Ageing Research Reviews 51 (2019) 85–96

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

The optimal treatment for improving cognitive function in elder people with mild cognitive impairment incorporating Bayesian network meta-analysis and systematic review

Jing-hong Liang[a,1], Wan-ting Shen[b,1], Jia-yu Li[a], Xin-yuan Qu[c], Jing Li[a], Rui-xia Jia[a], Ying-quan Wang[a], Shan Wang[a], Rong-kun Wu[a], Hong-bo Zhang[a], Lei Hang[a], Yong Xu[a,*], Lu Lin[d,**]

[a] Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, School of Public Health, Soochow University, Suzhou, PR China
[b] Department of Biological Sciences, Xi'an Jiaotong-Liverpool University, Suzhou, PR China
[c] Department of Epidemiology, School of Public Health, Medical College of Soochow University, Suzhou, PR China
[d] School of Nursing, Medical College of Soochow University, Suzhou, PR China

ARTICLE INFO

Keywords:
Mild cognitive impairment
Bayesian network meta-analysis
Systematic review
Cognitive intervention

ABSTRACT

It's widely acknowledged that, as a neurodegenerative aging disease representing an intermediate stage between cognitive intactness and Alzheimer's disease (AD), Mild cognitive impairment (MCI) poses an excessive burden on patients' well-being, family members, health-care providers as well as the whole society. This study focuses on three cognitive interventions proposed by Clare and Woods, which are, Cognitive stimulation (CS), Cognitive training (CT) and Cognitive rehabilitation (CR). Our Network meta-analysis (NMA) aims to compar them with one another to determine the optimal cognitive intervention for elderly adults with MCI in improving their cognitive function. We applied extensive strategies to preliminary literature retrieval to identify relevant randomized controlled trials (RCTs) which scrupulously compared any two of the three cognitive interventions with one another or any one of the three with a control group as the placebo or non-active group in treating elder patients with MCI in accordance with Petersen's criteria. Our NMA of cognitive interventions for patients diagnosed with MCI appraised the relative effectiveness of cognitive interventions across trials simultaneously. Our study attempts to summarize available data to suggest that CS (Mean difference [MD] = 0.95, 95% confidence interval [CI]:0.27, 1.70) and CT (MD = 0.70, [CI]:0.11,1.30) were significantly beneficial to MCI patients for improving their cognition status while CR (MD = 0.59, [CI]:-0.30,1.50) scored lowest. Our study suggested CS was most likely to be the best intervention for improving the cognitive function of MCI patients.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative aging disease that develops insidiously and is clinically characterized by cognitive and memory deterioration, executive dysfunction in daily activities and a multiplicity disturbance in behavioral and psychological activities (Di Iulio et al., 2010; Herrup, 2011; Zhang et al., 2013), which poses an excessive burden on patients' families, caregivers, health-care system even the whole society (Welsh-Bohmer et al., 2013; Wortmann, 2012). Nowadays, the world is comprised of more than 47 million people suffering from AD and the number is estimated to triple in 2050 (Mortby et al., 2018; Prince, 2019). The death rate of AD patients increased by 71% from 2000 to 2013 in the United state (Gaugler et al., 2016). In addition, the excessive expense of global economy in this area is reckoned to be around $315 billion (Herrera et al., 2016).

Severe deterioration of cognitive function in patients with AD is usually preceded by a preclinical phase but observed with only subtle cognitive decline symptoms over time (Gauthier et al., 2005). Therefore, as a transitional ageing stage between normal elderly adults and people with dementia (Petersen, 2004; Winblad et al., 2004), mild

* Corresponding author at: School of Public Health, Medical College of Soochow University, No. 199 Ren Ai Road, Suzhou, 215123, PR China.
** Corresponding author at: School of Nursing, Soochow University, No. 1 Shizi Street, Suzhou, 215006, PR China.
E-mail addresses: 13092616243@163.com (J.-h. Liang), 1307090249@qq.com (W.-t. Shen), 1174870379@qq.com (J.-y. Li), quxinyuan1016@126.com (X.-y. Qu), 348901000@qq.com (J. Li), 20174247027@stu.suda.edu.cn (R.-x. Jia), 2824854419@qq.com (Y.-q. Wang), 1170386307@qq.com (S. Wang), 2359881469@qq.com (R.-k. Wu), 1615798227@qq.com (H.-b. Zhang), 2536841069@qq.com (L. Hang), childhealth@suda.edu.cn (Y. Xu), linlu@suda.edu.cn (L. Lin).
[1] J-hL and W-tS contributed equally to the work presented here and therefore should be considered equivalent authors.

https://doi.org/10.1016/j.arr.2019.01.009
Received 7 August 2018; Received in revised form 16 December 2018; Accepted 9 January 2019
Available online 22 January 2019

cognitive impairment (MCI) was initially conceptualized as a memory impairment by Petersen et al. (1999) and during the past decade it was characterized by an objective cognitive deficit in global cognitive functioning and the ability to perform daily activities independently (Petersen et al., 2014, 2001).

MCI generally represents early-stage AD through authoritative assessment by several experts in this field (Akins, 2001; Morris, 2006; Morris et al., 2001). Compared with AD patients, the rapid growth in MCI patients can not be neglected when global population and prevalence is estimated to rise to over 2 billion people and by 10%–20% in the near future among ages over 60 respectively (Economic, U.N.D.o., Division, S.A.P., 2013; Petersen et al., 2018; Prince et al., 2013). It's imperative to implement instrumental and cost-effective measures to prevent a series of cognitive problems occurring to the MCI population due to increasing and widespread cognitive deterioration. Admittedly, there exists different kinds of cognitive therapies demonstrating their effectiveness in improving the cognitive ability in MCI patients: computerized cognitive training (CCT) (Barnes et al., 2009; Finn and McDonald, 2015), group-cognitive stimulation (De Marco et al., 2014; Moro et al., 2015), memory rehabilitation (Barekatain et al., 2016; Otani et al., 2013), as well as pharmacological treatment (Rodakowski et al., 2015; Wang et al., 2014), a promising treatment which remains highly controversial. Most of them were derived from Clare and Woods's research (Clare and Woods, 2004) which vividly divided cognitive interventions into three main categories, namely, cognitive training (CT), cognitive stimulation (CS) and cognitive rehabilitation (CR), which play an important part in enhancing cognitive function for patients with early-stage AD. CS, featuring engagement in a wide range of group-oriented social events, focuses on general improvement of individual cognitive functioning and behavior. CT mainly refers to guided practice incorporating a set of standardized tasks with a range of difficulty levels and is intended for improvement in specific cognitive domains with the potential for generalizing beyond standardized tasks. CR, as an individualized method with personally-relevant goals, should be implemented with flexibility, backed by healthcare provider engagement, be of sufficient duration in order to achieve the result of "optimal level of physical, psychological and social functioning" in the daily context (Clare et al., 2003c; Clare and Woods, 2004). Although there exists quite a bit noteworthy research on the effectiveness of various cognitive interventions associated with MCI (Buschert et al., 2012; Joosten-Weyn Banningh et al., 2013), there is still a need for relevant studies based on a comprehensive view from synthesized analyses incorporating more than two cognitive treatments simultaneously since there is a limitation of traditional approaches which focus on pair-wise analyses.

As clinical guidelines in some areas, network meta-analysis (NMA) is a synthetical approach which provides an overview by comparing multiple treatments for a disease simultaneously despite that such treatments can not generate a direct comparison among them (Lu and Ades, 2004; Mills et al., 2013; Salanti et al., 2008). Therefore, we conducted both a network meta-analysis and a systematic review to identify the optimal cognitive intervention from an macroscopic aspect for MCI patients.

2. Method

Our study was conducted in accordance with the PRISMA declaration for Network Meta-analysis and the Cochrane Handbook for the Systematic Review of Interventions (Higgins and Green, 2011; Hutton et al., 2015). All analyses were based on previous published studies and therefore no ethical approval and patients consent were required.

2.1. Literature search and selection criteria

We applied extensive strategies to preliminary literature retrival by searching PubMed, Cochrane Central register of controlled trials, PsycINFO, Embase, China National Knowledge Infrastructure database, Chinese Scientific Journal database, Chinese Biomedical Literature database, Wan Fang database, to identify relevant parallel-group and cross-over randomized controlled trials (RCTs) from their inception to 1 st July, 2018 which scrupulously compared any two of the three cognitive interventions(cognitive training, cognitive stimulation, cognitive rehabilitation) with one another or any one of the three with a control group(the placebo, non-active group) in treating elderly adults with MCI according to Petersen's MCI-criteria (Petersen et al., 2001).

Through both combined Medical Subject Headings (MeSH) and text-terms followed by Boolean logical operators, an exhaustive search was conducted by using the following MeSH terms without any language restrictions: "Cognitive dysfunctions", "Mild cognitive impairment", "Cognitive impairment", "Mild neurocognitive disorder", "Cognitive decline", "Cognitive intervention", "Cognitive training", "Cognitive stimulation", "Cognitive rehabilitation", "Cognitive method", "Cognitive therapy", "Cognitive assist", "Cognitive behavior therapy", "Cognitive aid", "Cognitive support", "Randomized controlled trials", as well as additional relevant conceptual keywords. Results were subjected to further examination if the paper was presented in a non-English format due to certain restrictions in language.

Additionally, we implemented a battery of recursive searches with the intention of making sure that all the studies were completed so that they met our eligibility criteria. Therefore, we screened all the bibliographies of obtained findings ranging from similar systematic reviews, meta-analyses to clinical guidelines of MCI. We also manually searched the proceedings from major international conferences on MCI or medicine so as not to miss any potential eligible trials. We processed the above screening records by using the Endnote X7 literature management software (Thompson ISI Research Soft, Philadelphia, Pennsylvania, USA).

2.2. Eligibility criteria and data abstraction

We screened all the included citations using the literature search strategies for final definitive eligible studies in accordance with the PICOS selection criteria. The inclusion and exclusion criteria was summarized in Table 1. Studies without a parallel methodology were excluded despite criteria mentioned above for it was necessary to balance the transitivity of numerously complex studies which could result in a more accurate analysis. Studies were summarized into three groups, namely CT, CS and CR according to the classification by Clare and Woods (Clare and Woods, 2004). The details of each cognitive intervention were shown in Table 1. The summarization process was conducted according to a rigorous criterion by four authors independently.

Based on the predefined protocol above, three independent authors identified the articles by reviewing the titles and abstracts of the included citations during the initial literature search. Duplicate studies were discarded simultaneously. Meanwhile, full-texts were retrieved for further evaluation in compliance with selection criteria if the article was potentially relevant. Finally, we abandoned studies which were published only in abstract form without any available data. Consensus was reached on all items if any disagreement existed.

2.3. Outcome measure and quality assessment

Firstly, we analyzed the global data and demographic characteristics of all the included studies. Two authors extracted the relevant data according to the pre-elaborated outcome measurement checklist which include the following essential items: major author responsible for the article, year of publication, origin of study (country), setting form, personal characteristics, duration of treatment, primary outcome. Our NMA-analysis analyzed an intersected endpoint——Mini-Mental-State-Examination(MMSE) (Folstein et al., 1975), as the primary outcome for validated assessment of the cognitive domain which is

Table 1
PICOS criteria and the characteristic of cognitive intervention.

PICOS	Inclusion Criteria	Exclusion Criteria
Population	Mild cognitive impairment was diagnosed by any proper clinical criteria, aged over 60 years old, without sex, race, region restriction.	Healthy ageing elderly adults, participants with Alzheimer's disease or other types of dementia, participants diagnosed with cognitive impairment but due to other disease.
Intervention	Patients with MCI treated by various cognitive interventions and properly for summarized in three main approaches, cognitive training, cognitive stimulation, cognitive rehabilitation.	Any cognitive intervention in combinatorial or multicomponent, the definition of cognitive intervention in study is vague.
Comparators	Cognitive interventions themselves or control group alone.	Placebo or control group in any combination with any cognitive intervention.
Outcomes	Primary: Cognitive function was evaluated by measurable cognitive screening instrument which must generate as a intersecting endpoint for our analysis.	Clinical assessment scale, biological indicator or other relevant outcome can not generate a conjunct endpoint for each included studies.
Study design	Both the parallel-group and cross-over RCTs have been published without year and language restriction.	Non-randomized controlled such as case-control study, cohort study, full-text but unpublished.

ChEI, Acetylcholinesterase inhibitor; MCI, Mild cognitive impairment; RCTs, Randomized controlled trials

Cognitive intervention	Essential characteristic
Cognitive stimulation	Group activities and discussions Social interaction Involves non-specific method with reality orientation or reminiscence therapy
Cognitive training	Cognitive or neuropsychological test Paper-and-pencil or computerized standardized task Memory training with daily activities ChEI application
Cognitive rehabilitation	Address cognitive difficulties A psychotherapeutic methods aim at dealing with individual everyday situation Tackle emotional responses Restore remaining memory by carrying out important, real-life practical skills Compensate impaired memory with the help of machine or techniques

represented by a continuous outcome and incorporates a directly proportional score (Altman and Bland, 1996). Therefore, we extracted the mean and standard deviation (SD) of the change from baseline and transformed it into a standard format to make sure that it was implemented successfully in our analysis. If the data we were to extract for our analysis (such as mean, SD or sample size) were not provided in the included literature, we would present them in another form by calculating other available values such as standard errors, confidence intervals, or other statistical indices as describe elsewhere which may clarify SD accordingly (Follmann et al., 1992; Hozo et al., 2005; Lipsey and Wilson, 2000). In order to ensure the stability and reliability of the result of combining parallel and cross-over trials, cross-over trials were analyzed similarly to parallel trials with data extracted only from the first period (Stedman et al., 2011).

Two independent authors assessed the quality of each included RCT, using the Cochrane risk of bias (ROB) tool which includes seven items and the included RCTs were judged as unclear, low or high bias level (Higgins and Green, 2011). Assessment of ROB was performed in Reviewer Manager (5.3 version (The Nordic Cochrane Centre Copenhagen, Denmark). For the selection bias, we consider it whether studies describe clearly the random sequence generation and specify the method of allocation concealment or not, if so, such kind of study would be accepted as in low risk of bias, otherwise, high risk. For the performance and detection bias, we regard them mainly based on whether the study was blind or not—participants, personnel and outcome assessors. For the attrition bias, we judge those studies as high risk whose relevant data was missing especially the primary outcome data which affects our further analysis directly. We appraise selective bias according to whether the study lacks some secondary outcome or reported the insufficient available data such as the characteristics of them. For any other potential bias, we classify them through the full-text searching for specific evidence that may led their results to bias such as less rigorous study deigns, or the obvious inconsistency compared with previous studies. All the above items judged as"unclear risk"of bias correspond with the study not addressing relevant items. The divergence was reconciled through discussion or objective adjudicationi by an experienced expert.

2.4. Synthesis analysis

Firstly, by synthesizing the essential data from all the included studies, we performed a conventional pair-wise meta-analysis for a quantitative analysis based on the random effects model. As the outcomes revealed on a continuous scale, we calculated the mean difference (MD) to pool the effect size, along with their respective 95% confidence intervals (CI). The reason why we conducted the quantitative analysis using I^2 statistics with higher values to indicate more heterogeneous increases especially substantial heterogeneity when I^2 was higher than 50% is that the traditional qualitative analysis which is represented by chi^2 combined with P value can only judge whether there is heterogeneity between studies but lacks the ability to calculate the magnitude of heterogeneity (Higgins and Thompson, 2002; Senn and Barnett, 2004). A comparison-adjusted funnel plot was constructed to judge whether a publication bias existed by visually observing the magnitude of asymmetry of the plot. Meanwhile, we also carried out relevant subgroup analyses based on the key features during the intervention, these groupings were treated as the covariates in our subgroup analyses. As a visual representation, we generated a network plot for each treatment which offers the evidence base and a concise description of their characteristics The above serial analyses were performed in STATA, version 14.0 (Stata Corp, College Station, TX).

The transitivity assumption was the crucial part in assessing the reliability of our NMA which aims to compare the similarities of clinical and methodological characteristics (eg, patient, experimental design, etc.) between studies. Therefore, we examined the baseline characteristic of participants, duration of intervention through available direct comparisons so that the following analysis could be conducted favorably (Caldwell et al., 2005; Jansen and Naci, 2013; Salanti, 2012). The Bayesian network meta-analysis has a categorical strength over traditional meta-analysis due to its ability to summarize comparisons between multifarious treatments concurrently (Lu and Ades, 2004), which allows for greater flexibility to use complex models and produce relatively scientific interpretations in terms of causal relationships.

Bayesian statistical model was implemented to compare the three cognitive interventions simultaneously by forming a connected network integrating direct and indirect evidence (Caldwell et al., 2005; Salanti et al., 2011, 2008; Salanti et al., 2009). In order to estimate the unique and primary outcome, our NMA was performed non-informatively prior to distributions and using the Markow chain Monte Carlo method under a Bayesian framework (Mavridis and Salanti, 2013; Valkenhoef and Kuiper, 2016). We choose the Gibbs sampling and Metropolis algorithm in this analysis. Relevant stimulation techniques allow three parallel chains to run simultaneously with different initial values in a randomly chosen state. Our model generated a total number of 50,000 iterations and the first 5,000 iterations were discarded to minimize bias of initial values when the chain reached its target distribution (Welton, 2012). Both the density plot and tract plot combined with the Brooks-Gelman-Rubin diagnostic statistics were taken into consideration by inspecting the trace “history” feature to ensure convergence (Brooks and AndrewGelman, 1998). Probability of which cognitive intervention would be the optimal intervention derived from proportion of the best ranking in all simulative operations (Dias et al., 2012). We ranked the three cognitive interventions using a hierarchical tool —— the surface under the cumulative ranking curve (SUCRA) was presented as a simple numerical summary statistic of cumulative ranking probability plots for each treatment. Higher SUCRA values indicates a higher likelihood that the treatment is on the top rank or is highly effective while zero represents that the treatment would be the worst to some extent (Salanti et al., 2011). The node-splitting approach was executed to statistically examine the inconsistency between direct and indirect evidence throughout the entire network frame where analysis derived *P*-values less than 0.05 indicates the probability of inconsistency (Chaimani et al., 2013; Dias et al., 2010; Higgins et al., 2012; van Valkenhoef and Dias, 2016). The analyses mentioned above regarding the Bayesian framework were performed in R language (X64 3.32 version) (Coreteam, 2014) by using both the “Gemtc” (version: 0.8–2) and “rjags” (version: 4–6).

3. Results

3.1. Baseline characteristics and quality of included studies

The schematic flow chart for selecting the included studies was shown in Fig. 1.

Of all the 17,878 studies that focus on the comparison among the three cognitive interventions obtained using the initial search strategy. 432 articles were discarded due to duplication, and 17,128 articles were removed from the remaining ones by screening their title and abstract. 318 researches that appeared to be potentially relevant were retrieved for further full-text appraisal. In addition, we retrieved by hand-search 24 relevant studies to make up for the insufficiency of electronic databases we pre-established (Egger et al., 2003) and 22 studies were judged as ineligible articles due to their unsuitable endpoint, or their failure to offer sufficient original data. We excluded the studies which used cognitive screening instruments similar to MMSE, such as K-MMSE (Korean-Mini-mental State Examination) (Hwang et al., 2012), C-MMSE (Chinese-Mini-mentalState Examination) (Chua et al., 2015). Eligibility criteria were comprised of miscellaneous cognitive interventions, which resulted in 13 articles in our Bayesian NMA finally (Barban et al., 2016; Buschert et al., 2011; Förster et al., 2011; Greenaway et al., 2013; Han et al., 2017; Jeong et al., 2016; Lam et al., 2012; Langoni et al., 2018; Rojas et al., 2013b; Rozzini et al., 2007b; Shimada et al., 2018; Tsolaki et al., 2010; Wei and Ji, 2014). All the authors participating in selection and appraisal in this section reached a unanimous agreement. The demographic characteristics of the 13 included articles are shown in Table 2. All included studies were randomized controlled studies (RCTs) and published from 2007 to 2018, enrolling a total of 1333 MCI patients. The active cognitive intervention involving 672 MCI patients were compared with the control group of 661 patients according to a randomly assigned approach. The median duration of the active group was 24 weeks (ranging from 4 to 54 weeks) and 23.93% (319) of patients enrolled were diagnosed with amnestic MCI and other form of MCI. The vast majority of participants were from Asia (854(64.06%), and Europe 379(28.43%), and all the included studies took place in either developed countries or developing countries but none in underdeveloped countries. 53% (777) participants were women and the mean score of MMSE ranged from 21.90 to 26.80 at baseline. Although we included both of the parallel and cross-over group of randomized controlled trials. Only the participants from three studies (Barban et al., 2016; Buschert et al., 2011; Han et al., 2017) were assigned to a cross-over design for launching the trail. The remaining ten were assigned to a parallel design. The quality of the included studies was described in Supplement Figs. 1 and 2 All the included studies had a low risk of bias in “Random sequence generation” and “Incomplete outcome data”. Only one study showed a high bias in such sections as “Blinding of participants and personnel”, “Blinding of outcome assessment”, and “Other bias” (Rojas et al., 2013b). Four studies (Lam et al., 2012b; Rozzini et al., 2007b; Tsolaki et al., 2011; Wei and Ji, 2014b) were judged to be at high risk of selective reporting, and three studies were judged to be at high risk of other biases (Barban et al., 2016; Greenaway et al., 2013; Rojas et al., 2013b). All of the included studies were rated as low risk of bias.

3.2. Pair-wise meta analysis and network meta-analysis results

No obvious heterogeneity was observed in the preliminary meta-analysis of all the included studies (See Table 3 and Supplement Fig. 3). The funnel plot did not indicate publication bias due to its symmetric distribution (Supplement Fig. 4). The abscissa axis and vertical axis of the funnel plot respectively represented the standard mean difference and the standard error of standard mean difference. Publication bias identification depends on whether the distribution of the studies are symmetrical in the inverted funnel. Each spot represented one included study. Studies of small sample size, low research accuracy, distributed at the bottom of the funnel plot while those of large sample size, high research accuracy, distributed at the top of the funnel plot, centralized toward the middle. We also conducted an Egger’s test to evaluate whether other biases existed (Supplement Fig. 6) . The *P*-value (0.521) being higher than 0.05 indicated the absence of an obvious bias in our study.

The visual network plot was conducted to display all the primary evidence regarding each cognitive intervention (Shown in Fig. 2). Each node represented a different treatment and its size depended on the number of patients that is directly examined. The nodes were joined by different thickness lines which generated to show whether there existed a direct relationship between treatments and the thickness was weighted according to the available direct evidence between them. From the network geometries, CT had the largest samples compared to the control group, and thus its node edge was the largest, followed by CS and CR. Each cognitive intervention held at least one direct evidence compared with the control group. And only CT and CS had three closed loops with CT, indicating that there existed direct evidence between them.

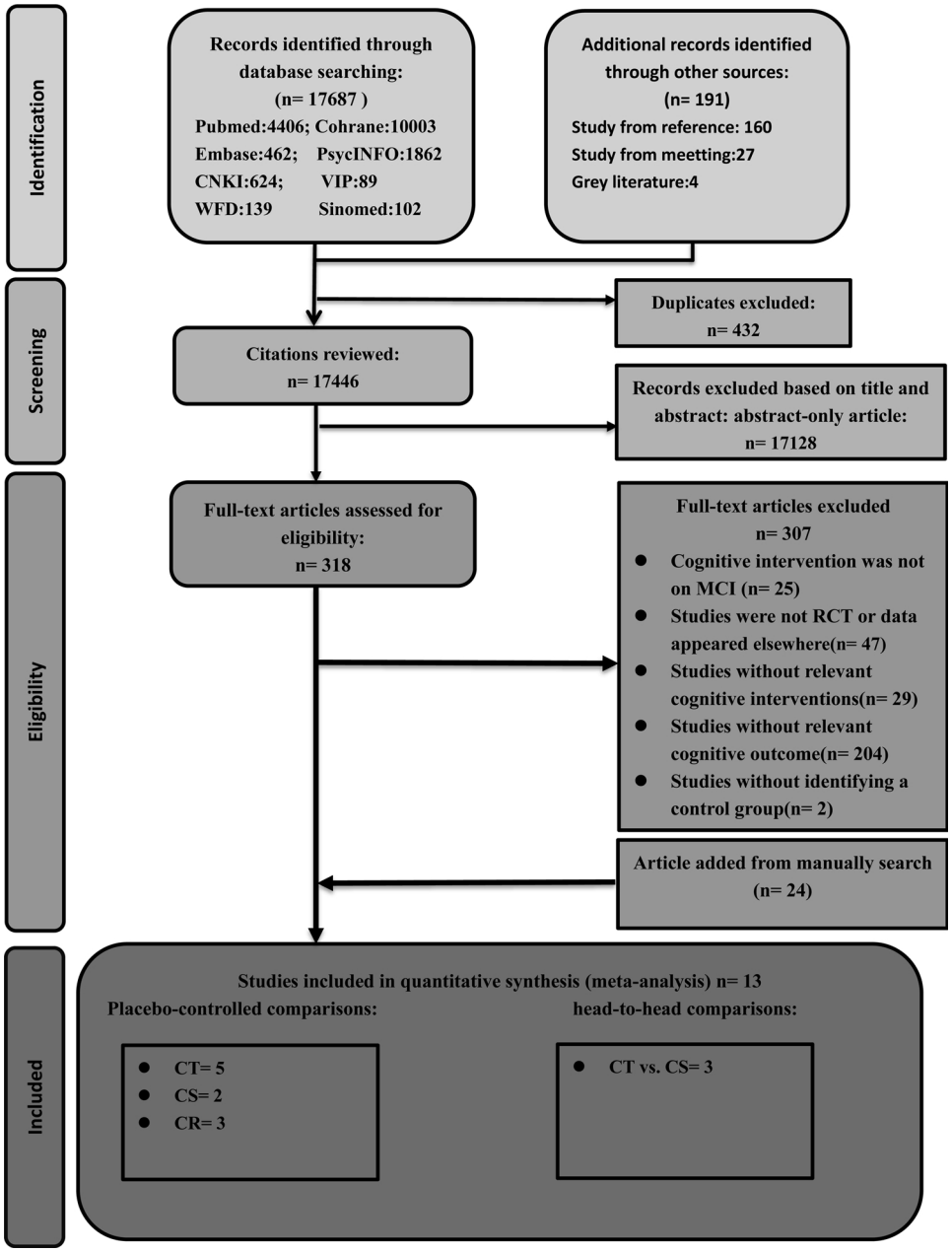


Fig. 1. Literature review flowchart. (CNKI, China National Knowledge Infrastructure database; CT, Cognitive Training; MCI, Mild cognitive impairment; CS, Cognitive stimulation; CR, Cognitive rehabilitation; RCT, Randomized controlled trial; VIP,Chinese scientific Journal database; WFD, Wan fang database).

A SUCRA line was drawn to rank the hierarchy of each cognitive intervention (shown in Fig. 3), which indicated that CS got the highest probability (SUCRA = 61.0%) in MCI treatment in terms of the cognitive domain compared with the other two cognitive interventions, although CT (SUCRA = 49.0%) also got a remarkable ranking among the three. CR (SUCRA = 45.9%) got an inferior ranking.

With the control group alone being the mutual contrast for comparison, CS (Mean difference [MD] = 0.95, 95%confidence interval [CI]:0.27, 1.70) and CT(MD = 0.70, [CI]:0.11,1.30) were associated with an significant improvement in the cognitive function based on MMSE while the MD (MD = 0.59, [CI]:-0.30,1.50) of CR showed a contrary statistic outcome (Shown in Table 3). Relatively reliable evidence could be drawn from absence of statistical inconsistency ($P > 0.05$, CS v.s Control group (CG) P-value = 0.271275, CT v.s CG P-value = 0.83015, CT v.s CS P-value = 0.9807) as is revealed by the node-splitting model ((Supplement Fig. 5), a scientific way to test for inconsistency between direct and indirect evidence which is used for valid comparison of the above-mentioned three cognitive interventions.

The subgroup analysis was shown in Table 3 combined with the total forest plot, which was divided into three subgroups. The setting group contains both group-based setting and individual-based setting, but only nine studies were included in this classification except for four studies (Förster et al., 2011; Greenaway et al., 2013; Jeong et al., 2016; Rozzini et al., 2007b; Wei and Ji, 2014) with different definitions. We divided the region group into Europe plus America group and Asia group, the technology group into new-technology group and traditional-method group. The results showed that both group-based setting (MD = 0.60, [CI]:0.43, 0.77, $P = 0.002$) and individual-based setting (MD = 0.45, [CI]:0.25, 0.64, $P = 0.019$) were capable of improving the cognitive function. The subgroups of new-technology (MD = 0.66, [CI]:0.34, 1.06, $P = 0.036$) and traditional (MD = 0.78, [CI]:0.20, 1.53, $P = 0.024$) also improved cognitive functioning and method there seemed to be little difference between them. In terms of region, the Europe and America (MD = 0.80, [CI]:0.24, 1.64, $P = 0.037$) groups

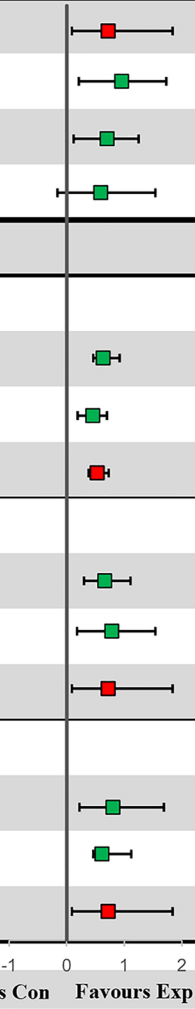
Table 2
Baseline chart.

Intervention	Study	RCT design	Age		Measure	Intervention format	Duration	Country	Major outcome
			Exp	Con					
Cognitive training	Barban, 2016	Cross-over	74.40 ± 5.70	72.90 ± 6.00	Process-based cognitive training computerized	Individual-based	24	Italy, Greece, Norway, Spain	RW-del, PF, MMSE
	Linda, 2012	Parallel	77.20 ± 6.30	78.30 ± 6.60	24-forms simplified "Tai Chi"	Group-based	54	Hongkong	MMSE, ADAS-Cog, NPI, CDR
	Chandra, 2018	Parallel	72.60 ± 7.80	71.90 ± 7.90	Fully qualified physical therapist	Group-based	24	Brazil	SWt, St, FRt, MMSE
	Xiu-hong, 2014	Parallel	66.73 ± 5.48	65.27 ± 4.63	Handball training program	Unclear	24	China	MMSE, ADL
	Hiroyuki, 2017	Parallel	71.60 ± 5.00	71.60 ± 4.90	Combined Activity Program	Individual-based	40	Japan	MMSE, WMS-LM II, TMT
Cognitive stimulation	Magda, 2010	Parallel	66.86 ± 8.79	68.45 ± 6.99	Cognitive stimulation and psychotherapeutic techniques	Group-based	20	Greece	MoCA, MMSE, ROCFT, FRSSD
	Galeno, 2013	Parallel	72.00 ± 14.29	76.93 ± 7.05	Cognitive stimulation training session	Group-based	24	Argentina	Mem-REC, SF, PhF, CDR, MMSE
Cognitive rehabilitation	Rozzini, 2007	Parallel	NR	NR	Multidimendional software	Unclear	54	Italy	BADL, MMSE,GDS, NPI
	Ji Won, 2017	Cross-over	73.74 ± 4.84	74.50 ± 6.44	Ubiquitous Spaced Retrieval-based Memory Advancement and Rehabilitation Training	Individual-based	4	Korea	WLMT, WLRT, SMCQ, GDS, MMSE
	Greenaway, 2013	Parallel	72.70 ± 6.90	72.30 ± 7.90	Memory support system	Unclear	24	USA	Ecog, QOL-AD, DRS-2, CES-D, CB, MMSE
CS v.s CT	Stefan, 2011	Parallel	74.50 ± 8.60	72.00 ± .7.10	Minute group-based cognitive intervention	Group-based	24	Germany	ADAS-Cog, MMSE
	Jee, 2016	Parallel	68.50 ± 8.50	70.80 ± 6.90	Group-and Home-Based Cognitive Intervention	Both	12	Korea	Modified ADAS-Cog, PMT, MMSE, CDR-SB, GDS-15, CGA-NPI, QOL-AD
	Verena, 2011	Cross-over	71.80 ± .8.60	70.70 ± 5.70	Stage-specfic cognitive intervention	Group-based	24	Germany	ADAS-Cog, MMSE, MADRS, QoL-AD

ADAS-Cog, Alzheimer's disease assessment scale; ADL, Activities of daily living; BADL, Basic Activities Daily Living; CB, Caregiver Burden; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CES-D, Centers for Epidemiological Studies-Depression; CGA-NPI, Caregiver-Administered Neuropsychiatric Inventory; Con, Control group; CS, Cognitive stimualtion; CT, Cognitive training; DRS-2, Dementia Rating Scale-2; Ecog, Everyday Cognition Memory Subscale Scores; Exp, Experiment group; GDS-15, 15-item version of the Geriatric Depression Scale; FRSSD, Functional Rating Scale of Symptoms of Dementia; FRt, Functional Reach Test; GDS, Geriatric Depression Scale; MADRS, Montgomery Asberg Depression Rating Scale; Mem-REC, Memory free recall; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatry Inventory; NR, Not report; PF, phonological fluency; PhF, phonological fluency; PMT, Prospective Memory Test; QoL-AD, Quality of Life-Alzheimer's Disease; RCT, Randomized controlled trial; ROCFT, visual-constructive abilities; RW-del, Rey words delayed recall; SF, semantic fluency; SMCQ, Subjective Memory Complaint Questionnaire; St, Sit/stand test; SWt, Stationary walk test; TMT, Trail-making test; WLMT, Word List Memory Test; WLRT, Word List Recall Test; WMS-LM II, The Wechsler Memory Scale-RevisedeLogical Memory II.

Table 3
The Forest plot of cognitive outcome based on MMSE.

Study	NO.studies	No.patients Exp	No.patients Con	Heterogeneity (I^2)	Mean difference(95%CI)	*P*-value
Overall	13	672	661	0%	0.72(0.03-1.81)	0.041
Cognitive stimulation	5	191	195	0%	0.95(0.27-1.70)	0.020
Cognitive training	8	433	414	0%	0.70(0.11-1.30)	0.034
Cognitive rehabilitatio	3	48	52	0%	0.59(-0.30-1.50)	0.524
Subgroup analysis						
1.Setting						
Group-based	6	232	345	0%	0.60(0.43-0.77)	0.002
Individual-based	3	206	209	0%	0.45(0.25-0.64)	0.019
Overall	9	438	554	0%	0.53(0.40-0.66)	<0.001
2.Technology						
New-technology	6	119	139	0%	0.66(0.34-1.06)	0.036
Traditional-method	7	553	522	0%	0.78(0.20-1.53)	0.024
Overall	13	672	661	0%	0.72(0.03-1.81)	0.041
3.Region						
Europe and America	8	211	268	0%	0.80(0.24-1.64)	0.037
Asia	5	430	424	0%	0.61(0.49-1.14)	0.017
Overall	13	641	692	0%	0.72(0.03-1.81)	0.041



Con, Control group; Exp, Experiment group; MMSE, Mini-Mental State Examination; NO, Number.

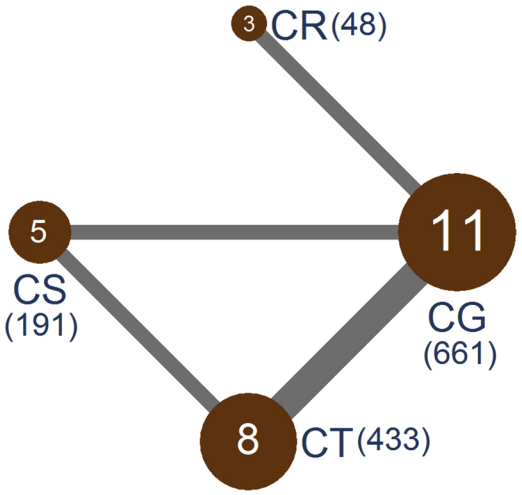


Fig. 2. Network of cognitive interventions comparison of cognition for the network meta-analysis. (CG, Control group; CR, Cognitive rehabilitation; CS, Cognitive stimulation; CT, Cognitive training).

showed a consistency with the Asia (MD = 0.61, [CI]:0.49, 1.14, $P = 0.017$) group that experienced a significant improvement in the cognitive function of MCI patients.

4. Discussion

As far as we are concerned, there is no previous study which has solved the problem which cognitive intervention is relatively the best intervention for MCI patients. Therefore, as the first NMA of cognitive interventions for MCI patients where indirect evidence was used to apprise the relative effectiveness of cognitive interventions across trials simultaneously, based on a summarization of available data, the result of our study suggest that the optimal intervention for cognitive decline is CS (SUCAR = 61.0%). The above findings can be reinforced by our previous meta-analyses (Liang et al., 2018).

Since MCI can cause substantial harm to both the society and the patient's family, it is imperative and urgent to provide scientific and reliable evidence to help MCI patients decrease or prevent the risk of developing AD by implementing relevant cognitive interventions. Nowadays, cognitive interventions were categorized into two major types, pharmacological interventions or non-pharmacological interventions. As a replaceable scientific first-line treatment,

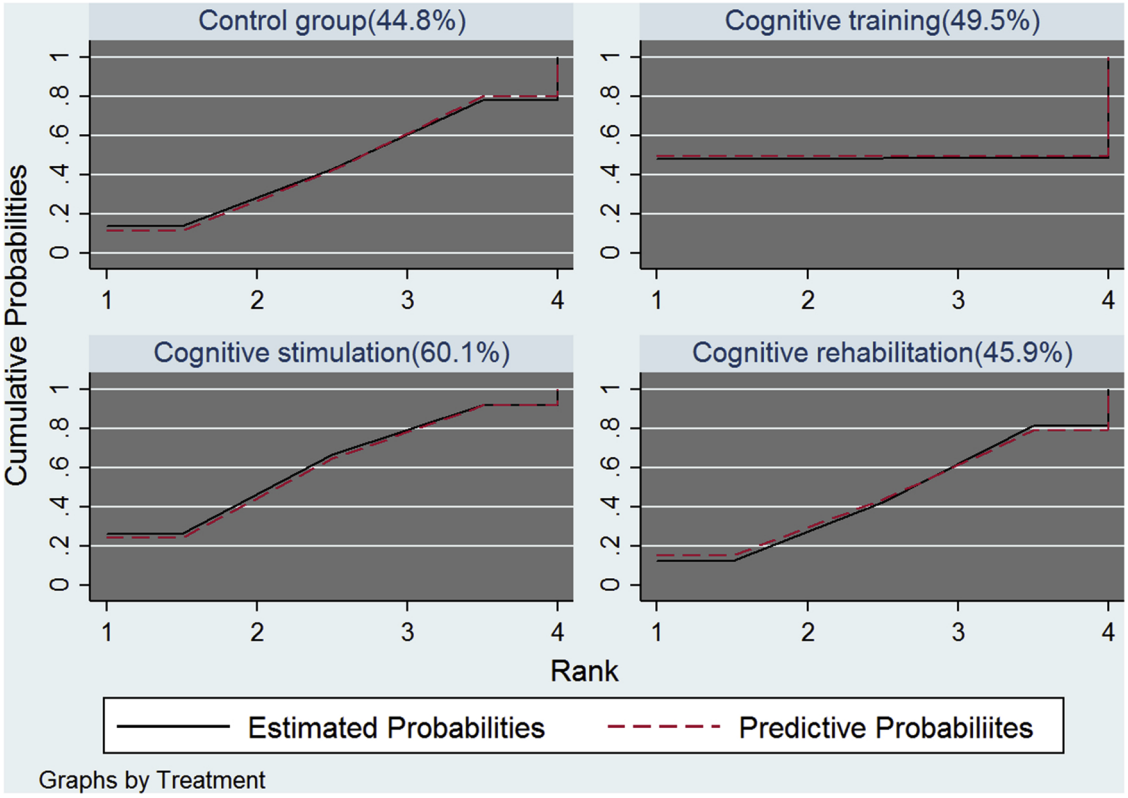


Fig. 3. The rankings of overall cognitive interventions based on SUCRA line.

pharmacological interventions such as donepezil, galanthamine, rivastigmine and other cholinesterase inhibitors (ChEI) (de Jager et al., 2012; Feldman et al., 2007; Oulhaj et al., 2016; Salloway et al., 2004; Sobow and Kloszewska, 2007; Winblad et al., 2008), as well as huperzine-A, an potent, reversible, selective inhibitor of Acetylcholinesterase (AchE) derived from Chinese herb Huperzia serrata, have demonstrated the potential for deferring cognitive decline or maintaining cognitive functioning (Wang et al., 2005; Xu et al., 1999). Some studies even found that elderly people diagnosed with AD experienced a significant improvement of cognitive ability after Huperzine-A treatment compared with those receiving conventional ChEI treatment (Kelley and Knopman, 2008; Little et al., 2008). However, undeniabllly, such interventions do not have a promising prospect due to their lacking in durative safety that might lead to some adverse effects (AEs) (Kavirajan and Schneider, 2007; Whalley et al., 2012) and high risk of contraindications (Rodakowski et al., 2015), thus confining their pervasive application.

The cognitive interventions summarized by Clare and Woods's (Clare and Woods, 2004) composed of cognitive training, cognitive stimulation and cognitive rehabilitation are defined as non-pharmacological interventions in most cases and sometimes are combined with pharmacological interventions as a complementary therapy (Clare et al., 2003b). These cognitive interventions not only address the problem of cognitive decline but also have a prominent effect on executive functioning, attention, memory, and so on (Rojas et al., 2013a; Simon et al., 2012). Furthermore, the cognitive interventions also play an essential role in assisting the clinical populations diagnosed with stroke, Parkinson's disease, and other cognitive disorders, whose preference proved the effectiveness of these cognitive interventions compared with pharmacological interventions (Faria et al., 2016; Floel, 2017; Leung et al., 2015; Towe et al., 2017). As the most conventional and regular cognitive treatment, CT, also defined by the Medical Research Council as all-inclusive term (Craig and Petticrew, 2013), can be grossly categorized as either remediation or compensation approaches (Cicerone et al., 2011). It's applicability and operability is much broader than those of the other cognitive interventions. CT was defined to include aerobic exercise (Cammisuli et al., 2017), individual-target training (Schwenk et al., 2016), and computerized cognitive training (Barnes et al., 2009), all of which have been examined of their efficacy and safety regarding cognitive domain. Physical exercise was the most frequently used intervention in cognitive training, and the types of exercise varied from "treadmill training" (Arcoverde et al., 2014), "whole-body vibration" (Christofoletti et al., 2008; Lam et al., 2018) to "walking tasks" (Venturelli et al., 2011) as the basic training and were executed repeatedly. There seems to be no significant difference in slowing down the cognitive impairment based on the intensity of training from moderate to high (Varela et al., 2012). This is probably due to the mechanization and inflexibility of CT which, as a guided practice, only uses standardized tasks. Nevertheless, CT was highly praised by plenty of clinical population with cognitive impairment even by healthy older adults (Corbett et al., 2015; Lampit et al., 2013). In spite of the preponderance of studies claiming that various cognitive trainings can maximumly help MCI patients with a categorical disadvantage in cognitive function, some studies puts forward the conservative argument that CT only provides subtle improvement in the cognitive ability (Finn and McDonald, 2011; Gaitan et al., 2013; Hwang et al., 2012). A number of factors should be taken into consideration, a notable factor being the sample size of different studies. This unsharp characteristic also clearly reflects that CT-group (847 samples) took up an overwhelming number of population samples compared with CS-group (386 samples) and CR-group (100 samples). Similarly, this perhaps can account for the reason why the ranking of CR was the lowest among the three cognitive interventions in our study. It may imply that some results could lead to an unconvincing theory caused by no more place for enough population samples throughout the whole research process (Arlati et al., 2017). The regional group was included in subgroup analysis to examine whether there was a difference among different regions. However, from the above analyzed results, the cognitive interventions took place in both Europe plus America (MD = 0.80, [CI]:0.24,1.64, P = 0.037) and Asia (MD = 0.61, [CI]:0.49,1.14,

P = 0.017) all seemed to have helped MCI patients achieve a higher cognitive performance. Few studies have arrived at this statement and most of them were interested in the clinical or economic impact of AD by making a comparison of different countries. Undoubtedly, with the rapid development of information technology, multitudinous cognitive interventions sprang up and developed the pivotal measures for supporting the long-term care for MCI patients during the past few years. Like the computerized cognitive training (Gooding et al., 2015; Lin et al., 2016), telerehabilitation interventions (Cotelli et al., 2017; Jelcic et al., 2014) and multidimensional software program (Rozzini et al., 2007a) are all performed by utilizing the cutting-edge technology related to computers, their practicability and maneuverability have been recognized but their effectiveness in cognitive improvement (MD = 0.50, [CI]:0.26,0.74,p:0.580) was not as obvious as conventional-intervention programs as indicted by our subgroup analysis (MD = 0.56, [CI]:0.19,0.93,p:0.726). Such studies have confirmed the consistency of this phenomenon. An important aspect worth consideration is the setting in which MCI patients received interventions, whether in group-based programs or face-to-face individual programs (Belleville et al., 2011; Hwang et al., 2012). Compared with the individual-based setting, the group-based setting had a more significant improvement in cognitive ability with its non-specific method particular in CS (Nakamura et al., 2016; Tsutsumimoto et al., 2016). CS held the highest ranking in our study which allows group-based patients to receive reminiscence therapy with emphasis on social interaction. In addition, CS also has the function to ameliorate the neuropsychiatric symptoms which can be assessed using Neuropsychiatric Inventory Questionnaire (NPI-Q) (Rozzini et al., 2007a; Steenland et al., 2012). Group-based programs aimed to obtain or maintain multidimensional communication and interaction between people underlying social engagement (Spector et al., 2008). In our study, due to the existence of the group-based setting, the ranking of CS was even higher than CT under the prerequisite that the sample size was far less than the latter. Cognitive rehabilitation, as the synthetical treatment involving a bio-psycho-social medical model (Ford, 1980) did not show a significant improvement in our NMA and thus got the lowest rank among the three cognitive interventions. Some studies indicate that cognitive impairment may be controlled successfully by engaging in rehabilitation strategy for its mission is to pursue an optimal level of physical, psychological and social functioning (Kurz et al., 2009; Otani et al., 2013). Reports on CR for MCI treatment are very limited. CR is performed using a mnemonic strategy supported by families or caregivers, which will increase the consumption of financial and material resources to some extent and thus delays the development of this cognitive program. The purposes of CR can simply be categorized into two aspects: one is to make the most advantage of the remaining memory ability, for example, identifying the optimal ways of getting important information or conducting essential, real-life practical skills (Hill et al., 1987); the other is to figure out appropriate ways of compensating for difficulties by applying memory-aid machine or adjusting the environment so that the requirements on memory can be reduced (Bourgeois, 1990; Clare et al., 2003a; Steenland et al., 2012).

As the unique target measurement, MMSE may be one of the most recognized and widely used mental status examinations, which was chosen exclusively in our study for further analysis (PH et al., 1994). The clinical utility of MMSE is highly supported as a primary screening test of cognitive function in the routine clinical examinations of elderly patients. The reason why we chose MMSE not only because of its advantages in quantified assessment for patients with a more objective or what is commonly a vague and subjective impression of cognitive disability, but also because of its usefulness in providing subjects with a simple method of cognitive assessment replacing bewildering various individual approaches (Tangalos et al., 1996). MMSE is a pioneering cognitive screening instrument with robustness and reliable evidence of its clinical utility, which solves the issue of selecting primary outcome in our study. In this context, the results from our study are likely to be more useful for decision-makers, service commissioners and paramedics.

We excluded the multicomponent treatment incorporating two or more cognitive interventions due to the synergistic effect of any combination among cognitive interventions which might introduce certain mixed elements into our outcome that will be unfavorable to our final analysis. However, abundant evidence has shown that this combination has a tendency of consistency with the cognitive intervention therapy alone(Borghini et al., 2017; Hampstead et al., 2017; Nakata et al., 2009). Like the combination therapies in pharmacological interventions (Alavi Naeini et al., 2014; Ownby, 2006), the Memantine, Donepezil, the combination of Memantine and Acetylcholinesterase inhibitor (AchEI) (Farrimond et al., 2012) have been proved to be particularly effective in improving the cognitive function in patients with cognitive disorders but they still have adverse effects. These linkages may suggest a rational intercommunity of physical therapy or pharmacological therapy but the disparity of safety underlines the importance of implementing a non-pharmacological intervention.

Instead of only putting various interventions into different categories such as physical exercise or cognitive stimulation, to the best advantage, our NMA took the lead in assessing each intervention individually and compared all major interventions simultaneously for MCI patients. From the methodological point of view, traditional meta-analysis only analyzes the effectiveness of one cognitive intervention against one control group for elderly adults diagnosed with MCI, but our NMA has overcome this limitation due to its strength in integrating more than two cognitive interventions to assess their efficacy concurrently. This sophisticated synthesis approach can be used in a certain leading condition, assuming primacy over most of previous studies. And it may be implemented as the evidence-based clinical guideline which is useful for healthcare policy makers, service commissioners or clinicians and caregivers when they are making choices among various kinds of treatments. In addition, the cognitive intervention of CCT is complex and multifaceted and the number of relevant trials is very small, which proves the particular significance of our NMA. Finally, we searched as many databases as possible to amplify the literature basis so asto prevent any omissions of potentially relevant articles.

The limitations of our NMA should also beduly discussed. First, the studies included in our NMA used the same scale as the basis, the outcomes of which were shown as a continuous variable. In the analysis section, we extracted the mean, SD, and sample size values at baseline and at last observation for analysis. However, the number of available studies became smaller since a few studies had lost their data. Second, there was a significant difference in sample size among different cognitive interventions, which may lead to an imprecise analysis. For example, CR (100 samples) had a relatively small sample population compared to the whole sample size (1333 samples). At last, only CT had relatively sufficient direct and indirect evidence, whereas CS, of which relevant studies provided few available data, and CR lacked direct evidence compared with CT and CS.

Quality of several studies potentially threatens the validity of our study (Greenaway et al., 2013a; Rojas et al., 2013a; Rozzini et al., 2010). Some of them lack the blindness in subject participation, personnel or outside assessors (Rojas et al., 2013a; Rozzini et al., 2010). Outcome of interest from four studies (Lam et al., 2012; Rozzini et al., 2010; Tsolaki et al., 2011; Wei and Ji, 2014a) with a high risk of reporting bias were reported insufficiently such as the data of characteristics, or the values of outcome needed to be transformed in our analysis. Three studies were judged as high risk of other bias as the sample size of one randomized controlled trail (Barban et al., 2016) with cross-over group design was comprised of three types of participants including the healthy elderly, the mild cognitive impairment and finally the mild Alzheimer's disease. Although its outcome output was introducing themselves respectively, furthermore, compared with the parallel group RCT, the trial with cross-over design would minimize certain biases generally (Sedgwick, 2015), but the other confounding

factors with subjects resulting the outcome directly may be generated simultaneously once the trial was conducted. Another study was also rated as high risk of other bias since its cognitive intervention program included part of cognitive training intervention (Rojas et al., 2013a). The remaining study held an insufficient reference for its evidence (Greenaway et al., 2013a). Some NMA giving the statement in their method only included the parallel trials (Wang et al., 2018; Wallis et al., 2018). Unlike these studies, we extracted the original data of parallel and cross-over RCTs from the first period for controlling the bias between them (DG et al., 2002), but some other biases may still exist due to various reasons of design of trials (Sedgwick, 2015), such as the difference of sample size, the types of each intervention and so on (DG and Medicine, 2002).

5. Conclusion

In conclusion, our study suggested that cognitive stimulation was the most effective cognitive intervention, followed by cognitive training and cognitive rehabilitation. The questions aforementioned suggest several directions for further research on the more available and intersecting outcomes of aspects such as Alzheimer's Disease Assessment Scale-Cognitive section (ADAS-Cog), Clinical Dementia Rating (CDR), as well as a clinical neuropsychiatric assessment scale, and Neuropsychiatric Inventory (NPI). Also, more basic trials, especially randomized controlled trials, need to be carried out to provide a comprehensive literature basis, which will facilitate the successful conduction of similar network meta-analyse.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding sources

This research was supported by Suzhou Science and Technology Development Project (Project No. SYS 201712).

Acknowledgments

We would like to gratefully acknowledge the help from the following authors: Jia-yan Qiu, Ling-long Zhou, Ya-xin Peng, Jing-yi Huang. We also thank Grisely from US and Qin-geng Liu from Australia for the help with language.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2019.01.009.

References

Akins, P.T., 2001. Does mild cognitive impairment represent early-stage Alzheimer disease? Arch. Neurol. 58, 1705.
Alavi Naeini, A.M., Elmadfa, I., Djazayery, A., Barekatain, M., Aghaye Ghazvini, M.R., Djalali, M., Feizi, A., 2014. The effect of antioxidant vitamins E and C on cognitive performance of the elderly with mild cognitive impairment in Isfahan, Iran: a double-blind, randomized, placebo-controlled trial. Eur. J. Nutr. 1255–1262.
Altman, D.G., Bland, J.M., 1996. Detecting skewness from summary information. BMJ (Clin. Res. ed.) 313, 1200.
Arcoverde, C., Deslandes, A., Moraes, H., Almeida, C., Araujo, N.B., Vasques, P.E., Silveira, H., Laks, J., 2014. Treadmill training as an augmentation treatment for Alzheimer's disease: a pilot randomized controlled study. Arq. Neuropsiquiatr. 72, 190–196.
Arlati, S., Zangiacomi, A., Greci, L., Santo, S.G., Franchini, F., Sacco, M., 2017. Virtual environments for cognitive and physical training in elderly with mild cognitive impairment: a pilot study, augmented reality, virtual reality and computer graphics. 4th International Conference, AVR 2017. Proceedings 10325, 86–106.
Barban, F., Annicchiarico, R., Pantelopoulos, S., Federici, A., Perri, R., Fadda, L., Carlesimo, G.A., Ricci, C., Giuli, S., Scalici, F., 2016. Protecting cognition from aging and Alzheimer's disease: a computerized cognitive training combined with reminiscence therapy. Int. J. Geriatr. Psychiatry 31, 340.
Barekatain, M., Alavirad, M., Tavakoli, M., Emsaki, G., Maracy, M.R., 2016. Cognitive rehabilitation in patients with nonamnestic mild cognitive impairment. J. Res. Med. Sci.
Barnes, D.E., Yaffe, K., Belfor, N., Jagust, W.J., DeCarli, C., Reed, B.R., Kramer, J.H., 2009. Computer-based cognitive training for mild cognitive impairment: results from a pilot randomized, controlled trial. Alzheimer Dis. Assoc. Disord. 23, 205–210.
Belleville, S., Clément, F., Mellah, S., Gilbert, B., Fontaine, F., Gauthier, S., 2011. Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. Brain: J. Neurol. 134, 1623–1634.
Borghini, A., Mercuri, A., Turchi, S., Bruno, M.R., Sicari, R., Picano, E., Andreassi, M.G., 2017. Effects of combined cognitive and physical training on telomere length in patients with mild cognitive impairment. Eur. Heart J. 872–873.
Bourgeois, M.S., 1990. Enhancing conversation skills in patients with Alzheimer'S disease using a prosthetic memory aid. J. Appl. Behav. Anal. 23, 29–42.
Brooks, S., AndrewGelman, 1998. General methods for monitoring convergence of iterative simulations. J. Comput. Graph. Stat. 7, 434–455.
Buschert, V.C., Friese, U., Teipel, S.J., Schneider, P., Merensky, W., Rujescu, D., Möller, H.J., Hampel, H., Buerger, K., 2011. Effects of a newly developed cognitive intervention in amnestic mild cognitive impairment and mild Alzheimer's disease: a pilot study. J. Alzheimers Dis. 25, 679–694.
Buschert, V.C., Giegling, I., Teipel, S.J., Jolk, S., Hampel, H., Rujescu, D., Buerger, K., 2012. Long-term observation of a multicomponent cognitive intervention in mild cognitive impairment. J. Clin. Psychiatry 73, e1492–1498.
Caldwell, D.M., Ades, A.E., Higgins, J.P., 2005. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ (Clin. Res. ed.) 331, 897–900.
Cammisuli, D.M., Innocenti, A., Franzoni, F., Pruneti, C., 2017. Aerobic exercise effects upon cognition in Mild Cognitive Impairment: a systematic review of randomized controlled trials. Arch. Ital. Biol. 155, 54–62.
Chaimani, A., Higgins, J.P., Mavridis, D., Spyridonos, P., Salanti, G., 2013. Graphical tools for network meta-analysis in STATA. PLoS One 8, e76654.
Christofoletti, G., Oliani, M.M., Gobbi, S., Stella, F., Bucken Gobbi, L.T., Renato, C.P., 2008. A controlled clinical trial on the effects of motor intervention on balance and cognition in institutionalized elderly patients with dementia. Clin. Rehabil. 22, 618–626.
Chua, K.K., Wong, A., Kwan, P.-L., Song, J.X., Chen, L.L., Chan, A.-T., Lu, J.H., Mok, V., Li, M., 2015. The efficacy and safety of the Chinese herbal medicine Di-Tan decoction for treating Alzheimer's disease: protocol for a randomized controlled trial. Trials.
Cicerone, K.D., Langenbahn, D.M., Braden, C., Malec, J.F., Kalmar, K., Fraas, M., Felicetti, T., Laatsch, L., Harley, J.P., Bergquist, T., 2011. Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. Arch. Phys. Med. Rehabil. 92, 519–530.
Clare, L., Woods, R.T., 2004. Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: a review. Neuropsychol. Rehabil. 14, 385–401.
Clare, L., Wilson, B.A., Carter, G., Hodges, J.R., 2003a. Cognitive rehabilitation as a component of early intervention in Alzheimer's disease: a single case study. Aging Ment. Health 7, 15.
Clare, L., Wilson, B.A., Carter, G., Hodges, J.R., 2003b. Cognitive rehabilitation as a component of early intervention in Alzheimer's disease: a single case study. Aging Ment. Health 7, 15–21.
Clare, L., Woods, R.T., Moniz Cook, E.D., Orrell, M., Spector, A., 2003c. Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. Cochrane Database Syst. Rev Cd003260.
Corbett, A., Owen, A., Hampshire, A., Grahn, J., Stenton, R., Dajani, S., Burns, A., Howard, R., Williams, N., Williams, G., Ballard, C., 2015. The effect of an online cognitive training package in healthy older adults: an online randomized controlled trial. J. Am. Med. Dir. Assoc. 990–997.
Coreteam, D., 2014. A Language and Environment for Statistical Computing.
Cotelli, M., Manenti, R., Brambilla, M., Gobbi, E., Ferrari, C., Binetti, G., Cappa, S.F., 2017. Cognitive telerehabilitation in mild cognitive impairment, Alzheimer's disease and frontotemporal dementia: a systematic review. J. Telemed. Telecare 1357633X17740390.
Craig, P., Petticrew, M., 2013. Developing and evaluating complex interventions: Reflections on the 2008 MRC guidance ☆. Int. J. Nurs. Stud. 50, 585–587.
de Jager, C.A., Oulhaj, A., Jacoby, R., Refsum, H., Smith, A.D., 2012. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. Int. J. Geriatr. Psychiatry 27, 592–600.
De Marco, M., Shanks, M.F., Venneri, A., 2014. Cognitive stimulation: the evidence base for its application in neurodegenerative disease. Curr. Alzheimer Res. 11, 469–483.
DG, A., JP, H., F, C., HV, W., & epidemiology, V. A. J. I. j. o. (2002). Meta-analyses involving cross-over trials: methodological issues.%A Elbourne DR. 31(1), 140-149.
DG, A., & medicine, E. D. J. S. i. (2002). Meta-analysis combining parallel and cross-over clinical trials. I: Continuous outcomes.%A Curtin F. 21(15), 2131-2144.
Di Iulio, F., Palmer, K., Blundo, C., Casini, A.R., Gianni, W., Caltagirone, C., Spalletta, G., 2010. Occurrence of neuropsychiatric symptoms and psychiatric disorders in mild Alzheimer's disease and mild cognitive impairment subtypes. Int. Psychogeriatr. 22, 629–640.
Dias, S., Welton, N.J., Caldwell, D.M., Ades, A.E., 2010. Checking consistency in mixed treatment comparison meta-analysis. Stat. Med. 29, 932–944.
Dias, S., Welton, N.J., Sutton, A.J., Ades, A.E., 2012. A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Med. Decis. Mak.
Economic, U.N.D.o., Division, S.A.P, 2013. World Population Policies /Department of Economic and Social Affairs Population Division. United Nations.
Egger, M., Juni, P., Bartlett, C., Holenstein, F., Sterne, J., 2003. How important are

comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. Health Technol. Assess. (Winchester, England) 7, 1–76.
Faria, A.L., Andrade, A., Soares, L., SB, I.B., 2016. Benefits of virtual reality based cognitive rehabilitation through simulated activities of daily living: a randomized controlled trial with stroke patients. J. Neuroeng. Rehabil. 1–12.
Farrimond, L.E., Roberts, E., McShane, R., 2012. Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review. BMJ Open 2.
Feldman, H.H., Ferris, S., Winblad, B., Sfikas, N., Mancione, L., He, Y., Tekin, S., Burns, A., Cummings, J., Ser, T., Inzitari, D., Orgogozo, J.M., Sauer, H., Scheltens, P., Scarpini, E., Herrmann, N., Farlow, M., Potkin, S., Charles, H.C., Fox, N.C., Lane, R., 2007. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. Lancet Neurol. 501–512.
Finn, M., McDonald, S., 2011. Computerised cognitive training for older persons with mild cognitive impairment: a pilot study using a randomised controlled trial design. Brain Impair. 187–199.
Finn, M., McDonald, S., 2015. Repetition-lag training to improve recollection memory in older people with amnestic mild cognitive impairment. A randomized controlled trial. Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn. 244–258.
Floel, A., 2017. Brain stimulation treatment for cognitive rehabilitation: can we improve learning and memory formation in aging and neurodegenerative disease? Brain stimulation. 2nd International Brain Stimulation Conference 361.
Follmann, D., Elliott, P., Suh, I., Cutler, J., 1992. Variance imputation for overviews of clinical trials with continuous response. J. Clin. Epidemiol. 45 (7), 769–773.
Folstein, M., Folstein, S., Mc Hugh, P., Folstein, M., Mchugh, P., Folstein, S., Mchugh, R.K., Mchugh, M., Mchugh, P., Folstein, M.F., 1975. Minimental State: a Practical Method for Grading the Cognitive State of Patient for the Clinican.
Ford, B., 1980. International Classification of Impairments, Disabilities and Handicaps: Exercises in Its Application in a Hospital Medical Record. World Health Organization.
Förster, S., Buschert, V.C., Teipel, S.J., Friese, U., Buchholz, H.G., Drzezga, A., Hampel, H., Bartenstein, P., Buerger, K., 2011. Effects of a 6-month cognitive intervention on brain metabolism in patients with amnestic MCI and mild Alzheimer's disease. J. Alzheimer Dis. 26 (Suppl. 3), 337–348.
Gaitan, A., Garolera, M., Cerulla, N., Chico, G., Rodriguez-Querol, M., Canela-Soler, J., 2013. Efficacy of an adjunctive computer-based cognitive training program in amnestic mild cognitive impairment and Alzheimer's disease: a single-blind, randomized clinical trial. Int. J. Geriatr. Psychiatry 28, 91–99.
Gaugler, J., James, B., Johnson, T., Scholz, K., Weuve, J., 2016. 2016 Alzheimer's disease facts and figures. Alzheimers Dement. 12, 459–509.
Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R.C., Ritchie, K., Broich, K., Belleville, S., Brodaty, H., Bennett, D., Chertkow, H., 2005. Mild cognitive impairment. Am. J. Geriatr. Psychiatry 13, 629–632.
Gooding, A.L., Choi, J., Fiszdon, J.M., Wilkins, K., Kirwin, P.D., van Dyck, C.H., Devanand, D., Bell, M.D., Rivera, M.M., 2015. Comparing three methods of computerised cognitive training for older adults with subclinical cognitive decline. Neuropsychol. Rehabil. 26, 1.
Greenaway, M.C., Duncan, N.L., Smith, G.E., 2013. The memory support system for mild cognitive impairment: randomized trial of a cognitive rehabilitation intervention. Int. J. Geriatr. Psychiatry 28, 402–409.
Hampstead, B.M., Sathian, K., Bikson, M., Stringer, A.Y., 2017. Combined mnemonic strategy training and high-definition transcranial direct current stimulation for memory deficits in mild cognitive impairment. World J. Biol. Psychiatry 3, 459–470.
Han, J.W., Son, K.L., Byun, H.J., Ko, J.W., Kim, K., Hong, J.W., Kim, T.H., Kim, K.W., 2017. Efficacy of the Ubiquitous Spaced Retrieval-based Memory Advancement and Rehabilitation Training (USMART) program among patients with mild cognitive impairment: a randomized controlled crossover trial. Alzheimers Res. Ther. 9, 39.
Herrera, A.C., Prince, M., Knapp, M., Karagiannidou, M., Guerchet, M., 2016. World Alzheimer Report 2016: Improving Healthcare for People With Dementia. Coverage, Quality and Costs Now and in the Future.
Herrup, K., 2011. Commentary on "Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." Addressing the challenge of Alzheimer's disease in the 21st century. Alzheimer's Dement.: J. Alzheimer's Assoc. 7, 335–337.
Higgins, J., Green, S.E., 2011. In: In: The Cochrane Collaboration (Ed.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 5. Naunyn-Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie, pp. S38.
Higgins, J.P., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21, 1539.
Higgins, J.P.T., Jackson, D., Barrett, J.K., Lu, G., Ades, A.E., White, I.R., 2012. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res. Synth. Methods 3, 98–110.
Hill, R.D., Evankovich, K.D., Sheikh, J.I., Yesavage, J.A., 1987. Imagery mnemonic training in a patient with primary degenerative dementia. Psychol. Aging 2, 204–205.
Hozo, S.P., Djulbegovic, B., Hozo, I., 2005. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med. Res. Methodol. 5 (1), 13.
Hutton, B., Salanti, G., Caldwell, D.M., Chaimani, A., Schmid, C.H., Cameron, C., Ioannidis, J.P.A., Straus, S., Thorlund, K., Jansen, J.P., 2015. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann. Intern. Med. 162, 777–784.
Hwang, H.R., Choi, S.H., Yoon, D.H., Yoon, B.N., Suh, Y.J., Lee, D., Han, I.T., Hong, C.G., 2012. The effect of cognitive training in patients with mild cognitive impairment and early Alzheimer's disease: a preliminary study. J. Clin. Neurol. (Seoul, Korea) 8, 190–197.
Jansen, J.P., Naci, H., 2013. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. BMC Med. 11, 159.
Jelcic, N., Agostini, M., Meneghello, F., Bussè, C., Parise, S., Galano, A., Tonin, P., Dam, M., Cagnin, A., 2014. Feasibility and efficacy of cognitive telerehabilitation in early Alzheimer's disease: a pilot study. Clin. Interv. Aging 2014, 1605–1611.
Jeong, J.H., Na, H.R., Choi, S.H., Kim, J., Na, D.L., Seo, S.W., Chin, J., Park, S.A., Kim, E.J., Han, H.J., Han, S.H., Yoon, S.J., Lee, J.H., Park, K.W., Moon, S.Y., Park, M.H., Choi, M.S., Han, I.W., Lee, J.H., Lee, J.S., Shim, Y.S., Kim, J.Y., 2016. Group- and home-based cognitive intervention for patients with mild cognitive impairment: a randomized controlled trial. Psychother. Psychosom. 85, 198–207.
Joosten-Weyn Banningh, L.W., Roelofs, S.C., Vernooij-Dassen, M.J., Prins, J.B., Olde Rikkert, M.G., Kessels, R.P., 2013. Long-term effects of group therapy for patients with mild cognitive impairment and their significant others: a 6- to 8-month follow-up study. Dementia (London, England) 81–91.
Kavirajan, H., Schneider, L.S., 2007. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. Lancet Neurol. 6, 782–792.
Kelley, B.J., Knopman, D.S., 2008. Alternative medicine and Alzheimer disease. Neurologist 14, 299–306.
Kurz, A., Pohl, C., Ramsenthaler, M., Sorg, C., 2009. Cognitive rehabilitation in patients with mild cognitive impairment. Int. J. Geriatr. Psychiatry 24, 163–168.
Lam, L.C., Chau, R.C., Wong, B.M., Fung, A.W., Tam, C.W., Leung, G.T., Kwok, T.C., Leung, T.Y., Ng, S.P., Chan, W.M., 2012. A 1-year randomized controlled trial comparing mind body exercise (Tai Chi) with stretching and toning exercise on cognitive function in older Chinese adults at risk of cognitive decline. J. Am. Med. Dir. Assoc. 13 568.e515-568.e520.
Lam, F.M.H., Liao, L.R., Kwok, T.C.Y., Pang, M.Y.C., 2018. Effects of adding whole-body vibration to routine day activity program on physical functioning in elderly with mild or moderate dementia: a randomized controlled trial. Int. J. Geriatr. Psychiatry 33.
Lampit, A., Hallock, H., Moss, R., Kwok, S., Rosser, M., Lukjanenko, M., 2013. A dose-response relationship between computerized cognitive training and global cognition in older adults. J. Nutr. Health Aging 803–804.
Langoni, C., Resende, T.L., Barcellos, A.B., Cecchele, B., Knob, M.S., Silva, T., Rosa, J., Diogo, T.S., Silva, I.F., Schwanke, C., 2018. Effect of exercise on cognition, conditioning, muscle endurance, and balance in older adults with mild cognitive impairment: a randomized controlled trial. J. Geriatr. Phys. Ther. 1.
Leung, I.H., Walton, C.C., Hallock, H., Lewis, S.J., Valenzuela, M., Lampit, A., 2015. Cognitive training in Parkinson disease: a systematic review and meta-analysis. Neurology 85, 1843–1851.
Liang, J.H., Xu, Y., Lin, L., Jia, R.X., Zhang, H.B., Hang, L., 2018. Comparison of multiple interventions for older adults with Alzheimer disease or mild cognitive impairment: a PRISMA-compliant network meta-analysis. Medicine 97, e10744.
Lin, F., Heffner, K.L., Ren, P., Tivarus, M.E., Brasch, J., Chen, D.G., Mapstone, M., Porsteinsson, A.P., Tadin, D., 2016. Cognitive and neural effects of vision-based speed-of-processing training in older adults with amnestic mild cognitive impairment: a pilot study. J. Am. Geriatr. Soc. 64, 1293–1298.
Lipsey, M.W., Wilson, D.B., (2000). Practical meta-analysis.
Little, J.T., Walsh, S., Aisen, P.S., 2008. An update on huperzine A as a treatment for Alzheimer's disease. Expert Opin. Investig. Drugs 17, 209–215.
Lu, G., Ades, A.E., 2004. Combination of direct and indirect evidence in mixed treatment comparisons. Stat. Med. 23, 3105–3124.
Mavridis, D., Salanti, G., 2013. A practical introduction to multivariate meta-analysis. Stat. Methods Med. Res. 22, 133–158.
Mills, E.J., Thorlund, K., Ioannidis, J.P., 2013. Demystifying trial networks and network meta-analysis. BMJ (Clin. Res. ed.) 346, f2914.
Moro, V., Condoleo, M.T., Valbusa, V., Broggio, E., Moretto, G., Gambina, G., 2015. Cognitive stimulation of executive functions in mild cognitive impairment: specific efficacy and impact in memory. Am. J. Alzheimers Dis. Other Demen. 153–164.
Morris, J.C., 2006. Mild cognitive impairment is early-stage Alzheimer disease. Arch. Neurol. 63, 15–16.
Morris, J.C., Storandt, M., Miller, J.P., Mckeel, D.W., Price, J.L., Rubin, E.H., Berg, L., 2001. Mild cognitive impairment represents early-stage Alzheimer disease. Arch. Neurol. 58, 397–405.
Mortby, M.E., Black, S.E., Gauthier, S., Miller, D., Porsteinsson, A., Smith, E.E., Ismail, Z., 2018. Dementia clinical trial implications of mild behavioral impairment. Int. Psychogeriatr. 30, 171.
Nakamura, K., Kasai, M., Nakai, M., Nakatsuka, M., Meguro, K., 2016. The group reminiscence approach can increase self-awareness of memory deficits and evoke a life review in people with mild cognitive impairment: the kurihara project data. J. Am. Med. Dir. Assoc. 17, 501–507.
Nakata, E., Kasai, M., Kasuya, M., Akanuma, K., Meguro, M., Ishii, H., Yamaguchi, S., Meguro, K., 2009. Combined memory and executive function tests can screen mild cognitive impairment and converters to dementia in a community: the Osaki-Tajiri project. Neuroepidemiology 103–110.
Otani, A., Matsumoto, S., Ueda, K., Nishi, U., 2013. Effects of Cognitive Rehabilitation in Outpatients With Mild Cognitive Impairment, International Psychogeriatrics. p. S187. .
Oulhaj, A., Jerneren, F., Refsum, H., Smith, A.D., de Jager, C.A., 2016. Omega-3 fatty acid status enhances the prevention of cognitive decline by B vitamins in mild cognitive impairment. J. Alzheimer's Dis.: JAD 50, 547–557.
Ownby, R.L., 2006. Donepezil and Vitamin E for Mild Cognitive Impairment, Current Psychiatry Reports. p. 9. .
Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. J. Intern. Med. 256, 183.
Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999. Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 56, 303.
Petersen, R.C., Doody, R., Kurz, A., Mohs, R.C., Morris, J.C., Rabins, P.V., Ritchie, K., Rossor, M., Thal, L., Winblad, B., 2001. Current concepts in mild cognitive

impairment. Arch. Neurol. 58, 1985–1992.
Petersen, R.C., Caracciolo, B., Brayne, C., Gauthier, S., Jelic, V., Fratiglioni, L., 2014. Mild cognitive impairment: a concept in evolution. J. Intern. Med. 275, 214–228.
Petersen, R.C., Lopez, O., Armstrong, M.J., Getchius, T.S.D., Ganguli, M., Gloss, D., Gronseth, G.S., Marson, D., Pringsheim, T., Day, G.S., 2018. Practice Guideline Update Summary: Mild Cognitive Impairment.
Prince, M., World Alzheimer report 2015: the global impact of dementia.
Prince, Martin, Bryce, Renata, Albanese, Ribeiro, 2013. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Demen. 9, 63–75.
Rodakowski, J., Saghafi, E., Butters, M.A., Skidmore, E.R., 2015. Non-pharmacological interventions for adults with mild cognitive impairment and early stage dementia: an updated scoping review. Mol. Aspects Med. 43–44, 38–53.
Rojas, G.J., Villar, V., Iturry, M., Harris, P., Serrano, C.M., Herrera, J.A., Allegri, R.F., 2013a. Efficacy of a cognitive intervention program in patients with mild cognitive impairment. Int. Psychogeriatr. 25, 825–831.
Rojas, G.J., Villar, V., Iturry, M., Harris, P., Serrano, C.M., Herrera, J.A., Allegri, R.F., 2013b. Efficacy of a cognitive intervention program in patients with mild cognitive impairment. Int. Psychogeriatr. 25, 825–831.
Rozzini, L., Costardi, D., Chilovi, B.V., Franzoni, S., Trabucchi, M., Padovani, A., 2007a. Efficacy of cognitive rehabilitation in patients with mild cognitive impairment treated with cholinesterase inhibitors. Int. J. Geriatr. Psychiatry 356–360.
Rozzini, L., Costardi, D., Chilovi, B.V., Franzoni, S., Trabucchi, M., Padovani, A., 2007b. Efficacy of cognitive rehabilitation in patients with mild cognitive impairment treated with cholinesterase inhibitors. Int. J. Geriatr. Psychiatry 22, 356–360.
Salanti, G., 2012. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res. Synth. Methods 3, 80–97.
Salanti, G., Higgins, J.P., Ades, A.E., Ioannidis, J.P., 2008. Evaluation of networks of randomized trials. Stat. Methods Med. Res. 17, 279–301.
Salanti, G., Marinho, V., Higgins, J.P., 2009. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. J. Clin. Epidemiol. 62, 857–864.
Salanti, G., Ades, A.E., Ioannidis, J.P., 2011. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J. Clin. Epidemiol. 64, 163–171.
Salloway, S., Ferris, S., Kluger, A., Goldman, R., Griesing, T., Kumar, D., Richardson, S., 2004. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. Neurology 651–657.
Schwenk, M., Sabbagh, M., Lin, I., Morgan, P., Grewal, G.S., Mohler, J., Coon, D.W., Najafi, B., 2016. Sensor-based balance training with motion feedback in people with mild cognitive impairment. J. Rehabil. Res. Dev. 945–958.
Senn, S., Barnett, V., 2004. Bayesian Approaches to Clinical Trials and Health-Care Evaluation. Wiley.
Shimada, H., Makizako, H., Doi, T., Park, H., Tsutsumimoto, K., Verghese, J., Suzuki, T., 2018. Effects of combined physical and cognitive exercises on cognition and mobility in patients with mild cognitive impairment: a randomized clinical trial. J. Am. Med. Dir. Assoc. 19, 584–591.
Simon, S.S., Yokomizo, J.E., Bottino, C.M., 2012. Cognitive intervention in amnestic Mild Cognitive Impairment: a systematic review (Structured abstract). Neurosci. Biobehav. Rev. 1163–1178.
Sobow, T., Kloszewska, I., 2007. Cholinesterase inhibitors in mild cognitive impairment: a meta-analysis of randomized controlled trials. Neurol. Neurochir. Pol. 41, 13–21.
Spector, A., Woods, B., Orrell, M., 2008. Cognitive stimulation for the treatment of Alzheimer's disease. Expert Rev. Neurother. 8, 751–757.
Stedman, M.R., Curtin, F., Elbourne, D.R., Kesselheim, A.S., Brookhart, M.A., 2011. Meta-analyses involving cross-over trials: methodological issues. Int. J. Epidemiol. 40 (6), 1732–1734. https://doi.org/10.1093/ije/dyp345.
Steenland, K., Karnes, C., Seals, R., Carnevale, C., Hermida, A., Levey, A., 2012. Late-life depression as a risk factor for mild cognitive impairment or Alzheimer's disease in 30 US Alzheimer's disease centers. J. Alzheimer Dis. 31, 265–275.
Towe, S.L., Patel, P., Meade, C.S., 2017. The acceptability and potential utility of cognitive training to improve working memory in persons living with HIV: a preliminary randomized trial. J. Assoc. Nurses AIDS Care: JANAC 28, 633–643.
Tsolaki, M., Kounti, F., Agogiatou, C., Poptsi, E., Bakoglidou, E., Zafeiropoulou, M., Soumbourou, A., Nikolaidou, E., Batsila, G., Siambani, A., 2010. Effectiveness of nonpharmacological approaches in patients with mild cognitive impairment. Neurodegener. Dis. 8, 138–145.
Tsutsumimoto, K., Doi, T., Shimada, H., Makizako, H., Suzuki, T., 2016. Effects of group exercise programmes on quality of life in older adults with mild cognitive impairment: preliminary results from a randomized controlled trial. Psychogeriatrics 327–328.
Valkenhoef, G.V., Kuiper, J., 2016. gemtc: Network Meta-Analysis Using Bayesian Methods. John Wiley Sons, Ltd.
van Valkenhoef, G., Dias, S., 2016. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Res. Synth. Methods 7, 80–93.
Varela, S., Ayan, C., Cancela, J.M., Martin, V., 2012. Effects of two different intensities of aerobic exercise on elderly people with mild cognitive impairment: a randomized pilot study. Clin. Rehabil. 26, 442–450.
Venturelli, M., Scarsini, R., Schena, F., 2011. Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. Am. J. Alzheimers Dis. Other Demen. 381–388.
Wallis, C.J.D., Klaassen, Z., Bhindi, B., Ye, X.Y., Chandrasekar, T., Farrell, A.M., Goldberg, H., Boorjian, S.A., Leibovich, B., Kulkarni, G.S., Shah, P.S., Bjarnason, G.A., Heng, D.Y.C., Satkunasivam, R., Finelli, A., 2018. First-line systemic therapy for metastatic renal cell carcinoma: a systematic review and network meta-analysis. Eur. Urol. 74 (3), 309–321.
Wang, W., Wang, L.N., Zhou, B., Zhang, X.H., 2005. Effect of huperzine A on memory function of patients with mild cognitive impairment. Chin. J. Clin. Rehabil. 23–25.
Wang, C., Yu, J.T., Wang, H.F., Tan, C.C., Meng, X.F., Tan, L., 2014. Non-pharmacological interventions for patients with mild cognitive impairment: a meta-analysis of randomized controlled trials of cognition-based and exercise interventions. J. Alzheimer's Dis.: JAD 42, 663–678.
Wang, F.F., Wu, Y., Zhu, Y.H., Ding, T., Batterham, R.L., Qu, F., Hardiman, P.J., 2018. Pharmacologic therapy to induce weight loss in women who have obesity/overweight with polycystic ovary syndrome: a systematic review and network meta-analysis. Obes. Rev. 19 (10), 1424–1445.
Wei, X.H., Ji, L.L., 2014. Effect of handball training on cognitive ability in elderly with mild cognitive impairment. Neurosci. Lett. 566, 98.
Welsh-Bohmer, K., Romero, H., Hayden, K., Plassman, B., Germain, C., Sano, M., Espeland, M., Craft, S., Monsch, A., Schneider, L., 2013. Challenges in international clinical trials to delay early symptomatic Alzheimer's disease. Alzheimers Demen. J. Alzheimers Assoc. 9, P137–P138.
Welton, N.J., 2012. Evidence Synthesis for Decision Making in Healthcare. John Wiley & Sons.
Whalley, L.J., Sharma, S., Fox, H.C., Murray, A.D., Staff, R.T., Duthie, A.C., Deary, I.J., Starr, J.M., 2012. Anticholinergic drugs in late life: adverse effects on cognition but not on progress to dementia. J. Alzheimer's Dis.: JAD 30, 253–261.
Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.O., Nordberg, A., Bäckman, L., Albert, M., Almkvist, O., 2004. Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J. Intern. Med. 256, 240–246.
Winblad, B., Gauthier, S., Scinto, L., Feldman, H., Wilcock, G.K., Truyen, L., Mayorga, A.J., Wang, D., Brashear, H.R., Nye, J.S., 2008. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology 70, 2024–2035.
Wortmann, M., 2012. Alzheimer's Disease International's efforts to make dementia a global health priority. Alzheimers Demen. 8, P238–P239.
Xu, S.S., Cai, Z.Y., Qu, Z.W., Yang, R.M., Cai, Y.L., Wang, G.Q., Su, X.Q., Zhong, X.S., Cheng, R.Y., Xu, W.A., Li, J.X., Feng, B., 1999. Huperzine-A in capsules and tablets for treating patients with Alzheimer disease. Zhongguo yao li xue bao [Acta pharmacologica Sinica] 486–490.
Zhang, S., Zhang, M., Cai, F., Song, W., 2013. Biological function of Presenilin and its role in AD pathogenesis. Transl. Neurodegener. 2, 15.