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Computerised cognitive training for maintaining cognitive function in cognitively healthy people in midlife (Review)

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[Intervention Review]

Computerised cognitive training for maintaining cognitive function in cognitively healthy people in midlife

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ABSTRACT

Background

Normal aging is associated with changes in cognitive function that are non-pathological and are not necessarily indicative of future neurocognitive disease. Low cognitive and brain reserve and limited cognitive stimulation are associated with increased risk of dementia. Emerging evidence now suggests that subtle cognitive changes, detectable years before criteria for mild cognitive impairment are met, may be predictive of future dementia. Important for intervention and reduction in disease risk, research also suggests that engaging in stimulating mental activity throughout adulthood builds cognitive and brain reserve and reduces dementia risk. Therefore, midlife (defined here as 40 to 65 years) may be a suitable time to introduce cognitive interventions for maintaining cognitive function and, in the longer term, possibly preventing or delaying the onset of clinical dementia.

Objectives

To evaluate the effects of computerised cognitive training interventions lasting at least 12 weeks for maintaining or improving cognitive function in cognitively healthy people in midlife.

Search methods

We searched up to 31 March 2018 in ALOIS (www.medicine.ox.ac.uk/alois), the specialised register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG). We ran additional searches in MEDLINE, Embase, PsycINFO, CINAHL, ClinicalTrials.gov, and the WHO Portal/ICTRP at 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to ensure that the search was as comprehensive and as up-to-date as possible, to identify published, unpublished, and ongoing trials.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We included randomised controlled trials (RCTs) or quasi-RCTs, published or unpublished, reported in any language. Participants were cognitively healthy people between 40 and 65 years of age (80% of study population within this age range). 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; 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

For preliminary screening of search results, we used a 'crowd' method to identify RCTs. At least two review authors working independently screened remaining citations against inclusion criteria; independently extracted data; and assessed the quality of the included trial, using the Cochrane risk of bias assessment tool. We used GRADE to describe the overall quality of the evidence.

Main results

We identified one eligible study that examined the effect of computerised cognitive training (CCT) in 6742 participants over 50 years of age, with training and follow-up duration of six months. We considered the study to be at high risk of attrition bias and the overall quality of the evidence to be low.

Researchers provided no data on our primary outcome. Results indicate that there may be a small advantage for the CCT group for executive function (mean difference (MD) -1.57, 95% confidence interval (CI) -1.85 to -1.29; participants = 3994; low-quality evidence) and a very small advantage for the control group for working memory (MD 0.09, 95% CI 0.03 to 0.15; participants = 5831; low-quality evidence). The intervention may have had little or no effect on episodic memory (MD -0.03, 95% CI -0.10 to 0.04; participants = 3090; low-quality evidence).

Authors' conclusions

We found low-quality evidence from only one study. We are unable to determine whether computerised cognitive training is effective in maintaining global cognitive function among healthy adults in midlife. We strongly recommend that high-quality studies be undertaken to investigate the effectiveness and acceptability of cognitive training in midlife, using interventions that last long enough that they may have enduring effects on cognitive and brain reserve, and with investigators following up long enough to assess effects on clinically important outcomes in later life.

PLAIN LANGUAGE SUMMARY

Computerised cognitive training for maintaining cognitive function in cognitively healthy people in midlife

Background

The terms 'cognition' and 'cognitive function' describe all the mental activities related to thinking, learning, remembering, and communicating. Normal changes in cognition become evident with aging. Also, diseases may affect cognition, principally dementia, which becomes increasingly common with increasing age from about 65 years onwards. Researchers have shown a great deal of interest in trying to prevent cognitive decline and dementia. It is known that being mentally active throughout life is associated with lower risk of dementia. Therefore, it is has been suggested that encouraging mental activity in midlife (which we define in this review as 40 to 65 years of age) might be an effective way of maintaining good cognitive function as people age. Cognitive training involves a set of standardised tasks intended to 'exercise the brain' in various ways. Programmes of cognitive training are often delivered by way of computers or mobile technology so that people can perform activities on their own at home. Increasingly, these are provided in commercial packages that are advertised to the general public. We wanted to know whether computerised cognitive training is an effective way for people between 40 and 65 years of age 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 the cognitive function of people 40 to 65 years of age who had taken part in computerised cognitive training lasting at least three months versus a control group that had not done so. For the comparison to be as fair as possible, it should have been decided randomly whether participants were assigned to the cognitive training group or the control group. We were primarily interested in overall measures of cognition. The choice of three months of intervention was somewhat arbitrary, but we thought it unlikely that shorter periods of training could have long-lasting effects.

What we found

We found that a lot of shorter studies had been conducted, but only one study met our criteria for this review. It took place in the UK and included two different types of online cognitive training. The control group participated in an online game that was not expected to have cognitive effects. This training lasted six months, and study authors measured cognition at the end of the training period. Resarchers randomised 6742 people in the study, but the dropout rate was high. We thought this put the results at high risk of bias; therefore we considered the quality of evidence provided by this study to be low, meaning that further research might well lead to different results. This study did not measure overall cognitive functioning - which we were most interested in - but it did measure some subtypes of cognitive function. The cognitive training group did slightly better on a test of reasoning, and the control group did very slightly better on a test of working memory, which is a very short-term type of memory. No evidence suggested that the groups differed in memory measured by a word-learning test.

Our conclusions

We were not able to tell whether taking part in computerised cognitive training in midlife has any lasting effects on cognitive function. We think this is an important question that should be investigated further in trials that test cognitive training over three months or longer. It will also be important for researchers to try to find the best ways to keep people motivated to persist with training.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Computerised cognitive training compared with control intervention in cognitively healthy people in midlife				
Patient or population: cognitively healthy people in midlife **Settings**: general population **Intervention**: computerised cognitive training **Comparison**: control intervention				
Outcomes	**Difference between CCT and control (95% CI)**[1]	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Global cognitive functioning	Not reported using a validated measure			
Cognitive subdomain: episodic memory, 6 months of follow-up	MD 0.03 lower (0.10 lower to 0.04 higher)	3090 participants (1 study)	⊕⊕○○ **low**[2]	CCT may lead to little or no improvement in episodic memory
Cognitive subdomain: executive functioning, 6 months of follow-up	MD 1.57 lower (1.85 lower to 1.29 lower)	3994 participants (1 study)	⊕⊕○○ **low**[2]	CCT possibly improves executive function compared to active control
Cognitive subdomain: working memory, 6 months of follow-up	MD 0.09 higher (0.03 higher to 0.15 higher)	5831 participants (1 study)	⊕⊕○○ **low**[2]	CCT possibly maintains working memory worse than active control, but the difference is deemed negligible
Cognitive subdomain: speed of processing	Not reported using a validated measure			
Quality of life	Not reported using a validated measure			
One or more serious adverse events	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).
CI: Confidence interval; **RR:** Risk Ratio

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

[1] The direction of the effect was standardised, so that lower values favour CCT and higher values favour control.
[2] Downgraded twice for attrition bias.

BACKGROUND

Description of the condition

Cognitive health across the life span is essential for independent function and active aging. 'Active aging' refers to the process of optimising opportunities for health, participation, and security (WHO 2016). 'Cognitive health' broadly refers to absence of cognitive impairment and preservation of cognitive structure; this is necessary if older adults are to achieve active aging (Depp 2012; Hendrie 2006). Older adults fear cognitive decline and dementia, among other reasons, for the threat that they pose to active aging and independence (Deary 2009; Lustig 2009).

Cognitively healthy adults undergo normal age-related changes in cognitive function, and they experience a reduction in neural resources as they age (Salthouse 2003; Shing 2008). A minor decline in some cognitive domains may be evident in adults in midlife. However, observers have noted considerable variability in cognitive function and brain structure between individuals and across the age span (Ronnlund 2015; Salthouse 2011). Large variations in cognitive health and function are seen at a population level, and lifetime trajectories of decline range from normal age-related decline through to subjective complaint, mild cognitive impairment (MCI), and clinical dementia (World Alzheimer Report 2014). Advances in research technologies have increased our understanding of the pathophysiological changes linked to dementia and indicate that the brain changes underlying dementia develop over a period of at least 20 to 30 years before the onset of symptoms (World Alzheimer Report 2014). However, differentiating between normal age-related changes and pathological changes due to slow progression of disease can be very difficult.

Differences in cognitive health and in individual susceptibility to the development of clinical dementia in late life may be due in part to variability in brain development and cognitive reserve (Barulli 2013; Stern 2009; Stern 2012). The concept of reserve can provide a theoretical explanation for differences between individuals with the same degree of brain pathology who present with a clinical dementia and are functionally impaired, and those who do not display any clinical symptoms and manage to maintain better levels of functioning (Stern 2012). Cognitive reserve is developed through educational attainment, occupation, and engagement in cognitive stimulating activities (Opedebeek 2016; World Alzheimer Report 2014). Lack of cognitive stimulation across the life span - and by inference reduced reserve - is a significant risk factor for reduced cognitive function and is associated with higher dementia risk (Norton 2014; World Alzheimer Report 2014).

Cross-sectional and longitudinal comparisons indicate that acquired knowledge generally increases until about age 60 (Salthouse 2011). Therefore the introduction of mentally stimulating activity in midlife (40 to 65) offers cognitively healthy people an opportunity to improve or maintain cognitive function and potentially to build reserve (Gates 2014). Even small improvements in cognitive function may lead to important benefits for everyday functioning, and any delay or reduction in age-related cognitive decline may substantially extend the period during which people can live independently (Hertzog 2008). Stimulating cognitive activity may improve cognitive function, leading to structural and functional neuroplasticity. Emerging research suggests that patterns of mental activity may influence the relationship between neuropathology and clinical dementia, with neural compensatory mechanisms the most likely mechanism, consistent with reserve models (Bennett 2014; Grady 2012).

Prospective epidemiological studies of cognitively stimulating leisure activities consistently report protective effects, including lower rates of cognitive decline and incident dementia (Marioni 2014; Verghese 2003; Wilson 2002). Prospective population and cohort studies also indicate benefits of mental activity, with lower rates of cognitive decline, less dementia pathology, and lower incidence of dementia reported (Beydoun 2014; Geda 2012; Landau 2012; Verghese 2003; Wilson 2012). For example, a meta-analysis of 22 cohort studies of dementia incidence revealed that individuals with higher levels of lifetime mental activity almost halved their risk of developing dementia (Valenzuela 2003). A five-year longitudinal cohort study, tracking more than 1000 cognitively healthy adults, indicated that the introduction of mental activities had a beneficial effect on cognition the following year, suggesting that intervention may be effective in countering age-related cognitive decline (Wilson 2012).

Investigators are examining new non-pharmacological interventions provided to build cognitive reserve, potentially maintaining better cognitive functioning with aging and delaying the onset of clinical dementia in later life (Acevedo 2007; Barnes 2011; Dresler 2013; Leifer 2003). Two models of cognitive enrichment have been developed, drawing on population studies of the benefits of mental activity and engagement: engagement through lifestyle within a complex environment, and engagement through instruction and practice interventions (Stine-Morrow 2014). Both models introduce novel complex mental activities for improving cognitive function that may preserve cognitive health, build cognitive reserve, combat age-related cognitive dysfunction, and promote active ageing (Amoyal 2012; Barnes 2011; Marquine 2012).

Description of the intervention

Cognitive training, frequently termed 'brain training' in commercial spheres, has been developed to provide mentally stimulating interventions to reduce age-related decline (Gates 2014). Such programmes introduce participants to novel activities with the aim of stimulating cognitive change and slowing cognitive aging (Park 2007). Although cognitive training may include traditional pen and paper tasks, it now more commonly takes the form of computer-based tasks, including exercises, games, and virtual reality (Gates 2010). Computerised cognitive training (CCT) programmes have been delivered in individual sessions and within groups, with supervision or privately at home; and studies show 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).

How the intervention might work

The theoretical premise behind cognitive intervention to improve cognitive function or to minimise age-related decline in cognitively healthy adults is that cognitively stimulating mental exercises will increase brain and cognitive reserve. Enhanced reserve may be associated with structural brain changes, such as increased brain volume, or with functional changes in neural activity (Stern 2012). Cognitive stimulation may lead to development of compensatory networks that work to maintain cognitive performance, and potentially to mask or prevent clinical manifestations of neurocognitive disease (Grady 2012). Evidence from animal studies indicates that new learning is associated with positive neuroplastic changes (Cotman 2007; Curlik 2013; Nithianantharajah 2006). Researchers have proposed a scaffold theory of compensatory activation to incorporate factors associated with age-related cognitive decline and factors that may enhance function and reserve (Park 2013). Computerised cognitive training may stimulate positive neuroplastic changes (Valenzuela 2003), including increasing neural volume and neural activity (i.e. compensatory neural networks) (Grady 2012; Park 2013), brain metabolism (Forster 2011), neurochemistry activation (Olesen 2004; Rosen 2011), and fluorodeoxyglucose uptake (Belleville 2012). However, research findings have been limited, and significant further investigation is required.

Although the evidence base is very limited, human trials of cognitive training suggest positive neural changes, including reduced β-amyloid burden (Landau 2012). Diverse studies investigating neurophysiological changes on 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 showing positive changes in brain metabolism, task-dependent brain activation, and resting-state networks (Belleville 2012; Berry 2010; Forster 2011). Thus, emerging evidence suggests that cognitively stimulating activities might be stimulate neuroplasticity and build brain reserve.

Why it is important to do this review

The potential of computerised cognitive interventions for enhancing cognitive health, and even for helping to prevent clinical dementia, and their accessibility and low implementation costs have led the American Alzheimer's Association to make recommendations for rapid development and testing of computerised cognitive intervention programmes (Alzheimers Association 2014). Increasing consumer demand for interventions to maintain cognitive function has resulted in a multi-billion dollar industry of commercial brain training computer software programmes that purport to maintain, and potentially enhance, cognitive function, yet often lack supportive data or independent research evaluation (Belleville 2012; Gates 2010; Sixsmith 2013).

Although research examining the effects of cognitive training in older adults is extensive and now spans several decades, results are inconclusive. The research literature has been characterised by significant variability in populations and interventions. Clinical trials have been criticised for poor specification of interventions, poor methodological rigour, small sample sizes, and failure to assign treatments randomly (Gates 2010; Kueider 2012; Papp 2009; Reijnders 2013; Walton 2014). Reviews have not always distinguished between the different types of cognitive interventions (Martin 2011). Results from studies in healthy adults have been inconsistent, with data showing negative findings from meta-analyses (e.g. Papp 2009), and more recent meta-analyses of computerised cognitive training in cognitively healthy adults, with defined intervention and clear eligibility criteria, have shown positive results on cognition (Kueider 2012; Lampit 2014a; Shao 2015). A significant limitation in the research, to be addressed by this review, is the paucity of studies examining cognitive interventions in midlife, with most studies focussing on young adults or older adults (over 60 years of age). For example, a comparative trial included younger (20 to 31 years) and older adults (65 to 80 years) but omitted those in midlife (Schmiedek 2010). Additionally, limited evidence shows generalisation and persistence of benefit over time (Park 2013). A robust review is therefore required to clarify the effects of cognitive training in midlife on global cognition, non-trained cognitive domains, and general function (Green 2014; Park 2013). The present review aims to address these gaps in the evidence and to examine critically the current research literature, including an evaluation of potential sources of bias and heterogeneity.

For individuals, fear of cognitive decline and dementia may be powerful motivators to seek preventive interventions. The World Alzheimer Report 2014 indicates that cognitively stimulating activities, including reading, playing musical instruments, and playing cards and board games, may be beneficial for improving and maintaining cognition and potentially preventing decline in the future, although most of these activities have not been investigated in clinical trials. Technology and computerised 'brain training' games and cognitive training programmes are being more actively investigated (Alzheimers Association 2014; Peretz 2011; Sixsmith 2013). However, the proliferation of computer-based commercial products purporting to improve cognitive function while reducing dementia risk is outpacing clinical research. In this context, this review will provide important information to the public so people can know whether the time, effort, and money they might invest to prevent cognitive decline is likely to be well spent.

From a research perspective, it is vital to review the evidence and to integrate clinical research into practice (Doody 2009). At this stage, reliable data are insufficient to provide clear guidelines for the implementation of intervention programmes. Recent primary studies have identified that the benefits of cognitive training may depend upon a number of factors including age, cognitive level, and non-cognitive factors (Lampit 2014a; Stine-Morrow 2014). Comparisons between single- and multiple-domain training suggest that multiple-domain training is better, and nascent evidence shows that different cognitive domains may respond differently to training, and hence may require specific interventions for different lengths of time (Lampit 2014a). Therefore, the present review of the effect size of interventions and stratification of data may highlight the 'dose', duration, and frequency of interventions necessary to achieve an effect.

Therefore, as well as informing consumers, this review may be useful to public health decision 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.

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

OBJECTIVES

To evaluate the effects of computerised cognitive training interventions lasting at least 12 weeks for maintaining or improving cognitive function in cognitively healthy people in midlife.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) or 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 results only 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 midlife. Midlife is defined as ranging from 40 to 65 years of age. At least 80% of the study population had to be in this age range. We covered participants in late life (65 or older) in a separate review (Gates 2019a). If the age range of participants in a trial did not coincide with our categories, we used the median and range, or the mean and standard deviation (SD), to help place studies into the most appropriate review.

We determined the cognitive status of participants by using the trial authors' own definitions of 'cognitively healthy'; we recorded these definitions. We excluded all studies reporting that more than 20% of participants had subjective memory complaints, or received a diagnosis, or were defined as having 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 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.

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, which involves repeated practice on standardised exercises of specified cognitive domain/s, for the purpose of enhancing cognitive function.

By 'active control', we mean all 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 controls', we refer to controls for which no intervention is applied that may be expected to have an effect on cognition.

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

from reviews of clinical trials (Lampit 2014a). Trials in cognitively healthy people with a duration of intervention as short as 12 weeks typically investigate cognitive enhancement rather than maintenance of cognitive function. It is recognised that the relationship between short-term cognitive training and maintenance of cognitive function over longer periods of time is unclear.
We excluded interventions that did not involve any form of computer delivery. We also excluded studies in which the investigator combined the experimental intervention with any other form of intervention, unless the added intervention was provided in a standardised manner to both experimental and control groups.

Types of outcome measures

Primary outcomes

- 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)
    - 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.

Secondary outcomes

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

- specific cognitive functioning subdomain: episodic memory;
- specific cognitive functioning subdomain: executive functioning;
- specific cognitive functioning subdomain: speed of processing;
- specific cognitive functioning subdomain: verbal fluency;
- specific cognitive functioning subdomain: attention/working memory;
- quality of life/psychological well-being, either generic or health-specific;
- daily function, such as measures of instrumental activities of daily living; or
- 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 from the cognitive scale that was highest in this hierarchy. For example, if a trial reported results on both the MMSE and the Clinical Dementia Rating scale (CDR), we used outcome data from 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 undertaken to evaluate vitamin and mineral supplementation, dietary interventions, and physical exercise interventions.

Outcomes to be included in the 'Summary of findings' table

We addressed 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.

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:

1. 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);
2. 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); the World Health Organization (WHO) Portal (which covers ClinicalTrials.gov (clinicaltrials.gov/); International Standard Randomized Controlled Trials Number (ISRCTN) (www.isrctn.com/); the Chinese Clinical Trials Register (ChiCTR) (who.int/ictrp/network/chictr/en/); the German Clinical Trials Register (GermanCTR) (who.int/ictrp/network/drks2/en/); the Iranian Registry of Clinical Trials (IRCT) (who.int/ictrp/network/irct2/en/); and the Netherlands National Trials Register (NTR) (who.int/ictrp/network/ntr/en/), plus others);
3. quarterly searches of the Cochrane Library's Central Register of Controlled Trials (CENTRAL); and
4. six-monthly searches of a number of grey literature sources, including 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 used in healthcare bibliographic databases for retrieval of reports on dementia, cognitive improvement, and cognitive enhancement trials can be viewed in the 'Methods used in reviews' section within the editorial information about the Cochrane Dementia and Cognitive Improvement Group.

We conducted additional searches in MEDLINE, Embase, PsycINFO, CINAHL, ClinicalTrials.gov, and the WHO Portal/ICTRP at www.apps.who.int/trialsearch, to ensure that the searches for this review were as comprehensive and as up-to-date as possible in identifying published, unpublished, and ongoing trials. We used this search strategy to retrieve reports of trials from MEDLINE (via the Ovid search platform - SP), as 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 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 complete extraction of trial details.

We used crowd-sourcing to screen the search results. We have presented details of this at www.medicine.ox.ac.uk/alois/content/modifiable-risk-factors. In brief, teams of volunteers will perform a 'first assess' of the search results. We recruited the crowd through the network called Students 4 Best Evidence (www.students4bestevidence.net). The crowd performed 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 a reading of title and abstract) whether the citation is describing a randomised or a quasi-randomised trial, irrespective of the citation topic. It is estimated that this removed 75% to 90% of the 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 disagreements resolved by a fifth independent review author.

We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), along with a 'Characteristics of excluded studies' table. We imposed no language restrictions.

Data extraction and management

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

Participant characteristics

- Gender
- Age (range, median, mean)
- Education (level and years of education)
- Baseline cognitive function
- Cognitive diagnostic status
- Duration of cognitive symptoms, if any
- 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 cognitive training
- Type and description of the control intervention
- 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 and obtained short-term (up to one year), medium-term (one to two years), and long-term results (longer than two years). Within these time periods, we extracted the latest data reported by the study (e.g. if the study reports data at six months, nine months, and one year, we extracted only one-year data and analysed these for the one-year (short-term) time point). For dichotomous outcomes (e.g. 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, along with the mean and SD of the change from baseline for each outcome at each time point. If change from baseline data were not available, we extracted the mean value at each time point. When necessary and possible, we approximated means and measures of dispersion from figures in the reports. For cross-over trials, we extracted data on the first treatment period only. Whenever possible, we extracted intention-to-treat data (i.e. analysing all patients according to the group randomisation); if these were not available, then we extracted and reported data from available case analyses. If neither 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 study 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 the Cochrane '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 'low risk', 'unclear risk', or 'high risk' of bias for each domain and provided a description of the reasoning for our rating. The general definitions used are reported in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We derived the 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 an effect size with a 95% confidence interval (CI). If only one trial contributed data to a comparison, or if all studies used the same instrument, this was a mean difference (MD). If trials used different instruments to assess the same outcome, the effect size was a standardised mean difference (SMD) (the between-group difference in mean values divided by the pooled SD). We expressed the treatment effect for dichotomous outcomes as a risk ratio (RR).

Unit of analysis issues

We included no cluster randomised or cross-over trials.

Dealing with missing data

Missing data for individual trials may bias effect estimates 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 evaluations of attrition bias via stratified analyses of the primary outcomes (Appendix 2). We analysed available information and did not contact study authors with a request to provide missing information. We did not impute missing data ourselves.

Assessment of heterogeneity

We aimed to inspect forest plots for the presence of heterogeneity and to calculate the variance estimate tau^2 as a measure of between-trial heterogeneity (DerSimonian 1986). As we identified only a single trial, we could not perform such an analysis.

Assessment of reporting biases

We did not identify enough trials to construct funnel plots with appropriate statistics to explore reporting biases and other biases related to small-study effects.

Data synthesis

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

We planned to use standard inverse-variance random-effects meta-analysis to combine outcome data across trials at the end of the trial (DerSimonian 1986); if possible, we planned to use at least one additional time point (see Primary outcomes and Data collection and analysis for definitions of time points). As we included only a single trial, we reported mean differences for the outcomes of interest in this trial. We conducted statistical analyses using Review Manager 5 (RevMan 2014), along with STATA, release 13 (Statacorp, College Station, Texas, USA). All P values are two-sided.

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

Subgroup analysis and investigation of heterogeneity

We did not identify enough trials to conduct protocol-defined subgroup analyses.

Sensitivity analysis

We did not identify enough trials to conduct protocol-defined sensitivity analyses.

R E S U L T S

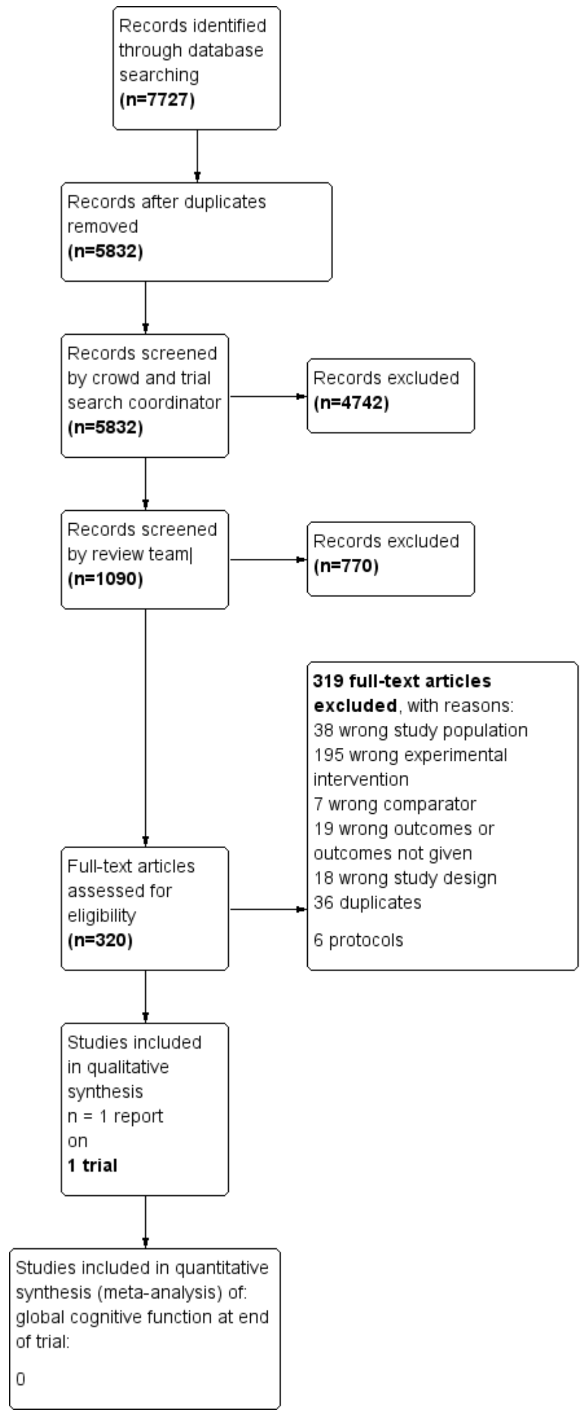
Description of studies

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 and the CDCIG Information Specialist assessed these studies at the title and abstract review level. In total, 1090 results remained after this assessment. The review author team then assessed these records. Of these, we assessed 317 full-text articles for eligibility and found that one study met our inclusion criteria for this review (Corbett 2015). We have depicted this process in Figure 1.

Figure 1. Study flow diagram.



Included studies

We have provided details of the included study in the Characteristics of included studies and have summarised them below.

Design

Corbett 2015 was a randomised controlled trial with three arms, consisting of two computerised cognitive training (CCT) interventions and an active control. Researchers assessed all outcomes after six months.

Sample size

Corbett 2015 randomised 6742 participants to three study arms.

Setting

The study took place in the United Kingdom (UK); all adults older than 50 were invited to take part in the study through a collaboration of the British Broadcasting Corporation (BBC), Alzheimer's Society UK, and the Medical Research Council.

Interventions

The two CCT interventions were (1) reasoning training (ReaCT), involving six tasks related to executive function, and (2) general cognitive training (GCT), targeting multiple cognitive domains, including memory, attention, and visuospatial ability. The active control group engaged in an Internet game requiring the re-ordering of statements. Study authors reported 2557 participants in the ReaCT group, 2432 participants in the GCT group, and 1753 participants in the control group. Those completing the study completed on average 112 training sessions over six months.

Participants

All participants were cognitively healthy. They had a mean age of 58.5 (SD 6.5) in the ReaCT arm, 59.1 (SD 6.4) in the GCT arm, and 59.1 (SD 6.6) in the control arm. More women than men participated in this study, accounting for 68.5% of all participants in the ReaCT experimental arm 1, 68.9% of all participants in the GCT experimental arm 2, and 62.4% of all participants in the control arm.

Outcomes

Researchers used five different outcome measures: (1) instrumental activities of daily living (IADLs), (2) Baddeley Grammatical Reasoning Test, (3) Spatial Working Memory (SWM), (4) digit span, and (5) verbal short-term memory. These are secondary outcomes in this review, and no measure was consistent with our primary outcome.

Excluded studies

We excluded 319 articles after we examined them in full text. Of these, we excluded nine because they focused on cognitively healthy people in late life (Desjardins-Crépeau 2016; Klusmann 2010; Lampit 2014; Lampit 2015; Legault 2011; Leung 2015; Peretz 2011; Shatil 2013; Van het Reve 2014), and we excluded eight because they included patients with MCI (Barnes 2013; Djabelkhir 2017; Fiatrone Singh 2014; Gooding 2016; Herrera 2012; Kwok 2013a; Optale 2010; Rozzini 2007). Two other Cochrane reviews have included these 17 studies (Gates 2019a; Gates 2019b). We excluded 195 studies because they investigated an intervention of less than 12 weeks' duration, or because they did not provide a computerised cognitive training intervention, and 18 because they used a study design that did not meet review criteria. We identified no ongoing trials in trial registers or conference proceedings. We have provided reasons for exclusion of the remainder in the Characteristics of excluded studies section.

Risk of bias in included studies

We have displayed graphically in Figure 2 risks of bias in the included study.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Corbett 2015 described both sequence generation and allocation concealment adequately, and we judged the study to be at low risk of bias in this domain.

Blinding

Corbett 2015 provided adequate blinding of participants, personnel (home-based intervention with no involvement of researchers), and outcome assessors (computer-collected data). Therefore, we judged the study to be at low risk of performance and detection bias.

Incomplete outcome data

For outcomes of interest, we found that final outcome data were missing for between 14% and 66% of participants in individual intervention groups. Study authors imputed final outcome data using the last observation carried forward (LOCF) method. Study authors stated that "reasons for withdrawal are not known due to the online format of intervention and study design" (Corbett 2015). We judged the study to be at high risk of bias for all outcomes, as imputing results using LOCF is likely to yield biased estimates in the presence of observed fractions of participants with missing outcome data at six months.

Selective reporting

We did not identify a trial registration nor a trial protocol. Relying on the published report, we considered the risk of reporting bias to be low, as all outcomes mentioned in the methods section were fully addressed in the results section.

Other potential sources of bias

We identified no other sources of bias.

Effects of interventions

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

See Summary of findings for the main comparison for the comparison of pooled data from both CCT interventions (ReaCT and GCT) versus active control.

Primary outcome: global cognitive function

Corbett 2015 did not examine the effects of training on any measure of global cognitive function.

Secondary outcomes

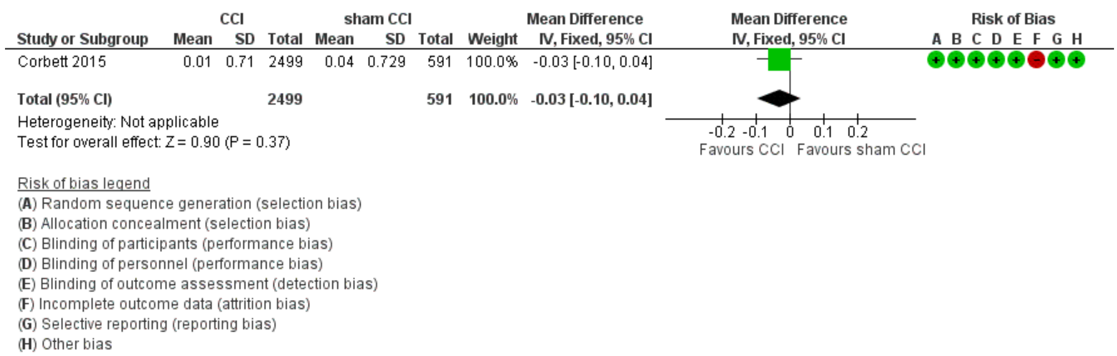
For all outcomes, negative values favour CCT.

Cognitive subdomain

Episodic memory

We found low-quality evidence on episodic memory measured as verbal learning (Analysis 1.1; Figure 3). We downgraded the level of evidence twice for very serious concern about the risk of attrition bias. There may be little or no difference in episodic memory performance between intervention and active control groups.(mean difference (MD) -0.03, 95% confidence interval (CI) -0.10 to 0.04; participants = 3090).

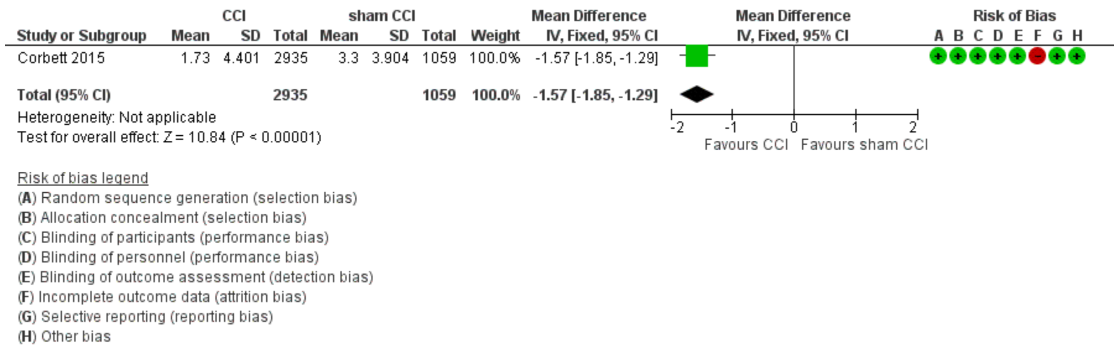
Figure 3. Forest plot of comparison: 1 CCI versus control, outcome: 1.1 Episodic memory, 6 months of follow-up.



Executive function

We found low-quality evidence on executive functioning measured by the Baddeley Grammatical Reasoning Test (Analysis 1.2; Figure 4). Again, we downgraded the level of evidence twice for very serious concern about the risk of attrition bias. The active intervention may provide benefit for executive function (MD -1.57, 95% CI -1.85 to -1.29; participants = 3994).

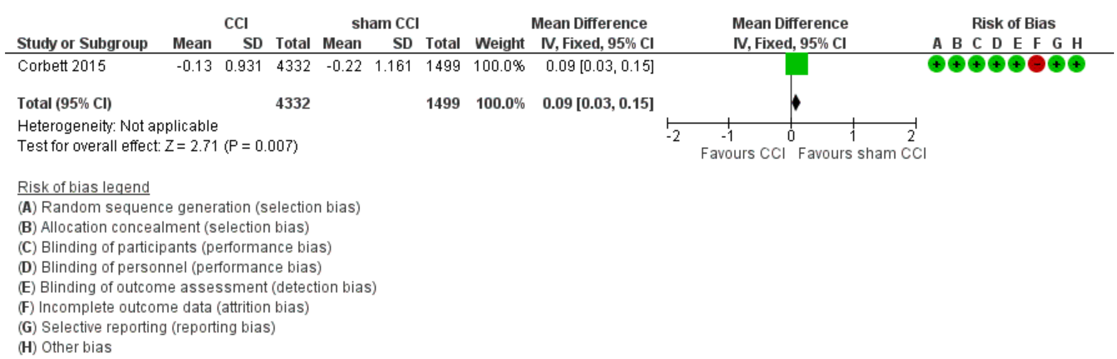
Figure 4. Forest plot of comparison: 1 CCI versus control, outcome: 1.2 Executive functioning, 6 months of follow-up.



Working memory

Researchers provided low-quality evidence on working memory measured by digit span (Analysis 1.3; Figure 5). Again, we downgraded the level of evidence twice for very serious concern about the risk of attrition bias. Results probably indicate a very small advantage of working memory for the control group (MD 0.09, 95% CI 0.03 to 0.15; participants = 5831).

Figure 5. Forest plot of comparison: 1 CCI versus control, outcome: 1.3 Working memory, 6 months of follow-up.



Cognitive function subdomain: speed of processing

The included study did not report this outcome.

Quality of life

The included study did not report this outcome.

Functional performance

Investigators measured daily function with instrumental activities of daily living (IADLs) as the study primary outcome measure.

We did not consider these data, as they were reported for only a subgroup of participants 60 years of age or older - not for our age group of interest.

Number of participants experiencing one or more serious adverse events

The included study did not report serious adverse events.

DISCUSSION

Summary of main results

This review identified only one randomised controlled trial (RCT) that was eligible for inclusion. In this trial, the intervention lasted for six months. This trial did not measure our primary outcome of interest: global cognitive functioning. We found low-quality evidence of an advantage at the end of the intervention period for the active intervention group on measures of executive functioning and of a very small advantage for the control group on working memory. We found low-quality evidence of little or no effect on episodic memory.

Overall completeness and applicability of evidence

The fundamental limitation of this review is that only one RCT was eligible for inclusion, and we caution against over-interpretation. The included trial suggested a small improvement in executive functioning from six months of training, but without longer-term follow-up, it is not possible to determine whether the benefit is enduring and represents maintenance of cognitive function or increased brain reserve.

Quality of the evidence

We judged the included study, Corbett 2015, to have high risk of bias for all outcomes, as the imputation technique used to deal with missing outcome data is likely to yield biased estimates in the presence of the observed proportion of participants with missing data. Analyses were compromised by anomalies in the data provided for the control group. Specifically, given values for the control group were different in general cognitive training (GCT) and reasoning training (ReaCT) comparisons. Additionally, it was difficult to extrapolate data from the published material, and we had concerns regarding the imputation model.

Potential biases in the review process

We conducted a very thorough search to identify relevant trials. We searched multiple data sources for published, unpublished, and ongoing studies. We did not restrict our search by language or publication type. We attempted to avoid bias at the review level by following guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and we used independent trial selection, data extraction, and quality assessment by at least two review authors. Nevertheless, our review is limited by the quality of the included trial, and overall, we have low confidence in the effect estimates reported here. Exclusion of interventions lasting less than 12 weeks - a central criterion in this series of reviews - led to the exclusion of 37% of identified studies (N = 123); as a result, extrapolating from these results to other computerised cognitive training (CCT) studies of shorter duration is inappropriate.

Agreements and disagreements with other studies or reviews

A limited number of trials of CCT in adults in midlife are available for comparison with our findings. Three meta-analyses of cognitive training in cognitively healthy adults from 50 years of age into late life indicate improved performance on non-trained measures of global cognition, executive function, and composite measures of cognitive function (Kueider 2012; Lampit 2014a; Shao 2015). However, evidence from clinical trials specifically in the midlife age range is limited, and results are contradictory. Regression analyses in Lee 2014, which we excluded because the intervention was too short, showed a positive impact of leisure physical and cognitive activities on episodic memory and executive function in adults in midlife (mean age 63), but contrary to what the reserve hypothesis would predict, employment did not have a positive influence. In contrast, Borness 2013, which we also excluded because duration of the intervention was too short, reported no benefit from training among employed adults with a mean age of 41 years.

AUTHORS' CONCLUSIONS

Implications for practice

Our review shows that randomised controlled trials in this age cohort are too few to test the hypothesis that cognitive interventions in midlife may help to maintain cognitive function over time. No implications for practice can be drawn at this time.

Implications for research

The Alzheimer's Association has recommended the development and testing of cognitive training because of its potential as an effective and accessible cognitive intervention to delay and potentially prevent clinical dementia (AA National Plan Milestone Workgroup 2014). Interventions that can be shown to have even small effects on cognition at the individual level could be important at the population level (Andrieu 2015). This review highlights the need to establish a coherent research agenda for computerised cognitive training (CCT) in midlife, which could lead to recommendations for implementation (including type, dose, duration, and intensity of training). A secondary objective would be to develop guidance and regulation codes for commercial products as 'medical devices' (AA National Plan Milestone Workgroup 2014).

Computerised cognitive training (CCT) interventions in midlife have the potential to maintain cognitive function via the development of brain and cognitive reserve. However, whether the introduction of CCT at midlife does in practice maintain cognitive function, reduce age-related cognitive decline, and ultimately prevent clinical dementia remains uncertain. High-quality trials that adhere fully to CONSORT guidance are necessary to investigate efficacy and mechanisms of interventions.

One consideration for future research with adults in midlife is how to maintain engagement in the intervention when multiple competing demands are present at this time of life, including employment, family commitments, and other leisure activities. Dropout was a significant issue in the included study. Strategies to support motivation and compliance are necessary. Entertainment or gamification and other incentives to complete training may be helpful, along with structured training times and supervision. Outcome measures should be relevant to this age cohort, especially as the idea of investing in brain health decades in the future may be too abstract and removed from current life demands. It is important to compare CCT with various levels of occupational demand, given that occupation is a primary source of cognitive stimulation in this age cohort and across the life span generally. It also would be useful to compare CCT with rest and with other leisure or recreational pursuits.

It is very important to note that studies in midlife with the long-term objective of maintaining cognitive function and ultimately of preventing or delaying clinical dementia must include longer-term follow-up to reveal whether any benefits are enduring and can be expected to have effects lasting into late life, when the risk of clinically important cognitive decline increases.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Corbett 2015

Methods	• **Design**: 3-arm randomised controlled trial with parallel-group design • **Recruitment period**: 2009 to 2009 • **No. of centres involved**: not reported • **Unit of randomisation**: individuals • **No. randomised**: 6742 • **Number of arms considered in this review**: 3 • **Maximum trial duration**: 6 months • **Funding by non-profit organisation**: This research was funded by Alzheimer's Society UK and Medical Research Council • **Funding by commercial organisation**: none reported • **Publication status**: full text report
Participants	• **Patients**: 2557 randomised, 2557 described at baseline in the experimental group; 2432 randomised, 2432 described at baseline in the experimental group; 1753 randomised, 1753 described at baseline in the control group • **Number of females**: 1752 of 2557 (69%) in experimental group 1; 1676 of 2432 (69%) in experimental group 2; 1093 of 1753 (62%) in control group • **Average age (SD)**: 58.5 (6.5) years in the experimental group 1; 59.1 (6.4) years in the experimental group 2; 59.1 (6.6) years in the control group • **Average (SD) education**: Experimental group 1: none: 44 (1.7%); primary school: 14 (0.6%); secondary school: 400 (15.6%); further education (A level): 777 (30.4%); university graduate/PG: 1322 (51.7%). Experimental group 2: none: 55 (2. 3%); primary school: 10 (0.4%); secondary school: 418 (17.2%); further education (A level): 717 (29.5%); university graduate/PG: 1230 (50.6%). Control group: none: 37 (2.1%); primary school: 9 (0.5%); secondary school: 320 (18.3%); further education (A level): 556 (31.7%); university graduate/PG: 831 (47.4%) • **Baseline cognitive function**: Baddeley Grammatical Reasoning Test 14.4 (5.3); Paired Associate Learning 3.5 (0.6); digit span 4.8 ladder (1.1). Overall, up to 2873/ 6742 (43%) of participants had age-associated impairment in reasoning • **Ethnicity**: Experimental group 1: 2478 white; 0 Indian; 25 Asian; 7 black; 47 other; 0 unclear. Experimental group 2: 2359 white; 0 Indian; 31 Asian; 4 black; 36 other; 2 unclear. Control group: 1707 white; 0 Indian; 10 Asian; 4 black; 32 other; 0 unclear • **APOE**: number of participants positive for APOE not reported
Interventions	• **Type of experimental intervention**: computerised CT, individualised; treatment duration 6 months. Intervention provided as individual training, without supervision • **Details of experimental intervention**: ReaCT focussed on 3 reasoning tasks and 3 problem-solving tasks • **Session duration**: 10 minutes daily in the experimental group • **Number of treatment sessions**: on average, 112 training sessions over 6 months • **Type of experimental intervention 2:** computerised CT, individualised; treatment duration not reported. Intervention provided as individual training, without supervision

	• **Details of experimental intervention 2**: GCT involved 6 cognitive tasks covering mathematics, attention, memory, and visuospatial ability • **Session duration**: 10 minutes daily in experimental group 2 • **Number of treatment sessions**: on average, 112 training sessions over 6 months • **Details of control intervention**: the control group performed equivalent Internet-based tasks involving a game in which people were asked to put a series of statements in correct numerical order • **Session duration**: 10 minutes daily in the control group • **Number of treatment sessions**: on average, 112 training sessions over 6 months
Outcomes	• **Cognitive functioning outcomes**: ○ Episodic memory measured with verbal short-term memory at 6 months, on a scale from not reported to not reported with higher values indicating benefit ○ Executive functioning measured with Baddeley Grammatical Reasoning Test at 6 months, on a scale from not reported to not reported with higher values indicating benefit ○ Working memory measured with digit span at 6 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 extracted**: none reported • **Safety outcome extracted**: none reported • **Available cognitive outcome, not considered in this review**: spatial working memory (SWM) with higher values indicating benefit • **Available physical functioning outcome, not considered for this review**: daily function measured with instrumental activities of daily living (IADLs) at 6 months with higher values indicating benefit. Outcome data on IADLs were reported for only a subgroup of participants 60 years of age or older
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Judgment**: random sequence adequately generated **Quote(s)**: "Participants were randomly assigned in equal proportions via simple randomization to receive ReaCT, GCT, or control. This was achieved by using a computer-generated randomization sequence to eliminate allocation bias"
Allocation concealment (selection bias)	Low risk	**Judgment**: adequate method of allocation concealment **Quote(s)**: "The online format enabled complete allocation concealment from investigators"

Blinding of participants (performance bias)	Low risk	**Judgment**: Study authors report that participants were blinded to treatment assigned **Quote(s)**: "Participants were blind to which group they were allocated"; "This was a double-blind 6-month online randomised 3-arm controlled trial"
Blinding of personnel (performance bias)	Low risk	**Judgment**: home-based; no involvement of therapists **Quote(s)**: "The online format enabled complete allocation concealment from investigators"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Judgment**: outcomes based on computer tests **Quote(s)**: "The online format enabled complete allocation concealment from investigators"
Incomplete outcome data (attrition bias) All outcomes	High risk	**Judgment:** we judged high risk of bias for all outcomes, as the imputation technique (last observation carried forward) is likely to yield biased estimates in the presence of observed fractions of participants with missing outcome data at 6 months *Comparison ReaCT reasoning and planning vs computerised tasks* • Outcome episodic memory: 1369 out of 2557 (54%) randomised were analysed in the experimental group, and 591 out of 1753 (34%) randomised were analysed in the control group • Outcome executive functioning: 1501 out of 2557 (59%) randomised were analysed in the experimental group, and 1059 out of 1753 (60%) randomised were analysed in the control group • Outcome working memory: 2236 out of 2557 (87%) randomised were analysed in the experimental group, and 1499 out of 1753 (86%) randomised were analysed in the control group *Comparison GCT multi-domain vs computerised tasks* • Outcome episodic memory: 1130 out of 2432 (46%) randomised were analysed in the experimental group, and

Corbett 2015 *(Continued)*

		591 out of 1753 (34%) randomised were analysed in the control group • Outcome executive functioning: 1434 out of 2432 (59%) randomised were analysed in the experimental group, and 1059 out of 1753 (60%) randomised were analysed in the control group • Outcome working memory: 2096 out of 2432 (86%) randomised were analysed in the experimental group, and 1499 out of 1753 (86%) randomised were analysed in the control group **Comment**: no data at 12 weeks were available for extraction **Quote(s)**: "The primary analysis was intention-to-treat and involved all participants who were randomized"; "Missing values were imputed by last observation carried forward for the 6-month outcome for individuals who completed the 3-month outcome assessment"
Selective reporting (reporting bias)	Low risk	**Judgment**: all outcomes indicated in the methods are reported in the results
Other bias	Low risk	**Judgment**: no other sources of bias are important

APOE: apolipoprotein E.
CT: computerised training.
GCT: general cognitive training.
IADL: instrumental activity of daily living.
PG: postgraduate.
ReaCT: reasoning training.
SD: standard deviation.
SWM: spatial working memory.

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

Study	Reason for exclusion
Adel 2013	Wrong study design
Alves 2014	Wrong intervention

(*Continued*)

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
Baniqued 2014	Adult population
Baniqued 2015	Aged under 30
Barban 2012	Duplicate
Barban 2016	Wrong study design
Barbosa 2015	Wrong intervention
Barcelos 2015	Wrong intervention
Barnes 2006	Intervention shorter than 12 weeks

(*Continued*)

Barnes 2009	Duplicate
Barnes 2013	Wrong patient population
Basak 2016	Intervention shorter than 12 weeks
Beck 2013	Wrong intervention
Belchior	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 study population: mean age is 41.3 years (SD 13.1), meaning that 46% were younger than 40 years (assuming a normal distribution of age)
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

(*Continued*)

Buitenweg 2017	Wrong intervention
Buiza 2008	Wrong intervention
Bures 2016	Intervention shorter than 12 weeks
Buschert 2011	Wrong intervention
Buschert 2011a	Duplicate
Buschert 2012	Wrong intervention
Buschert 2012a	Duplicate
Calkins 2011	Wrong intervention
Cammarata 2011	No outcome given
Cancela 2015	Wrong patient population
Candela 2015	Wrong intervention
Cantarella 2017	Intervention shorter than 12 weeks
Cao 2016	Wrong route of administration
Carretti 2013	Wrong intervention
Casutt 2014	Wrong outcomes
Chapman 2015	Wrong intervention
Chapman 2016	Wrong intervention
Chapman 2017	Wrong intervention
Cheng 2012	Wrong intervention
Cheng 2018	Wrong patient population
Cho 2002	Aged under 30
Cleverley 2012	Wrong intervention
Cohen-Mansfield 2014	Wrong intervention
Cohen-Mansfield 2014a	Wrong intervention

(*Continued*)

Cohen-Mansfield 2015	Wrong intervention
Cohen-Mansfield 2015a	Duplicate
Combourieu 2014	Wrong outcomes
Costa 2015	Wrong patient population
Danassi 2015	Duplicate
Dannhauser 2014	Wrong study design
de Almondes 2017	Intervention shorter than 12 weeks
de Macedo 2015	Wrong outcomes
De Vreese 1996	Wrong intervention
Desjardins-Crépeau 2016	Wrong patient population
Diamond 2015	Intervention shorter than 12 weeks
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

(*Continued*)

Fairchild 2010	Wrong intervention
Feng 2013	Wrong intervention
Feng 2015	Wrong intervention
Feng 2017	Wrong patient population
Fiatrone Singh 2014	Wrong patient population
Finn 2011	Intervention shorter than 12 weeks
Finn 2015	Intervention shorter than 12 weeks
Finn 2015a	Duplicate
Flak 2013	Study protocol
Flak 2014	Study protocol
Flak 2014a	Study protocol
Flak 2016	Study protocol
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

(*Continued*)

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
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
Hötting 2013	Intervention shorter than 12 weeks
Ignjatovic 2015	Aged under 30

(*Continued*)

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
Kivipelto 2014	Wrong intervention
Klusmann 2009	Duplicate
Klusmann 2010	Wrong patient population
Klusmann 2010a	Duplicate
Klusmann 2011	Aged under 30
Kudelka 2014	Intervention shorter than 12 weeks
Kwak 2015	Nature of intervention unclear

(*Continued*)

Kwak 2017	Nature of intervention unclear
Kwok 2013	Intervention shorter than 12 weeks
Kwok 2013a	Intervention shorter than 12 weeks
Lampit 2013	Wrong study design
Lampit 2014	Wrong patient population
Lampit 2015	Wrong patient population
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
Legault 2011	Wrong patient population
Leung 2015	Wrong patient population
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
Man 2012	Wrong comparator
Mann 2012	Wrong patient population
Margrett 2006	Wrong patient population

(*Continued*)

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

(*Continued*)

NCT02785315 2016	Wrong intervention
NCT02808676 2016	Wrong intervention
Neely 2013	Nature of intervention unclear
Ng 2015	Wrong intervention
Ngandu 2015	Wrong intervention
Ngandu 2015a	Wrong intervention
Nishiguchi 2015	Wrong intervention
Nouchi 2012	Intervention shorter than 12 weeks
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
Peretz 2011	Wrong patient population
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

(*Continued*)

Redick 2013	Aged under 30
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
Santos 2011	Wrong comparator
Schoene 2015	Duplicate
Schoene 2015a	Duplicate
Schumacher 2013	Intervention shorter than 12 weeks
Shah 2012	Wrong patient population
Shatil 2013	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

(Continued)

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
Tennstedt 2013	Study protocol
Tesky 2012	Wrong intervention
Tsai 2008	Duplicate
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
Van het Reve 2014	Wrong patient population
Vance 2007	Intervention shorter than 12 weeks
Vidovich 2009	Intervention shorter than 12 weeks

(*Continued*)

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	Intervention shorter than 12 weeks
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
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

(*Continued*)

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

DATA AND ANALYSES

Comparison 1. CCI versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodic memory, 6 months of follow-up	1	3090	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.10, 0.04]
2 Executive functioning, 6 months of follow-up	1	3994	Mean Difference (IV, Fixed, 95% CI)	-1.57 [-1.85, -1.29]
3 Working memory, 6 months of follow-up	1	5831	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.03, 0.15]

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Screening of references: Students 4 Best Evidence (title/abstract screening), Nicola Gates, Salman Karim.

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Overall interpretation of data: Nicola Gates, Anne Rutjes, Marcello Di Nisio, Salman Karim, Evrim March, Gabriel Martínez, 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.

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- SERI and Horizon 2020, Other.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol referred throughout to 'cognition-based interventions'. It was subsequently agreed that the widely used term 'cognitive training' accurately described the interventions of interest and was preferred.

Due to the lack of trials, we could not perform any of the planned stratified analyses by trial, participant, and intervention to explore between-trial heterogeneity (see also Appendix 2). Neither could we perform the protocol-defined funnel plot analyses or sensitivity analyses.

Before we published our protocol, we decided to use a hierarchy to select instruments for which we would analyse outcome data in the event of an outcome being assessed with more than one instrument or scale. As the hierarchy was being developed, it was not yet described in the protocol. However, the hierarchy was established before the start of data extraction for this review and the other two reviews related to this topic (Gates 2019a; Gates 2019b)