Ageing Research Reviews 56 (2019) 100965

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Non-pharmacological therapeutic strategy options for patients with dementia based on cognitive function—A Bayesian network meta-analysis of randomized controlled trials

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ARTICLE INFO

Keywords:
Dementia
Alzheimers disease
Non-pharmacological therapies
Bayesian network meta-analysis

ABSTRACT

Dementia represents one of the most common neurodegenerative disorders in older adults. However, it is still unclear whether non-pharmacological therapies (NPTs) are effective or not and which treatment should be preferred. We applied a series of search strategies to identify eligible randomized controlled trials on 1st October, 2018, investigating the effects of NPTs of dementia in the older persons. Pairwise and network meta-analyses were sequentially performed. A total of 31 trials were included, which enrolled 1895 participants and 7 NPTs. Compared with control group, all the NPTs included were statistically beneficial to cognitive function, and our study indicated Comprehensive Therapy(CT) [the surface under the cumulative ranking curve (SUCRA = 92.42%)] might be the best choice for dementia patients. Our study suggests CT might be the optimal NPT for improving the cognitive function of dementia patients. However, the above conclusions need to be further analyzed.

1. Introduction

Dementia, a neurodegenerative disease, has defied attempts to find preventive therapies or cure (Herrera et al., 2018a,b). Memories, executive function in daily activities and a sense of visuospatial or attention functioning were all be totally deprived brutally, with devastating consequences for their families, caregivers health-care system and even the whole society (Baharfuchs et al., 2013; Herrup and Dementia, 2011). The latest official report shows that the estimate of people suffering from Alzheimer's disease (AD) is reckoned to be around 50 million by the year of 2018, which will triple in 2050 compared with 46.8 million in 2012 (Association, 2018; Mortby et al., 2018; Prince et al., 2015). Moreover, there will be a new case of dementia every 3 s across the world, and the total estimated worldwide cost of dementia in 2018 is US$1 trillion while this figure will rise to US $2 trillion by 2030 (Association, 2018). These ever-increasing phenomena pose a significantly double burden both on society and economics (Albert et al., 2011; Ma et al., 1999)and the increasing estimated prevalence and incidence of AD emphasize the need for effective treatments (Katz et al., 2012). Accumulating evidence has suggested that the progression of AD is inevitable (Cummings et al., 2014), and there is a undoubted fact that the pharmacological treatment possesses an ability in maintaining or decreasing the rate of cognitive decline in older adults with early stage dementia (Stahl, 1998). However, given the emergence of various Adverse effects(AEs) and the high risk of contraindications of pharmacological treatment (Kavirajan and Schneider, 2007; Whalley et al., 2012), it is often used as the last resort compared with Non-pharmacological therapies(NPTs) in improving the well-being of AD patients (Health, 2006).

A battery of non-pharmacological trials has already been applied

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https://doi.org/10.1016/j.arr.2019.100965
Received 11 June 2019; Received in revised form 17 August 2019; Accepted 23 September 2019
Available online 31 October 2019

pervasively in an attempt to provide effective interventions to retard the progression of dementia. Recommended management methods highly supported by National Institute for Health and Care Excellence (NICE) for dementia-related symptoms involving NPTs have become increasingly accepted for controlling the progression of dementia or retarding the cognitive impairment to dementia, most notably AD. The most common NPTs, such as Cognitive stimulation therapy(CST), Cognitive rehabilitation(CR), Music therapy(MT), Reminiscence therapy(RT), as well as Computerized cognitive training(CCT), a special treatment focusing primarily on reducing underlying cognitive impairment or slowing its progression in AD patients (Hill et al., 2017), which has already been manifested by previous studies, and the NPTs mentioned above were generally demonstrated by previous studies on their efficacy not only in improving the cognition in AD patients but also executive functioning, behavior, and global quality of daily life (Luchsinger et al., 2005; Orrell et al., 2014; Thivierge et al., 2014). Also worth noting is that the more popular sensory interventions, namely, multisensory stimulation environment(MSSE), was aimed at helping people with severe or very severe dementia under a Snoezelen multisensory environment by stimulating the primary senses without the need for intellectual activity (Maseda et al., 2014; Sánchez et al., 2016a, b). Despite the surging interest in the role of NPTs, only limited attention has been given to the fact that cognitive treatment was the optimal among numerous NPTs due to a lack of a large sample size and relative scientific and reliable statistical method.

The present study has overcome this limitation by implementing a Bayesian network meta-analysis(NMA) which provides an overview by comparing two or more of the interventions simultaneously and ranking them even if there is absence of a direct evidence head-to-head between them. The precision of estimates of effects has increased more in NMA, allowing an integration of both direct and indirect treatment effect estimates (Thorlund and Mills, 2012), than in pairwise meta-analyses. Therefore, the main purpose of our study was to identify the optimal NPT for patients with dementia by summarizing and analyzing the available evidence.

2. Methods

2.1. Search strategies

Pubmed, Embase, the Cochrane Central Register of Controlled Trials, and PsyINFO, China National Knowledge Infrastructure database, Chinese Scientific Journal database, Chinese Biomedical Literature database, Wan Fang database, were utilized to search for the relevant randomized controlled trials(RCTs) published from the date of database inception to 1st October, 2018, comparing any NPTs with placebo or other NPTs as monotherapy in the acute treatment of patients with a primary diagnosis of major AD, other types of dementia according to standard clinical criteria.

We put no restrictions on year of publication or language, and the following Medical subject headings[MeSH] terms and free text terms combined with Boolean operators were used in search strategy: “Alzheimer’s disease”, “Dementia”, “Non-pharmacological therapy”, “Music therapy”, “Physical exercise”,” Computerized-based training”, “Reminiscence therapy”, “Cognitive stimulation therapy”, “Cognitive rehabilitation”, “Cognitive method”, “Cognitive therapy”, “Cognitive assist”, “Psychotherapy”, “Psychosocial therapy”, “Randomized controlled trial”. The bibliography lists of systematic reviews or meta-analyses referring to relevant treatment options for dementia were also used to perform recursive searches of literature which was published between Jan 1, 2000 and October 1, 2018. We conducted a manual-search strategy additionally as complementary retrieval from key journals, conference proceedings in case of the omission of eligible studies that were presented only with abstract. Our study was conducted and reported in accordance with a network meta-analysis of the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA-NMA) declaration (Hutton et al., 2015a). Details of PRISMA-NMA for our study were presented in **Supplement PRISMA-NMA**. All analyses were based on the basis of previous published studies and therefore there exists no requirement for ethical approval and patients’ consent. Based on the pre-established inclusion and exclusion criteria, two reviewers initially screened titles and abstracts independently and full-text studies were perused to examine the potentially eligible articles which may have been missed by the initial database search after eliminating irrelevant and duplicate studies. The details of search strategies for each database were summarized in **Supplement Search Strategies.**

Confirmation was necessary for the precision and completeness of data. All the searching records were downloaded in the Endnote version X9(Thompson ISI Research Soft, Philadelphia, PA, USA); managing and checking the citations were simultaneously performed to ensure the precision and completeness of data. Any divergence emerging during the search and literature selection was eventually settled by a team-discussion and if necessary, an expert was asked to arbitrate it.

2.2. Inclusion and exclusion criteria and data abstraction

We defined the target trials according to the predetermined selection criteria based on the PICOS criterion.

2.2.1. Study population

Older adults, aged more than 65 with dementia as diagnosed by clinical examination tool, such as the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association(NINCDS-ADRDA) criteria (Dubois et al., 2007; McKhann et al., 1984).

2.2.2. Intervention

Including any structured and conceptualized Non-pharmacological therapies, such as CCT, CST, CR, PE, and psychological therapy (PST).

2.2.3. Comparisons

Focused primarily on comparisons of the core therapeutic methods (CCT, MT, PE, CST, CR), and other types of NPTs or a Control group (CG), such as placebo, pharmacological therapy, and treatment as usual.

2.2.4. Outcomes

The primary outcome was the change of cognition, as measured by a rating clinical instrumental such as Mini-Mental State Examination (MMSE) (Folstein et al., 1975). The details of each type of NPT is show in Table 1. Disagreement appearing during this section was resolved by two authors. All the co-authors were consulted and consensus was reached after a team-discussion.

2.3. Outcome measures and quality appraisal

A pretested and customized data extraction form was performed to extract relevant data for each included trial by two authors, the following variables from all the included studies were collected in accordance with the Cochrane Consumers and Communication Review Group’s data extraction template (Shuster, 2011): name of first author and year of publication, study origin(country), participants’ characteristics, the duration of the NPTs and their CG, the primary outcome. The primary outcome of interest was the efficacy of all NPTs which evaluated the cognitive domain, as measured by relevant rating scale such as the MMSE. We then extracted the mean and standard deviation(SD) values of this continuous outcome at baseline and at last observation for calculating their change scores in these symptoms (Altman and Bland, 1996). Qualitative assessment for all trials included was implemented by using the Cochrane Collaboration tool for assessing and classifying the risk of bias in randomized controlled trials (Shuster, 2011). In case

Table 1
Description of Non-pharmacological therapy.

Type of Non-pharmacological therapy	Abbreviation	People	Goals	Methods	Example
Physical exercise	PE	Mild to moderate AD	Aiming at slowing cognitive decline and delaying the onset of cognitive impairment and dementia in adults	Interventions could include activities with mostly aerobic components such as walking or running or non-aerobic components such as strength exercises.	In PE, participants trained their lower body on a movement trainer which was performed from chairs. Participants were required to train three times a week for 30 minutes and the program changed between passive, motor-assisted or active resistive training of the legs as well as changes in direction (forward, reverse) every 5 minutes.
Computerized cognitive training	CCT	Mild to moderate AD	CCT is a safe, relatively inexpensive and scalable intervention that aims to maintain cognition in older adults.	CCT involves guided drill-and-practice on standardized tasks designed to load on specific cognitive processes, typically without explicit teaching of memory or problem-solving strategies, such as cognitive rationale, videogames, or virtual reality.	CCT employs the training neuropsychologic software which represents several parts of cognitive function (Memory, Intelligence, Language). A neuropsychologist sat beside the subject, chose the exercises, read the instructions along with the patient and gave all necessary clarifications.
Music therapy	MT	Mild to moderate AD	Music therapy is one of the nonpharmaceutical treatments for patients with dementia that aims to ease the patient's mind and reduce the behavioral and psychological symptoms of dementia.	In music therapy, recipients can be actively engaged in making music and singing, which defines an "interactive" method, or they can listen to music that a therapist plays or sings or to a CD player, which is considered a "passive" method.	MT consisted of the following sections. First, voice training was performed for 15 min. Second, a 15-min review of the former session in which the songs practiced during the previous week were sung. In the third section, participants practiced familiar songs with normal voicing for 20 min. 10-min section was a so-called recreation time at last.
Cognitive stimulation therapy	CST	Early stage of AD	Aiming at improving or at least maintaining cognitive or social function in a given domain.	CS is conducted within social activities and discussions, which often takes place in a group-session manner with various difficulty level	CS including multiple group activities under a social environment and multisensory stimulation (attention, language, problem-solving) was introduced if possible. [Such as adding some subjective content through their imagination in an ordinary picture after identifying and describing it, or calculating some easily identifiable work by group discussion, e.g., by discussing recent topics and the important life events (e.g., hobbies and meaningful activities they enjoyed).]
Cognitive rehabilitation	CR	Inconclusive	Aiming to help older adults obtain or maintain an optimal level of physical, psychological, and social function	CR targets situations in daily life, including learning or relearning important information, and maintaining this learning over time. Their family members sometimes work together with health care professionals	CR tackles directly memory difficulties by addressing practical aids and strategies, which are represented by identifying the best ways of taking important information or carrying out important real-life practical skills (such as spaced retrieval, face-name recall, verbal elaboration, concentration repetition).
Comprehensive therapy	CT	Severe AD	With the accompanying care of caregivers, nursing therapy aimed at helping dementia patients improve their quality of life, improve their cognitive ability and mental capacities. The key of its concept emphasizes "human-oriented".	The most commonly used and highly recommended nursing therapy mode is "3 + 1 holistic rehabilitation nursing mode", which involves any combination of two or over two therapies among the existing therapy in most cases.	For daily living care. To promote proper self-care of patients through mutual supervision and side-by-side assistance. When patients lack independence to complete their basic life, they should be given assistance and comfort. For sleeping, giving patients suitable room temperature, humidity, soft indoor light and comfortable sleeping environment, and play music selectively according to patients' characteristics when necessary to promote patients' sleep.
Psychosocial therapy	PST	Any stage	PST is a supportive, functionally-oriented strategy aimed at enabling individuals with dementia to improve or maintain their cognition, function, adaptive behavior, emotional competence, and quality of life.	PST can be divided into cognitive training methods, behaviour orientated concepts, emotional orientated approaches and family interventions which address the dementia patients, their caregivers and the adaptation of the environment.	As an interpersonal therapy which was formerly known as the conversational model of psychotherapy and has been used to treat a wide variety of disorders including depression, somatisation and self-harm, PST consisted of six sessions of psychodynamic interpersonal therapy with an experienced psychotherapist.
Control group	CG	Any stage	A control condition	Any control group that as a NPTs placebo, such as PT, WL, TAU.	

AD, Alzheimer's disease; NPT, non-pharmacological therapy; PT, pharmacological therapy; WL, wait-list; TAU, Treatment as usual.

of disagreement regarding the quality appraisal results between the 3 co-authors, the remaining co-authors were consulted, and disagreement was ultimately resolved with consensus.

2.4. Statistical analyses

According to the minimally informative prior distributions of Bayesian random effects model (Mengersen and Stojanovski, 2006), we first conducted a conventional pairwise meta-analyses of across comparisons available for each contrast. Due to the expected variation among various NPTs from assessment of method, standard random-effects models were carried out to compare the efficacy of various NPTs in terms of change in each outcome measure. As a visual representation of statistical heterogeneity, I^2 statistic was tested for assessing whether a substantial heterogeneity existed, of which the values 25%, 50%, 75% indicated mild, moderate and high heterogeneity respectively (Hutton et al., 2015b). For detecting whether any bias was generated, a comparison-adjusted funnel plot was made as a concise description, both analyzed with the Egger test (Seagroatt and Stratton, 1997). We constructed a network plot for offering all the existing relationships, with distinct treatment expressed by different nodes, and trials by lines joining appropriate nodes. Evaluates of effect sizes for each pairwise treatment comparison in terms of continuous outcome, mean difference (MD) was calculated both along with 95 % credible intervals(CrIs) as the pooled relative effect and estimate uncertainly respectively. The above sequence of analyses were conducted in STATA, version 14.0(Stata, Corp, College Station, TX). Prior to statistical analyses, as an essential assumption which would affect the reliability of our analyses, the transitivity assumption was further appraised independently by four authors through comparing different sets of treatment that were sufficiently similar to provide valid indirect inferences in order to make the clinical and methodological characteristics as similar as possible (e.g., patients, experimental design, the types of endpoints, etc.) for each included study. Three different chains under Markov Chain Monte Carlo (MCMC) model (Mavridis and Salanti, 2013; Valkenhoef and Kuiper, 2015) were set up to simulate initially with a randomly chosen state, and each chain produced 100,000 interactions with 20,000 burn-in samples for ensuring the minimum bias of initial values when the chain reached its target distribution (Brooks and Gelman, 1998). As an estimated probability which was used for ranking the targeted non-pharmacological treatment, the surface under the cumulative ranking curve (SUCRA) was presented as a simple numerical summary statistic cumulative ranking probability plot for each treatment (Page et al., 2016). SUCRA with a higher value denotes greater likelihood of a given treatment being in the top rank or highly effective while the value "zero" indicates that the treatment is certain to be the worst. The node-splitting technique was used for judging whether a consistency of direct and indirect estimates exists separately for each treatment comparison, often shown as *P*-values(Georgia et al., 2014; Salanti et al., 2014). The above analyses were performed using "Gemtc" package (version 0.8–2) and "rjags" (version 4–6) in R language (X64 3.32version) and WinBUGS(version 1.4.3, MRC Biostatistics Unit, Cambridge, UK). Details of WinBUGS's code were presented in **Supplement WinBUGS code**. We conducted sensitivity analysis to estimate the robustness of results after excluding studies with high risk of bias.

3. Results

3.1. Included studies characteristics and ROB quality assessment

14,554 publications were identified through database search and 56 were found by additional manual search, in which 13,916 were removed based on their titles or abstracts which did not fulfill the inclusion criteria. Based on the full-text review, 277 records were excluded due to various reasons: 106 Studies were not RCTs, 11 studies enrolled the participants who were not diagnosed with dementia, 42 studies were conducted without relevant therapies we defined in this study, 64 studies reported the data that could not be extracted. At last, only 31 RCTs were included. Details of the literature selection were shown in Fig. 1. All the authors taking part in selection and appraisal in this section reached a unanimous agreement.

The included 31 studies (Arroyo-Anlló et al., 2013; Bottino et al., 2005b; Capotosto et al., 2017b; Chen et al., 2017; Chen, 2013; Duru and Kapucu, 2016; Guo, 2016; Hsin et al., 2014; Ito et al., 2006; Jelcic et al., 2014; Jiang, 2015; Jing-Jy, 2010; Kwak et al., 2007; Lai et al., 2015; Lee et al., 2013; Li, 2016; Liu et al., 2013; Nakamae et al., 2014; Niu et al., 2010; Satoh et al., 2015; Spector et al., 2003a, 2003b; Spector et al., 2015; Suzuki et al., 2010; Vreugdenhil et al., 2012; Wang et al., 2007; Yang et al., 2015; Zhong et al., 2015) included 1895 participants intervened with 7 different NPTs, and provided sufficient data which published from 2003 to 2017. None of the trials deliberately were restricted to any region, thus 21 studies were published in English and 10 in Chinese, and 9 trials with 525 participants were conducted in either European or American countries while the remaining 22 RCTs with 1370 participants were originated from Asia and Oceania. The duration ranged from 4 to 144 weeks and the median treatment duration of these 7 NPTs was 12 weeks. The mean age of all samples ranged from 67.07 to 86.00 and their mean score of MMSE ranged from 11.08 ± 6.21 to 24.17 ± 2.93 at baseline. In nine (666 participants) studies, the ratio of male to female was more than 1, whereas the remainder 22(1229 participants) had mostly male participants. 3 trials (Capotosto et al., 2017a; Jing-Jy, 2010; Spector et al., 2015) elaborated on the progression of dementia while the subjects of 21 studies were AD patients. The demographic characteristics of these 31 studies are shown in Table 2.

All the 31 trials used a random allocation for subjects but few of them reported the way to generate random sequence. The vast majority of studies had a low or unclear risk of bias in "Blinding of participants and personnel" item and one study (Ito et al., 2007) described in details the blinding of outcome assessment. 8 RCTs (Spector et al., 2003a,b; Bottino et al., 2005b; Cynthia et al., 2014; Hsin et al., 2014; Ito et al., 2007; Jing-Jy, 2010; Lee et al., 2013; Spector et al., 2015) reported their approaches to allocation concealment. 9 studies(Spector et al., 2003a,b; Bottino et al., 2005b; Cynthia et al., 2014; Guo, 2016; Ito et al., 2007; Li, 2016; Niu et al., 2010; Satoh et al., 2015; Spector et al., 2015) were at low risk of bias concerned in selective reporting items and 8 studies (Spector et al., 2003a,b; Bottino et al., 2005a; Cynthia et al., 2014; Ito et al., 2007; Jing-Jy, 2010; Spector et al., 2015; Tárraga et al., 2006; Wu and Koo, 2015) were at low risk of other bias items. The overall quality of the included studies- was rated as low and unclear risk of bias, and only one study was rated as at a high risk of bias because of the absence of both blinding of participants and performer (Nakamae et al., 2014). Risk of bias of all included studies was reported in Supplement Fig. 1 and Supplement Fig. 2.

3.2. Traditional meta-analysis and network meta-analysis

From the preliminary conventional meta-analyses, moderate magnitude of global statistical heterogeneity was observed (I^2 = 48.0%, P = 0.006). The comparison-adjusted funnel was in relatively symmetric distribution on the two sides of the inverted funnel except for several small studies that were distributed outside the inverted funnel, which indicated there might exist publication bias(See in Supplement Fig. 3). The extra Egger's test to examine whether there existed a publication bias generated a *P*-value of 0.75, higher than 0.05, which indicated that no publication bias existed in our study (Shown in Supplement Fig. 4).

Fig. 2shows the direct comparisons which display as a visual network diagram for summarizing all the primary available evidence regarding each NPT. Each node represented a non-pharmacological treatment and its size depended on the number of patients directly involved. These nodes were bridged by different thickness lines for demonstrating whether there was a direct relationship between

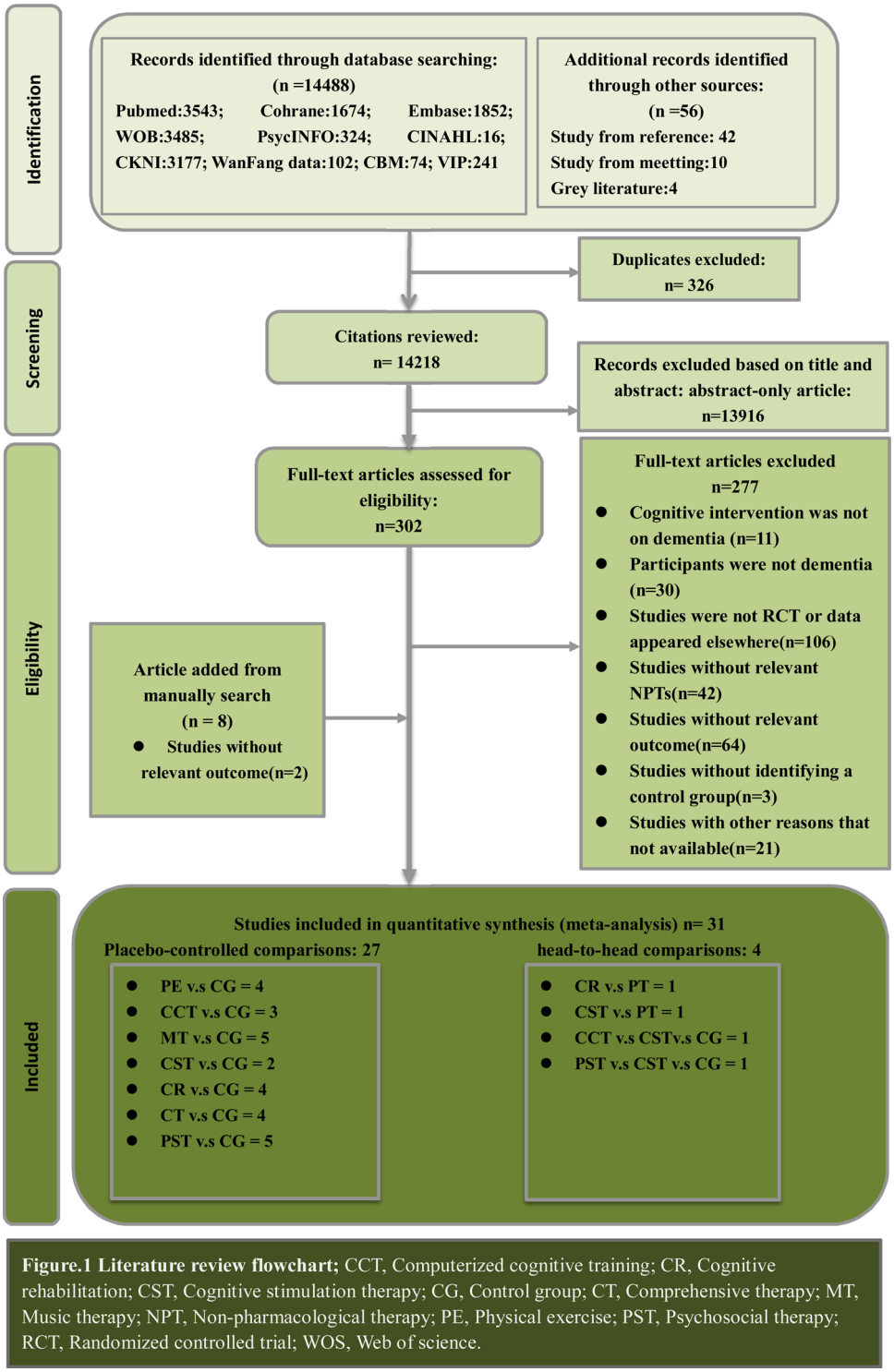


Figure.1 Literature review flowchart; CCT, Computerized cognitive training; CR, Cognitive rehabilitation; CST, Cognitive stimulation therapy; CG, Control group; CT, Comprehensive therapy; MT, Music therapy; NPT, Non-pharmacological therapy; PE, Physical exercise; PST, Psychosocial therapy; RCT, Randomized controlled trial; WOS, Web of science.

Fig. 1. Literature review flowchart; CCT, Computerized cognitive training; CR, Cognitive rehabilitation; CST, Cognitive stimulation therapy; CG, Control group; CT, Comprehensive therapy; MT, Music therapy; NPT, Non-pharmacological therapy; PE, Physical exercise; PST, Psychosocial therapy; RCT, Randomized controlled trial; WOS, Web of science.

interventions and the thickness was weighted based on available evidence between them. Each NPT had at least 1 controlled trial, and only CST had 2 closed loops between CCT and PST, thus there existed direct evidence between them.

For all the included NPTs, efficacy was shown to be statistically significant, superior to the CG. Comprehensive therapy(CT) (MD = 3.40, 95%CrI:2.10, 4.90), MT(MD = 3.0, 95%CrI:1.60, 4.40), PE(MD = 2.30, 95%CrI:1.30, 3.40), CR(MD = 1.90, 95%CrI:0.85, 3.10), CCT(MD = 1.7, 95%CrI:0.41, 2.90), CST(MD = 1.50, 95%CrI:0.65, 2.50), PST(MD = 1.20, 95%CrI:0.40, 2.00). CT was also significantly superior to CST(MD = 1.92, 95%CrI:0.24, 3.60), while CT and MT were both significantly inferior to PST[CT vs. PST(MD = -2.23, 95%CrI:-3.89, -0.63); MT vs. PST(MD = -1.77, 95%CrI:-3.40, -0.10)]. Treatment efficacy for improvement of cognitive function is shown in Fig. 3. The results of fixed model were consistent with the results based on random model. The above results were shown in Supplement Fig. 7

Table 2
Demographic Characteristics of Included Studies.

Source	Treatments and sample size	Diagnose	Age (mean ± SD)		Proportion of male(%)	Treatment Duration (Weeks)	Recruiting area	ROB
			Exp	Con				
Vreugdenhil et al. (2012)	PE = 20 vs. CG = 20	AD	73.50*	74.70*	40.00%	16	Australia	U
Kwak (2006)	PE = 15 vs. CG = 15	AD	79.67 ± 6.64	82.27 ± 7.09	NR	24	Korea	U
Yang et al. (2015)	PE = 25 vs. CG = 25	AD	72.00 ± 6.69	71.92 ± 7.28	34.00%	12	China	U
Arcoverde, 2014	PE = 10 vs. CG = 10	AD	78.50(64-81)	79.00(74-82)	45.00%	16	Brazil	L
Jelcic et al. (2014)	CCT = 7 vs. CR = 10	AD	86.00 ± 5.10	82.70 ± 6.00	29.41%	12	Italy	U
Tarraga, 2015	CCT = 15 vs.CST = 16 vs. CG = 12	AD	CCT: 75.80 ± 5.90 CST: 77.40 ± 4.70 CG: 76.90 ± 4.50		16.28%	24	Spain	L
Lee, 2013	CCT = 6 vs. CG = 7	AD	NR	NR	23.07%	6	HongKong	L
Chen, 2013	CCT = 19 vs. CG = 19	VD	76.79 ± 4.26	77.74 ± 4.05	52.63%	8	China	U
Chu, 2014	MT = 52 vs. CG = 52	AD	NR	NR	NR	4	Taiwan	U
(Arroyo-Anlló et al., 2013)	MT = 20 vs. CG = 20	AD	74.38 ± 3.56	75.15 ± 4.23	7.50%	12	Spain	U
Satoh et al. (2015)	MT = 10 vs. CG = 10	AD	78.10 ± 7.00	77.00 ± 6.10	30.00%	24	Japan	L
Suzuki, 2004	MT = 10 vs. CG = 13	Senile dementia	82.00 ± 8.42	85.23 ± 4.19	34.78%	8	Japan	U
Zhong et al. (2015)	MT = 28 vs. CG = 29	AD	78.10 ± 7.70	78.15 ± 6.50	64.91%	24	China	U
Capotosto et al. (2016)	CST = 20 vs. CG = 19	Mild to moderate dementia	88.25 ± 5.15	86.52 ± 5.55	30.77%	7	Italy	U
Spector et al. (2003a)	CST = 115 vs. CG = 86	AD	85.70 ± 6.20	84.70 ± 7.90	24.09%	7	USA	L
Niu et al. (2010)	CST = 16 vs. CG = 16	AD	80.56 ± 4.23	79.13 ± 4.38	78.13%	16	China	L
Bottino et al. (2004)	CR = 6 vs. CG = 7	AD	74.67 ± 6.98	72.86 ± 6.26	30.77%	20	Portugal	L
Guo, 2016	CR = 50 vs. CG = 50	AD	72.90 ± 5.60	73.60 ± 5.10	58.00%	12	China	L
Liu et al. (2013)	CR = 44 vs. CG = 43	AD	67.26 ± 8.98	66.55 ± 9.17	26.44%	144	China	U
Wang, 2007A	CR = 32 vs. CG = 31	VD	67.07 ± 7.91	67.48 ± 7.22	77.78%	12	China	U
Tang, 2008	CR = 28 vs. CG = 28	AD	78.07 ± 7.70	78.07 ± 7.70	77.78%	48	China	U
Chen et al. (2017)	CT = 112 vs. CG = 112	AD	72.30 ± 5.40	74.10 ± 5.60	52.23%	48	China	U
Lai et al. (2015)	CT = 30 vs. CG = 30	VD	67.82 ± 5.40	67.71 ± 5.30	55.00%	12	China	U
Jiang, 2015	CT = 38 vs. CG = 38	AD	74.66 ± 3.21	74.71 ± 3.18	53.95%	56	China	U
Li, 2016	CT = 30 vs. CG = 30	AD	74.49 ± 1.38	72.17 ± 3.19	55.00%	48	China	L
Aimee-Spector, 2015	PST = 25 vs. CG = 25	Mild to moderate dementia	69.00(62-80)	66.00(51-74)	40.00%	15	Turkey	L
Asiret, 2016	PST = 31 vs. CG = 30	AD	81.83 ± 4.87	82.26 ± 5.07	31.14%	12	Japan	U
Nakamae et al. (2014)	PST = 15 vs. CG = 15	AD&VD	84.76 ± 6.89	87.16 ± 4.57	NR	6	Taiwan	H
Wu and Koo (2015)	PST = 53 vs. CG = 50	Dementia	73.50 ± 7.30	73.60 ± 7.60	31.06%	6	Japan	L
Tomoko, 2007	PST = 20 vs. CST = 20 vs. CG = 20	VD	PST:82.90 ± 6.40 CST:81.90 ± 6.20 CG:82.10 ± 5.20		28.33%	12	Taiwan	L
Wang, 2007B	PST = 51 vs. CG = 51	Mild to moderate dementia	79.76 ± 6.29	78.92 ± 7.64	49.01%	8	USA	L

AD, Alzheimer's disease; CCT, Computerized cognitive training; CR, Cognitive rehabilitation; CST, Cognitive stimulation therapy; CT, Comprehensive therapy; MT, Music therapy; CG, Control group; PE, Physical exercise; PST, Psychosocial therapy; NPT, Non-pharmacological therapy; NR, Not report; ROB, Risk and bias; SD, standard deviation; VD, Vascular dementia;

* , mean.

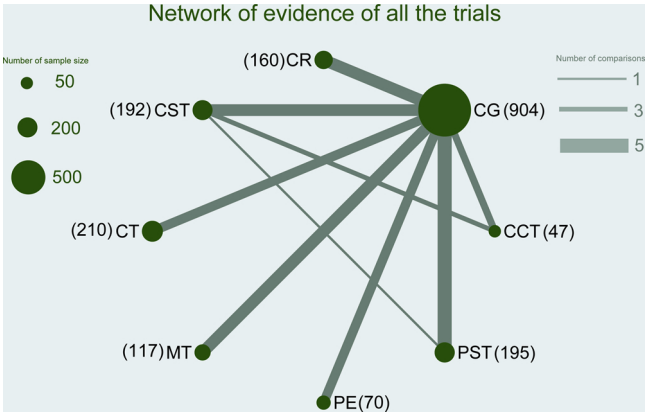


Fig. 2. Network of evidence of all the trials. CCT, Computerized cognitive training; CR, Cognitive rehabilitation; CST, Cognitive stimulation therapy; CG, Control group; CT, Comprehensive therapy; MT, Music therapy; NPT, Non-pharmacological therapy; PE, Physical exercise; PST, Psychosocial therapy.

and Supplement Table 2. Sensitivity analysis showed that after the exclusion of study with moderate or high risk of bias, the association in-between remained unchanged (Show in Supplement Fig. 6 & Supplement Table 1).

The SUCRA line was drawn for ranking the hierarchy of each NPT(See in Supplement SUCRA plot and Table 3), and CT (SUCRA = 92.42%) had the highest probability in dementia patients in terms of cognitive function compared with the other six active interventions, followed by two equally remarkable NPT–MT(SUCRA = 82.94%) and PE (SUCRA = 66.32%) while CR (SUCRA = 42.72%), CCT(SUCRA = 53.00%), and CST(SUCRA = 36.87%) had a relatively low probability, and PST(SUCRA = 22.55%) came bottom. Due to absence of statistical inconsistency ($p > 0.05$, CST vs. CCT p-value = 0.410325, PST vs. CST p-value = 0.38855) revealed by the node-splitting approach, a robust test was conducted to estimate whether an inconsistency existed between the direct and indirect evidence(Shown in Supplement Fig. 5).

4. Discussion

According to our results, in comparison with the CG, all the NPTs got a statistical significant improvement, and CT seemed to have a higher probability of helping older adults with dementia to improve their cognitive function while MT and PE are suboptimal and can be implemented as adjuvant cognitive therapies for dementia patients. The above findings can be reinforced by our previous meta-analyses (Liang et al., 2018, 2019).

Dementia is a fatal medical condition that can lead to a substantial dysfunction affecting patients' cognitive function, executive function and social functioning, and the AD is the most common one(Katzman, 2008). Although there existed more than hundreds of ongoing pharmacological treatment options, no cure halt the course of AD and most of them intended to treat AD but failed during the past 30 years (Dartigues, 2009). By 2050 if no effective treatment succeeds in delaying this disorder, more than 130 million may suffer from some forms of the disease (Herrera et al., 2018a,b).

The majority of cognitive interventions received a non-pharmacological guidance, and some non-pharmacological interventions are often considered as complementary therapies, which offer useful and versatile approaches to improving the outcome in AD patients (Javier et al., 2010), such as the CST, which was aimed at improving or at least maintaining cognitive or social function in a given domain, CR as a practical aids and strategies treatment, which was conducted by identifying the best ways of taking important information or carrying out important real-life practical skills. While the aforementioned two therapies obtained a relatively latter ranking in our results with regard to cognitive performance, levels of emotional and mental state were improved and there was a positive acceptance of the other activities and signs of happiness based on the relevant studies and other studies included (Clare et al., 2003; Jelcic et al., 2014). Some studies imply absence of group stimulation may represent a cause of AD, and lack of

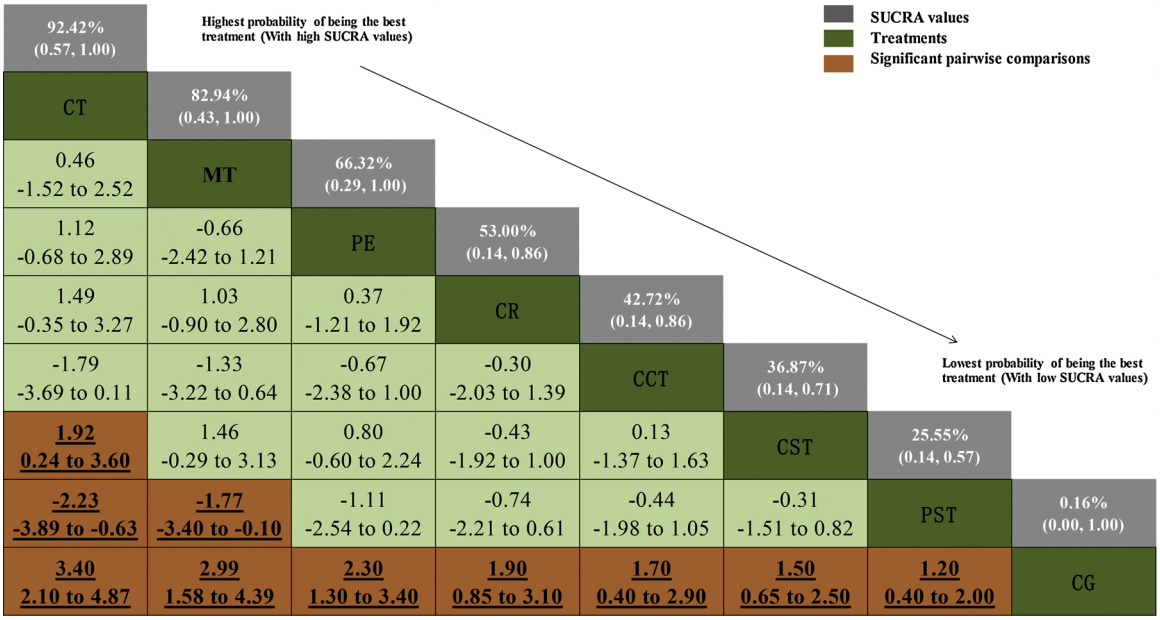
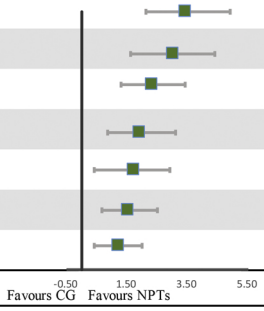


Fig. 3. Relative effect sizes of efficacy at post-treatment according to network meta-analysis(Random model).
Treatments are orders in the rank of their chance of being the best treatment. Numbers in grey boxes are SUCRA (the surface under the cumulative ranking curve) values and their CrIs (credible intervals), which represented the rank of the treatment. Significant pairwise comparisons are highlighted in orange, in bold and underlined. For efficacy in post-treatment, Mean differences (MDs) more than 0 favor the column-defining treatment, MDs lower than 0 favor the row-defining treatment. CCT, Computerized cognitive training; CR, Cognitive rehabilitation; CST, Cognitive stimulation therapy; CG, Control group; CT, Comprehensive therapy; MT, Music therapy; NPT, Non-pharmacological therapy; PE, Physical exercise; PST, Psychosocial therapy.

Table 3
Efficacy of different Non-pharmacological therapy compared to control group (Random model).

Treatments	Number of arms	Number of patients	Mean Difference(95%CrI)	SUCRA (95%CrI)
Comprehensive therapy	4	210	3.40 (2.10, 4.90)	92.42% (0.57, 1.00)
Music therapy	5	117	3.00 (1.60, 4.40)	82.94% (0.43, 1.00)
Physical exercise	4	70	2.30 (1.30, 3.40)	66.32% (0.29, 1.00)
Cognitive rehabilitation	5	160	1.90 (0.85, 3.10)	42.72% (0.14, 0.86)
Computerized cognitive training	6	192	1.70 (0.41, 2.90)	53.00% (0.14, 0.86)
Cognitive stimulation therapy	4	47	1.50 (0.65, 2.50)	36.87% (0.14, 0.71)
Psychosocial therapy	6	195	1.20 (0.40, 2.00)	25.55% (0.14, 0.57)



CG, Control group; CrI, Credible intervals; NPT, Non-pharmacological therapy; SUCRA, the surface under the cumulative ranking curve.

stimulation has presented more than the risk for suffering from dementia and indicator of the seriousness of the progression(Zanetti and Al, 2010; Zanetti et al., 2001). A large amount of evidence suggested the possibility that the combination of any two NPTs or more slowed down a higher rate of cognitive decline than the administration of one NPT alone, pharmacological intervention in particular. Its effect on reducing the risk factors of AD has been affirmed especially in cognitive function, as multiple mechanisms may exert a synergistic effect for clinically significant effects on global cognition (Ngandu et al., 2015). Based on this understanding of these potential factors in combination therapy, these potential factors can aid dementia patients in improving their cognitive function effectively, thus we added a comprehensive therapy (CT) as the complex therapy which has combined any of the existing therapies. While the thrust of CT in the lead has been highlighted to redouble efforts to identify dementia patients in need of help and then make that help available. It focuses on engaging in a series of activities of daily life with the help of nurses, family members or service commissioners whose emphasis is: human-oriented". But only a few of the studies can clarify the working mechanism of treatment. The positive effect of CT might, in other words, actually be undetectable. Equally remarkably, the result of MT has both statistical significance and obtains a relatively higher ranking among all NPTs. Lots of findings about MT indicate that MT can prevent or delay the cognitive dysfunction in dementia patients in the absence of new drugs by promoting changes in behavior and by managing vascular risk factors (Moreira et al., 2018; Steen et al., 2017). The uniqueness of MT is that the dementia patients can still maintain their ability to respond to music rhythm even though their cognitive function was destroyed. The interoperability between music and life has greatly helped dementia patients to improve their ability in realistic orientation, attention and language function (Smith, 1986). CCT can target single or multiple domains, allowing for the selection of what is most appropriate for a specific individual (Hill et al., 2017; Tárraga et al., 2006). The effectiveness of CCT in improving the cognitive ability of AD individuals has been validated by previous studies, particularly in meta-analyses. While there is little dispute about that, the efficacy of its global function improvement was actualized in Mild cognitive impairment (MCI) patients, assumed by one meta-analysis (Hill et al., 2017), what researchers have found in their studies provides evidence of a link between immersive technologies and cognitive function. And it is worth mentioning that CCT was the safe, relatively inexpensive and scalable treatment among these 7 NPTs (Lustig et al., 2009). In the face of multitude of disadvantages of conventional treatment failures, CCT may provide a relatively convenient approach to dealing with dementia epidemic, as it can be extrapolated from CCT's efficacy in various other age-related diseases like Stroke, Parkinson and so on(De et al., 2018; Patel et al., 2017). The Physical exercise is often conducted individually-tailored to each participant and led by a physiotherapist, along with a series of standard tasks at least (Clare et al., 2003). The efficacy of PE has been supported by evidence from many a study although its mechanism remains unclear. Several theories have been put forward to explain these observations. Some argue that patients can improve cognition by building up the coordination of their whole body muscles(Garuffi et al., 2013), and others reckon that the stimulation on nerve and vessel plays a role (Sayal, 2015). Taken together, these results suggest that PE tends to impose positive effect on dementia patients at the time of cognitive decline. Both the change in the improvement of mental health, loneliness, and the increase in the happiness are partly a consequence of the natural flow under the frame of PST (Spector et al., 2015), especially that the RT appears to have strong influence on coping with the affective disorder of dementia (Duru and Kapucu, 2016; Philbin et al., 2019). But it tends to lag behind in ranking in terms of cognitive performance. It is seen as a practical and available way of protecting dementia patients from extra mental disorders through cognitive- behavior therapy, supported therapy, instead of depending on professional therapy.

4.1. Strength

Despite decades of scientific research, a complicated matter is the fact that no one yet knows which NPT is relatively efficacious to slow down the progression of dementia. Our study presents an overview of the theoretical model for improving the global quality of life of dementia patients with relative efficacy and safety and provides a sound and scientific approach.

NMA is recommended over traditionally pairwise meta-analysis by World Health Organization as a basis for clinical guidelines (Kanters et al., 2016). This method is attractive for clinical researchers, policy makers when addressing their main concern of determining the best available treatment among multiple cognitive interventions.

4.2. Limitation

Quality of several studies potentially threatens the validity of our study, since most of them lack details in their methods of blinding of subject participants, personnel or outside assessors. And one study was rated as a high risk of bias in regard to blinding. Although we conducted a sensitivity analysis to address the potential residual confounding, most of the included studies were at moderate risk of bias.

We have not registered our study in PROSPERO with a protocol, which may potentially affect the quality of this study. In view of the fact that most of the endpoints in the original articles were presented as scale-based continuous variables, usually presented by cognitive screening instrument such as ADAS-cog(Alzheimer's Disease

Assessment Scale-Cognitive Subscale), MOCA(Montreal-cognitive assessment) or MMSE, our NMA used the same outcome as the basis, and the necessary data we extracted for further assessment included the mean, SD, and sample size values at baseline. Besides, quite a number of studies do not have the abovementioned data, which makes eligible studies even less. Last but not least, our analyses were only based on only one cognitive assessment instrument (MMSE), namely, a unique target measurement, which may be one of the most recognized and widely used mental status examinations. Bayesian NMA is so complex that it is hard for decision makers to explain the results, for example, based on the analysis of MMSE. It is most likely that CT was the best NPT. That might be under the limitations in the quality of included studies and CT as the combination therapy affected by plenty of confounding factors which may make our original results produce bias elsewhere compared with the single NPT.

5. Conclusion

Our findings suggest that there exist several viable options of NPT against dementia and the optimal NPT is Comprehensive therapy. The results are encouraging enough to suggest that further studies should rely on available outcomes of more comprehensive aspects rather than outcomes in a single domain, and more high-quality RCTs, which will facilitate the successful conduction of more similar network meta-analyses.

Funding sources

This research was supported by the Priority Academic Program Development of Jiangsu Higher Eduation Institutions(PAPD).

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

Acknowledgments

We would like to gratefully acknowledge the help from the following authors: Wenyong Liang, Hong Yao, Yaxin Peng and Dong Zhou. We acknowledge the Priority Academic Program Development of Jiangsu Higher Eduation.

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.2019.100965.

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