0.21$, $\tau^2 = 2.52$, $I^2 = 33\%$) for the long term (Fig. 14). The results demonstrated that there was no consistent conclusion on

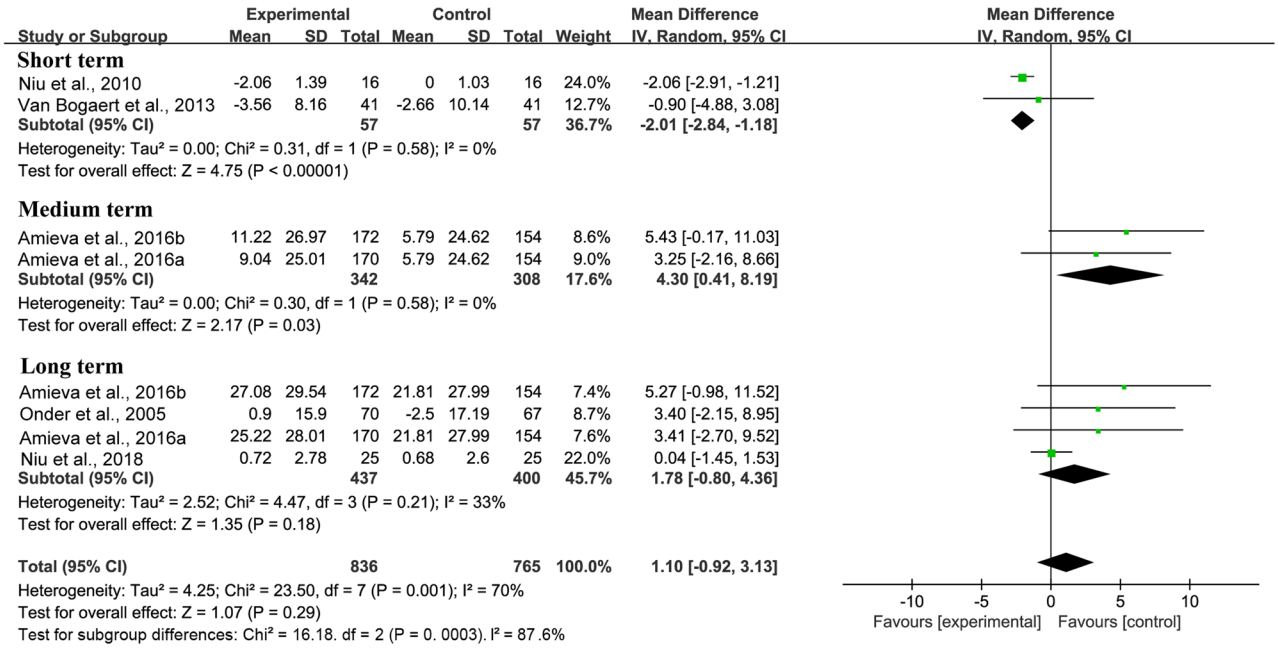

Fig.14 Effects of cognitive training on neuropsychiatric symptoms using NPI the Neuropsychiatric Inventory, Amieva et al., 2016 participants received cognitive training **a** as shown in Table 1. Amieva et al., 2016 participants received cognitive training **b** as shown in Table 1

cognitive training on neuropsychiatric symptoms compared with the control group.

Cognitive Rehabilitation

Only one study focused on the effect of cognitive rehabilitation on neuropsychiatric symptoms using NPI; it suggested that short-term cognitive rehabilitation had no effect on this outcome compared with the control condition ($p > 0.05$) (Brunelle-Hamann et al., 2015; Thivierge et al., 2014). One study found that there was no significant difference on the effect of cognitive rehabilitation on AD patients' neuropsychiatric symptoms after medium or long term interventions between the experimental group and control group (Amieva et al., 2016).

Follow-up

There was no significant change in NPI scores between the cognitive rehabilitation, cognitive stimulation and control groups at 4 weeks, 8 weeks or 40 weeks of follow-up ($p > 0.05$) (Brunelle-Hamann et al., 2015; Chapman et al., 2004; Thivierge et al., 2014). There were no data on the effect of cognitive training on AD patients' neuropsychiatric symptoms after follow up ended.

Depression

Cognitive Stimulation

There were no data on the effect of cognitive stimulation on AD patients' depression after short, medium or long term interventions.

Cognitive Training

Six studies were included in the analysis of the effects of cognitive training on participants' depression measured using GDS (Geriatric Depression Scale), CSDD (Cornell Scale for Depression in Dementia), MOSES (Multidimensional Observation Scales for Elderly Subjects), or MADRS (Montgomery-Asberg Depression Rating Scale). As Fig. 15 shows, the results showed that short-term cognitive training had positive effects on participants' depression (SMD = -0.48, 95% CI: -0.71, -0.24, $p < 0.0001$; $Q = 6.26$, df = 6, $p = 0.39$, $\tau^2 < 0.01$, $I^2 = 4\%$). But the results of two trials demonstrated that there was no statistical difference between the cognitive training and control groups on depression assessed using GDS or MADRS in the case of medium-term interventions ($p > 0.05$) (Yang et al., 2017; Amieva et al., 2016), we did not pool the data due to lack of the baseline score and the mean changes of the score of MADRS from Amieva's trial. In addition, two trial, (Amieva et al., 2016; Bergamasch et al., 2013), demonstrated the intervention effect of long-term cognitive training on depression measured using MADRS or CSDD. Due to due to lack of the baseline score and the mean changes of the score of MADRS in the Amieva et al (2016) trial, we performed qualitative analysis and found that the two RCTs both showed that no positive effect was found ($p > 0.05$) (Amieva et al., 2016; Bergamasch et al., 2013).

Cognitive Rehabilitation

Only one study, (Amieva et al., 2016), focused on the effect of cognitive rehabilitation on depression; it found that cognitive rehabilitation did not result in a statistically significant difference between the groups in the long term ($p > 0.05$). There were

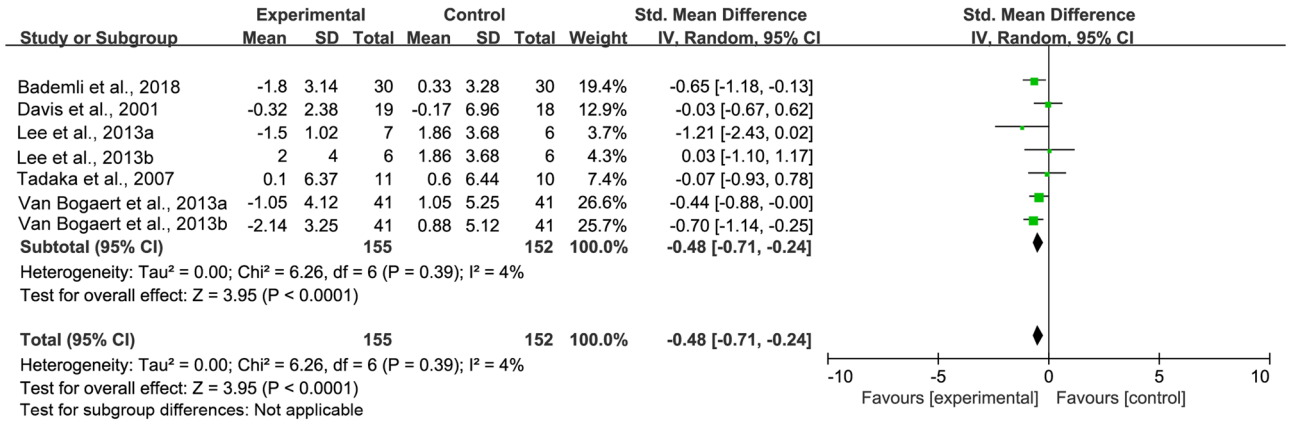

Fig 15. Effects of cognitive training on depression for the short term using CSDD, GDS, or MOSES CSDD, Cornell Scale for Depression in Dementia. GDS, the Geriatric Depression Scale. MOSES, Multidimensional Observation Scales for Elderly Subjects, Lee et al., 2013 participants received cognitive training **a** as shown in Table 1. Lee et al., 2013 participants received cognitive training **b** as shown in Table 1. Van Bogaert et al., 2013: depression measured using CSDD. Van Bogaert et al., 2013: depression measured using GDS.

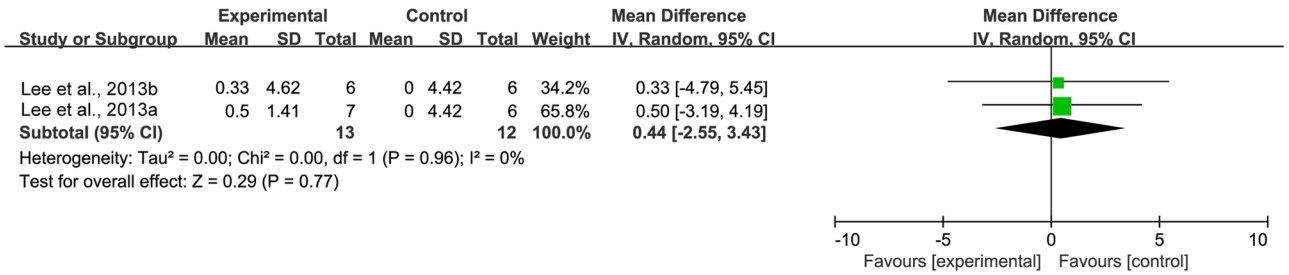

Fig.16 Effect of cognitive training on participant's depression after 6 weeks of follow-up usong GDS, the Geriatric Depression Scale. Lee et al., 2013: participants received cognitive training **a** as shown in Table 1. Lee et al., 2013: participants received cognitive training **b** as shown in Table 1.

no data on the effect of cognitive rehabilitation on AD patients' depression after the short term or medium intervention.

Follow-up

There was no positive effects of cognitive training on depression after 6 weeks of follow-up (MD = 0.44, 95% CI: -2.55, 3.43, $p = 0.77$; $Q < 0.01$, df = 1, $p = 0.96$, $\tau^2 < 0.01$, $I^2 < 0.01$) (Fig. 16). One study, (Tadaka et al., 2007), found that the same result existed after 24 weeks of follow-up using the depression subscale of MOSES. There were no data on the effect of cognitive stimulation or cognitive rehabilitation on AD patients' depression after follow up ended.

Quality of Life

Cognitive Stimulation

There were no data on the effect of cognitive stimulation on AD patients' quality of life after short, medium or long term interventions.

Cognitive Training

Four RCTs reported the effect of cognitive training on quality of life measured by QLA-P (Quality of Life-Patient) or Qol-AD (the Quality of Life in Alzheimer's Disease Scale). As Fig. 17 shows, the combined SMD of two trials was 0.10 (95% CI: -0.84, 1.03, $p = 0.84$; $Q = 5.09$, df = 1, $p = 0.02$, $\tau^2 = 0.37$, $I^2 = 80\%$) for the short term, indicating that there was no significant difference between the two groups. There were contradictory findings based on the results of Tao and Amieva assessed by Qol-AD for the medium term, so the data cannot be pooled due to lack of the baseline score and the mean changes in the Amieva' trial (Amieva et al., 2016; Tao et al., 2017). Only one study (Amieva et al., 2016), demonstrated the intervention effect of long-term cognitive training. After assessment using Qol-AD, it found no significant difference between the experimental group and the control group.

Cognitive Rehabilitation

Only one RCT examined the intervention effect of cognitive rehabilitation on quality of life using DQol (Dementia Quality of Life Questionnaire) and found that it did not affect quality of life in the short term (Brunelle-Hamann et al., 2015; Thivierge et al., 2014). The same finding was demonstrated in medium and long term interventions based on data from Amieva using Qol-AD (Amieva et al., 2016).

Follow-up

There was no significant difference in the efficacy of cognitive stimulation or cognitive rehabilitation after follow up ended based on assessment using DQol or QOL-AD between

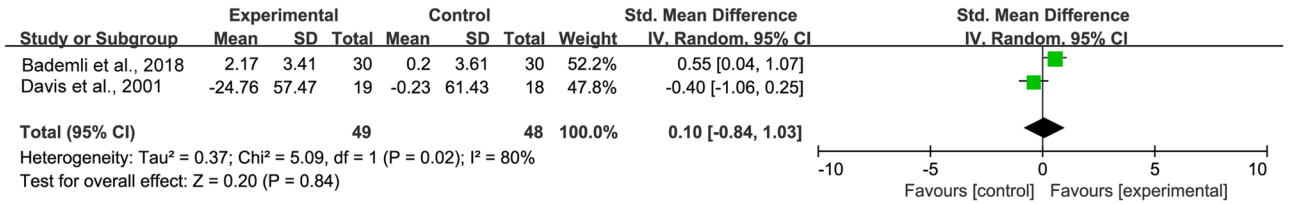

Fig.17 Effect of cognitive training on participant's quality of life for the short term using QLA-P or QQL-AD. QLA, Quality of Life Patient. QQL-AD, the Quality of Life in Alzheimer 's disease Scale

the experimental group and control group at 4 weeks, 8 weeks or 40 weeks of follow-up ($p > 0.05$) (Brunelle-Hamann et al., 2015; Chapman et al., 2004; Thivierge et al., 2014). There were no data on the effect of cognitive training on AD patients' quality of life after follow up ended.

Discussion

Twenty-five studies (2012 participants) were eventually included in this review. The majority of the studies focused on the intervention effect of cognitive training on global cognitive function, memory and noncognitive outcomes (IADL, ADL, and quality of life). We found that cognitive training may bring clearly beneficial improvements in global cognitive function after short, medium or long-term interventions. In addition, it was also helpful for improving depression in the patients after short term interventions. However, cognitive training did not maintain a positive effect on global cognitive function or depression after the intervention ended. Cognitive training may not affect participant's skill level on IADL or ADL. There were no consistent conclusions on the effects of cognitive training on memory and neuropsychiatric symptoms. Limited attention has been paid to the impact of cognitive stimulation and cognitive rehabilitation on these outcomes.

Effect of Cognitive Training on Global Cognitive Function

Cognitive training usually consists of guided practice on a series of standardised tasks designed to reflect particular cognitive functions such as memory, attention or problem-solving (Davis et al., 2001). The improvement of general cognitive function may be the most direct result of cognitive training. This review found that cognitive training using different intervention durations may improve this outcome, possibly by increasing the functional connectivity of the posterior default mode network and by producing functional changes in the medial temporal lobe and topological changes in the anterior cingulum of individuals with AD (Barban et al., 2017). Moreover, great attention must be paid to the fact that the difficulty of the training provided in the 13 RCTs included in the meta-analysis (Davis et al., 2001; Onder et al., 2005; Tadaka et al., 2007; Liu et al., 2008; Lee et al., 2013; Van Bogaert et al., 2013; Camargo et al., 2015; Zhang et al., 2016; Tao et al., 2017; Yang et al., 2017; Niu et al., 2018; Bademli et al., 2018; Trebbastoni et al., 2018) was not adapted to the patients' cognitive performance, and the researchers did not provide alternative interventions doses to better understand the clinical benefit of the interventions. However, caution is warranted when interpreting this finding due to the substantial heterogeneity in these studies and the probable risk of bias. Moreover, the content of cognitive training must be adjusted to keep pace with the patient's cognitive decline, and its intervention effect needs to be further explored.

Effect of Cognitive Training on Memory

Memory difficulty is one of the first symptoms of AD, and it continues to worsen over the course of the disease. Unfortunately, no evidence is available to provide strong suggestions for improving memory. There have been a few individual studies focusing on different subdomains of memory, and a wide diversity of measurement tools has revealed both positive and negative effects of cognitive intervention on memory. Therefore, we did not conduct quantitative synthesis based on the existing data. However, Alves et al. performed a meta-analysis (4 RCTs, 133 participants) of memory using standardized mean differences and found that cognitive intervention (cognitive training or cognitive stimulation) might not contribute to improvement in memory, including immediate auditory-verbal memory, immediate visuospatial memory, delayed auditory-verbal memory and delayed visuospatial memory (Alves et al., 2013). The interventions of two RCTs included in the Alves and colleagues study were directly related to memory (Cahn-Weiner et al., 2003; Niu et al., 2010). The conclusion, which was based on trials with small sample sizes, may be uncertain, and an understanding of the real effect of cognitive training on memory still requires further exploration.

Effect of Cognitive Training on Noncognitive Outcomes

As we found, there were contradictory conclusions regarding the effects of cognitive training on quality of life based on a few individual trials (Davis et al., 2001; Chapman et al., 2004; Brunelle-Hamann et al., 2015; Thivierge et al., 2014; Amieva et al., 2016; Tao et al., 2017; Bademli et al., 2018). Although the individual studies show that a medium term intervention of cognitive training may be beneficial for patients' ADL and IADL scores, further confirmation is needed to draw a reliable conclusion. Based on current knowledge, cognitive training might also not have a significantly positive effect on IADLs or ADLs, a finding that was similar to Alves' study (Alves et al., 2013; Oltra-Cucarella et al., 2016). A possible explanation for the absence of significant functional improvements is that none of the RCTs concentrated on improvements in ADLs and IADLs. Almost all of the interventions in the included RCTs consisted of academic activities related to cognition, and it seems rational that nonsignificant results were likely to be reported because of a lack of transfer to untrained domains.

Nevertheless, there was no consistent conclusion on cognitive training on neuropsychiatric symptoms compared with the control group, although cognitive training may result in small improvements in neuropsychiatric symptoms in the short term. However, this result is very questionable. Because the standard deviations were much smaller in the study of Niu's study (Niu et al., 2010), the Standard Error of the mean difference was much smaller in this study than in the study of Amieva trial (Amieva et al., 2016), and therefore this study got a much larger weight in the analysis although the sample size was much smaller.

Duration of Effect after the End of the Intervention

This is the first review to explore the persistence of training effects in individuals with AD after the end of the intervention. Our findings cannot give reliable conclusions relevant to this topic based on limited existing trials which is similar to Sherman's studies, which found no significant difference between the cognitive intervention group and the control group in MCI patients during the post intervention follow-up period (Sherman et al., 2017). It is rational to conclude that if a cognitive intervention is discontinued, the intervention effect will decrease and even gradually disappear for AD patients. This difference may also be because progressive alterations in the connectivity of regions of the middle temporal lobe (hippocampus and entorhinal) may arise as AD severity increases (Rasero et al., 2017), resulting in a decrease in the training effect. Until now, there have been no primary studies focusing on the long-term benefit of continuing cognitive intervention from the onset of AD to the end of life. Questions such as how long a cognitive intervention can delay the progression of AD, which form of cognitive intervention makes AD patients more compliant and how to adjust the intensity of cognitive intervention according to the severity of AD patients need to be further explored.

Strengths and Limitations

Our review has obvious advantages in the following areas. This is the largest review of AD patients (25 studies, 2012 participants) to date. Given the fact that AD is a progressive disease, this is also the first review comprehensively focusing on the role of intervention duration (short, medium, and long) on the effect of cognitive interventions. In addition, we examined the effects of cognitive interventions over time after the intervention ends.

However, there are inevitably several potential limitations to our study. Firstly, we did not conduct formal tests of publication bias, and we inspected funnel plots, Egger's tests only when at least 10 trials contributed to the outcome. Hence, we could not evaluate this for many outcomes, including all outcomes in the comparison groups. But we have tried our best to search related professional database, grey literature database and some systematic review' references and connect with the relevant authors to obtain original data to be sure not to miss important literature relevant to our topic. Second, there is no detailed discussion on the effect of cognitive stimulation and cognitive rehabilitation for AD patients due to the limited number of studies and contradictory results. In addition, Lee' study (Lee et al., 2013) was a three arm trial, while the Amieva study was a four arm trial (Amieva et al., 2016). When we extracted the data, the control group may have been compared more than once, which may have an impact on the accuracy of the results. Finally, compared with the registered protocol, we added memory as an expected outcome in consideration of its importance, and we chose intervention duration rather than intervention dose as a subgroup analysis. It was not possible to calculate the intervention dose due to inadequate information in the primary studies.

Suggestions for Further Research

Recommendations for research in the future are proposed based on our finding. First, studies should pay attention to the outcome measurements based on the same internationally recognized and well-established tools to make full use of the data for secondary analysis. Second, detailed information about the methodology of RCTs, such as random sequence generation, allocation concealment and blinding, is necessary to allow readers to evaluate the authenticity of RCTs and the reliability of their results. More high-quality and larger-scale RCTs are needed to verify the real effects of cognitive intervention on AD patients. Finally, the effect of adjusting the intensity of cognitive interventions to changes in the patients' cognitive condition and the role of intervention duration to modify the effect of cognitive intervention on patients' outcomes would be interesting topics worthy of exploration.

Conclusion

Cognitive training may produce clear improvements in global cognitive function whether after short, medium or long-term interventions, it is also helpful for improvement of depression in the patients after short term interventions. However, the positive effect of the intervention on global cognitive function and depression did not seem to be maintained after the interventions ended. Cognitive training may not affect the participant's skill level in IADL or ADL. There was no consistent conclusion on cognitive training on memory and neuropsychiatric symptoms. Little attention has been paid to the impact of cognitive stimulation and cognitive rehabilitation on these outcomes. More high quality and larger-scale RCTs are needed to confirm the real effects of cognitive intervention for AD patients.

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