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Computerised cognitive training for 12 or more weeks for maintaining cognitive function in cognitively healthy people in late life (Review)

Gates NJ, Rutjes AWS, Di Nisio M, Karim S, Chong LY, March E, Martínez G, Vernooij RWM

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[Intervention Review]

Computerised cognitive training for 12 or more weeks for maintaining cognitive function in cognitively healthy people in late life

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ABSTRACT

Background

Increasing age is associated with a natural decline in cognitive function and is the greatest risk factor for dementia. Cognitive decline and dementia are significant threats to independence and quality of life in older adults. Therefore, identifying interventions that help to maintain cognitive function in older adults or that reduce the risk of dementia is a research priority. Cognitive training uses repeated practice on standardised exercises targeting one or more cognitive domains and may be intended to improve or maintain optimal cognitive function. This review examines the effects of computerised cognitive training interventions lasting at least 12 weeks on the cognitive function of healthy adults aged 65 or older and has formed part of a wider project about modifying lifestyle to maintain cognitive function. We chose a minimum 12 weeks duration as a trade-off between adequate exposure to a sustainable intervention and feasibility in a trial setting.

Objectives

To evaluate the effects of computerised cognitive training interventions lasting at least 12 weeks on cognitive function in cognitively healthy people in late life.

Search methods

We searched to 31 March 2018 in ALOIS (www.medicine.ox.ac.uk/alois), and we performed additional searches of MEDLINE, Embase, PsycINFO, CINAHL, ClinicalTrials.gov, and the WHO Portal/ICTRP (www.apps.who.int/trialsearch), to ensure that the search was as comprehensive and as up-to-date as possible to identify published, unpublished, and ongoing trials.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs, published or unpublished, reported in any language. Participants were cognitively healthy people, and at least 80% of the study population had to be aged 65 or older. Experimental interventions adhered to the following criteria: intervention was any form of interactive computerised cognitive intervention - including computer exercises, computer

games, mobile devices, gaming console, and virtual reality - that involved repeated practice on standardised exercises of specified cognitive domain(s) for the purpose of enhancing cognitive function; the duration of the intervention was at least 12 weeks; cognitive outcomes were measured; and cognitive training interventions were compared with active or inactive control interventions.

Data collection and analysis

We performed preliminary screening of search results using a 'crowdsourcing' method to identify RCTs. At least two review authors working independently screened the remaining citations against inclusion criteria. At least two review authors also independently extracted data and assessed the risk of bias of included RCTs. Where appropriate, we synthesised data in random-effects meta-analyses, comparing computerised cognitive training (CCT) separately with active and inactive controls. We expressed treatment effects as standardised mean differences (SMDs) with 95% confidence intervals (CIs). We used GRADE methods to describe the overall quality of the evidence for each outcome.

Main results

We identified eight RCTs with a total of 1183 participants. The duration of the interventions ranged from 12 to 26 weeks; in five trials, the duration of intervention was 12 or 13 weeks. The included studies had moderate risk of bias, and the overall quality of evidence was low or very low for all outcomes.

We compared CCT first against active control interventions, such as watching educational videos. Negative SMDs favour CCT over control. Trial results suggest slight improvement in global cognitive function at the end of the intervention period (12 weeks) (standardised mean difference (SMD) -0.31, 95% confidence interval (CI) -0.57 to -0.05; 232 participants; 2 studies; low-quality evidence). One of these trials also assessed global cognitive function 12 months after the end of the intervention; this trial provided no clear evidence of a persistent effect (SMD -0.21, 95% CI -0.66 to 0.24; 77 participants; 1 study; low-quality evidence). CCT may result in little or no difference at the end of the intervention period in episodic memory (12 to 17 weeks) (SMD 0.06, 95% CI -0.14 to 0.26; 439 participants; 4 studies; low-quality evidence) or working memory (12 to 16 weeks) (SMD -0.17, 95% CI -0.36 to 0.02; 392 participants; 3 studies; low-quality evidence). Because of the very low quality of the evidence, we are very uncertain about the effects of CCT on speed of processing and executive function.

We also compared CCT to inactive control (no interventions). We found no data on our primary outcome of global cognitive function. At the end of the intervention, CCT may lead to slight improvement in episodic memory (6 months) (mean difference (MD) in Rivermead Behavioural Memory Test (RBMT) -0.90 points, 95% confidence interval (CI) -1.73 to -0.07; 150 participants; 1 study; low-quality evidence) but can have little or no effect on executive function (12 weeks to 6 months) (SMD -0.08, 95% CI -0.31 to 0.15; 292 participants; 2 studies; low-quality evidence), working memory (16 weeks) (MD -0.08, 95% CI -0.43 to 0.27; 60 participants; 1 study; low-quality evidence), or verbal fluency (6 months) (MD -0.11, 95% CI -1.58 to 1.36; 150 participants; 1 study; low-quality evidence). We could not determine any effects on speed of processing because the evidence was of very low quality.

We found no evidence on quality of life, activities of daily living, or adverse effects in either comparison.

Authors' conclusions

We found low-quality evidence suggesting that immediately after completion of the intervention, small benefits of CCT may be seen for global cognitive function when compared with active controls, and for episodic memory when compared with an inactive control. These benefits are of uncertain clinical importance. We found no evidence that the effect on global cognitive function persisted 12 months later. Our confidence in the results was low, reflecting the overall quality of the evidence. In five of the eight trials, the duration of the intervention was just three months. The possibility that more extensive training could yield larger benefit remains to be more fully explored.

We found substantial literature on cognitive training, and collating all available scientific information posed problems. Duration of treatment may not be the best way to categorise interventions for inclusion. As the primary interest of older people and of guideline writers and policymakers involves sustained cognitive benefit, an alternative would be to categorise by length of follow-up after selecting studies that assess longer-term effects.

PLAIN LANGUAGE SUMMARY

Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life

Background

The terms 'cognition' and 'cognitive function' describe all of the mental activities related to thinking, learning, remembering, and communicating. Normal changes in cognition occur with ageing. There are also diseases that affect cognition, principally dementia, which becomes increasingly common with increasing age from about 65 years onwards. It is known that being mentally active throughout life is associated with lower risk of dementia. Therefore, it has been suggested that encouraging mental activity might be an effective way of maintaining good cognitive function as people age. Cognitive training comprises a set of standardised tasks intended to 'exercise the brain' in various ways. Programmes of cognitive training are often delivered by computers or mobile technology, so that people can do this training on their own at home. Increasingly, these are available as commercial packages that are advertised to the general public.

We wanted to know whether long-term use of computerised cognitive training (CCT) is an effective way for people aged 65 and older to maintain good cognitive function as they age.

What we did

We searched the medical literature up to 15 March 2018 for trials that compared cognitive function of people aged 65 or older who had taken part in computerised cognitive training for a minimum of 12 weeks with cognitive function of a control group that had not done so. All participants should have been cognitively healthy at the start of the trials. For the comparison to be as fair as possible, it should have been decided randomly whether participants were in the cognitive training group or in the control group. We were primarily interested in overall measures of cognition. The choice of three months for the intervention was somewhat arbitrary, but we thought very short interventions were unlikely to have lasting effects, and we were interested in interventions that could be sustained over time.

What we found

We found eight trials with a total of 1183 participants to include in the review. Five trials provided CCT for three months, two for four months, and one for six months. We compared CCT with other activities, such as watching educational videos, and with no activity. We looked for effects on overall cognitive function and on specific cognitive functions, such as memory and thinking speed. All of the included studies had some design problems, which could have biased the results. Overall, we thought the quality of the evidence that we found was low or very low. This means we cannot be confident in the results, and that future research might well find something different. CCT may slightly improve overall cognitive function after 12 weeks of training; however, we found no evidence of a persistent effect 12 months after the intervention. We were unable to comment or found little evidence that CCT when compared with other activities may have a relevant effect on most of the specific cognitive functions that we examined. The longest trial found that compared to doing nothing, completing six months of CCT may have had a beneficial effect on memory. None of the included trials reported effects of cognitive training on quality of life or on daily activities, and none reported harmful effects of training.

Our conclusions

Compared to other activities, CCT may lead to slightly better overall cognitive function at the end of 12 weeks of training, but we found no evidence that the effect persists a year later. Compared to doing nothing, CCT may slightly improve memory at the end of six months of training. Although we excluded trials with less than 12 weeks of training, the trials that we included were still quite short for examining long-term effects as people age. A limitation of our review is that we did not include some trials with shorter training periods that did look for long-lasting effects, so it is possible that we missed some useful evidence. Many published studies have looked at computer training. Making sense of this substantial literature is difficult. It may be more helpful in the future to categorise trials by the duration of effects of training rather than by the duration of the training itself.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Computerised cognitive training compared with active control intervention in cognitively healthy people in late life

Patient or population: cognitively healthy people in late life

Settings: general population

Intervention: computerised cognitive training

Comparison: active control intervention

Outcomes	Difference between CCT and control (95% CI) ^{a*}	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Global cognitive function measured at the end of the intervention period (12 weeks)	SMD 0.31 lower (0.57 lower to 0.05 lower)	232 participants (2 studies)	⊕⊕⊕⊕ low^b	CCT may improve global cognitive function slightly compared with active control
Cognitive subdomain: episodic memory measured at the end of the intervention period (12 to 17 weeks)	SMD 0.06 higher (0.14 lower to 0.26 higher)	439 participants (4 studies)	⊕⊕⊕⊕ low^b	CCT may result in little to no difference in episodic memory compared with active control
Cognitive subdomain: speed of processing measured at the end of the intervention period (12 to 16 weeks)	SMD 0.63 lower (1.14 lower to 0.12 lower)	138 participants (2 studies)	⊕⊕⊕⊕ very low^c	It is uncertain whether CCT maintains speed of processing better than active control
Cognitive subdomain: executive functioning measured at the end of the intervention period (12 to 17 weeks)	SMD 0.04 lower (0.61 lower to 0.53 higher)	230 participants (3 studies)	⊕⊕⊕⊕ very low^c	It is uncertain whether CCT maintains executive functioning better than active control
Cognitive subdomain: working memory measured at the end of the intervention period (12 to 16 weeks)	SMD 0.17 lower (0.36 lower to 0.02 higher)	392 participants (3 studies)	⊕⊕⊕⊕ low^b	CCT may result in little to no difference in working memory compared with active control
Quality of life at the end of the intervention period	Not reported using a validated measure			
Number of participants experiencing 1 or more serious adverse events at the end of the intervention period	Not reported using a validated measure			

* 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; 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.

^aThe direction of the difference in effect was standardised so that lower values favour CCT and higher values favour control.

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^bDowngraded two levels for imprecision (confidence interval included effects that are not clinically relevant) and risk of bias.

^cDowngraded three levels for imprecision (confidence interval included effects that are not clinically relevant), inconsistency (high heterogeneity), and risk of bias.

Summary of findings 2.

Computerised cognitive training compared with inactive control in cognitively healthy people in late life

Patient or population: cognitively healthy people in late life

Settings: general population

Intervention: computerised cognitive training

Comparison: inactive control intervention

Outcomes	Difference between CCT and control (95% CI) ^{a*}	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Global cognitive function measured at the end of the intervention period	Not reported using a validated measure			
Cognitive subdomain: episodic memory measured at the end of the intervention period (6 months)	MD 0.90 lower (1.73 lower to 0.07 lower)	150 participants (1 study)	⊕⊕⊕⊕ low^b	CCT may improve slightly episodic memory when compared to inactive control
Cognitive subdomain: speed of processing measured at the end of the intervention period (12 to 16 weeks)	SMD 0.28 lower (0.82 lower to 0.26 higher)	204 participants (2 studies)	⊕⊕⊕⊕ very low^c	It is uncertain whether CCT maintains speed of processing better than inactive control
Cognitive subdomain: executive functioning measured at the end of the intervention period (12 weeks to 6 months)	SMD 0.08 lower (0.31 lower to 0.15 higher)	292 participants (2 studies)	⊕⊕⊕⊕ low^b	CCT may lead to little or no improvement in executive functioning when compared to inactive control
Cognitive subdomain: working memory measured at the end of the intervention period (16 weeks)	MD 0.08 lower (0.43 lower to 0.27 higher)	60 participants (1 study)	⊕⊕⊕⊕ low^b	CCT may lead to little or no improvement in working memory when compared to inactive control
Cognitive subdomain: verbal fluency measured at the end of the intervention period (6 months)	MD 0.11 lower (1.58 lower to 1.36 higher)	150 participants (1 study)	⊕⊕⊕⊕ low^b	CCT may lead to little or no improvement in verbal fluency when compared to inactive control
Quality of life at the end of the intervention period	Not reported using a validated measure			
Number of participants experiencing 1 or more serious adverse events at the end of the intervention period	Not reported using a validated measure			

* 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; SMD: standardised mean difference.

GRADE Working Group grades of evidence.

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Very low quality: we are very uncertain about the estimate.

^aThe direction of the difference in effect was standardised so that lower values favour CCT and higher values favour control.

^bDowngraded two levels for imprecision (confidence interval included effects that are not clinically relevant) and risk of bias.

^cDowngraded three levels for imprecision (confidence interval included effects that are not clinically relevant), inconsistency (high heterogeneity), and risk of bias.

BACKGROUND

Description of the condition

Cognitive health, dementia, and reserve

'Cognitive health' broadly refers to the absence of cognitive impairment and the preservation of cognitive structure. Maintaining cognitive health in later life is essential to allow older adults to achieve active ageing (Depp 2012; Hendrie 2006). 'Active ageing' refers to the process of optimising opportunities for health, participation, and security in later life (WHO 2016). Older adults themselves are increasingly interested in managing their own health and have expectations of positive ageing and a high quality of life (Brown 2004). Retirement age in many countries is being extended past age 65, and many older adults want to extend their working lives, requiring them to maintain cognitive health as long as possible. Cognitive decline and dementia are significant threats to independence and active ageing, and are significant concerns of older adults (Deary 2009; Lustig 2009).

Dementia is now one of the biggest global health challenges and may affect up to 135 million adults worldwide by 2050 (Prince 2013). The global cost of caring for people with dementia is currently estimated at USD315 billion (Wimo 2010). The World Health Organization 2017 Dementia Action Plan identifies reducing dementia risk as a major health objective (who.int/mental_health/neurology/dementia/action_plan_2017_2025/en/). In most cases, the onset of clinical dementia is gradual, with the underlying disease process probably starting years, or even decades, before symptoms present. Pharmacological treatments at present are very limited, and none are curative (Aisen 2011). The long prodromal and preclinical periods before dementia onset offer an opportunity to intervene to maintain cognitive function, thereby preventing or postponing the onset of clinical dementia (Leifer 2003). Postponing the onset of clinical dementia by just five years could potentially reduce disease prevalence by 50% (Brookmeyer 1998). Differences in individual susceptibility to the development of clinical dementia may in part be due to exposure to a number of positive and negative factors. Multiple potentially modifiable factors have been identified, including physical exercise, diet, and mentally stimulating activities (World Alzheimer Report 2014). Accordingly, new non-pharmacological lifestyle interventions are being investigated for their potential to prevent or delay dementia onset (Acevedo 2007; Dresler 2013).

Research evidence indicates that maintenance of cognitive health requires the development of optimal levels of brain and cognitive reserve across the lifespan (Stern 2012). 'Brain reserve' refers to structural tolerance of the brain to disease processes. 'Cognitive reserve' refers to functional differences in cognitive processes that may affect the way cognitive tasks are performed, which may in turn enhance resilience against threats to cognitive health. Thus, reserve provides a theoretical explanation for the differences between individuals with the same degree of disease in the brain who succumb to clinical dementia and are functionally impaired, and those who tolerate the pathology and maintain function (Stern 2012). Consistent with this notion of reserve is evidence from epidemiological and prospective studies that a lower incidence of Alzheimer's disease is found in people who have engaged in mentally stimulating activities (Marioni 2014; Marquine 2012; Stern 2012; Verghese 2003; Wilson 2002). Therefore, one intervention that has been proposed to increase cognitive health and improve

cognitive function in older adults is the introduction of novel mental activity (Park 2007).

Age-related cognitive decline

In cognitively healthy adults, some non-pathological changes in cognitive function naturally occur with increasing age (Salthouse 2003). Cognitive changes associated with normal ageing may contribute to deterioration in quality of life and may compromise functional capacity. Large variations in cognitive health and function are observed at a population level, and trajectories of decline are highly variable (Salthouse 2011). Cross-sectional and longitudinal comparisons indicate that whilst acquired knowledge generally increases until about age 60, there is a decrease in information processing efficiency from early adulthood, and beyond age 60, increasing age is associated with general negative cognitive change (Salthouse 2011). When cognitive difficulties are beyond those associated with normal ageing but performance of daily activities is not significantly affected, the term 'mild cognitive impairment' (MCI), or its synonym 'mild neurocognitive disorder', is applied. MCI is associated with an increased risk of progression to dementia (Petersen 2018).

Risk and protective factors

Although increasing age is the greatest risk factor for dementia, additional risk and protective factors have been linked with dementia in general, and with Alzheimer's disease in particular (World Alzheimer Report 2014). It has recently been suggested that after accounting for non-independence between risk factors, around a third of cases of dementia due to Alzheimer's disease worldwide might be attributable to potentially modifiable risk factors (Norton 2014). Accordingly, there is growing interest in addressing lifestyle factors to combat age-related cognitive decline, enhance cognitive function, and prevent the onset of clinical dementia (Barnes 2011; Dresler 2013). Addressing preventable risks, as by promoting cognitively stimulating activities, is a global health priority according to the World Health Organization 2017 Health Report Dementia Action Plan.

The links between stimulating leisure pursuits and cognitive health are strong. Epidemiological evidence indicates that the risk of developing dementia due to Alzheimer's disease is significantly reduced in individuals with higher educational or occupational attainment (Marioni 2012; Marquine 2012; Stern 2012). Cognitive lifestyle variables such as education, midlife occupation, and late life social engagement may also be associated with cognitive trajectories and morbidity (Marioni 2012; Marioni 2014). A broad spectrum of activities, including those with mental, physical, and social components, contribute to reducing risk for dementia (Karp 2006). Prospective studies also indicate that mental activity, even when commenced late in life, has positive benefits, with lowered rates of decline and lowered dementia incidence reported (Beydoun 2014; Geda 2012; Verghese 2003; Wilson 2002; Wilson 2012). In contrast, lack of cognitive stimulation, particularly across an individual's life course, is a significant risk factor (Norton 2014; World Alzheimer Report 2014). Therefore, introducing cognitively stimulating interventions – even in late life – has the potential to reverse the effects of reduced participation, promote cognitive health and active ageing, and improve quality of life (Amoyal 2012).

Description of the intervention

Cognitive interventions are diverse treatments based upon the distinct theoretical constructs of maintenance and improvement for the purposes of preventing decline, restoring reduced function, and compensating for impairment (Gates 2014). The clinical research literature refers to three forms of cognitive intervention based upon these theoretical models: cognitive training, cognitive stimulation, and cognitive rehabilitation (Baher-Fuchs 2013; Clare 2004; Gates 2014; Woods 2012).

Cognitive training is increasingly being applied in research and clinical settings for prevention of cognitive decline, and commercial training packages are widely available. 'Cognitive training' is defined as an intervention consisting of repeated practice on standardised exercises, targeting a specific cognitive domain or domains, for the purpose of benefiting cognitive function (Gates 2010). In cognitively healthy older adults, it is intended to maintain cognitive function, reduce age-related decline, and prevent or delay the development of clinical dementia. Recent investigations suggest that cognitive training may improve cognitive function (Petersen 2018). Computer-based cognitive training tasks, including computer exercises and computer games (which may involve mobile devices, gaming consoles, and virtual reality), offer a highly accessible low-cost, standardised means of training in specified cognitive domain(s) for the purpose of enhancing cognitive function. Computerised cognitive training can be provided in different ways, including individual exercises or games, group games, online games, and on-site games.

Several meta-analyses and randomised clinical trials of cognitive training in cognitively healthy adults and those at risk of dementia have reported significant benefits across multiple cognitive domains, global cognition, and composite measures of cognitive function (Alves 2013; Kelly 2014; Kueider 2012; Lampit 2014a; Shao 2015). Other meta-analyses of cognitive interventions in longitudinal trials have indicated that such interventions may reduce the risk of developing dementia and may reduce the rate of cognitive decline (Valenzuela 2006a; Valenzuela 2006b; Valenzuela 2009). Researchers investigating cognitive training in adults with subtle cognitive changes and MCI have concluded that it could improve global cognitive function and increase performance on domain-specific outcome measures, with some studies also reporting reduced rates of incident dementia (Cheng 2012; Gates 2011a; Herrera 2012; Hoyer 2006; Unverzagt 2012; Zehnder 2009). Additionally, some clinical trial results indicate that computerised and online cognitive training in adults without dementia may improve daily functioning and psychological well-being (Gordon 2013; Kueider 2012; Rebok 2014; Zelinski 2009), and some systematic reviews indicate that computerised cognitive training (CCT) might be beneficial for cognitive outcomes (Lampit 2014a), and even for non-cognitive outcomes such as well-being and functional outcomes (Edwards 2018).

In this review, we focus on primary prevention, that is, maintenance of cognitive function in cognitively healthy adults in late life (> 65 years of age) by means of CCT. Companion reviews have investigated the effects of CCT on cognitively healthy adults in midlife (40 to 65 years) and among people with MCI (Gates 2019a; Gates 2019b). We reviewed randomised controlled trials (RCTs) investigating the effects of CCT interventions over at least 12 weeks on cognitive performance, quality of life, and daily functioning. For any intervention designed to maintain or improve health, the

effect will be dependent on the exposure. For example, the effect of a drug, an exercise programme, or a dietary intervention would be influenced, respectively, by drug dose, time spent exercising, or proportion of meals meeting prescribed nutritional standards. For CCT, no consensus has been reached about the minimum or optimum exposure required to achieve cognitive effects. When the protocol for this review was designed, a minimum exposure was selected based on the judgement that it was implausible that short training courses would have long-term cognitive benefits. After discussion, an inclusion criterion of 12 weeks of exposure was chosen. This was an arbitrary threshold, as any threshold of duration or dose would be in this field, which was considered to represent an acceptable trade-off between biologically plausible effects and feasibility within a trial setting. This review forms part of a suite of reviews on modifiable risk factors for dementia and cognitive decline. Harmonisation of inclusion criteria with the other reviews in the suite was also a consideration.

How the intervention might work

Computerised programmes have been delivered in individual sessions and within groups, with supervision or privately at home, and there is wide variation in the 'dose' or length of each training session, the frequency of sessions, and the duration of training programmes, leading to significant heterogeneity in the literature (Gates 2014). However, the unifying theoretical premise behind cognitive training is that it will stimulate neuroplasticity, increase brain and cognitive reserve, and thereby maintain or improve cognitive function. It has also been suggested that cognitive stimulation may result in neural compensation, which is the development of compensatory networks maintaining cognitive performance, potentially masking or preventing clinical manifestation of neurocognitive disease (Grady 2012). Recently, to incorporate both factors associated with age-related cognitive decline and those thought to enhance function and reserve, a scaffold theory of compensatory activation has been proposed (Park 2013). The interventions that fall within the scope of this review are not expected to modify dementia pathology, but it is hypothesised that the increase in mentally stimulating activity that these interventions induce will have an impact on the development of clinical dementia (Bennett 2014).

Although the evidence base is very limited, human trials of cognitive training suggest positive neuroplastic changes, including reduced β -amyloid burden (Landau 2012), as a result of the intervention. A number of diverse studies investigating neurophysiological changes using functional magnetic resonance imaging have identified increased prefrontal and parietal activity and hippocampal activation (Olesen 2004; Rosen 2011; Suo 2012a; Valenzuela 2003). Electroencephalography and magnetic resonance spectrometry studies of cognitive training support the concept of functional neuroplasticity 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 prevalence and financial implications of dementia are such that small effects on cognitive decline, or on the incidence of dementia, may have a large impact on healthcare costs and the overall burden of dementia to society and to individuals

with the disease. The potential for computerised cognitive-based interventions to be effective in improving cognitive health and function, along with their low implementation and administration costs and their high availability and accessibility, has led to the American Alzheimer's Association's recommending development and testing of cognitive training as a research priority ([Alzheimer's Association 2014](#)).

To date, cognitive training research has been controversial, with insufficient data on which to base clear clinical guidelines for intervention. Results from meta-analyses have been inconsistent; negative findings have been reported, and opposing views have been published ([Lampit 2014a](#); [Papp 2009](#)). Clinical trials have been criticised for poor specification of interventions, poor methodological rigour, small sample sizes, failure to assign treatments randomly, lack of active control, limited outcome measures to determine transfer of benefit to non-trained functions, and lack of longitudinal design to determine persistence of benefit ([Gates 2010](#); [Green 2014](#); [Kueider 2012](#); [Papp 2009](#); [Park 2013](#); [Reijnders 2013](#); [Walton 2014](#)). Additionally, results reported in some previous reviews have been hard to interpret, as cognitively healthy and clinical populations have been combined, and diverse types of cognitive intervention have been analysed together (e.g. [Martin 2011](#)). Recent meta-analyses in cognitively healthy older adults with defined intervention eligibility criteria have shown positive effects on cognition ([Kueider 2012](#); [Lampit 2014a](#); [Shao 2015](#)). It is important to note that primary studies have identified that the benefits of CCT may depend upon a number of factors. Comparisons between single- and multiple-domain training suggest that multiple-domain training was better, consistent with increased global reserve ([Cheng 2012](#)), and nascent evidence suggests that different cognitive domains may respond differently to training, and hence may require different interventions for different durations ([Lampit 2014](#)).

For individuals, fear of cognitive decline and dementia may be a powerful motivator to seek preventive interventions. 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, maintaining, and preventing decline in cognitive functioning, although most of these activities have not been investigated in clinical trials. Technology and computerised 'brain training' games and cognitive training programmes are being investigated more actively ([Alzheimer's Association 2014](#); [Peretz 2011](#); [Sixsmith 2013](#)). However, the proliferation of computer-based commercial products purporting to improve cognitive function and reduce dementia risk has frequently outpaced thorough research into product benefits ([Gates 2014](#); [Lampit 2015](#)). The value of the brain training industry has reportedly risen from \$295 million in 2009 to \$2 billion to \$8 billion in 2015 (www.sharpbrains.com). In this context, it is important to assist clinicians and consumers to make informed choices that are based on evidence, take account of alternative cognitively stimulating activities, and protect against strong advertising claims.

A review is therefore warranted to investigate the efficacy of computerised cognitive interventions and to evaluate potential sources of bias and heterogeneity in the literature. If sufficient trials are identified, then it is important to examine intervention characteristics and other factors that may affect outcomes, along with examining transfer and persistence of benefit. Information

about adverse effects is also important, although behavioural interventions such as CCT are often perceived to be at 'low risk' for adverse effects ([Gates 2014](#)). The findings of this review should be useful for older adults, public health decision-making bodies, health 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.

OBJECTIVES

To evaluate the effects of computerised cognitive training interventions lasting at least 12 weeks on cognitive function in cognitively healthy people in late life.

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 we considered only results from the former. We included cross-over studies, but we extracted and analysed data from the first treatment period only.

Types of participants

We included studies of cognitively healthy people in late life. 'Late life' was defined as over 65 years of age, in line with the World Health Organization (WHO) definition (who.int/healthinfo/survey/ageingdefolder/en/). At least 80% of the study population had to be in this age range. We covered healthy participants in midlife (40 to 65 years) in a separate review ([Gates 2016a](#)). If the age range of participants in a trial did not coincide with our categories, then we used the median and range, or the mean and standard deviation (SD), to place studies into the most appropriate review.

For a study to be included, its authors should have attempted to exclude those who were not cognitively healthy or who had dementia. We accepted and recorded the trial authors' own definitions of 'cognitively healthy'. It was acceptable, for this purpose, for authors to have used a cut-off score on a cognitive test as an exclusion criterion. We accepted any cut-offs used in the studies, and we examined this as a possible source of heterogeneity.

We excluded all studies in which more than 20% of participants were reported to have subjective memory complaints, or to have received a diagnosis of any cognitive, neurological, psychiatric, or medical condition.

We contacted study authors if we needed further 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 of cognitive training interventions using interactive computerised technology of 12 or more weeks duration

compared with active or inactive control interventions. The rationale for this threshold is described in the Introduction section.

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 involves repeated practice on standardised exercises of specified cognitive 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 a planned intervention. These tasks can involve watching educational videos or playing computer games, with no particular training component. By 'inactive control', we refer to control groups in which no intervention is applied that may be expected to have an effect on cognition.

There was no minimum duration of follow-up. However, all included trials had to report outcomes at a minimum of one time point - 12 or more weeks after randomisation. Trials in cognitively healthy people with a duration as short as 12 weeks typically investigate cognitive enhancement rather than maintenance of cognitive function. We included these trials to give a full picture of the data, although it is recognised that the relationship between short-term cognitive enhancement 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 excluded studies in which the experimental intervention was combined 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

- Global cognitive functioning: measured using validated tests, for example (but not limited to):
 - * Mini Mental State Examination (MMSE);
 - * Alzheimer's Disease Assessment Scale (ADAS-Cog);
 - * Repeatable Battery for the 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 follow-up duration, as measured from randomisation (see also section [Data collection and analysis](#)). We also extracted and presented outcome data reported at other time points after randomisation, when available.

Secondary outcomes

Secondary outcomes are cognitive tests not included in the training programme, administered before and after training, that provide any validated measure of:

- specific cognitive functioning subdomain: episodic memory;
- specific cognitive functioning subdomain: speed of processing;
- specific cognitive functioning subdomain: executive function;
- specific cognitive functioning subdomain: attention/working memory;
- specific cognitive functioning subdomain: verbal fluency;

- quality of life/psychological well-being, either generic or health-specific;
- daily function, such as measures of instrumental activities of daily living; and
- number of participants experiencing one or more serious adverse event(s).

If a trial provided data on more than one cognitive scale for a specific outcome, we applied a hierarchy of cognition-related outcomes (manuscript in preparation) and used data on the cognitive scale that was highest in 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 to be included in the 'Summary of findings' table

We planned to address critical effectiveness outcomes in the 'Summary of findings' table for each review. We included all outcomes related to cognitive function on non-trained tasks and quality of life. We were able to include for the first comparison the following outcomes: (1) global cognitive functioning, (2) episodic memory, (3) speed of processing, (4) executive functioning, (5) working memory, (6) quality of life, and (7) adverse events. For the second comparison, we included the following outcomes: (1) episodic memory, (2) speed of processing, (3) executive functioning, (4) working memory, and (5) verbal fluency.

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 (CDCIG) - up to 31 March 2018.

ALOIS was maintained by the Information Specialist for the CDCIG and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy elderly populations. These studies are identified through:

- monthly searches of several major healthcare databases: MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, and Latin American Caribbean Health Sciences Literature (LILACS);
- monthly searches of several trial registers: University hospital Medical Information Network (UMIN) Clinical Trials Registry (Japan) (UMIN-CTR) (www.umin.ac.jp/ctr/index.htm); World Health Organization (WHO) portal (which covers ClinicalTrials.gov (clinicaltrials.gov)); International Standard Randomized Controlled Trials Number (ISRCTN) (www.isrctn.com/); Chinese Clinical Trials Register (ChiCTR) (who.int/ictrp/network/chictr/en/); German Clinical Trials Register (GermanCTR) (who.int/ictrp/network/drks2/en/); 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 of 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; and 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, CENTRAL, ClinicalTrials.gov, and the WHO Portal/ICTRP (www.apps.who.int/trialsearch), to ensure that the searches were as comprehensive and as up-to-date as possible, in identifying published, unpublished, and ongoing trials. 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 this protocol 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 are available at www.medicine.ox.ac.uk/alois/content/modifiable-risk-factors. In brief, teams of volunteers would perform 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 search 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 is describing a randomised or quasi-randomised trial, irrespective of the citation topic. It is estimated that this approach removes 75% to 90% of results retrieved. 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 a [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, GM), working independently, extracted trial information using a standardised and piloted extraction method, while referring also to a guidance document and resolving discrepancies by discussion or by involvement of a fifth review author. When possible, we extracted the following information related to characteristics of participants, interventions, and study design.

Participant characteristics

- Sex
- 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 computerised cognition-based intervention
- Type and description of the control condition
- Delivery mode (individualised, group sessions, supervised)
- Length of training sessions (in minutes)
- Frequency of sessions (per week)
- Duration of treatment programme
- Any concomitant treatments for which benefits can be isolated from the intervention

Methodological characteristics

- Trial design (individual or cluster-randomisation, parallel-group, factorial, or cross-over design)
- Number of participants
- Allocation to trial (randomisation, blind allocation)
- 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, as well as 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 reported data at six months, nine months, and one year, we

extracted only the one-year data and 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, and we determined the mean and the SD of the change from baseline for each outcome at each time point. If changes 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 trial authors if we could not obtain the 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 studies as having '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 provided 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 explained them in detail in [Appendix 2](#).

Measures of treatment effect

The measure of treatment effect for continuous outcomes was 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 or cross-over trials for inclusion.

Dealing with missing data

Missing data in 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 evaluated attrition bias in stratified analyses of the primary outcomes ([Appendix 2](#)). We analysed available information and did not contact study authors with requests to provide missing information, nor did we impute missing data ourselves.

Assessment of heterogeneity

We planned to examine heterogeneity in stratified analyses by trial, participant, and intervention. We also planned to visually inspect forest plots for the presence of heterogeneity and to calculate the variance estimate τ^2 as a measure of between-trial heterogeneity (DerSimonian 1986). We prespecified a τ^2 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 I^2 statistic and the corresponding χ^2 test to assist readers more familiar with these statistics (Higgins 2011). I^2 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 τ^2 over I^2 in interpretation of between-trial heterogeneity, as interpretation of I^2 can be largely affected by the precision of trials included in the meta-analysis (Rücker 2008). All P values are two-sided.

Assessment of reporting biases

We did not identify a sufficient number of trials to formally explore reporting biases and other biases related to small-study effects (see [Differences between protocol and review](#)).

Data synthesis

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

Additionally, 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), as well as in STATA, release 13 (Statacorp, College Station, Texas, USA).

GRADE and 'Summary of findings' table

We used GRADE to describe the quality of the overall body of evidence for each outcome in the 'Summary of findings' table (Guyatt 2008; Higgins 2011). We defined 'quality' as the degree of confidence that we can place in the estimates of treatment benefits and harms. Four ratings were possible: 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 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 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

Due to the limited number of trials identified, we were unable to conduct protocol-defined subgroup and sensitivity analyses (see [Differences between protocol and review](#)).

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 March 2018. In total, we retrieved 7727 records from the five searches. After de-duplication, 5832 remained. A crowd (through crowdsourcing) and the CDCIG Information Specialist assessed these at title and abstract levels. In total, 1090 results remained after this assessment. The review team then assessed these and five additional records identified through other sources. Of these, we assessed 325 full-text articles for eligibility and found that eight studies (reported in nine articles) were eligible for inclusion ([Desjardins-Crépeau 2016](#); [Klusmann 2010](#); [Lampit 2014](#); [Legault 2011](#); [Leung 2015](#); [Peretz 2011](#); [Shatil 2013](#); [van het Reve 2014](#)). This process is depicted in [Figure 1](#).

Figure 1. Study flow diagram.

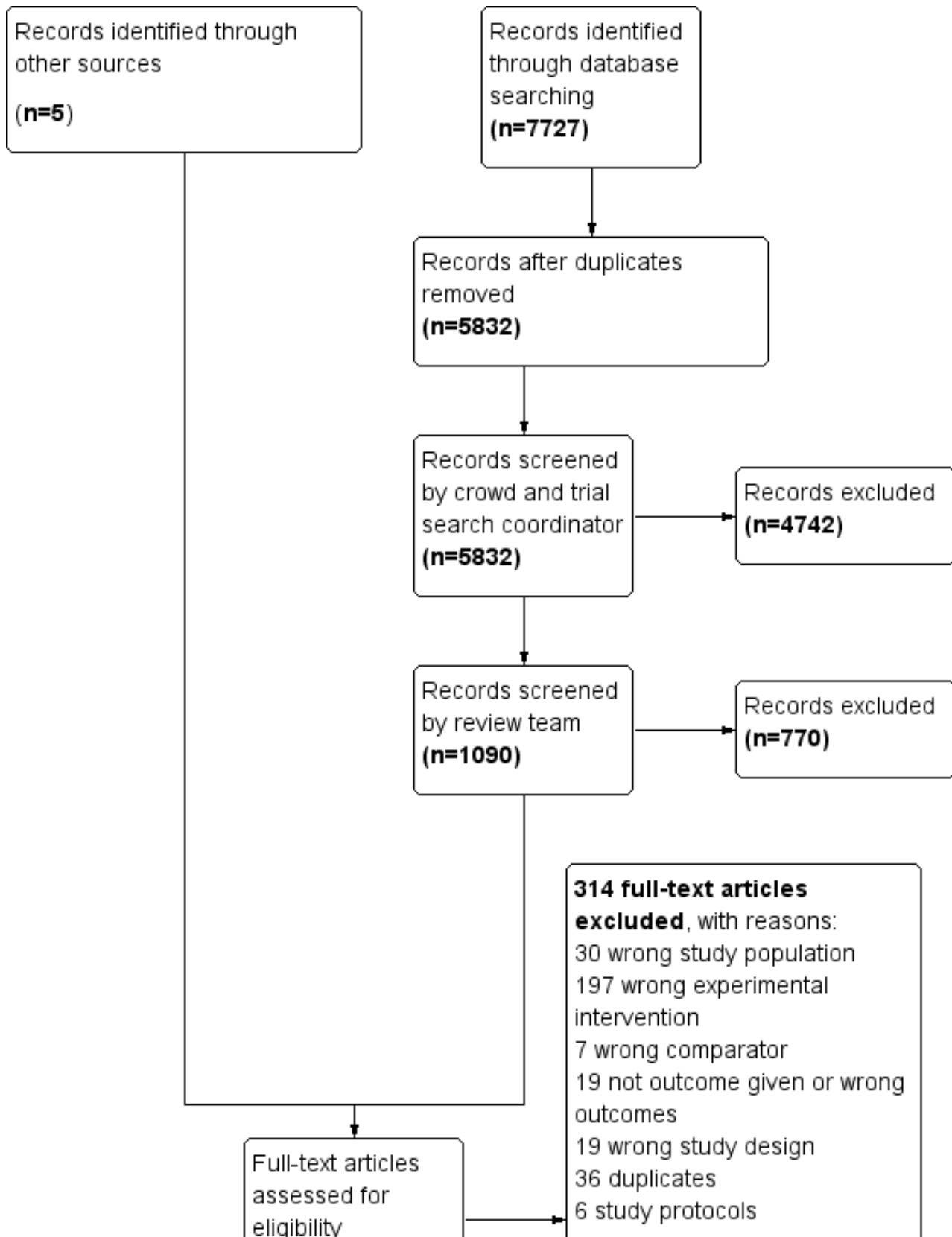
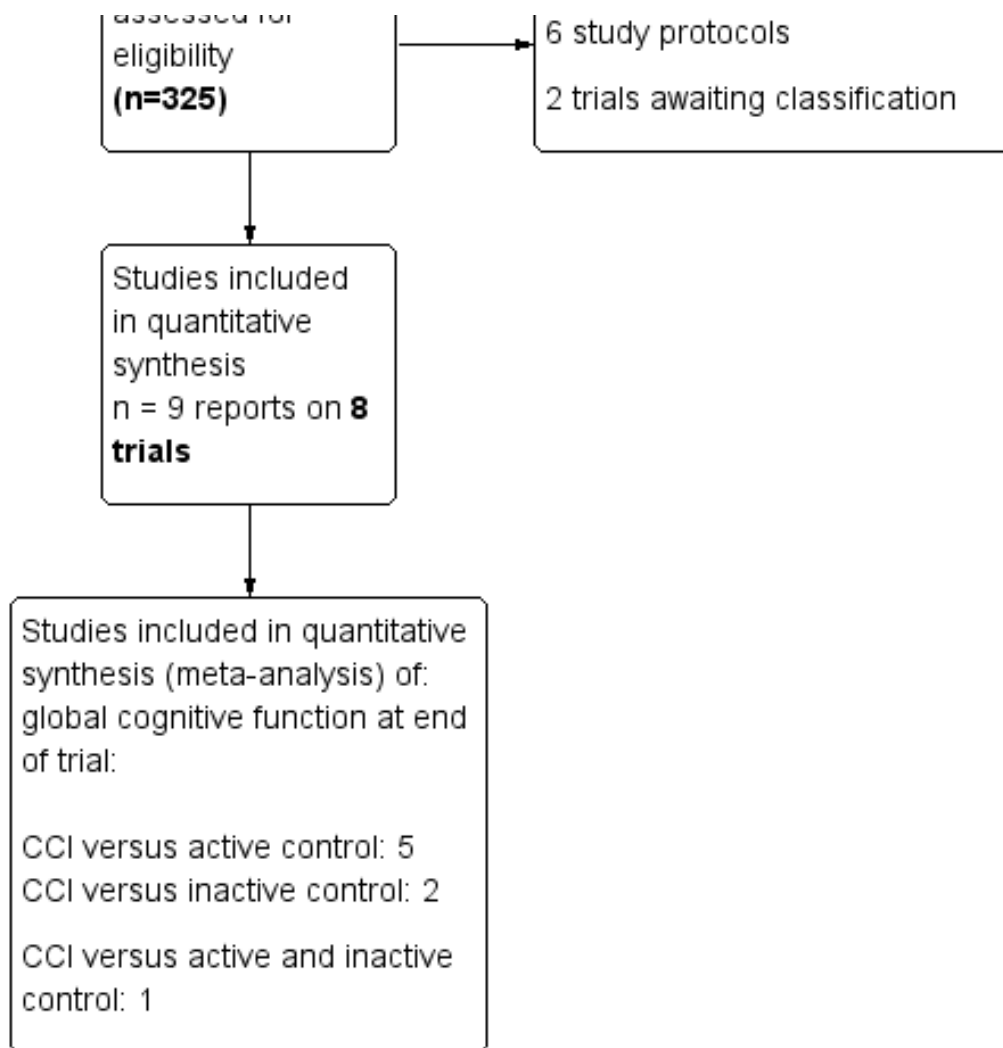


Figure 1. (Continued)



Included studies

We have provided details of the eight eligible studies in the [Characteristics of included studies](#) tables and have briefly summarised them below. Two additional studies meeting eligibility criteria are listed in the section [Characteristics of studies awaiting classification](#).

Design

All studies used a randomised controlled design. Three used a factorial 2 × 2 design (Desjardins-Crépeau 2016; Legault 2011; Peretz 2011), and the remainder used separate interventions in a parallel-group design.

Durations of the included interventions were three months (12 or 13 weeks) (Desjardins-Crépeau 2016; Lampit 2014; Leung 2015; Peretz 2011; van het Reve 2014), four months (16 or 17 weeks) (Legault 2011; Shatil 2013), and six months (Klusmann 2010). All studies assessed outcomes at the end of the intervention period. Lampit 2014 also assessed outcomes 15 months after randomisation, which was 12 months after the end of the intervention.

Sample size

Desjardins-Crépeau 2016 included 136 participants in total and reported data on 42 participants in the experimental group and 34 in the control group. Klusmann 2010 included 92 participants in the experimental group and 76 in the control group. Lampit 2014 randomised 41 people to the experimental group and 39 to the control group. Legault 2011 randomised 18 participants to cognitive training, 19 to the combined intervention (cognitive training and exercise), and 18 to control. Leung 2015 included 109 participants in the experimental group and 100 in the control group. Peretz 2011 randomised 84 participants to the experimental group and 71 to the control group. Shatil 2013 randomised 42 to 48 participants in each of the four arms of the study (total 180 participants). Finally, van het Reve 2014 randomised 84 participants to the intervention group and 98 to the control group.

Setting

Desjardins-Crépeau 2016 did not provide information regarding the setting. Klusmann 2010 undertook this investigation in Germany but provided few details about the setting. Lampit 2014, Leung 2015, and Peretz 2011 were single-centre studies conducted in Australia, Hong Kong, and Israel, respectively. Legault 2011 and

[Shatil 2013](#) were single-centre studies conducted in the USA. Fourteen centres from Switzerland and Germany participated in [van het Reve 2014](#).

Participants

All participants were cognitively healthy with a minimum age of 65 years or older, other than those in [Desjardins-Crépeau 2016](#), who were 60 years or older (the mean age in all groups in this study was > 70 years; therefore we considered that inclusion in this review was warranted). Mean ages ranged from 67 to 82 years. Most studies except [Legault 2011](#) reported a preponderance of women. None of the studies focused on high-risk groups for cognitive decline.

Interventions

CCT versus active control

[Desjardins-Crépeau 2016](#) compared computerised dual task cognitive exercises versus an active control (lessons to introduce participants to computers and diverse software, e.g. Word, Excel) and to the internet (e.g. search engines, websites, online games). Researchers randomised participants in both groups to receive either aerobic and resistance exercises or stretching and toning exercises in a 2 × 2 factorial design. [Lampit 2014](#) compared computerised COGPACK cognitive training exercises targeting five cognitive domains (memory, attention, response speed, executive functions, and language) versus an active control condition of watching educational videos and answering multiple choice questions. Similarly, [Leung 2015](#) compared computerised cognitive training exercises versus an active control of watching educational videos (e.g. history, science) followed by questions. [Peretz 2011](#) compared the CogniFit Personal Coach programme versus an active control of traditional computer games. [Legault 2011](#) compared a computerised memory domain training programme in small groups monitored by skilled trainers versus an active control of weekly health lectures provided by an instructor and promotion of group interaction.

CCT versus inactive control

[Klusmann 2010](#) compared a computer course that included multiple computer activities such as creative, co-ordinative, and memory tasks versus an inactive, no intervention control. [van het Reve 2014](#) compared a strength-balance-cognitive programme - the CogniPlus computerised cognitive training programme - versus a strength-balance programme.

CCT versus both active and inactive controls

We included [Shatil 2013](#) in our comparisons of computerised training versus both active and inactive controls. This study included four arms: (1) Cognifit, (2) Cognifit in combination with group-based supervised physical training, (3) supervised physical training, and (4) active control of book club reading. Therefore, we included [Shatil 2013](#) in comparisons of computerised cognitive training (Cognifit) plus physical training versus physical training as inactive control, and computerised cognitive training (Cognifit) versus book club reading as active control.

Outcomes

In this section, we describe outcome measures that we included in meta-analyses in this review (see [Types of outcome measures](#)). We describe instruments that address outcomes of interest to

this review but were not included in any meta-analyses in the [Characteristics of included studies](#) tables.

Primary outcome

Global cognitive function

[Lampit 2014](#) measured global cognitive functioning using a composite score of memory, speed, and executive function after 3 and 15 months of follow-up. [Peretz 2011](#) measured global cognitive functioning using an overall NexAde battery test composite score at three months.

Secondary outcomes

Cognitive function subdomain: episodic memory

Episodic memory was measured with the Rey Auditory Verbal Learning Test (RAVLT) by [Desjardins-Crépeau 2016](#), the Rivermead Behavioural Memory Test (RBMT) by [Klusmann 2010](#), the Logical Memory subtest of the Wechsler Memory Scale-III (WMS-III) by [Legault 2011](#) and [Leung 2015](#), and a memory recall test from the NexAde cognitive test battery by [Peretz 2011](#).

Cognitive function subdomain: speed of processing

[Shatil 2013](#) used the CogniFit neuropsychological evaluation subtest speed of visual information processing (SVP) to measure speed of processing. [Desjardins-Crépeau 2016](#) and [van het Reve 2014](#) used the Trail Making Test (TMT)-A, to measure speed of processing.

Cognitive function subdomain: executive function

[Legault 2011](#) used TMT-B and -A, and [van het Reve 2014](#) used TMT-B, to measure executive function. [Klusmann 2010](#) assessed executive function with the Stroop test, [Peretz 2011](#) used the Executive functions subtest of NexAde, and [Desjardins-Crépeau 2016](#) used the Color-Word Interference Test (CWIT) of the Delis-Kaplan Executive Functions System (CWIT-switching).

Cognitive function subdomain: working memory

Working memory was measured with the Digit Span by [Leung 2015](#), the NexAde Visuospatial working memory subtest by [Peretz 2011](#), and the auditory working memory (AM) subtest of Cognifit by [Shatil 2013](#).

Cognitive function subdomain: verbal fluency

Verbal fluency was measured via semantic verbal fluency by [Klusmann 2010](#).

Quality of life/psychological well-being

None of the included studies reported on these outcomes.

Daily functioning

None of the included studies reported on this outcome.

Number of participants experiencing one or more serious adverse events

None of the studies reported on this outcome.

Excluded studies

We excluded 311 full-text articles that we had examined in full text. Of these, we excluded one because it focused on cognitively healthy people in midlife ([Corbett 2015](#)), another because the age of

participants was given as ranging from 50 to 85 without means and standard deviations (Shah 2012), and eight because participants had mild cognitive impairment (Barnes 2013; Djabelkhir 2017; Fiatarone Singh 2014; Gooding 2016; Herrera 2012; Kwok 2013a; Optale 2010; Rozzini 2007). Nine of these trials are included in two other Cochrane reviews (Gates 2019a; Gates 2019b). We excluded 195 studies because they investigated an intervention shorter than 12 weeks, or because the intervention did not involve computerised

cognitive training, and 18 studies because they used the wrong study design. We did not identify any ongoing trials in trial registers or conference proceedings. Reasons for study exclusion can be found in [Characteristics of excluded studies](#).

Risk of bias in included studies

For graphical presentation of the risk of bias assessments, please see [Figure 2](#) and [Figure 3](#).

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

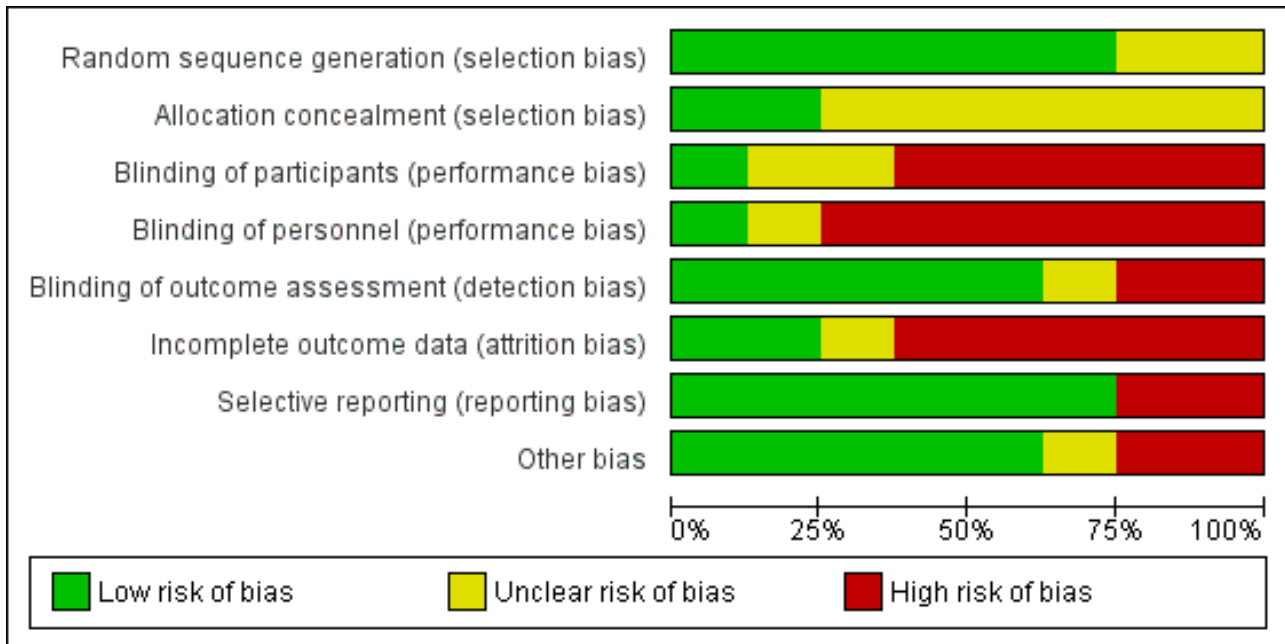


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Desjardins-Crépeau 2016	+	?	-	-	+	-	+	+
Klusmann 2010	+	?	-	-	+	-	+	+
Lampit 2014	+	+	+	-	+	+	-	+
Legault 2011	?	?	-	-	+	+	-	-
Leung 2015	+	?	-	-	-	?	+	?
Peretz 2011	+	+	-	+	+	-	+	+
Shatil 2013	?	?	?	?	?	-	+	-
van het Reve 2014	+	?	?	-	-	-	+	+

Allocation

We considered there to be low risk of selection bias for two studies, which reported adequate methods to generate random sequences and to conceal allocation (Lampit 2014; Peretz 2011). For three trials, we considered that there was an adequate method of random sequence generation but little or no information about allocation concealment; we therefore judged them to be at unclear risk (Klusmann 2010; Leung 2015; van het Reve 2014). In the remaining two trials, the risk of bias associated with both sequence generation

and concealment of allocation was unclear (Legault 2011; Shatil 2013).

Blinding

We considered there to be unclear risk of performance and detection bias for one study, which lacked information on blinding of participants, personnel, and outcome assessors (Shatil 2013). We considered two studies to be at high risk of performance bias because patients and personnel were not blinded to the treatment

assigned, but at low risk of detection bias because blinding of outcome assessors was described (Klusmann 2010; Legault 2011). Lampit 2014 described adequate blinding of participants and outcome assessors, but not of personnel, so we considered it to be at high risk of performance bias and low risk of detection bias. We considered Leung 2015 to be at high risk of both performance and detection bias because patients, personnel, and outcome assessors were not blinded. Peretz 2011 described blinding of personnel and outcome assessors, but not of participants, so we considered it to be at high risk of performance bias and low risk of detection bias. van het Reve 2014 did not report any details regarding blinding of participants but had high risk of both performance and detection bias because neither personnel nor outcome assessors were blinded.

Incomplete outcome data

We considered two studies to be at low risk of attrition bias (Lampit 2014; Legault 2011), and we judged one study to be at unclear risk because of lack of information about how missing data were handled (Leung 2015). We considered Klusmann 2010, Desjardins-Crépeau 2016, and Shatil 2013 to be at high risk of attrition bias because on average, less than 90% of randomised participants were analysed. Peretz 2011 stated that researchers used an intention-to-treat (ITT) analysis, but 18 participants in the experimental group and 16 in the control group did not complete the training and provided no data at baseline, follow-up, or both; we considered this to present high risk of attrition bias. We considered van het Reve 2014 to have high risk of attrition bias because only 82% and 78% of participants randomised to the two treatment groups were included in the statistical analyses.

Selective reporting

We considered five studies to be at low risk of reporting bias because all outcomes are described in the results section of the articles (Klusmann 2010; Leung 2015; Peretz 2011; Shatil 2013; van het Reve 2014). We considered two studies to be at high risk of reporting bias because we identified differences between the trial registry entry and the final article (Lampit 2014; Legault 2011).

Other potential sources of bias

We assessed Legault 2011 to be at high risk of bias for other reasons because the attendance rate in the combined CCT and physical activity group was statistically significantly better than in the physical activity only control group (Legault 2011). We assessed Shatil 2013 to be at high risk of bias for other reasons because Shatil works for the CogniFit company.

Effects of interventions

See: [Summary of findings for the main comparison](#); [Summary of findings 2](#)

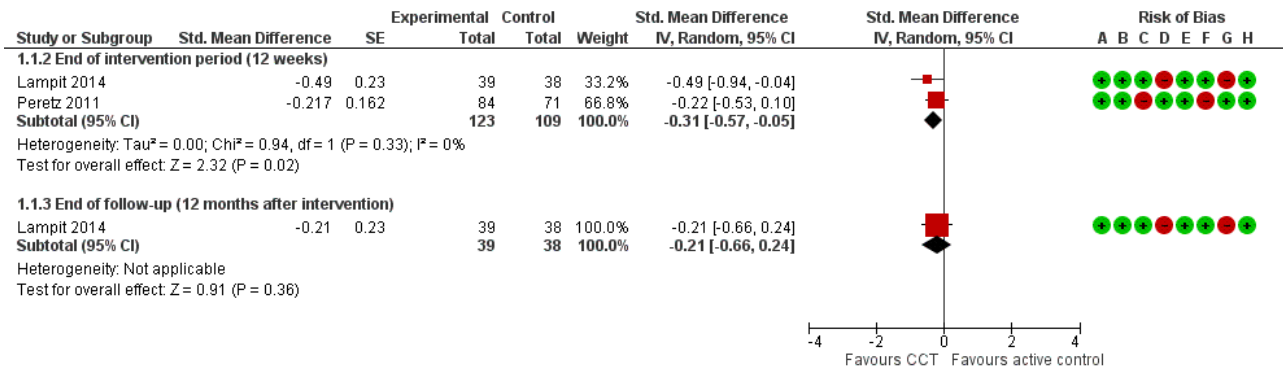
Comparison: computerised cognitive training versus active control

We refer to [Summary of findings for the main comparison](#) for an overview related to the comparison computerised cognitive training (CCT) versus active control. Unless otherwise stated, all outcomes were independent neuropsychological measures, not trained tasks, and any change would suggest transfer of training effects.

Primary outcome

Evidence on global cognitive function at end of trial was of low quality, downgraded for imprecision and risk of bias ([Analysis 1.1](#); [Figure 4](#)). Therefore we are uncertain of this result. Negative values favour the CCT group. Two studies contributed to the analysis at the end of the intervention period (12 weeks) (Lampit 2014; Peretz 2011), yielding a standardised mean difference (SMD) of -0.31 (95% confidence interval (CI) -0.57 to -0.05; 2 studies; 232 participants). One of these trials also assessed global cognitive function 12 months after completion of the intervention; this trial provided no clear evidence of a persistent effect (SMD -0.21, 95% CI -0.66 to 0.24; 77 participants; 1 study; low-quality evidence). Results at all time points were imprecise.

Figure 4. Forest plot of comparison: 1 Computerised cognition-based training versus active control, outcome: 1.1 Global cognitive function. Peretz 2011 published standard deviations as measure of spread for all outcomes. We deemed the published values for change from baseline values within groups to be more likely standard errors, and treated these as such.



Risk of bias legend
 (A) Random sequence generation (selection bias)
 (B) Allocation concealment (selection bias)
 (C) Blinding of participants (performance bias)
 (D) Blinding of personnel (performance bias)
 (E) Blinding of outcome assessment (detection bias)
 (F) Incomplete outcome data (attrition bias)
 (G) Selective reporting (reporting bias)
 (H) Other bias

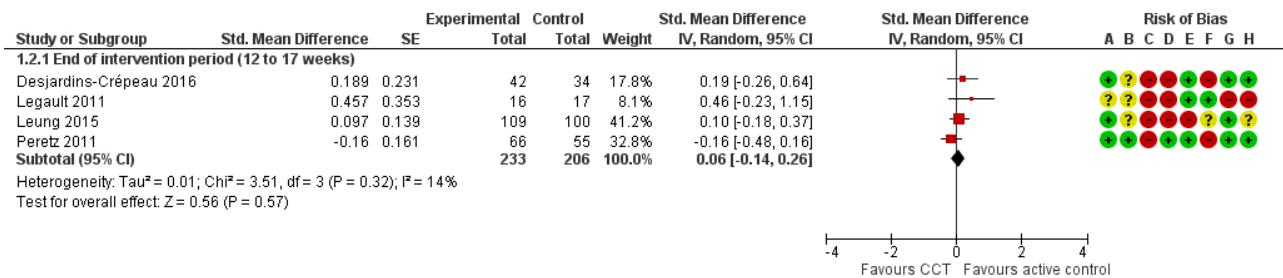
Secondary outcomes

Cognitive subdomain: episodic memory

Evidence on episodic memory at end of trial was of low quality, downgraded for imprecision and risk of bias (Analysis 1.2; Figure 5).

Therefore we are uncertain of this result. Negative values favour the CCT group. Four studies contributed to the analysis at the end of the intervention period (12 to 17 weeks) (Desjardins-Crépeau 2016; Legault 2011; Leung 2015; Peretz 2011), yielding an SMD of 0.06 (95% CI -0.14 to 0.26; 4 studies; 439 participants).

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



Risk of bias legend
 (A) Random sequence generation (selection bias)
 (B) Allocation concealment (selection bias)
 (C) Blinding of participants (performance bias)
 (D) Blinding of personnel (performance bias)
 (E) Blinding of outcome assessment (detection bias)
 (F) Incomplete outcome data (attrition bias)
 (G) Selective reporting (reporting bias)
 (H) Other bias

Cognitive subdomain: speed of processing

Two studies provided very low-quality evidence on speed of processing at the end of the intervention period (12 to 16 weeks) (Analysis 1.3) (Desjardins-Crépeau 2016; Shatil 2013). We downgraded the evidence for imprecision, inconsistency, and risk of bias. Therefore we are very uncertain of this result. Negative values favour the CCT group (SMD -0.63, 95% CI -1.14 to -0.12; 2 studies; 138 participants).

Cognitive subdomain: executive function

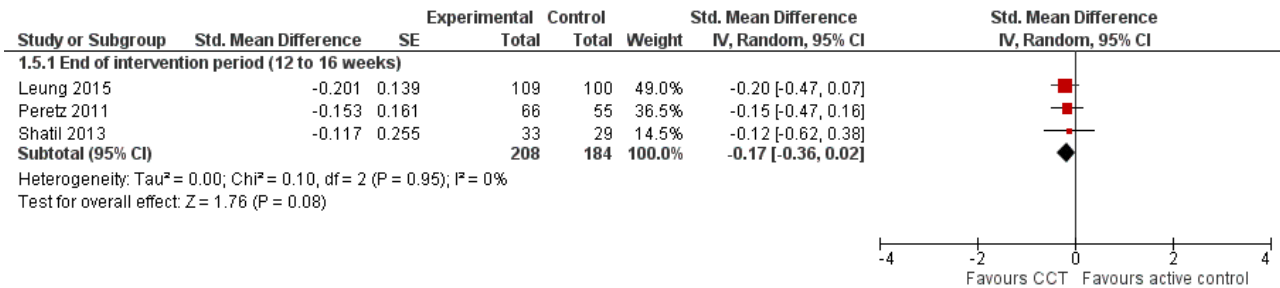
Evidence on executive function at end of trial was of very low quality, downgraded for imprecision, inconsistency, and risk of bias (Analysis 1.4). Therefore we are very uncertain of this result. Negative values favour the CCT group. Included studies at the end of the intervention period (12 to 17 weeks) were Desjardins-Crépeau 2016, Legault 2011, and Peretz 2011. The SMD was -0.04 (95% CI -0.61 to 0.53; 3 studies; 230 participants).

Cognitive subdomain: working memory

Evidence on working memory at the end of the intervention period (12 to 16 weeks) was of low quality (Analysis 1.5; Figure 6), downgraded for imprecision and risk of bias. Therefore we are

uncertain of this result. Negative values favour the CCT group. Three studies contributed to the analysis (Leung 2015; Peretz 2011; Shatil 2013), yielding an SMD of -0.17 (95% CI -0.36 to 0.02; 3 studies; 392 participants).

Figure 6. Forest plot of comparison: 1 Computerised cognition-based training versus active control, outcome: 1.5 Working memory.



Comparison: computerised cognitive training versus inactive control

We refer to Summary of findings 2 for an overview related to the comparison CCT versus inactive control. Unless otherwise stated, all outcomes were independent neuropsychological measures, not trained tasks, and any change would suggest transfer of training effects.

Primary outcome

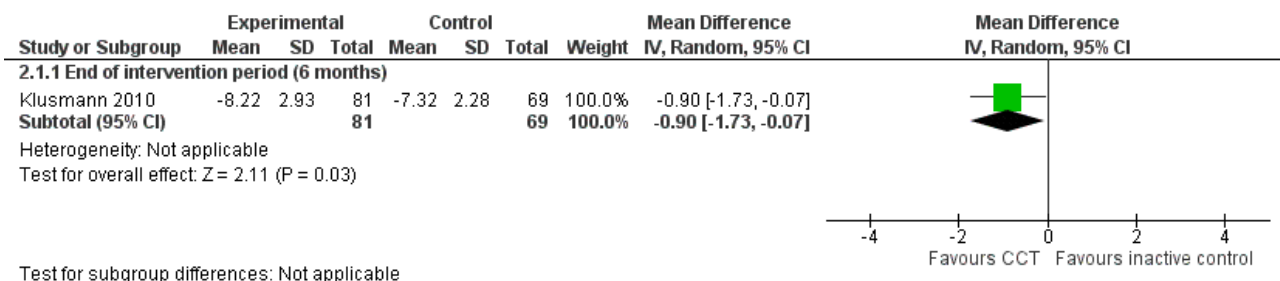
No studies provided data on global cognitive function at end of trial.

Secondary outcomes

Cognitive subdomain: episodic memory

Evidence on episodic memory at end of trial was of low quality, downgraded for imprecision and risk of bias (Analysis 2.1; Figure 7). Negative values favour the CCT group. The analysis at the end of the intervention period (six months) included one study and yielded a mean difference (MD) of -0.90 (95% CI -1.73 to -0.07; 150 participants) (Klusmann 2010).

Figure 7. Forest plot of comparison: 2 Computerised cognition-based training versus inactive control, outcome: 2.1 Episodic Memory.



Cognitive subdomain: speed of processing

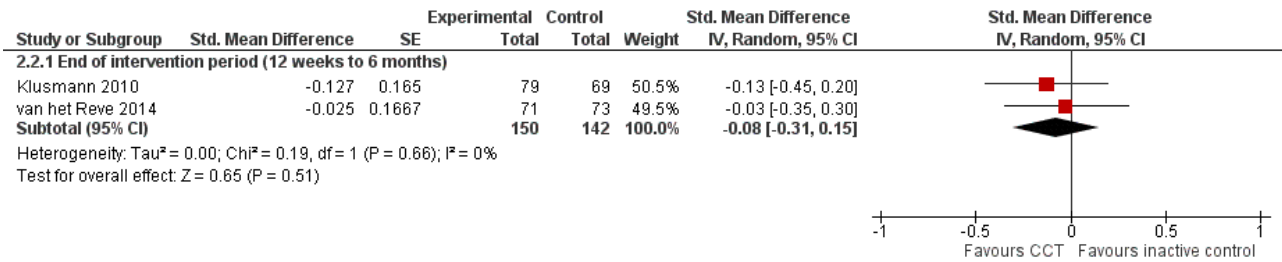
Two studies provided very low-quality evidence on speed of processing at the end of the intervention period (12 to 16 weeks) (Analysis 2.3) (Shatil 2013; van het Reve 2014). We downgraded the evidence for imprecision, inconsistency, and risk of bias. Therefore we are very uncertain of this result. Negative values favour CCT. The SMD was -0.28 (95% CI -0.82 to 0.26; 2 studies; 204 participants).

Cognitive subdomain: executive function

Evidence on executive function at the end of the intervention period (12 weeks to six months) was of low quality, downgraded

for imprecision and risk of bias (Analysis 2.2; Figure 8). Negative values favour the CCT group. The analysis included two studies and yielded an SMD of -0.08 (95% CI -0.31 to 0.15; 2 studies; 292 participants) (Klusmann 2010; van het Reve 2014). Results at individual time points were as follows: at the end of the intervention at 12 weeks: SMD -0.03 (95% CI -0.35 to 0.30; 1 study; 144 participants); and at the end of the intervention at six months: SMD -0.13 (95% CI -0.45 to 0.20; 1 study; 148 participants).

Figure 8. Forest plot of comparison: 2 Computerised cognition-based training versus inactive control, outcome: 2.2 Executive function.

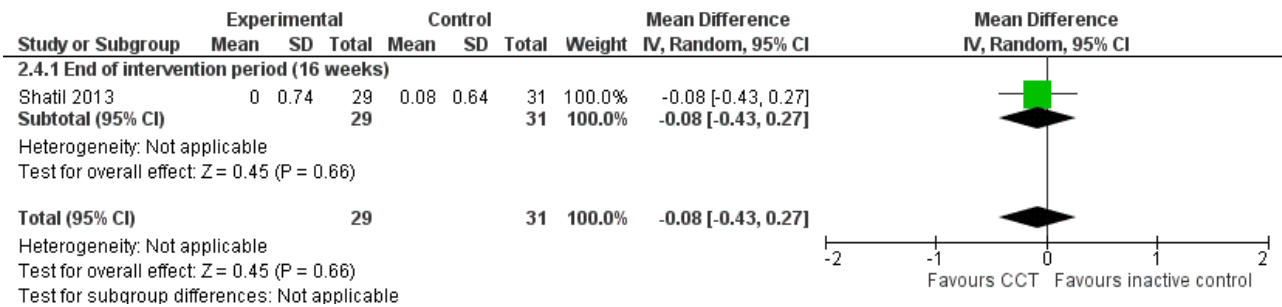


Cognitive subdomain: working memory

One study provided low-quality evidence on working memory (Analysis 2.4; Figure 9) (Shatil 2013). We downgraded the evidence because of imprecision and risk of bias. Negative values favour CCT.

At the end of the intervention period (16 weeks), the MD was -0.08 (95% CI -0.43 to 0.27; 1 study; 60 participants). This result means that, when compared with an inactive control, there may be little or no effect of CCT on working memory.

Figure 9. Forest plot of comparison: 2 Computerised cognition-based training versus inactive control, outcome: 2.4 Working memory.

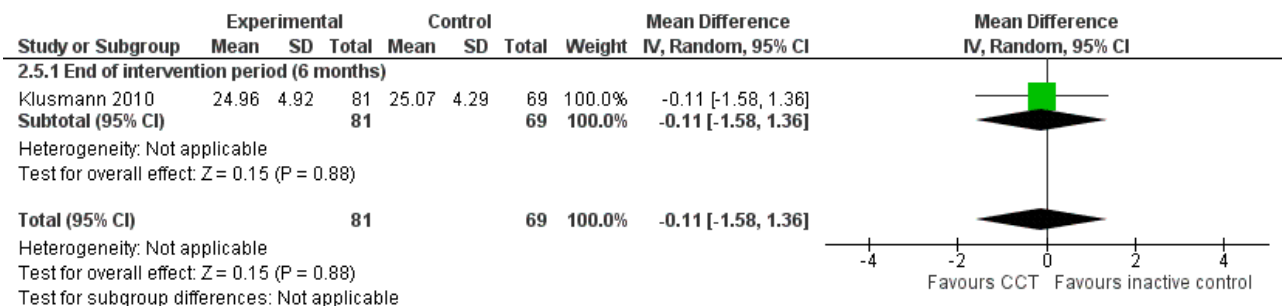


Cognitive subdomain: verbal fluency

One study provided low-quality evidence on verbal fluency at end of trial (Analysis 2.5; Figure 10) (Klusmann 2010). We downgraded the evidence for imprecision and risk of bias. Negative values favour

CCT. At the end of the intervention period (six months), the MD was -0.11 (95% CI -1.58 to 1.36; 1 study; 150 participants). This result means that, when compared with an inactive control, there may be little or no effect of CCT on verbal fluency.

Figure 10. Forest plot of comparison: 2 Computerised cognition-based training versus inactive control, outcome: 2.5 Verbal fluency.



Subgroup analyses and sensitivity analyses

We could perform no subgroup analyses as too few studies contributed to the meta-analyses (see Differences between protocol and review).

DISCUSSION

Summary of main results

Computerised cognitive training (CCT) compared to active control interventions at end of trial

We found low-quality evidence suggesting that when compared with an active control, CCT may slightly improve global cognitive function at the end of 12 weeks of training, but not at 12 months

after the end of training. CCT may have little or no effect on episodic memory and working memory. The quality of the evidence on speed of processing and executive function was very low, so we were unable to draw any conclusions about an effect of CCT on these outcomes.

Computerised cognitive training (CCT) compared to inactive control at end of trial

We found low-quality evidence suggesting that when compared with an inactive control, CCT may slightly improve episodic memory and may have little or no effect on executive function, working memory, or verbal fluency. The quality of the evidence on speed of processing was very low, so we were unable to draw any conclusions about an effect of CCT on this outcome.

Overall completeness and applicability of evidence

We made an *a priori* decision to operate a threshold around duration of exposure for inclusion in this review. As is evident from our PRISMA flow diagram, this threshold necessitated excluding a substantial proportion of the published literature. We did not deviate from our published protocol, but we recognise that our inclusion criteria may have led to the exclusion of potentially informative evidence.

Lack of long-term follow-up in the included studies meant that we found little evidence on the effect of CCT on maintenance of cognitive function over time. Ideally, follow-up should be long enough to allow age-related cognitive decline to occur.

We did not identify any trial that examined the outcomes quality of life, psychological well-being, daily functioning, and adverse events. These are all important outcomes for clinical decision-making and for potential consumers.

The extent to which CCT of duration shorter than 12 weeks can maintain or benefit cognitive function is not addressed by this review. For example, another review of computerised training in cognitively healthy elderly included 12 studies, nine of which provided training interventions of less than 12 weeks duration, and found that five short training programmes resulted in cognitive improvement across several cognitive domains (Shao 2015).

Quality of the evidence

We identified several limitations in the included studies, and we rated none as having low risk of bias. We considered only two studies to have low risk of selection bias (Lampit 2014; Peretz 2011), and we considered none to have low risk of performance bias. We judged that risk for, respectively, detection bias, attrition bias, and reporting bias was low in five studies (Desjardins-Cr peau 2016; Klusmann 2010; Lampit 2014; Legault 2011; Peretz 2011), three studies (Lampit 2014; Legault 2011; Shatil 2013), and six studies (Desjardins-Cr peau 2016; Klusmann 2010; Leung 2015; Peretz 2011; Shatil 2013; van het Reve 2014).

Overall, the quality of evidence was low or very low according to GRADE criteria, so we have low to very low confidence in the summary estimates of effects reported here. Identified issues with quality were mainly imprecision and risk of bias. Higher-quality evidence is required if we are to draw conclusions with greater certainty.

Potential biases in the review process

We used an exhaustive search strategy covering multiple data sources, considering full reports, abstracts, and other report types described in any language. We searched for unpublished and ongoing data, but we identified published data only. We did not detect publication bias, but this does not mean that we can rule out publication bias. We could not formally assess it in funnel plot evaluations because of the small number of studies identified.

Use of at least two independent review authors minimised bias at the review level. We followed Cochrane guidance and used a component approach to assess the methodological rigour of trials while applying GRADE to assess the quality of the overall body of evidence. We nevertheless are aware of some important limitations of this review. We had to choose a method to deal with the use of multiple instruments to measure a specific cognitive (sub)-domain within and across trials. We opted for use of a hierarchy that informed us which outcome data we should extract, so that for each cognitive outcome, data from a single validated instrument per trial contributed to analyses. The hierarchy of these outcomes can be consulted in the protocol of our review. As instruments differed across trials, we chose to use the standardised mean difference to combine outcome data across trials. An alternative strategy would have been 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, so that we could include a larger number of trials. The disadvantage of our approach is that interpretation of effect size (standardised mean difference (SMD)) is less intuitive than results reported on a natural scale. As there is little consensus on the threshold for minimal clinically important differences, we refrained from translating estimates of the SMD back to the natural scale of, for example, the Mini Mental State Examination (MMSE). We may have introduced between-trial heterogeneity by combining SMDs derived from multiple instruments, but the small number of trials identified did not allow us to assess such impact. As we had no access to individual participant data, we chose not to combine results on multiple instruments within a trial before combining results across trials, as this would put the summary estimates at high risk of ecological fallacy.

Agreements and disagreements with other studies or reviews

Results from other meta-analyses and individual clinical trials vary. Other recent meta-analyses of computerised cognitive programmes with no minimum training duration showed improvement in executive function, global composite scores, memory, and processing speed compared to controls and in non-cognitive outcomes including emotional well-being and everyday functioning (e.g. Gates 2011a; Gordon 2013; Kelly 2014a; Kueider 2012; Lampit 2014a; Rebok 2014; Shao 2015; Edwards 2018).

However, the overall evidence in cognitively healthy adults is mixed, and opposing professional views regarding the evidence base have been published (Lampit 2015; Ratner 2015). We identified a rather large number of reviews relative to the limited number of well-designed clinical trials. Diversity of interventions involving dose, duration, and intensity of cognitive training, along with methodological constraints such as lack of randomisation, small samples, and lack of blinding, may account for the disparate results

(Gates 2010; Kueider 2012; Mowszowski 2010; Papp 2009; Shao 2015; Steiner 2010).

AUTHORS' CONCLUSIONS

Implications for practice

At the current time, there is a lack of high-quality evidence to show that computerised cognitive training (CCT) for 12 or more weeks helps to maintain cognitive function in healthy older adults. It is important to emphasise that our conclusions are applicable only to studies that delivered cognitive training over at least 12 weeks. There may be important and relevant evidence from studies with shorter intervention periods. Despite our intention to examine generalisation of effects to objective measures of everyday functioning, we are able to comment only on training effects on cognitive outcomes.

Clinicians and consumers may find the field confusing and may note contradictory messages about research evidence and divisive debates in the research community (e.g. Lampit 2015; Ratner 2015). Fear of developing dementia is common among older adults, and there is increasing demand for interventions to address age-related and non-pathological cognitive decline. This goes along with the development and commercialisation of brain training products targeting older consumers. Although we found no strong evidence in support of CCT in this review, it remains possible that longer interventions - or shorter, higher-dose interventions - could help to maintain cognitive function.

Implications for research

Studies of CCT in cognitively healthy adults could be improved by careful consideration given to study design, including choice and measurement of outcomes and time points of follow-up. Selection of outcomes ought to address the principal objective of CCT - not only that training benefits the specific skills trained but also that those benefits *transfer* to improvement or maintenance of function on non-trained cognitive tasks, and *generalise* to non-cognitive domains such as daily functioning (Kelly 2014a), although the topic of transfer is debated (Zelinski 2009). In this review, we found that measures of functional performance that may indicate generalisation were absent from the identified studies. Inclusion of outcomes that could demonstrate effects on quality of life, psychiatric symptoms, mood, and daily functioning should be encouraged in future studies.

To accurately measure change in cognitive function, and to identify transfer and generalisation, selected outcomes should be sensitive to subtle and possibly non-linear changes, should have high reliability, should have alternate forms or be psychometrically robust for repeated use, and should have low risk of floor and ceiling effects. This is particularly relevant for cognitively healthy adults, in whom ceiling effects may dominate (i.e. how do you improve on normal?). We advocate for establishment of an international multi-disciplinary panel to develop a standardised core outcome set for cognitive assessments in older individuals with and without cognitive decline, to improve outcome reporting and facilitate evidence synthesis. Ideally, studies should measure change immediately after an intervention ends and then should monitor function over time. Future research studies should move towards investigating different types of training exercises,

differential effects of training on separate cognitive domains, and the impact of variability on the frequency, intensity, and duration of interventions. Furthermore, it would be helpful to assess effectiveness of training in realistic situations, including participants with health risk factors, comorbidities, and barriers to participation. Inactive controls are suitable for research examining possible neuroplastic mechanisms and brain reserve, and for inclusion in simple efficacy studies, and the clinical effectiveness and comparative studies described above will require an active control arm.

Improved reporting of study methods should be a priority because of the high proportion of unclear risks of bias, which could be improved through simple steps, such as adherence to CONSORT, improved data management to reduce the quantity of incomplete data, and development of methods to facilitate blinding of participants and personnel. Blinding of participants is especially important given the commercialisation of CCT, advertisements, and widespread community exposure, and an active control may partially address this potential bias.

The process of conducting this review has highlighted important methodological considerations for future updates and for other systematic reviews in this field. With hindsight, our 12 weeks duration inclusion criterion did not achieve what we hoped for. We had wanted to exclude studies in which exposure to training was modest and was unlikely to have meaningful, lasting effects. However, as is evident from comparisons of included and excluded studies, some excluded studies offered high-intensity training and hence an overall 'dose' of training that was higher than in many included studies. For future updates, various options are possible; it may be useful to consider dose of training and perhaps to perform meta-regression to look at the effects of dose on outcomes. Alternatively, length of follow-up may be a more useful inclusion criterion than duration of intervention. Although short-term effects are of scientific interest, for older people and for clinicians and policy makers, it is sustained benefits that matter most.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Desjardins-Crépeau 2016

Methods	<ul style="list-style-type: none"> • Design: 2 × 2 factorial RCT design • Recruitment period: not reported • No. of centres involved: not reported • Unit of randomisation: individuals • No. randomised: 136 participants • Number of arms considered in this review: 4 • Maximum trial duration: 12 weeks. • Funding by non-profit organisation: this study was supported by a Canadian Institutes of Health Research (CIHR) grant (#187596). One study author was supported by a doctoral fellowship from the CIHR, and the other study author was supported by the Canada Research Chair Programme • Funding by commercial organisation: none reported • Publication status: full-text report
Participants	<ul style="list-style-type: none"> • Patient flow: 136 participants were randomised, 91 completed the programme, and 76 were considered in the report. Each of 38 participants had aerobic and resistance (AR) and stretching and toning (ST) exercises. Of these, 22 in AR and 20 in ST received the computerised stimulation (experimental group), and 16 in AR and 18 in ST received computer lessons (control group), respectively • Number of females: arm with AR: 13 of 22 (59%) in experimental group, 8 of 16 (50%) in control group; arm with ST: 17 of 20 (85%) in experimental group, 15 of 18 (83%) in control group • Average age (SD): arm with AR: 72.7 (7.4) years in experimental group, 70.9 (7.4) years in control group; arm with ST: 73.2 (6.3) years in experimental group, 72.5 (7.0) years in control group • Average (SD) education: arm with AR: 14.4 (2.8) years in experimental group, 15.9 (2.1) years in control group; arm with ST: 14.1 (4.3) years in experimental group, 14.1 (3.8) years in control group • Baseline cognitive function: MMSE in arm with AR: 28.8 (1.3) in experimental group, 28.8 (1.0) in control group; MMSE in arm with ST: 29.4 (0.7) in experimental group, 28.5 (1.4) in control group • Selection criteria on cognition: community-dwelling participants were recruited from the research centre's participant pool. A telephone-based screening interview was used to assess the eligibility of each candidate. Exclusion criteria were as follows: history of neurological disease or major surgery in the year preceding the study, auditory or visual impairments that were not corrected, smoking, severe mobility limitations, any other contraindication to perform physical activity, currently engaged in any type of structured physical activity, high score on geriatric depression scale, < 60 years old • Ethnicity: not reported • APOE: number of participants positive for APOE not reported
Interventions	<p>Type of experimental intervention: computerised cognitive training group; treatment duration 12 weeks; intervention provided in small group format under supervision of a neuropsychologist student</p> <ul style="list-style-type: none"> • Details of experimental intervention: each weekly session of dual task (DT) training took place in a room with 10 computer stations and was supervised by a student in neuropsychology. Participants were trained on a computerised visual DT analog. The task consisted of 2 visual discrimination tasks performed separately and concurrently. The first task was a number discrimination task (3, 5, and 8), and the second was a shape discrimination task (circle, square, and diamond). Participants had to respond to the number or shape presented on the screen with a key press on the appropriate button identified on the keyboard. The DT consisted of 4 different blocks, each containing different types of trials • Type of concomitant treatment provided: arm with AR: included two 60-minute sessions/week for 12 weeks of physical exercise of cardiorespiratory fitness and lower body muscle strength; arm with ST included two 60-minute sessions/week for 12 weeks of series of exercises aimed at improving flexibility and general motor skills without a specific focus on increasing cardiorespiratory capacity or strength

Desjardins-Crépeau 2016 (Continued)

- **Session duration:** 60 minutes in the experimental group
- **Number of treatment sessions:** 12 in the experimental group
- **Treatment frequency:** 1 session per week
- **Maximum treatment duration in weeks:** 12 in the experimental group

Type of control intervention: inactive; treatment duration of 12 weeks; intervention provided in group format, under supervision

- **Details of control intervention:** computer lessons (control) condition consisted of introductory exercises to computers and diverse software (e.g. Word, Excel), as well as an introduction to the Internet (search engines, websites, online games, etc.). These sessions took place in the same computer room as the DT training programme and were taught by a student in neuropsychology
- **Type of concomitant treatment provided:** arm with AR: included two 60-minute sessions/week for 12 weeks of physical exercise of cardiorespiratory fitness and lower body muscle strength; arm with ST included two 60-minute sessions/week for 12 weeks of series of exercises aimed at improving flexibility and general motor skills without a specific focus on increasing cardiorespiratory capacity or strength
- **Session duration:** 60 minutes in the control group
- **Number of treatment sessions:** 12 in the control group
- **Treatment frequency:** 1 session per week
- **Maximum treatment duration in weeks:** 12 in the control group

Outcomes

- **Cognitive functioning outcomes considered**
 - * Episodic memory measured with Rey Auditory Verbal Learning Test, delayed at 12 weeks, on a scale from 0 to 15, with higher values indicating benefit
 - * Executive function measured in seconds with the Color-Word Interference Test (CWIT-switching) of the Delis-Kaplan Executive Functions System is based on the Stroop procedure 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
- **Physical functioning outcome considered:** none reported
- **Quality of life outcome considered:** none reported
- **Safety outcome considered:** none reported
- **Depression outcome considered:** none reported
- **Other outcome data on cognitive functioning, not considered in our meta-analyses**
 - * Episodic memory measured with Rey Auditory Verbal Learning Test, total 5 trials and immediate recall at 12 weeks, on a scale from not reported to not reported with higher values indicating benefit
 - * Executive function measured in seconds with the Color-Word Interference Test (CWIT-inhibition) of the Delis-Kaplan Executive Functions System is based on the Stroop procedure, TMT part B at 12 weeks on a scale from not reported to not reported with lower values indicating benefit
 - * Executive function measured in seconds with BDT-DT index at 12 weeks on a scale from not reported to not reported with higher values indicating benefit
 - * Speed of processing as measured in seconds with the Color-Word Interference Test (CWIT-color naming and seconds) of the Delis-Kaplan Executive Functions System is based on the Stroop procedure and BDT-simple tasks at 12 weeks in seconds, with lower values indicating benefit

Notes

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We combined data from ST and AR arms

Risk of bias
Bias

Authors' judgement **Support for judgement**

Desjardins-Crépeau 2016 (Continued)

Random sequence generation (selection bias)	Low risk	<p>Judgement: adequate random sequence generation</p> <p>Quote(s): "the study was carried on in waves of 16–32 participants randomly assigned to one of the four training combinations using the website randomization.com"</p>
Allocation concealment (selection bias)	Unclear risk	<p>Judgement: method of allocation concealment not reported</p> <p>Quote(s): "the study was carried on in waves of 16–32 participants randomly assigned to one of the four training combinations using the website randomization.com"</p>
Blinding of participants (performance bias)	High risk	<p>Judgement: blinding not feasible</p>
Blinding of personnel (performance bias)	High risk	<p>Judgement: blinding not feasible</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Judgement: explicit reporting of blinded outcome assessment</p> <p>Quote(s): "the evaluators at both pretest and posttest were blind to the group membership of participants"</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Judgement: we judged high risk of bias, as on average less than 90% of randomised participants were analysed</p> <p>Quote(s): "among the 125 participants who were enrolled in the study, 91 participants completed the program. Among those, three participants failed to participate in the posttest evaluations and two participants had invalid data due to illness at posttest examinations and were thus excluded from analyses"</p>
Selective reporting (reporting bias)	Low risk	<p>Judgement: all outcomes described in the methods section are adequately addressed in the results section</p>
Other bias	Low risk	<p>Judgement: no other sources of bias detected</p>

Klusmann 2010

Methods	<ul style="list-style-type: none"> • Design: 3-arm RCT with parallel-group design • Recruitment period: 2006 to 2008 • No. of centres involved: not reported • Unit of randomisation: individuals • No. randomised: 259 • Number of arms considered in this review: 2 • Maximum trial duration: 6 months • Funding by non-profit organisation: German Research Foundation (grant number 429) Doctoral Programme "Neuropsychiatry and Neuropsychology of Aging" (years covered: 2006 to 2008) to I.H. and the Gertrud and Hugo Adler Foundation (years covered: 2006 to 2008) • Funding by commercial organisation: none reported • Publication status: full-text report
Participants	<ul style="list-style-type: none"> • Patient flow: 92 randomised, 92 described at baseline in experimental group; 76 randomised, 76 described at baseline in control group • Number of females: 92 of 92 (100%) in experimental group 1; 76 of 76 (100%) in control group • Average age (SD): 74 (4.4) years in experimental group 1; 74 (4.3) years in control group • Average (SD) education: 12 (2.6) years in experimental group; 12 (2.8) years in control group

Klusmann 2010 (Continued)

- **Baseline cognitive function:** baseline cognitive function measured with: selection criteria on cognition overall: participants were screened to rule out the presence of cognitive impairment or depression and were included if they made no more than 4 errors on the Mini Mental State Examination (MMSE; 20) and scored less than 6 points on the 15-item short-form Geriatric Depression Scale (GDS-Sf; 21). Baseline mean MMSE (SD) was 28.76 (0.97)
- Selection criteria on cognition in experimental group: participants were screened to rule out the presence of cognitive impairment or depression and were included if they made no more than 4 errors on the Mini Mental State Examination (MMSE; 20) and scored less than 6 points on the 15-item short-form Geriatric Depression Scale (GDS-Sf; 21). Baseline mean MMSE (SD): 28.84 (0.94)
- **Selection criteria on cognition in control group:** participants were screened to rule out the presence of cognitive impairment or depression and were included if they made no more than 4 errors on the Mini Mental State Examination (MMSE; 20) and scored less than 6 points on the 15-item short-form Geriatric Depression Scale (GDS-Sf; 21). Mean baseline MMSE (SD): 28.62 (1.08)
- **Ethnicity:** not reported
- **APOE:** number of participants positive for APOE not reported

Interventions

Type of experimental intervention: computerised CT individualised; treatment duration of 26 weeks; intervention provided as individual training, under supervision

- **Details of experimental intervention:** the computer course covered heterogeneous and multi-faceted tasks such as learning how to operate with common software and hardware, writing, playing, calculating, surfing on the Internet, emailing, drawing, image editing, and videotaping
- **Session duration:** 90 minutes in experimental group
- **Number of treatment sessions:** 75 in experimental group
- **Treatment frequency:** not reported in experimental group
- **Maximum treatment duration in weeks:** 26 in experimental group

Type of control intervention: inactive; duration of 26 weeks; without supervision

- **Details of control intervention:** usual daily life/care
- **Type of concomitant treatment provided:** none reported
- **Session duration:** not reported in control group
- **Number of treatment sessions:** not reported in control group
- **Maximum treatment duration in weeks:** 26 in control group

Outcomes

- **Cognitive functioning outcomes considered**
 - * Episodic memory measured with Rivermead Behavioural Memory Test (RBMT), delayed story recall at 6.5 months, on a scale from 0 to not reported with higher values indicating benefit*
 - * Executive functioning measured with Stroop test at 6.5 months, on a scale from not reported to not reported with higher values indicating benefit
 - * Verbal fluency measured with semantic verbal fluency at 6.5 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
- **Other outcome data on cognitive functioning, not considered in our meta-analyses**
 - * Episodic memory measured with Rivermead Behavioural Memory Test (RBMT), immediate story recall at 6.5 months, on a scale from 0 to not reported with higher values indicating benefit*
 - * Episodic memory measured with Free and Cued Selective Reminding Test (FCSRT), short delay at 6.5 months, on a scale from 0 to 48 with higher values indicating benefit
 - * Episodic memory measured with Free and Cued Selective Reminding Test (FCSRT), long delay at 6.5 months, on a scale from 0 to 16 with higher values indicating benefit
 - * Executive function measured with Trail Making Test (TMT)-B/A at 6.5 months, on a scale from not reported to not reported with lower values indicating benefit

Klusmann 2010 (Continued)

*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.

Notes Baseline characteristics were reported for the randomised population, whereas outcome data are presented only for those with pretest and post-test evaluations

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Judgement: adequate random sequence generation</p> <p>Quote(s): "the randomization sequence for each of the seven study cohorts was generated using Research Randomizer (www.randomizer.org) by VK"</p>
Allocation concealment (selection bias)	Unclear risk	<p>Judgement: envelopes were not reported to be opaque. Although preparation of envelopes was done centrally by an independent research assistant, we are unsure if the nurse who was in charge of handing over the envelopes could foresee the codes kept in the envelopes</p> <p>Quote(s): "a study assistant prepared seven sets of 34 numbered envelopes containing the accordant randomization results (12 for the intervention groups each and 10 for the control group)"; "the sealed envelopes, all prepared before starting the examination of the first cohort and kept locked in a safe deposit box, were given on a daily basis to the study nurse in consecutive order. Envelopes were opened after the main part of the clinical baseline evaluation to have the participants of the exercise group undergo the additional stress ECG. If study candidates withdrew from the study or were excluded because of lacking eligibility criteria at a later point in time, the study assistant prepared additional envelopes containing the corresponding assignments of those who dropped out in the sequence of deposit"</p>
Blinding of participants (performance bias)	High risk	<p>Judgement: patients were not blinded to the treatment assigned</p> <p>Quote(s): "before participants were informed about their group assignment, at a second 2.5-hour appointment"; "finally, we used a single-, not a double-, blind design. However, to design a "placebo" control group would be methodologically challenging and, furthermore, to keep participants fully blinded would raise ethical questions"</p>
Blinding of personnel (performance bias)	High risk	<p>Judgement: blinding not feasible</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Judgement: explicit reporting of blinded outcome assessment. Therapists were also outcome assessors</p> <p>Quote(s): "participants and neuropsychological assessors were blinded to group allocation up to the completed baseline examination of the whole cohort (double blind); participants were then informed by mail. Assessors were kept blind at post-test by explicitly instructing the participants not to discuss any of the information regarding randomization and intervention with the research staff conducting the testing"</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Judgement: we judged high risk of bias, as on average less than 90% of randomised participants were analysed</p> <p>Quote(s): "259 participants to be randomized (91 for the exercise, 92 for the computer, and 76 for the control condition), of whom 12 participants (5 of the exercise and 7 of the computer condition) refused to participate after being informed about their group assignment and withdrew consent before treatment"</p>

Klusmann 2010 (Continued)

started. Thus, 247 (95.4% of randomized participants; ie, 86 for the exercise, 85 for the computer, and 76 for the control condition) women were allocated to the corresponding groups, of whom 230 (93.1% of baseline, 88.8% of randomized) returned for follow-up"; "three women of the computer group were excluded from analyses of pre-post change in one cognitive test each, due to incorrect test data assessment"

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 were detected

Lampit 2014

Methods	<ul style="list-style-type: none"> • Design: 2-arm RCT with parallel-group design • Recruitment period: 2011 to 2012 • No. of centres involved: 1 • Unit of randomisation: individuals • No. randomised: 80 • Number of arms considered in this review: 2 • Maximum trial duration: 15 months • Funding by non-profit organisation: this study was funded by the Dementia Collaborative Research Centres (DCRC) - Assessment and Better Care (ID PDCRC-CB50), in which HB is the director, as well as the Dreikurs Bequest. MV is a National Health and Medical Research Council of Australia Career Development Fellow (ID 1004156) • Funding by commercial organisation: none reported • Publication status: full-text report
Participants	<ul style="list-style-type: none"> • Patient flow: 41 randomised, 39 described at baseline in experimental group; 39 randomised, 38 described at baseline in control group • Number of females: 29 of 39 (74%) in experimental group 1; 24 of 38 (63%) in control group • Average age (SD): 72 (7.1) years in experimental group 1; 72 (5.3) years in control group • Education: experimental group 1: low education (≤ 10 years), 11/39 (28.2); control: low education (≤ 10 years), 11/38 (29%) • Baseline cognitive function: MMSE scores ranged from 24 to 30 (mean MMSE 28, SD 1.6). All participants had at least 1 established dementia risk factor, the most prevalent being subjective memory complaints (68.9% in women; 70.1% in men) • Selection criteria on cognition: intervention group: MMSE (SD): 28.2 (1.4). All participants had at least 1 established dementia risk factor, the most prevalent being subjective memory complaints (69%), hypertension (31%), hypercholesterolaemia (36%). Control group: MMSE (SD): 27.8 (1.8). All participants had at least 1 established dementia risk factor, the most prevalent being subjective memory complaints (71%), hypertension (53%), hypercholesterolaemia (37%) • Ethnicity: not reported. • APOE: number of participants positive for APOE not reported
Interventions	<p>Type of experimental intervention: computerised CT group; treatment duration of 12 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> • Details of experimental intervention: 24 exercises from the COGPACK package, version 8.1 (Marker Software), to cover the 5 cognitive domains: memory, attention, response speed, executive functions, and language • Type of concomitant treatment provided: none reported • Session duration: 30 to 45 minutes in experimental group • Number of treatment sessions: 36 in experimental group

Lampit 2014 (Continued)

- **Treatment frequency:** 3/week in experimental group
- **Maximum treatment duration in weeks:** 12 in experimental group

Type of control intervention: other; treatment duration of 12 weeks; intervention provided in group format, under supervision

- **Details of control intervention:** this control intervention was developed for general sensorimotor stimulation, computer use, socialisation, motivation, simple learning and memory demands, and other non-specific effects inherent to supervised CCI, and was used in a previous trial conducted by this group. Participants viewed 7 *National Geographic* videos per session on computer and answered multiple choice questions immediately after each presentation
- **Type of concomitant treatment provided:** none reported
- **Session duration:** 30 to 45 minutes in control group
- **Number of treatment sessions:** 36 in control group
- **Treatment frequency:** 3/week in control group
- **Maximum treatment duration in weeks:** 12 in control group

Outcomes

- **Cognitive functioning outcomes considered**
 - * Global cognitive functioning measured with composite score of memory, speed, and executive function at 3 and 15 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
- **Other outcome data on cognitive functioning, not considered in our meta-analyses:** none reported

*Study authors reported: "no adverse effects related to the intervention were recorded throughout the study period". As this is about attributed AEs only, we did not consider the data

Notes

Timecourse Trial. ACTRN12611000702910. The funding panel had no role in study design, data collection, data analysis, interpretation of data, writing of the report, or the decision to submit the paper for publication. There were also no systematic differences in protocol adherence in the CCI group (35.1 sessions, 97.5%) compared to the AC training group (34.7 sessions, 96.4%; $P = 0.581$)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Judgement: adequate random sequence generation</p> <p>Quote(s): "participants were randomised using a simple computer-generated randomisation sequence in a 1:1 ratio to either CCI or active control (AC) group"; from trial registration: "simple randomisation table created by a computer software"</p>
Allocation concealment (selection bias)	Low risk	<p>Judgement: allocation was done by the principal investigator, who does not seem to be involved with training or outcome assessment, and seems to be independent. Randomisation was organised centrally, and for this reason, we judged central randomisation</p> <p>Quote(s): "randomisation was conducted by the principal investigator (MV) and was concealed from the rest of the research team until the first day of training"; from trial registration: "allocation involved contacting the holder of the allocation schedule who was "off-site" or at central administration site"</p>

Lampit 2014 (Continued)

Blinding of participants (performance bias)	Low risk	<p>Judgement: an attempt was made to blind participants, as the 2 types of interventions were distinguishable, but as participants were blinded to the study hypothesis, we deem it likely that blinding was successful</p> <p>Quote(s): "participants were blinded to the study hypotheses. On-going participant blinding achieved by describing CCI as a "diversified set of cognitive exercises", and AC as comprehension and memory exercises"</p>
Blinding of personnel (performance bias)	High risk	<p>Judgement: blinding of therapists not feasible</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Judgement: outcome assessors explicitly reported to be blinded</p> <p>Quote(s): "assessors were blinded to group allocation"</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Judgement: for the outcome global cognitive functioning: 39 out of 41 (95%) randomised were analysed in experimental group, and 38 out of 39 (97%) randomised were analysed in control group. Statistical analyses were reported to be done according to the intent-to-treat principle. In the experimental group, 15/41 participants were not evaluated 12 months post training. In the control group, 10/39 patients were not evaluated 12 months post training. Although study authors reported that this was an intention-to-treat (ITT) analysis, they deemed the fraction of missing data was too large. MMRM incorporates a model for missing data values and so avoids discrete imputation or omission of cases. All analyses are therefore ITT. Twelve participants withdrew during the intervention period (8 in the CCI group, 4 in the AC group; 2-sided Chi² P = 0.347), and 10 additional participants (5 in each group) were lost to longitudinal follow-up (see Figure 1). No baseline sociodemographic or clinical differences were noted between dropouts and those who completed the intervention</p>
Selective reporting (reporting bias)	High risk	<p>Judgement: all outcomes described in the methods section are adequately addressed in the results section, but on the trial registration site, an additional primary outcome is listed that is described as post-hoc testing in the full publication. In addition, 2 instruments were dropped due to lack of feasibility</p> <p>Quote(s): "trial registration: first primary outcome (out of 2) - scores in (1) a computer-based adaptation of WAIS 4 Matrix Reasoning test; (2) Controlled Oral Word Association Test (COWAT); (3) Boston Naming Test (short versions); and (4) a computerised adaptation of the Recognition Memory Test and full text: These 4 tests were included in the more expansive post hoc Global Cognitive Score and full text: one test was initially planned but not implemented because of poor usability with our participants (Mindstreams Visual-Spatial Orientation test), and another test (Cogscreen) could not be implemented because of technical issues. These changes were documented in the trial registry"</p>
Other bias	Low risk	<p>Judgement: no other sources of bias were detected</p>

Legault 2011

Methods	<ul style="list-style-type: none"> • Design: 4-arm randomised single-blinded controlled trial with 2 × 2 factorial design • Recruitment period: 2008 to 2009 • No. of centres involved: 1 • Unit of randomisation: individuals • No. randomised: 73 • Number of arms considered in this review: 4
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Computerised cognitive training for 12 or more weeks for maintaining cognitive function in cognitively healthy people in late life (Review)

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Legault 2011 (Continued)

	<ul style="list-style-type: none"> • Maximum trial duration: 4 months • Funding by non-profit organisation: Department of Health and Human Services, National Institutes of Health (1R01AG029285 - 01A1), and the General Clinical Research Center of Wake Forest University Baptist Medical Center (M01-RR07122) • Funding by commercial organisation: none reported • Publication status: full-text report
Participants	<ul style="list-style-type: none"> • Patient flow: 18 randomised, 18 described at baseline in experimental group; 18 randomised, 18 described at baseline in control group • Number of females: 8 of 18 (44%) in experimental group 1; 7 of 18 (38%) in control group 1 • Average age (SD): 76 (5.2) years in experimental group 1; 75 (4.8) years in control group 1 • Education: experimental group 1: high school or less: 4 (22%), more than high school: 14 (78%); control group 1: high school or less: 5 (28%), more than high school: 13 (72%) • Baseline cognitive function: experimental group 1: selection criteria on cognition overall: community-dwelling persons, aged 70 to 85 years, who were at risk for cognitive decline but who did not have mild cognitive impairment • Selection criteria on cognition in experimental group: community-dwelling persons, aged 70 to 85 years, who were at risk for cognitive decline but who did not have mild cognitive impairment. Control group: community-dwelling persons, aged 70 to 85 years, who were at risk for cognitive decline but who did not have mild cognitive impairment • Ethnicity: experimental group: 17 white, 0 Indian, 0 Asian, 1 black, 0 other, 0 unclear; control group: 17 white, 0 Indian, 0 Asian, 1 black, 0 other, 0 unclear • Genetic marker: experimental group: present: 2 (17%), absent: 10 (83%); control group: present: 3 (25%), absent: 9 (75%)
Interventions	<p>Type of experimental intervention: computerised CT group; treatment duration of 17.2 weeks; intervention provided in small group format under supervision</p> <ul style="list-style-type: none"> • Details of experimental intervention: sessions were centre-based, conducted via computer, carried out with small groups of no more than 6 individuals, and monitored by skilled trainers. For each session, participants studied a list of 30 words, followed by a recognition test consisting of 30 studied words and 30 new words with each new word repeated once, and were asked to respond "yes" to study words and "no" to new items both times they occurred • Type of concomitant treatment provided: none in comparison 1; physical activity in comparison 2 • Session duration: 10 to 12 minutes in experimental group • Number of treatment sessions: 24 in experimental group • Treatment frequency: training consisted of 4 consecutive 10- to 12-minute sessions per day, administered 2 times per week for 2 months, which then tapered to 1 time per week for 2 additional months in experimental group • Maximum treatment duration in weeks: 17.2 in experimental group <p>Type of control intervention: inactive; treatment duration of 17.2 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> • Details of control intervention: Healthy Aging Education control intervention consisted of weekly lectures based on health education and was based on a programme developed originally at Stanford and adapted for the Lifestyle interventions and Independence for Elders pilot trial. Topics such as medications, foot care, travelling, and nutrition were covered • Type of concomitant treatment provided: none in comparison 1; physical activity in comparison 2 • Session duration: not reported in control group • Number of treatment sessions: not reported in control group • Treatment frequency: 1/week in control group • Maximum treatment duration in weeks: 17.2 in control group

Legault 2011 (Continued)

Outcomes

- **Cognitive functioning outcomes considered for both comparisons**
 - * Episodic memory measured with Logical Memory task from the Wechsler Memory Scale-III (LM2), Recall Total Score at 4 months, on a scale from 0 to not reported with higher values indicating benefit
 - * Executive functioning measured with Trails B Time-Trails A Time at 4 months, on a scale from 0 to not reported with lower 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
- **Other outcome data on cognitive functioning, not considered in our meta-analyses**
 - * Episodic memory measured with Logical Memory task from the Wechsler Memory Scale-III (LM1) - Supplemental Score, 1st Recall at 4 months, on a scale from 0 to not reported with higher values indicating benefit
 - * Episodic memory measured with Hopkins Verbal Learning Test (HVLT), immediate recall at 4 months, on a scale from 0 to not reported with higher values indicating benefit
 - * Episodic memory measured with Hopkins Verbal Learning Test (HVLT), delayed recall at 4 months, on a scale from 0 to not reported with higher values indicating benefit
 - * Executive functioning measured with Flanker Task, Incongruent-Congruent RTs at 4 months, on a scale from 0 to not reported with higher values indicating benefit
 - * Executive functioning measured with Task Switching, Switch-Non-switch RTs at 4 months, on a scale from 0 to not reported with higher values indicating benefit
 - * Executive functioning measured with Self-Ordered Pointing Task, % correct at 4 months, on a scale from 0 to not reported with higher values indicating benefit
 - * Executive functioning measured with 1-Back, % Hits-False Alarms at 4 months, on a scale from 0 to not reported with higher values indicating benefit
 - * Executive functioning measured with 2-Back, % Hits-False Alarms at 4 months, on a scale from 0 to not reported with higher values indicating benefit

Notes

As we pooled outcome data from the 2 comparisons within the trial, before pooling across trials, 50% of participants in the pooled experimental group and 50% in the pooled control group received standardised physical activity. Pooling was justified, as no interaction effect of physical activity was observed. Study authors stated: "Depending on the choice of outcome, two-armed full-scale trials may require fewer than 1000 participants (continuous outcome) or 2000 participants (categorical outcome)". One SAE occurred, but the trial authors did not report in which trial arm

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): "following this, they were randomly assigned with equal probability among the four experimental conditions"
Allocation concealment (selection bias)	Unclear risk	Judgement: method of allocation concealment not reported Quote(s): "following this, they were randomly assigned with equal probability among the four experimental conditions"
Blinding of participants (performance bias)	High risk	Judgement: blinding not feasible
Blinding of personnel (performance bias)	High risk	Judgement: blinding not feasible

Legault 2011 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Judgement: study described as "single-blinded", and at clinicaltrials.gov, it is explicitly described that outcome assessors were blinded</p> <p>Quote(s): "clinicaltrials.gov - Masking: Single Blind (Outcomes Assessor)"</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Judgement: for the outcome executive functioning: statistical analyses were reported to be done according to the intent-to-treat principle. Study authors described the analysis as being done according to the ITT principle, but we wonder if they referred only to the principle that the participant was analysed in the group to which he/she was randomised, regardless of cross-over. We are unsure if the 2 participants with missing data in the experimental group and the 1 in the control group were included in the analyses. We treated them as not analysed in our meta-analyses, in accordance with how the trial authors depicted their data in the tables</p>
Selective reporting (reporting bias)	High risk	<p>Judgement: all outcomes indicated in the methods section are adequately addressed in the results section, but at least 2 instruments (perceived cognitive functioning problems and quality of life) mentioned in NCT00688155 are not mentioned in the full publication</p>
Other bias	High risk	<p>Judgement: comparison 1: no other potential sources of bias detected; comparison 2: attendance rate in the combined CCI and physical activity group was statistically significantly better than in the physical activity only control group. The direction of bias would likely inflate CCI effects; we thus judged high risk of bias for comparison 2.</p> <p>Quote(s): "intervention attendance rates were higher in the CT and PACT groups: CT: 96%, PA: 76%, PACT: 90% (P = 0.004)"</p>

Leung 2015

Methods	<ul style="list-style-type: none"> • Design: 2-arm RCT with parallel-group design • Recruitment period: not reported • No. of centres involved: 1 • Unit of randomisation: individuals • No. randomised: not reported • Number of arms considered in this review: 2 • Maximum trial duration: 3 months • Funding by non-profit organisation: this work was supported by Health and Health Services Research Fund (No. 09100911) • Funding by commercial organisation: none reported • Publication status: full-text report
Participants	<ul style="list-style-type: none"> • Patient flow: unclear number randomised; 109 described at baseline in experimental group; 100 described at baseline in control group • Number of females: 87 of 109 (80%) in experimental group 1; 77 of 100 (77%) in control group 1 • Average age (SD): 70 (6.2) years in experimental group 1; 70 (6.6) years in control group 1 • Average (SD) education: 8.71 (3.84) years in experimental group; 9.49 (4.44) years in control group • Baseline cognitive function: selection criteria on cognition in experimental group: right-handed community-dwelling Chinese older adults at risk of cognitive decline, as indicated by their Montreal Cognitive Assessment (MoCA) scores falling into the range of 19 to 26. MoCA, Hong Kong version, mean total score 23.6 (SD 1.88). Selection criteria on cognition in control group: right-handed community-dwelling Chinese older adults at risk of cognitive decline, as indicated by their MoCA scores falling into the range of 19 to 26. MoCA, Hong Kong version, mean total score 23.8 (SD 1.97)

Leung 2015 (Continued)

	<ul style="list-style-type: none"> • Ethnicity: experimental group: white, Indian 109; Asian, Black, other unclear. Control group: white, Indian 100; Asian, Black, other unclear • APOE: number of participants positive for APOE not reported
Interventions	<p>Type of experimental intervention: computerised CT group; treatment duration 13 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> • Details of experimental intervention: for both CT and AC groups, each participant was assigned a laptop, a headset, and a mouse, all of which were used for performing cognitive exercises. They used the same laptop for their entire training • Type of concomitant treatment provided: none reported • Session duration: 60 minutes in experimental group • Number of treatment sessions: 39 in experimental group • Treatment frequency: 3/week in experimental group • Maximum treatment duration in weeks: 13 in experimental group <p>Type of control intervention: other; treatment duration 13 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> • Details of control intervention: participants in active control group ".were shown educational programs covering diverse topics (e.g., history, science, health information, and local social issues) on a group basis. Immediately after watching the video, they were instructed to answer several questions that were related to the video content" • Type of concomitant treatment provided: none reported • Session duration: 60 minutes in control group • Number of treatment sessions: 39 in control group • Treatment frequency: 3/week in control group • Maximum treatment duration in weeks: 13 in control group
Outcomes	<ul style="list-style-type: none"> • Cognitive functioning outcomes considered <ul style="list-style-type: none"> * Episodic memory measured with WMS-III Logical Memory Delayed recall at 3.25 months, on a scale from not reported to not reported with higher values indicating benefit* * Working memory measured with Digit Span, total at 3.25 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 • Other outcome data on cognitive functioning, not considered in our meta-analyses <ul style="list-style-type: none"> * Episodic memory measured with WMS-III Logical Memory Immediate recall at 3.25 months, on a scale from not reported to not reported with higher values indicating benefit* * Episodic memory measured with WMS-III Family Pictures Delayed recall at 3.25 months, on a scale from not reported to not reported with higher values indicating benefit * Episodic memory measured with WMS-III Family Pictures Immediate recall at 3.25 months, on a scale from not reported to not reported with higher values indicating benefit * Working memory measured with Digit Vigilance Test at 3.25 months, on a scale from not reported to not reported with higher values indicating benefit * Working memory measured with Visual Spatial Span, total at 3.25 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

Leung 2015 (Continued)

Random sequence generation (selection bias)	Low risk	<p>Judgement: adequate random sequence generation</p> <p>Quote(s): "the 209 participants were randomly assigned to the CT and AC groups by an experimenter blind to the cognitive status of the participants using computer-generated random sequences of numbers"</p>
Allocation concealment (selection bias)	Unclear risk	<p>Judgement: the method of concealment is unclear as it is not understandable why participants had to be "rearranged", and we suspect that participants were not allocated consecutively, while it remains unclear if allocation of a participant could be foreseen by the researcher</p> <p>Quote(s): "specifically, each participant ID was paired with a random number, and the order of the participants was rearranged based on the value of the assigned number (from smallest to largest)"</p>
Blinding of participants (performance bias)	High risk	<p>Judgement: patients were not blinded to treatment</p>
Blinding of personnel (performance bias)	High risk	<p>Judgement: research assistants could not be blinded, and they both supervised training and performed post-training assessments</p> <p>Quote(s): "a research assistant was present in each training session to keep track of their attendance and address any questions pertaining to the task instruction raised by the participants. These research assistants were also responsible for conducting the post-training assessments"</p>
Blinding of outcome assessment (detection bias) All outcomes	High risk	<p>Judgement: therapists, who could not be blinded, supervised training and perform post-training assessments</p> <p>Quote(s): "a research assistant was present in each training session to keep track of their attendance and address any questions pertaining to the task instruction raised by the participants. These research assistants were also responsible for conducting the post-training assessments"</p>
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>Judgement: reporting is inconclusive. Although according to the flow diagram it seems that 109 were randomised to experimental and 100 to control, we wonder if this merely reflects the number randomised who completed the follow-up assessment. There is no mention of intent-to-treat analyses, missing data, dropouts, or withdrawals, so that we judged risk as unclear</p> <p>Quote(s): "our final sample consisted of 209 older adults (...) who successfully completed the pre- and post-training assessment, of which 109 older adults were randomly assigned to the CT group (...) and 100 older adults were in the AC group".</p>
Selective reporting (reporting bias)	Low risk	<p>Judgement: all outcomes described in the methods section are adequately addressed in the results section</p>
Other bias	Unclear risk	<p>Judgement: the selection process is not clear because study authors do not indicate the number of participants actually screened, those excluded, and reasons for exclusion. It is not clear whether inclusion was consecutive, and study authors mention that baseline characteristics were "matched". With the latter, we assume they meant "comparable"</p> <p>Quote(s): "participants from the CT and AC groups were matched for their demographic characteristics"</p>

Peretz 2011

Methods	<ul style="list-style-type: none"> • Design: 2-arm RCT with factorial design • Recruitment period: not reported • No. of centres involved: 1 • Unit of randomisation: individuals • No. randomised: 155 • Number of arms considered in this review: 2 • Maximum trial duration: 3 months • Funding by non-profit organisation: none reported • Funding by commercial organisation: NexSig Cognifit • Publication status: full-text report
Participants	<ul style="list-style-type: none"> • Patient flow: 84 randomised, 84 described at baseline in experimental group; 71 randomized, 71 described at baseline in control group • Number of females: 56 of 84 (67%) in experimental group 1; 40 of 71 (56%) in control group 1 • Average age (SD): 68 (8.3) years in experimental group 1; 67 (7.2) years in control group 1 • Average (SD) education: 14.6 (2.8) years in experimental group; 15.1 (3.6) years in control group • Baseline cognitive function: MMSE 29.0 (SD 1.2) • Selection criteria on cognition overall: healthy • Ethnicity: not reported • APOE: number of participants positive for APOE not reported
Interventions	<p>Type of experimental intervention: computerised CT, individualised; treatment duration of 12 weeks; intervention provided as individual training, without supervision</p> <ul style="list-style-type: none"> • Details of experimental intervention: the personalised cognitive training programme selected for this study was the CogniFit Personal Coach. This programme's training regimen is based on the results of a baseline cognitive evaluation called the Neuropsychological Examination–CogniFit Personal Coach • Session duration: 20 to 30 minutes in experimental group • Number of treatment sessions: 36 in experimental group • Treatment frequency: 3/week in experimental group • Maximum treatment duration in weeks: 12 in experimental group <p>Type of control intervention: active computer; treatment duration of 12 weeks; intervention provided as individual training, without supervision</p> <ul style="list-style-type: none"> • Details of control intervention: "twelve classic computer games that significantly engage cognitive processing were selected to create the computer games program. This program shared several features with the personalized cognitive training program, including the baseline cognitive evaluation, a total of 24 sessions comprising 3 different tasks, and a similar graphic design (Appendix 2). However, it did not have the adaptive training features of the personalized cognitive training program" • Session duration: 25 minutes in control group • Number of treatment sessions: 36 in control group • Treatment frequency: 3/week in control group • Maximum treatment duration in weeks: 12 in control group
Outcomes	<ul style="list-style-type: none"> • Cognitive functioning outcomes considered <ul style="list-style-type: none"> * Global cognitive functioning measured with Overall score: NexAde battery at 3 months, on a scale from not reported to not reported with higher values indicating benefit * Episodic memory measured with Memory recall at 3 months, on a scale from not reported to not reported with higher values indicating benefit * Executive functioning measured with Executive functions at 3 months, on a scale from not reported to not reported with higher values indicating benefit * Working memory measured with Visuospatial working memory at 3 months, on a scale from not reported to not reported with higher values indicating benefit

Peretz 2011 (Continued)

- **Physical functioning outcome considered:** none reported
- **Quality of life outcome considered:** none reported
- **Safety outcome considered:** none reported
- **Depression outcome considered:** none reported
- **Other outcome data on cognitive functioning, not considered in our meta-analyses**
 - * Episodic memory measured with Memory recognition at 3 months, on a scale from not reported to not reported with higher values indicating benefit
 - * Episodic memory measured with Visuospatial learning at 3 months, on a scale from not reported to not reported with higher values indicating benefit
 - * Executive functioning measured with Focused attention at 3 months, on a scale from not reported to not reported with higher values indicating benefit
 - * Executive functioning measured with Mental flexibility at 3 months, on a scale from not reported to not reported with higher values indicating benefit
 - * Working memory measured with Sustained attention at 3 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)	Low risk	Judgement: adequate random sequence generation Quote(s): "random number generator"
Allocation concealment (selection bias)	Low risk	Judgement: adequate method of allocation concealment Quote(s): "encrypted codes"
Blinding of participants (performance bias)	High risk	Judgement: a large number of participants correctly identified their group assignment; this is assumed to be an indication of poor blinding of participants Quote(s): "..with investigators and participants being blind to group assignment. Participants received a CD containing either the cognitive training program or the computer games program. To preserve blindness, all CDs were labelled and packaged identically, and all graphics, fonts, opening screens, baseline evaluations and post-training evaluations were identical on both CDs. Personnel were kept unaware of the participants' group assignment, which was encrypted in the code number labels on the CDs"; ""Thirty-six percent of the subjects correctly identified their group assignment (21% personalized cognitive training, 15% games)"
Blinding of personnel (performance bias)	Low risk	Judgement: adequate method of therapist blinding Quote(s): "..with investigators and participants being blind to group assignment. Participants received a CD containing either the cognitive training program or the computer games program. To preserve blindness, all CDs were labelled and packaged identically, and all graphics, fonts, opening screens, baseline evaluations and post-training evaluations were identical on both CDs. Personnel were kept unaware of the participants' group assignment, which was encrypted in the code number labels on the CDs"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement: not clearly reported if outcome assessors were blinded, but all personnel were likely kept blinded to treatment assignment Quote(s): "personnel were kept unaware of the participants' group assignment, which was encrypted in the code number labels on the CDs"

Peretz 2011 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Judgement: for the outcome episodic memory, 66 out of 84 (79%) randomised were analysed in experimental group, and 55 out of 71 (77%) randomised were analysed in control group. Statistical analyses were reported to be done according to the intent-to-treat principle. Although study authors state that they used an ITT, 18 participants in experimental group and 16 in control group did not complete the training and had no data available at baseline, follow-up, or both</p> <p>Quote(s): "a total of 34 (22%) participants (18 in the cognitive training group and 16 in the computer games group) did not complete the training; the majority of those (n = 29) never began the home training"</p>
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 apparent risks of bias

Shatil 2013

Methods	<ul style="list-style-type: none"> • Design: 4-arm RCT with parallel-group design • Recruitment period: not reported • No. of centres involved: 1 • Unit of randomisation: individuals • No. randomised: 180 • Number of arms considered in this review: 4 • Maximum trial duration: 4 months • Funding by non-profit organisation: Beckman Insititute • Funding by commercial organisation: none reported • Publication status: full-text report
Participants	<ul style="list-style-type: none"> • Patient flow: 45 randomised, 33 described at baseline in experimental group 1; 48 randomised, 29 described at baseline in experimental group 2; 45 randomised, 31 described at baseline in experimental group 3; 42 randomised, 29 described at baseline in control group • Number of females: 23 of 33 (70%) in experimental group 1; 20 of 29 (69%) in experimental group 2; 22 of 31 (71%) in experimental group 3; 19 of 29 (66%) in control group 1 • Average age (SD): 80 (5.4) years in experimental group 1; 79 (5.5) years in experimental group 2; 79 (5.8) years in experimental group 3; 81 (5.3) years in control group 1 • Average (SD) education: experimental group 1: some college and above: 26 (78,8%); experimental group 2: some college and above: 17 (58,6%); experimental group 3: some college and above: 28 (90,3%); control group 1: some college and above: 23 (79,3%) • Baseline cognitive function: MMSE > 24 • Selection criteria on cognition overall: healthy • Ethnicity: not reported • APOE: number of participants positive for APOE not reported
Interventions	<p>Type of experimental intervention 1: computerised CT group; treatment duration of 16 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> • Details of experimental intervention: Cognifit • Session duration: 40 minutes in experimental group • Number of treatment sessions: 48 in experimental group • Treatment frequency: 3/week in experimental group • Maximum treatment duration in weeks: 16 in experimental group

Shatil 2013 (Continued)

Type of experimental intervention 2: mixed

- **Details of experimental intervention 2:** cognitive training as for experimental arm 1 in combination with group-based supervised physical training, which consisted of 3 weekly 45-minute sessions, with at least a 1-day interval between training days, during 16 weeks
- **Session duration:** 40 minutes in experimental group 2
- **Number of treatment sessions:** 48 in experimental group 2
- **Treatment frequency:** 3/week in experimental group 2
- **Maximum treatment duration in weeks:** 16 in experimental group 2

Type of control intervention 1: other; treatment duration of 16 weeks; intervention provided in group format, under supervision

- **Details of control intervention:** this group was assigned selected book excerpts to be read at home and held one 60-minute weekly meeting during which the best ways to achieve the goals advocated in the book were discussed. This group was classified as an active control group because it was compared with the Cognifit group
- **Session duration:** 60 minutes in control group
- **Number of treatment sessions:** 16 in control group
- **Treatment frequency:** 1/week in control group
- **Maximum treatment duration:** 16 in control group

Type of control intervention 2: other; intervention provided in group format, under supervision

- **Details of control intervention 2:** group-based supervised physical training. This group was classified as an inactive control group because it was compared with the mixed experimental intervention
- **Session duration:** 45 minutes in control group 2
- **Number of treatment sessions:** 48 in control group 2
- **Treatment frequency:** 3/week in control group 2
- **Maximum treatment duration in weeks:** 16 in control group 2

Outcomes

- **Cognitive functioning outcomes considered for both comparisons**
 - * Speed of processing measured with SVP at 4 months, on a scale from not reported to not reported with higher values indicating benefit
 - * Working memory measured with AM Cognifit at 4 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
- **Other outcome data on cognitive functioning, not considered in our meta-analyses**
 - Cognifit subtests

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): "following the screening subjects were randomized to the four intervention groups"
Allocation concealment (selection bias)	Unclear risk	Judgement: method of allocation concealment not reported

Shatil 2013 (Continued)

		Quote(s): "following the screening subjects were randomized to the four intervention groups"
Blinding of participants (performance bias)	Unclear risk	Judgement: no information reported
Blinding of personnel (performance bias)	Unclear risk	Judgement: no information reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Judgement: blinding of outcome assessment not reported Quote(s): "to measure change in cognitive function following the interventions, we used the CogniFit neuropsychological evaluation"
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement: 62 out of 93 (67%) randomised were analysed in experimental group, and 60 out of 87 (69%) randomised were analysed in control group Quotes: "55 participants (30.5%) left during the baseline testing period, while another battery of tests (to be reported elsewhere) were being administered; before the training interventions."; "three participants, two in the Cognitive Training Group and one in the Physical Activity Group, left the study, due to health problems. Thus, altogether, 58 subjects (32.2% among the 180 enlisted study participants) withdrew from the study and 122 adhered to it"
Selective reporting (reporting bias)	Low risk	Judgement: all outcomes indicated in the methods section are reported in the results section
Other bias	High risk	Judgement: potential high risk of bias because the main author (Shatil) is an employee of the CogniFit Company

van het Reve 2014

Methods	<ul style="list-style-type: none"> • Design: international multi-centre 2-arm RCT with parallel-group design • Recruitment period: 2011 to 2013 • No. of centres involved: 14 • Unit of randomisation: individuals • No. randomised: 182 • Number of arms considered in this review: 2 • Maximum trial duration: 3 months • Funding by non-profit organisation: none reported • Funding by commercial organisation: none reported • Publication status: full-text report
Participants	<ul style="list-style-type: none"> • Patient flow: 84 randomised, 69 described at baseline in experimental group; 98 randomised, 76 described at baseline in control group • Number of females: 49 of 69 (71%) in experimental group 1; 52 of 76 (68%) in control group 1 • Average age (SD): 81 (8.3) years in experimental group 1; 82 (6.3) years in control group • Education: experimental group 1: university/college 7 (10), vocational education 41 (59), no educated profession 21 (30), in a sitting position past profession 18 (26); control 1: university/college 4 (5), vocational education 52 (68), no educated profession 20 (26), in a sitting position past profession 15 (20) • Baseline cognitive function: selection criteria on cognition overall: healthy • Selection criteria on cognition: experimental group: MMSE score (mean ± SD): 27.6 ± 2.6; control group: MMSE score (mean ± SD): 27.7 ± 2.9 • Ethnicity: not reported

van het Reve 2014 (Continued)

- **APOE:** number of participants positive for APOE not reported*

Interventions	<p>Type of experimental intervention: computerised CT group; treatment duration of 12 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> • Details of experimental intervention: cognitive training, with the CogniPlus training programme • Type of concomitant treatment provided: strength-balance training • Session duration: 10 minutes in experimental group • Number of treatment sessions: 36 in experimental group • Treatment frequency: 3/week in experimental group • Maximum treatment duration in weeks: 12 in experimental group <p>Type of control intervention: other; treatment duration of 12 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> • Details of control intervention: exercise programme consisted of twice-weekly 30-minute progressive resistance training on age-adapted machines and 10-minute balance training during 12 weeks • Type of concomitant treatment provided: strength-balance training • Session duration: 40 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	<ul style="list-style-type: none"> • Cognitive functioning outcomes considered <ul style="list-style-type: none"> * Executive functioning measured with TMT-B at 3 months, on a scale from not reported to not reported with lower values indicating benefit * Speed of processing measured with TMT-A at 3 months, on a scale from not reported to not reported with lower 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 	
Notes	<p>Due to strength-balance training, which was given to both groups, we included the study in the inactive control comparison</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Judgement: adequate random sequence generation</p> <p>Quote(s): "to ensure allocation concealment, participants in each home were enrolled by the health care staff, and randomized by the person assessing the outcome measures using simple (unrestricted) randomisation.. based on a table of random numbers"</p>
Allocation concealment (selection bias)	Unclear risk	<p>Judgement: unclear allocation concealment</p> <p>Quote(s): "the assessor generated an unpredictable allocation sequence, which was concealed until assignment occurred. Each participant in every home received a two digit number (01, 02, 03, ...) resulting in a rank order of the participants. With the help of the random numbers table the assessor decided a priori to pick a number from the table with a pencil and go through the table either from bottom-right to upper-left in a diagonal way, horizontally from left-to-right or right-to-left, etc"</p>

van het Reve 2014 (Continued)

Blinding of participants (performance bias)	Unclear risk	<p>Judgement: patient blinding was not reported, but it is unlikely</p> <p>Quote(s): "blinding of the investigator was not possible because the investigator conducted part of the assessments"</p>
Blinding of personnel (performance bias)	High risk	<p>Judgement: investigators were not blinded</p> <p>Quote(s): "blinding of the investigator was not possible because the investigator conducted part of the assessments"</p>
Blinding of outcome assessment (detection bias) All outcomes	High risk	<p>Judgement: outcome assessment was not blinded</p> <p>Quote(s): "blinding of the investigator was not possible because the investigator conducted part of the assessments"</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Judgement: 69 out of 84 (82%) randomised were analysed in the experimental group, and 76 out of 98 (78%) randomised were analysed in the control group, although statistical analyses were reported to be done according to the intent-to-treat principle. In addition, 4 participants were re-assigned by investigators to the control group despite being initially randomised to the intervention group</p> <p>Quote(s): "a total of 156 participants completed the intervention (137 subjects living in the homes-for-the-aged and 19 subjects living in the vicinity) resulting in 14.3% attrition"; "Four participants that were not able to conduct the cognitive training due to vision problems were manually allocated to the SB group after randomization. Thus, we reported 98 participants in SB and 84 participants in SBC after this adaptation"</p>
Selective reporting (reporting bias)	Low risk	<p>Judgement: all outcomes indicated in the methods section are reported in the results section</p>
Other bias	Low risk	<p>Judgement: no other sources of bias detected</p> <p>Quote(s): none</p>

AC: active control.
 AE: adverse event.
 APOE: apolipoprotein E.
 AR: aerobics and resistance.
 BDT-DT: The Baddeley Dual Task
 CCI: computerised cognitive intervention.
 COWAT: Controlled Oral Word Association Test.
 CT: computed tomography.
 CWIT: Color-Word Interference Test.
 DT: dual task.
 FCSRT: Free and Cued Selective Reminding Test.
 GDS-Sf: short-form Geriatric Depression Scale.
 HVLT: Hopkins Verbal Learning Test.
 ITT: intention-to-treat.
 MMRM: mixed model for repeated measures.
 MMSE: Mini Mental State Examination.
 MoCA: Montreal Cognitive Assessment.
 RBMT: Rivermead Behavioural Memory Test.
 RCT: randomised controlled trial.
 RT: Reaction time.
 SAE: serious adverse event.
 SD: standard deviation.
 ST: stretching and toning.
 SVP: speed of visual information processing.

TMT: Trail Making Test.

WMS-III: Wechsler Memory Scale, Third Edition.

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
Ann 2012	Wrong patient population
Anon 2007	Nature of intervention unclear
Anon 2007a	Nature of intervention unclear
Apostolo 2014	Wrong patient population
Baglio 2011	Nature of intervention unclear
Ball 2002	Intervention shorter than 12 weeks
Ball 2002a	Duplicate
Ball 2006	Intervention shorter than 12 weeks
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
Banique 2014	Adult population
Banique 2015	Younger than 30 years of age
Barban 2012	Duplicate
Barban 2016	Wrong study design: cross-over trial that reported outcome data only at the end of trial, after cross-over had taken place
Barbosa 2015	Wrong intervention
Barcelos 2015	Wrong intervention

Study	Reason for exclusion
Barnes 2006	Intervention shorter than 12 weeks
Barnes 2009	Duplicate
Barnes 2013	Wrong patient population
Basak 2016	Intervention shorter than 12 weeks
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
Bier 2015	Wrong study design
Binder 2016	Intervention shorter than 12 weeks
Bittner 2013	Wrong study design
Borella 2010	Intervention shorter than 12 weeks
Borella 2013	Wrong intervention
Borella 2014	Duplicate
Borella 2017	Wrong intervention
Boripuntakul 2012	Wrong intervention
Borness 2013	Wrong patient population
Bottiroli 2009	Duplicate
Bottiroli 2009a	Intervention shorter than 12 weeks
Bozoki 2013	Intervention shorter than 12 weeks
Brehmer 2012	Intervention shorter than 12 weeks
Brum 2013	Duplicate
Buitenweg 2017	Wrong intervention
Buiza 2008	Wrong intervention
Bureš 2016	Intervention shorter than 12 weeks
Buschert 2011	Wrong intervention

Study	Reason for exclusion
Buschert 2011a	Duplicate
Buschert 2012	Wrong intervention
Buschert 2012a	Duplicate
Buschkuehl 2008	Wrong design. Not an RCT. Quote: "pseudorandomly assigned to either the experimental or the control group. Both groups were matched as closely as possible according to gender, age, body weight, and selected physical performance measures"
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
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

Study	Reason for exclusion
Dannhauser 2014	Wrong study design
de Almondes 2017	Intervention shorter than 12 weeks
de Macedo 2015	Wrong outcomes
De Vreesse 1996	Wrong intervention
Diamond 2015	Intervention shorter than 12 weeks
Dittmann-Kohli 1991	Wrong intervention
Djabelkhir 2017	Wrong patient population
Duncan 2009	Wrong intervention
Dwolatzky 2005	Intervention shorter than 12 weeks
Eckroth-Bucher 2009	Wrong patient population
Edwards 2005	Intervention shorter than 12 weeks
Edwards 2011	Intervention shorter than 12 weeks
Edwards 2015	Intervention shorter than 12 weeks
Edwards 2015a	Intervention shorter than 12 weeks
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
Fiatarone Singh 2014	Wrong patient population
Finn 2011	Intervention shorter than 12 weeks
Finn 2015	Intervention shorter than 12 weeks
Finn 2015a	Duplicate
Flak 2013	Intervention shorter than 12 weeks
Flak 2014	Intervention shorter than 12 weeks

Study	Reason for exclusion
Flak 2014a	Intervention shorter than 12 weeks
Flak 2016	Intervention shorter than 12 weeks
Foerster 2009	No outcome given
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
Gaitan 2013	Wrong patient population
Gajewski 2012	Intervention shorter than 12 weeks
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
Gooding 2016	Wrong patient population
Haesner 2015	Wrong study design
Haesner 2015a	Intervention shorter than 12 weeks
Haimov 2013	Intervention shorter than 12 weeks
Haimov 2013a	Intervention shorter than 12 weeks
Haimov 2013b	Intervention shorter than 12 weeks
Haimov 2013c	Duplicate
Haimov 2013d	Intervention shorter than 12 weeks
Haimov 2014	Intervention shorter than 12 weeks

Study	Reason for exclusion
Haimov 2014a	Intervention shorter than 12 weeks
Hardy 2015	Intervention shorter than 12 weeks
Hausmann 2012	Wrong intervention
Hayashi 2012	Wrong intervention
Hayslip B Jr 2016	Intervention shorter than 12 weeks
Heinzel 2014	Intervention shorter than 12 weeks
Herrera 2012	Wrong patient population
Hudak 2013	Intervention shorter than 12 weeks
Hughes 2014	Wrong population: participants with mild cognitive impairment
Hötting 2013	Intervention shorter than 12 weeks
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
Jeong 2016	Wrong intervention
Jobe 2001	Intervention shorter than 12 weeks
Jones 2013	Intervention shorter than 12 weeks
Kampanaros 2010	Wrong intervention
Kholin 2010	Intervention shorter than 12 weeks
Kim 2012	Wrong outcomes
Kim 2013	Intervention shorter than 12 weeks
Kim 2013a	Wrong outcomes
Kim 2015	Intervention shorter than 12 weeks
Kim 2015a	Intervention shorter than 12 weeks
Kim 2015b	Duplicate

Study	Reason for exclusion
Kivipelto 2014	Wrong intervention
Klusmann 2009	Duplicate
Klusmann 2010a	Duplicate
Klusmann 2011	Younger than 30 years of age
Kudelka 2014	Intervention shorter than 12 weeks
Kwak 2015	Nature of intervention unclear
Kwak 2017	Nature of intervention unclear
Kwok 2013	Intervention shorter than 12 weeks
Kwok 2013a	Wrong patient population
Lampit 2013	Wrong study design
Lavretsky 2016	Nature of intervention unclear
Law 2014	Intervention shorter than 12 weeks
Law 2014a	Duplicate
Lee 2013	Intervention shorter than 12 weeks
Lee 2013a	Intervention shorter than 12 weeks
Lee 2013b	Intervention shorter than 12 weeks
Lee 2014	Intervention shorter than 12 weeks
Lee 2015	Intervention shorter than 12 weeks
León 2015	Wrong comparator
Li 2010	Intervention shorter than 12 weeks
Linde 2014	Nature of intervention unclear
Mace 2015	Intervention shorter than 12 weeks
Mahncke 2006	Intervention shorter than 12 weeks
Maillot 2012	Wrong intervention. RCT meeting all inclusion criteria but those for the intervention: exergames, which we considered to be a combined intervention of physical exercise and computerised cognitive training; persons in the control group received no intervention
Man 2012	Wrong comparator
Mann 2012	Wrong patient population
Margrett 2006	Wrong patient population

Study	Reason for exclusion
Mayas 2014	Intervention shorter than 12 weeks
McAvinue 2013	Intervention shorter than 12 weeks
McDaniel 2014	Intervention shorter than 12 weeks
McDougall 2012	Intervention shorter than 12 weeks
Middleton 2012	Wrong intervention
Miller 2013	Intervention shorter than 12 weeks
Mohs 1998	Wrong intervention
Mombelli 2012	No outcome given
Moon 2013	Intervention shorter than 12 weeks
Mowszowski 2014	Intervention shorter than 12 weeks
Mowszowski 2014a	Duplicate
Mozolic 2010	Intervention shorter than 12 weeks
Mozolic 2011	Intervention shorter than 12 weeks
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
NCT02417558 2015	Nature of intervention unclear
NCT02462135 2014	No outcome given
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

Study	Reason for exclusion
Ngandu 2015	Wrong intervention
Ngandu 2015a	Wrong intervention
Nishiguchi 2015	Wrong intervention
Nouchi 2012	Intervention shorter than 12 weeks
Nouchi 2013	Intervention shorter than 12 weeks
Nozawa 2015	Intervention shorter than 12 weeks
O'Caoimh 2015	Intervention shorter than 12 weeks
Oei 2013	Intervention shorter than 12 weeks
Oliveira 2013	Intervention shorter than 12 weeks
Optale 2010	Wrong patient population
Otsuka 2015	Wrong study design
Park 2009	Nature of intervention unclear
Park 2014	Intervention shorter than 12 weeks
Payne 2012	Wrong intervention
Payne 2017	Intervention shorter than 12 weeks
Rahe 2015	Intervention shorter than 12 weeks
Rahe 2015a	Intervention shorter than 12 weeks
Rebok 2013	Intervention shorter than 12 weeks
Rebok 2014	Intervention shorter than 12 weeks
Redick 2013	Younger than 30 years of age
Requena 2016	Wrong intervention
Rizkalla 2015	Intervention shorter than 12 weeks
Rojas 2013	Wrong intervention
Rose 2015	Intervention shorter than 12 weeks
Rosen 2011	Intervention shorter than 12 weeks
Rozzini 2007	Wrong patient population
Ryu 2013	Wrong study design
Sakka 2015	Wrong study design

Study	Reason for exclusion
Santos 2011	Wrong comparator
Schoene 2015	Duplicate
Schoene 2015a	Duplicate
Schumacher 2013	Intervention shorter than 12 weeks
Shah 2012	Wrong patient population
Shatil 2014	Intervention shorter than 12 weeks
Shatil 2014a	Duplicate
Sisco 2013	Intervention shorter than 12 weeks
Slegers 2009	Wrong intervention
Smith 2009	Intervention shorter than 12 weeks
Smith-Ray 2014	Intervention shorter than 12 weeks
Smith-Ray 2015	Intervention shorter than 12 weeks
Smith-Ray 2015a	Duplicate
Solomon 2014	Wrong comparator
Song 2009	Wrong intervention
Stepankova 2014	Intervention shorter than 12 weeks
Stine-Morrow 2014	Intervention shorter than 12 weeks
Strenziok 2013	Duplicate
Strenziok 2014	Intervention shorter than 12 weeks
Sturz 2011	Wrong patient population
Sturz 2011a	Nature of intervention unclear
Sturz 2015	Duplicate
Styliadis 2015	Intervention shorter than 12 weeks
Styliadis 2015a	Duplicate
Suo 2012	Wrong outcomes
Szelag 2012	Intervention shorter than 12 weeks
Talib 2008	Intervention shorter than 12 weeks
Tappen 2014	Wrong intervention

Study	Reason for exclusion
Tennstedt 2013	Study protocol
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
van der Ploeg 2016	Wrong study design
Vance 2007	Intervention shorter than 12 weeks
Vidovich 2009	Intervention shorter than 12 weeks
Vidovich 2015	Intervention shorter than 12 weeks
Vidovich 2015a	Duplicate
von Bastian 2013	Intervention shorter than 12 weeks
Wadley 2007	Wrong study design
Walton 2015	Intervention shorter than 12 weeks
Wang 2013	Wrong intervention
Weicker 2013	Intervention shorter than 12 weeks
Wild-Wall 2012	Wrong outcomes
Williams 2014	Intervention shorter than 12 weeks
Willis 1986	Intervention shorter than 12 weeks
Willis 2006	Intervention shorter than 12 weeks
Willis 2006a	Duplicate
Willis 2007	Duplicate
Willis 2013	Intervention shorter than 12 weeks
Wojtynska 2011	Intervention shorter than 12 weeks
Wolinsky 2006	Intervention shorter than 12 weeks
Wolinsky 2006a	Intervention shorter than 12 weeks
Wolinsky 2010	Intervention shorter than 12 weeks
Wolinsky 2010a	Intervention shorter than 12 weeks

Study	Reason for exclusion
Wolinsky 2013	Intervention shorter than 12 weeks
Wolinsky 2015	Intervention shorter than 12 weeks
Yam 2014	Wrong intervention
Yassuda 2015	Intervention shorter than 12 weeks
Yip 2012	Intervention shorter than 12 weeks
Yoonmi 2012	Intervention shorter than 12 weeks
Youn 2011	Intervention shorter than 12 weeks
Zelinski 2011	Wrong study design
Zelinski 2011a	Intervention shorter than 12 weeks
Zhuang 2013	Wrong patient population
Zimmermann 2014	Intervention shorter than 12 weeks

Characteristics of studies awaiting assessment [ordered by study ID]

Boot 2013

Methods	<ul style="list-style-type: none"> • Country: USA • Design: 3-arm randomised controlled pilot trial with parallel-group design • Recruitment period: not reported • No. of centres involved: 1 • Unit of randomisation: individuals • No. randomised: 62 • Number of arms considered in this review: 3 • Maximum trial duration: 12 weeks • Funding by non-profit organisation: National Institute on Aging, NIA 3 PO1 AG017211, Project CREATE III, Center for Research and Education on Aging and Technology Enhancement • Funding by commercial organisation: none reported • Publication status: full-text report
Participants	<ul style="list-style-type: none"> • Participant profile: independent living Caucasian elderly, 90% retired, mean near visual acuity of 20/32 • Patient flow: 21 randomised, 21 described at baseline in experimental group; 21 randomised, 21 described at baseline in control group 1; 20 randomised, 20 described at baseline in control group 2 • Number of females: 14 of 21 (67%) in experimental group; 11 of 21 (52%) in control group 1; 11 of 20 (55%) in control group 2 • Average age (SD): 74 (1.2) years in experimental group; 75 (1.5) years in control group 1; 72 (1.4) in control group 2 • Average (SD) education: not reported • Baseline cognitive function: MMSE mean 29, SD 1.04

Boot 2013 (Continued)

	<ul style="list-style-type: none"> • Selection criteria on cognition: minimum score of 25 on the MMSE; ≤ 2 errors on Short Portable Mental Status Questionnaire; no significant memory deficits using the Wechsler Memory Scale, 3rd edition (Logical Memory subscale; age-adjusted criterion) • Ethnicity: 100% Caucasian • APOE: not reported
Interventions	<ul style="list-style-type: none"> • Type of experimental intervention: computerised CT, treatment duration 12 weeks; intervention provided as individual training at home, without supervision • Details of experimental intervention: Brain Fitness group. Video game intervention using the Nintendo DS Lite gaming system, Brain Age 2, with focus on memory, reaction time, language, and mathematical ability • Type of concomitant treatment provided: none • Session duration: 60 minutes in experimental group (planned); mean of 56 minutes (SD 6) in practice • Number of treatment sessions: 60 in experimental group • Treatment frequency: 5/week in experimental group • Maximum treatment duration: 12 weeks in experimental group • Type of control intervention 1: other; treatment duration 12 weeks; intervention provided as group training, under supervision • Details of control intervention 1: video game intervention using the Nintendo DS Lite gaming system, Mario Kart DS • Session duration: 60 minutes in control group (planned); mean of 22 minutes (SD 5) in practice • Number of treatment sessions: 60 in control group • Treatment frequency: 5/week in control group • Maximum treatment duration: 12 weeks in control group • Type of control intervention 2: no intervention • Details of control intervention 2: no contact group • Session duration: not applicable • Number of treatment sessions: not applicable • Treatment frequency: not applicable • Maximum treatment duration: not applicable
Outcomes	<p>Cognitive functioning outcome</p> <ul style="list-style-type: none"> • Physical functioning outcome to be considered: none measured <p>Quality of life outcome</p> <ul style="list-style-type: none"> • Depression outcome to be considered: none measured • Safety outcome to be considered: none measured
Notes	<p>* Values across the 6 subscales will be averaged</p> <p>This trial was identified thanks to a communication with Dr. Lampit and will be included in the meta-analysis in the next update of this review</p>

Stern 2011

Methods	<ul style="list-style-type: none"> • Design: 3-arm randomised controlled pilot trial with parallel-group design • Country: USA • Recruitment period: not reported • No. of centres involved: 1 • Unit of randomisation: individual • No. randomised: 60 (of which 40 considered in this review)
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Stern 2011 (Continued)

	<ul style="list-style-type: none"> • Number of arms considered in this review: 3 • Maximum trial duration: 6 months • Funding by non-profit organisation • Funding by commercial organisation • Publication status: full-text report
Participants	<ul style="list-style-type: none"> • Type of participants: cognitive healthy elderly with (corrected-to) normal vision, with no past or current medical, neurological, or psychiatric disorder • Patient flow: 20 randomised, 17 described at baseline in experimental group; 20 randomised, 18 described at baseline in experimental group 2; 20 randomised, 19 described at baseline in control group • Number of females: 10 of 17 (59%) in experimental group 1; 9 of 18 (50%) in experimental group 2; 11 of 19 (58%) in control group • Average age (SD): 66 (4.5) years in experimental group 1; 66 (4.0) years in experimental group 2; 67 (4.2) years in control group • Average (SD) education: 15.65 (2.55) years in experimental group; 16.28 (2.61) years in experimental 2 group; 15.74 (2.54) years in control group • Baseline cognitive function: DRS total score 140.7 (SD 2.88) in experimental group 1; 140.7 (SD 2.33) in experimental group 2; and 140.2 (SD 2.76) in control group • Selection criteria on cognition: Mattis Dementia Rating Scale (DRS) total score 135 or higher included. Neuropsychological test data from baseline assessment battery were subsequently reviewed to ensure absence of dementia or MCI • Ethnicity: not reported • APOE: not reported
Interventions	<p>Type of experimental intervention 1: computerised CT, treatment duration 12 weeks; intervention provided as individual training, under supervision</p> <ul style="list-style-type: none"> • Details of experimental intervention: Space Fortress, played with emphasis on attention* • Type of concomitant treatment provided: none reported • Session duration: 60 minutes in experimental group • Number of treatment sessions: 36 in experimental group • Treatment frequency: 3/week in experimental group • Maximum treatment duration: 12 weeks in experimental group <p>Type of experimental intervention 2: computerised CT, treatment duration 12 weeks; intervention provided as individual training, under supervision</p> <ul style="list-style-type: none"> • Details of experimental intervention: Space Fortress, played with standard instructions* • Type of concomitant treatment provided: none reported • Session duration: 60 minutes in experimental group • Number of treatment sessions: 36 in experimental group • Treatment frequency: 3/week in experimental group • Maximum treatment duration: 12 weeks in experimental group <p>Type of control intervention 1: passive; treatment duration 12 weeks</p> <ul style="list-style-type: none"> • Details of control intervention: no intervention • Session duration: not applicable in control group • Number of treatment sessions: not applicable in control group • Treatment frequency: not applicable in control group • Maximum treatment duration: not applicable in control group
Outcomes	<p>Cognitive functioning outcomes</p> <ul style="list-style-type: none"> • Physical functioning outcome to be considered: none measured • Quality of life outcome to be considered: none measured

Stern 2011 (Continued)

- **Depression outcome to be considered:** none measured
- **Safety outcome to be considered:** none measured

Notes

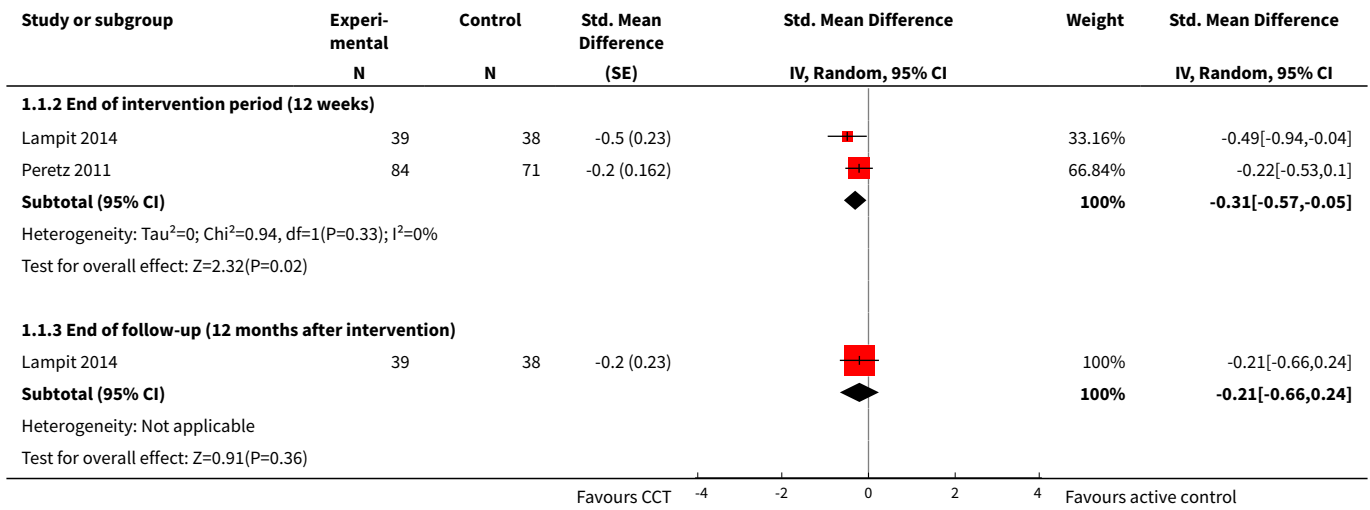
* In the systematic review by [Lampit 2014a](#), the trial arm playing Space Fortress under specific experimental conditions (emphasis change) was not included. Instead, the trial arm playing Space Fortress with standard instructions was included

This trial was identified thanks to a communication with Dr. Lampit and will be included in the meta-analysis in the next update of this review

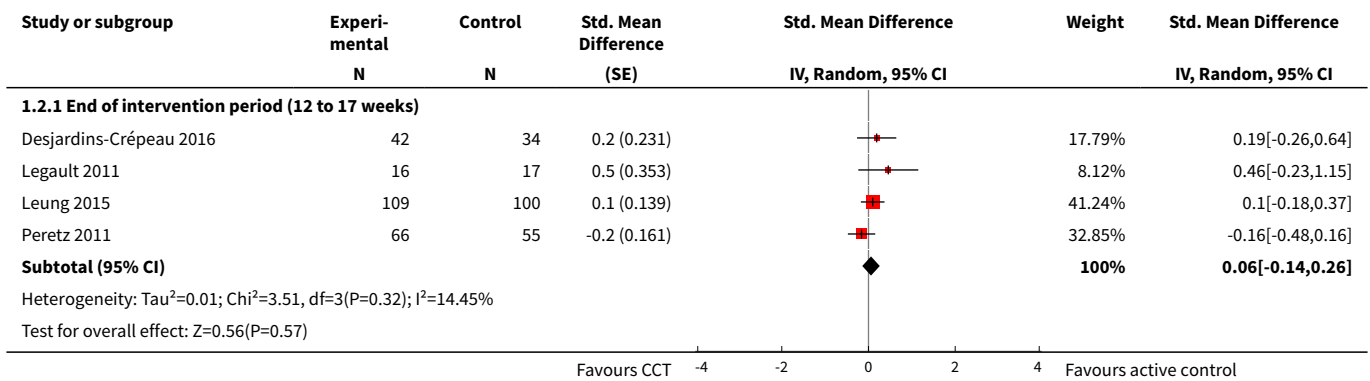
DATA AND ANALYSES
Comparison 1. Computerised cognition-based training versus active control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global cognitive function	2		Std. Mean Difference (Random, 95% CI)	Subtotals only
1.2 End of intervention period (12 weeks)	2	232	Std. Mean Difference (Random, 95% CI)	-0.31 [-0.57, -0.05]
1.3 End of follow-up (12 months after intervention)	1	77	Std. Mean Difference (Random, 95% CI)	-0.21 [-0.66, 0.24]
2 Episodic memory	4		Std. Mean Difference (Random, 95% CI)	Subtotals only
2.1 End of intervention period (12 to 17 weeks)	4	439	Std. Mean Difference (Random, 95% CI)	0.06 [-0.14, 0.26]
3 Speed of processing	2		Std. Mean Difference (Random, 95% CI)	Subtotals only
3.1 End of intervention period (12 to 16 weeks)	2	138	Std. Mean Difference (Random, 95% CI)	-0.63 [-1.14, -0.12]
4 Executive function	3		Std. Mean Difference (Random, 95% CI)	Subtotals only
4.1 End of intervention period (12 to 17 weeks)	3	230	Std. Mean Difference (Random, 95% CI)	-0.04 [-0.61, 0.53]
5 Working memory	3		Std. Mean Difference (Random, 95% CI)	Subtotals only
5.1 End of intervention period (12 to 16 weeks)	3	392	Std. Mean Difference (Random, 95% CI)	-0.17 [-0.36, 0.02]

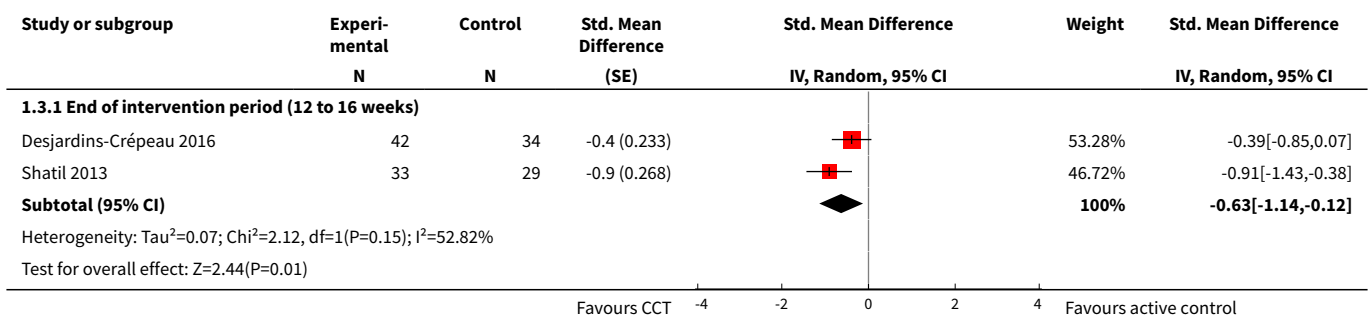
Analysis 1.1. Comparison 1 Computerised cognition-based training versus active control, Outcome 1 Global cognitive function.



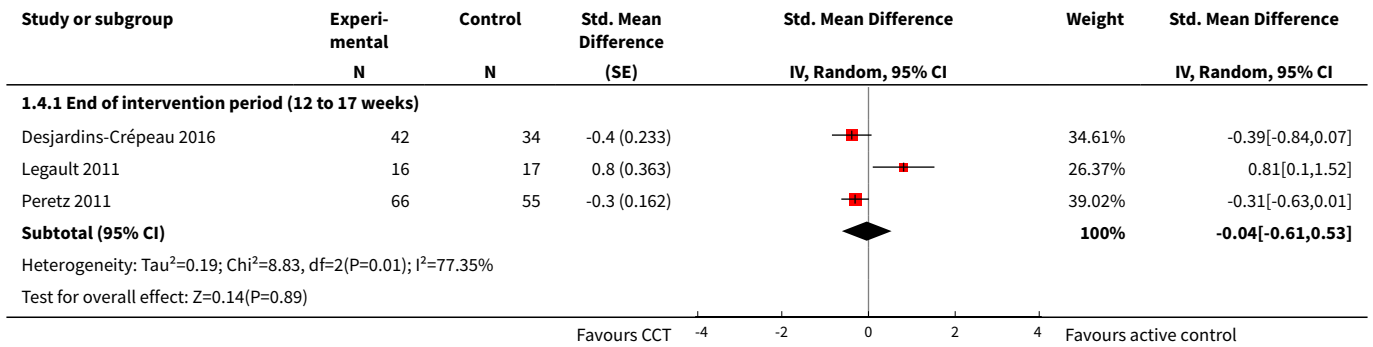
Analysis 1.2. Comparison 1 Computerised cognition-based training versus active control, Outcome 2 Episodic memory.



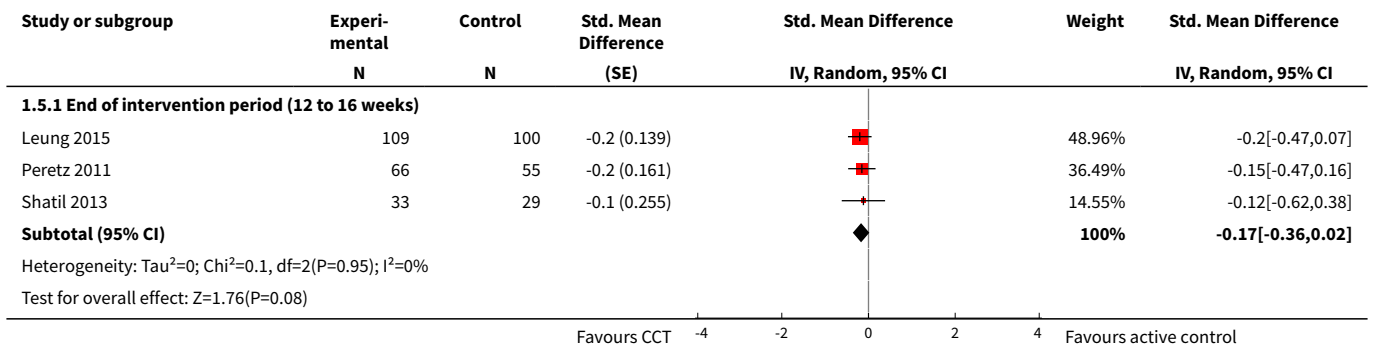
Analysis 1.3. Comparison 1 Computerised cognition-based training versus active control, Outcome 3 Speed of processing.



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



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

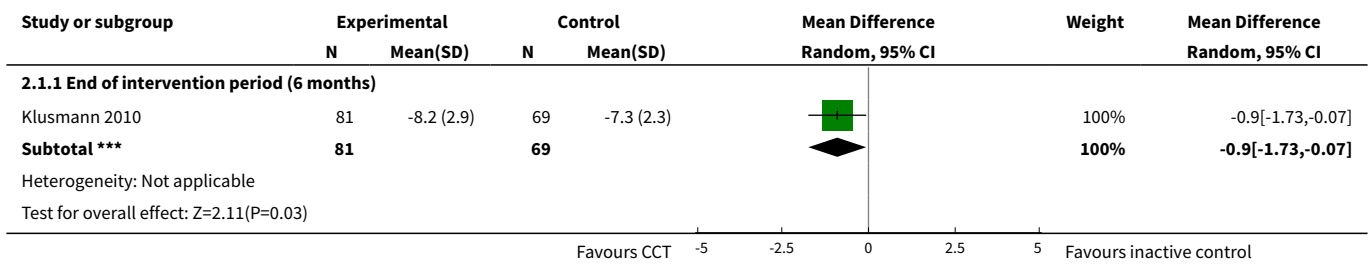


Comparison 2. Computerised cognition-based training versus inactive control

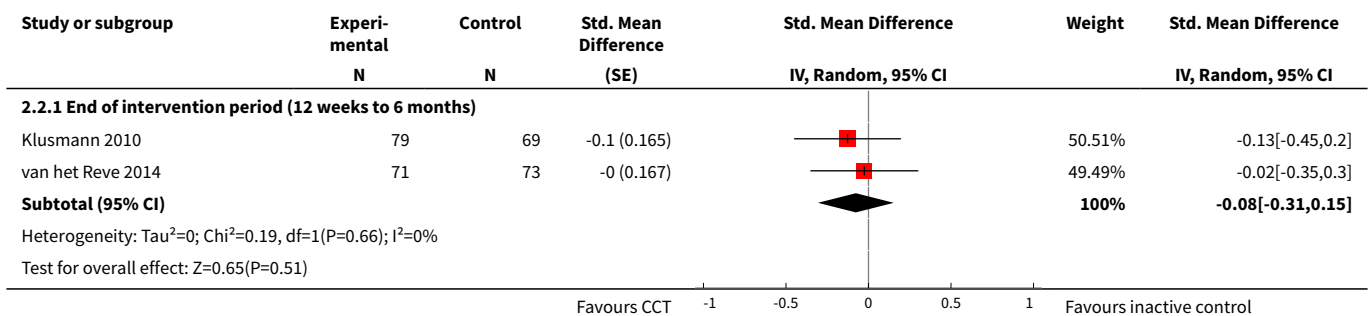
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodic Memory	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 End of intervention period (6 months)	1	150	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.73, -0.07]
2 Executive function	2		Std. Mean Difference (Random, 95% CI)	Subtotals only
2.1 End of intervention period (12 weeks to 6 months)	2	292	Std. Mean Difference (Random, 95% CI)	-0.08 [-0.31, 0.15]
3 Speed of processing	2		Std. Mean Difference (Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 End of intervention period (12 to 16 weeks)	2	204	Std. Mean Difference (Random, 95% CI)	-0.28 [-0.82, 0.26]
4 Working memory	1	60	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.43, 0.27]
4.1 End of intervention period (16 weeks)	1	60	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.43, 0.27]
5 Verbal fluency	1	150	Mean Difference (IV, Random, 95% CI)	-0.11 [-1.58, 1.36]
5.1 End of intervention period (6 months)	1	150	Mean Difference (IV, Random, 95% CI)	-0.11 [-1.58, 1.36]

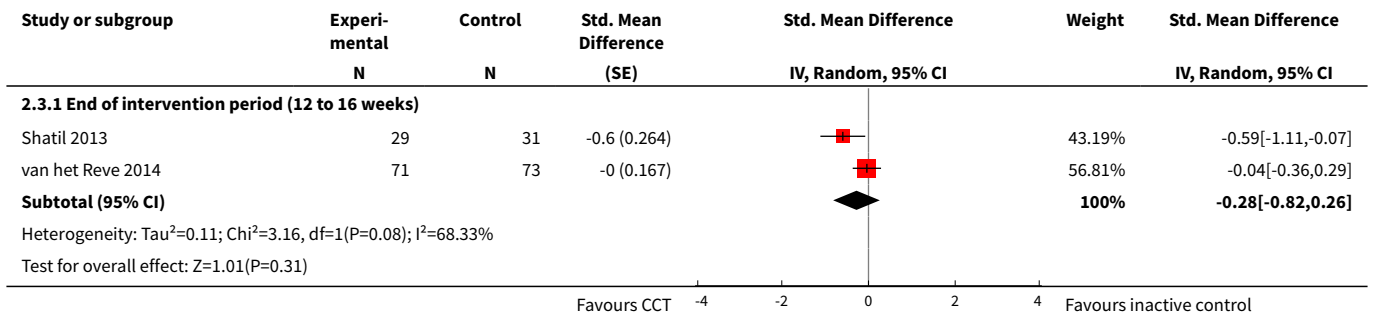
Analysis 2.1. Comparison 2 Computerised cognition-based training versus inactive control, Outcome 1 Episodic Memory.



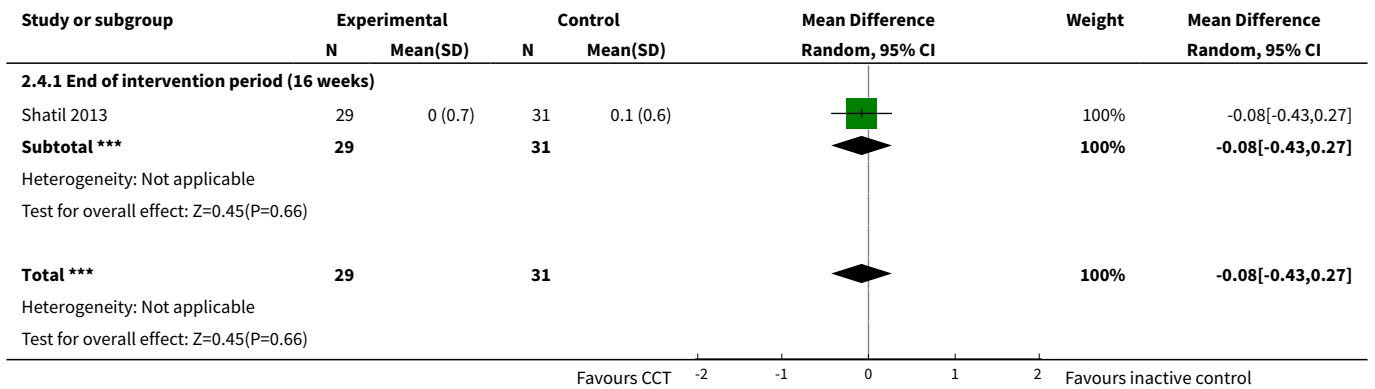
Analysis 2.2. Comparison 2 Computerised cognition-based training versus inactive control, Outcome 2 Executive function.



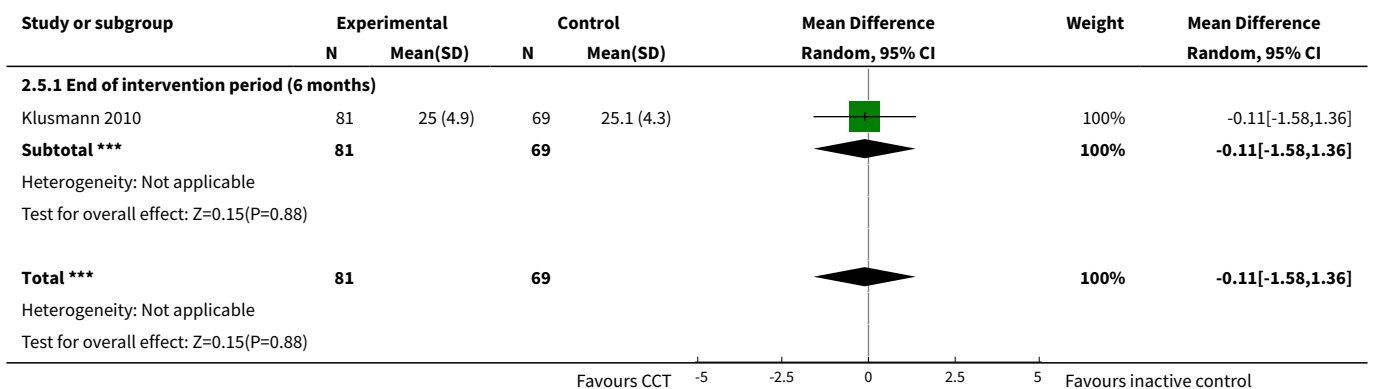
Analysis 2.3. Comparison 2 Computerised cognition-based training versus inactive control, Outcome 3 Speed of processing.



Analysis 2.4. Comparison 2 Computerised cognition-based training versus inactive control, Outcome 4 Working memory.



Analysis 2.5. Comparison 2 Computerised cognition-based training versus inactive control, Outcome 5 Verbal fluency.



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 March 2018]	Basic search: COG	Jan 2015: 31
	[Studies within ALOIS are coded COG if the intervention is a cognitive-based intervention]	Jul 2015: 4
		Feb 2016: 2
		Jul 2016: 0
		Mar 2018: 0
MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP) [Date of most recent search: 31 March 2018]	1. "cognitive stimulation".ti,ab.	Jan 2015: 1455
	2. cognitive ADJ3 train*.ti,ab.	Jul 2015: 70
	3. "cognitive exercis*".ti,ab.	Feb 2016: 303
	4. "brain train*".ti,ab.	Jul 2016: 423
	5. (memory adj3 train*).ti,ab.	Mar 2018: 489
	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	

(Continued)

26. *Cognition/
27. *Cognition Disorders/
28. Memory/
29. Memory Disorders/
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.

(Continued)

- 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 - directly sent to core author team]**

- 74. 68 NOT 73 **[results minus 'no brainer' results - for the crowd to screen]**

Embase	1. aging/	Jan 2015: 1289
1974-24 January 2018 (Ovid SP)	2. aged/	Jul 2015: 163
[Date of most re- cent search: 31 March 2018]	3. middle aged/	Feb 2016: 380
	4. mild cognitive impairment/	Jul 2016: 268
	5. elderly.ti,ab.	Mar 2018: 640
	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/	

(Continued)

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 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.

(Continued)

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	1. exp Aging/	Jan 2015: 166
1806-January week 2 2018 (Ovid SP)	2. exp Cognitive Impairment/	Jul 2015: 20
	3. "cognit* impair*".ti,ab.	Feb 2016: 25
[Date of most re- cent search: 31 March 2018]	4. MCI.ti,ab.	Jul 2016: 12
	5. AAMI.ti,ab.	Mar 2018: 70
	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.	
	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.	

(Continued)

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

(Continued)

56. 52 and 53 and 54 and 55

57. 51 not 56

CINAHL (EBSCO-host)		Jan 2015: 390
		Jul 2015: 13
[Date of most recent search: 31 March 2018]		Feb 2016: 57
		Jul 2016: 12
		Mar 2018: 125
ISI Web of Science [includes: Web of Science (1945-present); BIOSIS Previews (1926-present); MEDLINE (1950-present); Journal Citation Reports]; BIOSIS Previews	("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 Mar 2018: 268
LILACS (BIREME)		Jan 2015: 4
		Jul 2015: 0
[Date of most recent search: 31 March 2018]		Feb 2016: 0
		Jul 2016: 0
		Mar 2018: 0
CENTRAL (via CRSO)	#1 MeSH descriptor: [Aged, 80 and over] explode all trees	Jan 2015: 274
	#2 MeSH descriptor: [Aged] explode all trees	Jul 2015: 11
[Date of most recent search: 31 March 2018]	#3 MeSH descriptor: [Middle Aged] explode all trees	Feb 2016: 57
	#4 MeSH descriptor: [Mild Cognitive Impairment] explode all trees	Jul 2016: 4
	#5 "cognit* impair*" or MCI	Mar 2018: 125
	#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 #7 or #8 or #9 or #10 or #11 or #12	

(Continued)

- #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)	Jan 2015: 17
	Jul 2015: 4
[Date of most recent search: 31 March 2018]	Feb 2016: 2
	Jul 2016: 0
	Mar 2018: 4

ICTRP Search Portal (http://apps.who.int/trialssearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov;	Jan 2015: 22
	Jul 2015: 3
	Feb 2016: 1
	Jul 2016: 0
	Mar 2018: 4

(Continued)

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]

[Date of most recent search: 31 March 2018]

TOTAL before de-duplication	Jan 2015: 3981
	Jul 2015: 332
	Feb 2016: 935
	Jul 2016: 754
	Mar 2018: 1725
	TOTAL: 7727
TOTAL after de-duplication	TOTAL: 5832
TOTAL after first assessment by the Crowd and CDCIG Information Specialists	Jan 2015: 604
	Jul 2015: 60
	Feb 2016: 164
	Jul 2016: 73
	Mar 2018: 189
	TOTAL: 1090

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

Item	Definition
<i>Design-related characteristics*</i>	

Computerised cognitive training for 12 or more weeks for maintaining cognitive function in cognitively healthy people in late life (Review)

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(Continued)

Concealment of allocation (avoiding selection bias)	Guidance from the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> 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: <ul style="list-style-type: none"> • if a credible sham procedure was used; or if a placebo supplement or pill was used that was reported to be identical in appearance from the experimental intervention, and the specific outcome or group of outcomes is/are likely to be influenced by lack of blinding; or • if blinding is absent or suboptimal and the specific outcome, such as mortality, is not likely to be influenced by lack of blinding
Blinding of outcome assessment (avoiding detection bias)	<p><i>For self-reported/partner-reported outcomes</i></p> <p>Low risk of bias will be judged if:</p> <ul style="list-style-type: none"> • 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 <p><i>For other outcomes</i></p> <ul style="list-style-type: none"> • Outcome assessment was considered to be blinded if the outcome assessment was reported to be blinded
Statistical analyses (avoiding attrition bias)	<p><i>For continuous outcomes</i></p> <p>Low risk of bias will be judged if:</p> <ul style="list-style-type: none"> • at least 90% of randomised participants were analysed AND the difference in percentage of participants not analysed was 5% or lower across trial arms; or • 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, and simple methods such as "last observation carried forward" or "baseline carried forward" will be considered inappropriate <p><i>For binary outcomes of rare events</i></p> <p>Low risk of bias will be judged if:</p> <ul style="list-style-type: none"> • the event rate is low (e.g. incidence of dementia) AND at least 95% of randomised participants 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 <p><i>For binary outcomes of non-rare events</i></p> <p>Low risk of bias will be judged if:</p> <ul style="list-style-type: none"> • at least 90% of randomised participants 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

(Continued)

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), short-term (up to 1 year), medium-term (1 to 2 years), and longer-term results (more than 2 years)

Treatment-related characteristics

Treatment and control	The analyses will be stratified by:
Treatment duration	<ul style="list-style-type: none"> • 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 in multiple domains (yes/no); or • mode of delivery <ul style="list-style-type: none"> * training supervision (yes /no); or * group training (yes/no) <p>The analyses will be stratified into > 3 sessions per week (yes/no), length of training sessions > 30 minutes (yes/no) based upon previous findings (Lampit 2014) and total number of sessions</p> <p>The minimum treatment duration of 3 months is considered short-term, 3 to 12 months as medium-term, and 12 months as long-term</p>

Participant-related characteristics

Participant-related criteria	Gender, level of education (in years)
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* The descriptions depicted in this Table are provided in addition to the guidance available in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Stratified analyses are performed only for the primary outcome and only if about 10 RCTs contribute to the analyses.

FEEDBACK

Included studies, 16 December 2019

Summary

Feedback submitted by Henry Mahncke

Comment : To the Editors,

We read with great interest your recently published review “Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life.” The review could have been a timely evidence-based analysis that helped to clarify key issues in the field of computerised cognitive training (CCT). However, the decision to include only studies that employed 12 or more weeks of cognitive training unfortunately renders the review of very limited scientific or clinical value.

The choice to include only studies employing 12 or more weeks of cognitive training is problematic for multiple reasons:

First, the decision itself does not have a scientific basis, as the authors of the review themselves state. The decision is mentioned briefly in several places in the Cochrane review: 1. In the introduction, with the statement “The inclusion criterion of an intervention duration of 12 or more weeks is consistent with cognitive training recommendations (Lampit 2015).” No other reference to the literature supporting the decision is provided. The reference Lampit 2015(1) appears to be to a single randomized controlled trial, of a single CCT intervention that is specifically titled “a pilot study.” In that reference, 12 weeks of cognitive training is used, but no specific justification for that length of time is discussed, nor is a general recommendation made that this is the minimum required amount of cognitive training for efficacy. It seems possible from the pattern of citations that the authors intended to cite the Lampit 2014a meta-analysis here. However that meta-analysis also does not support the review’s statement and in fact makes no analysis of duration of training in weeks and specifically concludes that shorter and longer training doses are statistically equivalently effective.

2. In the methods, with the statement “The minimum treatment duration was set at 12 weeks to evaluate the effects of training on meaningful long-term outcomes...” However, requiring training duration of 12 or more weeks does not relate the meaningful long-term outcomes – that goal would have been accomplished by requiring follow-up assessments at 12 or more weeks.

3. The statement continues “...and to make a comment about the minimum ‘dose’ of training that may be required to effect an enduring change.” However, no comment can be made on the minimum ‘dose’ of training that may be required to effect an enduring change if short duration trials are excluded – that goal would have been accomplished by including trials of various durations, and conducting an analysis to evaluate the effect of training duration (or more correctly, delivered dose) on outcomes.

4. “Previous research suggests that acute brain changes can be seen following eight weeks of training (Engvig 2014); however, we are unable to find any evidence that such brain changes endure.” This is a peculiar statement. It is quite well accepted in modern neuroscience that plastic brain changes are the mechanism by which learning and memory work – including memory for skills trained earlier than 8 weeks ago. Perhaps the authors mean to say that longitudinal brain imaging studies of cognitive training are lacking, which is a limitation in the field but does not relate to how the inclusion criteria for a meta-analysis of behavioral results should be defined.

5. “We therefore made an arbitrary judgement that at least 12 weeks of regular cognitive training would be required for an enduring effect of intervention.” The arbitrariness of this decision proves fatal for the fundamental purpose of the review to synthesize the entirety of the evidence.

We are aware of no published evidence that trials with training duration under 12 weeks are ineffective and those with training duration over 12 weeks are effective, likely because analyzing trials by weeks of duration (instead of total hours of training) is generally not accepted as a reasonable basis for distinguishing trials.

We see no reasonable scientific basis for this inclusion criterion in the Cochrane review – and neither do the authors, who describe their judgement in the review itself as “arbitrary.”

Second, the criterion does not achieve its stated goal – and in fact achieves a nonsensical result. A duration of twelve weeks of training reveals very little about how much training was delivered. As written, the review would exclude an 8 week trial requiring 5 hours per week of cognitive training (40 hours total) and include a trial of 12 weeks requiring 1 hour per week of cognitive training (12 hours total) with the intention “to make a comment about the minimum ‘dose’ of training that may be required to effect an enduring change.”

This issue directly affects the quality of the results in the review. As a straightforward example, the IMPACT study(2) (N=487, requiring 5 hours of training per week for 8 weeks for a total of 40 hours) was excluded, however a study explicitly described as an independent replication(3) of IMPACT (N=209, requiring 3 hours of training per week for 13 weeks for a total of 39 hours) was included. These trials delivered equivalent doses of cognitive training, yet one is included in the Cochrane review and one is not.

Simply looking at the 8 trials included in the review reveals a startling range of total number of hours of cognitive training delivered over 12 week periods. A quick check of the methods sections shows that over a three month period the trials included in the Cochrane review deliver anywhere from 6(4) to 60(5) hours of training.

Furthermore, while a study(4) with only 6 hours of cognitive training is included in the Cochrane review (under the belief that 12 weeks of training at 30 minutes per week is an adequate dose), multiple studies are excluded that provided a significantly higher dose of cognitive training in under 12 weeks that include follow-up assessments that extend the total trial duration to greater than 12 weeks (e.g., 10 hours of training with a 10-year of follow-up(6), 30 hours of training with a 1-year follow-up(7), 40 hours of training with a 6-month follow-up(2); see next section for further details). This is a clearly nonsensical result.

Overall, the use of this criterion fails to achieve the Cochrane review’s stated goal of including trials that deliver at least a “minimum dose of training.”

Third, the criterion results in the elimination of virtually all published clinical trials from the review.

This has two significant consequences:

Removal of the vast majority of published trials: The inclusion table from the review counts 114 publications as excluded for <12 weeks of cognitive training duration – almost 15 times as many as were included in the review. While careful inclusion criteria regarding trial design and execution metrics are admirable in a meta-analysis, a tremendous number of the studies excluded are randomized controlled trials that would otherwise meet the inclusion criteria of the Cochrane review – with the sole exception that the cognitive training period was <12 weeks.

If a single inclusion criterion for a clinical trial results in the exclusion of the vast majority of the otherwise eligible patients, it would be appropriate to state that the trial design is ungeneralizable and the results cannot be interpreted for the patient population at it exists in the real world. The Cochrane review suffers precisely this flaw.

Removal of the largest and most carefully designed and executed published trials: The four largest and most carefully designed/executed trials of cognitive training are comprehensively excluded because each employed training durations of <12 weeks. These trials include 6,921 participants – almost 6 times as many as were included in the Cochrane review.

1. ACTIVE: The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study was the first study explicitly designed as a pivotal study to evaluate the efficacy of cognitive training in healthy older adults. It enrolled 2,832 healthy older adults, evaluated outcomes at 2(8), 5(9), and 10-year(6) follow-up visits, and documented improvements in directly trained cognitive domains(6,8,9) and generalization to a variety of functional(10,11) and real-world measures(12).
2. IHAMS: The Iowa Healthy and Active Minds Study was designed as a sequel to ACTIVE to replicate the core results from speed training with three main design differences: use of an active control, involvement of a broader age range of participants, and comparison of training location models. IHAMS enrolled 681 healthy older adults, followed outcomes over a one-year period, and documented improvements in directly trained cognitive function and generalization to real-world measures(13,14).
3. IMPACT: The Improvement in Cognition with Plasticity-based Adaptive Cognitive Training study was designed as a pivotal trial for an auditory speed training program. IMPACT enrolled 487 healthy older adults, followed outcomes over a six-month period, and documented improvements in directly trained measures, composite cognitive function measures, and self-report measures(2,15).
4. BGTT: This study was designed as an evaluation of brain training in collaboration with the British television show *Bang Goes The Theory*. This trial enrolled 2,921 healthy older adults, followed outcomes over a six-month period, and documented improvements in directly trained measures, composite cognitive function measures, and functional measures(7).

Each of these trials is a gold-standard randomized controlled trial, with an a priori data analysis plan, and intent-to-treat analysis, and careful randomization and blinding procedures. As a result, these publications have had a real impact on the field – with a combined total of well over 2,500 citations to the initial publications for each study.

Overall, the Cochrane review has excluded a) most of the RCT evidence on CCT and b) the highest quality scientific literature on CCT. As a result, it is difficult to interpret the conclusions of Cochrane review as generalizable to the scientific field or to clinical practice.

Other reviews of CCT have not chosen to suffer from this limitation. Three examples include

1. Lampit(16) identified 52 trials meeting inclusion criteria similar to the Cochrane review, including all studies with 4 or more total hours of cognitive training delivered.
2. Mewborn(17) identified 97 trials meeting inclusion criteria similar to the Cochrane review (except including both computerized and non-computerized interventions, and including healthy aging and MCI populations), including studies without limitation regarding dose.
3. Edwards(18) identified 17 trials meeting inclusion criteria similar to the Cochrane review in a review a single type of CCT (speed training), including trials with ~10 hours of cognitive training delivered over 5 weeks.

Notably, each of these reviews comes to the opposite conclusion of the Cochrane review – stating that their respective meta-analyses document that cognitive training results in statistically and clinically significant improvement.

As a result of these issues, every single sentence of the authors plain language summary on page 3 is incorrect and misleading to its audience:

1. “It is not yet possible to say for certain whether or not computerised cognitive training can help older people to maintain good cognitive function.” The authors chose to exclude more than 100 publications, including those from the four largest and most carefully designed and well conducted studies of cognitive training, each of which documented that computerized cognitive training can help older people to maintain good cognitive function. Unsurprisingly the authors then find it difficult to come to a conclusion. In fact, it is “yet possible to say for certain whether or not computerized cognitive training can help older people to maintain good cognitive function” – the authors could do so by including the available well-designed and well-conducted studies. This precise question has been answered in multiple careful meta-analyses each of which was available to prior to the publication of the Cochrane review16–18.
2. “Although we excluded very short trials (< 3 months) from this review, the trials that we found were still quite short for examining long-term effects as people age.” The authors chose to exclude multiple large scale trials with follow-up periods ranging from 3 months to 10 years. It is misleading and not scientifically appropriate to exclude multiple studies that evaluate long-term effects and then state that the authors were not able to find trials that could examine long-term effects.
3. “We think it is important to do more research to find out whether longer periods of training work better, and whether training can produce lasting effects.” While this may be the authors’ personal beliefs, and of course further research is always appealing, there is simply nothing in the review that justifies the belief that longer periods of training might work better. The authors did not find positive effects because they excluded studies with <12 weeks of cognitive training – not because studies of >12 weeks have not yet been done. In addition, Multiple studies already have been done with multi-month and multi-year follow-ups to evaluate whether “training can produce lasting effects” – however, those studies were excluded from the review.

Cochrane's first goal is "To produce high-quality, relevant, up-to-date systematic reviews and other synthesized research evidence to inform health decision making." Unfortunately, the current review does not achieve its goal due to this crucial design error.

It is difficult to see how this review can be amended or corrected given this fundamental flaw. Any conclusion – even that insufficient evidence existed to evaluate the efficacy of the included studies – would have note that that vast majority of studies, including the largest studies, studies with higher doses of cognitive training of cognitive training, and studies with longer follow-up periods, were all excluded.

In an effort to be helpful, we suggest: "We found little evidence from the included studies to suggest that 12 or more weeks of CCT improves cognition in healthy older adults. However, our limited confidence in the results reflects the exclusion of more than 100 publications with cognitive training periods of under 12 weeks, including multiple studies with substantially larger patient populations, substantially higher doses of cognitive training, and substantially longer follow-up periods than the studies included in this review. The possibility that each of these variables could affect the results of the analysis remains to be more fully explored."

More appropriately, we suggest that this review should be retracted, and re-conducted with appropriate inclusion criteria.

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Declaration of Interest

Do you have any affiliation with or involvement in any organisation with a financial interest in the subject matter of your comment?

HM and MM are employed at and hold stock in Posit Science, a company that develops cognitive training programs. KB holds stock in Posit Science. JE has no conflict of interest.

Reply

We thank Dr. Mahncke and colleagues for their comments regarding the Cochrane Review: 'Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life.'

Dr. Mahncke and colleagues' primary criticism is of our decision to require a 12-week minimum duration of the computerised cognitive training (CCT) intervention, which led to exclusion of a large number of trials with shorter intervention periods.

Regarding the use of the two references 'Lampit 2015' and 'Lampit 2014a' as background to this decision, we agree that these are referenced incorrectly and we apologise for this mistake. We agree that these papers do not support the minimum 12-week exposure criterion.

This review was conceived as part of a set of reviews concerned with lifestyle modifications which could help to maintain cognitive function in later life and, in particular, contribute to preventing or delaying the onset of dementia. The reviews were intended to focus on sustainable interventions and to look for enduring effects. One of the intervention domains identified as being of interest was increasing cognitive activity and, with an eye to sustainability, a decision was made to restrict the focus to computer-delivered interventions (computerised cognitive training, CCT).

Trials of any intervention which measure cognitive outcomes in cognitively healthy adults fall along a spectrum. At one end are cognitive enhancement trials. Cognitive enhancement is typically the aim of interventions directed at younger adults. The interventions are often short and can be of high intensity. At the other end are trials looking to prevent cognitive decline or dementia. These trials are most often conducted in older adults, although we know that the duration of neurodegenerative diseases is such that mid-life may also be a key period for neuroprotection. Indeed, for cognitive activity, the evidence on education as a protective factor against dementia suggests that whole-life timescales may be relevant.

The distinction between cognitive enhancement (or improvement from baseline) and prevention of cognitive decline and dementia is an important one and, in recent years, the policy of the Cochrane Dementia and Cognitive Improvement Group has to been to regard these as sufficiently distinct topics to merit separate reviews.

We would maintain that the majority of the trials excluded from this review on the basis of duration of intervention <12 weeks are best viewed as cognitive enhancement trials and are not directly relevant to the question this review seeks to address. As acknowledged above, this is a spectrum, not a dichotomy, but – in order to avoid producing a review dominated by cognitive enhancement effects – some threshold had to be chosen, which inevitably had to be a matter of judgment.

We understand Dr. Mahncke and colleagues to be suggesting that, if a threshold is to be imposed, then dose (total hours delivered and/or frequency) would be a better basis for that threshold than overall duration of intervention. We agree that this is an alternative approach and that it was misleading to refer in the review to "a minimum dose of intervention" rather than to a minimum duration. However, selecting a dose cut-off would have been equally arbitrary. Certainly there is no clear dose-response relationship in the literature. For example, Lampit 2014, in a subgroup analysis in their review, found no evidence of benefit from training >3 times/week compared to less frequent training.

Dr. Mahncke and colleagues also make the point that the objectives of the review would be better addressed by concentrating on duration of follow-up, not duration of exposure to the intervention. We think this is a valid argument. The review is being updated with new lead

authors and the inclusion criteria will be amended in the update so that all CCT trials which assess outcomes 12 weeks or longer after randomisation will be eligible, regardless of total dose of CCT or duration of exposure.

As far as this edition of the review is concerned, we published a peer-reviewed protocol in which the PICO elements, including the 12-week threshold for duration of eligible interventions were clearly stated. This criterion was repeated several times in the abstract of the review, the Plain Language Summary and the Discussion, where it was clearly stated that the conclusions did not apply to shorter training programmes. In the amended version of the review published with this response, we have – for even greater transparency – also inserted the duration criterion into the title and further emphasised the restriction of scope in other sections, in order that the findings are not over-generalised. We accept that the rationale for the duration criterion could have been better explained, but not that the review was misleading. Mahncke and colleagues may not consider that the review asked the best question, but it did address the question asked.

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Dr J McCleery, Dr T Quinn (CDCIG Coordinating Editors)

WHAT'S NEW

Date	Event	Description
11 February 2020	New citation required and conclusions have changed	Comments/feedback received and errors corrected in response. Title changed to reflect this. Conclusions changed
11 February 2020	Amended	Errors corrected in response to comments received. Title changed to reflect this. Conclusions changed

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Completion of the protocol: Nicola Gates, Anne Rutjes, Marcello Di Nisio, Salman Karim, Jennifer Ware, Lee Yee Chong, Evrim March, Robin Vernooij.

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DECLARATIONS OF INTEREST

Nicola J Gates: 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.

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 in Advisory Boards for Daiichi-Sankyo, Aspen, and Pfizer, and consultancy fees for Daiichi-Sankyo, Bayer Health Care, and Leo Pharma outside the submitted work.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

[Appendix 2](#) describes the features we planned to use in stratified analyses to explore between-trial heterogeneity. We also planned to explore bias associated with small study size, such as publication bias, in funnel plot analyses. As our protocol required the inclusion of 10 trials for such analyses to be meaningful, we omitted stratified and funnel plot analyses. We also omitted the protocol-defined sensitivity analysis for the primary outcome. Latter analyses would include high-quality trials only, with high quality planned to be defined using results of the stratified analyses. As stratified analyses could not be performed, we omitted this sensitivity analyses. We also planned to perform sensitivity analyses according to the definitions used for MCI or dementia, namely, restricting analyses to trials applying internationally accepted definitions. As none of the trials reported such outcomes, we could not perform any analyses for this patient relevant outcome. We used a hierarchy to select instruments from which we would analyse the outcome data. We made the decision to use the hierarchy before we began to extract data.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cognition; *Computer-Assisted Instruction; *Healthy Aging; Age Factors; Cognitive Dysfunction [*prevention & control]; Dementia [prevention & control]; Memory, Episodic; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Aged; Aged, 80 and over; Humans; Middle Aged