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Review

Study designs and statistical analyses in randomized controlled trials of non-pharmacological preventive and therapeutic interventions for dementia continuum : A statistical review

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Introduction

Non-pharmacological interventions for dementia prevention in people with risk factors for cognitive decline, treatment and care in patients with mild cognitive impairment (MCI) and dementia, and reducing the burden on caregivers of patients with dementia play significant roles in preventive and therapeutic interventions. Various systematic reviews and meta-analyses have attempted to synthesize the effects of preventive and therapeutic interventions across clinical trials to assess their effectiveness and acceptability ; however, the variations in study designs among the clinical trials and the low quality of the clinical trial methodology are barriers to deriving reliable conclusions. For instance, systematic reviews evaluating the effectiveness of non-pharmacological interventions in preventing cognitive decline among older people (Yao et al., 2020) and at-risk individuals due to age or cognitive frailty (Whitty et al., 2020) have been performed recently ; however, these reviews commonly identified a difficulty in drawing a unified conclusion on the effectiveness of non-pharmacological preventive interventions due to the heterogeneity in study designs and the low quality of studies. Hu et al. (2022) assessed the utility of four non-pharmacological interventions (physical activity, cognitive intervention, multicomponent of physical activity and cognitive intervention, and nutrition) in people with MCI through an overview of systematic reviews and network meta-analyses. In this study, of the 42 randomized controlled trials (RCTs) included, the quality of 40 (95%) RCTs was considered questionable. In a systematic review of non-pharmacological interven-

認知症領域の非薬物介入のランダム化対照試験の試験デザインと統計解析法 : 統計的レビュー

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tions for improving activities of daily living in people with moderate to severe dementia, the certainty of evidence was moderate or low, partially due to the heterogeneity between the included studies (Na et al., 2019). We consider that these issues are caused by the complexity of the study design and implementation due to the difficulty in homogeneous implementation of non-pharmacological interventions among participants and the involvement of many healthcare professionals in delivering the interventions.

To address these issues, the use of adequate methodologies of study design and statistical analysis that can improve the quality of study results and the generalization of interventions in practice, is encouraged. The components that characterize the design and analysis include the target population, control arm, randomization, number of arms, primary outcome, blinding, number of measurement time points after baseline assessment, sample size, primary analysis, and analysis sets. To the best of our knowledge, only a limited number of reviews on non-pharmacological interventions have focused on these components. In this study, we aimed to investigate the study designs and statistical analyses used in the RCTs of the following types of non-pharmacological interventions : (i) dementia prevention in people with risk factors for cognitive decline, (ii) treatment and care in patients with MCI and dementia, and (iii) burden reduction of caregivers of patients with dementia. Based on the findings of this review, we offer common practical recommendations for investigators to design RCTs on nonpharmacological preventive and therapeutic interventions.

Materials and Methods

In this study, we focused on the review of study designs and statistical analyses of the RCTs showing evidence of non-pharmacological preventive and therapeutic interventions. Therefore, as sources of such RCTs, we selected the Clinical Practice Guidelines for Dementia 2017 in Japan (Japanese Society of Neurology, 2017) and the Cochrane Database of Systematic Reviews (https://www.cochranelibrary.com/cdsr/about-cdsr) that reviewed and authorized the evidence of non-pharmacological preventive and therapeutic interventions by multiple medical experts. We extracted RCTs on non-pharmacological interventions cited in the Clinical Practice Guidelines for Dementia 2017 in Japan and 23 Cochrane Review reports selected from Cochrane Database of Systematic Reviews using the words "dementia", "alzheimer's disease", or "mild cognitive impairment" in March 2020 (Abraha et al., 2017 ; Bahar-Fuchs et al., 2013 ; Bahar-Fuchs et al., 2019 ; Cook et al., 2012 ; Deshmukh et al., 2018 ; Forbes et al., 2015 ; Gates et al., 2019a ; Gates et al., 2019b ; Gates et al., 2020 ; Herke et al., 2018 ; Karkou & Meekums, 2017 ; Lai et al., 2019 ; Lins et al., 2014 ; Liu et al., 2018 ; Martin et al., 2011 ; Möhler et al., 2018 ; Neal & Wright, 2003 ; Orgeta et al., 2020 ; van der Steen et al., 2018 ; Vernooij-Dassen et al., 2011 ; Woods et al., 2012 ; Woods et al., 2018 ; Young et al., 2015). In the Clinical Practice Guidelines for Dementia 2017, the editorial committee conducted searches in MEDLINE, PubMed, and Japan Medical Abstracts Society using relevant keywords on non-pharmacological intervention. A qualitative systematic review was carried out for 63 studies published between January 2000 and April 2015. The committee rated each selected study's grade of evidence for the effectiveness of non-pharmacological interventions. In addition to these studies, we included 196 studies reviewed in the 23 Cochrane Review reports. After excluding review articles, duplicated articles, and articles not written in English, we selected 200 studies and recorded the following variables : publication year, target population (individuals with normal cognition, MCI, or dementia ; caregivers only ; mixed population [two or more populations such as individuals with MCI and individuals

with dementia]), type of intervention (dietary intervention, cognitive intervention, exercise therapy, animal therapy, art therapy, music therapy, reminiscence therapy, validation therapy, multidomain intervention, psychoeducational intervention, cognitive-behavioral therapy, counseling, general support, multidomain intervention for caregivers), study design (parallel-group randomized controlled trial, cluster randomized trial, crossover trial), control arm (observation, usual care, other type of intervention, no description), randomization (simple randomization, block randomization, stratified randomization, minimization method, cluster randomization, no description), number of arms, blinding (blinded to the outcome assessment, unblinded, no description), follow-up period, number of time points for outcome measurements after baseline assessment, description of primary outcome, number of outcomes, outcome domain(s) (cognition/memory, behavioral and psychological symptoms of dementia [BPSD], activities of daily living [ADL], physical outcome, quality of life [QOL], biological outcome, onset of dementia, onset of MCI, adherence to intervention, depression among caregivers, caregiver burden, caregivers' knowledge, QOL of caregivers, stress among caregivers, and other category), sample size, analysis sets (intention-to-treat, full analysis set, per protocol set, no description), primary analysis (t-test, analysis of variance [ANOVA], analysis of covariance [ANCOVA], repeated-measures ANOVA, regression model analysis including logistic regression and Cox proportional hazard model, mixed-effects model, mixed-effects model for repeated measures [MMRM], and generalized estimating equations, others [e.g., chi-square test and nonparametric test], no description), and description of sample size rationale. Two statisticians (RH and AH) independently investigated the variables for quality control. All 199 papers that included the results of 200 studies we reviewed are presented in the appendix.

Types of non-pharmacological interventions

Non-pharmacological interventions can be divided into interventions for patients with dementia and those for caregivers. The Clinical Practice Guidelines for Dementia 2017 in Japan and the Cochrane Review reports reviewed the literature on RCTs on the following non-pharmacological interventions.

1) Dietary intervention (Herke et al., 2018)

Dietary intervention is designed to modify the mealtime environment of people with dementia, improve the mealtime behavior of people with dementia or their caregivers, or integrate aspects of both to improve food and fluid intake and nutritional status.

2) Cognitive intervention (cognitive stimulation, cognitive training, and cognitive rehabilitation) (Bahar-Fuchs et al., 2013 ; Woods et al., 2012)

Cognitive stimulation aims to improve general cognitive function and sociality through various activities in personalized or group settings. Cognitive training focuses on specific areas of cognitive function, such as memory, attention, and problem solving, and uses paper- or computer-based tasks tailored to an individual's level of function. Cognitive rehabilitation is a personalized intervention that sets goals for each patient to improve their ADL. It is performed in a real-life setting, and it rarely involves interventions that target specific cognitive functions.

3) Exercise therapy (Forbes et al., 2015 ; Young et al., 2015)

Exercise therapy includes aerobic exercises, muscle strengthening training, and balance training, and it is often performed in combination with multiple exercise therapies.

4) Animal therapy (Lai et al., 2019)

Animal therapy is thought to help people with dementia by providing companionship and support of animals in daily activities. This may improve physical and mental health outcomes, including better mood and fewer problematic behaviors.

5) Art therapy (Deshmukh et al., 2018)

Art therapy is a form of psychotherapy that uses art media as the primary mode of communication.

6) Music therapy (van der Steen et al., 2018)

Music therapy includes listening to music, singing, playing musical instruments, and rhythmic exercises, all of which are often conducted in combination.

7) Reminiscence therapy (Woods et al., 2018)

In reminiscence therapy, the listener listens to the life history of the older adult in a receptive, empathetic, and supportive manner. The goal is to support older adults' mental health through therapy, specifically to enhance their self-esteem and promote good interpersonal relationships.

8) Validation therapy (Neal & Wright, 2003)

Validation therapy is based on the general principle of validation, acceptance of reality, and the personal truth of another individual's experience. The specific interventions and techniques used within this approach involve behavioral and psychotherapeutic methods to meet the needs of individuals at different stages of dementia.

9) Psychoeducational intervention (Hébert et al., 2003 ; Walter & Pinquart, 2020)

Psychoeducational intervention includes passive information provision and active skills training. The goal is to transmit knowledge and skills regarding dementia, caregiving, available services, and stress coping mechanisms.

10) Cognitive-behavioral therapy (Akkerman & Ostwald, 2004 ; Walter & Pinquart, 2020)

Cognitive-behavioral therapy aims to modify behavioral, cognitive, and affective responses to caregiving, as well as to directly change the mental health of the caregiver. We categorized mindfulness-based stress reduction interventions into cognitive-behavioral therapy in this study.

11) Counseling (Salfi et al., 2005 ; Walter & Pinquart, 2020)

Counseling includes assessment and planning. It is tailored to specific problems of individual caregivers or dyads of caregivers and care recipients.

12) General support (Winter & Gitlin, 2006 ; Walter & Pinquart, 2020)

General support refers to unstructured specialist-led and caregiver-group-led support that focuses on creating opportunities for discussing caregiving issues and emotions.

Types of randomization (Friedman et al, 2015 ; Donner & Klar, 2000)

Simple randomization is a method that assigns participants to each treatment group using a prespecified ratio. For example, if there are two treatment arms, groups A and B, a simple randomization procedure assigns participants to group A with probability p and participants to group B with probability 1-p. Block randomization is a method that assigns participants to each treatment group in a prespecified ratio for each block of a certain number of participants. This method avoids serious imbalances in the number of participants assigned to each group. Stratified randomization is a method that performs randomization within each stratum (or subgroup) and is usually categorized based on the status of a prognostic factor. Incorporation of stratification into randomization enhanced the similarity of prognostic factor(s), called comparability, between the groups we compared. The minimization method assigns participants to each treatment group in a manner that dynamically adjusts the allocation ratio to balance the distribution of prespecified prognostic factors among the treatment groups. Apart from these randomization methods, cluster randomization randomly assigns social units or clusters of individuals, rather than individuals themselves, to different intervention groups.

Results

Characteristics of participants and studies

Table 1 shows the descriptive characteristics of the

Table 1. Descriptive characteristics of the studies on each target population (n = 200)

	Normal cognition n = 31	Mild cognitive impairment n = 19	Dementia n = 126	Caregivers only n = 22	Mixed population n = 2
Mean age, median (range)	72.3 (58.9-86.9)	71.5 (58.5-80.1)	80.4 (66.5-88.7)	63.3 (46.9-74.0)	74.7 (74.0-75.4)
Percent of female, median (range)	68.2 (39.0-100.0)	58.0 (41.9-85.2)	68.7 (0.0-100.0)	81.0 (0.0-100.0)	57.1 (57.1-57.1)
Mean of education year, median (range)	14.2 (4.0-16.3)	10.9 (5.7-16.4)	8.8 (2.3-14.6)	14.3 (14.1-14.4)	8.4 (7.0-9.8)
Publication year, n (%)					
≤ 1999	5 (16.1)	0 (0.0)	15 (11.9)	0 (0.0)	0 (0.0)
2000 (224)*	0 (0.0)	0 (0.0)	2 (1.6)	1 (4.5)	0 (0.0)
2001 (169)*	2 (6.5)	0 (0.0)	3 (2.4)	0 (0.0)	0 (0.0)
2002 (265)*	2 (6.5)	1 (5.3)	2 (1.6)	0 (0.0)	0 (0.0)
2003 (287)*	0 (0.0)	0 (0.0)	5 (4.0)	3 (13.6)	0 (0.0)
2004 (289)*	0 (0.0)	0 (0.0)	6 (4.8)	3 (13.6)	0 (0.0)
2005 (330)*	2 (6.5)	0 (0.0)	7 (5.6)	1 (4.5)	0 (0.0)
2006 (328)*	3 (9.7)	0 (0.0)	6 (4.8)	1 (4.5)	0 (0.0)
2007 (245)*	5 (16.1)	1 (5.3)	4 (3.2)	6 (27.3)	0 (0.0)
2008 (288)*	0 (0.0)	0 (0.0)	4 (3.2)	0 (0.0)	0 (0.0)
2009 (275)*	0 (0.0)	0 (0.0)	6 (4.8)	0 (0.0)	0 (0.0)
2010 (312)*	3 (9.7)	2 (10.5)	8 (6.3)	2 (9.1)	0 (0.0)
2011 (335)*	1 (3.2)	1 (5.3)	9 (7.1)	0 (0.0)	0 (0.0)
2012 (350)*	1 (3.2)	2 (10.5)	8 (6.3)	0 (0.0)	0 (0.0)
2013 (401)*	2 (6.5)	2 (10.5)	9 (7.1)	2 (9.1)	0 (0.0)
2014 (396)*	2 (6.5)	5 (26.3)	8 (6.3)	1 (4.5)	0 (0.0)
2015 (395)*	2 (6.5)	1 (5.3)	9 (7.1)	1 (4.5)	0 (0.0)
2016 (394)*	1 (3.2)	1 (5.3)	9 (7.1)	1 (4.5)	2 (100.0)
2017 (416)*	0 (0.0)	1 (5.3)	3 (2.4)	0 (0.0)	0 (0.0)
2018 (457)*	0 (0.0)	2 (10.5)	3 (2.4)	0 (0.0)	0 (0.0)
Type of intervention, n (%)					
Dietary intervention	1 (3.2)	0 (0.0)	3 (2.4)	0 (0.0)	0 (0.0)
Cognitive intervention	17 (54.8)	17 (89.5)	41 (32.5)	0 (0.0)	2 (100.0)
Exercise therapy	6 (19.4)	2 (10.5)	12 (9.5)	0 (0.0)	0 (0.0)
Animal therapy	0 (0.0)	0 (0.0)	7 (5.6)	0 (0.0)	0 (0.0)
Art therapy	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
Music therapy	0 (0.0)	0 (0.0)	17 (13.5)	0 (0.0)	0 (0.0)
Reminiscence therapy	0 (0.0)	0 (0.0)	18 (14.3)	0 (0.0)	0 (0.0)
Validation therapy	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
Multidomain intervention	7 (22.6)	0 (0.0)	9 (7.1)	0 (0.0)	0 (0.0)
Psychoeducational intervention	0 (0.0)	0 (0.0)	7 (5.6)	7 (31.8)	0 (0.0)
Cognitive-behavioral therapy	0 (0.0)	0 (0.0)	0 (0.0)	10 (45.5)	0 (0.0)
Counseling	0 (0.0)	0 (0.0)	3 (2.4)	0 (0.0)	0 (0.0)
General support	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)
Multidomain intervention for caregiver	0 (0.0)	0 (0.0)	5 (4.0)	4 (18.2)	0 (0.0)

*Figures in parentheses indicate the number of publications of clinical trials related to dementia, which were extracted using the search keywords ("Dementia" [Mesh] OR dementia) AND (clinical trial [Filter]) in PubMed.

Table 2. Study designs and randomization methods by target population and type of intervention (n = 200)

Target population	Type of intervention	Study design		
		Parallel-group randomized controlled trials	Cluster randomized trials	Crossover trials
Normal cognition n = 31	Total, n (%)	28 (90.3)	2 (6.5)	1 (3.2)
	Dietary intervention	1 (100.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	15 (88.2)	1 (5.9)	1 (5.9)
	Exercise therapy	5 (83.3)	1 (16.7)	0 (0.0)
	Multidomain intervention	7 (100.0)	0 (0.0)	0 (0.0)
Mild cognitive impairment n = 19	Total, n (%)	19 (100.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	17 (100.0)	0 (0.0)	0 (0.0)
	Exercise therapy	2 (100.0)	0 (0.0)	0 (0.0)
Dementia n = 126	Total, n (%)	99 (78.6)	18 (14.3)	9 (7.1)
	Dietary intervention	2 (66.7)	1 (33.3)	0 (0.0)
	Cognitive intervention	35 (85.4)	2 (4.9)	4 (9.8)
	Exercise therapy	11 (91.7)	1 (8.3)	0 (0.0)
	Animal therapy	2 (28.6)	4 (57.1)	1 (14.3)
	Art therapy	2 (100.0)	0 (0.0)	0 (0.0)
	Music therapy	14 (82.4)	1 (5.9)	2 (11.8)
	Reminiscence therapy	14 (77.8)	3 (16.7)	1 (5.6)
	Validation therapy	2 (100.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	7 (77.8)	1 (11.1)	1 (11.1)
	Psychoeducational intervention	3 (42.9)	4 (57.1)	0 (0.0)
	Counseling	2 (66.7)	1 (33.3)	0 (0.0)
	Multidomain intervention for caregiver	5 (100.0)	0 (0.0)	0 (0.0)
Caregivers only n = 22	Total, n (%)	22 (100.0)	0 (0.0)	0 (0.0)
	Psychoeducational intervention	7 (100.0)	0 (0.0)	0 (0.0)
	Cognitive-behavioral therapy	10 (100.0)	0 (0.0)	0 (0.0)
	General support	1 (100.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	4 (100.0)	0 (0.0)	0 (0.0)
Mixed population n = 2	Total, n (%)	1 (50.0)	0 (0.0)	1 (50.0)
	Cognitive intervention	1 (50.0)	0 (0.0)	1 (50.0)

participants and the included studies. Between 2000 and 2018, the number of annually published studies on normal cognition, MCI, dementia, and caregivers ranged from 0-5, 0-5, 2-9, and 0-6, respectively. The medians of the mean age enrolled in the studies for normal cognition (72.3 years old) and MCI (71.5 years old) were similar, while that for dementia was 80.4 years old. The median percentage of female participants with normal cognition, MCI, and dementia was approximately 60-70%. The median of the mean duration of education in the normal cognition, MCI, and dementia patients gradually decreased from 14.2 to 8.8 years. In studies targeting caregivers, the median of the mean age was 63.3 years, and the median percentage of female participants was 81.0%. The median of the mean education was 14.3 years. The most and second-most interventions evaluated in the studies were cognitive interventions (n=17, 54.8%) and multidomain therapy (n=7, 22.6%) for normal cognition, cognitive interventions (n=17, 89.5%) and exercise therapy (n=2, 10.5%) for MCI, cognitive interventions (n=41, 32.5%) and reminiscence ther-

Table 2. (continued)

Target population	Type of intervention	Randomization		
		Simple randomization	Block randomization	Stratified randomization
Normal cognition $n = 31$	Total, n (%)	4 (12.9)	1 (3.2)	5 (16.1)
	Dietary intervention	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	3 (17.6)	0 (0.0)	3 (17.6)
	Exercise therapy	0 (0.0)	1 (16.7)	1 (16.7)
	Multidomain intervention	1 (14.3)	0 (0.0)	1 (14.3)
Mild cognitive impairment $n = 19$	Total, n (%)	4 (21.1)	2 (10.5)	2 (10.5)
	Cognitive intervention	2 (11.8)	2 (11.8)	2 (11.8)
	Exercise therapy	2 (100.0)	0 (0.0)	0 (0.0)
Dementia $n = 126$	Total, n (%)	13 (10.3)	6 (4.8)	23 (18.3)
	Dietary intervention	1 (33.3)	0 (0.0)	0 (0.0)
	Cognitive intervention	8 (19.5)	2 (4.9)	8 (19.5)
	Exercise therapy	1 (8.3)	0 (0.0)	3 (25.0)
	Animal therapy	1 (14.3)	0 (0.0)	1 (14.3)
	Art therapy	0 (0.0)	0 (0.0)	0 (0.0)
	Music therapy	0 (0.0)	2 (11.8)	5 (29.4)
	Reminiscence therapy	0 (0.0)	0 (0.0)	4 (22.2)
	Validation therapy	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	1 (11.1)	2 (22.2)	0 (0.0)
	Psychoeducational intervention	0 (0.0)	0 (0.0)	1 (14.3)
	Counseling	1 (33.3)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	0 (0.0)	0 (0.0)	1 (20.0)
Caregivers only $n = 22$	Total, n (%)	3 (13.6)	2 (9.1)	2 (9.1)
	Psychoeducational intervention	0 (0.0)	1 (14.3)	1 (14.3)
	Cognitive-behavioral therapy	3 (30.0)	0 (0.0)	0 (0.0)
	General support	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	0 (0.0)	1 (25.0)	1 (25.0)
Mixed population $n = 2$	Total, n (%)	0 (0.0)	0 (0.0)	2 (100.0)
	Cognitive intervention	0 (0.0)	0 (0.0)	2 (100.0)

apy (n=18, 14.3%) for dementia, and cognitive-behavioral therapy (n=10, 45.5%) and psychoeducational interventions (n=7, 31.8%) for caregivers. In Table S1, we also show the number of studies published each year according to the type of intervention.

Study designs

In studies on normal cognition, MCI, dementia, and caregivers, the number (percentage) of parallel-group RCTs was 28 (90.3%), 19 (100%), 99 (78.6%), and 22 (100%), respectively; those of cluster RCTs were 2 (6.5%), 0 (0%), 18 (14.3%), and 0 (0%), respectively (Table 2). Studies on normal cognition, MCI, dementia, and caregivers approximately 10-20% applied simple randomization (or stratified randomization). In the studies on dementia, 18 (14.3%) studies used cluster randomization. Approximately 50% of the studies in each target population did not describe the randomization methodology. The number of arms evaluated in each study and the presence or absence of blinding are presented in Table 3. While the majority of studies on MCI, dementia, and caregivers compared two arms (73.7% for MCI, 72.2% for dementia, and 86.4% for caregivers), 64.5% of the studies on normal

Table 2. (continued)

Target population	Type of intervention	Randomization		
		Minimization method	Cluster randomization	No description
Normal cognition $n = 31$	Total, n (%)	1 (3.2)	2 (6.5)	18 (58.1)
	Dietary intervention	0 (0.0)	0 (0.0)	1 (100.0)
	Cognitive intervention	0 (0.0)	1 (5.9)	10 (58.8)
	Exercise therapy	1 (16.7)	1 (16.7)	2 (33.3)
	Multidomain intervention	0 (0.0)	0 (0.0)	5 (71.4)
Mild cognitive impairment $n = 19$	Total, n (%)	0 (0.0)	0 (0.0)	11 (57.9)
	Cognitive intervention	0 (0.0)	0 (0.0)	11 (64.7)
	Exercise therapy	0 (0.0)	0 (0.0)	0 (0.0)
Dementia $n = 126$	Total, n (%)	5 (4.0)	18 (14.3)	61 (48.4)
	Dietary intervention	0 (0.0)	1 (33.3)	1 (33.3)
	Cognitive intervention	0 (0.0)	2 (4.9)	21 (51.2)
	Exercise therapy	0 (0.0)	1 (8.3)	7 (58.3)
	Animal therapy	0 (0.0)	4 (57.1)	1 (14.3)
	Art therapy	1 (50.0)	0 (0.0)	1 (50.0)
	Music therapy	0 (0.0)	1 (5.9)	9 (52.9)
	Reminiscence therapy	3 (16.7)	3 (16.7)	8 (44.4)
	Validation therapy	0 (0.0)	0 (0.0)	2 (100.0)
	Multidomain intervention	0 (0.0)	1 (11.1)	5 (55.6)
	Psychoeducational intervention	0 (0.0)	4 (57.1)	2 (28.6)
	Counseling	0 (0.0)	1 (33.3)	1 (33.3)
	Multidomain intervention for caregiver	1 (20.0)	0 (0.0)	3 (60.0)
Caregivers only $n = 22$	Total, n (%)	2 (9.1)	0 (0.0)	13 (59.1)
	Psychoeducational intervention	1 (14.3)	0 (0.0)	4 (57.1)
	Cognitive-behavioral therapy	1 (10.0)	0 (0.0)	6 (60.0)
	General support	0 (0.0)	0 (0.0)	1 (100.0)
	Multidomain intervention for caregiver	0 (0.0)	0 (0.0)	2 (50.0)
Mixed population $n = 2$	Total, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	0 (0.0)	0 (0.0)	0 (0.0)

cognition evaluated three arms or more. The number (percentages) of blinded studies were 8 (25.8%), 16 (84.2%), 78 (61.9%), and 5 (22.7%) for normal cognition, MCI, dementia, and caregivers, respectively, but 22 (71.0%) studies on normal cognition did not describe the blinding status. Studies with blinding increased slightly as the years progressed (Figure S1 (a)). The type of control arm evaluated in the studies varied depending on the type of intervention irrespective of the target population (Table 3). In studies on normal cognition, MCI, dementia, and caregivers, >70% of the studies had a follow-up period of ≤ 6 months, and approximately 50% of the studies had two or more measurement time points after baseline assessment (Table 4).

Primary outcome

More than 50% of the studies did not describe the primary outcome in each target population (Table 5), and this was observed in each publication year (Figure S1(b)). In the studies on normal cognition, dementia, and caregivers, 40-50% used 2-5 outcomes. The most and second-most frequently measured outcomes were cognition/memory (n=26, 83.9%) and ADL

Table 3. Number of arms, blinding, and control arm by target population and type of intervention (n = 200)

Target population	Type of intervention	Number of arms				
		2	3	4	5	6
Normal cognition n = 31	Total, n (%)	11 (35.5)	10 (32.3)	9 (29.0)	0 (0.0)	1 (3.2)
	Dietary intervention	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	6 (35.3)	7 (41.2)	4 (23.5)	0 (0.0)	0 (0.0)
	Exercise therapy	4 (66.7)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)
	Multidomain intervention	1 (14.3)	1 (14.3)	4 (57.1)	0 (0.0)	1 (14.3)
Mild cognitive impairment n = 19	Total, n (%)	14 (73.7)	3 (15.8)	1 (5.3)	0 (0.0)	1 (5.3)
	Cognitive intervention	12 (70.6)	3 (17.6)	1 (5.9)	0 (0.0)	1 (5.9)
	Exercise therapy	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dementia n = 126	Total, n (%)	91 (72.2)	29 (23.0)	5 (4.0)	1 (0.8)	0 (0.0)
	Dietary intervention	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	26 (63.4)	11 (26.8)	3 (7.3)	1 (2.4)	0 (0.0)
	Exercise therapy	9 (75.0)	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Animal therapy	5 (71.4)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Art therapy	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Music therapy	13 (76.5)	4 (23.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Reminiscence therapy	13 (72.2)	4 (22.2)	1 (5.6)	0 (0.0)	0 (0.0)
	Validation therapy	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	7 (77.8)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)
	Psychoeducational intervention	6 (85.7)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
	Counseling	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Caregivers only n = 22	Total, n (%)	19 (86.4)	3 (13.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Psychoeducational intervention	7 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive-behavioral therapy	8 (80.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
	General support	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	3 (75.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mixed population n = 2	Total, n (%)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

(n=8, 25.8%) for normal cognition; those were cognition/memory (n=18, 94.7% for MCI; n=79, 62.7% for dementia) and BPSD (n=8, 42.1% for MCI; n=87, 69.0% for dementia) for MCI and dementia. The most and second-most frequently measured caregiver-related outcomes were depression among caregivers (n=14, 63.6%) and caregiver burden (n=9, 40.9%), respectively. Table S2 shows the outcome measures used as primary outcomes.

Statistical considerations

Sample size: The median number of participants included per trial for normal cognition, MCI, dementia, and caregivers were 106, 40, 58, and 92, respectively (Table 6). Eleven (57.9%) studies on MCI enrolled ≤ 50 patients, whereas 17 (54.8%) studies on normal cognition enrolled >100 participants. The sample size varied throughout the study period (Figure S1 (c)). Only 20-25% of studies in each target population calculated the sample size using power analysis (Table 6). More than 50% of the studies did not describe the power analysis throughout the study period (Figure S1(d)).

Analysis set: The number (percentage) of studies

Table 3. (continued)

Target population	Type of intervention	Blinding		
		Blinded to the outcome assessment	Unblinding	No description
Normal cognition $n = 31$	Total, n (%)	8 (25.8)	1 (3.2)	22 (71.0)
	Dietary intervention	1 (100.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	2 (11.8)	0 (0.0)	15 (88.2)
	Exercise therapy	3 (50.0)	0 (0.0)	3 (50.0)
	Multidomain intervention	2 (28.6)	1 (14.3)	4 (57.1)
Mild cognitive impairment $n = 19$	Total, n (%)	16 (84.2)	1 (5.3)	2 (10.5)
	Cognitive intervention	14 (82.4)	1 (5.9)	2 (11.8)
	Exercise therapy	2 (100.0)	0 (0.0)	0 (0.0)
Dementia $n = 126$	Total, n (%)	78 (61.9)	6 (4.8)	42 (33.3)
	Dietary intervention	1 (33.3)	1 (33.3)	1 (33.3)
	Cognitive intervention	29 (70.7)	0 (0.0)	12 (29.3)
	Exercise therapy	9 (75.0)	0 (0.0)	3 (25.0)
	Animal therapy	3 (42.9)	2 (28.6)	2 (28.6)
	Art therapy	0 (0.0)	0 (0.0)	2 (100.0)
	Music therapy	12 (70.6)	1 (5.9)	4 (23.5)
	Reminiscence therapy	11 (61.1)	0 (0.0)	7 (38.9)
	Validation therapy	2 (100.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	3 (33.3)	0 (0.0)	6 (66.7)
	Psychoeducational intervention	4 (57.1)	1 (14.3)	2 (28.6)
	Counseling	3 (100.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	1 (20.0)	1 (20.0)	3 (60.0)
Caregivers only $n = 22$	Total, n (%)	5 (22.7)	7 (31.8)	10 (45.5)
	Psychoeducational intervention	3 (42.9)	1 (14.3)	3 (42.9)
	Cognitive-behavioral therapy	1 (10.0)	6 (60.0)	3 (30.0)
	General support	0 (0.0)	0 (0.0)	1 (100.0)
	Multidomain intervention for caregiver	1 (25.0)	0 (0.0)	3 (75.0)
Mixed population $n = 2$	Total, n (%)	0 (0.0)	0 (0.0)	2 (100.0)
	Cognitive intervention	0 (0.0)	0 (0.0)	2 (100.0)

using the intention-to-treat or full analysis sets for normal cognition, MCI, dementia, and caregivers was 10 (32.2%), 4 (21.1%), 30 (23.8%), and 7 (31.5%), respectively, although 60-70% of studies in each target population did not describe the analysis sets (Table 6).

Primary analysis : ANCOVA, repeated-measures ANOVA, and mixed-effects model were frequently used in each target population (Table 6).

Discussion

We comprehensively reviewed the study designs and statistical analyses of RCTs that evaluated the effects of non-pharmacological preventive interventions in participants with normal cognition and therapeutic interventions in patients with MCI and dementia along with interventions to reduce the burden on caregivers. In each target population, >70% of the trials had a follow-up period ≤ 6 months. About 50% of the studies on normal cognition or caregivers had a sample size of >100, while 50% of the studies on people with MCI or dementia had a sample size of ≤ 50. Furthermore, among the number of publications of clinical trials related to dementia that were extracted

Table 3. (continued)

Target population	Type of intervention	Type of control arm			
		Observation	Usual care	Other types of intervention	No description
Normal cognition $n = 31$	Total, n (%)	15 (48.4)	1 (3.2)	14 (45.2)	1 (3.2)
	Dietary intervention	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	10 (58.8)	0 (0.0)	6 (35.3)	1 (5.9)
	Exercise therapy	3 (50.0)	0 (0.0)	3 (50.0)	0 (0.0)
	Multidomain intervention	2 (28.6)	0 (0.0)	5 (71.4)	0 (0.0)
Mild cognitive impairment $n = 19$	Total, n (%)	4 (21.1)	1 (5.3)	14 (73.7)	0 (0.0)
	Cognitive intervention	4 (23.5)	1 (5.9)	12 (70.6)	0 (0.0)
	Exercise therapy	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)
Dementia $n = 126$	Total, n (%)	16 (12.7)	58 (46.0)	50 (39.7)	2 (1.6)
	Dietary intervention	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)
	Cognitive intervention	8 (19.5)	11 (26.8)	21 (51.2)	1 (2.4)
	Exercise therapy	3 (25.0)	4 (33.3)	5 (41.7)	0 (0.0)
	Animal therapy	0 (0.0)	5 (71.4)	2 (28.6)	0 (0.0)
	Art therapy	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)
	Music therapy	0 (0.0)	10 (58.8)	7 (41.2)	0 (0.0)
	Reminiscence therapy	3 (16.7)	12 (66.7)	3 (16.7)	0 (0.0)
	Validation therapy	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	0 (0.0)	5 (55.6)	4 (44.4)	0 (0.0)
	Psychoeducational intervention	0 (0.0)	4 (57.1)	2 (28.6)	1 (14.3)
	Counseling	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	0 (0.0)	1 (20.0)	4 (80.0)	0 (0.0)
Caregivers only $n = 22$	Total, n (%)	2 (9.1)	5 (22.7)	15 (68.2)	0 (0.0)
	Psychoeducational intervention	0 (0.0)	3 (42.9)	4 (57.1)	0 (0.0)
	Cognitive-behavioral therapy	1 (10.0)	1 (10.0)	8 (80.0)	0 (0.0)
	General support	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	1 (25.0)	0 (0.0)	3 (75.0)	0 (0.0)
Mixed population $n = 2$	Total, n (%)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)
	Cognitive intervention	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)

using the search keywords ("Dementia" [Mesh] OR dementia) AND (clinical trial [Filter]) in PubMed (see Table 1), the percentage of studies of non-pharmacological interventions investigated in this study was less than 10% throughout the study period. These results possibly indicate that it would be difficult to conduct RCTs of non-pharmacological interventions (especially, with a long-term follow-up period given a large sample size), probably because of the complexity of implementing the interventions. To address this issue, the establishment of nationwide study groups for administering and implementing adequate and well-controlled RCTs is desired for each type of nonpharmacological intervention (or target population).

In the remainder of this section, based on the findings of our review, we suggest the following for consideration when designing and analyzing non-pharmacological preventive and therapeutic intervention studies.

Common points to be considered in designing and conducting randomized controlled trials of nonpharmacological interventions

The complexity of interventions varies depending on the number of study staff delivering the interven-

Table 4. Follow-up period and number of measurement time points by target population and type of intervention (n = 200)

Target population	Type of intervention	Follow-up period			
		≤ 6 months	7-12 months	≥ 13months	No description
Normal cognition n = 31	Total, n (%)	27 (87.1)	1 (3.2)	3 (9.7)	0 (0.0)
	Dietary intervention	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	13 (76.5)	1 (5.9)	3 (17.6)	0 (0.0)
	Exercise therapy	6 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	7 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mild cognitive impairment n = 19	Total, n (%)	13 (68.4)	4 (21.1)	2 (10.5)	0 (0.0)
	Cognitive intervention	11 (64.7)	4 (23.5)	2 (11.8)	0 (0.0)
	Exercise therapy	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dementia n = 126	Total, n (%)	99 (78.6)	19 (15.1)	7 (5.6)	1 (0.8)
	Dietary intervention	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	32 (78.0)	7 (17.1)	2 (4.9)	0 (0.0)
	Exercise therapy	11 (91.7)	1 (8.3)	0 (0.0)	0 (0.0)
	Animal therapy	6 (85.7)	0 (0.0)	1 (14.3)	0 (0.0)
	Art therapy	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)
	Music therapy	15 (88.2)	2 (11.8)	0 (0.0)	0 (0.0)
	Reminiscence therapy	15 (83.3)	3 (16.7)	0 (0.0)	0 (0.0)
	Validation therapy	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	7 (77.8)	0 (0.0)	1 (11.1)	1 (11.1)
	Psychoeducational intervention	3 (42.9)	3 (42.9)	1 (14.3)	0 (0.0)
	Counseling	2 (66.7)	0 (0.0)	1 (33.3)	0 (0.0)
	Multidomain intervention for caregiver	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)
Caregivers only n = 22	Total, n (%)	20 (90.9)	0 (0.0)	2 (9.1)	0 (0.0)
	Psychoeducational intervention	5 (71.4)	0 (0.0)	2 (28.6)	0 (0.0)
	Cognitive-behavioral therapy	10 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	General support	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mixed population n = 2	Total, n (%)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)

tion, the interactions involved, and the degree of flexibility allowed in their delivery. In such interventions, to improve the quality of study results, there are several points that should be adequately addressed in designing and conducting RCTs of non-pharmacological intervention : First, standardization of materials and equipment used in the study as well as the intensity of interaction between deliverers (e.g., clinicians and caregivers) and participants. Second, pre-trial training was implemented to improve the homogeneity of the intervention, using a standard operating procedure manual. Third, the degree of flexibility of the intervention allowed in the study (e.g., change in timing and number of interventions) should be clarified. Fourth, data were collected on the quality of the delivered intervention and monitored during the study. The general guidelines for planning and conducting non-pharmacological interventions is also provided by the extended CONSORT statement for non-pharmacological treatment (Boutron et al., 2008).

Table 4. (continued)

Target population	Type of intervention	Number of time points for measurements after baseline assessment		
		1	2	3
Normal cognition $n = 31$	Total, n (%)	17 (54.8)	7 (22.6)	3 (9.7)
	Dietary intervention	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	7 (41.2)	5 (29.4)	3 (17.6)
	Exercise therapy	5 (83.3)	1 (16.7)	0 (0.0)
	Multidomain intervention	5 (71.4)	1 (14.3)	0 (0.0)
Mild cognitive impairment $n = 19$	Total, n (%)	9 (47.4)	9 (47.4)	1 (5.3)
	Cognitive intervention	8 (47.1)	8 (47.1)	1 (5.9)
	Exercise therapy	1 (50.0)	1 (50.0)	0 (0.0)
Dementia $n = 126$	Total	57 (45.2)	46 (36.5)	10 (7.9)
	Dietary intervention	1 (33.3)	1 (33.3)	0 (0.0)
	Cognitive intervention	21 (51.2)	12 (29.3)	5 (12.2)
	Exercise therapy	7 (58.3)	5 (41.7)	0 (0.0)
	Animal therapy	2 (28.6)	4 (57.1)	1 (14.3)
	Art therapy	1 (50.0)	0 (0.0)	0 (0.0)
	Music therapy	4 (23.5)	7 (41.2)	2 (11.8)
	Reminiscence therapy	9 (50.0)	8 (44.4)	0 (0.0)
	Validation therapy	1 (50.0)	1 (50.0)	0 (0.0)
	Multidomain intervention	5 (55.6)	3 (33.3)	0 (0.0)
	Psychoeducational intervention	4 (57.1)	2 (28.6)	1 (14.3)
	Counseling	1 (33.3)	1 (33.3)	0 (0.0)
	Multidomain intervention for caregiver	1 (20.0)	2 (40.0)	1 (20.0)
Caregivers only $n = 22$	Total, n (%)	12 (54.5)	7 (31.8)	0 (0.0)
	Psychoeducational intervention	5 (71.4)	0 (0.0)	0 (0.0)
	Cognitive-behavioral therapy	5 (50.0)	5 (50.0)	0 (0.0)
	General support	1 (100.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	1 (25.0)	2 (50.0)	0 (0.0)
Mixed population $n = 2$	Total, n (%)	1 (50.0)	1 (50.0)	0 (0.0)
	Cognitive intervention	1 (50.0)	1 (50.0)	0 (0.0)

Randomization and blinding

Of 200 studies we investigated, twenty (10.0%) and eleven (5.5%) studies employed cluster randomization and crossover designs, respectively ; however, these designs have several known limitations. Specifically, the clustering effect (i.e., intraclass correlation coefficients) should be accounted for when calculating the sample size and performing statistical analysis, and blinding is not always feasible in cluster randomized trials (Boutron et al., 2011). Carryover and period effects should be adequately addressed in the study design or statistical modeling in studies employing crossover designs. Considering that the primary outcome with placebo effects, such as cognition/memory and BPSD, is often used, an individual randomization design might be better in many cases.

Outcomes

A total of 187 studies (94.5%) used multiple primary outcomes. As dementia is a multifaceted condition with long-term disease progression, evaluating the effectiveness of therapeutic interventions for MCI and dementia based on multiple outcomes may be useful. Guidelines on drug development for Alzheim-

Table 4. (continued)

Target population	Type of intervention	Number of time points for measurements after baseline assessment		
		4	≥ 5	Other*
Normal cognition $n = 31$	Total, n (%)	2 (6.5)	2 (6.5)	0 (0.0)
	Dietary intervention	0 (0.0)	1 (100.0)	0 (0.0)
	Cognitive intervention	1 (5.9)	1 (5.9)	0 (0.0)
	Exercise therapy	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	1 (14.3)	0 (0.0)	0 (0.0)
Mild cognitive impairment $n = 19$	Total, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	0 (0.0)	0 (0.0)	0 (0.0)
	Exercise therapy	0 (0.0)	0 (0.0)	0 (0.0)
Dementia $n = 126$	Total, n (%)	4 (3.2)	8 (6.3)	1 (0.8)
	Dietary intervention	0 (0.0)	1 (33.3)	0 (0.0)
	Cognitive intervention	2 (4.9)	1 (2.4)	0 (0.0)
	Exercise therapy	0 (0.0)	0 (0.0)	0 (0.0)
	Animal therapy	0 (0.0)	0 (0.0)	0 (0.0)
	Art therapy	0 (0.0)	1 (50.0)	0 (0.0)
	Music therapy	2 (11.8)	2 (11.8)	0 (0.0)
	Reminiscence therapy	0 (0.0)	1 (5.6)	0 (0.0)
	Validation therapy	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	0 (0.0)	1 (11.1)	0 (0.0)
	Psychoeducational intervention	0 (0.0)	0 (0.0)	0 (0.0)
	Counseling	0 (0.0)	0 (0.0)	1 (33.3)
	Multidomain intervention for caregiver	0 (0.0)	1 (20.0)	0 (0.0)
Caregivers only $n = 22$	Total, n (%)	0 (0.0)	3 (13.6)	0 (0.0)
	Psychoeducational intervention	0 (0.0)	2 (28.6)	0 (0.0)
	Cognitive-behavioral therapy	0 (0.0)	0 (0.0)	0 (0.0)
	General support	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	0 (0.0)	1 (25.0)	0 (0.0)
Mixed population $n = 2$	Total, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	0 (0.0)	0 (0.0)	0 (0.0)

*One study with time-to-event outcomes was categorized into "Other".

er's disease (Food and Drug Administration, 2018 ; Committee for Medical Products for Human Use, 2018) also recommend the use of multiple primary outcomes. From a statistical point of view, however, we recommend testing one primary outcome, which is recognized as the most compelling measure among stakeholders such as patients, caregivers, and clinicians, because the use of multiple primary outcomes complicates the sample size calculation and causes problems with the multiplicity of statistical testing.

Repeated measures data analysis

Of the 103 studies with repeated measures data in this review, 38 (36.9%) did not use appropriate analysis for repeated measures data. RCTs of non-pharmacological interventions often collect repeated measures data, which are typically obtained from multiple measurements of the outcome(s) of interest. For such repeated measures data, it is recommended to use repeated measures data analysis that can account for correlations among measures within a patient by representing the individual effects of participants as a ran-

Table 5. Outcome information by target population and type of intervention (n = 200)

Target population	Type of intervention	Description of primary outcome
Normal cognition n = 31	Total, n (%)	13 (41.9)
	Dietary intervention	0 (0.0)
	Cognitive intervention	7 (41.2)
	Exercise therapy	4 (66.7)
	Multidomain intervention	2 (28.6)
Mild cognitive impairment n = 19	Total, n (%)	6 (31.6)
	Cognitive intervention	5 (29.4)
	Exercise therapy	1 (50.0)
Dementia n = 126	Total, n (%)	44 (34.9)
	Dietary intervention	0 (0.0)
	Cognitive intervention	13 (31.7)
	Exercise therapy	2 (16.7)
	Animal therapy	2 (28.6)
	Art therapy	0 (0.0)
	Music therapy	7 (41.2)
	Reminiscence therapy	9 (50.0)
	Validation therapy	0 (0.0)
	Multidomain intervention	4 (44.4)
	Psychoeducational intervention	4 (57.1)
	Counseling	1 (33.3)
	Multidomain intervention for caregiver	2 (40.0)
Caregivers only n = 22	Total, n (%)	10 (45.5)
	Psychoeducational intervention	4 (57.1)
	Cognitive-behavioral therapy	3 (30.0)
	General support	0 (0.0)
	Multidomain intervention for caregiver	3 (75.0)
Mixed population n = 2	Total, n (%)	1 (50.0)
	Cognitive intervention	1 (50.0)

dom effect. Among them, the MMRM method, a type of mixed-effects model that includes both fixed (group-specific) effects and random (individual-specific) effects, is a powerful approach in repeated measures data analysis. When analyzing repeated measures data with missing observations, it is well known that the exclusion of participants with missing data from the analysis causes a serious bias in the interventional effect estimation (Mallinckrod et al., 2018). MMRM often provides better inferences for interventional effects at the time point of interest under repeated measures data with missing observations, but the software implication of MMRM requires a certain level of understanding of statistical methodologies and programming techniques. This may be the reason why only two studies used MMRM in this study.

Sample size calculation

Only 20-25% of studies in each target population performed a power analysis. When planning RCTs, the statistical hypothesis for the primary outcome(s) and the sample size rationale based on this hypothesis should be adequately determined. The rationale for the sample size required to evaluate the statistical hypothesis is also important for an appropriate interpretation of the study results. When the sample size

Table 5. (continued)

Target population	Type of intervention	Number of outcomes			
		1	2-5	6-10	≥ 11
Normal cognition $n = 31$	Total, n (%)	3 (9.7)	14 (45.2)	10 (32.3)	4 (12.9)
	Dietary intervention	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	3 (17.6)	8 (47.1)	5 (29.4)	1 (5.9)
	Exercise therapy	0 (0.0)	2 (33.3)	2 (33.3)	2 (33.3)
	Multidomain intervention	0 (0.0)	3 (42.9)	3 (42.9)	1 (14.3)
Mild cognitive impairment $n = 19$	Total, n (%)	0 (0.0)	3 (15.8)	8 (42.1)	8 (42.1)
	Cognitive intervention	0 (0.0)	3 (17.6)	7 (41.2)	7 (41.2)
	Exercise therapy	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)
Dementia $n = 126$	Total, n (%)	9 (7.1)	59 (46.8)	49 (38.9)	9 (7.1)
	Dietary intervention	0 (0.0)	1 (33.3)	2 (66.7)	0 (0.0)
	Cognitive intervention	0 (0.0)	14 (34.1)	21 (51.2)	6 (14.6)
	Exercise therapy	1 (8.3)	8 (66.7)	3 (25.0)	0 (0.0)
	Animal therapy	2 (28.6)	4 (57.1)	1 (14.3)	0 (0.0)
	Art therapy	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)
	Music therapy	3 (17.6)	10 (58.8)	3 (17.6)	1 (5.9)
	Reminiscence therapy	1 (5.6)	11 (61.1)	5 (27.8)	1 (5.6)
	Validation therapy	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	0 (0.0)	4 (44.4)	4 (44.4)	1 (11.1)
	Psychoeducational intervention	1 (14.3)	4 (57.1)	2 (28.6)	0 (0.0)
	Counseling	1 (33.3)	0 (0.0)	2 (66.7)	0 (0.0)
	Multidomain intervention for caregiver	0 (0.0)	1 (20.0)	4 (80.0)	0 (0.0)
Caregivers only $n = 22$	Total, n (%)	1 (4.5)	11 (50.0)	9 (40.9)	1 (4.5)
	Psychoeducational intervention	0 (0.0)	4 (57.1)	3 (42.9)	0 (0.0)
	Cognitive-behavioral therapy	0 (0.0)	5 (50.0)	4 (40.0)	1 (10.0)
	General support	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	1 (25.0)	1 (25.0)	2 (50.0)	0 (0.0)
Mixed population $n = 2$	Total, n (%)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)
	Cognitive intervention	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)

is not determined based on a statistical hypothesis, it is better to clearly state that the sample size is based on the feasibility of participant enrollment during the study period.

Conclusion

This review elucidated the current status of study designs and statistical analyses in RCTs of non-pharmacological preventive and therapeutic interventions for dementia continuum. Based on the findings of this review, we offer suggestions for consideration when planning and conducting randomized controlled trials on non-pharmacological interventions in the future. In particular, the appropriate choice of one primary outcome, use of statistical analysis for repeated measures data, and sample size calculation based on power analysis are important for improving the quality of study results. Although, there may be a possible selection bias in this study because we did not select the literature based on the method recommended for selecting articles for a systematic review (Rethlefsen et al., 2021). To address selection bias, further studies based on a systematic review approach are war-

Table 5. (continued)

Target population	Type of intervention	Outcome domain*			
		Cognition / Memory	BPSD	ADL	Physical outcome
Normal cognition $n = 31$	Total, n (%)	26 (83.9)	5 (16.1)	8 (25.8)	6 (19.4)
	Dietary intervention	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	Cognitive intervention	16 (94.1)	2 (11.8)	6 (35.3)	0 (0.0)
	Exercise therapy	4 (66.7)	2 (33.3)	0 (0.0)	3 (50.0)
	Multidomain intervention	6 (85.7)	1 (14.3)	2 (28.6)	2 (28.6)
Mild cognitive impairment $n = 19$	Total, n (%)	18 (94.7)	8 (42.1)	5 (26.3)	1 (5.3)
	Cognitive intervention	16 (94.1)	8 (47.1)	4 (23.5)	0 (0.0)
	Exercise therapy	2 (100.0)	0 (0.0)	1 (50.0)	1 (50.0)
Dementia $n = 126$	Total, n (%)	79 (62.7)	87 (69.0)	33 (26.2)	12 (9.5)
	Dietary intervention	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
	Cognitive intervention	39 (95.1)	24 (58.5)	16 (39.0)	1 (2.4)
	Exercise therapy	9 (75.0)	6 (50.0)	4 (33.3)	6 (50.0)
	Animal therapy	3 (42.9)	5 (71.4)	3 (42.9)	3 (42.9)
	Art therapy	2 (100.0)	2 (100.0)	1 (50.0)	0 (0.0)
	Music therapy	5 (29.4)	17 (100.0)	3 (17.6)	0 (0.0)
	Reminiscence therapy	13 (72.2)	12 (66.7)	3 (16.7)	0 (0.0)
	Validation therapy	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	3 (33.3)	7 (77.8)	2 (22.2)	1 (11.1)
	Psychoeducational intervention	3 (42.9)	6 (85.7)	1 (14.3)	0 (0.0)
	Counseling	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	2 (40.0)	4 (80.0)	0 (0.0)	0 (0.0)
Caregivers only $n = 22$	Total, n (%)	3 (13.6)	6 (27.3)	3 (13.6)	0 (0.0)
	Psychoeducational intervention	0 (0.0)	2 (28.6)	1 (14.3)	0 (0.0)
	Cognitive-behavioral therapy	1 (10.0)	3 (30.0)	1 (10.0)	0 (0.0)
	General support	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	2 (50.0)	1 (25.0)	1 (25.0)	0 (0.0)
Mixed population $n = 2$	Total, n (%)	2 (100.0)	1 (50.0)	2 (100.0)	0 (0.0)
	Cognitive intervention	2 (100.0)	1 (50.0)	2 (100.0)	0 (0.0)

ranted, although we focused on studies included in the Clinical Practice Guidelines for Dementia 2017 in Japan and the Cochrane Database of Systematic Reviews.

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References

Abraha I, Rimland JM, Lozano-Montoya I, Dell'Aquila G, Vélez-Díaz-Pallarés M, Trotta FM, Cruz-Jentoft AJ, Cherubini A (2017) Simulated presence therapy for dementia. Cochrane Database Syst Rev 4: CD011882

Akkerman RL, Ostwald SK (2004) Reducing anxiety in Alzheimer's disease family caregivers: the effectiveness of a nine-week cognitive-behavioral intervention. Am J Alzheimers Dis Other Demen 19: 117-123

Table 5. (continued)

Target population	Type of intervention	Outcome domain*			
		QOL	Biological outcome	Onset of dementia	Onset of MCI
Normal cognition $n = 31$	Total, n (%)	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Dietary intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Exercise therapy	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mild cognitive impairment $n = 19$	Total, n (%)	4 (21.1)	1 (5.3)	1 (5.3)	1 (5.3)
	Cognitive intervention	4 (23.5)	0 (0.0)	1 (5.9)	1 (5.9)
	Exercise therapy	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
Dementia $n = 126$	Total, n (%)	30 (23.8)	3 (2.4)	1 (0.8)	0 (0.0)
	Dietary intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	11 (26.8)	1 (2.4)	1 (2.4)	0 (0.0)
	Exercise therapy	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
	Animal therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Art therapy	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Music therapy	5 (29.4)	2 (11.8)	0 (0.0)	0 (0.0)
	Reminiscence therapy	8 (44.4)	0 (0.0)	0 (0.0)	0 (0.0)
	Validation therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Psychoeducational intervention	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Counseling	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Caregivers only $n = 22$	Total, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Psychoeducational intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive-behavioral therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	General support	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention for caregiver	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mixed population $n = 2$	Total, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Bahar-Fuchs A, Clare L, Woods B (2013) Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. Cochrane Database Syst Rev 6 : CD003260

Bahar-Fuchs A, Martyr A, Goh AM, Sabates J, Clare L (2019) Cognitive training for people with mild to moderate dementia. Cochrane Database Syst Rev 3 : CD013069

Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P ; CONSORT Group (2008) Methods and processes of the CONSORT Group : example of an extension for trials assessing nonpharmacologic treatments. Ann Intern Med 148Z W60-66

Boutron I, Ravaud P, Moher D (2011) Randomized Clinical Trials of Non-pharmacological Treatments. Location : CRC Press pp 3-10

Committee for Medical Products for Human Use (CHMP) (2018) Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease. https://www.ema.europa.eu/en/clinical-investigation-medicines-treatment-alzheimers-disease (accessed 31 May 2022).

Cook EDM, Swift K, James I, Malouf R, De Vugt M, Verhey F (2012) Functional analysis-based interventions for challenging behaviour in dementia. Cochrane Database Syst Rev 2 : CD006929

Deshmukh SR, Holmes J, Cardno A (2018) Art therapy for people with dementia. Cochrane Database Syst Rev 9 :

Table 5. (continued)

Target population	Type of intervention	Outcome domain*			
		Adherence to intervention	Depression among caregivers	Caregiver burden	QOL of caregivers
Normal cognition *n* = 31	Total, *n* (%)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Dietary intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Exercise therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Mild cognitive impairment *n*= 19	Total, *n* (%)	2 (10.5)	1 (5.3)	1 (5.3)	1 (5.3)
	Cognitive intervention	2 (11.8)	1 (5.9)	1 (5.9)	1 (5.9)
	Exercise therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dementia *n* = 126	Total, *n* (%)	2 (1.6)	11 (8.7)	18 (14.3)	8 (6.3)
	Dietary intervention	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
	Cognitive intervention	0 (0.0)	5 (12.2)	6 (14.6)	1 (2.4)
	Exercise therapy	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)
	Animal therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Art therapy	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)
	Music therapy	0 (0.0)	0 (0.0)	1 (5.9)	1 (5.9)
	Reminiscence therapy	0 (0.0)	1 (5.6)	3 (16.7)	2 (11.1)
	Validation therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Multidomain intervention	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)
	Psychoeducational intervention	0 (0.0)	1 (14.3)	1 (14.3)	2 (28.6)
	Counseling	0 (0.0)	1 (33.3)	1 (33.3)	0 (0.0)
	Multidomain intervention for caregiver	1 (20.0)	2 (40.0)	2 (40.0)	2 (40.0)
Caregivers only *n* = 22	Total, *n* (%)	2 (9.1)	14 (63.6)	9 (40.9)	6 (27.3)
	Psychoeducational intervention	1 (14.3)	3 (42.9)	4 (57.1)	2 (28.6)
	Cognitive-behavioral therapy	1 (10.0)	7 (70.0)	3 (30.0)	4 (40.0)
	General support	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)
	Multidomain intervention for caregiver	0 (0.0)	3 (75.0)	1 (25.0)	0 (0.0)
Mixed population *n*= 2	Total, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

CD011073

Donner A, Klar N (2000) Design and Analysis of Cluster Randomization Trials in Health Research. WILEY.

Food and Drug Administration (2018) Early Alzheimer's disease, developing drugs for treatment guidance for industry (draft guidance). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/alzheimers-disease-developing-drugs-treatment-guidance-industy (accessed 31 May 2022).

Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S (2015) Exercise programs for people with dementia. Cochrane Database Syst Rev 4 : CD006489

Friedman LM, Furberg CD, DeMets DL, Reboussin DM, Granger CB (2015) Fundamentals of clinical trials. springer.

Gates NJ, Rutjes AW, Di Nisio M, Karim S, Chong LY, March E, Martínez G, Vernooij RW (2019a) Computerised cognitive training for maintaining cognitive function in cognitively healthy people in midlife. Cochrane Database Syst Rev 3 : CD012278

Gates NJ, Vernooij RW, Di Nisio M, Karim S, March E, Martínez G, Rutjes AW (2019b) Computerised cognitive training for preventing dementia in people with mild cognitive impairment. Cochrane Database Syst Rev 3 : CD012279

Table 5. (continued)

Target population	Type of intervention	Outcome domain*		
		Caregiver's knowledge	Stress among caregivers	Other category
Normal cognition $n = 31$	Total, n (%)	0 (0.0)	0 (0.0)	5 (16.1)
	Dietary intervention	0 (0.0)	0 (0.0)	1 (100.0)
	Cognitive intervention	0 (0.0)	0 (0.0)	3 (17.6)
	Exercise therapy	0 (0.0)	0 (0.0)	1 (16.7)
	Multidomain intervention	0 (0.0)	0 (0.0)	0 (0.0)
Mild cognitive impairment $n = 19$	Total, n (%)	0 (0.0)	0 (0.0)	3 (15.8)
	Cognitive intervention	0 (0.0)	0 (0.0)	3 (17.6)
	Exercise therapy	0 (0.0)	0 (0.0)	0 (0.0)
Dementia $n = 126$	Total, n (%)	3 (2.4)	6 (4.8)	35 (27.8)
	Dietary intervention	1 (33.3)	0 (0.0)	2 (66.7)
	Cognitive intervention	0 (0.0)	2 (4.9)	9 (22.0)
	Exercise therapy	0 (0.0)	0 (0.0)	3 (25.0)
	Animal therapy	0 (0.0)	0 (0.0)	1 (14.3)
	Art therapy	0 (0.0)	0 (0.0)	0 (0.0)
	Music therapy	0 (0.0)	0 (0.0)	1 (5.9)
	Reminiscence therapy	1 (5.6)	2 (11.1)	6 (33.3)
	Validation therapy	0 (0.0)	0 (0.0)	1 (50.0)
	Multidomain intervention	0 (0.0)	1 (11.1)	3 (33.3)
	Psychoeducational intervention	0 (0.0)	0 (0.0)	2 (28.6)
	Counseling	0 (0.0)	1 (33.3)	3 (100.0)
	Multidomain intervention for caregiver	1 (20.0)	0 (0.0)	4 (80.0)
Caregivers only $n = 22$	Total, n (%)	6 (27.3)	7 (31.8)	18 (81.8)
	Psychoeducational intervention	3 (42.9)	2 (28.6)	5 (71.4)
	Cognitive-behavioral therapy	1 (10.0)	5 (50.0)	8 (80.0)
	General support	0 (0.0)	0 (0.0)	1 (100.0)
	Multidomain intervention for caregiver	2 (50.0)	0 (0.0)	4 (100.0)
Mixed population $n = 2$	Total, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
	Cognitive intervention	0 (0.0)	0 (0.0)	0 (0.0)

*Some are overlapped. BPSD, behavioral and psychological symptoms of dementia ; ADL, activities of daily living ; QOL, quality of life ; MCI, mild cognitive impairment.

Gates NJ, Rutjes AW, Di Nisio M, Karim S, Chong LY, March E, Martínez G, Vernooij RW (2020) Computerised cognitive training for 12 or more weeks for maintaining cognitive function in cognitively healthy people in late life. Cochrane Database Syst Rev 2 : CD012277

Hébert R, Lévesque L, Vézina J, Lavoie JP, Ducharme F, Gendron C, Préville M, Voyer L, Dubois MF (2003) Efficacy of a psychoeducative group program for caregivers of demented persons living at home : a randomized controlled trial. J Gerontol B Psychol Sci Soc Sci 258 : S58-67

Herke M, Fink A, Langer G, Wustmann T, Watzke S, Hanff AM, Burckhardt M (2018) Environmental and behavioural modifications for improving food and fluid intake in people with dementia. Cochrane Database Syst Rev 7 : CD011542

Hu M, Hu H, Shao Z, Gao Y, Zeng X, Shu X, Huang J, Shen S, Wu IXY, Xiao LD, Feng H (2022) Effectiveness and acceptability of non-pharmacological interventions in people with mild cognitive impairment : Overview of systematic reviews and network meta-analysis. J Affect Disord 311 : 383-390

Japanese Society of Neurology (2017) Ninchisyo Shikkan Shinryo Guideline 2017 (Clinical Practice Guidelines for Dementia 2017). Tokyo, Japan : Igakushoin pp 67-293

Table 6. Considerations for statistical analyses by target population and type of intervention (n = 200)

	Normal cognition n = 31	Mild cognitive impairment n = 19	Dementia n = 126	Caregivers only n = 22	Mixed population n = 2
Sample size, median (range)	106.0 (15.0-6742.0)	40.0 (17.0-223.0)	58.0 (11.0-653.0)	92.0 (28.0-329.0)	334.5 (321.0-348.0)
≤ 50, n (%)	7 (22.6)	11 (57.9)	56 (44.4)	8 (36.4)	0 (0.0)
51-100	7 (22.6)	5 (26.3)	39 (31.0)	4 (18.2)	0 (0.0)
>100	17 (54.8)	3 (15.8)	31 (24.6)	10 (45.5)	2 (100.0)
Power analysis, n (%)	6 (19.4)	5 (26.3)	27 (21.4)	5 (22.7)	0 (0.0)
Analysis sets, n (%)					
ITT	9 (29.0)	4 (21.1)	28 (22.2)	6 (27.3)	0 (0.0)
FAS	1 (3.2)	0 (0.0)	2 (1.6)	1 (4.5)	0 (0.0)
PPS	0 (0.0)	2 (10.5)	2 (1.6)	2 (9.1)	0 (0.0)
No description	21 (67.7)	13 (68.4)	94 (74.6)	13 (59.1)	2 (100.0)
Primary analysis, n (%)					
t-test	3 (9.7)	4 (21.1)	14 (11.1)	0 (0.0)	0 (0.0)
ANOVA	0 (0.0)	1 (5.3)	9 (7.1)	1 (4.5)	0 (0.0)
ANCOVA	8 (25.8)	3 (15.8)	18 (14.3)	11 (50.0)	0 (0.0)
Repeated measures ANOVA	13 (41.9)	4 (21.1)	33 (26.2)	4 (18.2)	0 (0.0)
Regression model analysis	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
Mixed-effects model	4 (12.9)	5 (26.3)	27 (21.4)	3 (13.6)	2 (100.0)
MMRM	1 (3.2)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Generalized estimating equations	0 (0.0)	0 (0.0)	5 (4.0)	2 (9.1)	0 (0.0)
Others	2 (6.5)	2 (10.5)	16 (12.7)	0 (0.0)	0 (0.0)
No description	0 (0.0)	0 (0.0)	1 (0.8)	1 (4.5)	0 (0.0)

ITT, intention-to-treat ; FAS, full analysis set ; PPS, per-protocol set ; ANOVA, analysis of variance ; ANCOVA, analysis of covariance ; MMRM, mixed-effects model for repeated measures.

Karkou V, Meekums B (2017) Dance movement therapy for dementia. Cochrane Database Syst Rev 2 : CD011022

Lai NM, Chang SMW, Ng SS, Tan SL, Chaiyakunapruk N, Stanaway F (2019) Animal-assisted therapy for dementia. Cochrane Database Syst Rev 11 : CD013243

Lins S, Hayder-Beichel D, Rücker G, Motschall E, Antes G, Meyer G, Langer G (2014) Efficacy and experiences of telephone counselling for informal carers of people with dementia. Cochrane Database Syst Rev 9 : CD009126

Liu Z, Sun YY, Zhong BL (2018) Mindfulness-based stress reduction for family carers of people with dementia. Cochrane Database Syst Rev 8 : CD012791

Mallinckrod CH, Lane PW, Schnell D, Peng Y, Mancuso JP (2018) Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. Drug Inf J 42 : 303-319

Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F (2011) Cognition-based interventions for healthy older people and people with mild cognitive impairment. Cochrane Database Syst Rev 1 : CD006220

Möhler R, Renom A, Renom H, Meyer G (2018) Personally tailored activities for improving psychosocial outcomes for people with dementia in long-term care. Cochrane Database Syst Rev 2 : CD009812

Na R, Yang JH, Yeom Y, Kim YJ, Byun S, Kim K, Kim KW (2019) A Systematic Review and Meta-Analysis of Non-pharmacological Interventions for Moderate to Severe Dementia. Psychiatry Investig 16 : 325-335

Neal M, Wright PB (2003) Validation therapy for dementia. Cochrane Database Syst Rev 3 : CD001394

Orgeta V, McDonald KR, Poliakoff E, Hindle JV, Clare L, Leroi I (2020) Cognitive training interventions for dementia and mild cognitive impairment in Parkinson's disease. Cochrane Database Syst Rev 2 : CD011961

Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB ; PRISMA-S Group (2021) PRISMA-

S : an extension to the PRISMA Statement for reporting literature searches in systematic reviews. Syst Rev 10 : 39

Salfi J, Ploeg J, Black ME (2005) Seeking to understand telephone support for dementia caregivers. West J Nurs Res 27 : 701-721

van der Steen JT, Smaling HJ, van der Wouden JC, Bruinsma MS, Scholten RJ, Vink AC (2018) Music-based therapeutic interventions for people with dementia. Cochrane Database Syst Rev 7 : CD003477

Vernooij-Dassen M, Draskovic I, McCleery J, Downs M (2011) Cognitive reframing for carers of people with dementia. Cochrane Database Syst Rev 11 : CD005318

Walter E, Pinquart M (2020) How effective are dementia caregiver interventions? An updated comprehensive meta-analysis. Gerontologist 60 : 609-619

Whitty E, Mansour H, Aguirre E, Palomo M, Charlesworth G, Ramjee S, Poppe M, Brodaty H, Kales HC, Morgan-Trimmer S, Nyman SR, Lang I, Walters K, Petersen I, Wenborn J, Minihane AM, Ritchie K, Huntley J, Walker Z, Cooper C (2020) Efficacy of lifestyle and psychosocial interventions in reducing cognitive decline in older people : systematic review. Ageing Res Rev 62 : 101113

Winter L, Gitlin LN (2006) Evaluation of a telephone-based support group intervention for female caregivers of community-dwelling individuals with dementia. Am J Alzheimers Dis Other Demen 21 : 391-397

Woods B, Aguirre E, Spector AE, Orrell M (2012) Cognitive stimulation to improve cognitive functioning in people with dementia. Cochrane Database Syst Rev 2 : CD005562

Woods B, O'Philbin L, Farrell EM, Spector AE, Orrell M (2018) Reminiscence therapy for dementia. Cochrane Database Syst Rev 3 : CD001120

Yao S, Liu Y, Zheng X, Zhang Y, Cui S, Tang C, Lu L, Xu N (2020) Do non-pharmacological interventions prevent cognitive decline? a systematic review and meta-analysis. Transl Psychiatry 10 : 19

Young J, Angevaren M, Rusted J, Tabet N (2015) Aerobic exercise to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev 4 : CD005381.

Appendix

Table S1. Number of studies published in each year by types of intervention (n = 200)

Type of intervention	Publication year				
	≤ 1999 n = 20	2000 n = 3	2001 n = 5	2002 n = 5	2003 n = 8
Cognitive intervention, n (%)	11 (55.0)	1 (33.3)	1 (20.0)	2 (40.0)	2 (25.0)
Validation therapy, n (%)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multidomain intervention for caregivers, n (%)	1 (5.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (25.0)
Psychoeducational intervention, n (%)	1 (5.0)	0 (0.0)	1 (20.0)	0 (0.0)	3 (37.5)
Multidomain intervention, n (%)	1 (5.0)	0 (0.0)	0 (0.0)	2 (40.0)	1 (12.5)
Reminiscence therapy, n (%)	1 (5.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Dietary intervention, n (%)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Music therapy, n (%)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Animal therapy, n (%)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cognitive-behavioral therapy, n (%)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Exercise therapy, n (%)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	0 (0.0)
Counseling, n (%)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Art therapy, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General support, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table S1. (continued)

Type of intervention	Publication year				
	2004 n = 9	2005 n = 10	2006 n = 10	2007 n = 16	2008 n = 4
Cognitive intervention, n (%)	2 (22.2)	5 (50.0)	3 (30.0)	7 (43.8)	0 (0.0)
Validation therapy, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multidomain intervention for caregivers, n (%)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychoeducational intervention, n (%)	1 (11.1)	1 (10.0)	2 (20.0)	2 (12.5)	1 (25.0)
Multidomain intervention, n (%)	1 (11.1)	1 (10.0)	0 (0.0)	1 (6.2)	0 (0.0)
Reminiscence therapy, n (%)	1 (11.1)	0 (0.0)	1 (10.0)	1 (6.2)	0 (0.0)
Dietary intervention, n (%)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Music therapy, n (%)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
Animal therapy, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cognitive-behavioral therapy, n (%)	1 (11.1)	0 (0.0)	0 (0.0)	3 (18.8)	0 (0.0)
Exercise therapy, n (%)	1 (11.1)	0 (0.0)	2 (20.0)	1 (6.2)	3 (75.0)
Counseling, n (%)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Art therapy, n (%)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
General support, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.2)	0 (0.0)

Table S1. (continued)

Type of intervention	Publication year				
	2009 $n = 6$	2010 $n = 15$	2011 $n = 11$	2012 $n = 11$	2013 $n = 15$
Cognitive intervention, *n* (%)	1 (16.7)	3 (20.0)	4 (36.4)	3 (27.3)	5 (33.3)
Validation therapy, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multidomain intervention for caregivers, *n* (%)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Psychoeducational intervention, *n* (%)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Multidomain intervention, *n* (%)	0 (0.0)	1 (6.7)	2 (18.2)	0 (0.0)	3 (20.0)
Reminiscence therapy, *n* (%)	0 (0.0)	2 (13.3)	1 (9.1)	4 (36.4)	0 (0.0)
Dietary intervention, *n* (%)	0 (0.0)	1 (6.7)	1 (9.1)	0 (0.0)	0 (0.0)
Music therapy, *n* (%)	1 (16.7)	3 (20.0)	1 (9.1)	2 (18.2)	3 (20.0)
Animal therapy, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cognitive-behavioral therapy, *n* (%)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	2 (13.3)
Exercise therapy, *n* (%)	3 (50.0)	3 (20.0)	1 (9.1)	2 (18.2)	1 (6.7)
Counseling, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Art therapy, *n* (%)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)
General support, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

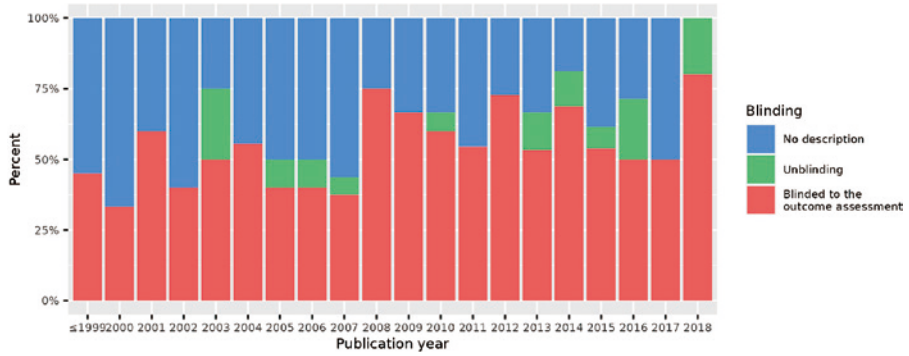
Table S1. (continued)

Type of intervention	Publication year				
	2014 $n = 16$	2015 $n = 13$	2016 $n = 14$	2017 $n = 4$	2018 $n = 5$
Cognitive intervention, *n* (%)	8 (50.0)	4 (30.8)	6 (42.9)	4 (100.0)	5 (100.0)
Validation therapy, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multidomain intervention for caregivers, *n* (%)	0 (0.0)	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)
Psychoeducational intervention, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multidomain intervention, *n* (%)	1 (6.2)	1 (7.7)	1 (7.1)	0 (0.0)	0 (0.0)
Reminiscence therapy, *n* (%)	2 (12.5)	2 (15.4)	2 (14.3)	0 (0.0)	0 (0.0)
Dietary intervention, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Music therapy, *n* (%)	2 (12.5)	2 (15.4)	1 (7.1)	0 (0.0)	0 (0.0)
Animal therapy, *n* (%)	1 (6.2)	2 (15.4)	3 (21.4)	0 (0.0)	0 (0.0)
Cognitive-behavioral therapy, *n* (%)	1 (6.2)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)
Exercise therapy, *n* (%)	1 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Counseling, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Art therapy, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General support, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

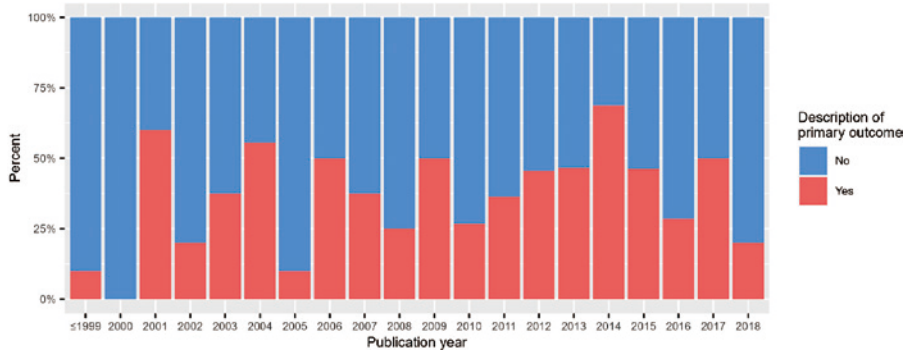
Table S2. Outcome measures used as primary outcome by types of interventions

Intervention	Outcome measures used as primary outcome
Cognitive intervention	Mini-Mental State Examination (8), Alzheimer's Disease Assessment Scale-Cognitive subscale (3), Rey Auditory Verbal Learning Test (3), Bayer Activities of Daily Living Scale (2), Brief Story Recall (2), Minimum Data Set-Home Care Instrumental Activities of Daily Living Scale (2), Neuropsychiatric Inventory (2), Phonemic and Semantic Fluency (2), Rey-Osterrieth Complex Figure Test (2), Short Story Test (2), Verbal Naming Test (2), Avoidance of specific driving situations (1), Boston Naming Test (1), Brief Assessment of Prospective Memory-Short Form (1), Brief test of attention (1), Cambridge Cognitive Examination-Revised (1), Canadian Occupational Performance Measure (1), CANTAB Stockings of Cambridge problems solved in minimum moves score (1), Clinician Interview-Based Impression of Change (1), Complex figure test (1), Complex Reaction Time (1), DemTect (1), Direct Measure of Training (1), Driving difficulty (1), Everyday Problems Test (1), FAS phonemic fluency test (1), Hong Kong List Learning Test (1), Letter verbal fluency (1), Mattis Dementia Rating Scale (1), Memo (1), Mindstreams battery (1), Mindstreams Stroop Interference test (1), Nuremberg Aging Observation Scale (1), Observed Tasks of Daily Living (1), Phonological Verbal Fluency Test (1), Quality of Life Questionnaire (1), Raven's Coloured Matrices (1), Recall test (1), Repeatable Battery for the Assessment of Neuropsychological Status (1), Self-Care of Heart Failure Index (1), Semantic verbal fluency (1), The rate of patients alive and without moderately severe to severe dementia (1), Texas Functional Living Scale (1), Timed Instrumental Activities of Daily Living (1), Trail Making Test (1), Visual Verbal Learning Test (1), Word Fluency test (1), Word recall (1), 15-dimensional instrument (1)
Exercise therapy	Letter and category fluency (2), Trail Making Test (2), AI score for the 3 tracking trials (1), Category Verbal Fluency Test (1), Chinese Version Verbal Learning Test (1), Digit Span (1), Digit Symbol Substitution Test (1), Eriksen Flanker Test (1), Katz Activities of Daily Living score (1), List learning test (1), Neurobehavioral Cognitive Status Examination (1), Quantitative electroencephalogram (1), Rey Auditory Verbal Learning Test (1), Rivermead Behavioural Memory Test (1), Stroop Test (1), Useful Field of View (1), Wechsler Memory Scale-Revised (1)
Animal therapy	Multidimensional Observation Scale for Elderly Subjects (1), Nursing Home Behavior Problem Scale (1)
Music therapy	Cohen-Mansfield Agitation Inventory (3), Alzheimer's Disease-Related Quality of Life (1), Behavior Pathology in Alzheimer's Disease Rating Scale (1), Dementia Care Mapping (1), Dementia Quality of Life (1), Geriatric Depression Scale (1), Hamilton Scale (1), Neuropsychiatric Inventory (1)
Reminiscence therapy	Quality of Life-Alzheimer's Disease Scale (3), Multidimensional Observation Scale for Elderly Subjects (2), Autobiographical Memory Interview (1), Clinical Dementia Rating (1), Cornell Scale for Depression in Dementia (1), General Health Questionnaire-28 item version (1), Self Reported Quality of Life Scale (1), Short Form-12 (1), Social Engagement Scale (1)
Multidomain intervention	Agitation Behavior Mapping Instrument (1), Cornell Scale for Depression in Dementia (1), Eriksen Flanker Task (1), Hamilton Depression Rating Scale (1), Hopkins Verbal Learning Test (1), Neuropsychiatric Inventory (1), Presence of the target behavior (1), Rating Anxiety in Dementia (1), Self-Ordered Pointing Task (1), Sickness Impact Profile (1), Spatio-Temporal Walking Parameters (1), Task Switching Test (1), Trail Making Test (1), Wechsler Memory Scale-III (1), 1-Back Tests (1), 2-Back Tests (1), 36-item Short-Form Health Survey (1)
Psychoeducational intervention	Revised Memory and Problem Behavior Checklist (2), Adapted-Gilleard Problem Checklist (1), Center for Epidemiologic Studies-Depression Scale (1), Cohen-Mansfield Agitation Inventory (1), Neuropsychiatric Inventory (1), Quality of Life-Alzheimer's Disease Scale (1), The proportion of patients receiving neuroleptic treatment (1), Zarit Burden Interview (1)
Cognitive-behavioral therapy	Beck Anxiety Inventory (1), Center for Epidemiologic Studies Depression Scale (1), Hamilton Anxiety Scale (1), Revised Memory and Behavior Problems Checklist (1)
Counseling	Time to institutionalization (1)
Multidomain intervention for caregiver	Center for Epidemiologic Studies Depression Scale (2), Caregiver upset (1), Confidence in managing the target problem behavior (1), Frequency of the problem behavior (1), Hospital Anxiety and Depression Scale (1), Informant Questionnaire for Cognitive Decline in the Elderly (1), Medication Appropriateness Index (1), Pittsburgh Agitation Scale (1), Responses to the semi-structured interviews (1), Revised Memory and Behavior Problem Checklist (1), Zarit Burden Interview (1)

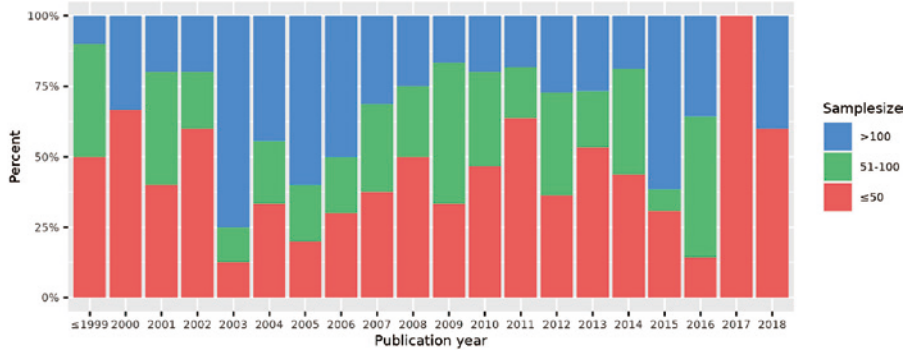
Figures in parentheses indicate the counts used as the primary outcome.



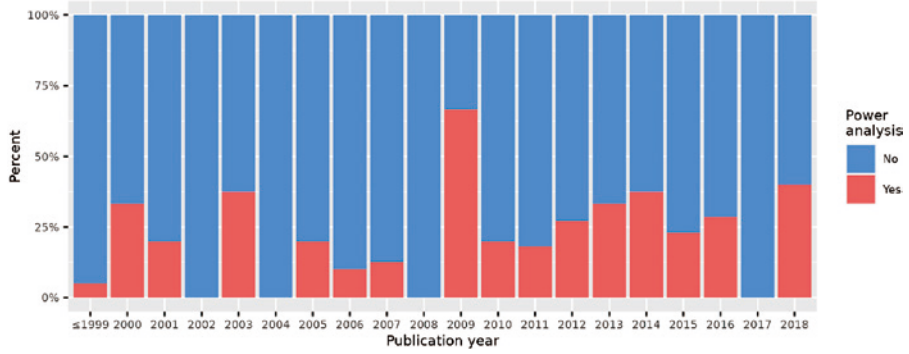
(a) Blinding



(b) Primary outcome



(c) Sample size



(d) Power analysis

Figure S1. Trends of study design quality with publication years

References to studies included in this review

Akanuma K, Meguro K, Meguro M, Sasaki E, Chiba K, Ishii H, Tanaka N（2011） Improved social interaction and increased anterior cingulate metabolism after group reminiscence with reality orientation approach for vascular dementia. Psychiatry Res 192：183-187

Akkerman RL, Ostwald SK（2004） Reducing anxiety in Alzheimer's disease family caregivers：the effectiveness of a nine-week cognitive-behavioral intervention. Am J Alzheimers Dis Other Demen 19：117-123

Alloni A, Quaglini S, Panzarasa S, Sinforiani E, Bernini S（2018） Evaluation of an ontology-based system for computerized cognitive rehabilitation. Int J Med Inform 115：64-72

Amieva H, Robert PH, Grandoulier AS, Meillon C, De Rotrou J, Andrieu S, Berr C, Desgranges B, Dubois B, Girtanner C, Joël ME, Lavallart B, Nourhashemi F, Pasquier F, Rainfray M, Touchon J, Chêne G, Dartigues JF（2016） Group and individual cognitive therapies in Alzheimer's disease：the ETNA3 randomized trial. Int Psychogeriatr 28：707-717

Baines S, Saxby P, Ehlert K（1987） Reality orientation and reminiscence therapy. A controlled cross-over study of elderly confused people. Br J Psychiatry 151：222-231

Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, Plymate SR, Fishel MA, Watson GS, Cholerton BA, Duncan GE, Mehta PD, Craft S（2010） Effects of aerobic exercise on mild cognitive impairment：a controlled trial. Arch Neurol 67：71-79

Bakken RC, Carey JR, Di Fabio RP, Erlandson TJ, Hake JL, Intihar TW（2001） Effect of aerobic exercise on tracking performance in elderly people：a pilot study. Phys Ther 81：1870-1879

Baldelli MV, Pirani A, Motta M, Abati E, Mariani E, Manzi V（1993） Effects of reality orientation therapy on elderly patients in the community. Arch Gerontol Geriatr 17：211-218

Baldelli MV, Boiardi R, Fabbo A, Pradelli JM, Neri M（2002） The role of reality orientation therapy in restorative care of elderly patients with dementia plus stroke in the subacute nursing home setting. Arch Gerontol Geriatr Suppl 8：15-22

Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, Morris JN, Rebok GW, Smith DM, Tennstedt SL, Unverzagt FW, Willis SL；Advanced Cognitive Training for Independent and Vital Elderly Study Group（2002） Effects of cognitive training interventions with older adults：a randomized controlled trial. JAMA 288：2271-2281

Barban F, Annicchiarico R, Pantelopoulos S, Federici A, Perri R, Fadda L, Carlesimo GA, Ricci C, Giuli S, Scalici F, Turchetta CS, Adriano F, Lombardi MG, Zaccarelli C, Cirillo G, Passuti S, Mattarelli P, Lymperopoulou O, Sakka P, Ntanasi E, Moliner R, Garcia-Palacios A, Caltagirone C（2016） Protecting cognition from aging and Alzheimer's disease：a computerized cognitive training combined with reminiscence therapy. Int J Geriatr Psychiatry 31：340-348

Barnes DE, Santos-Modesitt W, Poelke G, Kramer AF, Castro C, Middleton LE, Yaffe K（2013） The Mental Activity and eXercise（MAX）trial：a randomized controlled trial to enhance cognitive function in older adults. JAMA Intern Med 173：797-804

Beauchamp N, Irvine AB, Seeley J, Johnson B（2005） Worksite-based internet multimedia program for family caregivers of persons with dementia. Gerontologist 45：793-801

Bergamaschi S, Arcara G, Calza A, Villani D, Orgeta V, Mondini S（2013） One-year repeated cycles of cognitive training（CT）for Alzheimer's disease. Aging Clin Exp Res 25：421-426

Blom MM, Zarit SH, Groot Zwaaftink RB, Cuijpers P, Pot AM（2015） Effectiveness of an Internet intervention for family caregivers of people with dementia：results of a randomized controlled trial. PLoS One 10

Boller B, Jennings JM, Dieudonné B, Verny M, Ergis AM（2011） Recollection training and transfer effects in Alzheimer's disease：effectiveness of the repetition-lag procedure. Brain Cogn 78：169-177

Bottino CM, Carvalho IA, Alvarez AM, Avila R, Zukauskas PR, Bustamante SE, Andrade FC, Hototian SR, Saffi F, Câmargo CH（2005） Cognitive rehabilitation combined with drug treatment in Alzheimer's disease patients：a pilot study. Clin Rehabil 19：861-869

Breuil V, De Rotrou J, Forette F, Tortrat D, Ganansia-Ganem A, Frambourt A, Moulin F, Boller, F（1994） Cognitive stimulation of patients with dementia：preliminary results. Int J Geriat Psychiatry 9：211-217

Brown KW, Coogle CL, Wegelin J（2016） A pilot randomized controlled trial of mindfulness-based stress reduction for caregivers of family members with dementia. Aging Ment Health 20：1157-1166

Brueggen K, Kasper E, Ochmann S, Pfaff H, Webel S, Schneider W, Teipel S（2017） Cognitive rehabilitation in Alzheimer's disease：a controlled intervention trial. J Alzheimers Dis

57 : 1315-1324

Buiza C, Etxeberria I, Galdona N, González MF, Arriola E, López de Munain A, Urdaneta E, Yanguas JJ (2008) A randomized, two-year study of the efficacy of cognitive intervention on elderly people : the Donostia longitudinal study. Int J Geriatr Psychiatry 23 : 85-94

Burgio L, Stevens A, Guy D, Roth DL, Haley WE (2003) Impact of two psychosocial interventions on white and African American family caregivers of individuals with dementia. Gerontologist 43 : 568-579

Buschert VC, Friese U, Teipel SJ, Schneider P, Merensky W, Rujescu D, Möller HJ, 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

Cahn-Weiner DA, Malloy PF, Rebok GW, Ott BR (2003) Results of a randomized placebo-controlled study of memory training for mildly impaired Alzheimer's disease patients. Appl Neuropsychol 10 : 215-223

Camberg L, Woods P, Ooi WL, Hurley A, Volicer L, Ashley J, Odenheimer G, McIntyre K (1999) Evaluation of simulated presence : a personalized approach to enhance well-being in persons with Alzheimer's disease. J Am Geriatr Soc 47 : 446-452

Cavallo M, Hunter EM, van der Hiele K, Angilletta C (2016) Computerized structured cognitive training in patients affected by early-stage Alzheimer's disease is feasible and effective : a randomized controlled study. Arch Clin Neuropsychol 31 : 868-876

Ceccato E, Vigato G, Bonetto C, Bevilacqua A, Pizziolo P, Crociani S, Zanfretta E, Pollini L, Caneva PA, Baldin L, Frongillo C, Signorini A, Demoro S, Barchi E (2012) STAM protocol in dementia : a multicenter, single-blind, randomized, and controlled trial. Am J Alzheimers Dis Other Demen 27 : 301-310

Cerasa A, Gioia MC, Salsone M, Donzuso G, Chiriaco C, Realmuto S, Nicoletti A, Bellavia G, Banco A, D'amelio M, Zappia M, Quattrone A (2014) Neurofunctional correlates of attention rehabilitation in Parkinson's disease : an explorative study. Neurol Sci 35 : 1173-1180

Chang BL (1999) Cognitive-behavioral intervention for homebound caregivers of persons with dementia. Nurs Res 48 : 173-182

Chang BL, Nitta S, Carter PA, Markham YK (2004) Perceived helpfulness of telephone calls — providing support for caregivers of family members with dementia. J Gerontol Nurs 30 : 14-21

Chang CC, Lin LC (2005) Effects of a feeding skills training programme on nursing assistants and dementia patients. J Clin Nurs 14 : 1185-1192

Chapman SB, Weiner MF, Rackley A, Hynan LS, Zientz J (2004) Effects of cognitive-communication stimulation for Alzheimer's disease patients treated with donepezil. J Speech Lang Hear Res 47 : 1149-1163

Charlesworth G, Burnell K, Crellin N, Hoare Z, Hoe J, Knapp M, Russell I, Wenborn J, Woods B, Orrell M (2016) Peer support and reminiscence therapy for people with dementia and their family carers : a factorial pragmatic randomised trial. J Neurol Neurosurg Psychiatry 87 : 1218-1228

Chenoweth L, King MT, Jeon YH, Brodaty H, Stein-Parbury J, Norman R, Haas M, Luscombe G (2009) Caring for Aged Dementia Care Resident Study (CADRES) of person-centred care, dementia-care mapping, and usual care in dementia : a cluster-randomised trial. Lancet Neurol 8 : 317-325

Christofoletti G, Oliani MM, Gobbi S, Stella F, Bucken Gobbi LT, Renato Canineu 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

Clare L, Linden DE, Woods RT, Whitaker R, Evans SJ, Parkinson CH, van Paasschen J, Nelis SM, Hoare Z, Yuen KS, Rugg MD (2010) Goal-oriented cognitive rehabilitation for people with early-stage Alzheimer disease : a single-blind randomized controlled trial of clinical efficacy. Am J Geriatr Psychiatry 18 : 928-939

Coen RF, Flynn B, Rigney E, O'Connor E, Fitzgerald L, Murray C, Dunleavy C, McDonald M, Delaney D, Merriman N, Edgeworth J (2011) Efficacy of a cognitive stimulation therapy programme for people with dementia. Ir J Psychol Med 28 : 145-147

Cohen-Mansfield J, Libin A, Marx MS (2007) Nonpharmacological treatment of agitation : a controlled trial of systematic individualized intervention. J Gerontol A Biol Sci Med Sci 62 : 908-916

Conradsson M, Littbrand H, Lindelof N, Gustafson Y, Rosendahl E (2010) Effects of a high-intensity functional exercise programme on depressive symptoms and psychological well-being among older people living in residential care facilities : a cluster-randomized controlled trial. Aging Ment Health 14 : 565-576

Cooke M, Moyle W, Shum D, Harrison S, Murfield J (2010) A randomized controlled trial exploring the effect of music on quality of life and depression in older people with dementia. J Health Psychol 15 : 765-776

Coon DW, Thompson L, Steffen A, Sorocco K, Gallagher-Thompson D (2003) Anger and depression management : psychoeducational skill training interventions for women caregivers of a relative with dementia. Gerontologist 43 : 678-689

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 16 : 990-997

Costa A, Peppe A, Serafini F, Zabberoni S, Barban F, Caltagirone C, Carlesimo GA (2014) Prospective memory performance of patients with Parkinson's disease depends on shifting aptitude : evidence from cognitive rehabilitation. J Int Neuropsychol Soc 20 : 717-726

Coyne ML, Hoskins L (1997) Improving eating behaviors in dementia using behavioral strategies. Clin Nurs Res 6 : 275-290

Craik FI, Winocur G, Palmer H, Binns MA, Edwards M, Bridges K, Glazer P, Chavannes R, Stuss DT (2007) Cognitive rehabilitation in the elderly : effects on memory. J Int Neuropsychol Soc 13 : 132-142

Dabelko-Schoeny H, Phillips G, Darrough E, DeAnna S, Jarden M, Johnson D, Lorch G (2014) Equine-assisted intervention for people with dementia. Anthrozoös 27 : 141-155

Davis KK, Mintzer M, Dennison Himmelfarb CR, Hayat MJ, Rotman S, Allen J (2012) Targeted intervention improves knowledge but not self-care or readmissions in heart failure patients with mild cognitive impairment. Eur J Heart Fail 14 : 1041-1049

Davis RN, Massman PJ, Doody RS (2001) Cognitive intervention in Alzheimer disease : a randomized placebo-controlled study. Alzheimer Dis Assoc Disord 15 : 1-9

De Vreese LP, Neri M, Boiardi R, Ferrari P, Belloi L, Salvioli G (1996) Memory training and drug therapy act differently on memory and metamemory functioning : evidence from a pilot study. Arch Gerontol Geriatr 22 : 9-22

Desjardins-Crépeau L, Berryman N, Fraser SA, Vu TT, Kergoat MJ, Li KZ, Bosquet L, Bherer L (2016) Effects of combined physical and cognitive training on fitness and neuropsychological outcomes in healthy older adults. Clin Interv Aging 11 : 1287-1299

Djabelkhir L, Wu YH, Vidal JS, Cristancho-Lacroix V, Marlats F, Lenoir H, Carno A, Rigaud AS (2017) Computerized cognitive stimulation and engagement programs in older adults with mild cognitive impairment : comparing feasibility, acceptability, and cognitive and psychosocial effects. Clin Interv Aging 12 : 1967-1975

Dunlosky J, Cavallini E, Roth H, McGuire CL, Vecchi T, Hertzog C (2007) Do self-monitoring interventions improve older adult learning? J Gerontol B Psychol Sci Soc Sci 62 : 70-76

Edwards JD, Wadley VG, Vance DE, Wood K, Roenker DL, Ball KK (2005) The impact of speed of processing training on cognitive and everyday performance. Aging Ment Health 9 : 262-271

Eggermont LH, Knol DL, Hol EM, Swaab DF, Scherder EJ (2009) Hand motor activity, cognition, mood, and the rest-activity rhythm in dementia : a clustered RCT. Behav Brain Res 196 : 271-278

Eggermont LH, Swaab DF, Hol EM, Scherder EJ (2009) Walking the line : a randomised trial on the effects of a short term walking programme on cognition in dementia. J Neurol Neurosurg Psychiatry 80 : 802-804

Eloniemi-Sulkava U, Notkola IL, Hentinen M, Kivelä SL, Sivenius J, Sulkava R (2001) Effects of supporting community-living demented patients and their caregivers : a randomized trial. J Am Geriatr Soc 49 : 1282-1287

Fabre C, Chamari K, Mucci P, Massé-Biron J, Préfaut C (2002) Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. Int J Sports Med 23 : 415-421

Farran CJ, Gilley DW, McCann JJ, Bienias JL, Lindeman DA, Evans DA (2004) Psychosocial interventions to reduce depressive symptoms of dementia caregivers : a randomized clinical trial comparing two approaches. J Ment Health Aging 10 : 337-350

Farran CJ, Gilley DW, McCann JJ, Bienias JL, Lindeman DA, Evans DA (2007) Efficacy of behavioral interventions for dementia caregivers. West J Nurs Res 29 : 944-960

Fiatarone Singh MA, Gates N, Saigal N, Wilson GC, Meiklejohn J, Brodaty H, Wen W, Singh N, Baune BT, Suo C, Baker MK, Foroughi N, Wang Y, Sachdev PS, Valenzuela M (2014) The Study of Mental and Resistance Training (SMART) study — resistance training and/or cognitive training in mild cognitive impairment : a randomized, double-blind, double-sham controlled trial. J Am Med Dir Assoc 15 : 873-880

Finkel S, Czaja SJ, Schulz R, Martinovich Z, Harris C, Pezzuto D (2007) E-care : a telecommunications technology intervention for family caregivers of dementia patients. Am J Geriatr Psychiatry 15 : 443-448

Folkerts AK, Dorn ME, Roheger M, Maassen M, Koerts J, Tucha O, Altgassen M, Sack AT, Smit D, Haarmann L, Kalbe E (2018) Cognitive stimulation for individuals with Parkinson's disease dementia living in long-term care : preliminary data from a randomized crossover pilot study. Parkinsons Dis 2018 : 8104673

Fossey J, Ballard C, Juszczak E, James I, Alder N, Jacoby R, Howard R (2006) Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia : cluster randomised trial. BMJ 332 : 756-761

Friedmann E, Galik E, Thomas SA, Hall PS, Chung SY, McCune S (2015) Evaluation of a pet-assisted living intervention for improving functional status in assisted living residents with mild to moderate cognitive impairment : a pilot study. Am J Alzheimers Dis Other Demen 30 : 276-289

Galante E, Venturini G, Fiaccadori C (2007) Computer-based cognitive intervention for dementia : preliminary results of a randomized clinical trial. G Ital Med Lav Ergon 29 : B26-32

Gallagher-Thompson D, Gray HL, Tang PC, Pu CY, Leung LY, Wang PC, Tse C, Hsu S, Kwo E, Tong HQ, Long J, Thompson LW (2007) Impact of in-home behavioral management versus telephone support to reduce depressive symptoms and perceived stress in Chinese caregivers : results of a pilot study. Am J Geriatr Psychiatry 15 : 425-434

Gant JR, Steffen AM, Lauderdale SA (2007) Comparative outcomes of two distance-based interventions for male caregivers of family members with dementia. Am J Alzheimers Dis Other Demen 22 : 120-128

Giovagnoli AR, Manfredi V, Parente A, Schifano L, Oliveri S, Avanzini G (2017) Cognitive training in Alzheimer's disease : a controlled randomized study. Neurol Sci 38 : 1485-1493

Gitlin LN, Winter L, Corcoran M, Dennis MP, Schinfeld S, Hauck WW (2003) Effects of the home environmental skill-building program on the caregiver-care recipient dyad : 6-month outcomes from the Philadelphia REACH Initiative. Gerontologist 43 : 532-546

Gitlin LN, Winter L, Dennis MP, Hodgson N, Hauck WW (2010) Targeting and managing behavioral symptoms in individuals with dementia : a randomized trial of a nonpharmacological intervention. J Am Geriatr Soc 58 : 1465-1474

Giuli C, Papa R, Lattanzio F, Postacchini D (2016) The effects of cognitive training for elderly : results from my mind project. Rejuvenation Res 19 : 485-494

Gonyea JG, O'Connor MK, Boyle PA (2006) Project CARE : a randomized controlled trial of a behavioral intervention group for Alzheimer's disease caregivers. Gerontologist 46 : 827-832

Gonzalez J, Mayordomo T, Torres M, Sales A, Meléndez JC (2015) Reminiscence and dementia : a therapeutic intervention. Int Psychogeriatr 27 : 1731-1737

Gooding AL, Choi J, Fiszdon JM, Wilkins K, Kirwin PD, van Dyck CH, Devanand D, Bell MD, Rivera Mindt M (2016) Comparing three methods of computerised cognitive training for older adults with subclinical cognitive decline. Neuropsychol Rehabil 26 : 810-821

Gormley N, Lyons D, Howard R (2001) Behavioural management of aggression in dementia : a randomized controlled trial. Age Ageing 30 : 141-145

Greenaway MC, Duncan NL, Smith GE (2013) The memory support system for mild cognitive impairment : randomized trial of a cognitive rehabilitation intervention. Int J Geriatr Psychiatry 28 : 402-409

Guétin S, Portet F, Picot MC, Pommié C, Messaoudi M, Djabelkir L, Olsen AL, Cano MM, Lecourt E, Touchon J (2009) Effect of music therapy on anxiety and depression in patients with Alzheimer's type dementia : randomised, controlled study. Dement Geriatr Cogn Disord 28 : 36-46

Haight BK, Gibson F, Michel Y (2006) The Northern Ireland life review/life storybook project for people with dementia. Alzheimers Dement 2 : 56-58

Hattori H, Hattori C, Hokao C, Mizushima K, Mase T (2011) Controlled study on the cognitive and psychological effect of coloring and drawing in mild Alzheimer's disease patients. Geriatr Gerontol Int 11 : 431-437

Hébert R, Lévesque L, Vézina J, Lavoie JP, Ducharme F, Gendron C, Préville M, Voyer L, Dubois MF (2003) Efficacy of a psychoeducative group program for caregivers of demented persons living at home : a randomized controlled trial. J Gerontol B Psychol Sci Soc Sci 58 : S58-67

Heiss WD, Kessler J, Slansky I, Mielke R, Szelies B, Herholz K (1993) Activation PET as an instrument to determine therapeutic efficacy in Alzheimer's disease. Ann N Y Acad Sci 695 : 327-331

Herrera C, Chambon C, Michel BF, Paban V, Alescio-Lautier B (2012) Positive effects of computer-based cognitive train-

ing in adults with mild cognitive impairment. Neuropsychologia 50 : 1871–1881

Hill RD, Sheikh JI, Yesavage JA（1988） Pretraining enhances mnemonic training in elderly adults. Exp Aging Res 14 : 207–211

Hill RD, Allen C, McWhorter P（1991） Stories as a mnemonic aid for older learners. Psychol Aging 6 : 484–486

Hou RJ, Wong SY, Yip BH, Hung AT, Lo HH, Chan PH, Lo CS, Kwok TC, Tang WK, Mak WW, Mercer SW, Ma SH（2014） The effects of mindfulness-based stress reduction program on the mental health of family caregivers : a randomized controlled trial. Psychother Psychosom 83 : 45–53

Hsieh CJ, Chang C, Su SF, Hsiao YL, Shih YW, Han WH, Lin CC（2010） Reminiscence group therapy on depression and apathy in nursing home residents with mild to moderate dementia. J Exp Clin Med 2 : 72–78

Hsu MH, Flowerdew R, Parker M, Fachner J, Odell-Miller H（2015） Individual music therapy for managing neuropsychiatric symptoms for people with dementia and their carers : a cluster randomised controlled feasibility study. BMC Geriatr 15 : 84

Huang HL, Shyu YI, Chen MC, Chen ST, Lin LC（2003） A pilot study on a home-based caregiver training program for improving caregiver self-efficacy and decreasing the behavioral problems of elders with dementia in Taiwan. Int J Geriatr Psychiatry 18 : 337–345

Jelcic N, Cagnin A, Meneghello F, Turolla A, Ermani M, Dam M（2012） Effects of lexical-semantic treatment on memory in early Alzheimer disease : an observer-blinded randomized controlled trial. Neurorehabil Neural Repair 26 : 949–956

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 9 : 1605–1611

Kallio EL, Öhman H, Hietanen M, Soini H, Strandberg TE, Kautiainen H, Pitkälä KH（2018） Effects of cognitive training on cognition and quality of life of older persons with dementia. J Am Geriatr Soc 66 : 664–670

Kao CC, Lin LC, Wu SC, Lin KN, Liu CK（2016） Effectiveness of different memory training programs on improving hyperphagic behaviors of residents with dementia : a longitudinal single-blind study. Clin Interv Aging 11 : 707–720

Kawashima R, Okita K, Yamazaki R, Tajima N, Yoshida H, Taira M, Iwata K, Sasaki T, Maeyama K, Usui N, Sugimoto K（2005） Reading aloud and arithmetic calculation improve frontal function of people with dementia. J Gerontol A Biol Sci Med Sci 60 : 380–384

Kemoun G, Thibaud M, Roumagne N, Carette P, Albinet C, Toussaint L, Paccalin M, Dugué B（2010） Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. Dement Geriatr Cogn Disord 29 : 109–114

Kim S（2015） Cognitive rehabilitation for elderly people with early-stage Alzheimer's disease. J Phys Ther Sci 27543–27546

Klusmann V, Evers A, Schwarzer R, Schlattmann P, Reischies FM, Heuser I, Dimeo FC（2010） Complex mental and physical activity in older women and cognitive performance : a 6-month randomized controlled trial. J Gerontol A Biol Sci Med Sci 65 : 680–688

Kolanowski A, Litaker M, Buettner L, Moeller J, Costa PT Jr（2011） A randomized clinical trial of theory-based activities for the behavioral symptoms of dementia in nursing home residents. J Am Geriatr Soc 59 : 1032–1041

Kramer AF, Hahn S, McAuley E, Cohen NJ, Banich MT, Harrison C, Chason J, Boileau RA, Bardell L, Colcombe A, Vakil E（2001） Exercise, aging and cognition : healthy body, healthy mind? In A.D. Fisk, & W. Rogers（Eds.）, Human Factors Interventions for the Health Care of Older Adults（pp. 91–120）. Lawrence Erlbaum Associates Publishers

Kwok TC, Bai X, Li JC, Ho FK, Lee TM（2013） Effectiveness of cognitive training in Chinese older people with subjective cognitive complaints : a randomized placebo-controlled trial. Int J Geriatr Psychiatry 28 : 208–215

Lai CK, Chi I, Kayser-Jones J（2004） A randomized controlled trial of a specific reminiscence approach to promote the well-being of nursing home residents with dementia. Int Psychogeriatr 16 : 33–49

Lampit A, Hallock H, Moss R, Kwok S, Rosser M, Lukjanenko M, Kohn A, Naismith S, Brodaty H, Valenzuela M（2014） The timecourse of global cognitive gains from supervised computer-assisted cognitive training : a randomised, active-controlled trial in elderly with multiple dementia risk factors. J Prev Alzheimers Dis 1 : 33–39

Langlois F, Vu TT, Chassé K, Dupuis G, Kergoat MJ, Bherer L（2013） Benefits of physical exercise training on cognition and quality of life in frail older adults. J Gerontol B Psychol Sci Soc Sci 68 : 400–404

Law LL, Barnett F, Yau MK, Gray MA（2014） Effects of functional tasks exercise on older adults with cognitive impair-

ment at risk of Alzheimer's disease : a randomised controlled trial. Age Ageing 43 : 813-820

Lawrence BJ, Gasson N, Johnson AR, Booth L, Loftus AM (2018) Cognitive training and transcranial direct current stimulation for mild cognitive impairment in parkinson's disease : a randomized controlled trial. Parkinsons Dis 26 : 4318475

Lee GY, Yip CC, Yu EC, Man DW (2013) Evaluation of a computer-assisted errorless learning-based memory training program for patients with early Alzheimer's disease in Hong Kong : a pilot study. Clin Interv Aging 8 : 623-633

Legault C, Jennings JM, Katula JA, Dagenbach D, Gaussoin SA, Sink KM, Rapp SR, Rejeski WJ, Shumaker SA, Espeland MA ; SHARP-P Study Group (2011) Designing clinical trials for assessing the effects of cognitive training and physical activity interventions on cognitive outcomes : the Seniors Health and Activity Research Program Pilot (SHARP-P) study, a randomized controlled trial. BMC Geriatr 11 : 27

Leung NT, Tam HM, Chu LW, Kwok TC, Chan F, Lam LC, Woo J, Lee TM (2015) Neural plastic effects of cognitive training on aging brain. Neural Plast 2015 : 535618

Levine B, Stuss DT, Winocur G, Binns MA, Fahy L, Mandic M, Bridges K, Robertson IH (2007) Cognitive rehabilitation in the elderly : effects on strategic behavior in relation to goal management. J Int Neuropsychol Soc 13 : 143-152

Lin LC, Huang YJ, Su SG, Watson R, Tsai BW, Wu SC (2010) Using spaced retrieval and Montessori-based activities in improving eating ability for residents with dementia. Int J Geriatr Psychiatry 25 : 953-959

Lin Y, Chu H, Yang CY, Chen CH, Chen SG, Chang HJ, Hsieh CJ, Chou KR (2011) Effectiveness of group music intervention against agitated behavior in elderly persons with dementia. Int J Geriatr Psychiatry 26 : 670-678

Loewenstein DA, Acevedo A, Czaja SJ, Duara R (2004) Cognitive rehabilitation of mildly impaired Alzheimer disease patients on cholinesterase inhibitors. Am J Geriatr Psychiatry 12 : 395-402

Lord TR, Garner JE (1993) Effects of music on Alzheimer patients. Percept Mot Skills 76 : 451-455

Mador JE, Giles L, Whitehead C, Crotty M (2004) A randomized controlled trial of a behavior advisory service for hospitalized older patients with confusion. Int J Geriatr Psychiatry 19 : 858-863

Mahncke HW, Connor BB, Appelman J, Ahsanuddin ON, Hardy JL, Wood RA, Joyce NM, Boniske T, Atkins SM, Merzenich MM (2006) Memory enhancement in healthy older adults using a brain plasticity-based training program : a randomized, controlled study. Proc Natl Acad Sci U S A 103 : 12523-12528

Mapelli D, Di Rosa E, Nocita R, Sava D (2013) Cognitive stimulation in patients with dementia : randomized controlled trial. Dement Geriatr Cogn Dis Extra 3 : 263-271

Margrett JA, Willis SL (2006) In-home cognitive training with older married couples : individual versus collaborative learning. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 13 : 173-195

Márquez-González M, Losada A, Izal M, Pérez-Rojo G, Montorio I (2007) Modification of dysfunctional thoughts about caregiving in dementia family caregivers : description and outcomes of an intervention programme. Aging Ment Health 11 : 616-625

Marriott A, Donaldson C, Tarrier N, Burns A (2000) Effectiveness of cognitive-behavioural family intervention in reducing the burden of care in carers of patients with Alzheimer's disease. Br J Psychiatry 176 : 557-562

Melendez JC, Torres M, Redondo R, Mayordomo T, Sales A (2017) Effectiveness of follow-up reminiscence therapy on autobiographical memory in pathological ageing. Int J Psychol 52 : 283-290

Moniz-Cook E, Elston C, Gardiner E, Agar S, Silver M, Win T, Wang M (2008) Can training community mental health nurses to support family carers reduce behavioural problems in dementia? an exploratory pragmatic randomised controlled trial. Int J Geriatr Psychiatry 23 : 185-191

Morgan S, Woods RT (2012) Life review with people with dementia in care homes : a preliminary randomised controlled trial. Dementia : Non-Pharmacological Therapies 1 : 43-59

Narme P, Clément S, Ehrlé N, Schiaratura L, Vachez S, Courtaigne B, Munsch F, Samson S (2014) Efficacy of musical interventions in dementia : evidence from a randomized controlled trial. J Alzheimers Dis 38 : 359-369

Neely AS, Vikstrom S, Josephsson S (2009) Collaborative memory intervention in dementia : caregiver participation matters. Neuropsychol Rehabil 19 : 696-715

O'Donnell RM (2013) Mindfulness-based stress reduction as an intervention among family caregivers of persons with neurocognitive disorders [Masters thesis]. The University of Arizona

Oken BS, Zajdel D, Kishiyama S, Flegal K, Dehen C, Haas M,

Kraemer DF, Lawrence J, Leyva J（2006） Randomized, controlled, six-month trial of yoga in healthy seniors : effects on cognition and quality of life. Altern Ther Health Med 12 : 40-47

Oken BS, Fonareva I, Haas M, Wahbeh H, Lane JB, Zajdel D, Amen A（2010） Pilot controlled trial of mindfulness meditation and education for dementia caregivers. J Altern Complement Med 16 : 1031-1038

Olsen C, Pedersen I, Bergland A, Enders-Slegers MJ, Ihlebæk C（2016） Effect of animal-assisted activity on balance and quality of life in home-dwelling persons with dementia. Geriatr Nurs 37 : 284-291

Olsen C, Pedersen I, Bergland A, Enders-Slegers MJ, Patil G, Ihlebaek C（2016） Effect of animal-assisted interventions on depression, agitation and quality of life in nursing home residents suffering from cognitive impairment or dementia : a cluster randomized controlled trial. Int J Geriatr Psychiatry 31 : 1312-1321

Onder G, Zanetti O, Giacobini E, Frisoni GB, Bartorelli L, Carbone G, Lambertucci P, Silveri MC, Bernabei R（2005） Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease : randomised controlled trial. Br J Psychiatry 187 : 450-455

Optale G, Urgesi C, Busato V, Marin S, Piron L, Priftis K, Gamberini L, Capodieci S, Bordin A（2010） Controlling memory impairment in elderly adults using virtual reality memory training : a randomized controlled pilot study. Neurorehabil Neural Repair 24 : 348-357

O'Shea E, Devane D, Cooney A, Casey D, Jordan F, Hunter A, Murphy E, Newell J, Connolly S, Murphy K（2014） The impact of reminiscence on the quality of life of residents with dementia in long-stay care. Int J Geriatr Psychiatry 29 : 1062-1070

París AP, Saleta HG, de la Cruz Crespo Maraver M, Silvestre E, Freixa MG, Torrellas CP, Pont SA, Nadal MF, Garcia SA, Bartolomé MV, Fernández VL, Bayés AR（2011） Blind randomized controlled study of the efficacy of cognitive training in Parkinson's disease. Mov Disord 26 : 1251-1258

Petrelli A, Kaesberg S, Barbe MT, Timmermann L, Fink GR, Kessler J, Kalbe E（2014） Effects of cognitive training in Parkinson's disease : a randomized controlled trial. Parkinsonism Relat Disord 20 : 1196-1202

Piccolini C, Amadio L, Spazzafumo L, Moroni S, Freddi A（1992） The effects of a rehabilitation program with mnemotechniques on the institutionalized elderly subject. Arch Gerontol Geriatr 15 : 141-149

Pivi GA, da Silva RV, Juliano Y, Novo NF, Okamoto IH, Brant CQ, Bertolucci PH（2011） A prospective study of nutrition education and oral nutritional supplementation in patients with Alzheimer's disease. Nutr J 10 : 98

Proctor R, Burns A, Powell HS, Tarrier N, Faragher B, Richardson G, Davies L, South B（1999） Behavioural management in nursing and residential homes : a randomised controlled trial. Lancet 354 : 26-29

Quayhagen MP, Quayhagen M, Corbeil RR, Roth PA, Rodgers JA（1995） A dyadic remediation program for care recipients with dementia. Nurs Res 44 : 153-159

Quayhagen MP, Quayhagen M, Corbeil RR, Hendrix RC, Jackson JE, Snyder L, Bower D（2000） Coping with dementia : evaluation of four nonpharmacologic interventions. Int Psychogeriatr 12 : 249-265

Raglio A, Bellelli G, Traficante D, Gianotti M, Ubezio MC, Gentile S, Villani D, Trabucchi M（2010） Efficacy of music therapy treatment based on cycles of sessions : a randomised controlled trial. Aging Ment Health 14 : 900-904

Raglio A, Bellandi D, Baiardi P, Gianotti M, Ubezio MC, Zanacchi E, Granieri E, Imbriani M, Stramba-Badiale M（2015） Effect of active music therapy and individualized listening to music on dementia : a multicenter randomized controlled trial. J Am Geriatr Soc 63 : 1534-1539

Raglio A, Oasi O, Gianotti M, Manzoni V, Bolis S, Ubezio MC, Gentile S, Villani D, Stramba-Badiale M（2010） Effects of music therapy on psychological symptoms and heart rate variability in patients with dementia. a pilot study. Curr Aging Sci 3 : 242-246

Rapp S, Brenes G, Marsh AP（2002） Memory enhancement training for older adults with mild cognitive impairment : a preliminary study. Aging Ment Health 6 : 5-11

Rasmusson DX, Rebok GW, Bylsma FW, Brandt J（1999） Effects of three types of memory training in normal elderly. Aging Neuropsychol Cogn 6 : 56-66

Requena C, Maestú F, Campo P, Fernández A, Ortiz T（2006） Effects of cholinergic drugs and cognitive training on dementia : 2-year follow-up. Dement Geriatr Cogn Disord 22 : 339-345

Richards KC, Beck C, O'Sullivan PS, Shue VM（2005） Effect of individualized social activity on sleep in nursing home residents with dementia. J Am Geriatr Soc 53 : 1510-1517

Ridder HM, Stige B, Qvale LG, Gold C（2013） Individual music therapy for agitation in dementia : an exploratory ran-

domized controlled trial. Aging Ment Health 17 : 667-678

Robb SS, Stegman CE, Wolanin MO (1986) No research versus research with compromised results : a study of validation therapy. Nurs Res 35 : 113-118

Rolland Y, Pillard F, Klapouszczak A, Reynish E, Thomas D, Andrieu S, Rivière D, Vellas B (2007) Exercise program for nursing home residents with Alzheimer's disease : a 1-year randomized, controlled trial. J Am Geriatr Soc 55 : 158-165

Rozzini L, Costardi D, Chilovi BV, Franzoni S, Trabucchi M, Padovani A (2007) Efficacy of cognitive rehabilitation in patients with mild cognitive impairment treated with cholinesterase inhibitors. Int J Geriatr Psychiatry 22 : 356-360

Rusted J, Sheppard L, Waller D (2006) A multi-centre randomized control group trial on the use of art therapy for older people with dementia. Group Analysis 39 : 517-536

Sakamoto M, Ando H, Tsutou A (2013) Comparing the effects of different individualized music interventions for elderly individuals with severe dementia. Int Psychogeriatr 25 : 775-784

Santana-Sosa E, Barriopedro MI, López-Mojares LM, Pérez M, Lucia A (2008) Exercise training is beneficial for Alzheimer's patients. Int J Sports Med 29 : 845-850

Särkämö T, Tervaniemi M, Laitinen S, Numminen A, Kurki M, Johnson JK, Rantanen P (2014) Cognitive, emotional, and social benefits of regular musical activities in early dementia : randomized controlled study. Gerontologist 54 : 634-650

Serino S, Pedroli E, Tuena C, De Leo G, Stramba-Badiale M, Goulene K, Mariotti NG, Riva G (2017) A novel virtual reality-based training protocol for the enhancement of the "mental frame syncing" in individuals with Alzheimer's disease : a development-of-concept trial. Front Aging Neurosci 9 : 240

Serrani Azcurra DJ (2012) A reminiscence program intervention to improve the quality of life of long-term care residents with Alzheimer's disease : a randomized controlled trial. Braz J Psychiatry 34 : 422-433

Shatil E (2013) Does combined cognitive training and physical activity training enhance cognitive abilities more than either alone? A four-condition randomized controlled trial among healthy older adults. Front Aging Neurosci 5 : 8

Simmons SF, Zhuo X, Keeler E (2010) Cost-effectiveness of nutrition interventions in nursing home residents : a pilot intervention. J Nutr Health Aging 14 : 367-372

Spector A, Thorgrimsen L, Woods B, Royan L, Davies S, Butterworth M, Orrell M (2003) Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia : randomised controlled trial. Br J Psychiatry 183 : 248-254

Spector A, Orrell M, Davies S, Woods B (2010) Can reality orientation be rehabilitated? Development and piloting of an evidence-based programme of cognition-based therapies for people with dementia. Neuropsychol Rehabil 11 : 377-397

Stanley MA, Calleo J, Bush AL, Wilson N, Snow AL, Kraus-Schuman C, Paukert AL, Petersen NJ, Brenes GA, Schulz PE, Williams SP, Kunik ME (2013) The peaceful mind program : a pilot test of a cognitive-behavioral therapy-based intervention for anxious patients with dementia. Am J Geriatr Psychiatry 21 : 696-708

Steffen AM (2000) Anger management for dementia caregivers : a preliminary study using video and telephone interventions. Behav Ther 31 : 281-299

Steinberg M, Leoutsakos JM, Podewils LJ, Lyketsos CG (2009) Evaluation of a home-based exercise program in the treatment of Alzheimer's disease : the Maximizing Independence in Dementia (MIND) study. Int J Geriatr Psychiatry 24 : 680-685

Stevens J, Killeen M (2006) A randomised controlled trial testing the impact of exercise on cognitive symptoms and disability of residents with dementia. Contemp Nurse 21 : 32-40

Subramaniam P, Woods B, Whitaker C (2014) Life review and life story books for people with mild to moderate dementia : a randomised controlled trial. Aging Ment Health 18 : 363-375

Sung HC, Lee WL, Li TL, Watson R (2012) A group music intervention using percussion instruments with familiar music to reduce anxiety and agitation of institutionalized older adults with dementia. Int J Geriatr Psychiatry 27 : 621-627

Svansdottir HB, Snaedal J (2006) Music therapy in moderate and severe dementia of Alzheimer's type : a case-control study. Int Psychogeriatr 18 : 613-621

Tadaka E, Kanagawa K (2007) Effects of reminiscence group in elderly people with Alzheimer disease and vascular dementia in a community setting. Geriatr Gerontol Int 7 : 167-173

Teri L, Gibbons LE, McCurry SM, Logsdon RG, Buchner DM, Barlow WE, Kukull WA, LaCroix AZ, McCormick W, Larson EB (2003) Exercise plus behavioral management in patients with Alzheimer disease : a randomized controlled trial. JAMA 290 : 2015-2022

Teri L, Huda P, Gibbons L, Young H, van Leynseele J (2005)

STAR : a dementia-specific training program for staff in assisted living residences. Gerontologist 45 : 686-693

Teri L, McCurry SM, Logsdon R, Gibbons LE (2005) Training community consultants to help family members improve dementia care : a randomized controlled trial. Gerontologist 45 : 802-811

Thivierge S, Jean L, Simard M (2014) A randomized cross-over controlled study on cognitive rehabilitation of instrumental activities of daily living in Alzheimer disease. Am J Geriatr Psychiatry 22 : 1188-1199

Thodberg K, Sørensen LU, Videbech PB, Poulsen PH, Damgaard V, Keseler I, Edwards D, Christensen JW (2016) Behavioral responses of nursing home residents to visits from a person with a dog, a robot seal or a toy cat. Anthrozoös 29 : 107-121

Thorgrimsen L, Schweitzer P, Orrell M (2002) Evaluating reminiscence for people with dementia : a pilot study. Arts in Psychotherapy

Thornley J, Hirjee H, Vasudev A (2016) Music therapy in patients with dementia and behavioral disturbance on an inpatient psychiatry unit : results from a pilot randomized controlled study. Int Psychogeriatr 28 : 869-871

Tibaldi V, Aimonino N, Ponzetto M, Stasi MF, Amati D, Raspo S, Roglia D, Molaschi M, Fabris F (2004) A randomized controlled trial of a home hospital intervention for frail elderly demented patients : behavioral disturbances and caregiver's stress. Arch Gerontol Geriatr Suppl 9 : 431-436

Toseland R, Diehl M, Freeman K, Manzanares T, Naleppa M, Mccallion P (1997) The impact of validation group therapy on nursing home residents with dementia. J Appl Gerontol 16 : 31-50

Trebbastoni A, Imbriano L, Podda L, Rendace L, Sacchetti ML, Campanelli A, D'Antonio F, de Lena C (2018) Cognitive training in patients with Alzheimer's disease : Findings of a 12-month randomized controlled trial. Curr Alzheimer Res 15 : 452-461

Tremont G, Davis JD, Papandonatos GD, Ott BR, Fortinsky RH, Gozalo P, Yue MS, Bryant K, Grover C, Bishop DS (2015) Psychosocial telephone intervention for dementia caregivers : a randomized, controlled trial. Alzheimers Dement 11 : 541-548

Valentí Soler M, Agüera-Ortiz L, Olazarán Rodríguez J, Mendoza Rebolledo C, Pérez Muñoz A, Rodríguez Pérez I, Osa Ruiz E, Barrios Sánchez A, Herrero Cano V, Carrasco Chillón L, Felipe Ruiz S, López Alvarez J, León Salas B, Cañas Plaza JM, Martín Rico F, Abella Dago G, Martínez Martín P (2015) Social robots in advanced dementia. Front Aging Neurosci 7 : 133

Valentijn SA, van Hooren SA, Bosma H, Touw DM, Jolles J, van Boxtel MP, Ponds RW (2005) The effect of two types of memory training on subjective and objective memory performance in healthy individuals aged 55 years and older : a randomized controlled trial. Patient Educ Couns 57 : 106-114

Van Bogaert P, Tolson D, Eerlingen R, Carvers D, Wouters K, Paque K, Timmermans O, Dilles T, Engelborghs S (2016) SolCos model-based individual reminiscence for older adults with mild to moderate dementia in nursing homes : a randomized controlled intervention study. J Psychiatr Ment Health Nurs 23 : 568-575

Van de Winckel A, Feys H, De Weerdt W, Dom R (2004) Cognitive and behavioural effects of music-based exercises in patients with dementia. Clin Rehabil 18 : 253-260

Van der Ploeg ES, Eppingstall B, Camp CJ, Runci SJ, Taffe J, O'Connor DW (2013) A randomized crossover trial to study the effect of personalized, one-to-one interaction using Montessori-based activities on agitation, affect, and engagement in nursing home residents with Dementia. Int Psychogeriatr 25 : 565-575

Van Haitsma KS, Curyto K, Abbott KM, Towsley GL, Spector A, Kleban M (2015) A randomized controlled trial for an individualized positive psychosocial intervention for the affective and behavioral symptoms of dementia in nursing home residents. J Gerontol B Psychol Sci Soc Sci 70 : 35-45

Van het Reve E, de Bruin ED (2014) Strength-balance supplemented with computerized cognitive training to improve dual task gait and divided attention in older adults : a multicenter randomized-controlled trial. BMC Geriatr 14 : 134

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 26 : 381-388

Vidovich MR, Lautenschlager NT, Flicker L, Clare L, McCaul K, Almeida OP (2015) The PACE study : a randomized clinical trial of cognitive activity strategy training for older people with mild cognitive impairment. Am J Geriatr Psychiatry 23 : 360-372

Vink AC, Zuidersma M, Boersma F, de Jonge P, Zuidema SU, Slaets JP (2013) The effect of music therapy compared with general recreational activities in reducing agitation in people with dementia : a randomised controlled trial. Int J Geriatr

Psychiatry 28 : 1031-1038

Vreugdenhil A, Cannell J, Davies A, Razay G (2012) A community-based exercise programme to improve functional ability in people with Alzheimer's disease : a randomized controlled trial. Scand J Caring Sci 26 : 12-19

Wallis GG, Baldwin M, Higginbotham P (1983) Reality orientation therapy — a controlled trial. Br J Med Psychol 56 : 271-277

Wenborn J, Challis D, Head J, Miranda-Castillo C, Popham C, Thakur R, Illes J, Orrell M (2013) Providing activity for people with dementia in care homes : a cluster randomised controlled trial. Int J Geriatr Psychiatry 28 : 1296-1304

Whitebird RR, Kreitzer M, Crain AL, Lewis BA, Hanson LR, Enstad CJ (2013) Mindfulness-based stress reduction for family caregivers : a randomized controlled trial. Gerontologist 53 : 676-686

Williams CL, Tappen RM (2008) Exercise training for depressed older adults with Alzheimer's disease. Aging Ment Health 12 : 72-80

Winter L, Gitlin LN (2006) Evaluation of a telephone-based support group intervention for female caregivers of community-dwelling individuals with dementia. Am J Alzheimers Dis Other Demen 21 : 391-397

Woods RT, Bruce E, Edwards RT, Elvish R, Hoare Z, Hounsome B, Keady J, Moniz-Cook ED, Orgeta V, Orrell M, Rees J, Russell IT (2012) REMCARE : reminiscence groups for people with dementia and their family caregivers-effectiveness and cost-effectiveness pragmatic multicentre randomised trial. Health Technol Assess 16 : 1-116

Woods RT (1979) Reality orientation and staff attention : a controlled study. Br J Psychiatry 134 : 502-507

Wu HS, Lin LC, Su SC, Wu SC (2014) The effects of spaced retrieval combined with errorless learning in institutionalized elders with dementia : recall performance, cognitive status, and food intake. Alzheimer Dis Assoc Disord 28 : 333-339

Yamagami T, Takayama Y, Maki Y, Yamaguchi H (2012) A randomized controlled trial of brain-activating rehabilitation for elderly participants with dementia in residential care homes. Dement Geriatr Cogn Dis Extra 2 : 372-380

Zisselman MH, Rovner BW, Shmuely Y, Ferrie P (1996) A pet therapy intervention with geriatric psychiatry inpatients. Am J Occup Ther 50 : 47-51

Study designs and statistical analyses in randomized controlled trials of non-pharmacological preventive and therapeutic interventions for dementia continuum : A statistical review

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Background : Various systematic reviews of non-pharmacological interventions involving the target population of normal cognition, mild cognitive impairment (MCI), dementia, or caregivers of patients with dementia have attempted to synthesize the effects of interventions ; however, the variations in study designs and the low quality of clinical trial methodology are barriers to deriving reliable conclusions.

Aim : We comprehensively investigated the study designs and statistical analyses used in randomized controlled trials (RCTs) of non-pharmacological preventive or therapeutic interventions for the four target populations, offering common practical recommendations for designing RCTs on non-pharmacological interventions.

Results : We reviewed 200 RCTs (31 on normal cognition, 19 on MCI, 126 on dementia, 22 on caregivers, and 2 on mixed populations). In each target population, >70% of the trials had a follow-up period ≤ 6 months. About 50% of the studies on normal cognition or caregivers had a sample size of >100, while 50% of the studies on people with MCI or dementia had a sample size of ≤ 50. Only 20-25% of studies in each target population performed a power analysis.

Conclusions : Based on the findings of this review, we offer suggestions for future consideration when planning and conducting RCTs on nonpharmacological interventions.

Keywords : Randomized controlled trial ; dementia ; non-pharmacological interventions ; systematic review

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