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Computerised cognitive training for preventing dementia in people with mild cognitive impairment (Review)

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[Intervention Review]

Computerised cognitive training for preventing dementia in people with mild cognitive impairment

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ABSTRACT

Background

The number of people living with dementia is increasing rapidly. Clinical dementia does not develop suddenly, but rather is preceded by a period of cognitive decline beyond normal age-related change. People at this intermediate stage between normal cognitive function and clinical dementia are often described as having mild cognitive impairment (MCI). Considerable research and clinical efforts have been directed toward finding disease-modifying interventions that may prevent or delay progression from MCI to clinical dementia.

Objectives

To evaluate the effects of at least 12 weeks of computerised cognitive training (CCT) on maintaining or improving cognitive function and preventing dementia in people with mild cognitive impairment.

Search methods

We searched to 31 May 2018 in ALOIS (www.medicine.ox.ac.uk/alois) and ran additional searches in MEDLINE, Embase, PsycINFO, CINAHL, ClinicalTrials.gov, and the WHO portal/ICTRP (www.apps.who.int/trialsearch) to identify published, unpublished, and ongoing trials.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs in which cognitive training via interactive computerised technology was compared with an active or inactive control intervention. Experimental computerised cognitive training (CCT) interventions had to adhere to the following criteria: minimum intervention duration of 12 weeks; any form of interactive computerised cognitive training, including computer exercises, computer games, mobile devices, gaming console, and virtual reality. Participants were adults with a diagnosis of mild cognitive impairment (MCI) or mild neurocognitive disorder (MND), or otherwise at high risk of cognitive decline.

Data collection and analysis

Two review authors independently extracted data and assessed risk of bias of the included RCTs. We expressed treatment effects as mean differences (MDs) or standardised mean differences (SMDs) for continuous outcomes and as risk ratios (RRs) for dichotomous outcomes. We used the GRADE approach to describe the overall quality of evidence for each outcome.

Main results

Eight RCTs with a total of 660 participants met review inclusion criteria. Duration of the included trials varied from 12 weeks to 18 months. Only one trial used an inactive control. Most studies were at unclear or high risk of bias in several domains. Overall, our ability to draw conclusions was hampered by very low-quality evidence. Almost all results were very imprecise; there were also problems related to risk of bias, inconsistency between trials, and indirectness of the evidence.

No trial provided data on incident dementia. For comparisons of CCT with both active and inactive controls, the quality of evidence on our other primary outcome of global cognitive function immediately after the intervention period was very low. Therefore, we were unable to draw any conclusions about this outcome.

Due to very low quality of evidence, we were also unable to determine whether there was any effect of CCT compared to active control on our secondary outcomes of episodic memory, working memory, executive function, depression, functional performance, and mortality. We found low-quality evidence suggesting that there is probably no effect on speed of processing (SMD 0.20, 95% confidence interval (CI) -0.16 to 0.56; 2 studies; 119 participants), verbal fluency (SMD -0.16, 95% CI -0.76 to 0.44; 3 studies; 150 participants), or quality of life (mean difference (MD) 0.40, 95% CI -1.85 to 2.65; 1 study; 19 participants).

When CCT was compared with inactive control, we obtained data on five secondary outcomes, including episodic memory, executive function, verbal fluency, depression, and functional performance. We found very low-quality evidence; therefore, we were unable to draw any conclusions about these outcomes.

Authors' conclusions

Currently available evidence does not allow us to determine whether or not computerised cognitive training will prevent clinical dementia or improve or maintain cognitive function in those who already have evidence of cognitive impairment. Small numbers of trials, small samples, risk of bias, inconsistency between trials, and highly imprecise results mean that it is not possible to derive any implications for clinical practice, despite some observed large effect sizes from individual studies. Direct adverse events are unlikely to occur, although the time and sometimes the money involved in computerised cognitive training programmes may represent significant burdens. Further research is necessary and should concentrate on improving methodological rigour, selecting suitable outcomes measures, and assessing generalisability and persistence of any effects. Trials with long-term follow-up are needed to determine the potential of this intervention to reduce the risk of dementia.

PLAIN LANGUAGE SUMMARY

Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Background

The terms 'cognition' and 'cognitive function' describe all of the mental activities related to thinking, learning, remembering, and communicating. There are normal changes in cognition with age, There are also diseases that affect cognition, principally dementia, in which cognition is impaired to the point of affecting a person's ability to manage daily activities. More common than dementia is a condition often described as mild cognitive impairment (MCI), in which mild impairment of cognition, more than expected from age alone, can be detected on testing, but by which daily functioning is largely unaffected. For some people, MCI is a stage on the way to developing dementia. There is a lot of interest in anything that might prevent further decline in cognition in people with MCI. One thing that has been suggested as a means of doing this is computerised cognitive training (CCT). Cognitive training consists of a set of standardised tasks intended to 'exercise the brain' in various ways. These days, cognitive training exercises are often delivered via computers or mobile technology, so that people can do them on their own at home. We wanted to know whether CCT is an effective way for people with MCI to maintain their cognitive function and reduce their risk of going on to develop dementia.

What we did

We searched the medical literature up to 15 March 2018 for trials in which a group of people with MCI had participated in CCT for at least 12 weeks and had been compared with another group that had not received any CCT. This 'control' group could have taken part in an alternative activity instead, or group members could have received no intervention at all. For the comparison to be as fair as possible, it should have been decided at random whether people were in the CCT or control group. We were primarily interested in whether study participants developed dementia and in their overall cognitive function, but we also looked for evidence on particular cognitive skills, daily activities, quality of life, mood, or mental well-being, and any harmful effects.

What we found

We found eight trials with 660 participants to include in the review. Seven of the trials (623 participants) compared CCT to an alternative activity. None of the included trials examined development of dementia, so this review presents no evidence on whether taking part in computerised cognitive training will help to prevent dementia. Our main finding in relation to all of the other outcomes in which we were interested was that the overall quality of the evidence was very low. This very low quality was mainly due to small sample sizes, problems with study methods, and differences between trials. Therefore, although we found some evidence for a few benefits of CCT for cognition, we were highly uncertain about study results and consider it likely that future research might lead to different results.

Our conclusions

Unfortunately, it is not yet possible to answer our review question with any certainty. We think it remains an important area for further study. We would like to see larger studies, which would be more able to detect effects of CCT, and longer studies, which are needed to show whether there are any benefits, whether benefits are long-lasting, and whether there is a chance of preventing or delaying the development of dementia.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Computerised cognitive training compared with active control in people with mild cognitive impairment

Patient or population: patients with mild cognitive impairment
Settings: general population
Intervention: computerised cognitive training
Comparison: active control

Outcomes	Differences between CCT and control (95% CI)*	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Global cognitive functioning (follow-up ranging from 3 months up to 2 years)	SMD 0.53 lower (1.06 lower to 0.01 lower)	407 participants (5 studies)	⊕◯◯◯ **very low**[b]	It is uncertain whether CCT maintains global cognitive functioning better than active control
Episodic memory (follow-up ranging from 3 months up to 2 years)	SMD 0.79 lower (1.54 lower to 0.04 lower)	223 participants (5 studies)	⊕◯◯◯ **very low**[b]	It is uncertain whether CCT improves episodic memory compared to active control
Speed of processing (follow-up ranging from 3 months up to 2 years)	SMD 0.20 higher (0.16 lower to 0.56 higher)	119 participants (2 studies)	⊕⊕◯◯ **low**[c]	CCT may have little or no effect on speed of processing
Executive functioning (follow-up ranging from 3 months up to 2 years)	SMD 0.31 lower (0.90 lower to 0.28 higher)	150 participants (3 studies)	⊕◯◯◯ **very low**[b]	It is uncertain whether CCT improves executive functioning better than active control
Working memory (follow-up ranging from 3 months up to 9 months)	SMD 0.88 lower (1.73 lower to 0.03 lower)	72 participants (3 studies)	⊕◯◯◯ **very low**[d]	It is uncertain whether CCT improves working memory compared to active control
Verbal fluency (follow-up ranging from 3 months up to 18 months)	SMD 0.16 lower (0.76 lower to 0.44 higher)	150 participants (3 studies)	⊕⊕◯◯ **low**[c]	CCT may have little or no effect on speed of processing
Quality of life (3 months of follow-up)	MD 0.40 higher (1.85 higher to 2.65 lower)	19 participants (1 study)	⊕⊕◯◯ **low**[c]	CCT may have little or no effect on quality of life

* The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CCT: computerised cognitive training; CI: confidence interval; MD: mean difference; RR: risk ratio; SMD: standardised mean difference

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]The direction of the difference in effect was standardised, so that lower values favour CCT and higher values favour control.
[b]Downgraded three levels for imprecision (confidence interval included effects that are not clinically relevant), inconsistency (high heterogeneity), and risk of bias.
[c]Downgraded two levels for imprecision (confidence interval included effects that are not clinically relevant) and risk of bias.
[d]Downgraded four levels for imprecision (confidence interval included effects that are not clinically relevant), inconsistency (high heterogeneity), indirectness, and risk of bias.

BACKGROUND

Description of the condition

Mild cognitive impairment

Normal ageing is associated with decline in many core cognitive functions (Salthouse 2003). When cognition deteriorates beyond normal age-related change, but the ability to complete ordinary activities of daily function remains largely intact, the condition is described as mild cognitive impairment (MCI). In some people, MCI is an intermediate state on the pathway from normal cognition to dementia. When several cognitive domains are involved and function in daily activities has deteriorated significantly, the diagnosis is changed to that of dementia. However, there is no clear demarcation between normal cognition and mild cognitive impairment, or between mild cognitive impairment and dementia, and it is impossible to identify the specific points of conversion (Aisen 2011; Albert 2011).

One review identified 16 different classification and measurement approaches for MCI (Matthews 2008); there remains no standard definition of MCI accepted for use in clinical trials (Stephan 2013). The National Institute on Aging (NIA)-Alzheimer's Association published criteria for MCI in 2011 (Albert 2011), but the criteria suggested earlier by Petersen are still commonly used in clinical research (Petersen 1999). Clinical subtypes have been introduced based on the presence or absence of a primary memory impairment (amnestic or non-amnestic MCI), and on the number of cognitive domains affected (single domain or multiple domains) (Petersen 2009; Winblad 2004). Further subdivisions can be made depending on the suspected underlying cause of cognitive deficits, for example, MCI due to Alzheimer's disease (MCI-AD) and MCI due to vascular disease (also termed 'vascular cognitive impairment no dementia' (VCIND)). The term 'mild neurocognitive disorder' is broadly synonymous with MCI.

The prevalence of MCI is more than double than that of dementia (Petersen 2009). A recent review suggests a prevalence of MCI of 6.7% in those aged 60 to 64 years, increasing to 25.2% among those aged 80 to 84 (Petersen 2018). However prevalence rates vary depending on the diagnostic criteria used. When 18 different definitions of MCI were mapped, prevalence estimates were found to range from 0.1% to 42%, and 'conversion' rates to dementia were found to be generally low (Stephan 2007). Prevalence and conversion rates in specialist settings are higher than those observed in population-based studies, with the adjusted annual conversion rate from MCI to dementia of 9.6% in specialist settings compared to 4.9% in the general population (Mitchell 2009). A large number of individuals with a diagnosis of MCI do not go on to develop dementia, and between 14% and 40% revert to normal cognitive function for their age (Koepsell 2012). Mild cognitive difficulties in themselves have functional and psychological ramifications for quality of life (Mitchell 2009).

Dementia

Dementia is usually a progressive syndrome of cognitive and functional decline. Although most commonly associated with 'forgetfulness', dementia, by definition, involves impairments in more than one cognitive domain, and impairments in language, executive function, complex attention, and social cognition are commonly identified. As the syndrome progresses, those affected become increasingly dependent on care from others for all activities of daily living (e.g. feeding, bathing, taking medication). Dementia is one of the principal causes of disease, disability, and decreased quality of life among older adults and is now identified as one of the biggest global health challenges. It may affect up to 135 million adults worldwide by 2050 (Prince 2013). The global economic cost of care for people with dementia is currently estimated at $315 billion (Wimo 2010).

Dementia is sometimes referred to as a neurocognitive disorder, as in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-V; APA 2013); the two terms may be used interchangeably. Subtypes of dementia are distinguished by the underlying brain pathology. The four most common subtypes of dementia include:

- dementia due to Alzheimer's disease (AD), which accounts for an estimated 60% to 70% of all dementia cases;
- vascular dementia (VaD);
- dementia with Lewy bodies (DLB); and
- frontotemporal dementia (FTD).

Accurate diagnosis of subtypes can be difficult, especially when the clinical disease is severe. Mixed pathology is commonly reported, with more than 80% of cases having some features of AD (Jellinger 2006; WHO 2012).

Alzheimer's disease (AD), the most common cause of dementia, is now known to have a long prodromal period. In those with AD, MCI - the symptomatic pre-dementia phase - offers an opportunity to introduce interventions that may prevent or postpone the onset of clinical dementia (Leifer 2003). Delaying progression from MCI to dementia would lead to a reduction in the incidence of dementia, with a significant reduction in associated costs to society and improved quality of life for individuals. Postponement of dementia onset by five years may reduce prevalence by 50% (Brookmeyer 1998). No drugs are currently available that can reduce the risk of progression from MCI to dementia (Russ 2012). As a result, investigations are focusing on non-pharmacological interventions that may delay clinical progression (Acevedo 2007; Dresler 2013).

Risk and protective factors for MCI and dementia

Age is the strongest risk factor for dementia. However, research has identified several additional risk and protective factors linked with

late-onset dementia in general and with AD in particular (World Alzheimer Report 2014). The World Health Organization 2017 Dementia Action Plan reports that reducing such risks is a major health objective to reduce disability (who.int/mental_health/neurology/dementia/action_plan_2017_2025/en/). Epidemiological evidence suggests that AD shares many risk factors with vascular dementia; these include cerebrovascular disease, type 2 diabetes, midlife obesity, midlife hypertension, smoking, and physical inactivity (Pendlebury 2009; WHO 2012; World Alzheimer Report 2014). It has recently been suggested that, after non-independence between risk factors is accounted for, around a third of AD cases worldwide might be attributable to potentially modifiable risk factors (Norton 2014), including alcohol intake, depression, diet, physical exercise, education, and mental activity (Barnes 2011; de Bruijn 2013; Diniz 2013; Erickson 2011; Jorm 2001). Lifestyle factors could increase or decrease risk of dementia (Amoyal 2012; Karp 2006).

Mental activity has been identified as a potentially important protective factor. Epidemiological studies indicate that lifelong cognitively stimulating experiences, including education and occupation and leisure activities, are linked to improved late-life cognition, reduced risk of cognitive decline, and lower incidence of AD (Barnes 2011; Marioni 2014; Verghese 2003; Wilson 2002). Lack of education has been identified in meta-analyses as a particularly strong predictor of dementia (Beydoun 2014). However, prospective studies indicate that even when mental activity is commenced late in life, it may have positive effects on cognition, with lowered rates of decline and lowered dementia incidence reported (Geda 2012; Wilson 2010; Wilson 2012). Cognitively stimulating activity may therefore offer an opportunity to maintain cognitive function, or to prevent or delay further deterioration, among those in early stages of cognitive decline.

Description of the intervention

This review focuses on randomised controlled trials (RCTs) investigating the effects of computerised cognitive training (CCT) interventions for maintenance of cognition and prevention of dementia in people with mild cognitive impairment. 'Cognitive training' has been operationally defined as an intervention consisting of repeated practice on standardised cognitive exercises targeting specific cognitive domains for the purpose of stimulating cognitive function (Gates 2010; Gates 2014; Kueider 2012). Although cognitive training may include traditional pen and paper tasks, it more commonly takes the form of computer-based tasks, including exercises, games, and virtual reality. Computerised cognitive training may be delivered in individual sessions or within groups, with supervision or privately at home.

How the intervention might work

The underlying premise of cognitive training is that intensive cognitive exercises may build up or restore brain and cognitive reserve, providing greater resilience against neuropathology and maintaining function (Liberati 2012). 'Brain reserve' refers to structural tolerance of the brain to disease and may be evident in increased brain volume; 'cognitive reserve' refers to functional differences in neural activity and cognitive processes (Sterne 2012). Up to 33% of individuals functioning independently without clinical dementia have the same volume of disease pathology as those with clinical dementia (Neuropathology Group 2001). The concept of reserve provides a theoretical explanation for the differences between those who succumb to AD pathology and develop clinical dementia, and those who tolerate the disease and maintain function (Sterne 2012). It has been further suggested that cognitive stimulation may result in neural plasticity and neural compensation, that is, in the development of compensatory networks maintaining cognitive performance and potentially masking or preventing the clinical manifestation of neurocognitive disease (Grady 2012; Park 2013).

Although the evidence base is very limited, some human trials of cognitive training have suggested positive neuroplastic changes. Diverse changes have been reported, including neurochemical activation (Olesen 2004; Rosen 2011), altered fluorodeoxyglucose uptake (Belleville 2012), and reduced β-amyloid burden (Landau 2012). Several diverse studies investigating neurophysiological changes seen on functional magnetic resonance imaging (fMRI) have identified increased prefrontal and parietal activity and hippocampal activation (Olesen 2004; Rosen 2011; Suo 2012a; Valenzuela 2003). Electroencephalography (EEG) and magnetic resonance spectrometry (MRS) studies of cognitive training support the concept of functional neural plasticity post training, with results indicating positive changes in brain metabolism, task-dependent brain activation, and resting-state networks (Belleville 2012; Berry 2010; Förster 2011). However, the research is limited, and significant further investigation is required.

Why it is important to do this review

The potential of CCT to be an effective intervention to maintain cognitive function, or to reduce the risk of clinical dementia, along with its low implementation costs and its high availability and accessibility, has led to the American Alzheimer's Association recommending rapid development and testing of such training (Alzheimer's Association 2014). However, the evidence base to date has been inconclusive, with mixed results reported. Several prior reviews exist, but these include mixed populations and varied interventions, and they need to be updated (Bahar-Fuchs 2013; Martin 2011). Earlier reviews have been critical of clinical trials for poor specification of interventions, small sample sizes, failure to assign treatments randomly, and lack of longitudinal follow-up - all factors that may contribute to heterogeneous results (Gates 2010; Gates 2014; Kueider 2012; Mowszowski 2010;

Papp 2009; Reijnders 2013; Walton 2014). Additional methodological criticisms with an impact upon valid evaluation of cognitive training include lack of differentiation between interventions, lack of adequate control conditions to isolate intervention benefit, a limited number of trials with active controls, and limited outcome measures to determine generalisation to non-trained cognitive domains and persistence of benefits (Gates 2010; Green 2014; Mowszowski 2010; Park 2013; Walton 2014). Primary studies have identified that the benefits of cognitive training may depend upon several factors including age, cognitive level, and non-cognitive factors (Lampit 2014; Stine-Morrow 2014). Therefore a robust review is warranted to investigate the efficacy of computerised cognitive training for people with MCI on non-trained cognitive domains, and to evaluate potential sources of bias and heterogeneity in the literature. If sufficient trials are identified, then it is important to examine the intervention characteristics and other factors that may affect outcomes.

There has been a proliferation of commercial brain training products purporting to improve cognitive function and reduce dementia risk. For older people, fear of cognitive decline and dementia may be a powerful motivator to seek such preventive interventions. However the development of such programmes has frequently outpaced thorough research into product benefits (Gates 2014; Lampit 2015). The World Alzheimer Report 2014 has reported that cognitively stimulating activities, including reading, playing musical instruments, and playing cards and board games, may be beneficial for improving and maintaining while preventing decline in cognitive functioning, although most of these activities have not been investigated in clinical trials. In this context of confusing and potentially misleading claims, this review is important to provide potential consumers with information on how best to spend time, effort, and money they might invest to prevent cognitive decline.

As well as informing individuals, the findings of this review may be useful to public health decision-making bodies, healthcare practitioners, and researchers, providing them with a comprehensive synthesis of information about the current state of the evidence, and identifying research gaps and unanswered questions in the field.

We also refer readers to companion reviews on the effects of computerised cognitive training on healthy people at midlife and in late life (Gates 2019a; Gates 2019b).

OBJECTIVES

To evaluate the effects of at least 12 weeks of computerised cognitive training (CCT) on maintaining or improving cognitive function and preventing dementia in people with mild cognitive impairment.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs, published or unpublished, reported in any language. Full reports and other types of reports, such as conference abstracts, were eligible for inclusion. We included studies involving both randomised and non-randomised trial arms but considered only results from the former. We included cross-over studies but extracted and analysed data from the first treatment period only.

Types of participants

We included studies of people with a diagnosis of mild cognitive impairment (MCI) or mild neurocognitive disorder (MND), or from a population at high risk of cognitive decline.

We accepted diagnoses of MCI, MND, and risk of cognitive decline made by the authors of each clinical trial and recorded the definitions used. These could include diagnostic assessment and/or subjective memory complaints with reduced scores on cognitive tests such as the Mini Mental State Examination. In all cases, an attempt should have been made by the trial authors to exclude dementia, and it was acceptable for the purpose of excluding dementia for a study to have used a cognitive score cut-off. Again, we accepted whatever cut-off study authors used, and we explored this as a possible source of heterogeneity.

We excluded studies of adults with a diagnosis of dementia, any other neurological condition, or psychiatric illness.

We contacted study authors if we needed clarification to determine health status. If we received no response, clinical experts in our review group classified the trials or listed them as 'Studies awaiting classification'.

Types of interventions

We included studies that compared cognitive training interventions using interactive computerised technology versus active or inactive control interventions over at least 12 weeks.

Experimental interventions had to adhere to the following criteria: any form of interactive computerised cognitive intervention, including computer exercises, computer games, mobile devices, gaming console, and virtual reality, that involve repeated practice on standardised exercises including a specified cognitive domain or domains, for the purpose of enhancing cognitive function.

By 'active control', we mean all those control conditions that involve unguided computer- and/or screen-based tasks that are not planned as interventions. These tasks can involve watching educational videos or playing computer games with no particular training component. By 'inactive control', we refer to control groups

for which no intervention is applied that may be expected to have an effect on cognition.

The minimum treatment duration was set at 12 weeks, and all included trials had to report outcomes at a minimum of one time point 12 or more weeks after randomisation. To evaluate the effects of training on meaningful long-term outcomes, it was necessary to make a judgement about the minimum 'dose' of training that may be required to effect an enduring change. Previous research suggests that acute brain changes can be seen following eight weeks of training (Engvig 2014), but we are unable to find any evidence that such brain changes persist. Most studies examining the benefits of brain and cognitive reserve identify long-term cognitive stimulation from years of education. We therefore made an arbitrary judgement that at least 12 weeks of regular cognitive training would be required for intervention to have an enduring effect. Addtionally, this time frame is consistent with recommendations from reviews of clinical trials (Lampit 2014a). It is recognised that the relationship between short-term cognitive training effects and maintenance of cognitive function over longer periods of time is unclear.

We excluded interventions that did not involve any form of computer delivery. We also excluded studies where researchers combined the experimental intervention with any other form of intervention, unless the added intervention was provided in a standardised manner to both experimental and control groups.

Types of outcome measures

Primary outcomes

Primary outcomes included the following.

- Incidence of all-cause dementia (measured as a dichotomous outcome).
- Global cognitive function (measured as a continuous outcome).

Global cognitive functioning could be measured using any validated tests, for example (but not limited to):

- Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog);
- Mini Mental State Examination (MMSE);
- Repeatable Battery for Assessment of Neuropsychological Status (RBANS); and
- Cambridge Cognition Examination (CAMCOG).

The main time point of interest was 'end of trial', defined as the time point with the longest period of follow-up from randomisation (see also section Data collection and analysis). We also extracted and presented outcome data reported at other time points after randomisation.

Secondary outcomes

Secondary outcomes included the following.

- Cognitive tests not included in the training programme, administered before and after training, that are any validated measure of:
    - episodic memory;
    - executive functioning;
    - speed of processing;
    - attention/working memory; or
    - verbal fluency.
- Quality of life/psychological well-being, either generic or disease-specific.
- Daily function, such as measures of instrumental activities of daily living.
- Number of participants experiencing one or more serious adverse events.

If a trial provided data on more than one cognitive scale for a specific outcome, we applied a predetermined hierarchy of cognitive outcome scales and used data on the cognitive scale that was highest on this hierarchy. For example, if a trial reported results on both the Mini Mental State Examination and the Clinical Dementia Rating scale (CDR), we used outcome data from the MMSE in our quantitative analyses. The order of a scale in the hierarchy was determined by the frequency of its use in a large set of 79 trials, evaluating vitamin and mineral supplementation, dietary interventions, and physical exercise interventions.

Outcomes included in the 'Summary of findings' table

We addressed critical effectiveness outcomes in a 'Summary of findings' table for each comparison. We planned to include all outcomes related to cognitive function on non-trained tasks and quality of life. For the comparison CCT versus active control, we were able to include the following outcomes: (1) global cognitive functioning, (2) episodic memory, (3) speed of processing, (4) executive functioning, (5) working memory, (6) verbal fluency, and (7) quality of life. For the comparison CCT versus inactive control, we were able to include the following outcomes: (1) global cognitive functioning, (2) episodic memory, (3) executive functioning, (4) verbal fluency, (5) depression, and (6) functional performance.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois) - the specialised register of the Cochrane Dementia and Cognitive Improvement Group - up to 31 May 2018.

The Information Specialist for the CDCIG maintained ALOIS, which contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive en-

hancement in the healthy elderly populations. These studies are identified through:

- monthly searches of several major healthcare databases: MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, and Latin American Caribbean Health Sciences Literature (LILACS);
- monthly searches of several trial registers: the University hospital Medical Information Network Clinical Trials Registry (Japan) (UMIN-CTR) (www.umin.ac.jp/ctr/index.htm); the World Health Organization (WHO) portal (which covers ClinicalTrials.gov (clinicaltrials.gov/); International Standard Randomized Controlled Trials Number (ISRCTN) (www.isrctn.com/); the Chinese Clinical Trials Register (ChiCTR) (who.int/ictrp/network/chictr/en/); the German Clinical Trials Register (GermanCTR) (who.int/ictrp/network/drks2/en/); the Iranian Registry of Clinical Trials (IRCT) (who.int/ictrp/network/irct2/en/); and the Netherlands National Trials Register (NTR) (who.int/ictrp/network/ntr/en/), plus others);
- quarterly searches of the Central Register of Controlled Trials, in the Cochrane Library (CENTRAL); and
- six-monthly searches of several grey literature sources: Institute for Scientific Information (ISI) Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS, see About ALOIS on the ALOIS website (www.medicine.ox.ac.uk/alois).
Details of the search strategies run in healthcare bibliographic databases, used for retrieval of reports of dementia, cognitive improvement, and cognitive enhancement trials, can be viewed in the 'Methods used in reviews' section within the editorial information about the Cochrane Dementia and Cognitive Improvement Group.
We conducted additional searches in MEDLINE, Embase, PsycINFO, CINAHL, ClinicalTrials.gov, and the WHO Portal/International Clinical Trials Registry Platform (ICTRP) (www.apps.who.int/trialsearch), to ensure that the searches were as comprehensive and as up-to-date as possible. The search strategies used are shown in Appendix 1.

Searching other resources

We screened the reference lists of all included trials. In addition, we screened the reference lists of recent systematic reviews, health technology assessment reports, and subject-specific guidelines identified through www.guideline.gov. We restricted the search to those guidelines meeting National Guideline Clearinghouse (NGC) 2013 published inclusion criteria.
We contacted experts in the field and companies marketing included interventions to request additional randomised trial reports not identified by the search.

Data collection and analysis

We used the protocol for this review alongside instructions for data extraction, quality assessment, and statistical analyses generated by the editorial board of CDCIG, and based in part on a generic protocol approved by the Cochrane Musculoskeletal Group for another series of reviews (da Costa 2012; da Costa 2014; Reichenbach 2010; Rutjes 2009a; Rutjes 2009b; Rutjes 2010).

Selection of studies

If multiple reports described the same trial, we included all of them to allow extraction of complete trial details.
We used crowdsourcing to screen the search results. Details of this approach have been described at www.medicine.ox.ac.uk/alois/content/modifiable-risk-factors. In brief, teams of volunteers performed a 'first assess' on the search results. The crowd was recruited through the network called Students For Best Evidence (www.students4bestevidence.net). The crowd provided an initial screen of the results using an online tool developed for the Cochrane EMBASE project, but tailored for this programme of work. The crowd decided (based on reading of title and abstract) whether the citation was describing a randomised trial or a quasi-randomised trial, irrespective of the citation topic. We then screened the remaining results (titles and abstracts). Four independent review authors (NG, EM, SK, RV) assessed the full text of studies for eligibility, with any disagreements resolved by a fifth independent review author.
We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table (Moher 2009). We did not impose any language restrictions.

Data extraction and management

Five review authors (NG, MN, SK, RV, AR), working independently, extracted trial information using a standardised and piloted extraction method, referring also to a guidance document, and resolving discrepancies by discussion, or by involvement of an independent review author. Where possible, we extracted the following information related to characteristics of participants, interventions, and study design.

Participant characteristics

- Gender
- Age (range, median, mean)
- Education (level and years of education)
- Baseline cognitive function
- Cognitive diagnostic status
- Duration of cognitive symptoms
- Ethnicity
- Apo-E genotype
- Vascular risk factors (hypertension, diabetes, hyperlipidaemia)

- Body mass index (BMI)
- Depression and stress
- Physical activity
- Work status

Intervention characteristics

- Type and description of cognition-based intervention
- Type and description of the control condition
- Delivery mode (individualised, group intervention, supervision)
- Length of training sessions (intensity)
- Frequency of sessions per week (dose)
- Duration of treatment programme
- Presence of supervision
- Group or individual
- Any concomitant treatments

Methodological characteristics

- Trial design (individual or cluster randomisation; parallel-group, factorial, or cross-over design)
- Number of participants
- Outcome measures used
- Duration of follow-up as measured from randomisation
- Duration of follow-up as measured from end of treatment
- Source of financial support
- Publication status

If outcome data were available at multiple time points within a given trial, we extracted data at 12 weeks, along with short-term (up to one year), medium-term (one to two years), and long-term results (more than two years). Within these time periods, we extracted the latest data reported by the study (e.g. if the study reports data at six months, nine months, and one year, we extracted only the one-year data, and we analysed these for the one-year (short-term) time point). For dichotomous outcomes (such as number of participants experiencing one or more serious adverse events), we extracted from each trial the number of participants with each outcome at each time point. For continuous outcomes, we extracted the number of participants for whom the outcome was measured, as well as the mean and standard deviation (SD) of the change from baseline for each outcome at each time point. If change from baseline data were not available, we extracted the mean value at each time point. When necessary and possible, we approximated means and measures of dispersion from figures in the reports. For cross-over trials, we extracted data on the first treatment period only. Whenever possible, we extracted intention-to-treat data (i.e. analysing all participants according to the group randomisation); if this information was not available, we extracted and reported data from available case analyses. If none of these data were available, we considered data from per-protocol analyses. We contacted the trial authors if we could not obtain necessary data from the trial report.

Assessment of risk of bias in included studies

After completion of a standardised training session provided by AR, one member of the review author team and one experienced review author provided by the editorial team independently assessed the risk of bias in each of the included trials, using Cochrane's 'Risk of bias' tool (Higgins 2011), and resolved disagreements by consensus. We assessed the risk of bias potentially introduced by suboptimal design choices with respect to sequence generation, concealment of allocation, blinding of participants and caregivers, blinded outcome assessment, selective outcome reporting, and incomplete outcome data, including the type of statistical analysis used (true intention-to-treat vs other). Based on the aforementioned criteria, we rated the studies as 'low risk', 'unclear risk', or 'high risk' of bias for each domain, including a description of the reasoning for our rating. The general definitions used are reported in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We derived review-specific definitions in part from a previously published systematic review (Rutjes 2012), and we have explained them in detail in Appendix 2.

Measures of treatment effect

The measure of treatment effect for continuous outcomes was an effect size (standardised mean difference), defined as the between-group difference in mean values divided by the pooled SD. In case a single trial contributed to a comparison, or if all studies used the same instrument, we used the mean difference to describe and analyse results. We expressed the treatment effect for dichotomous outcomes as a risk ratio (RR) with a 95% confidence interval (CI).

Unit of analysis issues

We identified no cluster-randomised trials for inclusion. We included one cross-over study, but we extracted and analysed data from the first treatment period only.

Dealing with missing data

Missing data in the individual trials may put study estimates of effects at high risk of bias and may lower the overall quality of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group (www.gradeworkinggroup.org). We dealt with missing data in our 'Risk of bias' assessments and planned evaluation of attrition bias in stratified analyses of the primary outcomes (Appendix 2; Differences between protocol and review). We analysed available information and did not contact study authors with a request to provide missing information, nor did we impute missing data ourselves.

Assessment of heterogeneity

We planned to examine between-trial heterogeneity in stratified analyses by trial, participant, and intervention. As the number

of trials identified was too small to permit meaningful analyses, we refrained from performing such analyses (Differences between protocol and review). We visually inspected forest plots for the presence of heterogeneity and calculated the variance estimate tau² as a measure of between-trial heterogeneity (DerSimonian 1986). We prespecified a tau² of 0.04 to represent low heterogeneity, 0.09 to represent moderate heterogeneity, and 0.16 to represent high heterogeneity between trials (Spiegelhalter 2004). In addition, we used the I² statistic and the corresponding Chi² test to assist readers more familiar with these statistics (Higgins 2011). I² describes the percentage of variation across trials attributable to heterogeneity rather than to chance, with values of 25%, 50%, and 75% interpreted as low, moderate, and high (respectively) between-trial heterogeneity. We preferred tau² over I² in interpreting between-trial heterogeneity, as interpretation of I² can be largely affected by the precision of trials included in the meta-analysis (Rcker 2008). All P values are two-sided.

Assessment of reporting biases

We did not identify enough trials to construct funnel plots to explore reporting biases and other biases related to small-study effects (Differences between protocol and review).

Data synthesis

We reported summary and descriptive statistics (means and SDs) for participant and intervention characteristics.

We used standard inverse-variance random-effects meta-analysis to combine outcome data across trials at end of trial (DerSimonian 1986), and, if possible, at least one additional time point (see Primary outcomes and Data collection and analysis for definitions of time points). We conducted statistical analyses in Review Manager 5 (RevMan 2014) and in STATA, release 14 (Statacorp, College Station, Texas, USA).

GRADE and 'Summary of findings' tables

We used GRADE to describe the quality of the overall body of evidence for each outcome in the 'Summary of findings' tables (Guyatt 2008; Higgins 2011). We defined quality as the degree of confidence that we can place in the estimates of treatment benefits and harms. There were four possible ratings: high, moderate, low, and very low. Rating evidence as 'high quality' implies that we are confident in our estimate of the effect and further research is very unlikely to change this. A rating of 'very low' quality implies that we are very uncertain about the obtained summary estimate of the effect. The GRADE approach rates evidence from RCTs that do not have serious limitations as 'high quality'. However, several factors can lead to downgrading of the evidence to 'moderate', 'low', or 'very low'. The degree of downgrading is determined by the seriousness of these factors: study limitations (risk of bias); inconsistency; indirectness of evidence; imprecision; and publication bias (Guyatt 2008; Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We did not identify enough trials to conduct subgroup analyses.

Sensitivity analysis

For the primary outcome, we performed one sensitivity analysis, including only those trials that used an internationally accepted definition of MCI.

RESULTS

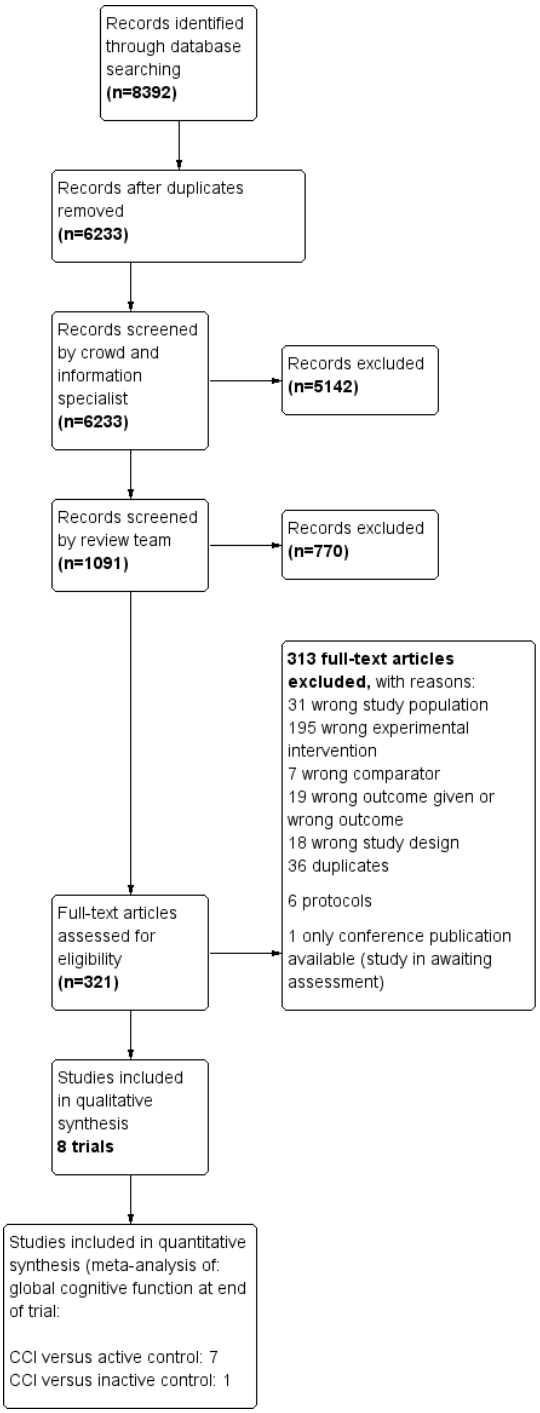
Description of studies

See Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification, and Characteristics of ongoing studies.

Results of the search

We conducted searches in January 2015, July 2015, February 2016, July 2016, and May 2018. In total, we retrieved 8392 records through the five searches. After de-duplication, 6233 records remained. A crowd and the CDCIG Information Specialist assessed these records at the title and abstract level. In total, 1091 results remained after this assessment. We then screened these records. Of these, we assessed 321 full-text articles for eligibility, and we included eight studies in the review (Barnes 2013; Djabelkhir 2017; Fiatarone Singh 2014; Gooding 2016; Herrera 2012; Kwok 2013a; Optale 2010; Rozzini 2007). We have depicted this process in Figure 1.

Figure 1. Study flow diagram.



Included studies

We have provided study details in the Characteristics of included studies section and have briefly summarised them below. We included in this review eight studies with a total of 660 participants.

Design

All studies are RCTs, with seven comparing CCT versus an active control and one versus an inactive control condition.

Study durations were 12 weeks (Kwok 2013a), three months (Barnes 2013; Djabelkhir 2017), four months (Gooding 2016), six months (Optale 2010), nine months (Herrera 2012), 12 months (Rozzini 2007), and 18 months (Fiatarone Singh 2014).

Sample size

Barnes 2013 randomised 126 participants to four different treatment arms (including one control arm), each with 31 or 32 participants. Djabelkhir 2017 randomised 10 participants to the experimental arm and 10 to the control arm. Fiatarone Singh 2014 randomised 51 participants to the experimental arms and 49 to the control arms. Gooding 2016 randomised 96 participants to the three arms of interest (the number of participants randomised to each arm is not reported). Herrera 2012 randomised 11 participants to both intervention and control groups. Kwok 2013a was the largest trial, with 111 participants randomised to the experimental arm and 112 to the control arm. Optale 2010 randomised 18 participants to each of the intervention and control groups. Finally, Rozzini 2007 randomised 15 participants to the intervention group and 22 to the control group.

Setting

Barnes 2013 was conducted at a single centre in the USA. Djabelkhir 2017 was conducted at a single centre in France. Fiatarone Singh 2014 was conducted in Australia. Gooding 2016 was conducted at four different sites in the USA; Herrera 2012 at a single centre in France; Kwok 2013a at six community centres randomly chosen from three districts in Hong Kong; Optale 2010 at a single centre; and Rozzini 2007 at two centres in Italy.

Participants

Four studies included participants with established MCI at baseline. Diagnostic criteria were consistent with Petersen criteria in Djabelkhir 2017, Herrera 2012 (Petersen 2004 criteria), Fiatarone Singh 2014 (Petersen 1999 criteria), and Rozzini 2007 (Petersen 2001 criteria). Optale 2010 included participants with a memory deficit defined by a corrected total score below 15.76 on the Verbal Story Recall (VSR) test. Barnes 2013, Gooding 2016, and Kwok 2013a included participants with self-reported or informant-reported cognitive complaints at baseline and satisfied our inclusion criteria, as participants had reduced scores on standardised dementia screening tests.

The mean age of participants in experimental and control groups ranged from 70 to 82 years. Rozzini 2007 gave an age range for participants (63 to 78 years), and Gooding 2016 gave only the median age for those who completed the study (76 years).

Interventions

Barnes 2013 used a 2 × 2 factorial design by which all participants received computerised training (Posit Science software) (MA-I) or active mental control educational videos (MA-C), along with an exercise regimen (EX-I) or a sham exercise regimen (EX-C) (Barnes 2013). We have included this study in comparison 1: computerised cognition-based interventions versus active control.

Djabelkhir 2017 treated the intervention group with a computerised multi-domain software programme (KODRO) and trained the control group to use a tablet PC and stiimulate social interactions among participants. We have included this study in comparison 1: computerised cognition-based interventions versus active control.

Fiatarone Singh 2014 used a 2 × 2 factorial design involving cognitive training (CT) with Cogpack computer-based exercises or sham cognitive training (watching educational videos followed by a set of questions), as well as progressive resistance training (PRT) or sham PRT (stretching and seated callisthenics exercises). We included all participants receiving CT (Cogpack) in the experimental group and all participants receiving sham CT in the active control group. We included these data in comparison 1: computerised cognition-based interventions versus active control.

Gooding 2016 included three study arms. One arm received computerised cognitive training in the BrainFitness programme, another arm received the same BrainFitness programme and a motivational therapeutic milieu (not included in the analysis). The third arm played computer games. We have included this study in comparison 1: computerised cognition-based interventions (BrainFitness programme only) versus active control.

Kwok 2013a provided 12 weekly sessions of computerised training focused on attention, memory, and reasoning as the experimental intervention. The control group received a series of health-related educational lectures on prevention of mood disorder, heart disease, diabetes, and stroke. We have included this study in comparison 1: computerised cognition-based interventions versus active control.

Herrera 2012 allocated the intervention group to computerised memory and attention task training programmed in Java, while the control group participated in activities such as finding names

of countries and corresponding capitals, organising a list of purchases by categories, and finding similarities and differences. We have included this study in comparison 1: computerised cognition-based interventions versus active control.

Optale 2010 provided virtual reality training as the experimental intervention and music therapy as the control intervention. We have included this study in comparison 1: computerised cognition-based interventions versus active control.

Rozzini 2007 included three study arms. One arm received CT through a computerised multi-domain software programme (TNP software) plus a cholinesterase inhibitor; another arm received a cholinesterase inhibitor only; and the third arm received neither CT nor cholinesterase inhibitor treatment (not included in the analysis). We have included data from the first two arms in comparison 2: computerised cognition-based interventions versus inactive control.

Outcomes

Here we describe outcome measures addressing outcomes of interest to our review that we included in one or more meta-analyses. We refer to the Characteristics of included studies table for other instruments reported by trial authors that we did not select for any meta-analyses. We have described under Types of outcome measures the method used to select outcome measures for inclusion.

Primary outcomes

Global cognitive function

Eight studies measured global cognitive function as an outcome. Four studies measured global cognitive functioning using the MMSE (Djabelkhir 2017; Optale 2010; Rozzini 2007; with the modified MMSE (mMMSE) used in Gooding 2016); Kwok 2013a used the Chinese equivalent of the Mattis Dementia Rating Scale; and Fiatarone Singh 2014 used ADAS-Cog.

Barnes 2013 used a composite score change at three months to measure global cognitive functioning. We could not include this outcome in the meta-analyses (see Effects of interventions).

Secondary outcomes

Cognitive function subdomain: episodic memory

One study used the Rey Auditory Verbal Learning Test (RAVLT) to measure episodic memory (Barnes 2013). Fiatarone Singh 2014 used the Wechsler Memory Scale (WMS) Logical Memory I (immediate) at 6 months and 18 months; Gooding 2016 used the WMS Logical Memory II (delayed). Optale 2010, and Rozzini 2007 used non-specified story recall. Herrera 2012, and Djabelkhir 2017 measured episodic memory using a list learning task: the 16-Item free recall (FR) and cued recall (CR) test (16-FR/CR test).

Cognitive function subdomain: executive functioning

Two studies used Trails B to measure executive functioning (Barnes 2013; Djabelkhir 2017).

Fiatarone Singh 2014 measured executive function on the Similarities subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III) at 6 and 18 months; Optale 2010 used dual task performance to measure executive functioning; and Rozzini 2007 measured executive functioning using Raven's coloured matrices.

Cognitive function subdomain: speed of processing

Two studies used Trails A to measure speed of processing (Barnes 2013; Djabelkhir 2017).

Fiatarone Singh 2014 measured speed of processing using the Symbol Digit Modality Test (SDMT) at 6 months and 18 months.

Cognitive function subdomain: verbal fluency

Several studies measured verbal fluency using letter verbal fluency (number of words generated beginning with specified letters), including Barnes 2013, which measured in one minute all the words the attendee could remember, words not stated, one attempt; Djabelkhir 2017, which measured in two minutes all the words the attendee could remember, starting with the letter P, attempts not stated; Fiatarone Singh 2014, which used the Controlled Oral Words Association Test,(COWAT); Optale 2010, which measured in one minute all the words the attendee could remember, starting with the letters C, P, and S, attempts not stated; and Rozzini 2007, which measured in one minute all the words the attendee could remember, words not stated, attempts not stated.

Cognitive function subdomain: working memory

Three studies used the digit span to measure working memory: Djabelkhir 2017 (WAIS, 4th edition), Herrera 2012 (not stated), and Optale 2010 (WAIS procedure).

Quality of life/Psychological well-being

Two studies measured depression using the Geriatric Depression Scale (Optale 2010; Rozzini 2007): Djabelkhir 2017 measured

depression using the Goldberg Scale, and Gooding 2016 measured depression using the Beck Depression Inventory.
Djabelkhir 2017 measured quality of life using the quality of life scale for older French people.

Functional performance

Only three studies measured this outcome: Fiatarone Singh 2014 and Rozzini 2007 measured daily function with the BAYER - Activities of Daily Living scale (B-ADL), and Optale 2010 used the Activities of Daily Living - Function scale.

Number of participants experiencing one or more serious adverse events

Optale 2010 reported mortality at six months.

Excluded studies

We excluded 312 full-text articles during the full-text screening. Of these, we excluded one because it focused on cognitively healthy people in midlife (Corbett 2015), and we excluded nine because they focused on cognitively healthy people in late life (Desjardins-Crépeau 2016; Klusmann 2010; Lampit 2014; Lampit 2015; Legault 2011; Leung 2015; Peretz 2011; Shatil 2013; Van het Reve 2014). Two other Cochrane reviews have included these 10 studies (Gates 2019a; Gates 2019b). We excluded 195 reports that investigated an intervention because it was provided for less than 12 weeks or because it did not involve computerised cognitive training; and we excluded 18 because the study did not use an eligible study design. We identified no ongoing trials in the trial registers or conference proceedings. One study is awaiting classification because, at the time of the final search, it was available only as a conference abstract from which eligibility could not be determined (not clear how cognitive training was delivered). Reasons for exclusion of studies can be found in the Characteristics of excluded studies table.

Risk of bias in included studies

For details, please see Characteristics of included studies. Figure 2 and Figure 3 display study level and aggregate results of the risk of bias assessments.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

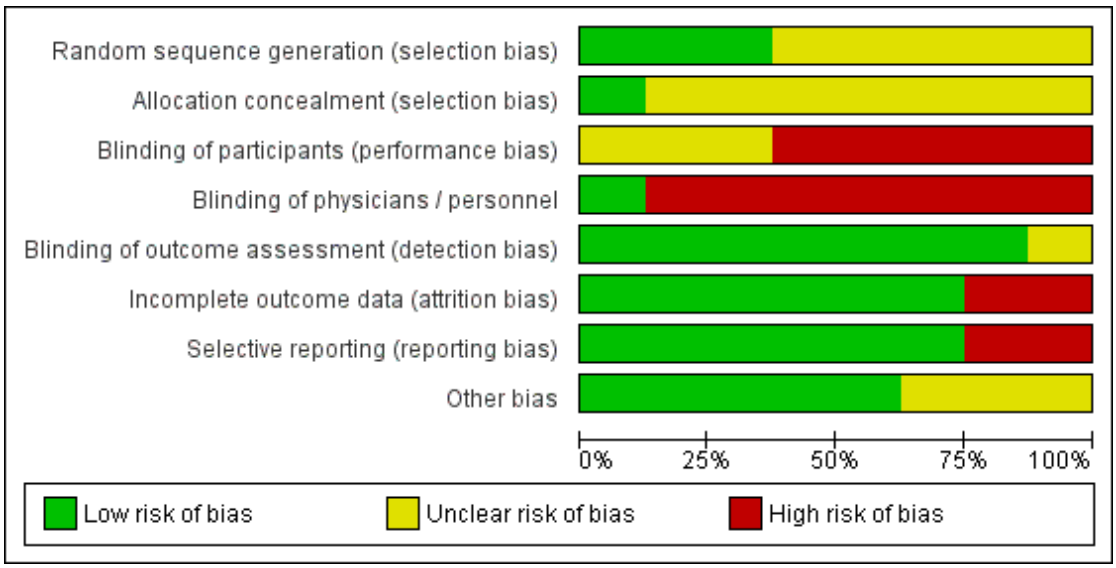


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

One study has low risk of selection bias due to adequate random sequence generation and allocation concealment (Fiatarone Singh 2014). Two studies have unclear risk of selection bias because allocation concealment was not described in sufficient detail, although the study authors described an adequate method for generating a random sequence (Barnes 2013; Djabelkhir 2017). The remaining studies did not describe any method for sequence generation nor allocation concealment (Gooding 2016; Herrera 2012; Kwok 2013a; Optale 2010; Rozzini 2007); we also judged these studies to be at unclear risk of selection bias.

Blinding

We considered Barnes 2013 to have high risk of performance bias because participants were not blinded to the type of intervention. However, both study personnel and outcome assessors were adequately blinded to the study treatment; therefore we judged the risk of detection bias to be low. We judged Fiatarone Singh 2014, Djabelkhir 2017, and Herrera 2012 to have unclear risk of performance bias for participants and high risk of performance bias for personnel, who were not blinded. However, study authors described adequate blinding of outcome assessors, giving these studies low risk of detection bias. We considered Kwok 2013a, Optale 2010, and Rozzini 2007 to be at high risk of performance bias due to lack of blinding for participants and personnel, but at low risk of detection bias as outcome assessors were adequately blinded. Gooding 2016 did not blind participants nor physicians (high risk of performance bias), and we identified unclear risk of detection bias due to lack of information regarding blinding of outcome assessors.

Incomplete outcome data

We considered six studies to be at low risk of attrition bias (Barnes 2013; Djabelkhir 2017; Fiatarone Singh 2014; Herrera 2012; Kwok 2013a; Rozzini 2007). We judged risk of attrition bias to be high in Gooding 2016 because 77% of randomised participants were analysed. In Optale 2010, 83% of participants randomised to the intervention arm and 89% randomised to the control arm were analysed; we judged this to put the study at high risk of attrition bias.

Selective reporting

We considered six studies to be at low risk of reporting bias (Barnes 2013; Djabelkhir 2017; Fiatarone Singh 2014; Gooding 2016; Herrera 2012; Rozzini 2007). We judged the remaining two studies to be at high risk of reporting bias. Optale 2010 did not report one outcome that was described as measured and Kwok 2013a incompletely reported outcome data described as non-significant.

Other potential sources of bias

We identified no other sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

Comparison 1: computerised cognition-based interventions versus active control

See Summary of findings for the main comparison for the comparison CCT versus active control. Although Barnes 2013 reported eligible outcome data for all cognitive outcomes, we could not include these data in our meta-analyses because the data were reported as standardised mean changes (z-scores). Therefore, we report these results separately.

Primary outcomes

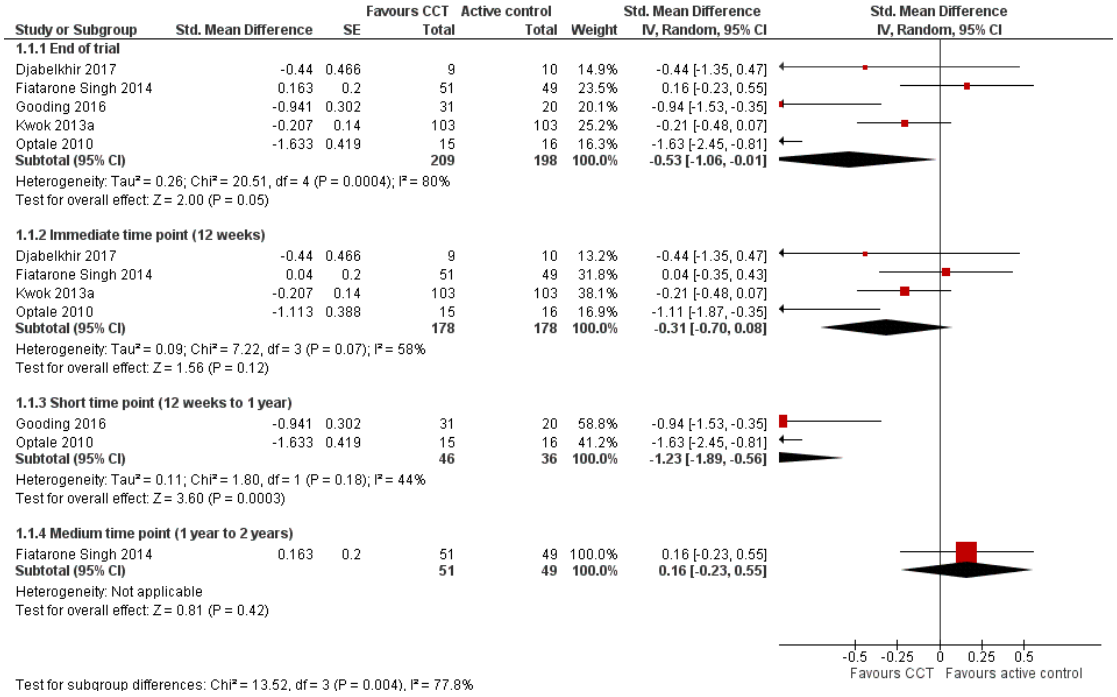
Incidence of dementia

We found no data on the incidence of dementia.

Global cognitive function

Evidence on global cognitive function at end of trial (Analysis 1.1; Figure 4) was very low quality, downgraded because of imprecision, inconsistency, and risk of bias. Therefore we are very uncertain of this result. Negative values favour the CCT group. Analysis of global cognitive function at end of follow-up gives a standardised mean difference (SMD) of -0.53 (95% confidence interval (CI) -1.06 to -0.01; 5 studies; 407 participants). Results at individual time points are as follows: immediate time point (12 weeks) SMD -0.31 (95% CI -0.70 to 0.08; 4 studies; 356 participants); short-term time point (12 weeks to one year) SMD -1.23 (95% CI -1.89 to -0.56; 2 studies; 82 participants); and medium-term time point (one to two years) SMD 0.16 (95% CI -0.23 to 0.55; 1 study; 100 participants).

Figure 4. Forest plot of comparison: 1 Computerised cognition-based interventions versus active control, outcome: 1.1 Global cognitive function.



Trial with outcome data not included in the meta-analyses

Barnes 2013 derived a composite score from six distinct cognitive instruments at three months. Higher values indicated improvement. Study authors reported there were no significant differences between groups (P from interaction = 0.26). In the comparison between groups also receiving sham exercise, the mean change in z-score was 0.17 in the CCT group (95% CI 0.03 to 0.31) and 0.16 in the educational DVD group (95% CI 0.05 to 0.26). In the comparison between groups also receiving aerobic exercise, the mean z-score change was 0.22 in the CCT group (95% CI 0.12 to 0.33) and 0.08 in the educational DVD control group (95% CI -0.004 to 0.17). Overall we deemed the quality of this evidence to be very low (downgraded for imprecision, indirectness of the study population, and risk of bias).

Sensitivity analyses

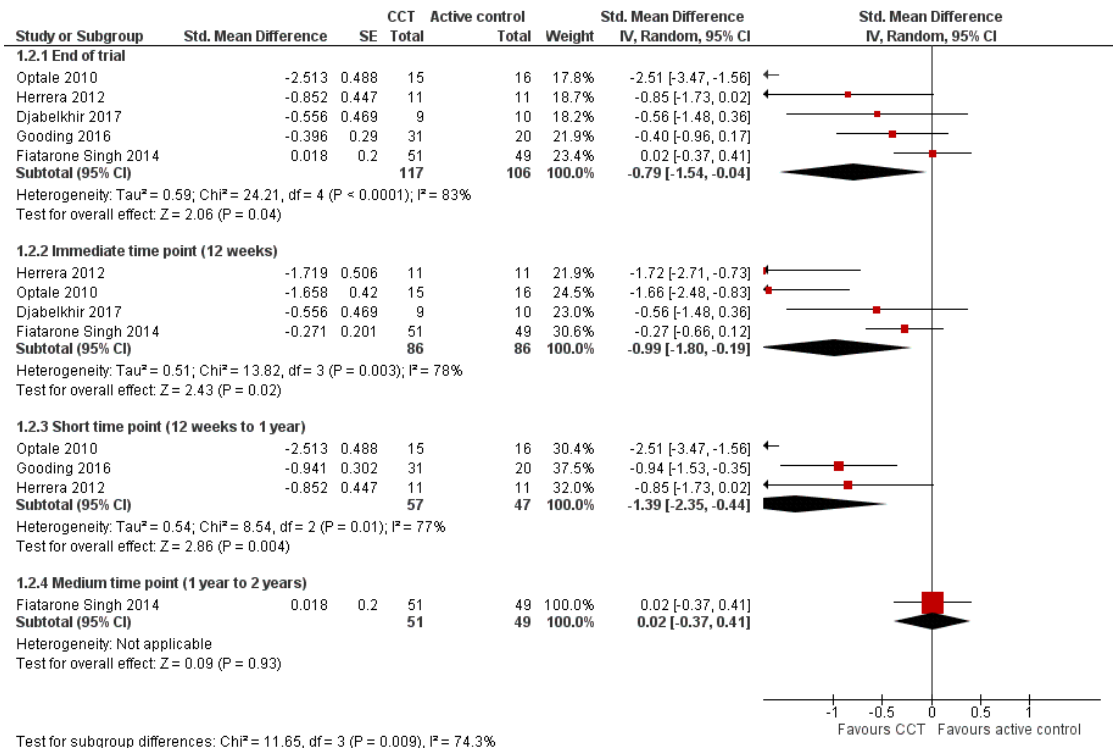
We conducted a prespecified sensitivity analysis including only trials in which MCI was diagnosed on the basis of internationally accepted diagnostic criteria. Two studies with 119 participants contributed to this analysis (Djabelkhir 2017; Fiatarone Singh 2014). At our main time point of interest - end of trial - we found no clear evidence of an effect of training: SMD 0.01 (95% CI -0.51 to 0.52; Tau² = 0.05; I² = 29%). We considered this to be low-quality evidence (downgraded for imprecision and risk of bias).

Secondary outcomes

Cognitive subdomain: episodic memory

Evidence regarding episodic memory at end of trial (Analysis 1.2; Figure 5) was very low quality, downgraded because of imprecision, inconsistency, and risk of bias. Therefore we are very uncertain about this result. Negative values favour the CCT group. Analysis at end of follow-up gives an SMD of -0.79 (95% CI -1.54 to -0.04; 5 studies; 223 participants). Results at individual time points are as follows: immediate time point (12 weeks) SMD -0.99 (95% CI -1.80 to -0.19; 4 studies; 172 participants); short-term time point (12 weeks to one year) SMD -1.39 (95% CI -2.35 to -0.44; 3 studies; 104 participants); and medium-term time point (one to two years) SMD 0.02 (95% CI -0.37 to 0.41; 1 study; 100 participants).

Figure 5. Forest plot of comparison: 1 Computerised cognition-based interventions versus active control, outcome: 1.2 Episodic memory.



Trial with outcome data not included in the meta-analyses

Barnes 2013 reported outcome data on verbal learning and memory (RAVLT), number of words learned, as standardised mean changes (z-scores) at three months. Higher values indicated improvement. Study authors reported no significant differences between groups (P from interaction = 0.38). In the comparison between groups receiving sham exercise, the mean change in z-score was 0.13 in the CCT group (95% CI -0.11 to 0.37) and 0.33 in the educational DVD group (95% CI 0.09 to 0.58). In the comparison between groups receiving aerobic exercise, the mean change in z-score was -0.04 in the CCT group (95% CI -0.42 to 0.33) and 0.14 in the educational DVD control group (95% CI -0.14 to 0.43). We judged the quality of this evidence to be very low (downgraded for imprecision, indirectness of the study population, and risk of bias).

Cognitive subdomain: speed of processing

Evidence regarding speed of processing at end of trial (Analysis 1.3) was low quality, downgraded because of imprecision and risk of bias. Negative values favour the CCT group. Analysis at end of follow-up gives an SMD of 0.20 (95% CI -0.16 to 0.56; 2 trials; 119 participants). This result is imprecise but indicates there may be little or no difference in the speed of processing between intervention and control groups. Results at individual time points are as follows: immediate time point (12 weeks) SMD 0.11 (95% CI -0.25 to 0.47; 2 studies; 119 participants) and medium-term time point (one to two years) SMD 0.14 (95% CI -0.25 to 0.53; 1 study; 100 participants).

Trial with outcome data not included in the meta-analyses

Barnes 2013 reported outcome data on Trail Making test part A as standardised mean changes (z-scores) at three months. Lower values indicated improvement. Study authors reported no significant differences between groups (P from interaction = 0.24). In the comparison between groups receiving sham exercise, the mean change in z-score was -0.03 in the CCT group (95% CI -0.50 to 0.44) and -0.36 in the educational DVD group (95% CI -0.58 to -0.15). In the comparison between groups receiving aerobic exercise, the mean change in z-score was -0.36 in the CCT group (95% CI -0.63 to -0.08) and -0.12 in the educational DVD con-

trol group (95% CI -0.32 to 0.07). We judged the quality of this evidence to be very low (downgraded for imprecision, indirectness of the study population, and risk of bias).

Cognitive subdomain: executive function

Evidence regarding executive function at end of trial (Analysis 1.4) was very low quality, downgraded because of imprecision, inconsistency, and risk of bias. Therefore we are very uncertain about this result. Negative values favour the CCT group. Analysis at end of follow-up gives SMD -0.31 (95% CI -0.90 to 0.28; 3 studies; 150 participants). Results at individual time points are as follows: immediate time point (12 weeks) SMD -0.18 (95% CI -0.50 to 0.14; 3 studies; 150 participants); short-term time point (12 weeks to one year) SMD -0.81 (95% CI -1.54 to -0.07; 1 study; 31 participants); and medium-term time point (one to two years) SMD 0.08 (95% CI -0.31 to 0.48; 1 study; 100 participants).

Trial with outcome data not included in the meta-analyses

Barnes 2013 reported outcome data on Trail Making test part B as standardised mean changes (z-scores) at three months. Lower values indicated improvement. No differences between groups were found (P from interaction = 0.31). In the comparison between groups receiving sham exercise, the mean change in z-score was 0.13 in the CCT group (95% CI -0.21 to 0.48) and -0.22 in the educational DVD group (95% CI -0.45 to 0.002). In the comparison between groups receiving aerobic exercise, the mean change in z-score was -0.25 in the CCT group (95% CI -0.51 to 0.01) and -0.18 in the educational DVD control group (95% CI -0.49 to 0.13). We judged the quality of this evidence to be very low (downgraded for imprecision, indirectness of the study population, and risk of bias).

Cognitive subdomain: working memory

Evidence regarding working memory at end of trial (Analysis 1.5) was very low quality, downgraded because of imprecision, inconsistency, indirectness, and risk of bias. Therefore we are very uncertain about this result. Negative values favour the CCT group. Analysis at end of follow-up gives SMD -0.88 (95% CI -1.73 to -0.03; 3 studies; 72 participants). Results at individual time points are as follows: immediate time point (12 weeks) SMD -0.66 (95% CI -1.26 to -0.06; 3 studies; 72 participants) and short-term time point (12 weeks to one year) SMD -1.29 (95% CI -1.88 to -0.69; 2 studies; 53 participants).

Cognitive subdomain: verbal fluency

Evidence regarding verbal fluency at end of trial (Analysis 1.6) was low quality, downgraded because of imprecision and risk of bias. Negative values favour the CCT group. Analysis at end of follow-up gives SMD -0.16 (95% CI -0.76 to 0.44; 3 studies; 150 participants). Results at individual time points are as follows: immediate time point (12 weeks) SMD -0.02 (95% CI -0.46 to 0.42; 3 studies; 150 participants), short-term time point (12 weeks to one year) SMD -0.78 (95% CI -1.51 to -0.04; 1 study; 31 participants), and medium-term time point (one to two years) SMD 0.17 (95% CI -0.22 to 0.57; 1 study; 100 participants).

Trial with outcome data not included in the meta-analyses

Barnes 2013 reported outcome data on verbal fluency - number of words, by letter, as standardised mean changes (z-scores) at three months. Higher values indicated improvement. Researchers found no differences between groups (P from interaction = 0.57). In the comparison between groups receiving sham exercise, the mean change in z-score was 0.24 in the CCT group (95% CI -0.11 to -0.58) and -0.05 in the educational DVD group (95% CI -0.33 to 0.24). In the comparison between groups receiving aerobic exercise, the mean change in z-score was 0.22 in the CCT group (95% CI -0.15 to 0.58) and 0.08 in the educational DVD control group (95% CI -0.21 to 0.37). We judged the quality of this evidence to be very low (downgraded for imprecision, indirectness of the study population, and risk of bias).

Depression

Evidence regarding depression at end of trial (Analysis 1.7) was very low quality, downgraded because of imprecision, indirectness, and risk of bias. Negative values favour CCT. Analysis at end of follow-up gives SMD of -0.77 (95% CI -2.07 to 0.52; 3 studies; 101 participants). Results at individual time points are as follows: immediate time point (12 weeks) SMD 0.22 (95% CI -0.68 to 1.13; 1 study; 19 participants) and short-term time point (12 weeks to one year) SMD -1.26 (95% CI -3.11 to 0.59; 2 studies; 82 participants).

Functional performance

Evidence regarding functional performance (Analysis 1.8) was very low quality, downgraded because of imprecision, indirectness, and risk of bias. Therefore we are very uncertain about this result. Negative values favour CCT. Analysis at end of follow-up gives SMD 0.09 (95% CI -0.51 to 0.70; 2 studies; 131 participants). Results at individual time points are as follows: immediate time point (12 weeks) SMD 0.33 (95% CI -0.02 to 0.67; 2 studies; 131 participants), short-term time point (12 weeks to one year) SMD -0.29 (95% CI -1.00 to 0.41; 1 study; 31 participants), and medium-term time point (one to two years) SMD 0.34 (95% CI -0.06 to 0.73; 1 study; 100 participants).

Quality of life

Evidence regarding quality of life at end of trial (12 weeks) (Analysis 1.9) was low quality, downgraded because of imprecision and risk of bias. Negative values favour CCT. The mean difference (MD) was 0.40 (95% CI -1.85 to 2.65; 1 study; 19 participants). This result indicates that there may be little or no difference in quality of life between intervention and control groups.

Serious adverse events: mortality

Evidence regarding serious adverse events: mortality (Analysis 1.10) comes from a single study and was very low quality, downgraded because of imprecision (double downgrading) and risk of bias (Optale 2010). At short-term follow-up (12 weeks to one year), the risk ratio (RR) was 0.50 (95% CI 0.05 to 5.04; 1 study; 36 participants).

Comparison 2: computerised cognition-based interventions versus inactive control

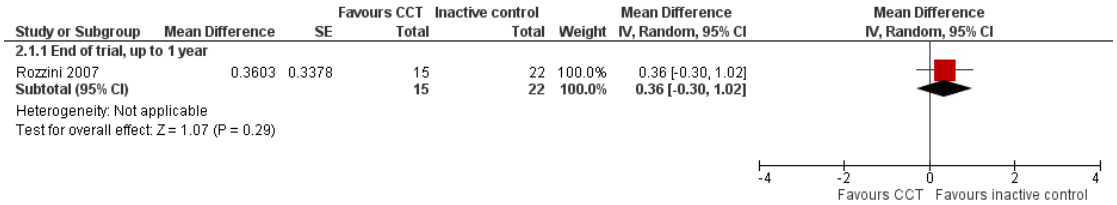
See Summary of findings 2 for the comparison CCT versus inactive control. This comparison included only one study (Rozzini 2007). No data on incidence of dementia were available.

Primary outcomes

Global cognitive function

Evidence on global cognitive function at end of trial (12 months) (Analysis 2.1; Figure 6) was very low quality, downgraded because of imprecision, indirectness, and risk of bias. Therefore we are very uncertain about this result. The MD was 0.36, favouring the inactive control group (95% CI -0.30 to 1.02; 37 participants).

Figure 6. Forest plot of comparison: 2 Computerised cognition-based interventions versus inactive control, outcome: 2.1 Global cognitive function.



Sensitivity analyses

As only a single trial contributed to the comparison, we performed no sensitivity analysis.

Secondary outcomes

Cognitive subdomain: episodic memory

Evidence regarding episodic memory at end of trial (12 months) (Analysis 2.2) was very low quality, downgraded because of imprecision, indirectness, and risk of bias. Therefore we are very uncertain about this result. The MD was -2.70, favouring CCT (95% CI -5.00 to -0.40; 37 participants).

Cognitive subdomain: executive function

Evidence regarding executive function at end of trial (12 months) (Analysis 2.3) was very low quality, downgraded because of imprecision, indirectness, and risk of bias. Therefore we are very uncertain about this result. Negative values favour the CCT group. Analysis at end of follow-up gives MD -2.70 (95% CI -6.21 to 0.81; 37 participants).

Cognitive subdomain: verbal fluency

Evidence regarding verbal fluency at end of trial (Analysis 2.4) was very low quality, downgraded because of imprecision, indirectness, and risk of bias. Negative values favour the CCT group. Therefore we are very uncertain about this result. Analysis at end of follow-up gives MD 1.90 (95% CI -4.50 to 8.30; 37 participants).

Depression

Evidence regarding depression at end of trial (Analysis 2.5) was very low quality, downgraded because of imprecision, indirectness, and risk of bias. Therefore we are very uncertain about this result.

Negative values favour CCT. Analysis at end of follow-up gives MD -1.30 (95% CI -2.61 to 0.01; 37 participants).

Functional performance

Evidence regarding functional performance (Analysis 2.6) was very low quality, downgraded because of imprecision, indirectness, and risk of bias. Therefore we are very uncertain about this result. Negative values favour CCT. Analysis at end of follow-up gives MD 0.00 (95% CI -0.48 to 0.48; 37 participants).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Computerised cognitive training compared with inactive control in people with mild cognitive impairment

Patient or population: patients with mild cognitive impairment
Settings: general population
Intervention: computerised cognitive training
Comparison: inactive control

Outcomes	Difference between CCT and control (95% CI)*	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Global cognitive functioning (measured at 12 months of follow-up)	MD 0.36 lower (0.30 lower to 1.02 higher)	37 participants (1 study)	⊕◯◯◯ **very low**[b]	It is uncertain whether CCT maintains global cognitive functioning better than inactive control
Episodic memory (measured at 12 months of follow-up)	MD 2.70 lower (5.00 lower to 0.40 lower)	37 participants (1 study)	⊕◯◯◯ **very low**[b]	It is uncertain whether CCT improves episodic memory compared to inactive control
Executive function (measured at 12 months of follow-up)	MD 2.70 lower (6.21 lower to 0.81 higher)	37 participants (1 study)	⊕◯◯◯ **very low**[b]	It is uncertain whether CCT improves executive function compared to inactive control
Verbal fluency (measured at 12 months of follow-up)	MD 1.90 higher (4.50 lower to 8.30 higher)	37 participants (1 study)	⊕◯◯◯ **very low**[b]	It is uncertain whether CCT improves verbal fluency compared to inactive control
Depression (measured at 12 months of follow-up)	MD 1.30 lower (2.61 lower to 0.01 higher)	37 participants (1 study)	⊕◯◯◯ **very low**[b]	It is uncertain whether CCT improves depression compared to inactive control
Functional performance (measured at 12 months of follow-up)	MD 0.00 lower (0.48 lower to 0.48 higher)	37 participants (1 study)	⊕◯◯◯ **very low**[b]	It is uncertain whether CCT improves functional performance compared to inactive control

* The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CCT: computerised cognitive training; CI: confidence interval; MD: mean difference; RR: risk ratio

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]The direction of the difference in effect was standardised so that lower values favour CCT and higher values favour control
[b]Downgraded 3 levels for imprecision (confidence interval included effects that are not clinically relevant), risk of bias, and indirectness (cholinesterase inhibitors were included in the comparison which is not an approved medication for MCI patients)

DISCUSSION

Summary of main results

This review examined the effects of computerised cognitive training (CCT), compared to active or inactive controls, on cognitive function in adults with mild cognitive impairment (MCI). Eight randomised controlled trials (RCTs) with a total of 660 participants were included. None of the studies reported on the incidence of dementia. All evidence was low or very low quality.

Seven trials compared CCT to a variety of active control interventions. Evidence was low quality (two outcomes) or very low quality (all other outcomes), and 95% confidence intervals (CIs) of the effect estimates were very wide, so we are very uncertain about all effect estimates. In our analyses, CCT appeared to improve performance on the primary outcome global cognition, and on secondary outcomes episodic memory and working memory, compared to active controls. However, these results are based on very low-quality evidence. We found no evidence for effects on the cognitive subdomains of speed of processing, verbal fluency, and executive function, nor on functional performance, quality of life, depression, and serious adverse events, although, again, a high level of uncertainty is associated with all these results.

One small study compared CCT versus an inactive control intervention. Evidence for all outcomes was very low quality, so we were very uncertain about all results. With this caveat, CCT was favoured for episodic memory and executive function, but researchers found no evidence of effects on global cognition (primary outcome) nor on any of the secondary outcomes.

Overall completeness and applicability of evidence

The search was very broad including multiple data sources, all article forms, and publications in any language, so it is unlikely that relevant trials were missed. We searched for unpublished and ongoing data, but we had to rely on published data only to complete analyses. Although we did not detect publication bias, we could not formally assess this via funnel plot evaluations because of the small number of trials identified. Our objective was to measure treatment effects in participants with MCI at baseline, but we also included trials that sampled participants with cognitive deficits not meeting the MCI diagnosis (Barnes 2013; Optale 2010). We restricted inclusion to trials with a treatment duration of at least 12 weeks, and we excluded a significant number of trials with shorter periods of intervention. Although we think that a shorter treatment duration is less likely to result in treatment effects, our decision implies that our results may not be applicable to intervention programmes of shorter duration. An important limitation of this review is that we did not identify any trial with sufficiently long follow-up to measure effects on the incidence of all-cause dementia.

Quality of the evidence

We restricted inclusion to RCTs that we deemed to use the most valid approach in measuring treatment effects related to this topic. We identified several limitations of the included studies, and we classified none as having low risk of bias. We judged that only one study described adequate methods of both randomisation and allocation concealment and hence had low risk of selection bias (Fiatarone Singh 2014). We considered none of the included studies to have low risk of performance bias. Most studies had low risk of detection, attrition, and reporting bias.

Upon applying GRADE criteria, we considered the quality of evidence across outcomes to be very low or low, indicating that our confidence in the effect estimate is limited and, for most outcomes, very limited. Identified issues involving quality were due to imprecision, inconsistency, indirectness, and risk of bias.

Potential biases in the review process

We adhered to high standards in conducting our review, with at least two review authors independently performing trial selection, data extraction, and quality assessment to minimise bias and transcription errors. Tools used for quality assessment of trials and the overall body of evidence are those advised by the Cochrane Collaboration and the GRADE Working Group. We faced an important challenge in this and in our other Cochrane reviews evaluating CCT: the use of multiple instruments to measure a specific cognitive outcome within and across trials. Whereas others may have preferred to consider a single preferred instrument for each cognitive domain, using the mean difference to combine outcome data across trials, we preferred to use a hierarchy to select outcome data from a single validated instrument, employing the standardised mean difference (SMD) to combine outcome data across trials. Both strategies have advantages and disadvantages. For example, with the first approach, most trials will not be considered in the meta-analyses, as studies reported large variation in the use of instruments. The advantage is that all outcome data can be easily interpreted on the natural scale. The advantage of using a hierarchy is that it allows for inclusion of all trials but makes interpretation of effect size (SMD) less intuitive. In addition, some claim that combining data derived from multiple instruments increases between-trial heterogeneity. However, empirical evidence that supports such a claim is lacking in the field of cognitive functioning. Yet another method is to consider all reported outcome data for a specific cognitive domain, and to combine outcome data from all instruments within a trial before pooling across trials. Although this method may be valid if individual patient data are available, we deem the risk of ecological fallacy to be high when only group means are available. For this reason, we did not use such an approach. Some trials reported outcome data as z-score changes, and even after we consulted several experienced statisticians, we were unable to transform these data to allow inclusion in the meta-

analyses. A future update of this review would benefit from clear author descriptions regarding the type of z-score used and access to data supplements where estimates with confidence intervals are provided on the natural scale for each instrument.
In summary, our review is limited by the quality of included trials and the diversity of instruments reported to measure outcomes.

Agreements and disagreements with other studies or reviews

When we applied our rigorous quality assessment methods, we found only very low-quality evidence for any beneficial effects of CCT. Two recent reviews have reported some positive results. In a recent review - Hill 2016 - review authors found an overall positive effect on cognition across 17 MCI trials (Hedges' g = 0.35, 95% CI 0.20 to 0.51) and small to moderate effects for global cognition, attention, working memory, learning, memory, and psychosocial functioning, including depressive symptoms. In a meta-analysis, Chandler 2016 examined the effects of cognitive interventions on more general outcome measures in MCI, including activities of daily living, mood, and quality of life; review authors identified only six computerised cognitive intervention studies and found that researchers reported benefits for mood (depression, anxiety, and apathy) among participants given the intervention compared to those given controls.
However, overall, the literature remains mixed. In adults with MCI or preclinical and early dementia, the number of clinical trials remains rather limited and studies show considerable differences between trial interventions and study methods (Gates 2014). Although multiple reviews of cognitive interventions in MCI have reported significant immediate and longer-term benefits for cognitive function, they reported on different types of interventions such as CCT, along with cognitive stimulation and remediation, or they included mixed populations (e.g. Chandler 2016; Coyle 2014; Kurz 2009; Reijnders 2013; Simon 2012).
Subjective cognitive decline (SCD) is another cognitive category that includes healthy older adults who report concerns about a decline in cognitive function, although their performance on cognitive tests is within normal limits (Jessen 2014). Emerging evidence suggests that SCD may represent a preclinical phase of Alzheimer's disease. Therefore it is noteworthy that a recent meta-analyses of interventions in SCD showed benefits for cognitive outcomes following cognitive training, even compared to active controls (Smart 2017).

AUTHORS' CONCLUSIONS

Implications for practice

It is accepted that mild cognitive impairment (MCI) may represent a transitional state between normal aging and clinical dementia in some individuals; therefore it has been seen as an optimal period for intervention.

We were unable to draw any firm conclusions about the efficacy of computerised cognitive training (CCT) because of the quality of available evidence gathered for this review. However, our results suggest that CCT may have positive effects on global cognitive function, episodic memory, and working memory, when compared to involvement in other cognitively stimulating activities.

Implications for research

Adults with MCI and subjective cognitive decline (SCD) may possibly benefit from CCT in terms of improved cognitive function. This intervention therefore warrants longer-term and larger-scale trials of improved methodological quality to examine effects on cognition, conversion to dementia, daily functioning, mental well-being and quality of life.

Key methodological considerations for future studies relate to selection of outcome measures, duration of follow-up, and study design. First, greater attention must be paid to generalisation of benefits from trained tasks to other cognitive activities and daily function. For any programme of CCT to be useful, training must demonstrate transfer of benefits from trained to untrained tasks, and then generalisation to global function, real-world skills, daily function, and mental health. Selected outcomes should be sensitive to subtle, and possibly non-linear change; must have high reliability; are available in alternative forms or are psychometrically robust for repeated use; and are not affected by floor and ceiling effects.

Second, assessing the maintenance of any training gains is important. Studies with longer follow-up are needed to measure change immediately after the intervention ends and then over time.

Third, improved reporting of study methods should be a matter of priority because of the high proportion of unclear risks of bias. Studies should adhere to CONSORT, improve data management to reduce reporting of incomplete data, and develop methods to facilitate blinding of participants and personnel. Blinding of participants is especially important given the commercialisation of CCT, advertisement, and widespread community exposure; an active control comparison arm may partially address this potential bias.

In summary, high-quality longitudinal studies with appropriately selected outcome measures are required to determine whether CCT can contribute to maintaining cognitive function and preventing further cognitive decline and progression to clinical dementia in people with MCI.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barnes 2013

Methods	• **Design**: 4-arm RCT with factorial design • **Recruitment period**: 2008 to 2009 • **No. of centres involved**: 1 • **Unit of randomisation**: individuals • **No. randomised**: 126 • **Number of arms considered in this review**: 4 • **Maximum trial duration**: 3 months • **Funding by non-profit organisation**: this study was funded through a Career Development Award from the National Institute on Aging (grant K01-AG024069), the Alzheimer's Association (grant IIRG-06-27306), the University of California School of Medicine, and the Institutes of Health/National Center for Research Resources/University of California, San Francisco-Clinical and Translational Science Institute (grant KL2 RR024130) • **Funding by commercial organisation**: none reported • **Publication status**: full-text report
Participants	• **Type of MCI:** participants with self-reported cognitive complaints at baseline • **Patient flow**: 31 randomised, 31 described at baseline in experimental group; 32 randomised, 32 described at baseline in experimental group 2, 31 randomised, 31 described at baseline in experimental group 3; 32 randomised, 32 described at baseline in control group • **Number of females**: 18 of 31 (58%) in experimental group 1; 20 of 32 (63%) in experimental group 2; 21 of 31 (68%) in experimental group 3; 20 of 32 (63%) in control group 1 • **Average age (SD)**: 74 (5.7) years in experimental group 1; 75 (6.1) years in experimental group 2; 71 (5.5) years in experimental group 3; 74 (6.3) years in control group 1 • **Average (SD) education**: 16.8 (2.3) years in experimental group 1; 16.7 (2.2) years in experimental group 2; 15.6 (2.8) years in experimental group 3; 16.3 (2.1) years in control group 1 • **Baseline cognitive function**: instrument to measure baseline cognitive function not reported • **Selection criteria on cognition overall**: mean modified Mini Mental State examination score: 94.4; experimental group 1: global cognition (3MS) score, mean (SD): 94.4 (3.9); experimental group 2: global cognition (3MS) score, mean (SD): 94 (5.2); experimental group 3: global cognition (3MS) score, mean (SD): 94.6 (5.6); control group 1: global cognition (3MS) score, mean (SD): 94.8 (4.7) • **Ethnicity**: experimental group 1: 0 white, 0 Indian, 0 Asian, 22 black, 0 other, 9 unclear; experimental group 2: 0 white, 0 Indian, 0 Asian, 21 black, 0 other, 11 unclear; experimental group 3: 0 white, 0 Indian, 0 Asian, 17 black, 0 other, 14 unclear; control group 1: 0 white, 0 Indian, 0 Asian, 22 black, 0 other, 10 unclear • **APOE**: number of participants positive for APOE not reported

Interventions	• **Type of experimental intervention 1**: computerised CT and sham exercise (stretching) • **Details of experimental intervention**: intervention provided as individual training, without supervision. Games designed to enhance the speed and accuracy of visual and auditory processing (Posit Science). For the first 6 weeks, games focused on visual tasks, and for the second 6 weeks, games focused on auditory tasks • **Type of experimental intervention 2**: computerised CT and aerobic exercise • **Details of experimental intervention 2**: computerised CT as in experimental arm 1 but with concomitant aerobic exercise • **Type of experimental intervention 3**: other • **Details of experimental intervention 3**: DVDs of educational lectures on art, history, and science and aerobic exercise • **Type of control intervention**: other • **Details of control intervention**: DVDs of educational lectures on art, history, and science and sham exercise (stretching) • S**ession duration**: 60 minutes in all groups • **Number of treatment sessions**: 36 in all groups • **Treatment frequency**: 3/week in all groups • **Maximum treatment duration**: 12 weeks in all groups
Outcomes	• **Cognitive functioning outcomes considered** ○ Global cognitive functioning measured with composite score change at 3 months, on a scale from not reported to not reported with higher values indicating benefit ○ Episodic memory measured with RAVLT, no. of words learned at 3 months, on a scale from not reported to not reported with higher values indicating benefit ○ Executive functioning measured with Trails B at 3 months, on a scale from not reported to not reported with lower values indicating benefit ○ Speed of processing measured with Trails A at 3 months, on a scale from not reported to not reported with lower values indicating benefit ○ Verbal fluency measured with no. of words by letter at 3 months, on a scale from not reported to not reported with higher values indicating benefit • **Physical functioning outcome considered**: none reported • **Quality of life outcome considered**: none reported • **Safety outcome considered**: none reported • **Depression outcome considered**: none reported • **Available cognitive functioning outcomes not considered in this review** ○ Episodic memory measured with RAVLT No. of words recalled at 3 months, on a scale from not reported to not reported with higher values indicating benefit ○ Executive functioning measured with EFT Congruent reaction time at 3 months, on a scale from not reported to not reported with higher values indicating benefit ○ Executive functioning measured with EFT Incongruent reaction time at 3 months, on a scale from not reported to not reported with higher values indicating benefit ○ Speed of processing measured with DSST, No. correct at 3 months, on a scale from not reported to not reported with higher values indicating benefit ○ Speed of processing measured with Useful Field of View (UFOV) Processing

	speed at 3 months, on a scale from not reported to not reported with higher values indicating benefit ○ Verbal fluency measured with No. of words, by category at 3 months, on a scale from not reported to not reported with higher values indicating benefit ○ Visuospatial function (UFOV) on a scale from not reported to not reported with higher values indicating benefit
Notes	• Experimental trial arm 1 includes participants who received mental activity intervention and group exercise control (stretching and relaxation) • Control arm 1 includes participants who received mental activity control and group exercise control (stretching and relaxation); • Experimental trial arm 2 includes participants who received mental activity intervention as experimental trial arm 1 in combination with group exercise intervention (aerobic exercise and strength training) • Experimental trial arm 3 includes participants who received mental activity control (same as control arm 1) in combination with group exercise intervention (aerobic exercise and strength training)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Judgement**: random sequence adequately generated **Quote(s)**: "participants were randomized in blocks of 4. The randomization sequence was prepared in advance by using a random-number generator on a computer"
Allocation concealment (selection bias)	Unclear risk	**Judgement**: study authors state that allocation was concealed, although the method of allocation concealment is not reported **Quote(s)**: "research staff involved with enrolment and outcome assessment were unaware of the randomization sequence and blinded to group assignment"
Blinding of participants (performance bias)	High risk	**Judgement**: patients were not blinded to the type of intervention **Quote(s)**: "study participants were unaware of study hypotheses and were told that the goal of the study was to compare the effects of different physical and mental activity programs"
Blinding of physicians / personnel	Low risk	**Judgement**: therapists were blinded to study treatment **Quote(s)**: "research staff involved with enrolment and outcome assessment were un-

Barnes 2013 (*Continued*)

		aware of the randomization sequence and blinded to group assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Judgement**: therapists were blinded to study treatment **Quote(s)**: "research staff involved with enrolment and outcome assessment were unaware of the randomization sequence and blinded to group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Judgement**: 32 out of 32 (100%) randomised to the experimental group were analysed, and 31 out of 31 (100%) randomised to the control group were randomised; the statistical analyses were reported to be done according to the intent-to-treat principle; 9/32 in experimental and 3/31 in control withdrew from study but were included in the final analysis **Quote(s)**: "all analyses were performed using intent-to-treat principles"
Selective reporting (reporting bias)	Low risk	**Judgement**: all outcomes mentioned in the methods section are reported in the results section
Other bias	Low risk	**Judgement**: no other sources of bias are apparent

Djabelkhir 2017

Methods	• **Design**: 2-arm RCT with parallel-group design • **Recruitment period**: December 2014 to July 2015 • **No. of centres involved**: 1 hospital in France • **Unit of randomisation**: individuals • **No. randomised**: 20 (10 participants each arm) • **Number of arms considered in this review**: 2 • **Maximum trial duration**: 3 months (12 weeks) • **Funding by non-profit organisation**: none described • **Funding by commercial organisation**: computerised cognitive exercises web platform (KODRO) was provided by the company • **Publication status**: full-text report
Participants	• **Patient flow**: 53 participants were screened and 20 were randomised: 10 participants received computerised cognitive stimulation (Intervention) (CCS) and 10 received computerised cognitive engagement (control) (CCE) • **Number of females**: intervention (CCS): 7 of 10 (70%); control (CCE): 6 of 10 (60%)

	• **Average age (SD)**: intervention (CCS): 75.2 (6.4); control (CCE): 78.2 (7.0) • **Education (college degree or higher, n (%)): i**ntervention (CCS): 4 (44.4%); control (CCE): 6 (60%) • **Baseline cognitive function in MMSE (mean, SD)**: intervention (CCS): 27.7 (1.9); control (CCE): 27.4 (2.0) • **Selection criteria:** inclusion criteria: community-dwelling older adults (≥ 60 years) meeting MCI criteria according to Petersen; mini Mental Status Examination (MMSE) score > 24; reported a subjective memory complaint, preferably corroborated by an informant; performed at/below 1.5 standard deviations (SDs) from the mean for age and education on more than 1 neuropsychological test, with preserved or minimal impairment in functional abilities; absence of dementia. Exclusion criteria: psychiatric and neurological disorders (e.g. bipolar disorder, schizophrenia, stroke, Parkinson's disease, epilepsy); history of alcohol or other substance abuse; sensory and/or motor deficits affecting the use of a tablet PC • **Ethnicity**: not reported • **APOE**: not reported
Interventions	• **Type of experimental intervention**: computerised cognitive training (CCS), group; treatment duration of 3 months (12 weeks); intervention provided in small group format under trained neuropsychologist supervision • **Details of experimental intervention**: intervention group attended 1 group session per week (5 to 7 participants) for 3 months (12 sessions in total). The CCS programme was designed to stimulate several cognitive domains with computerised cognitive exercises and social interactions among participants. Each session was conducted as follows: presentation of the day's programme, recall of the last session and discussion (15 minutes). Cognitive exercises on tablet with a short break between exercises (60 minutes). Feedback and group discussion about the session (15 minutes). Computerised cognitive exercises were selected from the institution version of KODRO (Altera-Group, Paris, France), a web-based platform that provided several applications (e.g. appointment and event reminding, cognitive games, communication, entertainment, videos and a library) tailored to older adults • **Type of concomitant treatment provided**: not stated • **Session duration**: 90 minutes in experimental group • **Number of treatment sessions**: 12 in experimental group • **Treatment frequency**: 1 session per week • **Maximum treatment duration in months**: 3 months (12 sessions) in experimental group • **Type of control intervention**: inactive; control group (CCE) attended 1 group session per week (5 to 7 participants) for 3 months (12 sessions in total). Each session lasted 90 minutes and was conducted by a trained neuropsychologist blinded to assessment • **Details of control intervention**: CCE programme was designed to train participants to use a tablet PC and to stimulate social interactions among participants. CCE participants were involved in a casual atmosphere, while the content was preprogrammed. A specific topic was defined for each session, and participants were invited to explore different applications related to this. For example, for the theme "compensating for memory problems", participants discovered the calendar and learned to schedule an appointment on it. During sessions, participants were invited to suggest

	a theme, and the neuropsychologist showed applications associated with the theme • **Type of concomitant treatment provided**: not stated • **Session duration**: 90 minutes in control group. • **Number of treatment sessions**: 12 in control group • **Treatment frequency**: 1/week in control group • **Maximum treatment duration in months**: 3 months (12 sessions) in control group
Outcomes	• **Cognitive functioning outcome considered** ○ Global cognitive function with MMSE on a scale from 0 to 30 with higher values indicating benefit ○ Episodic memory measured with 16-FR/CR test on a scale from not reported to not reported with higher values indicating benefit ○ Executive function measured in seconds with TMT-B at 12 weeks on a scale from not reported to not reported with lower values indicating benefit ○ Speed of processing measured with TMT-A at 12 weeks, on a scale from not reported to not reported with lower values indicating benefit ○ Working memory with the Backward Digit Span from the Wechsler Adult Intelligent Scale (WAIS) 4th edition, on a scale from not reported to not reported with higher values indicating benefit ○ Verbal fluency measured in number of words with letter P in 2 minutes • **Physical functioning outcome considered**: none reported • **Quality of life outcome considered**: quality of life was assessed using the quality of life scale for older French people (Echelle de Qualité de Vie adpatée aux Personnes Agées) • **Safety outcome considered**: none reported • **Depression outcome considered**: depression symptoms measured with Goldberg Anxiety and Depression Scales, on a scale from not reported to not reported with lower values indicating benefit • **Other outcome data on cognitive functioning not considered in our meta-analyses** ○ Episodic memory measured with Visuospatial memory test from the cognitive efficiency profile, on a scale from not reported to not reported with higher values indicating benefit ○ Executive function measured with TMT-B error on a scale from not reported to not reported with lower values indicating benefit ○ Verbal fluency measured with Category Fluency, on a scale from not reported to not reported with higher values indicating benefit
Notes	KODRO provided access to the software; study authors reported no conflict of interest in the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	**Judgement**: adequate method of random sequence generation **Quote(s):** "patients were assigned to either a computerized CS (CCS) group or a computerized cognitive engagement (CCE) group with a simple computerized randomization procedure
Allocation concealment (selection bias)	Unclear risk	**Judgement**: no description provided
Blinding of participants (performance bias)	Unclear risk	**Judgement**: study described as single-blinded; however, it is not clear if and how participants were blinded **Quote(s)**: "we designed a randomized single-blind study conforming to Consolidated Standards of Reporting Trials criteria for pilot and feasibility studies"
Blinding of physicians / personnel	High risk	**Judgement**: therapists could not be blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Judgement:** blinded outcome assessment **Quote(s)**: "these were carried out by an experienced neuropsychologist blinded to the intervention"
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Judgement:** no participants were lost to follow-up **Quote(s)**: "none of the participants discontinued the intervention. Only one participant in the CCS group did not perform the M3 assessment for medical reasons (surgery), resulting in 19 subjects for the final analyses"
Selective reporting (reporting bias)	Low risk	**Judgement**: all outcomes indicated in the methods section are reported in the results section
Other bias	Low risk	**Judgement**: no other sources of bias are apparent

Fiatarone Singh 2014

Methods	• **Design**: international 4-arm RCT with factorial design • **Quote study design**: "randomized, fully-factorial, double-blind, double sham training-controlled clinical trial" • **Recruitment period**: not reported • **No. of centres involved**: not reported • **Unit of randomisation**: individuals • **No. randomised**: 100 • **Number of arms considered in this review**: 4 • **Maximum trial duration**: 18 months • **Funding by non-profit organisation**: this study was funded by a National Health and Medical Research Council (NH&MRC) of Australia Dementia Research Grant, project grant ID No. 512672, from 2008 to 2011(https://www.nhmrc.gov.au). Additional funding for a research assistant position was sourced from the NHMRC Program Grant ID No. 568969, and the project was supported by the University of Sydney and the University of New South Wales • **Funding by commercial organisation**: none reported • **Publication status**: full-text report
Participants	• **Type of MCI**: MCI consistent with the Petersen 1999 criteria • **Patient flow**: 24 randomised, 24 described at baseline in experimental group 1 (CT and sham physical exercise); 27 randomised, 27 described at baseline in experimental group 2 (CT and physical exercise); 27 randomised, 27 described at baseline in control group 1 (double sham); 22 randomised, 22 described at baseline in control group 2 (physical exercise and sham CT) • **Number of females overall**: 68 of 100 (68%) • **Average age (SD) overall**: 70 (6.7) years • **Average (SD) education**: not reported • **Baseline cognitive function**: instrument to measure baseline cognitive function not reported • **Selection criteria on cognition overall**: Clinical Dementia Rating Algorithm (0 to 4): 0.14 (0.22); 71% rated 0, 29% rated 0.5; Mini Mental State Exam: 27 (1) (23 to 29) • **Ethnicity**: not reported • **APOE**: number of participants positive for APOE not reported
Interventions	• **Type of experimental intervention**: computerised CT group, treatment duration 24 weeks; intervention provided in group format, under supervision • **Details of experimental intervention**: "CT intervention involved computer-based multimodal and multidomain exercises targeting memory, executive function, attention, and speed of information processing. The training used the COGPACK program". Participants also received progressive resistance training (PRT) performed with exercise or sham exercise (factorial design) • **Session duration**: 75 minutes in experimental group • **Number of treatment sessions**: 48 in experimental group • **Treatment frequency**: 2/week in experimental group • **Maximum treatment duration**: 24 in experimental group • **Type of control intervention**: usual care, treatment duration 24 weeks; intervention provided in group format, under supervision • **Details of control intervention**: sham cognitive consisted of watching 5 short

	National Geographic videos, followed by a set of 15 questions (3/video) regarding the presented material. Sham exercise consisted of stretching and seated callisthenics, designed so as not to notably increase heart rate or aerobic capacity, nor improve balance, enhance strength, or other physiological outcomes. PRT was performed with pneumatic resistance machines (Keiser Sports Health Equipment, Ltd., Gloucestershire, UK), which were used for training at high intensity, with 3 sets of 8 repetitions of each of 56 exercises/session for most major muscle groups (chest press, leg press, seated row, standing hip abduction, knee extension) • **Session duration**: 60 minutes in control group • **Number of treatment sessions**: 48 in control group • **Treatment frequency**: 2/week in control group • **Maximum treatment duration**: 24 in control group
Outcomes	• **Cognitive functioning outcomes considered** ○ Global cognitive functioning measured with ADAS-Cog at 6 and 18 months, on a scale from not reported to not reported with lower values indicating benefit ○ Episodic memory measured with Logical Memory II (delayed) at 6 and 18 months, on a scale from not reported to not reported with higher values indicating benefit* ○ Executive functioning measured with WAIS-III Similarities at 6 and 18 months, on a scale from not reported to not reported with higher values indicating benefit ○ Speed of processing measured with SDMT at 6 and 18 months, on a scale from not reported to not reported with higher values indicating benefit ○ Verbal fluency measured with COWAT at 6 and 18 months, on a scale from not reported to not reported with higher values indicating benefit • **Physical functioning outcome considered** ○ Daily function measured with BAYER-ADL scale at 6 and 18 months, on a scale from not reported to not reported with lower values indicating benefit • **Quality of life outcome considered**: none reported • **Safety outcome considered**: none reported • **Depression outcome considered**: none reported • **Available cognitive functioning outcomes not considered in this review** ○ Global cognitive functioning measured with Global Cognition Domain at 6 and 18 months, on a scale from not reported to not reported with higher values indicating benefit ○ Episodic memory measured with BVRT at 6 and 18 months, on a scale from not reported to not reported with higher values indicating benefit ○ Episodic memory measured with Logical Memory I (immediate) at 6 months, on a scale from not reported to not reported with higher values indicating benefit* ○ Executive functioning measured with WAIS-III Matrices at 6 and 18 months, on a scale from not reported to not reported with higher values indicating benefit ○ Verbal fluency measured with Category Fluency at 6 and 18 months, on a scale from not reported to not reported with higher values indicating benefit *Our hierarchy did not indicate a preference for the delayed subscale over the immediate subscale. Whenever both immediate and delayed subscales were available, the delayed subscale was included in the meta-analyses, as it was thought to be more clinically relevant

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Judgement**: adequate method of random sequence generation **Quote(s)**: "a concealed, computer-generated sequence of randomly permuted blocks.. in a 1:1:1:1 ratio to each of the 4 intervention arms, stratified by sex and age (<75 and 75 years), was generated by a research assistant not otherwise involved in the study via a statistical website"
Allocation concealment (selection bias)	Low risk	**Judgement**: adequate method of concealment allocation **Quote(s)**: "assignments were then placed in sealed opaque envelopes and delivered to participants by the recruitment officer"
Blinding of participants (performance bias)	Unclear risk	**Judgement**: study described as double-blinded; however, it is not clear if patients were blinded **Quote(s)**: "all training was fully supervised by research assistants from exercise physiology or physical therapy backgrounds"
Blinding of physicians / personnel	High risk	**Judgement**: researchers supervising training were not blinded **Quote(s)**: "all training was fully supervised by research assistants from exercise physiology or physical therapy backgrounds"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Judgement**: blinded outcome assessment **Quote(s)**: "blinded assessors administered all outcome measures at baseline, 6 and 18 months"
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Judgement**: Comparison 1: 24 out of 24 (100%) randomised were analysed in experimental group 1, and 27 out of 27 (100%) randomised were analysed in control group 1 Comparison 2: 27 out of 27 (100%) randomised were analysed in experimental group 2, and 22 out of 22 (100%) ran-

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		domised were analysed in control group 2. Statistical analyses were reported to be done according to the intent-to-treat principle **Quote(s)**: "all patients randomised were included in the analysis"; "n = 100 for all outcomes"
Selective reporting (reporting bias)	Low risk	**Judgement**: all outcomes indicated in the methods section are reported in the results section
Other bias	Low risk	**Judgement**: no other sources of bias are apparent

Gooding 2016

Methods	• **Design**: 3-arm RCT with parallel-group design • **Recruitment period**: not reported • **No. of centres involved**: 4 (participants were recruited through the Memory Disorders Center (MDC) at Columbia University, which includes the Alzheimer's Disease Research Center (ADRC), Doctors Private Offices at the Neurological Institute, and the Memory Disorders Clinic at the New York State Psychiatric Institute (NYSPI), as well as through the Department of Geriatric Psychiatry at the VA Connecticut Healthcare System) • **Unit of randomisation**: individuals • **No. randomised**: 96 (data reported for 74 participants who completed the study - 20 participants in the control group, 31 in the computerised cognitive training group, and 23 in the cognitive vitality programme) • **Number of arms considered in this review**: 3 • **Maximum trial duration**: 4 months • **Funding by non-profit organisation**: funded by a grant from the Alzheimer's Association (IIRG-09-131861) and by a Department of Veterans Affairs RR&D Career Development Award (RRD-B4146V) • **Funding by commercial organisation**: none stated • **Publication status**: full-text report
Participants	• **Patient flow**: A total of 96 participants were recruited for this study and completed the baseline neuropsychological evaluation. Of these, 74 participants completed the full treatment, 7 completed partial treatment, and 15 did not complete any portion of the assigned treatment. The overall study attrition rate was 23%. Among those who did not complete treatment, 6 participants dropped out after the baseline neuropsychological evaluation, 4 dropped out after completing a portion of the 2-month follow-up evaluation, and 12 dropped out after completing the full 2-month follow-up evaluation **Data provided only for 74 participants who completed the study:** • **Number of females, n (%)**: 43 (58.1%) • **Average age (SD)**: 75.79 (8.75) • **Education (years) (mean, SD): 15.14 (2.58)** • **Baseline cognitive function in mMMSE (mean, SD)**: 50.58 (2.72)

	• **Selection criteria:** study sample was recruited through the Memory Disorders Center (MDC) at Columbia University and the VA Connecticut Healthcare System. Inclusion criteria: diagnosis of subclinical cognitive decline established by (1) subjective or informant memory complaints; (2) verbal memory impairment, as measured by > 0. 5 SD decline on Wechsler Memory Scale-Revised (WMS-R) Logical Memory (LM)-II, or Buschke Selective Reminding Test (BSRT); (3) normal general cognitive function, as determined by Mini Mental State Examination (MMSE) score > 24; and (4) normal independent functioning as determined by physician report and > 75 percentile score on Independent Living Scales (ILS) • **Ethnicity (%)**: non-Hispanic white 59.5%, African American 17.6%, Hispanic/ Latino 17.6%, Asian: 5.4% • **APOE**: not reported
Interventions	• **Type of experimental intervention (2 arms):** ○ **1 arm computerised cognitive training (CCT) and 2 arms cognitive vitality training (CVT)**: treatment phase sessions were provided in individual or group format, twice per week, with each session lasting approximately 60 minutes. Total exposure was the same for all treatment groups and required approximately 30 hours of training within a 16-week period • **Details of experimental intervention**: ○ **CCT**: programme incorporated repeated drill-and-practice exercises involving memory, attention, and executive functions within domain-specific training modules that allow for adaptive training with titrated difficulty levels. Software used was BrainFitness version 2.0.1 ○ **CVT**: participants in the CVT group completed the same exercises as the CCT group using the BrainFitness programme described above, but within an incorporated motivational therapeutic milieu based on the principles put forth by NEAR (allowed to personalise incidental features in the training programme (i.e. can set personal goals rather than follow clinician-set goals)), provided choice over aspects of the training activity (i.e. can select module of choosing and set personal time constraints), and allowed to conceptualise the training into a meaningful, real-world situation (i.e. training programme embedded into the context of high-interest or real-world themes, such as sport games or simulating a business transaction).**This arm was not included in the analysis** **Type of concomitant treatment provided**: not stated • **Session duration**: 60 minutes in experimental group • **Number of treatment sessions**: twice a week for 16-week period in experimental group • **Treatment frequency**: 2 sessions per week • **Maximum treatment duration in months**: 16 weeks in experimental group • **Type of control intervention**: active; control group, treatment phase sessions were provided in individual or group format, twice per week, with each session lasting approximately 60 minutes. Total exposure was the same for all treatment groups and required approximately 30 hours of training within a 16-week period • **Details of control intervention**: participants assigned to the ACG worked on various commercially available computer games and puzzles (e.g. BrainAge, Sudoku, crossword puzzles). Participants in this group worked on computerised games in a similar format to individuals in the CCT group (either at the hospital or remotely from home), and treatment dosage and intensity were identical to the CCT group (i.e. total

	of 2 hours per week) • **Type of concomitant treatment provided**: not stated • **Session duration**: 60 minutes in control group • **Number of treatment sessions**: twice a week for 16-week period in control group • **Treatment frequency**: 2 sessions per week • **Maximum treatment duration in months**: 16 weeks in control group
Outcomes	• **Cognitive functioning outcomes considered** ○ Global cognitive function with mMMSE on a scale from not reported with higher values indicating benefit ○ Episodic memory with WMS-R-II subtest, on a scale from not reported to not reported with higher values indicating benefit ○ Working memory with the Wechsler Adult Intelligence Scale-Revised Digit Span subtest on a scale from not reported to not reported with higher values indicating benefit (data not reported in the study) • **Physical functioning outcome considered**: none reported • **Quality of life outcome considered**: none reported • **Safety outcome considered**: none reported • **Depression outcome considered**: depression symptoms measured with Beck Depression Inventory 2nd Edition, on a scale from not reported to not reported with lower values indicating benefit • **Other outcome data on cognitive functioning not considered in our meta-analyses** ○ Episodic memory measured with BSRT verbal learning and memory, WMS-R LM-I, WMS-R Visual reproductions I and II
Notes	Funded by a grant from the Alzheimer's Association (IIRG-09-131861) and a Department of Veterans Affairs RR&D Career Development Award (RRD-B4146V); study authors report no conflict of interest in the study The third arm (CVT) consisted of CCT plus a motivational therapeutic milieu and was not included in the analysis due to the ACG that did not receive the motivational therapeutic milieu intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Judgement:** no methods for randomisation described **Quote(s):** "this randomised clinical trial used a test-re-test treatment controlled design with recruited patients randomly assigned to one of three research arms - computerised cognitive training (CCT), cognitive vitality training (CVT), or an active control group (ACG)"

Gooding 2016 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	**Judgement:** no methods for allocation concealment described
Blinding of participants (performance bias)	High risk	**Judgement**: blinding not feasible **Quote(s)**: none
Blinding of physicians / personnel	High risk	**Judgement**: blinding not feasible **Quote(s)**: none
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Judgement:** no methods for blinding the outcome assessor described
Incomplete outcome data (attrition bias) All outcomes	High risk	**Judgement:** high proportion of participants were lost to follow-up **Quote(s)**: "a total of 96 participants were recruited for this study, and completed the baseline neuropsychological evaluation. Of those, 74 participants completed the full treatment, 7 completed a partial portion of the treatment, and 15 did not complete any portion of the assigned treatment. The overall study attrition rate was 23%"
Selective reporting (reporting bias)	Low risk	**Judgement**: all outcomes described in the methods section are adequately addressed in the results section
Other bias	Low risk	**Judgement**: no other sources of bias are apparent

Herrera 2012

Methods	• **Design**: 2-arm RCT with parallel-group design • **Recruitment period**: not reported to not reported • **No. of centre involved**: 1 • **Unit of randomisation**: individuals • **No. randomised**: 22 • **Number of arms considered in this review**: 2 • **Maximum trial duration**: 9 months • **Funding by non-profit organisation**: unclear • **Funding by commercial organisation**: unclear • **Publication status**: full-text report
Participants	• **Type of MCI:** amnestic MCI multiple domains subtype (A-MCImd) consistent with Petersen 2004 criteria • **Patient flow**: 11 randomised, 11 described at baseline in experimental group; 11 randomised, 11 described at baseline in control group

	• **Number of females**: 5 of 11 (45%) in experimental group 1; 6 of 11 (55%) in control group 1 • **Average age (SD)**: 75 (2.0) years in experimental group 1; 78 (1.4) years in control group 1 • **Average (SD) education**: not reported. Experimental group 1: primary: 54%; secondary: 36%; more than secondary: 10%. Control group 1: primary: 37%; secondary: 45%; more than secondary: 18% • **Baseline cognitive function**: 3 selection criteria on cognition overall: 1) participants meet definition criteria for A-MCImd (Petersen 2004); 2) all patients had memory complaint; and 3) have normal general cognitive functioning as determined by a Mini-Mental State Examination (MMSE) score ≥ 24. • **Selection criteria on cognition**: experimental group 1: amnestic MCI multiple domains subtype (A-MCImd, according to Petersen 2004). All participants had memory complaint, usually verified by an informant. MMSE, mean (SD): 27.36 (0. 53). Control group 1: amnestic MCI multiple domains subtype (A-MCImd, according to Petersen 2004). All participants had memory complaint, usually verified by an informant. MMSE, mean (SD): 27.18 (0.40) • **Ethnicity**: not reported • **APOE:** number of participants positive for APOE not reported
Interventions	• **Type of experimental intervention**: computerised CT group; treatment duration 12 weeks; Intervention provided in group format, under supervision • **Details of experimental intervention**: training involved a memory task and an attention task. It was programmed in Java (Release 1.4) and conducted on a Microsoft Windows-based computer. Stimuli were pictures belonging to various categories (e.g. animals, flowers, objects of everyday life) and common words pronounced by the computer. Each picture was 256 × 256 pixels in size. Responses to training tasks were given using a tactile screen, a standard keyboard (using only 2 keys), and a computer mouse. For attention training, we used response time tasks to yes/no choice; for memory training, we used recognition memory tasks with forced choice • **Type of concomitant treatment provided**: none reported • **Session duration**: 60 minutes in experimental group • **Number of treatment sessions**: 24 in experimental group • **Treatment frequency**: 2/week in experimental group • **Maximum treatment duration in weeks**: 12 in experimental group • **Type of control intervention**: other; treatment duration 12 weeks; Intervention provided as individual training, under supervision • **Details of control intervention**: cognitive activities consisting of exercises in which participants were asked to find names of countries and corresponding capitals, to organise a list of purchases in categories, to find similarities and differences, to choose a newspaper article and bar all the letters "A", to read a text and then answer questions, to tell a story or construct a sentence from a list of words in disorder, etc. • **Session duration**: 60 minutes in control group • **Number of treatment sessions**: 24 in control group • **Treatment frequency**: 2/week in control group • **Maximum treatment duration in weeks**: 12 in control group
Outcomes	• **Cognitive functioning outcome considered** ○ Episodic memory measured with 16-item free and cued reminding test (16-

	FR/CR test) at 3 and 9 months, on a scale from 0 to 16 with higher values indicating benefit ○ Working memory measured with Digit span test, backward (type of digit span test used not stated) at 3 and 9 months, on a scale from 0 to not reported with higher values indicating benefit • **Physical functioning outcome considered**: none reported • **Quality of life outcome considered**: none reported • **Safety outcome considered**: none reported • **Depression outcome considered**: none reported • **Available cognitive functioning outcomes not considered in this review** ○ Episodic memory measured with MMSE-recall of 3 words at 3 months, on a scale from 0 to not reported with higher values indicating benefit ○ Episodic memory measured with Doors recognition subtest (doors and people battery) set A/12 at 3 and 9 months, on a scale from 0 to not reported with higher values indicating benefit ○ Episodic memory measured with Doors recognition subtest (doors and people battery) set B/12 at 3 and 9 months, on a scale from 0 to not reported with higher values indicating benefit ○ Episodic memory measured with 12-word-list recall test from BEM-144 memory battery (Signoret 1991) at 3 and 9 months, on a scale from 0 to 12 with higher values indicating benefit ○ Episodic memory measured with recall of the Rey-Osterrieth Complex Figure at 3 and 9 months, on a scale from 0 to 36 with higher values indicating benefit ○ Episodic memory measured with delayed matching-to-sample 48 test (DMS48 test)-set 1 expressed as recognition score (%) at 3 and 9 months, on a scale from 0 to not reported with higher values indicating benefit ○ Working memory measured with Digit span test, forward, at 3 months, on a scale from 0 to not reported with higher values indicating benefit
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Judgement**: no methods for randomising participants have been described **Quote(s)**: "the 22 patients were randomly assigned into two groups (11 patients per group): a group that performed training (Trained group) and a group that participated in stimulating cognitive activities (Control group)"
Allocation concealment (selection bias)	Unclear risk	**Judgement**: no description provided
Blinding of participants (performance bias)	Unclear risk	**Judgement**: blinding not reported and interventions are clearly different. Nevertheless, depending on the information partic-

		ipants received, blinding could have been successful. As trial authors did not measure this, we judged unclear risk of bias
Blinding of physicians / personnel	High risk	**Judgement**: therapists could not be blinded **Quote(s)**: "three trained neuropsychologists were involved in the study: one administered and scored the pre-tests, post-tests, and follow-up tests (this person was kept blind to the group membership of patients) , one supervised training, and one supervised cognitive activities"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Judgement**: assessors were blinded to the treatment assigned, although the method of blinding is not described in detail **Quote(s)**: "three trained neuropsychologists were involved in the study: one administered and scored the pre-tests, post-tests, and follow-up tests (this person was kept blind to the group membership of patients) , one supervised training, and one supervised cognitive activities"
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Judgement**: 11 out of 11 (100%) randomised were analysed in the experimental group, and 11 out of 11 (100%) randomised were analysed in the control group. It is not clearly reported if all randomised participants were evaluated for this test, so for statistical analyses, we used the number randomised as the number analysed
Selective reporting (reporting bias)	Low risk	**Judgement**: all outcomes described in the methods section are adequately addressed in the results section
Other bias	Unclear risk	**Judgement**: the selection process for participants is not described in sufficient detail; few baseline characteristics are described, not allowing a judgement whether between-group baseline imbalances occurred in this small trial

Kwok 2013a

Methods	• **Design**: 2-arm randomised controlled pilot trial with parallel-group design • **Recruitment period**: not reported • **No. of centres involved**: 6 • **Unit of randomisation**: individuals • **No. randomised**: 223 • **Number of arms considered in this review**: 2 • **Maximum trial duration**: 9 months • **Funding by non-profit organisation**: CADENZA, a Jockey Club Initiative for Seniors • **Funding by commercial organisation**: none described • **Publication status**: full-text report
Participants	• **Type of MCI:** not addressed • **Patient flow**: 111 randomised, 111 described at baseline in experimental group; 112 randomised, 112 described at baseline in control group • **Number of females**: 97 of 111 (87%) in experimental group; 93 of 112 (83%) in control group • **Average age (SD)**: 75 (5.8) years in experimental group; 75 (5.8) years in control group • **Average (SD) education**: no formal education 6 (5.4%); below or at primary level 84 (75.7%); secondary or above 21 (18.9%) in experimental group; no formal education 14 (12.5%); below or at primary level 72 (64.3%); secondary or above 26 (23.2%) in control group • **Baseline cognitive function**: measured with CMSS and CMMSE • **Selection criteria on cognition**: subjective memory complaints: score ≥ 3 on Chinese Memory Symptoms Scale (mean 4.2, SD 0.8 in experimental group; mean 4.0, SD 0.8 in control group); no dementia: score ≥ 20 on Chinese version of Mini Mental State Examination (mean 25.6, SD 2.5 in experimental group; mean 25.7, SD 2.5 in control group) • **Ethnicity**: 111 Asian in experimental group; 112 Asian in control group • **APOE**: number of participants positive for APOE not reported
Interventions	• **Type of experimental intervention**: computerised CT, treatment duration 12 weeks; intervention provided as group training, under supervision • **Details of experimental intervention**: CCT based on ACTIVE trial protocol, with focus on attention, memory, and reasoning • **Type of concomitant treatment provided**: none • **Session duration**: 90 minutes in experimental group • **Number of treatment sessions**: 12 in experimental group • **Treatment frequency**: 1/week in experimental group • **Maximum treatment duration**: 12 weeks in experimental group • **Type of control intervention**: other; treatment duration 12 weeks; intervention provided as group training, under supervision • **Details of control intervention**: "series of health-related educational lectures in small groups on prevention of mood disorder, heart diseases, diabetes, and stroke" • **Session duration**: 90 minutes in control group • **Number of treatment sessions**: 12 in control group • **Treatment frequency**: 1/week in control group • **Maximum treatment duration**: 12 weeks in control group

Outcomes	• **Cognitive functioning outcome considered** ○ Global cognitive functioning measured with total score of the Chinese version of Mattis Dementia Rating Scale (CDRS) at 12 weeks on a scale from 0 to 144, with higher values indicating benefit • **Physical functioning outcome considered**: none • **Quality of life outcome considered**: none • **Depression outcome considered**: none • **Safety outcome considered**: none • **Available cognitive functioning outcomes not considered in this review** ○ CDRS subscale: attention at 12 weeks and 9 months on a scale from 0 to 37 with higher values indicating benefit ○ CDRS subscale: initiation/perseveration at 12 weeks and 9 months on a scale from 0 to 37 with higher values indicating benefit ○ CDRS subscale: construction at 12 weeks and 9 months on a scale from 0 to 6 with higher values indicating benefit ○ CDRS subscale: conceptualisation at 12 weeks and 9 months on a scale from 0 to 39 with higher values indicating benefit ○ CDRS subscale: memory at 12 weeks and 9 months on a scale from 0 to 25 with higher values indicating benefit
Notes	Although Kwok 2013a measured global cognitive function at 9 months of follow-up, they did not report data for the entire study population

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Judgement**: method of allocation not reported **Quote(s)**: "single-blind randomized placebo-controlled trial"
Allocation concealment (selection bias)	Unclear risk	**Judgement**: method of allocation concealment not reported **Quote(s)**: none
Blinding of participants (performance bias)	High risk	**Judgement**: blinding not feasible **Quote(s)**: none
Blinding of physicians / personnel	High risk	**Judgement**: blinding not feasible **Quote(s)**: none
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Judgement**: outcome assessor explicitly reported to be blind **Quote(s)**: "trained research assistant who was blind to treatment assignment"

Kwok 2013a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	**Judgement**: 103 out of 111 (93%) randomised in experimental group were analysed, and 103 out of 112 (92%) randomised in control group were analysed. Fraction with missing data below 10% **Quote(s)**: none; "the authors did not mention analyses to be in line with intent-to-treat principles, neither did they report on imputation techniques"
Selective reporting (reporting bias)	High risk	**Judgement**: incomplete reporting of non-significant outcome data for the overall group. For example, outcome data for the CDRS total score were not abstractable for the overall group but were reported for subgroups with low, moderate, or high educational baseline values
Other bias	Low risk	**Judgement**: none detected

Optale 2010

Methods	• **Design**: 2-arm randomised controlled pilot trial with parallel-group design • **Recruitment period**: not reported • **No. of centres involved**: 1 • **Unit of randomisation**: individuals • **No. randomised**: 36 • **Number of arms considered in this review**: 2 • **Maximum trial duration**: 6 months • **Funding by non-profit organisation**: Consorzio Sociale CPS gestore centro servizi "Anni Sereni" Rest-Home, Scorzè, Venice, Italy (to Gabriele Optale). Cosimo Urgesi was supported by the Scientific Institute (IRCCS) Eugenio Medea (Ricerca Corrente 2009, Italian Ministry of Health) • **Funding by commercial organisation**: none reported • **Publication status**: full-text report
Participants	• **Type of MCI:** not applicable; diagnosis of MCI was not required • **Patient flow**: 18 randomised, 15 described at baseline in experimental group; 18 randomised, 16 described at baseline in control group • **Number of females**: 10 of 15 (67%) in experimental group 1; 11 of 16 (69%) in control group 1 • **Average age (SD)**: 79 (10.9) years in experimental group 1; 82 (5.0) years in control group 1 • **Average (SD) education**: 5.3 (2.4) years in experimental group; 6 (3.5) years in control group • **Baseline cognitive function**: measured with selection criteria on cognition overall: presence of memory deficits as documented by a corrected total score at the Verbal Story Recall (VSR) Test below the cut-off value (15.76)

	• **Selection criteria on cognition**: presence of memory deficits as documented by a corrected total score at the Verbal Story Recall (VSR) test below the cut-off value (15. 76). Corrected MMSE score ranged from 9.7 to 29.3, with 9 participants in experimental group presenting a score below the cut-off value (23.8) and ranging from 13.1 to 29, and with 12 participants in control group presenting a score below the cut-off value (23.8) • **Ethnicity**: not reported • **APOE**: number of participants positive for APOE not reported
Interventions	• **Type of experimental intervention**: computerised CT, individualised; treatment duration 24 weeks; intervention provided as individual training, under supervision • **Details of experimental intervention**: virtual reality memory training that involved auditory stimulation and virtual reality experiences in path finding. VR experiences are administered through a head-mounted display V6. The VR system runs on a notebook PC • **Type of concomitant treatment provided**: both groups participated in recreational expressive activities (reading/discussing newspapers and magazines, watching TV documentaries, participating in creative and painting workshops) and assisted-mobility activities during training • **Session duration**: 30 minutes in experimental group • **Number of treatment sessions**: 60 in experimental group • **Treatment frequency**: 3/week during first 3 months (36 sessions); 2/week in subsequent 3 months (24 sessions) in experimental group • **Maximum treatment duration, in weeks**: 24 in experimental group • **Type of control intervention**: other; treatment duration 24 weeks; intervention provided as individual training, under supervision • **Details of control intervention**: "individual face-to-face training sessions using music therapy" • **Session duration**: 30 minutes in control group • **Number of treatment sessions**: 60 in control group • **Treatment frequency**: 3/week during first 3 months (36 sessions); 2/week in subsequent 3 months (24 sessions) in control group • **Maximum treatment duration, in weeks**: 24 in control group
Outcomes	• **Cognitive functioning outcomes considered** ○ Global cognitive functioning measured with Mini Mental State Examination at 3 and 6 months, on a scale from 0 to 30, with higher values indicating benefit ○ Episodic memory measured with Verbal Story Recall at 3 and 6 months, on a scale from 0 to 28, with higher values indicating benefit ○ Executive functioning measured with Dual Task Performance at 3 and 6 months, on a scale from not reported to not reported with higher values indicating benefit ○ Working memory measured with Digit Span ('WAIS procedure') at 3 and 6 months, on a scale from not reported to not reported with higher values indicating benefit ○ Verbal fluency measured with Phonemic Verbal Fluency at 3 and 6 months, on a scale from not reported to not reported with higher values indicating benefit ("The PVF requires the participant to produce in 1 minute all the words he or she can remember, starting with the letters C, P, and S")

	• **Physical functioning outcome considered** ○ Daily function measured with Activities of Daily Living - functions at 3 and 6 months, on a scale from 0 to 60, with lower values indicating benefit • **Quality of life outcome considered**: none reported • **Safety outcome considered**: ○ Mortality measured at 6 months • **Depression outcome considered** ○ Depression measured with Geriatric Depression Scale at 3 and 6 months, on a scale from 0 to 15, with lower values indicating benefit • **Available cognitive functioning outcomes not considered in this review** ○ Executive functioning measured with Cognitive Estimation Test at 3 and 6 months, on a scale from not reported to not reported with higher values indicating benefit
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Judgement**: method for generating random sequence is not clearly reported **Quote(s)**: "for each replicate, half of the participants were randomly allocated to the EG, whereas the remaining participants were allocated to the CG"
Allocation concealment (selection bias)	Unclear risk	**Judgement**: method of allocation concealment is not reported **Quote(s)**: "for each replicate, half of the participants were randomly allocated to the EG, whereas the remaining participants were allocated to the CG"
Blinding of participants (performance bias)	High risk	**Judgement**: patients were not blinded **Quote(s)**: "a randomized controlled single-blind procedure was used, in which the examiner administrating the clinical and neuropsychological tests remained unaware of the participants' allocations to the EG or CG"
Blinding of physicians / personnel	High risk	**Judgement**: therapist supervising the training was not blinded **Quote(s)**: "a randomized controlled single-blind procedure was used, in which the examiner administrating the clinical and neuropsychological tests remained unaware of the participants' allocations to the EG or CG"

Optale 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Judgement**: the outcome assessor was explicitly described to be blinded to the intervention assigned **Quote(s)**: "the examiner administrating the clinical and neuropsychological tests remained unaware of the participants' allocations to the EG or CG"
Incomplete outcome data (attrition bias) All outcomes	High risk	**Judgement**: 15 out of 18 (83%) randomised in experimental group were analysed, and 16 out of 18 (89%) randomised in control group were analysed. We judged high risk of bias, as the percentage randomised but not analysed exceeded 10%; a complete case analyses was performed **Quote(s)**: "one experimental group (EG) participant and 2 control group (CG) participants died before completing the booster training. Furthermore, 2 EG participants left the rest home and went back to their families before completing the booster phase. Because we aimed to investigate the effects of both the initial and the booster training phases, the 5 participants yielding incomplete data were not included in the analyses"
Selective reporting (reporting bias)	High risk	**Judgement**: 1 out of 13 outcomes was not consistently performed for unclear reasons **Quote(s)**: "the Trail Making Test was also part of the evaluation protocol but could not be administered to most participants and was not included in the final analysis"
Other bias	Unclear risk	**Judgement**: no other potential risks of bias detected.

Rozzini 2007

Methods	• **Design**: 3-arm RCT with parallel-group design • **Recruitment period**: not reported • **No. of centres involved**: 2 • **Unit of randomisation**: individuals • **No. randomised**: 37 • **Number of arms considered in this review**: 2 • **Maximum trial duration**: 12 months • **Funding by non-profit organisation**: unclear • **Funding by commercial organisation**: unclear • **Publication status**: full-text report
Participants	• **Type of MCI:** consistent with Petersen 2001 criteria • **Patient flow**: 15 randomised, 15 described at baseline in experimental group; 22 randomised, 22 described at baseline in control group • **Number of females**: unknown in experimental group 1; unknown in control group 1 • **Average age (SD)**: median age (min to max) is 63 to 78 years in experimental group 1 • **Average (SD) education**: not reported • **Baseline cognitive function**: instrument to measure baseline cognitive function not reported • **Selection criteria on cognition overall**: MCI Petersen criteria • **Ethnicity**: not reported • **APOE**: number of participants positive for APOE not reported
Interventions	• **Type of experimental intervention**: computerised CT; intervention provided as individual training, under supervision • **Details of experimental intervention**: multi-dimensional software (TNP software) • **Type of concomitant treatment provided**: "the patients treated with ChEIs (n ¼37) received at baseline donepezil (n =26; 70%), rivastigmine (n = 6; 16%) and galantamine (n = 5; 14%) as per the clinician's judgment at different dosages (donepezil 5-10 mg/ daily; rivastigmine 1, 5-3 mg/b.i.d. or higher; galantamine 4-8 mg/b.i.d. or higher). There were no statistical differences in the distributions of drugs between the treated groups" • **Session duration**: 60 minutes in experimental group • **Number of treatment sessions**: 60 in experimental group • **Treatment frequency**: 5/week in experimental group • **Maximum treatment duration, in weeks**: 12 in experimental group • **Type of control intervention**: other; treatment duration not reported; intervention provided as individual training, without supervision • **Details of control intervention**: cholinesterase inhibitors • **Session duration**: not reported in control group • **Number of treatment sessions**: not reported in control group
Outcomes	• **Cognitive functioning outcomes considered** ○ Global cognitive functioning measured with MMSE at 12 months, on a scale from not reported to not reported with higher values indicating benefit ○ Episodic memory measured with short story at 12 months, on a scale from not reported to not reported with higher values indicating benefit

	○ Executive functioning measured with Raven's coloured matrices at 12 months, on a scale from not reported to not reported with higher values indicating benefit ○ Verbal fluency measured with Letter verbal fluency at 12 months, on a scale from not reported to not reported with higher values indicating benefit • **Physical functioning outcome considered** ○ Daily function measured with BADL at 12 months, on a scale from not reported to not reported with lower values indicating benefit • **Quality of life outcome considered** ○ Not reported • **Safety outcome considered**: none reported • **Depression outcome considered** ○ Depression measured with Geriatric Depression Scale at 1 year, on a scale from 0 to 15, with lower values indicating benefit • **Available cognitive functioning outcome not considered in this review** ○ Verbal fluency measured with Semantic verbal fluency at 12 months, on a scale from not reported to not reported with higher values indicating benefit
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Judgement**: method of random sequence generation not reported **Quote(s)**: "randomisation was made by a member of the research team"
Allocation concealment (selection bias)	Unclear risk	**Judgement**: method of allocation not reported **Quote(s)**: "randomisation was made by a member of the research team"
Blinding of participants (performance bias)	High risk	**Judgement**: blinding not feasible **Quote(s)**: none
Blinding of physicians / personnel	High risk	**Judgement**: blinding not feasible **Quote(s)**: none
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Judgement**: blinded outcome assessors **Quote(s)**: "the administration of the pre-post neuropsychological measures and the training program were conducted by two different experienced neuropsychologist, blinded to the subjects' group status"

Incomplete outcome data (attrition bias) All outcomes	Low risk	**Judgement**: 15 out of 15 (100%) randomised in experimental group were analysed, and 22 out of 22 (100%) randomised in control group were analysed. From the Table, it seems that all included patients were considered for inclusion in the analysis, although this is not clearly reported in the text
Selective reporting (reporting bias)	Low risk	**Judgement**: all outcomes indicated in the methods section are reported in the results section
Other bias	Unclear risk	**Judgement**: participants characteristics are not described and the selection process is not reported; it is unclear if participants were included consecutively

16-FR/CR test: 16-item free and cued reminding test (also RI-RI-16: rappel libre / rappel indicé à 16 items)
3MS: Mini Mental State Examination.
ACG: active control group.
ADAS-Cog: Alzheimer's Disease Assessment Scale Cognitive.
A-MCImd: amnestic MCI multiple domains subtype.
APOE: apolipoprotein E.
BADL: Brief Activities of Daily Living.
BAYER-ADL: Bayer Activities of Daily Living Scale.
BSRT: Buschke Selective Reminding Test.
BVRT: Benton Visual Retention Test.
CCE: computerised cognitive engagement.
CCS: computerised cognitive stimulation.
CG: control group.
ChEI: cholinesterase inhibitor.
CMMSE: Chinese version of Mini-Mental State Examination.
CMSS: Chinese Memory Symptoms Scale
COWAT: Controlled Oral Word Association Test.
CT: cognitive training.
CVT: cognitive vitality training.
DSST: Digit Symbol Substitution Test.
EFT: Eriksen Flanker Test
EG: experimental group.
ILS: independent living scales.
LM: logical memory.
MCI: mild cognitive impairment.
mMMSE: modified Mini Mental State Examination.
MMSE: Mini Mental State Examination.
NEAR: Neuropsychological and Educational Approach to Remediation model of treatment
PRT: progressive resistance training.
RAVLT: Rey Auditory Verbal Learning Test.

RCT: randomised controlled test.
SD: standard deviation.
SDMT: Symbol Digit Modality Test.
TMT-B and -A: Trail Making Test-B and -A.
UFOV: useful field of view.
WAIS: Wechsler Adult Intelligence Scale.
WMS-R: Wechsler Memory Scale-Revised.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adel 2013	Wrong study design
Alves 2014	Wrong intervention
Alves 2014a	Wrong intervention
Anderson 2014	Intervention shorter than 12 weeks: 8-week intervention period (2-arm trial; n = 67; likely cognitive healthy; mean age 63 years; extension of earlier trial)
Ann 2012	Wrong patient population
Apostolo 2014	Wrong patient population
Baglio 2011	Nature of intervention unclear
Ball 2002	Intervention shorter than 12 weeks: 5- to 6-week intervention period with 2- to 3-week booster period at 11 and 35 months (4-arm trial ACTIVE; n = 2832; cognitively healthy; mean age 74 years)
Ball 2002a	Duplicate
Ball 2006	Intervention shorter than 12 weeks. Multiple reports for excluded trial: Ball 2002 (trial ACTIVE)
Ball 2013	Intervention shorter than 12 weeks
Ballesteros 2014	Duplicate
Ballesteros 2014a	Duplicate
Ballesteros 2015	Duplicate
Ballesteros 2015a	Duplicate
Ballesteros 2017	Intervention shorter than 12 weeks
Bamidis 2015	Wrong study design

(*Continued*)

Baniqued 2014	Adult population
Baniqued 2015	Younger than 30 years of age
Barban 2012	Duplicate
Barban 2016	Wrong study design
Barbosa 2015	Wrong intervention
Barcelos 2015	Wrong intervention
Barnes 2006	Intervention shorter than 12 weeks
Barnes 2009	Duplicate
Basak 2016	Intervention shorter than 12 weeks: 2 week intervention period (2-arm trial; n = 46; cognitively healthy; mean age 69 years)
Beck 2013	Wrong intervention
Belchior 2007	Wrong outcomes
Belchior 2008	Wrong outcomes
Belleville 2006	Wrong intervention
Belleville 2014	Wrong outcomes
Berry 2010	Intervention shorter than 12 weeks: 3 to 5 weeks (2-arm trial: n = 32; cognitively healthy; mean age 72 years)
Bier 2015	Wrong study design
Binder 2016	Intervention shorter than 12 weeks
Bittner 2013	Wrong study design
Borella 2010	Intervention shorter than 12 weeks: 2 weeks (2-arm trial; n = 40; cognitively healthy; mean age 69 years)
Borella 2013	Wrong intervention
Borella 2014	Duplicate
Borella 2017	Wrong intervention
Boripuntakul 2012	Wrong intervention

(*Continued*)

Borness 2013	Wrong patient population
Bottiroli 2009	Duplicate
Bottiroli 2009a	Intervention shorter than 12 weeks: 3 training sessions (2-arm trial; n = 44; cognitively healthy; mean age 66 years)
Bozoki 2013	Intervention shorter than 12 weeks: 6-week intervention period (2-arm trial; n = 60; cognitively healthy; mean age 69 years)
Brehmer 2012	Intervention shorter than 12 weeks: 5-week intervention period (2-arm trial stratified by younger and older age groups; n = 45 in old age groups, n = 55 in young age groups; cognitively healthy; mean age 64 years in old age groups, 26 in young age groups)
Brum 2013	Duplicate
Buitenweg 2017	Wrong intervention
Buiza 2008	Wrong intervention
Bureš 2016	Intervention shorter than 12 weeks
Buschert 2011	Wrong intervention
Buschert 2011a	Duplicate
Buschert 2012	Wrong intervention
Buschert 2012a	Duplicate
Calkins 2011	Wrong intervention
Cammarata 2011	No outcome given
Cancela 2015	Wrong patient population
Candela 2015	Wrong intervention
Cantarella 2017	Intervention shorter than 12 weeks
Cao 2016	Wrong route of administration
Carretti 2013	Wrong intervention
Casutt 2014	Wrong outcomes
Chapman 2015	Wrong intervention

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Chapman 2016	Wrong intervention
Chapman 2017	Wrong intervention
Cheng 2012	Wrong intervention
Cheng 2018	Wrong patient population
Cho 2002	Younger than 30 years of age
Cleverley 2012	Wrong intervention
Cohen-Mansfield 2014	Wrong intervention
Cohen-Mansfield 2014a	Wrong intervention
Cohen-Mansfield 2015	Wrong intervention
Cohen-Mansfield 2015a	Duplicate
Combourieu 2014	Wrong outcomes
Corbett 2015	Wrong patient population
Costa 2015	Wrong patient population
Danassi 2015	Duplicate
Dannhauser 2014	Wrong study design
de Almondes 2017	Intervention shorter than 12 weeks
de Macedo 2015	Wrong outcomes
De Vreese 1996	Wrong intervention
Desjardins-Crépeau 2016	Wrong patient population
Diamond 2015	Intervention shorter than 12 weeks: 7-week intervention period (2-arm trial; n = 64; cognitively healthy; mean age 66 years)
Dittmann-Kohli 1991	Wrong intervention
Duncan 2009	Wrong intervention

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Dwolatzky 2005	Intervention shorter than 12 weeks: multiple reports for excluded trial: Wolinsky 2015 (IHAMS study) . This citation refers to the trial registration NCT01165463
Eckroth-Bucher 2009	Wrong patient population
Edwards 2005	Intervention shorter than 12 weeks: maximum 12 sessions (2-arm SKILL trial; n = 126; participants with initial processing speed or processing difficulty; mean age 76 years)
Edwards 2011	Intervention shorter than 12 weeks: multiple reports for Edwards 2005 (SKILL trial)
Edwards 2015	Intervention shorter than 12 weeks: planned treatment duration 10 to 12 weeks, but less than 12 weeks provided on average
Edwards 2015a	Duplicate
Efthymiou 2011	Wrong comparator.
Engvig 2014	Wrong study design
Fabre 2002	Wrong intervention
Faille 2007	Nature of intervention unclear
Fairchild 2010	Wrong intervention
Feng 2013	Wrong intervention
Feng 2015	Wrong intervention
Feng 2017	Wrong patient population
Finn 2011	Intervention shorter than 12 weeks
Finn 2015	Intervention shorter than 12 weeks: 4-week intervention period (2-arm trial; n = 41; participants with MCI; mean age 75 years)
Finn 2015a	Duplicate
Flak 2013	Study protocol
Flak 2014	Study protocol
Flak 2014a	Study protocol
Flak 2016	Study protocol
Foerster 2009	No outcome given

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Forloni 2012	No outcome given
Forster 2011	Wrong intervention
Fortman 2013	Wrong comparator
Gagnon 2012	Wrong study design
Gagnon 2012a	Intervention shorter than 12 weeks: 2-week intervention period (2-arm trial; n = 24; participants with MCI; mean age 68 years)
Gaitan 2013	Wrong patient population
Gajewski 2012	Intervention shorter than 12 weeks: cognitive training over 16 weeks, of which 12 concerned computerised cognitive training (4-arm trial; n = 141; cognitively healthy; mean age 71 years)
Gajewski 2017	Intervention shorter than 12 weeks
Garcia-Campuzano 2013	Nature of intervention unclear
Gates 2011	Study protocol
Gill 2016	Wrong intervention
Gillette 2009	No outcome given
Giovannini 2015	No outcome given
Giuli 2016	Wrong intervention
Giuli 2017	Wrong intervention
Golino 2017	Wrong intervention
Haesner 2015	Wrong study design
Haesner 2015a	Intervention shorter than 12 weeks: 8-week intervention (2-arm trial; n = 80, 40 cognitively healthy and 40 with subjective memory complaints; mean age 70 years)
Haimov 2013	Duplicate
Haimov 2013a	Duplicate
Haimov 2013b	Intervention shorter than 12 weeks: 8-week intervention period (2-arm study; n = 51; likely cognitively healthy; mean age 72 years)

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Haimov 2013c	Duplicate
Haimov 2013d	Intervention shorter than 12 weeks: multiple reports for Haimov 2013b
Haimov 2014	Intervention shorter than 12 weeks: multiple reports for Haimov 2013b
Haimov 2014a	Intervention shorter than 12 weeks: multiple reports for Haimov 2013b
Hardy 2015	Intervention shorter than 12 weeks: 10-week intervention period (2-arm trial; n = 9919; cognitively healthy; mean age 39 years; subgroup data by age can be analysed)
Hausmann 2012	Wrong intervention
Hayashi 2012	Wrong intervention
Hayslip B Jr 2016	Intervention shorter than 12 weeks
Heinzel 2014	Intervention shorter than 12 weeks: 4-week intervention period (2-arm trial; n = 60; 2-arm trial stratified by younger and older age groups; n = 30 in old age groups, n = 30 in young age groups; cognitively healthy; mean age 66 years in old age groups, 26 in young age groups)
Hudak 2013	Intervention shorter than 12 weeks: 10-week intervention period (3-arm trial; n = 53; cognitively healthy; mean age 82 years)
Hötting 2013	Intervention shorter than 12 weeks: 6 sessions during 1 month (4-arm trial; n = 33; cognitively healthy; mean age 49 years)
Ignjatovic 2015	Younger than 30 years of age
Irigaray 2012	Wrong intervention
Israel 1997	Nature of intervention unclear
ISRCTN70130279	Wrong intervention
Jackson 2012	Nature of intervention unclear
Jansen 2012	Wrong intervention
Jean 2010	Intervention shorter than 12 weeks: 3-week intervention period (2-arm trial; n = 22; participants with MCI; mean age 69 years)
Jeong 2016	Wrong intervention
Jobe 2001	Intervention shorter than 12 weeks: multiple reports for excluded trial: Ball 2002 (trial ACTIVE)
Jones 2013	Intervention shorter than 12 weeks: multiple reports for Ball 2002 (trial ACTIVE)

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Kampanaros 2010	Wrong intervention
Kholin 2010	Intervention shorter than 12 weeks: 30-day intervention period (2-arm trial; n = 60; participants with MCI; age not reported; conference abstract)
Kim 2012	Wrong outcomes
Kim 2013	Intervention shorter than 12 weeks: 10-week intervention period (2-arm trial; n = 20; participants with MCI or dementia; mean age 69 years)
Kim 2013a	Wrong outcomes
Kim 2015	Nature of intervention unclear
Kim 2015a	Intervention shorter than 12 weeks: 8-week intervention period (2-arm trial; n = 28; cognitively healthy; mean age 72 years)
Kim 2015b	Duplicate
Kivipelto 2014	Wrong intervention
Klusmann 2009	Duplicate
Klusmann 2010	Wrong patient population
Klusmann 2010a	Duplicate
Klusmann 2011	Younger than 30 years of age
Kudelka 2014	Intervention shorter than 12 weeks: 8-week intervention period (4-arm trial; n = 96; cognitively healthy; mean age 65 years)
Kwak 2015	Nature of intervention unclear
Kwak 2017	Nature of intervention unclear
Kwok 2013	Intervention shorter than 12 weeks: 8-week intervention period (2-arm trial; n = 194; mean MMSE score 25.92; mean age 75 years)
Lampit 2013	Wrong study design
Lampit 2014	Wrong patient population
Lampit 2015	Wrong outcomes
Lavretsky 2016	Nature of intervention unclear

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Law 2014	Intervention shorter than 12 weeks: 10-week intervention period (2-arm trial; n = 83; participants with MCI; mean age 74 years)
Law 2014a	Duplicate
Lee 2013	Intervention shorter than 12 weeks: 6-week intervention period (2-arm trial; n = 30; mean MMSE-K 26; mean age 72 years)
Lee 2013a	Intervention shorter than 12 weeks: 8-week intervention period (2-arm trial; n = 31; cognitively healthy; mean age 65 years)
Lee 2013b	Intervention shorter than 12 weeks: multiple reports for Lee 2013a
Lee 2014	Intervention shorter than 12 weeks: 8-week intervention period (2 2-arm pilots trials; n = 31 & n = 39; likely cognitively healthy; age not reported; conference abstract that is part of multiple reports for Lee 2015)
Lee 2015	Intervention shorter than 12 weeks: 8-week intervention period (2-arm trial; n = 39; cognitively healthy; mean age 65 years)
Legault 2011	Wrong patient population
Leon 2015	Wrong comparator
Leung 2015	Wrong patient population
Li 2010	Intervention shorter than 12 weeks: intervention period 5 weeks (2-arm trial; n = 20; cognitively healthy; mean age 76 years)
Linde 2014	Nature of intervention unclear
Mace 2015	Intervention shorter than 12 weeks: 3-week intervention period (2-arm trial; n = 43; mild cognitive complaints; mean age 78 years)
Mahncke 2006	Intervention shorter than 12 weeks: 8 to 10 weeks (2-arm trial; n = 182; cognitively healthy; mean age 71 years)
Man 2012	Wrong comparator
Mann 2012	Wrong study population
Margrett 2006	Wrong patient population
Mayas 2014	Intervention shorter than 12 weeks: 20 sessions provided in 10- to 12-week intervention period (n = 27; 2-arm trial; cognitively healthy; mean age 69)

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McAvinue 2013	Intervention shorter than 12 weeks: 5-week intervention period (n = 36; 2-arm trial; likely cognitively healthy; mean age 70)
McDaniel 2014	Intervention shorter than 12 weeks: 8-week intervention period (n = 96; 4-arm trial, cognitively healthy, mean age 65 years)
McDougall 2012	Intervention shorter than 12 weeks: 6-week intervention period (n = 41; 2-arm trial; likely cognitively healthy; mean age 75)
Middleton 2012	Wrong intervention
Miller 2013	Intervention shorter than 12 weeks: 8-week intervention period (n = 69; 2-arm trial; cognitively healthy; mean age 81.8)
Mohs 1998	Wrong intervention
Mombelli 2012	No outcome given
Moon 2013	Intervention shorter than 12 weeks: 10-week intervention period (n = 38; likely participants with MCI; age not reported; conference abstract only)
Mowszowski 2014	Intervention shorter than 12 weeks: 7-week intervention period (n = 53; participants with memory complaints, MCI or late life depression; mean age 66)
Mowszowski 2014a	Duplicate
Mozolic 2010	Intervention shorter than 12 weeks: 8-week intervention period (n = 66; mean age 69; cognitively healthy participants)
Mozolic 2011	Intervention shorter than 12 weeks: multiple reports for Mozolic 2010
Muller 2011	Nature of intervention unclear
Na 2013	Duplicate
Na 2014	Nature of intervention unclear
Naismith 2014	Duplicate
Navarro 2006	Intervention shorter than 12 weeks: 14 sessions; intervention duration not reported, but maximal follow-up duration was 84 days (2-arm trial; n = 80; likely cognitively healthy; mean age 66 years)
NCT00544856	Nature of intervention unclear
NCT02417558 2015	Nature of intervention unclear
NCT02462135 2014	No outcome given

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NCT02480738 2012	No outcome given
NCT02512627 2015	No outcome given
NCT02747784 2016	Wrong patient population
NCT02774083 2015	Wrong comparator
NCT02785315 2016	Wrong intervention
NCT02808676 2016	Wrong intervention
Neely 2013	Nature of intervention unclear
Ng 2015	Wrong intervention
Ngandu 2015	Wrong intervention
Ngandu 2015a	Wrong intervention
Nishiguchi 2015	Wrong intervention
Nouchi 2012	Intervention shorter than 12 weeks: 4-week intervention period (2-arm trial; n = 32; cognitively healthy; mean age 69)
Nouchi 2013	Intervention shorter than 12 weeks
Nozawa 2015	Intervention shorter than 12 weeks: 8-week intervention period (3-arm trial; n = 37; cognitively healthy; mean age 68)
O'Caoimh 2015	Intervention shorter than 12 weeks
Oei 2013	Intervention shorter than 12 weeks: 4-week intervention period (5-arm trial; n = 75; cognitively healthy; mean age 21)
Oliveira 2013	Intervention shorter than 12 weeks: 10-week intervention period. (2-arm cohort study; n = 182; subjective memory complaints; mean age not reported, all over 50 years of age, conference abstract only)
Otsuka 2015	Wrong study design
Park 2009	Nature of intervention unclear
Park 2014	Intervention shorter than 12 weeks: 2-week intervention period (2-arm trial; n = 40; cognitively healthy; mean age 70)
Payne 2012	Wrong intervention

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Payne 2017	Intervention shorter than 12 weeks
Peretz 2011	Wrong patient population
R000001637	Nature of intervention unclear
Rahe 2015	Intervention shorter than 12 weeks: 6.5-week intervention period (2-arm trial; n = 30; cognitively healthy; mean age 67 years)
Rahe 2015a	Intervention shorter than 12 weeks: 7-week intervention period (3-arm trial; n = 81; cognitively healthy; mean age 68 years)
Rebok 2013	Intervention shorter than 12 weeks: multiple reports for excluded trial: Ball 2002 (trial ACTIVE)
Rebok 2014	Intervention shorter than 12 weeks: multiple reports for excluded trial: Ball 2002 (trial ACTIVE)
Redick 2013	Younger than 30 years of age
Requena 2016	Wrong intervention
Rizkalla 2015	Intervention shorter than 12 weeks: 4-week intervention period (2-arm trial; n = 56; cognitively healthy; mean age 73 years)
Rojas 2013	Wrong intervention
Rose 2015	Intervention shorter than 12 weeks: 1-month intervention period (2-arm trial; n = 59; cognitively healthy; mean age 67 years)
Rosen 2011	Intervention shorter than 12 weeks: 2-month intervention period (2-arm pilot trial; n = 12; participants with MCI; mean age 74)
Ryu 2013	Wrong study design
Sakka 2015	Wrong study design
Santos 2011	Wrong comparator
Schoene 2015	Duplicate
Schoene 2015a	Duplicate
Schumacher 2013	Intervention shorter than 12 weeks: 10-week intervention period (3-arm trial; n = 63; cognitively healthy participants; mean age 72; conference abstract)
Shah 2012	Wrong patient population
Shatil 2013	Wrong patient population

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Shatil 2014	Intervention shorter than 12 weeks: 8-week intervention period (2-arm trial; n = 140; cognitively healthy; mean age 68)
Shatil 2014a	Duplicate citation
Sisco 2013	Intervention shorter than 12 weeks: multiple reports for excluded trial: Ball 2002 (trial ACTIVE)
Slegers 2009	Wrong intervention
Smith 2009	Intervention shorter than 12 weeks: 8-week intervention period (2-arm trial IMPACT; n = 487; cognitively healthy; mean age 75 years)
Smith-Ray 2014	Intervention shorter than 12 weeks: 10-week intervention period (2-arm trial; n = 45; cognitively healthy; mean age 72)
Smith-Ray 2015	Intervention shorter than 12 weeks: 10-week intervention period (2-arm trial; n = 51; cognitively healthy; mean age 82)
Smith-Ray 2015a	Duplicate
Solomon 2014	Wrong comparator
Song 2009	Wrong intervention
Stepankova 2014	Intervention shorter than 12 weeks: 5-week intervention period (3-arm trial; n = 68; cognitively healthy; mean age 68 years)
Stine-Morrow 2014	Intervention shorter than 12 weeks: CCT intervention period 10 weeks (3-arm trial; n = 461; cognitively healthy; mean age 73 years)
Strenziok 2013	Duplicate
Strenziok 2014	Intervention shorter than 12 weeks: 6-week intervention period (3-arm trial; n = 42; cognitively healthy; mean age 69 years)
Sturz 2011	Wrong patient population
Sturz 2011a	Nature of intervention unclear
Sturz 2015	Duplicate
Styliadis 2015	Intervention shorter than 12 weeks: 8-week intervention (5-arm trial; n = 70; participants with MCI; mean age 71 years)
Styliadis 2015a	Duplicate
Suo 2012	Wrong outcomes

(*Continued*)

Szelag 2012	Intervention shorter than 12 weeks: 8-week intervention period (3-arm trial; n = 30; cognitively healthy; mean age 69 years)
Talib 2008	Intervention shorter than 12 weeks: 4-session intervention period (2-arm trial; n = 23; cognitively healthy; mean age 68 years)
Tappen 2014	Wrong intervention
Tennstedt 2013	Study protocol: multiple reports for excluded trial: Ball 2002 (trial ACTIVE)
Tesky 2012	Wrong intervention
Tsai 2008	Wrong study design
Tsolaki 2013	Nature of intervention unclear
Tucker-Drob 2009	Wrong study design
van den Berg 2016	Intervention shorter than 12 weeks: 2-week intervention period (2-arm trial; n = 58; rehabilitation inpatients with MMSE $\geq$ 21 (mean MMSE 26 with SD = 3 in experimental and 27 with SD = 3 in control); mean age 80 years)
van der Ploeg 2016	Wrong study design
Van het Reve 2014	Wrong patient population
Vance 2007	Intervention shorter than 12 weeks: 2 to 3 months (n = 159; cognitively healthy but with speed of processing impairment; mean age 75 years)
Vidovich 2009	Intervention shorter than 12 weeks: multiple reports for excluded trial: Vidovich 2015 (PACE trial)
Vidovich 2015	Intervention shorter than 12 weeks: 5-week intervention period (2-arm trial; n = 160; participants with MCI; mean age 75 years; PACE trial)
Vidovich 2015a	Duplicate
von Bastian 2013	Intervention shorter than 12 weeks: 4-week intervention period (2-arm trial; n = 57 in the elderly subgroup; cognitively healthy; mean age 69 years in the elderly subgroup)
Wadley 2007	Wrong study design
Walton 2015	Intervention shorter than 12 weeks: 4-week intervention period (2-arm trial; n = 28; cognitively healthy; mean age 64 years)
Wang 2013	Wrong intervention

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Weicker 2013	Intervention shorter than 12 weeks: 4-week intervention period (2-arm trial; n = not reported; cognitively healthy; age 60 to 75 years; conference abstract)
Wild-Wall 2012	Wrong outcomes
Williams 2014	Intervention shorter than 12 weeks: 3-week intervention period (3-arm trial; n = 103; mild impairment in cognition, expressed concern about cognitive changes, or mild dementia - mean MMSE = 25.3; mean age 86 years)
Willis 1986	Intervention shorter than 12 weeks: 2-week intervention period (2-arm trial; n = 229; cognitively stable and cognitively declined participant subgroups; mean age 73 years)
Willis 2006	Intervention shorter than 12 weeks: multiple reports for excluded trial: Ball 2002 (trial ACTIVE)
Willis 2006a	Duplicate
Willis 2007	Duplicate
Willis 2013	Intervention shorter than 12 weeks: multiple reports for excluded trial: Ball 2002 (trial ACTIVE)
Wojtynska 2011	Intervention shorter than 12 weeks: 6-week intervention period (2-arm trial, stratified by 3 cognitive strata; n = 34 MCI, n = 29 AD, n = 12 cognitively healthy; participants with MCI and early dementia; mean age 69 years; conference abstract)
Wolinsky 2006	Intervention shorter than 12 weeks: multiple reports for excluded trial: Ball 2002 (trial ACTIVE)
Wolinsky 2006a	Intervention shorter than 12 weeks: multiple reports for excluded trial: Ball 2002 (trial ACTIVE)
Wolinsky 2010	Intervention shorter than 12 weeks: multiple reports for excluded trial: Ball 2002 (trial ACTIVE)
Wolinsky 2010a	Intervention shorter than 12 weeks: multiple reports for excluded trial: Ball 2002 (trial ACTIVE)
Wolinsky 2013	Intervention shorter than 12 weeks: multiple reports for excluded trial: Wolinsky 2015 (IHAMS study)
Wolinsky 2015	Intervention shorter than 12 weeks: 5- to 6-week intervention period with booster at 11 months (4-arm trial; n = 681; cognitively healthy; 50 to 64 years, n = 455; and 65 years and above, n = 226; Iowa Healthy and Active Minds Study (IHAMS study)
Yam 2014	Wrong intervention
Yassuda 2015	Intervention shorter than 12 weeks: 8-session intervention period (2-arm trial; n = 60; participants without depression/dementia; mean age not reported; conference abstract)
Yip 2012	Intervention shorter than 12 weeks: 5-week intervention period (3-arm trial; n = 56; participants with acquired brain injury and subjective memory complaints; mean age 52 years)

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Yoonmi 2012	Intervention shorter than 12 weeks: 6-week intervention period (2-arm trial; n = 30; cognitively healthy; aged 65 to 80 years)
Youn 2011	Intervention shorter than 12 weeks: 5-week intervention period (2-arm trial; n = 40; participants with subjective memory complaints; mean age 69 years)
Zelinski 2011	Wrong study design
Zelinski 2011a	Intervention shorter than 12 weeks: multiple reports for excluded trial: Smith 2009 (IMPACT)
Zhuang 2013	Wrong patient population
Zimmermann 2014	Intervention shorter than 12 weeks: 6-week intervention period (2-arm trial; n = 20; cognitively healthy; mean age 68 years)

MMSE: Mini Mental State Examination.

DATA AND ANALYSES

Comparison 1. Computerised cognition-based interventions versus active control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global cognitive function	5		Std. Mean Difference (Random, 95% CI)	Subtotals only
1.1 End of trial	5	407	Std. Mean Difference (Random, 95% CI)	-0.53 [-1.06, -0.01]
1.2 Immediate time point (12 weeks)	4	356	Std. Mean Difference (Random, 95% CI)	-0.31 [-0.70, 0.08]
1.3 Short time point (12 weeks to 1 year)	2	82	Std. Mean Difference (Random, 95% CI)	-1.23 [-1.89, -0.56]
1.4 Medium time point (1 year to 2 years)	1	100	Std. Mean Difference (Random, 95% CI)	0.16 [-0.23, 0.55]
2 Episodic memory	5		Std. Mean Difference (Random, 95% CI)	Subtotals only
2.1 End of trial	5	223	Std. Mean Difference (Random, 95% CI)	-0.79 [-1.54, -0.04]
2.2 Immediate time point (12 weeks)	4	172	Std. Mean Difference (Random, 95% CI)	-0.99 [-1.80, -0.19]
2.3 Short time point (12 weeks to 1 year)	3	104	Std. Mean Difference (Random, 95% CI)	-1.39 [-2.35, -0.44]
2.4 Medium time point (1 year to 2 years)	1	100	Std. Mean Difference (Random, 95% CI)	0.02 [-0.37, 0.41]
3 Speed of processing	2		Std. Mean Difference (Random, 95% CI)	Subtotals only
3.1 End of trial	2	119	Std. Mean Difference (Random, 95% CI)	0.20 [-0.16, 0.56]
3.2 Immediate time point (12 weeks)	2	119	Std. Mean Difference (Random, 95% CI)	0.11 [-0.25, 0.47]
3.3 Medium time point (1 year to 2 years)	1	100	Std. Mean Difference (Random, 95% CI)	0.14 [-0.25, 0.53]
4 Executive function	3		Std. Mean Difference (Random, 95% CI)	Subtotals only
4.1 End of trial	3	150	Std. Mean Difference (Random, 95% CI)	-0.31 [-0.90, 0.28]
4.2 Immediate time point (12 weeks)	3	150	Std. Mean Difference (Random, 95% CI)	-0.18 [-0.50, 0.14]
4.3 Short time point (12 weeks to 1 year)	1	31	Std. Mean Difference (Random, 95% CI)	-0.81 [-1.54, -0.07]
4.4 Medium time point (1 year to 2 years)	1	100	Std. Mean Difference (Random, 95% CI)	0.08 [-0.31, 0.48]
5 Working memory	3		Std. Mean Difference (Random, 95% CI)	Subtotals only
5.1 End of trial	3	72	Std. Mean Difference (Random, 95% CI)	-0.88 [-1.73, -0.03]
5.2 Immediate time point (12 weeks)	3	72	Std. Mean Difference (Random, 95% CI)	-0.66 [-1.26, -0.06]
5.3 Short time point (12 weeks to 1 year)	2	53	Std. Mean Difference (Random, 95% CI)	-1.29 [-1.88, -0.69]
6 Verbal fluency	3		Std. Mean Difference (Random, 95% CI)	Subtotals only
6.1 End of trial	3	150	Std. Mean Difference (Random, 95% CI)	-0.16 [-0.76, 0.44]
6.2 Immediate time point (12 weeks)	3	150	Std. Mean Difference (Random, 95% CI)	-0.02 [-0.46, 0.42]
6.3 Short time point (12 weeks to 1 year)	1	31	Std. Mean Difference (Random, 95% CI)	-0.78 [-1.51, -0.04]

6.4 Medium time point (1 year to 2 years)	1	100	Std. Mean Difference (Random, 95% CI)	0.18 [-0.22, 0.57]
7 Depression	3		Std. Mean Difference (Random, 95% CI)	Subtotals only
7.1 End of trial	3	101	Std. Mean Difference (Random, 95% CI)	-0.77 [-2.07, 0.52]
7.2 Immediate time point (12 weeks)	1	19	Std. Mean Difference (Random, 95% CI)	0.22 [-0.68, 1.13]
7.3 Short time point (12 weeks to 1 year)	2	82	Std. Mean Difference (Random, 95% CI)	-1.26 [-3.11, 0.59]
8 Functional performance	2		Std. Mean Difference (Random, 95% CI)	Subtotals only
8.1 End of trial	2	131	Std. Mean Difference (Random, 95% CI)	0.09 [-0.51, 0.70]
8.2 Immediate time point (12 weeks)	2	131	Std. Mean Difference (Random, 95% CI)	0.33 [-0.02, 0.67]
8.3 Short time point (12 weeks to 1 year)	1	31	Std. Mean Difference (Random, 95% CI)	-0.29 [-1.00, 0.41]
8.4 Medium time point (1 year to 2 years)	1	100	Std. Mean Difference (Random, 95% CI)	0.34 [-0.06, 0.73]
9 Quality of life	1		Mean Difference (Random, 95% CI)	Subtotals only
9.1 End of trial; 12 weeks	1	19	Mean Difference (Random, 95% CI)	0.4 [-1.85, 2.65]
10 Serious adverse events: mortality	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
10.1 Short time point (12 weeks to 1 year)	1	36	Risk Ratio (IV, Fixed, 95% CI)	0.5 [0.05, 5.04]

Comparison 2. Computerised cognition-based interventions versus inactive control

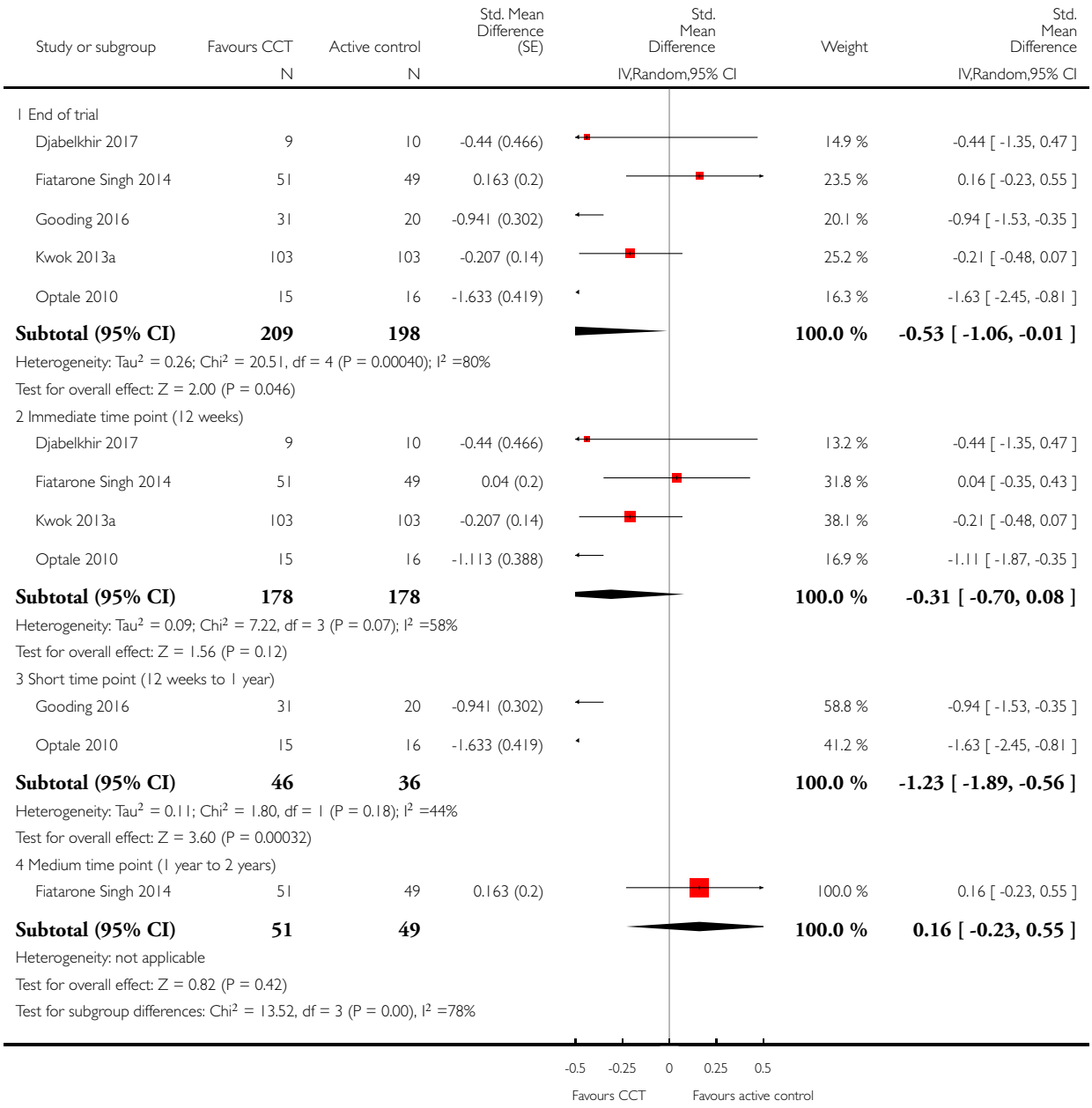
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global cognitive function	1		Mean Difference (Random, 95% CI)	Subtotals only
1.1 End of trial, up to 1 year	1	37	Mean Difference (Random, 95% CI)	0.36 [-0.30, 1.02]
2 Episodic memory	1		Mean Difference (Random, 95% CI)	Subtotals only
2.1 End of trial, up to 1 year	1	37	Mean Difference (Random, 95% CI)	-2.7 [-3.00, -0.40]
3 Executive function	1		Mean Difference (Random, 95% CI)	Subtotals only
3.1 End of trial, up to 1 year	1	37	Mean Difference (Random, 95% CI)	-2.7 [-6.21, 0.81]
4 Verbal fluency	1		Mean Difference (Random, 95% CI)	Subtotals only
4.1 End of trial, up to 1 year	1	37	Mean Difference (Random, 95% CI)	1.90 [-4.50, 8.30]
5 Depression	1		Mean Difference (Random, 95% CI)	Subtotals only
5.1 End of the trial, up to 1 year	1	37	Mean Difference (Random, 95% CI)	-1.3 [-2.61, 0.01]
6 Functional performance	1		Mean Difference (Random, 95% CI)	Subtotals only
6.1 End of trail, up to 1 year	1	37	Mean Difference (Random, 95% CI)	0.0 [-0.48, 0.48]

Analysis 1.1. Comparison 1 Computerised cognition-based interventions versus active control, Outcome 1 Global cognitive function.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 1 Computerised cognition-based interventions versus active control

Outcome: 1 Global cognitive function



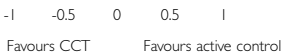
Analysis 1.2. Comparison 1 Computerised cognition-based interventions versus active control, Outcome 2 Episodic memory.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 1 Computerised cognition-based interventions versus active control

Outcome: 2 Episodic memory

Study or subgroup	CCT N	Active control N	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 End of trial						
Optale 2010	15	16	-2.513 (0.488)		17.8 %	-2.51 [-3.47, -1.56]
Herrera 2012	11	11	-0.852 (0.447)		18.7 %	-0.85 [-1.73, 0.02]
Djabelkhir 2017	9	10	-0.556 (0.469)		18.2 %	-0.56 [-1.48, 0.36]
Gooding 2016	31	20	-0.396 (0.29)		21.9 %	-0.40 [-0.96, 0.17]
Fiatarone Singh 2014	51	49	0.018 (0.2)		23.4 %	0.02 [-0.37, 0.41]
Subtotal (95% CI)	**117**	**106**			**100.0 %**	**-0.79 [-1.54, -0.04]**
Heterogeneity: Tau² = 0.59; Chi² = 24.21, df = 4 (P = 0.00007); I² =83%						
Test for overall effect: Z = 2.06 (P = 0.040)						
2 Immediate time point (12 weeks)						
Herrera 2012	11	11	-1.719 (0.506)		21.9 %	-1.72 [-2.71, -0.73]
Optale 2010	15	16	-1.658 (0.42)		24.5 %	-1.66 [-2.48, -0.83]
Djabelkhir 2017	9	10	-0.556 (0.469)		23.0 %	-0.56 [-1.48, 0.36]
Fiatarone Singh 2014	51	49	-0.271 (0.201)		30.6 %	-0.27 [-0.66, 0.12]
Subtotal (95% CI)	**86**	**86**			**100.0 %**	**-0.99 [-1.80, -0.19]**
Heterogeneity: Tau² = 0.51; Chi² = 13.82, df = 3 (P = 0.003); I² =78%						
Test for overall effect: Z = 2.43 (P = 0.015)						
3 Short time point (12 weeks to 1 year)						
Optale 2010	15	16	-2.513 (0.488)		30.4 %	-2.51 [-3.47, -1.56]
Gooding 2016	31	20	-0.941 (0.302)		37.5 %	-0.94 [-1.53, -0.35]
Herrera 2012	11	11	-0.852 (0.447)		32.0 %	-0.85 [-1.73, 0.02]
Subtotal (95% CI)	**57**	**47**			**100.0 %**	**-1.39 [-2.35, -0.44]**
Heterogeneity: Tau² = 0.54; Chi² = 8.54, df = 2 (P = 0.01); I² =77%						
Test for overall effect: Z = 2.86 (P = 0.0043)						
4 Medium time point (1 year to 2 years)						
Fiatarone Singh 2014	51	49	0.018 (0.2)		100.0 %	0.02 [-0.37, 0.41]
Subtotal (95% CI)	**51**	**49**			**100.0 %**	**0.02 [-0.37, 0.41]**



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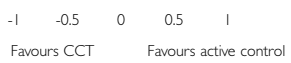
Study or subgroup	CCT N	Active control N	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Heterogeneity: not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Chi^2 = 11.65, df = 3 (P = 0.01), I^2 =74%						



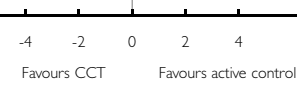
Analysis 1.3. Comparison 1 Computerised cognition-based interventions versus active control, Outcome 3 Speed of processing.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 1 Computerised cognition-based interventions versus active control

Outcome: 3 Speed of processing

Study or subgroup	CCT N	Active control N	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 End of trial						
Djabelkhir 2017	9	10	0.509 (0.468)		15.4 %	0.51 [-0.41, 1.43]
Fiatarone Singh 2014	51	49	0.14 (0.2)		84.6 %	0.14 [-0.25, 0.53]
Subtotal (95% CI)	**60**	**59**			**100.0 %**	**0.20 [-0.16, 0.56]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.53, df = 1 (P = 0.47); I^2 =0.0%						
Test for overall effect: Z = 1.07 (P = 0.28)						
2 Immediate time point (12 weeks)						
Djabelkhir 2017	9	10	0.509 (0.468)		15.4 %	0.51 [-0.41, 1.43]
Fiatarone Singh 2014	51	49	0.032 (0.2)		84.6 %	0.03 [-0.36, 0.42]
Subtotal (95% CI)	**60**	**59**			**100.0 %**	**0.11 [-0.25, 0.47]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.88, df = 1 (P = 0.35); I^2 =0.0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
3 Medium time point (1 year to 2 years)						
Fiatarone Singh 2014	51	49	0.14 (0.2)		100.0 %	0.14 [-0.25, 0.53]



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Study or subgroup	CCT N	Active control N	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**51**	**49**			**100.0 %**	**0.14 [-0.25, 0.53]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Chi^2 = 0.13, df = 2 (P = 0.94), I^2 =0.0%						

Analysis 1.4. Comparison 1 Computerised cognition-based interventions versus active control, Outcome 4 Executive function.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 1 Computerised cognition-based interventions versus active control

Outcome: 4 Executive function

Study or subgroup	CCT N	Active control N	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 End of trial						
Djabelkhir 2017	9	10	-0.419 (0.465)		24.1 %	-0.42 [-1.33, 0.49]
Fiatarone Singh 2014	51	49	0.084 (0.2)		45.7 %	0.08 [-0.31, 0.48]
Optale 2010	15	16	-0.809 (0.375)		30.2 %	-0.81 [-1.54, -0.07]
Subtotal (95% CI)	**75**	**75**			**100.0 %**	**-0.31 [-0.90, 0.28]**
Heterogeneity: Tau^2 = 0.16; Chi^2 = 4.79, df = 2 (P = 0.09); I^2 =58%						
Test for overall effect: Z = 1.02 (P = 0.31)						
2 Immediate time point (12 weeks)						
Djabelkhir 2017	9	10	-0.419 (0.465)		12.5 %	-0.42 [-1.33, 0.49]
Fiatarone Singh 2014	51	49	-0.034 (0.2)		67.4 %	-0.03 [-0.43, 0.36]
Optale 2010	15	16	-0.531 (0.366)		20.1 %	-0.53 [-1.25, 0.19]
Subtotal (95% CI)	**75**	**75**			**100.0 %**	**-0.18 [-0.50, 0.14]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.72, df = 2 (P = 0.42); I^2 =0.0%						

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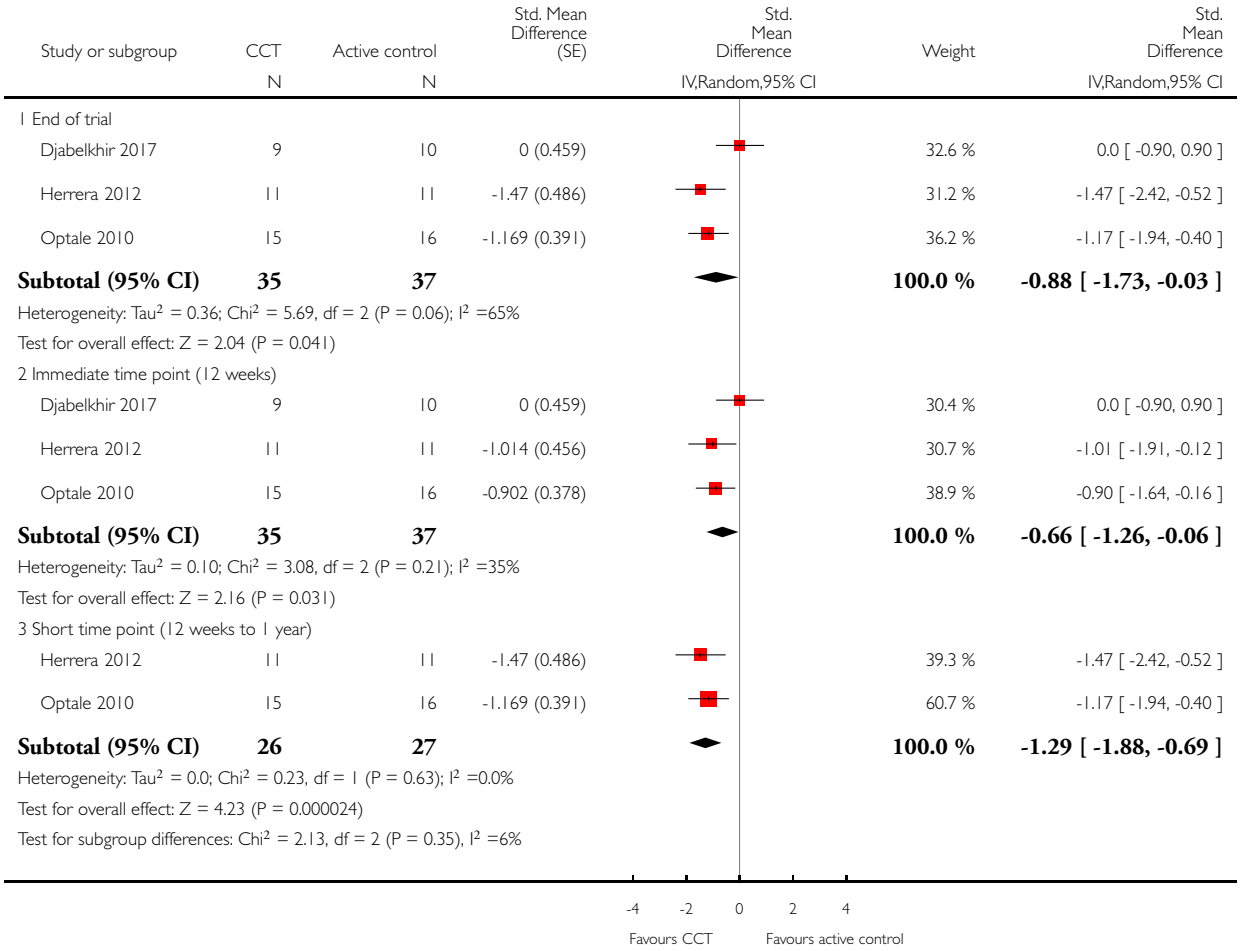
Study or subgroup	CCT N	Active control N	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Test for overall effect: Z = 1.11 (P = 0.27)						
3 Short time point (12 weeks to 1 year)						
Optale 2010	15	16	-0.809 (0.375)		100.0 %	-0.81 [-1.54, -0.07]
Subtotal (95% CI)	**15**	**16**			**100.0 %**	**-0.81 [-1.54, -0.07]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.16 (P = 0.031)						
4 Medium time point (1 year to 2 years)						
Fiatarone Singh 2014	51	49	0.084 (0.2)		100.0 %	0.08 [-0.31, 0.48]
Subtotal (95% CI)	**51**	**49**			**100.0 %**	**0.08 [-0.31, 0.48]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.42 (P = 0.67)						
Test for subgroup differences: Chi^2 = 4.73, df = 3 (P = 0.19), I^2 =37%						

Analysis 1.5. Comparison 1 Computerised cognition-based interventions versus active control, Outcome 5 Working memory.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 1 Computerised cognition-based interventions versus active control

Outcome: 5 Working memory

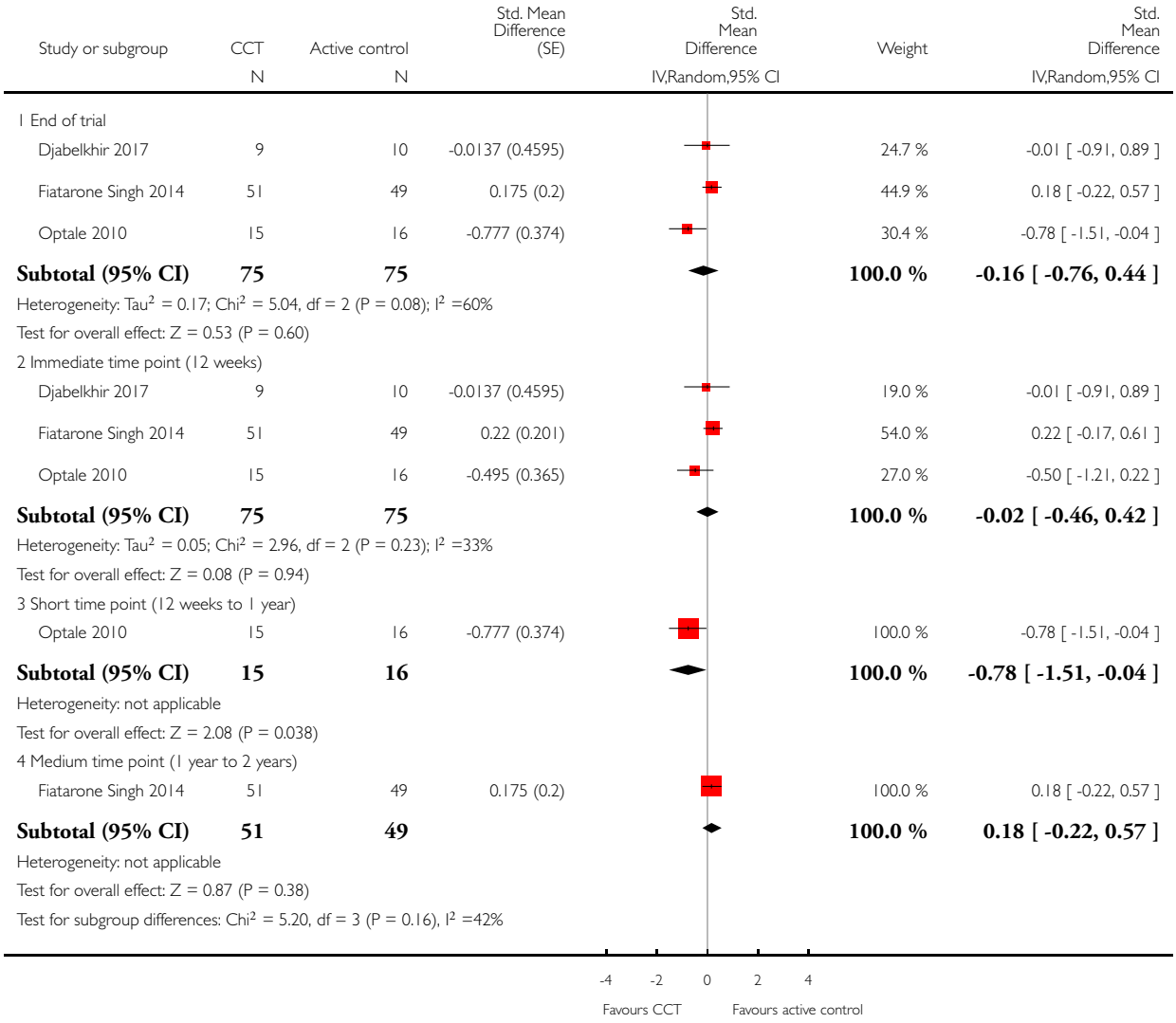


Analysis 1.6. Comparison 1 Computerised cognition-based interventions versus active control, Outcome 6 Verbal fluency.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 1 Computerised cognition-based interventions versus active control

Outcome: 6 Verbal fluency

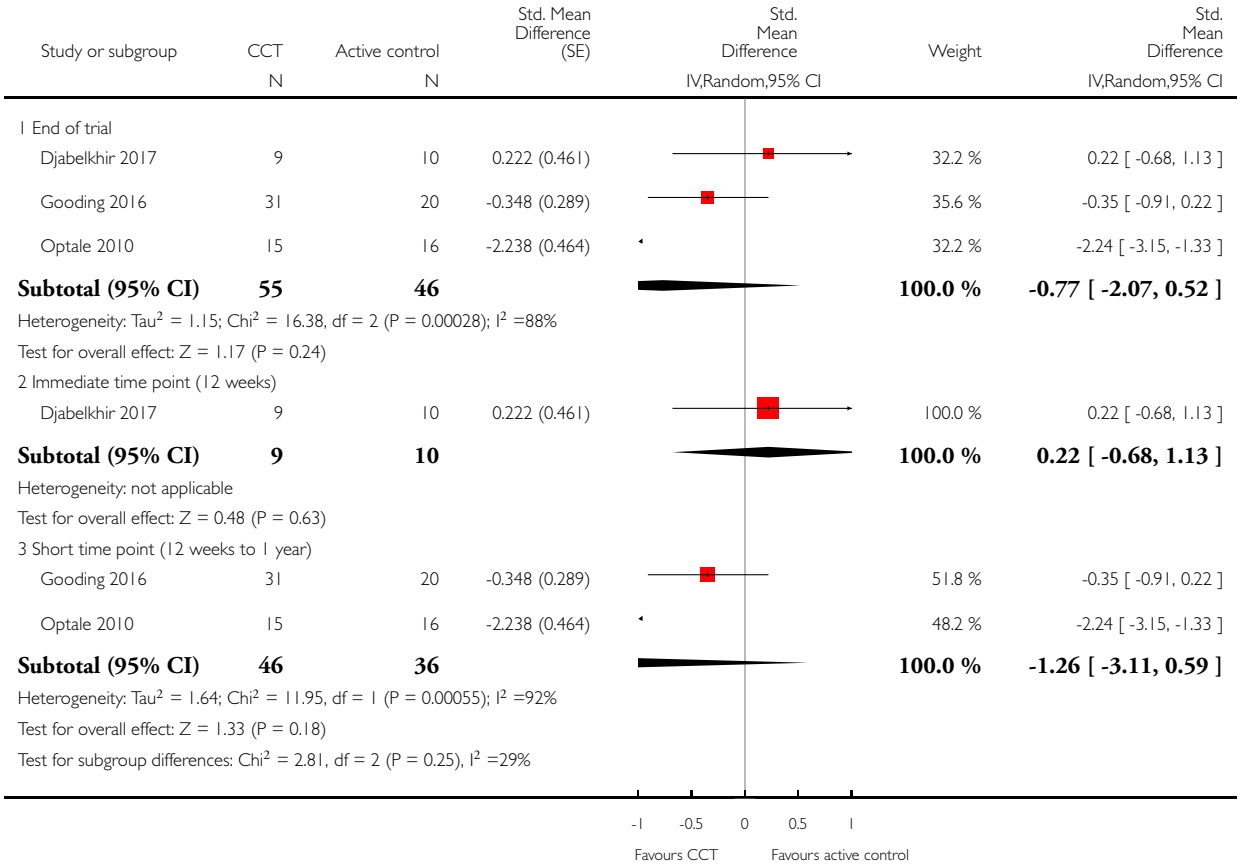


Analysis 1.7. Comparison 1 Computerised cognition-based interventions versus active control, Outcome 7 Depression.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 1 Computerised cognition-based interventions versus active control

Outcome: 7 Depression

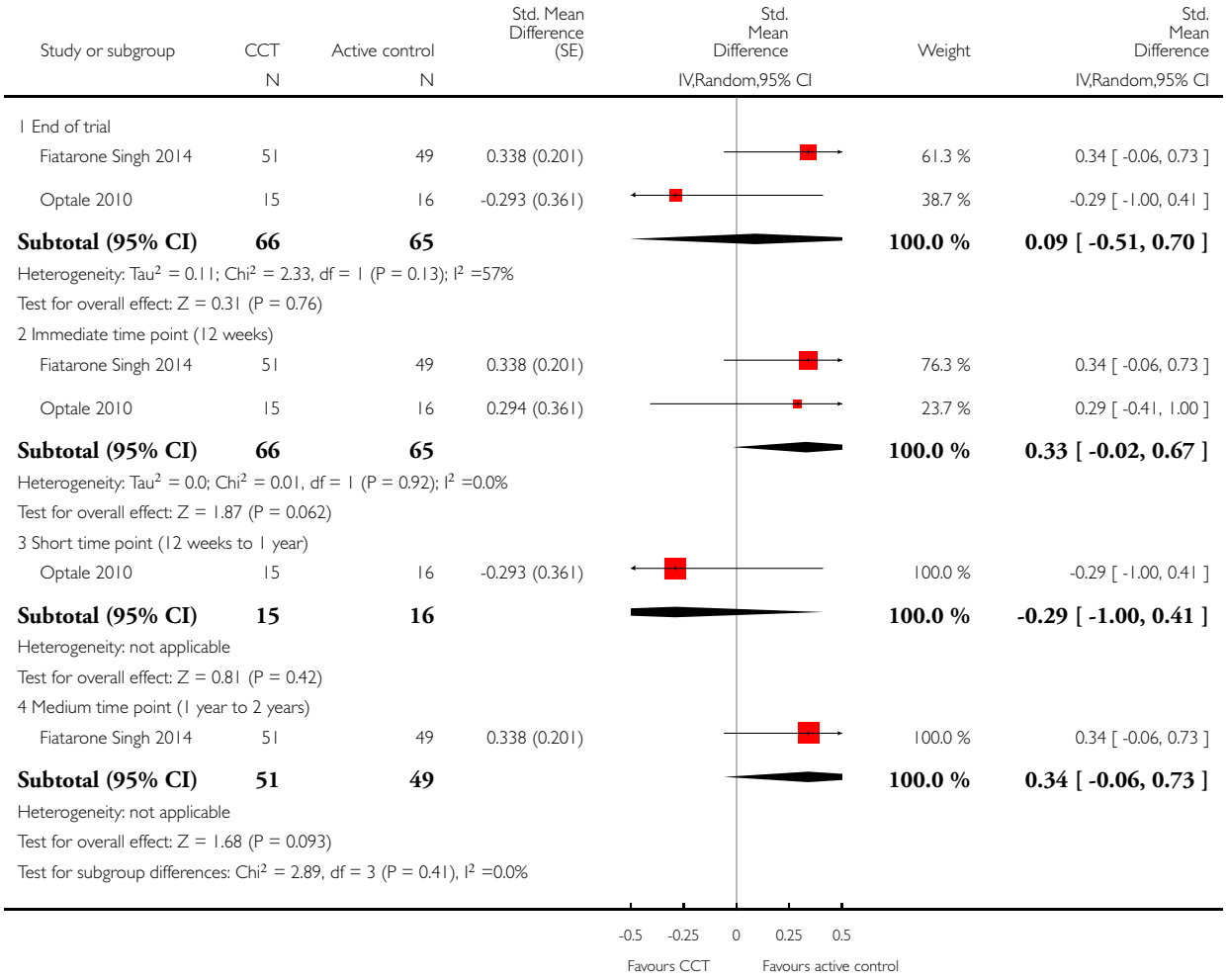


Analysis 1.8. Comparison 1 Computerised cognition-based interventions versus active control, Outcome 8 Functional performance.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 1 Computerised cognition-based interventions versus active control

Outcome: 8 Functional performance

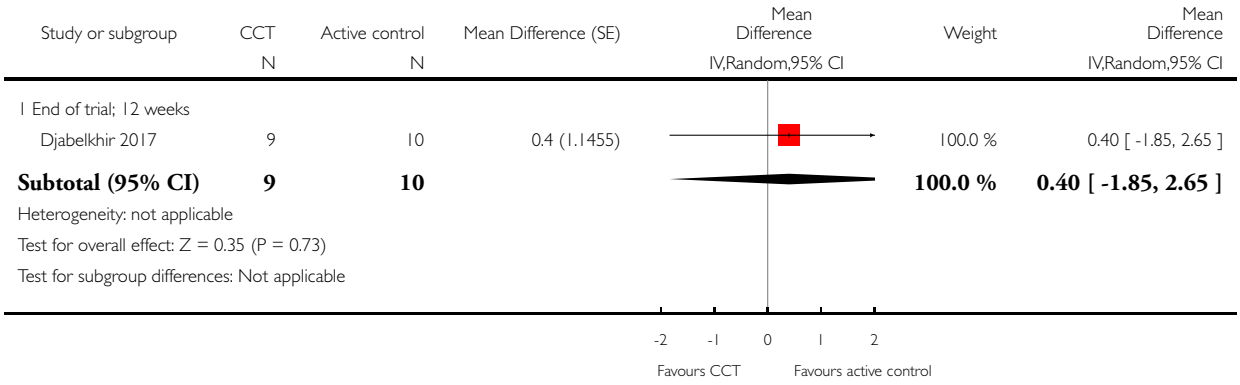


Analysis 1.9. Comparison 1 Computerised cognition-based interventions versus active control, Outcome 9 Quality of life.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 1 Computerised cognition-based interventions versus active control

Outcome: 9 Quality of life

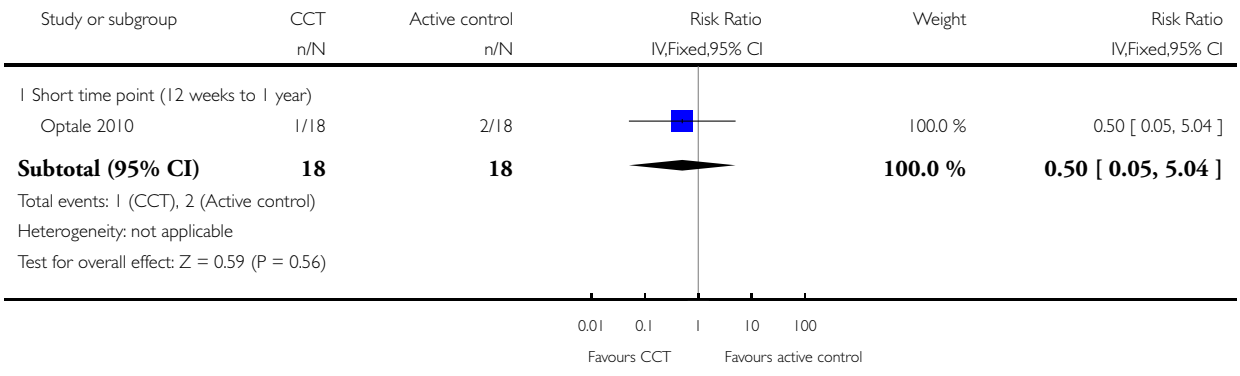


Analysis 1.10. Comparison 1 Computerised cognition-based interventions versus active control, Outcome 10 Serious adverse events: mortality.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 1 Computerised cognition-based interventions versus active control

Outcome: 10 Serious adverse events: mortality



Analysis 2.1. Comparison 2 Computerised cognition-based interventions versus inactive control, Outcome 1 Global cognitive function.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 2 Computerised cognition-based interventions versus inactive control

Outcome: 1 Global cognitive function

Study or subgroup	Favours CCT N	Inactive control N	Mean Difference (SE)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 End of trial, up to 1 year						
Rozzini 2007	15	22	0.3603 (0.3378)		100.0 %	0.36 [-0.30, 1.02]
Subtotal (95% CI)	**15**	**22**			**100.0 %**	**0.36 [-0.30, 1.02]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.07 (P = 0.29)						

Analysis 2.2. Comparison 2 Computerised cognition-based interventions versus inactive control, Outcome 2 Episodic memory.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 2 Computerised cognition-based interventions versus inactive control

Outcome: 2 Episodic memory

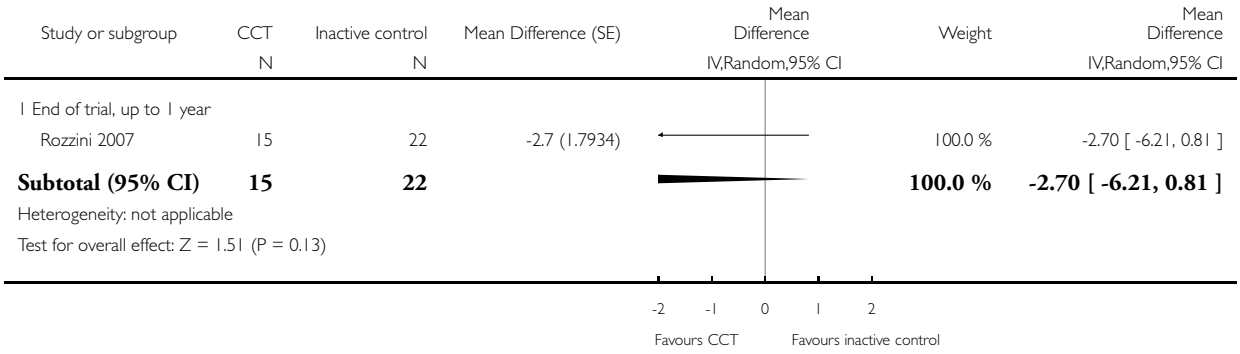
Study or subgroup	CCT N	Inactive control N	Mean Difference (SE)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 End of trial, up to 1 year						
Rozzini 2007	15	22	-2.7 (1.172)		100.0 %	-2.70 [-5.00, -0.40]
Subtotal (95% CI)	**15**	**22**			**100.0 %**	**-2.70 [-5.00, -0.40]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.30 (P = 0.021)						

Analysis 2.3. Comparison 2 Computerised cognition-based interventions versus inactive control, Outcome 3 Executive function.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 2 Computerised cognition-based interventions versus inactive control

Outcome: 3 Executive function

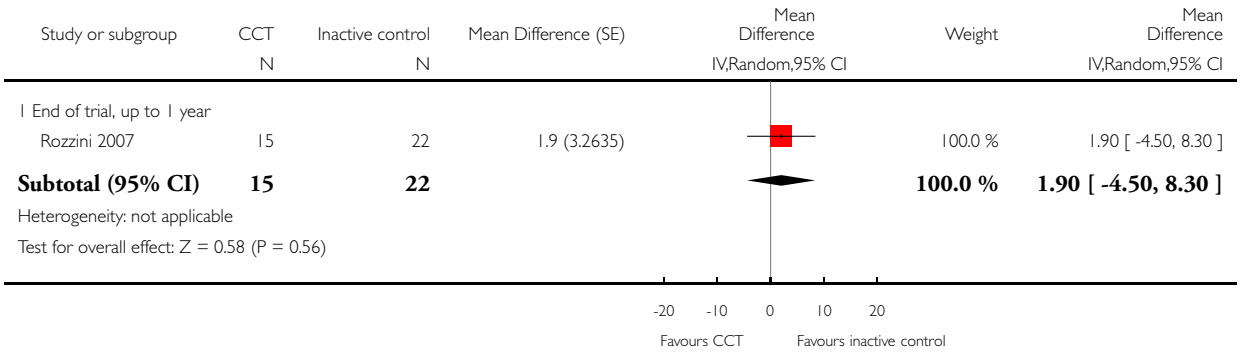


Analysis 2.4. Comparison 2 Computerised cognition-based interventions versus inactive control, Outcome 4 Verbal fluency.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 2 Computerised cognition-based interventions versus inactive control

Outcome: 4 Verbal fluency

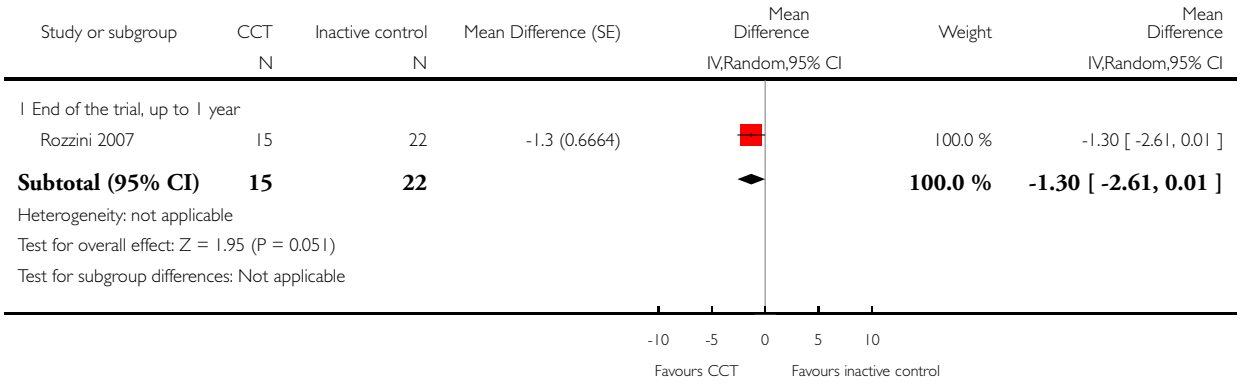


Analysis 2.5. Comparison 2 Computerised cognition-based interventions versus inactive control, Outcome 5 Depression.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 2 Computerised cognition-based interventions versus inactive control

Outcome: 5 Depression

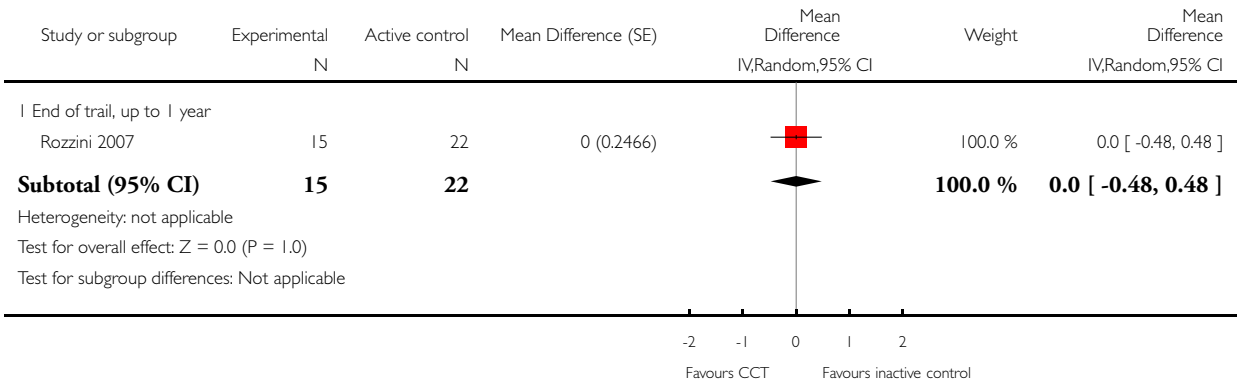


Analysis 2.6. Comparison 2 Computerised cognition-based interventions versus inactive control, Outcome 6 Functional performance.

Review: Computerised cognitive training for preventing dementia in people with mild cognitive impairment

Comparison: 2 Computerised cognition-based interventions versus inactive control

Outcome: 6 Functional performance



APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
ALOIS (www.medicine.ox.ac.uk/alois) [Date of most recent search: 31 May 2018]	Basic search: COG [Studies within ALOIS are coded COG if the intervention is a cognitive-based intervention]	Jan 2015: 31 Jul 2015: 4 Feb 2016: 2 Jul 2016: 0 May 2018: 1
MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP) [Date of most recent search: 31 May 2018]	1. "cognitive stimulation".ti,ab. 2. cognitive ADJ3 train*.ti,ab. 3. "cognitive exercis*".ti,ab. 4. "brain train*".ti,ab. 5. (memory adj3 train*).ti,ab. 6. "memory rehab*".ti,ab. 7. "memory enhance*".ti,ab. 8. "poetry-based stimulation".ti,ab. 9. "cognitive flexibility".ti,ab. 10. "brain exercis*".ti,ab. 11. "cognitive rehab*".ti,ab. 12. "mnemonic train*".ti,ab. 13. CST.ti,ab. 14. (mental adj3 activit*).ti,ab. 15. "cognitive intervention*".ti,ab. 16. "cognitive motor intervention*".ti,ab. 17. "cognition based intervention*".ti,ab. 18. "cognitive enrich*".ti,ab. 19. Cognitive Therapy/ mt 20. or/1-19 21. *aging/ 22. Aged 23. "Aged, 80 and over" 24. Middle Aged 25. Age Factors 26. *Cognition/ 27. *Cognition Disorders/ 28. Memory/ 29. Memory Disorders/	Jan 2015: 1455 Jul 2015: 70 Feb 2016: 303 Jul 2016: 423 May 2018: 703

(*Continued*)

	30. Brain/ 31. Mild Cognitive Impairment/ 32. Executive Function/ 33. (cognit* ADJ3 (func* OR declin* OR reduc* OR impair* OR improve* OR deficit* OR progress* 34. OR perform*)).ti,ab 35. "mental perform*".ti,ab. 36. memory.ti,ab. 37. "executive function*".ti,ab. 38. MCI.ti,ab. 39. AAMI.ti,ab. 40. ACMI.ti,ab. 41. ARCD.ti,ab. 42. CIND.ti,ab. 43. (nMCI OR aMCI OR mMCI OR MCIa).ti,ab. 44. Dementia/ 45. Alzheimer Disease/ 46. dement*.ti,ab. 47. alzheimer*.ti,ab. 48. "old* age*".ti,ab. 49. elderly.ti,ab. 50. "middle age*".ti,ab. 51. "old*adults".ti,ab. 52. seniors.ti,ab. 53. "senior citizens".ti,ab. 54. "community dwelling".ti,ab. 55. pensioners.ti,ab. 56. or/21-55 57. randomized controlled trial.pt. 58. controlled clinical trial.pt. 59. randomized.ab. 60. placebo.ab. 61. drug therapy.fs. 62. randomly.ab. 63. trial.ab. 64. groups.ab. 65. or/57-64 66. exp animals/ not humans.sh. 67. 65 NOT 66 68. 67 AND 56 AND 20 **[all results]** 69. ("cognitive stimulation" OR "cognitive training").ti. 70. *Cognition 71. *Aging/ 72. and/69-71 73. 72 AND 57 **['no brainer' results - di-**	

(*Continued*)

	rectly sent to core author team] 74. 68 NOT 73 **[results minus 'no brainer' results - for the crowd to screen]**	
Embase 1974-24 January 2018 (Ovid SP) [Date of most recent search: 31 May 2018]	1. aging/ 2. aged/ 3. middle aged/ 4. mild cognitive impairment/ 5. elderly.ti,ab. 6. MCI.ti,ab. 7. AAMI.ti,ab. 8. ACMI.ti,ab. 9. ARCD.ti,ab. 10. CIND.ti,ab. 11. (nMCI or aMCI or mMCI or MCIa).ti,ab. 12. "old* age*".ti,ab. 13. elderly.ti,ab. 14. "middle age*".ti,ab. 15. "old* aadults".ti,ab. 16. seniors.ti,ab. 17. "senior citizens".ti,ab. 18. "community dwelling".ti,ab. 19. pensioners.ti,ab. 20. ("aged sample" or "aged population" or "older sample" or "older population").ti,ab 21. "CDR 0.5".ti,ab. 22. (cognit* adj3 (func* or declin* or reduc* or impair* or improve* or deficit* or progress* or perform* or abilit*)).ti,ab 23. or/1-22 24. *cognition/ 25. memory/ or episodic memory/ 26. executive function/ 27. attention/ 28. "mental perform*".ti,ab. 29. memory.ti,ab. 30. dementia/ 31. Alzheimer disease/ 32. dement*.ti,ab. 33. alzheimer*.ti,ab. 34. or/24-33 35. randomized controlled trial/ 36. controlled clinical trial/ 37. (randomly adj2 allocat*).ab. 38. (randomly adj2 divide*).ab. 39. randomi?ed.ab. 40. (controlled adj7 (study or design or	Jan 2015: 1289 Jul 2015: 163 Feb 2016: 380 Jul 2016: 268 May 2018: 796

(*Continued*)

	trial)).ti,ab. 41. "double-blind*".ti,ab. 42. "single blind*".ti,ab. 43. groups.ab. 44. or/35-43 45. "cognitive stimulation".ti,ab. 46. (cognitive adj3 train*).ti,ab. 47. "cognitive exercis*".ti,ab. 48. "brain train*".ti,ab. 49. (memory adj3 train*).ti,ab. 50. "memory enhance*".ti,ab. 51. "memory rehab*".ti,ab. 52. "brain exercis*".ti,ab. 53. "cognitive rehab*".ti,ab. 54. "cognitive rehab*".ti,ab. 55. "mnemonic train*".ti,ab. 56. CST.ti,ab. 57. (mental adj3 activit*).ti,ab. 58. "cognitive intervention*".ti,ab. 59. "cognitive motor intervention*".ti,ab. 60. "cognition based intervention*".ti,ab. 61. "cognitive enrich*".ti,ab. 62. "reality orientation".ti,ab. 63. (memory adj2 game*).ti,ab. 64. or/45-63 65. 23 and 34 and 44 and 64 66. ("cognitive stimulation" or "cognitive training").ti,ab. 67. cognition/ 68. (MCI or "mild cognitive impairment" or elderly or "old* adults" or "middle age*").ti 69. 66 and 67 and 68 70. 35 and 69 71. 65 not 70	
PSYCINFO 1806-January week 2 2018 (Ovid SP) [Date of most recent search: 31 May 2018]	1. exp Aging/ 2. exp Cognitive Impairment/ 3. "cognit* impair*".ti,ab. 4. MCI.ti,ab. 5. AAMI.ti,ab. 6. ACMI.ti,ab. 7. ARCD.ti,ab. 8. CIND.ti,ab. 9. (nMCI or aMCI or mMCI or MCIa).ti,ab. 10. "old* age*".ti,ab. 11. elderly.ti,ab. 12. "middle age*".ti,ab.	Jan 2015: 166 Jul 2015: 20 Feb 2016: 25 Jul 2016: 12 May 2018: 84

(*Continued*)

	13. “old* adults”.ti,ab. 14. seniors.ti,ab. 15. “senior citizens”.ti,ab. 16. “community dwelling”.ti,ab. 17. pensioners.ti,ab. 18. or/1-17 19. randomi?ed.ti. 20. (randomly adj2 allocat*).ab. 21. (randomly adj2 divide*).ab. 22. RCT.ti,ab. 23. “double-blind*”.ti,ab. 24. “single blind*”.ti,ab. 25. “randomi?ed trial”.ab. 26. “randomi?ed control* trial”.ab. 27. “random allocation”.ab. 28. “controlled clinical trial”.ti,ab. 29. (controlled adj4 (study or design or trial)).ti,ab. 30. or/19-29 31. “cognitive stimulation”.ti,ab. 32. (cognitive adj3 train*).ti,ab. 33. “cognitive exercis*”.ti,ab. 34. “brain train*”.ti,ab. 35. (memory adj3 train*).ti,ab. 36. “memory enhance*”.ti,ab. 37. “memory rehab*”.ti,ab. 38. “brain exercis*”.ti,ab. 39. “cognitive rehab*”.ti,ab. 40. “cognitive rehab*”.ti,ab. 41. “mnemonic train*”.ti,ab. 42. CST.ti,ab. 43. (mental adj3 activit*).ti,ab. 44. “cognitive intervention*”.ti,ab. 45. “cognitive motor intervention*”.ti,ab. 46. “cognition based intervention*”.ti,ab. 47. “cognitive enrich*”.ti,ab. 48. “reality orientation”.ti,ab. 49. (memory adj2 game*).ti,ab. 50. or/31-49 51. 18 and 30 and 50 52. *Cognition/ 53. (MCI or “mild cognitive impairment” or elderly or “old* adults” or “middle age*”).ti 54. (“cognitive stimulation” or “cognitive training”).ti,ab. 55. 19 or 20 or 21 56. 52 and 53 and 54 and 55 57. 51 not 56	

(*Continued*)

CINAHL (EBSCOhost) [Date of most recent search: 31 May 2018]		Jan 2015: 390 Jul 2015: 13 Feb 2016: 57 Jul 2016: 12 May 2018: 181
ISI Web of Science [includes: Web of Science (1945-present); BIOSIS Previews (1926-present); MEDLINE (1950-present); Journal Citation Reports]; BIOSIS Previews [Date of most recent search: 31 May 2018]	("mild cognitive impairment" OR elderly OR "age* subjects" OR "old* adult*" OR "middle age*" OR MCI) AND TOPIC: ("randomly allocated" OR "random allocation" OR randomised OR randomized OR RCT OR "controlled trial" OR "double blind" OR "single blind") AND TOPIC: ("cognit* stim*" OR "cognit* train*" OR puzzle OR "brain train*" OR "cognit* exercis*" OR "brain exercis*" OR "memory exercis*" OR "brain gam*" OR "cognit* gam*" OR "memory gam*" OR sudoku OR crossword* OR "reality orientation") AND TOPIC: (cognition OR dementia OR memory OR "executive function" OR alzheimer*) Timespan: All years. Search language=Auto	Jan 2015: 333 Jul 2015: 44 Feb 2016: 108 Jul 2016: 35 May 2018: 408
LILACS (BIREME) [Date of most recent search: 31 May 2018]		Jan 2015: 4 Jul 2015: 0 Feb 2016: 0 Jul 2016: 0 May 2018: 0
CENTRAL (*via CRSO)* [Date of most recent search: 31 May 2018]	#1 MeSH descriptor: [Aged, 80 and over] explode all trees #2 MeSH descriptor: [Aged] explode all trees #3 MeSH descriptor: [Middle Aged] explode all trees #4 MeSH descriptor: [Mild Cognitive Impairment] explode all trees #5 "cognit* impair*" or MCI #6 elderly #7 "old* adults" #8 "old* age*" #9 "old* sample" #10 senior citizens #11 pensioners #12 seniors #13 #1 or #2 or #3 or #4 or #5 or #6 or #	Jan 2015: 274 Jul 2015: 11 Feb 2016: 57 Jul 2016: 4 May 2018: 210

(*Continued*)

	7 or #8 or #9 or #10 or #11 or #12 #14 MeSH descriptor: [Cognition] explode all trees #15 MeSH descriptor: [Dementia] explode all trees #16 cognit* #17 memory #18 "executive function*" #19 processing #20 "mental perform*" #21 dement* #22 alzheimer* #23 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 #24 "cognitive stimulation" #25 "cognitive training" #26 "brain train*" #27 "brain gam*" #28 "memory train*" or "memory game*" #29 puzzle* #30 crossword* #31 sudoku* #32 "mental game*" #33 "mental agil*" #34 "cognitive exercis*" #35 "mental exercis*" #36 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 #37 #13 and #23 and #36	
Clinicaltrials.gov (www.clinicaltrials.gov) [Date of most recent search: 31 May 2018]		Jan 2015: 17 Jul 2015: 4 Feb 2016: 2 Jul 2016: 0 May 2018: 4
ICTRP Search Portal (http://apps.who.int/trialsearch) [includes Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service - Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]		Jan 2015: 22 Jul 2015: 3 Feb 2016: 1 Jul 2016: 0 May 2018: 4

(*Continued*)

[Date of most recent search: 31 May 2018]		
TOTAL before de-duplication		Jan 2015: 3981 Jul 2015: 332 Feb 2016: 935 Jul 2016: 754 May 2018: 2390 **TOTAL: 8392**
TOTAL after de-duplication		**TOTAL: 6233**
TOTAL after first assessment by the Crowd and CDCIG Information Specialists		Jan 2015: 604 Jul 2015: 60 Feb 2016: 164 Jul 2016: 73 May 2018: 190 **TOTAL: 1091**

Appendix 2. Definitions of design, patient, and intervention characteristics as applied in the stratified analyses exploring between-trial variations in intervention effects

ITEM	DEFINITION
Design-related characteristics*	
Concealment of allocation (avoiding selection bias)	Guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* will be used to judge bias related to sequence generation and concealment of allocation using the 2 Cochrane 'Risk of bias' items (Higgins 2011). From these, the statistician will derive a single variable to be used in the stratified analysis: allocation concealment will be judged at low risk of bias if the investigators responsible for patient selection were unable to suspect before allocation which treatment was next. Concealment will be downgraded to high risk of bias if there is evidence of inadequate sequence generation (Rutjes 2012)
Blinding of patients and personnel (avoiding performance bias)	Low risk of bias will be judged: - if a credible sham procedure was used; or if a placebo supplement or pill was used that was reported to be identical in appearance to the experimental intervention and the specific outcome or group of outcomes is/are likely to be influenced by lack of blinding - if blinding is absent or suboptimal and the specific outcome, such as mortality, is not likely to be influenced by lack of blinding

(*Continued*)

Blinding of outcome assessment (avoiding detection bias)	*For self-reported/partner-reported outcomes:* Low risk of bias will be judged if self-report outcomes were assessed AND blinding of patients was considered adequate AND there was no information to suggest that there was an investigator involved during the process of outcome assessment; OR if blinding of investigators performing the outcome assessment was reported AND an attempt to blind patients was reported *For other outcomes:* Outcome assessment was considered to be blinded if outcome assessment was reported to be blinded
Statistical analyses (avoiding attrition bias)	*For continuous outcomes:* Low risk of bias will be judged: - if at least 90% of the patients randomised were analysed AND the difference in percentage of participants not analysed was 5% or lower across trial arms - for trials using imputations to handle missing data: the percentage of participants with missing data did not exceed 20% AND the difference in percentage of participants with imputed data was 5% or lower across trial arms AND applied imputation methods were judged to be appropriate. Multiple imputation techniques will be considered appropriate, simple methods such as 'last observation carried forward' or 'baseline carried forward' will be considered inappropriate *For binary outcomes of rare events:* Low risk of bias will be judged if the event rate is low (e.g. incidence of dementia) AND at least 95% of the patients randomised were analysed AND there is no evidence of differential reasons for missing data that may alter the estimate AND the rate of missing data does not exceed the expected event rates *For binary outcomes of non-rare events:* Low risk of bias will be judged if at least 90% of the patients randomised were analysed AND the difference in percentage of participants not analysed was 5% or lower across trial arms AND there is no evidence of differential reasons for missing data that may alter the estimate AND the rate of missing data does not exceed the expected event rates
Trial size	The cut-off to distinguish small from larger trials will be determined by a sample size calculation on the primary outcome
Publication status	Full journal article vs other type or unpublished material
Follow-up duration	For the cognitive outcomes, we will group studies according to these follow-up cut-offs to describe immediate results (up to 12 weeks) and short-term (up to 1 year), medium-term (1 to 2 years) , and longer-term results (more than 2 years)

(*Continued*)

Treatment-related characteristics	
Treatment and control Treatment duration	Analyses will be stratified by • control intervention (placebo vs no intervention vs usual care, where no intervention refers to RCTs with standardised concurrent treatments in both experimental and control arms • training multiple domains (yes/no) • mode of delivery ○ training supervision (yes/no) ○ group training (yes/no) Analyses will be stratified into session length > 30 minutes (yes/no), frequency > 3 sessions per week (yes/no), based upon previous findings (Lampit 2014), and total number of sessions. The minimum treatment duration of 3 months is considered short term, 3 to 12 months as medium term, and 12 months as long term. For the outcome all-cause dementia, only outcome data at 1 year of follow-up or longer will be considered, and therefore the grouping will include short-term (up to 1 year), medium-term (1 to 2 years), and longer-term results (more than 2 years)
Participant-related characteristics	
Cognition and participant-related criteria	Gender, level of education (in years), ApoE-4 (yes/no), baseline age (mid-life vs late-life vs other), and time since diagnoses

*The descriptions given in this table are provided in addition to the guidance provided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Stratified analyses are performed only for the primary outcome if about 10 RCTs contributed to the analyses

CONTRIBUTIONS OF AUTHORS

Completion of the protocol: NG, SK, AR, RV.

Screening of references: Students For Best Evidence (title/abstract screening), NG, SK, GM, RV.

Acquisition of data: NG, RV, MdN, SK, EM, AR, GV.

'Risk of bias' assessments and GRADE-ing: NG, RV, MdN, SK, EM, AR, GM.

Statistical analysis: AR.

SoF & GRADE-ing: RV.

Overall interpretation of data: NG, RV, MdN, EM, AR, GM.

Manuscript preparation: NG, AR, RV, EM, GM.

DECLARATIONS OF INTEREST

Nicola J Gates - none known

Robin WM Vernooij - none known

Marcello Di Nisio - Di Nisio declares partial funding by a grant for the project 'OPERAM: OPtimising therapy to prevent Avoidable hospital admissions in the Multi-morbid elderly' supported by the European Union's Horizon 2020 research and innovation programme under the grant agreement No 6342388. Di Nisio reports participation to Advisory Boards for Daiichi-Sankyo, Aspen, and Pfizer, and consultancy fees for Daiichi-Sankyo, Bayer Health Care, and Leo Pharma outside the submitted work.

Salman Karim - none known

Evrim March - none known

Gabriel Martínez - none known

Anne WS Rutjes - Dr. Rutjes declares partial funding by a grant for the project 'OPERAM: OPtimising therapy to prevent Avoidable hospital admissions in the Multi-morbid elderly' supported by the European Union's Horizon 2020 research and innovation programme under the grant agreement No 6342388, and by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0137.

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

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- SERI and Horizon 2020, Other.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We planned stratified analyses to explore between-trial heterogeneity according to the features outlined in Appendix 2, and we planned to prepare funnel plots to explore the impact of publication bias and other biases associated with small sample size. By protocol, we indicated that about 10 trials should contribute to the analysis for it to be meaningful. As the number of trials identified was substantially lower, we refrained from undertaking such analyses. We planned to perform one sensitivity analysis for the primary outcome, including high-quality trials only. We aimed to define high quality by using results of the stratified analyses. As stratified analyses could not be performed, we refrained from conducting sensitivity analyses. Although not described in our published protocol, we made the decision to use a hierarchy to select outcome data before starting data extraction. The hierarchy itself was also established before any trial in this and two other Cochrane reviews had started (Gates 2019a; Gates 2019b).

INDEX TERMS

Medical Subject Headings (MeSH)

Cognition; Cognitive Dysfunction [*complications]; Computer-Assisted Instruction [*methods]; Dementia [*prevention & control]; Disease Progression; Executive Function; Memory, Episodic; Quality of Life; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Aged; Humans; Middle Aged