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*Research Article*

# Cognitive Training for People with Mild to Moderate Dementia: A Systematic Review and Meta-Analysis of Cognitive Effects

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## Abstract

**Objectives:** To assess the cognitive training effectiveness on cognitive results in adults with a diagnosis of dementia and a mild-moderate level of severity. **Method:** We developed specific search strategies for Ovid MEDLINE and EMBASE, among other databases. We included randomized controlled trials published in any language. Two independent reviewers performed the study selection and the extraction of the relevant data and assessed the risk of bias using the Cochrane Collaboration's Risk of Bias tool. A random-effects model meta-analysis of changes from baseline using standardized mean differences (SMD) was conducted. Subgroup analyses were performed. The GRADEPro tool was used to assess the quality of the evidence. **Results:** 18 trials were included with a total of 1483 patients. The meta-analyses revealed that cognitive training, compared to a control group, may have large positive effects at end of treatment on overall cognitive function (SMD: 0.92; 95% CI 95% 0.35 to 1.48) and on delayed memory and language fluency in patients with mild-moderate dementia, as well as a more discrete positive effect on semantic (low-quality evidence). Moderate-quality evidence showed that cognitive training could have a moderate positive effect on the immediate memory (SMD: 0.69, 95% CI 0.42 to 0.97) and, in the medium term, on verbal fluency. Cognitive training may also be associated with a significant slower clinical progression of dementia (low-quality evidence). **Conclusions:** Cognitive training may be effective at improving overall cognitive function, memory and cognitive impairment progression in patients with mild to moderate dementia. Additional long-term follow-up research is needed.

***Keywords:*** *cognitive training, dementia, effectiveness, systematic review, meta-analysis, memory*

## Introduction

Dementia, a group of disorders characterized by cognitive impairment that affects one or more cognitive domains, is a major cause of disability and dependence among older people worldwide, with very important morbidity and mortality associated [1]. Dementia interferes with patient daily function and independence and causes anxiety and frustration, having a significant impact not only on individuals but also on their caregivers, families, communities and societies. This personal and social impact is not negligible since, in 2015, dementia affected 47 million people worldwide and recent estimations show nearly 9,9 million new cases every year; a figure that is predicted to increase to 75 million in 2030 and 132 million by 2050 [2].

In patients with the milder stages of dementia, the interventions designed to improve cognitive functioning and memory problems can potentially minimise the risk of excess disability and may allow the person greater independence. Although no cure is yet available for any of the irreversible causes of dementia, several treatments have been proposed for slowing cognitive symptoms progression, improving the patient's quality of life, and delaying the need for specialized care. The treatments for dementia can be pharmacological, non-pharmacological, or both. Currently, drugs such as cholinesterase inhibitors and memantine provide limited benefits, so there is a growing interest in non-

pharmacological treatments for patients with dementia [3-5]. Several types of non-pharmacological interventions focused on cognitive function have been described in people with dementia. Although there is considerable inconsistency in the terminology used in the literature about the types of cognitive interventions, they arise from different disciplines and aim very different objectives. So, these interventions can be classified into three broad categories [4,6]: cognitive stimulation (group approach emphasising on social interaction and aim for general improvement in cognitive function), cognitive rehabilitation (approach with individualised goals aimed to improve everyday function and activities of daily living) [7,8] and cognitive training.

Cognitive training traditionally involves the repeated practice of a set of standardized and guided tasks, delivered mainly in paper and pencil or computer, designed to train individuals on relatively well-defined particular cognitive areas such as memory, attention or executive functions [3,7,9]. In line with the principles of neuroplasticity and cognitive remediation therapy [10], this intervention is based on the hypothesis that the repetition of a set of standardized cognitive tasks with increasing levels of difficulty could promote synaptic growth and repair processes [11] improving or preserving functional capacity in the area being trained beyond the immediate context of the training session. Cognitive training may be presented in various formats and settings such as outpatient consultations, hospital facilities or even the patient's home, as well as in individual or group sessions.

The potential advantages of cognitive function training have been studied for years, especially in healthy elderly [12,13] and in people with mild cognitive impairment [9]. However, and although in recent years there has been an increase in scientific interest in this intervention [8,14,15], the effects of cognitive training in people with mild to moderate dementia diagnosis according to standardised criteria remain unclear. Therefore, the aim of this systematic review and meta-analysis is to assess the cognitive training effectiveness for cognitive results in adult patients with a well-established diagnosis of dementia and a mild to moderate level of severity.

## Materials and Methods

The current study was conducted and reported according to the PRISMA standards for systematic reviews and meta-analyses [16]. This review was not registered, and no published review protocol exists, although methods and eligibility criteria were specified in advance and collected according to the protocol.

### Search and study selection

The search strategies were developed according to the PICO format using free and controlled terminology to identify relevant studies. We search the following electronic databases until October 2018: Ovid MEDLINE (R), EMBASE (Evidence-Based Medicine), Cochrane Central Register of Controlled Trials (CENTRAL), International Clinical Trials Registry Platform (ICTRP) Search Portal (which includes ClinicalTrials.gov plus other records) and ClinicalTrials.gov. The article type was restricted to RCT, but no limits were applied for publication dates or language. Details of the search strategies are presented in Supplementary Table 1. In addition, the reference lists of identified studies were manually reviewed for additional potentially relevant studies and the authors were contacted in case of identifying unpublished data. References identified were imported into Covidence software (www.covidence.org) [17] where duplicate references were identified and removed.

Two reviewers independently (JEML and JMM) filtered titles and abstracts according to the eligibility criteria. Afterward, the full-text articles of potentially relevant studies and those whose inclusion was doubtful were obtained to verify that explicitly met the inclusion/exclusion criteria.

**Table 1.** Characteristics of included studies (n=18)

| Study demographics | | | | | | | | Intervention design | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study, Year** | **Study Group** | **N** | **Mean Age (DE)** | **Male (Female)** | **Educational level (years), mean (DE)** | **Medications for dementia** | **Baseline MMSE score, mean (DE)** | **Length (weeks)** | **Sessions/ week** | **Format and delivery** | **Trainer** |
| Amieva, 2016 | Cognitive training | 170 | 78.5 (7.2) | 69 (99) | Primary school 59 (34.7%); secondary school 50(29.4%); baccalaureate and more 40(23.5%) | 152 (89.4%) | 21.5 (3.2) | 96 | 1 during the first 3 months and 1 every 6 weeks (for the next 21 months) | Paper and pencil, individual | Psychologists and medical staff |
| | Reminiscence therapy | 172 | 78.8 (6.9) | 61 (108) | Primary school 58 (33.7%); secondary school 53(30.8%); baccalaureate and more 42 (26.8%) | 155 (90.1%) | 21.1 (3.1) | 96 | 1 during the first 3 months and 1 every 6 weeks (for the next 21 months) | Paper and pencil, individual | NR |
| | Individualized cognitive rehabilitation | 157 | 78.9 (6.2) | 64 (92) | Primary school 56 (35.7%); secondary school 42(26.8%); baccalaureate and more 30 (19.1%) | 136 (86.6%) | 21.6 (3.0) | 96 | 1 during the first 3 months and 1 every 6 weeks (for the next 21 months) | Paper and pencil, individual | Psychologist |
| | Control (usual care) | 154 | 78.7 (6.5) | 63 (90) | Primary school 51 (33.1%); secondary school 45(29.2%); baccalaureate and more 32 (20.8%) | 133 (86.4%) | 21.6 (3.3) | NR | NR | NR | NR |
| Barban, 2016 | Training-rest | 42 | 76.7 (5.7) | 13 (29) | 8.8 (3.6) | NR | 23.4 (1.9) | 12 | 2 | Computerized (SOCIABLE) in small groups | Trained cognitive therapist |
| | Rest-training | 39 | 76.9 (5.7) | 11 (28) | 9.2 (3.7) | NR | 23.4 (1.7) | 12 | NR | NR | NR |
| Bergamaschi, 2013 | Cognitive training | 16 | 78.2 (5.50) | NR | 7.25 (3.24) | NR | 20.25 (2.95) | 20 | 5 | Paper and pencil tasks, in small-4 patients group | Expert neuropsychologist |
| | Control | 16 | 77.7 (5.06) | NR | 5.61 (2.30) | NR | 21.94 (2.01) | 20 | NR | Daily multiple sessions of non-specific cognitive activities at Day Centre | NR |
| Fernandez-Calvo, 2011 | EABB | 15 | 75.8 (4.27) | 9 (6) | 7.46 (1.84) | NR | 19.33 (2.48) | 12 | 3 | Computerized games, Individual | Occupational therapist and psychologist |
| | EAPI | 15 | 75.6 (4.55) | 8 (7) | 8.40 (2.77) | NR | 20.00 (2.92) | 12 | 3 | NR | NR |
| | Waiting list (Control) | 15 | 75.87 (4.15) | 8 (7) | 7.26 (3.34) | NR | 20.44 (1.90) | 12 | NA | NA | NA |
| Galante, 2007 | Cognitive training | 7 | NR | NR | NR | NR | 22.9 (3.1) | 4 | 3 | Computerized exercises, individually | Neuropsychologist |
| | Control | 4 | NR | NR | NR | NR | 23.1 (1.8) | 4 | 3 | Semi-structured interview | Neuropsychologist |
| Giovagnoli, 2017 | Cognitive training | 13 | 71.7 (7.88) | 3 (10) | 6.92 (2.46) | NR | 23.62 (1.94) | 12 | 2 | NR | Neuropsychologist |
| | Active music therapy | 13 | 73.9 (7.74) | 7 (6) | 10.46 (5.3) | NR | 22.85 (6.28) | 12 | 2 | Rhythmical and melodic instruments | Music therapist |
| | Neuroeducation (control) | 13 | 75.3 (5.56) | 5 (8) | 7.31 (4.01) | NR | 21.15 (3.48) | 12 | 2 | Interview | Neurology |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Heiss, 1993 | Cognitive training | 18 | 65.9 (6.28) | 9 (9) | NR | NR | 20.55 (4.42) | 24 | 2 | Computerized and individual tasks | NR |
| | Cognitive training + Pyritinol 600 mg twice daily | 17 | 67.2 (8.51) | 8 (9) | NR | NR | 21.64 (4.55) | 24 | 2 | Computerized and individual tasks | NR |
| | Cognitive training + phosphatidylserine 200 mg twice daily | 18 | 66.7 (6.93) | 10 (8) | NR | NR | 20.88 (4.73) | 24 | 2 | Computerized and individual tasks | NR |
| | Control | 17 | 66.6 (10.17) | 10(7) | NR | NR | 20.23 (4.10) | 24 | 2 | Conversations | NR |
| Huntley, 2017 | Cognitive training | 15 | 79.4 (6.19) | 9 (6) | 12.33 (2.94) | NR | 26.00 (2.30) | 8 | NR | Computerized and paper and pencil, individually | NR |
| | Control (active) | 15 | 80.1 (5.19) | 9 (6) | 12.57 (2.82) | NR | 25.93 (2.09) | 8 | NR | NR | NR |
| Jelcic, 2012 | LSS | 20 | 82.9 (3.6) | 2 (18) | 6.7 (2.9) | NR | 24.4 (2.8) | 12 | 2 | Paper and pencil in groups | Neuropsychologist |
| | UCS | 20 | 81.8 (5.5) | 5 (15) | 8.25 (3.6) | NR | 25 (2.6) | 12 | 2 | NA | Neuropsychologist |
| Jelcic, 2014 | LSS-tele | 7 | 86.0 (-5.1) | 2 (5) | 6 (3.5) | NR | 23.7 (2.8) | 12 | 2 | Remote control based on telecommunications in small groups (3-4 participants) | Experienced neuropsychologist |
| | LSS-direct | 10 | 82.7 (-6) | 3 (7) | 6.7 (3.3) | NR | 24.9 (2.5) | 12 | 2 | Paper and pencil in small groups (3-4 participants) | Experienced neuropsychologist |
| | Control | 10 | 82.3 (5.9) | 1 (9) | 8.7 (3.7) | NR | 24.8 (2.7) | 12 | 2 | Face to face exercises | Experienced neuropsychologist |
| Kallio, 2018 | Cognitive training | 76 | 82.6 (5.5) | 26 (50) | 32 (<8 Years) | 60 (33% taking anticholinergics) | 21.00 (4.3) | 12 | 2 | Paper and pencil tasks in group / individual | Experienced neuropsychologist |
| | Control | 71 | 83.6 (5.4) | 15 (56) | 36 (<8 Years) | 62 (37% taking anticholinergics) | 19.90 (3.9) | NR | NR | NR | NR |
| Lee, 2013 | TELP | 6 | NR | 3 (3) | Nil 16.7%; <2 years 16.7%; 3-6 years 33.2%; Secondary 16.7%; University 16.7% | NR | 17.0 (3.5) | 6 | 2 | Computerized with a touch pen input device, individually | Experienced Occupational therapists |
| | CELP | 7 | NR | 1 (6) | Nil 42.8%; <2 years 14.3%; 3-6 years 28.6%; Secondary 14.3%; University 0% | NR | 15.3 (2.7) | 6 | 2 | Training manual, paper and pencil | Experienced Occupational therapists |
| | Waiting list (Control) | 6 | NR | 2 (4) | Nil 33.3%; <2 years 16.7%; 3-6 years 16.7%; Secondary 33.3%; University 0% | NR | 17.6 (4.7) | 6 | 2 | Games | NR |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mapelli, 2013 | Cognitive stimulation | 10 | 82.6 (4.85) | NR | 4.6 (1.5) | NR | 20.1 (4.2) | 8 | 5 | Paper and pencil exercises in groups | Therapist not specified |
| | Placebo (occupational therapy) | 10 | 84.5 (5.06) | NR | 4.3 (1.82) | NR | 19.7 (3.8) | 8 | 5 | Different activities | Therapist not specified |
| | Control | 10 | 84.7 (4.42) | NR | 4.0 (1.15) | NR | 18.8 (2.68) | NR | NR | NR | Therapist not specified |
| Nousia, 2018 | Cognitive training | 25 | 76.2 (5.14) | 9 (16) | 8.08 (3.01) | NR | NR | 15 | 2 | Paper and pencil and computer-based, individually | Individual therapist |
| | Control | 25 | 76.3 (5.38) | 5 (20) | 8.92 (2.83) | NR | NR | 15 | NR | Usual standard clinical care | NR |
| Quayhagen, 1995 | Cognitive stimulation | 25 | NR | NR | NR | NR | 109.8 (12.0) DRS | 12 | 6 | Paper and pencil, individually | NR |
| | Placebo (passive cognitive stimulation) | 28 | NR | NR | NR | NR | 110.0 (12.2) DRS | 12 | NR | Paper and pencil, individually | NR |
| | Waiting list (passive control) | 25 | NR | NR | NR | NR | 109.2 (11.7) DRS | NR | NR | NR | NR |
| Silva, 2017 | Memo + | 17 | 71.7 (5.15) | NR | 5.18 (3.68) | NR | 21.53 (3.01) | 6 | 2 | Computerized, individually | Neuropsychologist |
| | Sense Cam | 17 | 75.4 (5.26) | NR | 4.76 (3.47) | NR | 21.88 (3.33) | 6 | 2 | Paper and pencil exercises, individually | Neuropsychologist |
| | Diary (control) | 17 | 73.82 (5.74) | NR | 6.76 (4.63) | NR | 22.82 (1.85) | 6 | 2 | Paper and pencil exercises, individually | NR |
| Trebbastoni, 2018 | Cognitive training | 45 | 74.2 (6.97) | 19 (23) | 8.64 (4.21) | 2% memantine 20 mg; 78% AChEIs; 27% Donezepil 5 mg; 24% Donezepil 10 mg; 7% Rivastigmine 4.6 mg; 20% Rivastigmine 9.5 mg | 22.20 (2.37) | 24 | 2 | Paper and pencil, in group | Experienced neuropsychologist |
| | Control | 85 | 6.0 (6.46) | 33 (7) | 8.40 (4.12) | 2% Memantine 20 mg; 88% AChEIs; 40% Donezepil 5 mg; 18% Donezepil 10 mg; 12% Rivastigmine 4.6 mg; 20% Rivastigmine 9.5 mg | 22.89 (2.72) | NR | NR | NR | Experienced neuropsychologist |
| Tsantali, 2017 | Cognitive training | 17 | 73.4 (5.7) | NR | 9.9 (4.2) | NR | 23.2 (1.6) | 16 | 3 | Pencil and paper tasks, individualized | Licensed psychologists with sufficient clinical experience |
| | Cognitive stimulation | 17 | 73.3 (4.9) | NR | 9.8 (4.0) | NR | 22.5 (0.9) | 16 | 3 | NR | Licensed psychologists with sufficient clinical experience |
| | Control | 21 | 74.2 (5.6) | NR | 9.5 (4.1) | NR | 23.1 (1.4) | 16 | NA | NR | NR |

NR: Not Reported; NA: Not Applicable

## Eligibility criteria

### *Study population*

Eligible studies had to include adult patients with a medical diagnosis of any subtype of dementia. Diagnosis of dementia should be based on established clinical or research diagnostic criteria, including any published version until October 2018 of following classifications: the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV/V), the International Classification of Diseases (ICD), the National Institute of Neurological and Communicative Disorders Alzheimer´s Disease and Related Disorders Association (NINCDS-ADRDA, including the criteria defined by the National Institute on aging-Alzheimer's Association Workgroups on diagnostic guidelines for Alzheimer´s disease-NIA-AA) or the National Institute of Neurological Disorders and Stroke and Association International and pour la Recherché et l´Énseignement en Neurosciences (NINDS-AIREN). In addition, participants included should have a level of severity of dementia between mild to moderate. Dementia severity was determined from inclusion criteria in primary trials according to ranges of scores on a standardised scale, such as scores of 3-5 points on Global Dementia Score (GDS), Mini-Mental State Examination (MMSE)>14 or Clinical Dementia Rating (CDR) between 0.5 and 1) [18].

### *Types of interventions*

Eligible studies had to analyze the results of cognitive training repeatedly over time and with a follow-up of, at least, one month. The intervention could be carried out individually or in group sessions, administered on pencil and paper or through computerised exercises and applied in any context, both face-to-face (outpatient, day hospitals, residences) and non-face-to-face or home-based (use of digital platforms). Any form of control group was permissible, including groups receiving active control (placebo), waiting list or standard treatment (clinic consultations, medication, contact with a community mental health team or day-care or support from voluntary organizations). Studies in which cognitive training was combined with another different cognitive or experimental intervention (i.e., brain stimulation or physical activity) were excluded.

### *Outcomes*

We included studies analysing outcomes connected with cognitive functions, including overall cognitive function, cognitive impairment progression and specific function for each cognitive domain such as memory, attention, language, executive function, processing speed, verbal fluency and visual-spatial ability, all of them based on standardized instruments. Short-term as well as long-term data were considered for our review. All of them were measured at end of treatment (considered as the first post-intervention assessment) and in the medium term (3 to 12 months post-intervention).

### *Study design*

Eligible studies were randomized controlled trials (RCTs) (including cross-over design), in any language.

## Data extraction

All relevant data from each included trial were independently extracted by two reviewers (JEML and JMM) with the help of standardized and specifically designed data entry form at Covidence software. Data extracted included detailed characteristics of provided interventions (training program, group sizes, duration and frequency of intervention, etc), sample characteristics (sample size, country, age, gender, education, etc), data on any side effects as well as cognitive and non-cognitive outcomes and significant findings (time points of measurement, drop-outs, significant findings, etc). When data could not be extracted from study reports, we contacted the authors requesting summary data. Subsequently, all extracted data were exported to RevMan v.5.3 for further analysis.

### Risk of bias assessment

Risk of bias in individual studies was assessed using the Cochrane Collaboration's Risk of Bias tool for clinical trials [19] and the studies were judged with "low risk", "high risk" or "undetermined risk". The ratings were done independently by two reviewers (JEML and JMM) who discussed the disagreements together.

### Data analysis and quality of evidence

Whenever data were available, a random-effects meta-analysis was conducted in RevMan v.5.3 for Windows program for each outcome. We used mean differences (MDs) with 95% CIs of post-training change between cognitive training and control groups whenever studies used the same outcome measure, whereas we used standardised mean differences (SMDs) when the same outcome was assessed by different measures. In cases where the standard deviation for difference was not available, it was calculated from the baseline and post-treatment group, means and standard deviation, assuming a 0.8 correlation coefficient between the measurements at the baseline and follow-up time points [20,21]. Effects were interpreted using Cohen´s convention [22] as 0.2 compromised a small effect, 0.5 comprised a moderate effect size, and 0.8 comprised a large effect size. For analysis of multiple arm studies in which more than one experimental group was compared, we combined data from all conditions that we judged to fit our definition of cognitive training into a single group using a formula [23]. When the trial included more than one control group (i.e., standard treatment and placebo), we used in the analysis data from both control conditions by splitting the sample size of the experimental group into two separate groups [23]. In the case of cross-over trials, we used only data from before cross-over. We chose data, where possible, from validated and published tests for evaluating each outcome and cognitive measures were classified into specific cognitive domains according to manuals on neuropsychological questionnaires [24,25]. In cases with repeated post-intervention assessments separate comparisons were conducted to assess outcomes at end of treatment (i.e., immediately post-intervention), and in medium term (up to 12 months post-intervention). Clinical heterogeneity was assessed by exploring the variability between participants, interventions and outcomes, while $I^2$ value statistic and forest plots visual inspection were used to test statistical heterogeneity between studies [26]. We interpreted the heterogeneity as follows [27]: 0 to 40%: not important/low heterogeneity; 30% to 60%: moderate heterogeneity; 75% to 100%: considerable heterogeneity. Where substantial heterogeneity was detected, we explored the sources of heterogeneity by conducting subgroup analyses and when at least three studies were available for each subgroup, we explored the sources of heterogeneity by performing subgroup analyses. The following moderating factors were included in our analysis plan: type of diagnosis of dementia, dementia severity at baseline, type and the total duration of the cognitive training program. In addition, funnel plots were evaluated through a visual examination for identifying possible publication bias and a sensitivity analysis was applied to determine whether overall effect size was affected by the quality of the included studies.

Moreover, we judged the certainty of the evidence contributing to these outcomes according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria [28,29], and a 'Summary of findings' tables was presented with the GRADEpro software support.

## Results

### Study selection

After 665 duplicate search results were removed, 2239 studies were initially screened for eligibility, of which 1837 were excluded based on title or abstract. Four hundred two full-text articles were considered potentially relevant and were assessed for eligibility, of which 384 met exclusion criteria such as the inclusion of other types of populations or interventions, among other reasons. Finally, 18 RCTs were included in the systematic review (published in 19 articles). Figure 1 shows a PRISMA diagram illustrating the study selection progress.

## Characteristics of included studies

Overall, the 18 studies included in this review encompassed 1483 participants (cognitive training, n= 576, control group, n=457 and other cognitive interventions, n=411). Mean participant age ranged from 65 [30] and 86 years [31], and about 50% of participants were women. Mean schooling years ranged from 4 and 12 years and acetylcholinesterase inhibitors (up to 88%) [32] and anticholinergics (up to 37%) [33] were the pharmacological treatments most commonly used (when this data was reported). Throughout the studies, individuals with different types of dementia and severity were included. Thus, in 16 trials, the only presumed aetiology was Alzheimer's disease, while in two trials [34,35] other aetiologies were also suspected (i.e., vascular dementia, Parkinson's disease, Lewy body dementia, among others). Mean MMSE scores at baseline ranged from 16.6 [36] and 25.9 points (Table 1) [37]. In addition, the type, delivery format and program of cognitive training varied considerably across included studies. In fact, of a total of 21 cognitive training interventions, 17 studies were multidomain cognitive training and 4 single domain training [31,36,37]. Group cognitive training was conducted in 6 of the interventions [31,33,35,36,38-40], while 14 were mainly individual training and 1 was applied in combination (individual and group) [33]. Seven studies [30,31,35,37,41-43] used digital support, 9 studies used conventional format (activities in pencil and paper) and two studies [36,44] used a mixed format (digital and conventional). The duration of cognitive training sessions ranged from 4 weeks [42] to approximately 96 weeks (Table 1) [34].

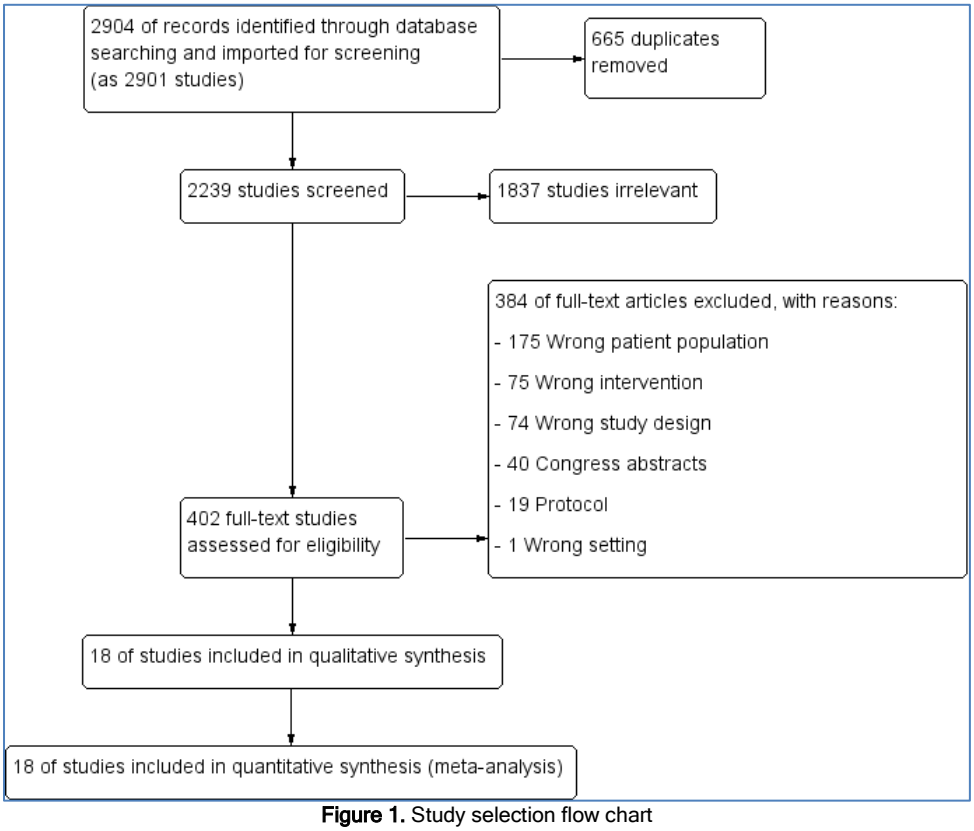


**Figure 1.** Study selection flow chart

## Risk of bias across included studies

The risk of bias assessment of the included RCTs is illustrated in Figure 2. All included studies were described as RCTs, but sequence generation and allocation concealment were insufficiently described in more than 50% of the studies (n=10), leading to unclear risk of selection bias. The vast majority (72.2%) of the studies did not describe in sufficient detail the blinding procedure for participants and personnel, and we considered high risk of performance bias

in 5 studies [30,34,37,39,43]. The risk of blinding of the outcome assessors was considered low for most of the studies (61.1%), but in 3 studies [30,43,45] we assumed that the outcome assessors were not masked, leading to detection bias. Attrition bias was considered high for 7 studies [30,32,34-36,45,46], although we found no evidence of this type of bias in 4 studies [33,37,41,47]. The reporting bias was judged as high for 44.4% of the studies and we found other sources of bias in two studies [33,34] regarding baseline imbalances detected between study groups (i.e., use of anti-dementia drugs, cognitive status or number of hospitalized patients).

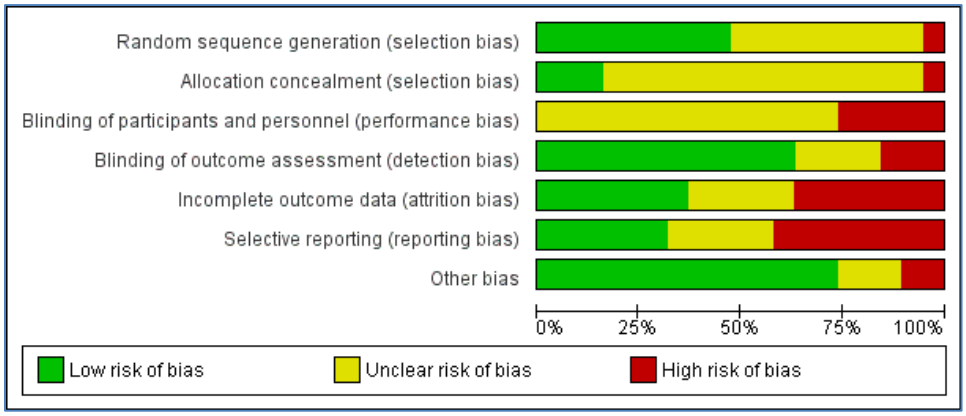


**Figure 2.** Risk of bias graph of randomized controlled trials included

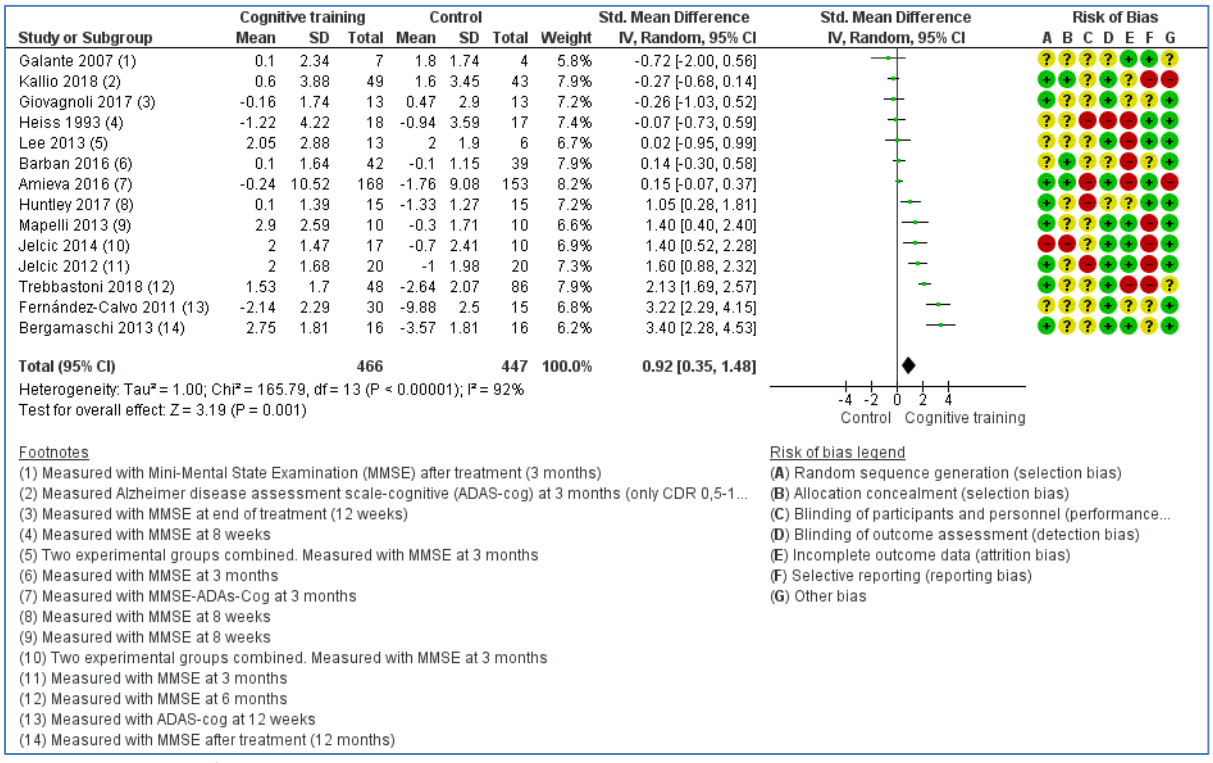


**Figure 3.** Forest plot: cognitive training vs control immediately post-intervention; outcome: Change in an overall measure of cognition

## Effects of cognitive training

### *Overall cognitive function*

For overall cognitive function, 14 studies were included in the analysis. The overall effect of cognitive training on overall cognition immediately ends intervention assessed with screening measures (typically the MMSE) was large in comparison with a control group (SMD: 0.92, 95% CI from 0.35 to 1.48; 14 trials; 913 participants; Figure 3). Although

we did not detect clear evidence of publication bias (Figure 4), the quality of evidence for this finding was low due to very serious heterogeneity ($I^2$=92%). In a sensitivity analysis in which we removed from meta-analysis studies with a higher risk of bias, we still found low-quality evidence of a high effect of cognitive training on overall cognition at end of training (SMD: 1.05, 95% CI 0.29 to 1.82; 11 trials; 530 participants).

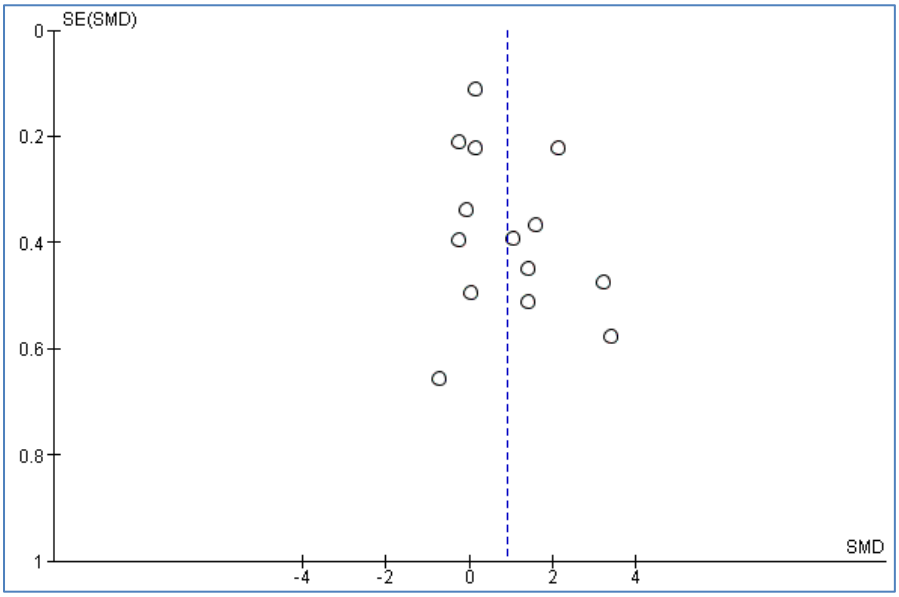


**Figure 4.** Funnel plot of cognitive training vs control immediately post-intervention; outcome: Change in an overall measure of cognition

In the medium term, 3 to 12 months post-intervention, the quality of evidence was very low, and we were unable to determine whether there is any effect of cognitive training on overall cognition (SMD: 1.49, 95% CI: from 0.03 to 2.94, 5 trials; 224 participants; Figure 5) due to quality concerns related to risk of bias, heterogeneity and imprecision.

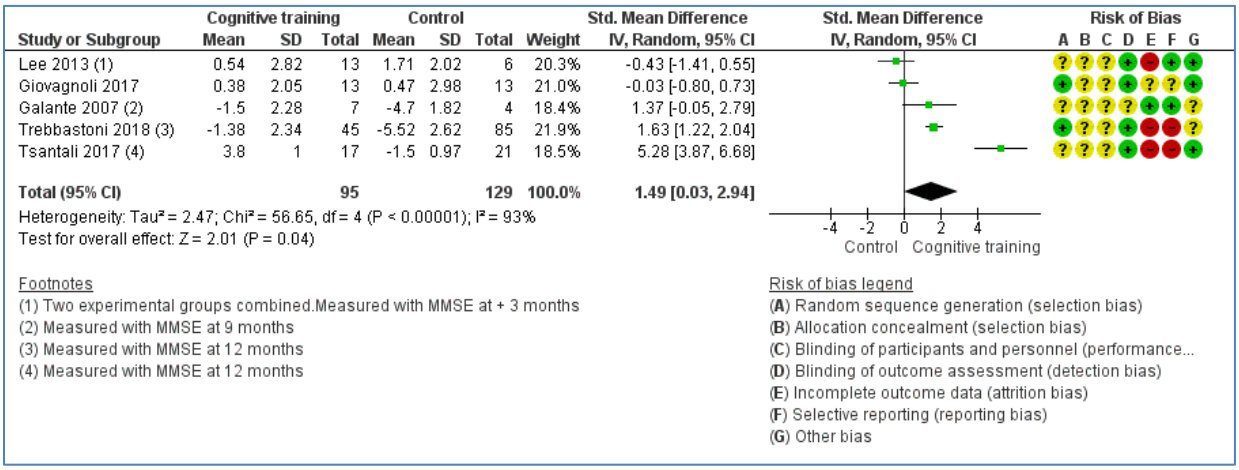


**Figure 5.** Forest plot: cognitive training vs control in the medium term (3 to 12 months post-intervention); outcome: Change in an overall measure of cognition

### *Cognitive impairment progression*

In comparison with a control group, we found a large effect of cognitive training on cognitive impairment progression at end of treatment (SMD: 0.99; 95% CI 0.44 to 1.55; 4 trials; 187 participants; Figure 6). However, due to concerns regarding heterogeneity (not explained by the subgroup analysis) and imprecision, the quality of the evidence was rated as low.

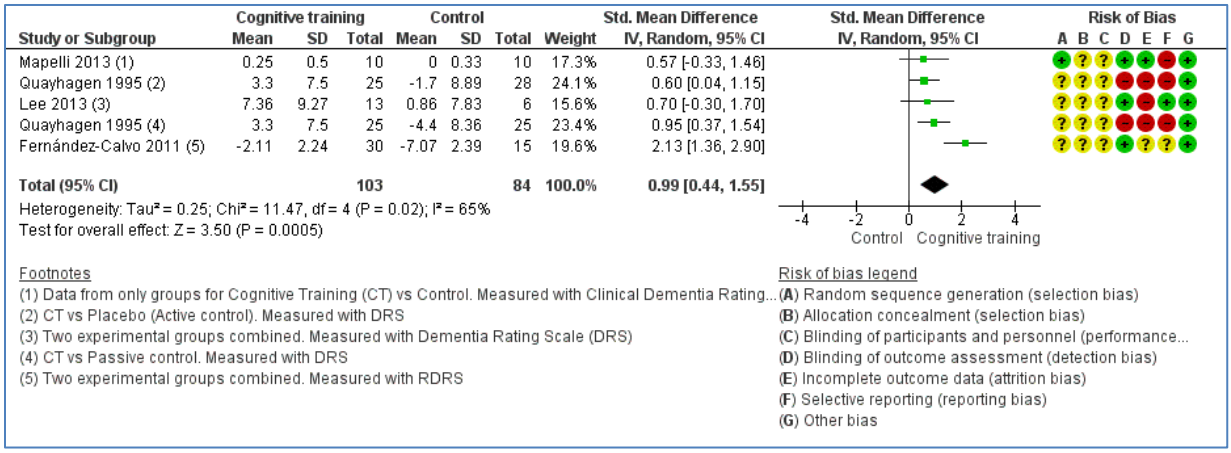


**Figure 6.** Forest plot: cognitive training vs control immediately post-intervention; outcome: Cognitive impairment progression

However, when cognitive impairment progression was assessed in medium term, it was not possible to determine whether there is an effect of cognitive training compared to a control group in terms of progression of cognitive impairment because of the very low quality of evidence, both in our main analysis (SMD 0.51; 95% CI from 07 to 0.94; 2 trials; 98 participants; Figure 7) and in a sensitivity analysis in which we removed studies with a higher risk of bias (SMD: 0.29; 95% CI from -0.68 to 1.27). Quality of the evidence was downgraded due to concerns regarding the risk of bias and imprecision.

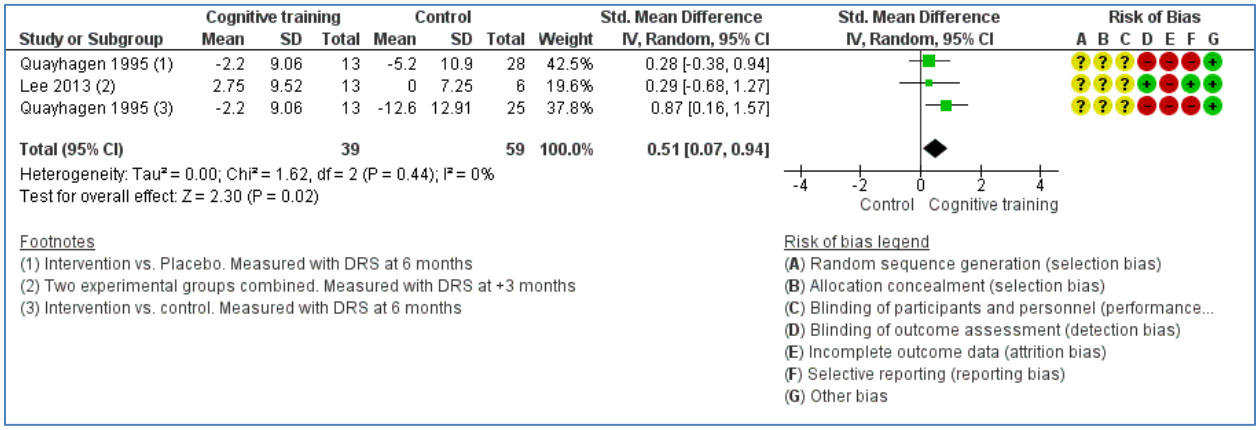


**Figure 7.** Forest plot: cognitive training vs control in the medium term (3 to 12 months post-intervention); outcome: Cognitive impairment progression

### *Specific domain function*

**Delayed memory:** Eight studies reported delayed memory outcomes. Although cognitive training showed a large positive effect on delayed memory of patients with mild to moderate dementia immediately end of training (SMD: 1.11; 95% CI from 0.59 to 1.63; 8 trials; 408 participants; Figure 8), the quality of evidence related to this outcome was low due to very serious inconsistency. However, in the medium term, we are unable to determine whether cognitive training had an effect on delayed memory relative to a control condition because the quality of evidence was very low (SMD: 0.77; 95% CI from -0.10 to 1.65; 4 trials; 225 participants).

**Immediate memory:** We found moderate-quality evidence showing a moderate effect size in comparison to a control group at end of training (SMD: 0.69; 95% CI from 0.42 to 0.97; 12 trials; 503 participants; Figure 9), but in the medium term four studies found no evidence of an effect of cognitive training on immediate memory (SMD: 0.47; 95% CI from -0.01 to 0.96; 7 trials; 334 participants) and quality of evidence was estimated as very low due to concerns regarding imprecision and inconsistency.

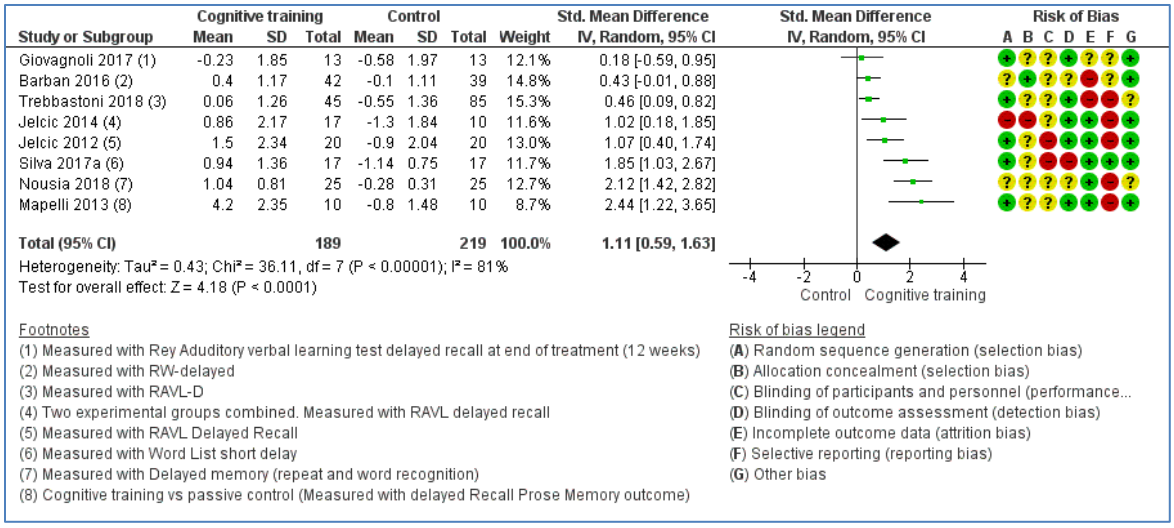


**Figure 8.** Forest plot: cognitive training vs control immediately post-intervention; outcome: Delayed memory

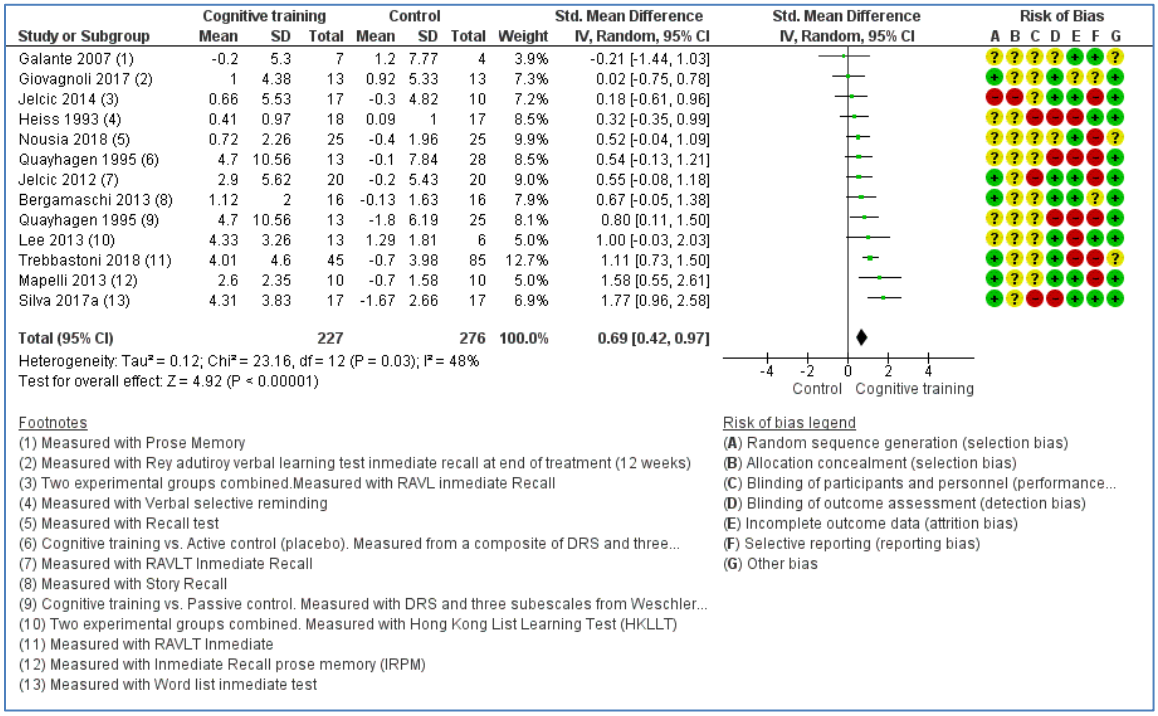


**Figure 9.** Forest plot: cognitive training vs control immediately post-intervention; outcome: Immediate memory

**Working memory:** Despite 10 trials reported data about working memory outcome, we are unable to determine whether cognitive training had an effect relative to a control condition at end of training because the quality of evidence was very low (SMD: 0.67; 95% CI from 0.13 to 1.21; 10 trials; 403 participants), meanly due to concerns about imprecision and inconsistency. This was also true in the medium term (SMD: 0.52; 95% CI from -0.29 to 1.34; 4 trials; 198 participants).

**Language:** We found a large effect favouring cognitive training in comparison to a control group on language domain, specifically subtype naming, at end of training (SMD: 1.19; 95% CI from 0.69 to 1.69; 6 trials; 296 participants). However, because of inconsistency and imprecision, the quality of evidence for this finding was estimated as low. In the medium term, we are uncertain of any effect of cognitive training on this outcome due to very low quality of evidence (SMD: 0.56; 95% CI from -0.74 to 1.86; 3 trials; 179 participants).

**Verbal fluency:** At end of training, we were unable to determine whether there is an effect of cognitive training relative to a control intervention on verbal fluency (SMD: 0.51; 95% CI from 0.13 to 0.89; 9 trials; 349 participants) due to quality of evidence was estimated as very low. However, in the medium term, we found moderate-quality evidence showing that a moderate effect of cognitive training on verbal fluency of patients with mild to moderate dementia (SMD: 0.54; 95% CI from 0.24 to 0.83; 4 trials; 198 participants, Figure 10).

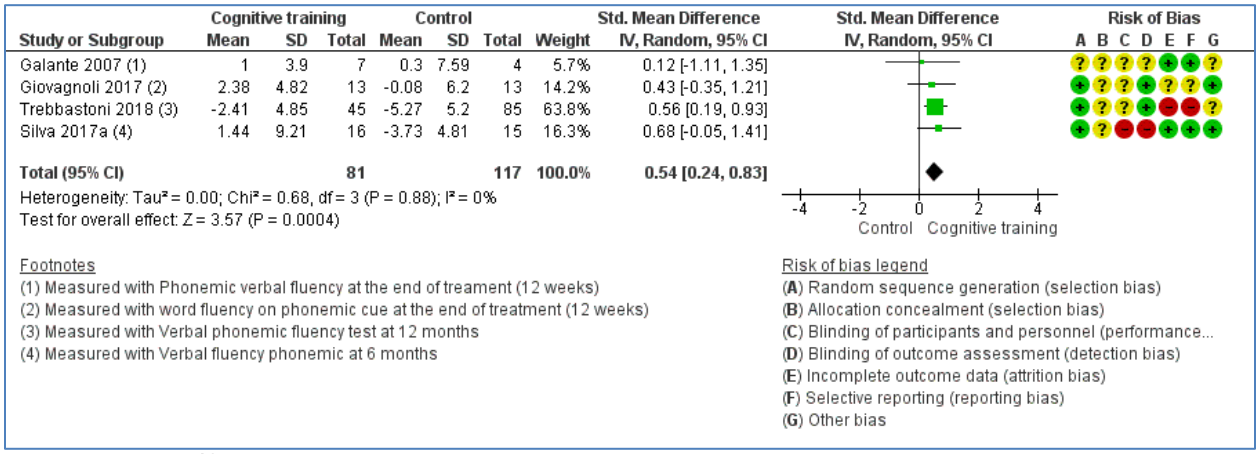


**Figure 10.** Forest plot: cognitive training vs control immediately post-intervention; outcome: Verbal fluency

**Semantic fluency:** We found that cognitive training had a moderate effect in comparison to a control group on semantic fluency at end of training (SMD: 0.64; 95% CI from 0.17 to 1.10; 7 trials; 319 participants), although the quality of evidence for this outcome was rated as low due to concerns related to imprecision and inconsistency. However, we are unable to determine whether this effect may be maintained in the medium term (SMD: 0.30; 95% CI from -0.65 to 1.24; 3 trials; 167 participants), due to the quality of evidence was very low owning to serious concerns about inconsistency and imprecision.

**Executive function:** Because the quality of evidence was very low, we are unable to determine whether, relative to a control group, cognitive training had an effect on executive function both immediately after training (SMD: 0.67; 95% CI from 0.12 to 1.22; 8 trials; 386 participants) and in the medium term (SMD: 0.36; 95% CI from -0.16 to 0.89; 4 trials; 246 participants). Main quality concerns were related to heterogeneity and imprecision.

**Speed of information processing:** We were unable to determine whether there was any effect of cognitive training in comparison to a control group on processing speed severity at end of training due to the very low quality of evidence (SMD: 0.45; 95% CI from -0.18 to 1.08; 6 trials; 197 participants). In the medium term, data for this outcome were available from only two studies and our results were inconclusive (SMD: -0.44; 95% CI from -1.10 to 0.22; 2 trials; 37 participants) (low-quality evidence).

### *Sensitivity analysis*

We conducted a comparison of the main analysis and a new analysis for all outcomes in which studies with a high risk of bias were removed. This comparison did not lead to a change in estimated treatment effect (SMD) for any of the cognitive outcomes.

### Subgroup's analysis

### *Type of diagnosis of dementia*

In order to explore the relationship between factors such as type of diagnosis of dementia, dementia severity at baseline, type and the total duration of the cognitive training program and cognitive training outcomes, we evaluated the results in predefined subgroups (Figure 11).

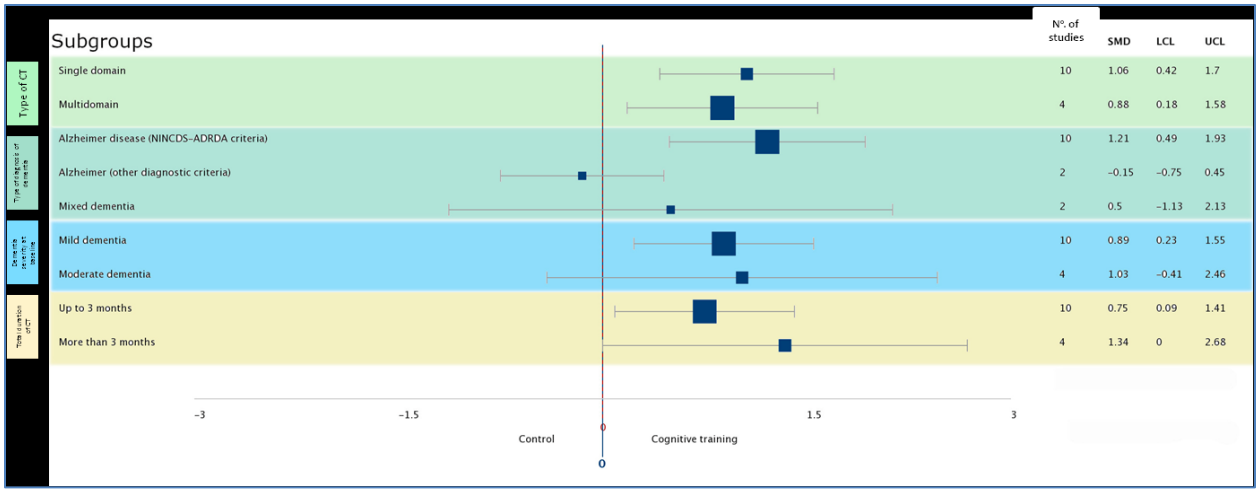


**Figure 11.** Subgroup analyses of moderators of the effect of cognitive training on overall cognition immediately post-intervention in patients with mild to moderate dementia. CT: Cognitive Training; SMD: Standardized Mean Difference; LCL: Low Confidence Limit; UCL: Upper Confidence Limit

Although, in general terms, we did not find significant differences between the subgroups analyzed for overall cognitive function, we found a significant trend (qualitative and quantitative) suggesting a larger effect in favour of cognitive training in patients with Alzheimer's dementia diagnosed according to the NINCDS-ADRDA criteria than in other types of dementia ($\chi^2$=8.04, df=2, $p$=0.02). However, we detected unexplained substantial heterogeneity between the trials within each subgroup (patients with Alzheimer's type dementia: $I^2$=94%; patients with other diagnoses of dementia: $I^2$=89%). Therefore, the effect estimations for each subgroup are uncertain, since the results of the individual trials are inconsistent. Regarding cognitive impairment progression, we did not find significant differences in the analysis of subgroups, but we detected a significant quantitative difference suggesting a larger effect in favour of cognitive training in patients with Alzheimer's dementia diagnosed according to the NINCDS-ADRDA criteria than in other types of dementia ($p$=0.005). However, the number of trials and participants included in each subgroup was very small (between 1 and 3 trials), so the analysis may not have sufficient power to detect subgroup differences.

***Dementia severity at baseline***

Subgroup analysis suggested that the effects observed by cognitive training on the delayed memory and executive function were attenuated in the subgroup of patients with milder degrees of dementia compared to the subgroup of patients with a moderate degree of dementia ($p$=0.03 and $p$=0.0001, respectively). However, a far smaller number of trials and participants contributed data to the moderate dementia subgroup (1 trial, 20 participants) than to the male subgroup (7 and 8 trials, 366 and 388 participants, respectively), meaning that the analysis is unlikely to produce useful findings.

***Type of the cognitive training program***

Although multidomain cognitive training was associated with a significant larger effect compared to single domain training on domains such as verbal fluency ($p$=0.03), semantic fluency ($p$=0.04) and executive function ($p$=0.02), substantial unexplained heterogeneity was identified between the trials within each of these subgroups and the validity of the treatment effect estimate for each subgroup is uncertain.

***Total duration of the cognitive training program***

There was also a significant effect for cognitive training duration on semantic fluency and processing speed ($p$=0.001 and $p$=0.0003, respectively) so that the greatest effects were associated with cognitive training administered more than three months versus cognitive training administered up to three months. However, a smaller number of

trials and participants contributed data to the more than three months subgroup than to the up to three months subgroup, meaning that the analysis may not be able to detect subgroup differences.

## Discussion

The main findings of our meta-analysis are that, for people with a diagnosis of dementia and a mild-moderate level of severity, cognitive training interventions compared to a passive or active control groups likely result in a large effect in immediate memory (moderate-quality of evidence) and probably will result in a large positive effect immediately after treatment on overall cognition, cognitive impairment progression as well as on the specific cognitive domains of delayed memory and language (low-quality of evidence). Furthermore, we found that cognitive training may have a moderate positive effect on semantic fluency (low-quality of evidence). For other cognitive outcomes, the evidence is very uncertain, although we also found effects in favour of cognitive training immediately after treatment on other cognitive domains such as operative memory, verbal fluency or executive function (very-low quality of evidence). In the medium term (between 3 and 12 months after treatment) we found that cognitive training, in comparison with the control group, probably has a moderate positive effect on verbal fluency in patients with mild-moderate dementia (moderate-quality of evidence), but the quality of the evidence concerning the effects of cognitive training on cognition and cognitive impairment progression is very low. We found no evidence of a significant effect of cognitive training in the medium term on other outcomes such as memory (delayed, immediate or operative), language, semantic fluency or executive function (very low-quality of evidence).

Our review includes 18 RCTs (1483 participants), of which 10 (55.5%) have been published in the last 4 years and 15 (83.3%) were carried out in European countries, especially in Italy. Only three of the included studies were conducted in non-European countries (USA, China, and Brazil) and were published prior to 2013, but the extent to which findings of the current review are applicable to individuals in other countries is not clear. Our meta-analyses demonstrated moderate/substantial, even in some cases, considerable heterogeneity. This heterogeneity can probably be related to specific characteristics of the patients (i.e., different dementia stages, mean ages, comorbidities or education levels), interventions and the outcomes measure scales. For example, the studies included interventions clinically heterogeneous from the point of view of the format (some used paper and pencil while other used computerized platforms), from the point of view of the objective (addressed to individual cognitive domains or to multiple domains), as well as from the point of view of the method used (focused on practice or learning). Furthermore, we also found differences in the clinical context in which intervention was applied (home/community setting) and the frequency for the administration of interventions (varying from 1 or 2 sessions per week and up to 6 sessions per week). It is likely that this clinical heterogeneity had contributed significantly to the statistical heterogeneity observed in our review. For addressing this heterogeneity, we performed a random-effects meta-analysis and we explored possible causes of heterogeneity among results of studies through pre-specified subgroup analyses. In this sense, although our subgroup analyses did not find a significant impact in any of the pre-specified subgroups, we found non-significant trends suggesting that trials including only populations with Alzheimer's dementia according to the NINCDS-ADRDA criteria were associated with larger positive effects on cognitive function and on cognitive impairment progression than trials which mixed populations with different types of dementia.

The results of our study are consistent with previous systematic reviews and meta-analysis [8,14,20,48,49] on the effects of cognitive training in people with dementia in overall cognitive function compared to a control group and at the end of treatment. However, it is noting that given the small number of studies and participants included in some cases, the accuracy could be limited [48] and that none of the published reviews on cognitive training included, exclusively, patients with a diagnosis of dementia using specific and well-established diagnostic criteria which could

explain the small differences found concerning the number of included studies and results obtained. In contrast with these consistencies, other more recent meta-analyses [8] did not find solid evidence about any effect of cognitive training on the overall cognitive function compared to an active control group (SMD 0.22, 95% CI 0.74 to 1.18). The effects of cognitive training among published reviews on specific cognitive domains in patients with dementia are very heterogeneous. Funnel plots were performed in order to detect possible publication bias, but in no case, we downgraded the quality of the evidence for this reason since none of the visual examination of funnel plots (overall cognitive function, immediate memory and operative memory) clearly revealed an apparent asymmetry. However, it is noting that the approach we used may have underestimated the true risk of this bias.

Strengths of our study are: (1) we applied a strict set of eligibility criteria, especially regarding diagnosis and severity of dementia (mild to moderate); (2) the effects of cognitive training on different cognitive subdomains were analysed and classified temporarily (immediately post-intervention and in the medium term); and (3) a subgroup analysis was conducted to explore the detected heterogeneity and additionally, possible modifiers were included, which are often not taken into account by researchers and which are important when evaluating the results of cognitive interventions. However, our review is not exempt from certain limitations. First, to perform the search only a limited number of databases were explored, which could have resulted in the lack of identification of other relevant evidence. However, the databases explored are the main databases used in medicine and psychology, which also include records from other published and unpublished sources. Second, since there is no clear definition of cognitive training and it is difficult to distinguish with other cognitive interventions (such as cognitive rehabilitation and stimulation), it is possible that in some cases the intervention may have been misclassified. To try to resolve this limitation, we clearly define the characteristics which the intervention should meet to be considered as cognitive training and we excluded combinations of interventions that could add complexity and confounding factors. Third, given the small number of studies and participants included in the meta-analyses for some outcomes, the results may not have reached statistical significance due to lack of power.

## Conclusions

Low-quality evidence suggests that cognitive training results in positive large effects immediately after treatment on overall cognition, cognitive impairment progression and specific cognitive domains, such as memory and language, in people with a diagnosed dementia and a mild to moderate level of severity.

In the medium term, cognitive training probably has a positive moderate effect on verbal fluency in this population, although due to the very low quality of the evidence for other cognitive outcomes, the effects of cognitive training in the medium term are uncertain. Future studies with rigorous methods that minimize the risks of bias and provide long-term follow-up are needed.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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