Exercise interventions for preventing dementia or delaying cognitive decline in people with mild cognitive impairment (Protocol)


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Exercise interventions for preventing dementia or delaying cognitive decline in people with mild cognitive impairment

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the effects of exercise interventions for preventing dementia in people with mild cognitive impairment.

We refer to Forbes 2015b and Forbes 2015c for the review protocols on exercise interventions for maintaining cognitive function in cognitively healthy people in mid and late life.
**BACKGROUND**

**Description of the condition**

*Mild cognitive impairment and dementia*

Prior to the onset of dementia, there can be a prodromal stage termed ‘mild cognitive impairment’ (MCI). MCI typically captures those individuals whose cognitive deficits are beyond those typically seen in normal aging and who are at a high risk of future dementia. Here we define MCI, of the amnestic subtype, as a state where individuals have subjective and objective memory impairment that is inconsistent with age, but normal physical and global cognitive functioning and normal performance in non-memory cognitive domains. The main focus of these criteria is to detect memory problems due to prodromal Alzheimer’s disease (AD). However, not all forms of MCI evolve into dementia (e.g. clinically diagnosed AD) and therefore there have been calls for broader, more inclusive criteria. In 2003, an International Working Group (IWG) developed consensus criteria and expanded the definition of MCI to include objective and subjective impairments in any cognitive domain (*Winblad* 2004). Similarly, the Petersen criteria have been expanded (*Petersen* 2004). In the last five years new criteria have been proposed, including the National Institute on Aging-Alzheimer’s Association (NIA-AA) (*Albert 2011*) criteria for preclinical/prodromal states and updated versions of the IWG criteria (*Dubois* 2014).

Dementia is a syndrome of cognitive and functional decline that is usually progressive. Although most commonly associated with ‘forgetfulness’, memory is not the only function that is affected. Other higher cortical functions such as orientation, comprehension, learning, language, and judgement are often affected. In most cases, the onset of dementia is gradual. In the early stages of the illness, cognitive deficits are relatively mild, but still impact on the ability to perform some normal daily activities. As the syndrome progresses, those affected become increasingly dependent on others for all activities of daily living.

**Types of MCI and dementia**

There are numerous different definitions of MCI, with different focuses (e.g. neuropsychological impairment such as memory versus non-memory) (*Matthews 2007*), prevalence (*Stephan 2007*) and risk of progression to dementia (*Matthews 2008*). Further subdivisions can be made depending on the suspected underlying cause of cognitive deficits, and this has led to the distinction between MCI due to AD and MCI due to vascular disease (termed vascular cognitive impairment no dementia: VCIND). Moreover, attempts have been made to develop new criteria to capture early preclinical states including, for example, pre-MCI that captures individuals with impaired executive function and language, higher apathy scores, and lower left hippocampal volumes compared to normal controls (*Duara* 2011). Still, there is no standardised definition of MCI accepted for use in clinical trials (*Christa Maree Stephan 2013*), but adaptations of the criteria suggested by *Petersen 1999* are commonly used.

Subtypes of dementia are distinguished by the underlying pathology. The four most common subtypes are Alzheimer’s disease (AD) (accounting for an estimated 60% to 70% of all dementia cases), vascular dementia (VaD), dementia with Lewy Bodies (DLB), and frontotemporal dementia (FTD). Accurate diagnosis of the subtypes may be difficult. Mixed pathology is common, with more than 80% of cases having some features of Alzheimer’s disease (*Jellinger 2006; WHO 2012*). However, the older the age the more mixed pathology is present in the brain, and this additional pathology (e.g. vascular) presented next to AD often determines whether a person expresses clinical symptoms (*Savva 2009*).

**Prevalence of MCI and dementia**

In the population-based UK Medical Research Council (MRC) Cognitive Function and Ageing Study (CFAS), when 18 different definitions of MCI were mapped the range of prevalence estimates was found to be variable (0.1% to 42.0%), and conversion rates to dementia generally low (*Stephan 2007*). However, prevalence and conversion rates in specialist settings have been reported to be higher than population-based studies (adjusted conversion rate from MCI to dementia 9.6% versus 4.9%) (*Mitchell 2009*).

The risk of dementia increases with age; only 2% to 10% of cases start before the age of 65 (*WHO 2012*). A WHO report estimates that there were 35.6 million people with dementia in the world in 2010, and that this figure would double every 20 years to reach 65.7 million in 2030 (*WHO 2012*). However, there is a degree of uncertainty about the expected increase in prevalence of dementia. Recent research from the Cognitive Function and Ageing Study (*Matthews 2013*) and work from Denmark (*Christensen 2013*) suggest that age-specific prevalence of dementia may be declining in developed countries, which supports the possibility that there may be modifiable risk factors. Nevertheless, because of population aging, the number of overall cases continues to rise.

**Risk factors**

Although age is the strongest risk factor, other risk factors for AD have been identified. Genetic mutations and modifiers have been identified that play a major role in early onset AD, but are less established and may play a lesser role in the much commoner late-onset disease (*Kim 2014*). Epidemiological evidence (*WHO 2014*) suggests that AD shares many risk factors with vascular disease, including type 2 diabetes, midlife obesity, midlife hypertension, smoking, and physical inactivity (*WHO 2012*). Furthermore, nutrition (B vitamins, antioxidants, omega 3 fatty acids), education, and social and mental stimulation have been proposed to have a protective effect (*Voss 2013; WHO 2012*).

Physical activity or exercise has been identified as an effective strategy that may improve the symptoms of dementia or delay its progression (*Forbes 2015a; Lautenschlager 2010; Middleton 2009*). A recent longitudinal study found that men who exercised regularly had the lowest relative risk of dementia, and these results were greater than for any other identified healthy lifestyle factor (including a healthy body mass index, eating sufficient fruits and vegetables, not smoking, and consuming a low/moderate amount of alcohol; *Elwood 2013*). Numerous epidemiological studies further support the likelihood that regular physical activity may reduce the risk of cognitive decline and dementia in older adults (*Dik 2003; Larson 2006; Podewils 2005; Yaffe 2001*). Longitudinal studies, such as the Nurses’ Health Study in Women (*n = 18,766; Weuve 2004*) with follow-up of up to 15 years, and the Honolulu-Asia Aging Study in men (*n = 2257; Abbott 2004; Taaffe 2008*) with follow-up of over three decades, found that higher levels of physical activity were associated with better cognitive performance and...
lower risk of cognitive decline (Weuve 2004) and dementia (Taaffe 2008). These findings were supported by recent meta-analyses of prospective cohort studies (Blondell 2014; Sofi 2011).

**Description of the intervention**

This review focuses on randomised controlled trials (RCTs) investigating the effect of exercise on cognitive decline and the incidence of dementia in individuals with MCI.

Currently there is no cure for any subtype of dementia, but the identification and targeting of modifiable risk factors such as exercise may offer opportunities to modify its onset and course.

The definitions of exercise interventions for this review are as follows:

- **Physical activity** refers to “body movement that is produced by the contraction of skeletal muscles and that increases energy expenditure” (Chodzko-Zajko 2009).
- **Exercise** refers to “planned, structured, and repetitive movement to improve or maintain one or more components of physical fitness” (Chodzko-Zajko 2009).
- **Aerobic exercise** refers to “exercises in which the body’s large muscles move in a rhythmic manner for sustained periods,” and resistance exercise refers to “exercise that causes muscles to work or hold against an applied force or weight” (Chodzko-Zajko 2009).

**How the intervention might work**

There are several potential mechanisms that link exercise programmes to improved cognitive function. Putative biological mechanisms for each are summarised very briefly in Appendix 1. For a detailed examination of the potential mechanism(s) the reader is directed to three recent reviews (Erickson 2014; Phillips 2014; Voss 2013). Briefly, exercise improves cardiovascular and vascular health by reducing blood pressure (Fleg 2012), arterial stiffness (Fleg 2012), oxidative stress (Covas 2002), systemic inflammation (Lavie 2011), and by enhancing endothelial function (Ghisi 2010), all of which are associated with the maintenance of cerebral perfusion (Ainslie 2008; Churchill 2002; Rogers 1990). Recent evidence supports the hypothesis that cardiovascular health, including cardiorespiratory fitness, is linked to cognitive function (Gauthier 2015). In addition, insulin resistance or glucose intolerance or both are associated with amyloid plaque formation (Farris 2003; Wareham 2000; Watson 2003), which is a feature of AD. Elevated plasma glucose has been associated with poorer cognitive performance (Crane 2013). There is also accumulating evidence that AD is associated with brain insulin resistance (Talbot 2012). Therefore, the well-known impact of exercise on enhancing insulin sensitivity and improving glucose control (Ryan 2000) may be linked with improved cognitive function. Exercise may also preserve neuronal structure and promote neurogenesis, synaptogenesis, and angiogenesis (formation of nerve cells, the gaps between them, and blood vessels, respectively) (Bugg 2011; Kleim 2002), which may be associated with exercise-induced elevation in brain-derived neurotrophic factor (BDNF) (Vaynman 2004), and insulin-like growth factors (Cotman 2007). Animal and human studies investigating the role of BDNF provide evidence that this molecule supports the health and growth of neurons and may regulate neuroplasticity (adaptability of the brain) as we age (Cheng 2003; Vaynman 2004). Intlekofer 2013 recently reported that exercise reinstates hippocampal function by enhancing the expression of BDNF and other growth factors that promote neurogenesis, angiogenesis (formation of blood vessels), and synaptic plasticity. Taken together, animal and human studies indicate that exercise provides a powerful stimulus that can counteract the molecular changes that underlie the progressive loss of hippocampal function in advanced age and AD (Erickson 2012; Voss 2013).

Several clinical studies have investigated the effects of aerobic exercise on healthy adults. A previous Cochrane review that included 12 RCTs of aerobic exercise programmes for older people without known cognitive impairment reported no beneficial effect (Young 2015). They conclude that it remains possible that aerobic exercise may be beneficial for particular subgroups of people, or that more intense exercise programmes could be beneficial (Young 2015).

Few studies have examined the effects of resistance training on cognitive function, and there is some evidence that resistance-only training may provide a beneficial effect (Cassilhas 2007; Lium-Ambrose 2010; Liu-Ambrose 2012). Although some evidence exists on the effects of exercise programmes on cognitive function, the most effective modality to deliver any exercise programme (e.g. frequency, intensity, duration, and modality of exercise) is yet to be evaluated (Forbes 2015).

**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. Robust assessments are needed of the effect size of interventions and of the ‘dose’ and duration of intervention necessary to achieve an effect.

People with MCI will be interested in determining effective interventions in preventing or delaying further cognitive decline.

Although nutritional and behavioural interventions are often perceived to be ‘low risk’, they are not necessarily without the potential to cause harm. For example, trials have found high doses of vitamin E to be associated with higher rates of side effects than placebo (Bjelakovic 2012; Brigelius-Flohe 2007) and exercise carries a risk of injury in older people (Chodzko-Zajko 2009).

This review may be of interest to healthcare providers who diagnose people with MCI as well as to those who provide primary care, and to policy makers.

**OBJECTIVES**

To evaluate the effects of exercise interventions for preventing dementia in people with mild cognitive impairment.

We refer to Forbes 2015b and Forbes 2015c for the review protocols on exercise interventions for maintaining cognitive function in cognitively healthy people in mid and late life.
METHODS

Criteria for considering studies for this review

Types of studies
Included in the review are randomised or quasi-randomised controlled trials, published or unpublished, reported in any language. We will include studies involving both randomised and non-randomised trial arms, but we will only consider results from the former. We may include cross-over studies, but we will extract and analyse data from the first treatment period only. We will include trials irrespective of the length of follow-up after the intervention has finished.

Types of participants
We will include studies of people diagnosed with mild cognitive impairment.

The adaptations of criteria suggested by Petersen 1999 are commonly used to identify 'mild cognitive impairment'. We will include other measures of cognitive status as determined by the study authors' own definitions of 'mild cognitive impairment', and we will record these definitions.

We will contact authors if we need further clarification to determine health status. If there is no response, then clinical experts in the respective review groups will classify the trials, or we will list them as 'Studies awaiting classification'.

Types of interventions
We will include studies comparing the effects of the described exercise interventions with control interventions that are not expected to have specific risk-modifying effects. The control arms would typically involve placebo/social interaction or no intervention/usual care. The minimum treatment duration is set at 12 weeks for all interventions. There is no minimum duration of follow-up. However, all included trials will report outcomes for at least one time point 12 weeks or more after randomisation. Trials in cognitively healthy people with a duration as short as 12 weeks will typically be investigating cognitive enhancement rather than maintenance of cognitive function. We will include these trials in order to give a full picture of the data, although we recognise that the relationship between short-term cognitive enhancement and maintenance of cognitive function over longer periods of time is unclear.

The following experimental interventions are eligible: aerobic, resistance, or combined exercise regimens.

Types of outcome measures

Primary outcomes
The primary outcome concerns:

- Incidence of dementia

- overall cognitive functioning measured with any validated measure, for example, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog); The Mini Mental State Examination (MMSE); Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); Cambridge Cognition Examination (CAMCOG).

Secondary outcomes
Secondary outcomes are any validated measures of:

- specific cognitive functioning subdomain: episodic memory
- specific cognitive functioning subdomain: executive functioning
- specific cognitive functioning subdomain: speed of processing
- quality of life, either generic or disease-specific
- clinical global impression
- functional performance

Where studies include validated biomarkers (e.g. beta-amyloid or tau in cerebrospinal fluid, structural MRI or amyloid imaging) as well as cognitive outcomes, we will extract biomarker data.

Outcomes to be included in the Summary of Findings Table
Critical effectiveness outcomes, to be addressed in the 'Summary of findings' table for each review, will include all outcomes related to cognitive functioning and quality of life.

Search methods for identification of studies

Electronic searches
We will search ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's (CDCIG) specialised register.

ALOIS is maintained by the Trials Search Co-ordinator for the Cochrane Dementia and Cognitive Improvement Group, and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy elderly populations. The studies are identified through:

1. Monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO, and LILACS;
2. Monthly searches of a number of trial registers: ISRCTN; UMIN (Japan’s Trial Register); the WHO portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials, and the Netherlands National Trials Register, plus others);
3. Quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
4. Six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS, see About ALOIS on the ALOIS website (www.medicine.ox.ac.uk/alois).

Details of the search strategies run in healthcare bibliographic databases, used for the 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 will run additional searches in MEDLINE, EMBASE, PsycINFO, CINAHL, ClinicalTrials.gov, and the WHO Portal/ICTRP at http://apps.who.int/trialsearch to ensure that the searches for each suite of reviews are as comprehensive and up-to-date as possible to identify published, unpublished and ongoing trials. The search strategy we will use for the retrieval of reports of trials from MEDLINE (via the Ovid SP platform) can be seen in Appendix 2.

Searching other resources
We will screen reference lists of all included trials. In addition, we will screen reference lists of recent systematic reviews, health technology assessment reports, and subject-specific guidelines identified through www.guideline.gov. We will restrict the search to those guidelines meeting NGC’s 2013 inclusion criteria published in this year or later.

We will contact experts in the field and companies marketing included interventions, in order to provide additional randomised trial reports that are not identified by the search.

Data collection and analysis
We will use 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 describe the same trial, we will include all of them to allow complete extraction of the trial details.

We will use crowdsourcing to screen the search results. Details of this have been described here: www.medicine.ox.ac.uk/alois/contentmodifiable-risk-factors. In brief, teams of volunteers will perform a ‘first assess’ on the search results. The volunteers will be recruited through the author team and the Cochrane Dementia Group’s institutions. They will screen the results using an online tool developed for the Cochrane EMBASE project but tailored for this programme of work. The crowd will decide based on a reading of title and abstract whether the citation is describing a randomised or quasi-randomised trial, irrespective of the citations topic. We estimate that this will remove 75% to 90% of results retrieved. The author team will then screen the remaining results.

Data extraction and management
Two review authors, working independently, will extract trial information using a standardised and piloted extraction method, referring also to a guidance document, and resolving discrepancies by discussion, or by the involvement of a third review author. Where possible, we will extract the following information related to characteristics of participants, intervention, 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

Intervention characteristics
• Type of exercise programme (e.g. aerobic, walking, cycling)
• description of the control condition
• duration and frequency of treatment sessions
• duration of treatment programme
• any concomitant treatments

We will extract cardiorespiratory or strength changes as reported; we expect them to involve increases in maximal oxygen consumption (VO2max), six-minute walk test, sit to stand, and or maximal strength (one repetition-maximum; 1-RM).

Methodological characteristics
• trial design (individual or cluster randomisation; parallel-group, factorial, or cross-over design)
• number of participants
• outcome measures used
• duration of follow-up as measured from randomisation
• duration of follow-up as measured from end of treatment
• source of financial support
• publication status

If outcome data are available at multiple time points within a given trial, we will group them with topic-specific cut-offs to describe short-term (up to one year), medium-term (one to two years) and longer-term results (more than two years). Within these time periods, we will extract the longest available data reported by the study (for example, if the study reports data at six months, nine months and one year, we will extract only the one-year data and will analyse these for the one-year (short-term) time point. For dichotomous outcomes (such as incident MCI or dementia), we will extract from each trial the number of participants with each outcome at each time point. For continuous outcomes, we will extract the number of participants in whom the outcome was measured, and the mean and standard deviation of the change from baseline for each outcome at each time point. If changes from baseline data are not available, we will extract the mean value at each time point. When necessary and if possible, we will approximate means and measures of dispersion from figures in the reports. For cross-over trials, we will extract data on the first treatment period only. Whenever possible, we will extract intention-to-treat data i.e. analysing all participants according to the group randomisation; if this is not available, then we will extract and report data from available case analyses. If neither of these data are available, we will consider data from per protocol analyses. We will contact the authors if we cannot 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 AWSR, one member of the author team and one experienced review author provided by the editorial team will independently assess the risk of bias in each of the included trials, using the Cochrane ‘Risk of bias’ tool (Higgins 2011), and resolving disagreements by
consensus. We will assess 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 analyses used (true intention-to-treat versus other). The general definitions that we will use are reported in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). The review-specific definitions described in Appendix 3 are in part derived from a previously published systematic review (Rutjes 2012).

Measures of treatment effect
The measure of treatment effect for continuous outcomes will be an effect size (standardised mean difference), defined as the between-group difference in mean values divided by the pooled standard deviation (SD). We will express the treatment effect for dichotomous outcomes as a risk ratio (RR) with a 95% confidence interval (CI).

Unit of analysis issues
If we include cluster-randomised trials, we aim to extract outcome data from analyses that take the effect of clustering into account (for example, an odds ratio with its confidence interval). When this is not possible, we will attempt to account for clustering by reducing the trial to its 'effective sample size', dividing the original sample size by the design effect, as described in Section 16.3.4 of the Cochrane Handbook (Higgins 2011; Rao 1992).

Dealing with missing data
Missing data in the individual trials may put the study estimates of effects at a high risk of bias and may lower the overall quality of the evidence according to GRADE (Higgins 2011). We will deal with missing data in our 'Risk of bias' assessments and plan to evaluate attrition bias in stratified analyses of the primary outcomes (Appendix 3). We will thus analyse the available information and will not contact authors with a request to provide missing information, nor will we impute missing data ourselves.

Assessment of heterogeneity
We will examine heterogeneity in stratified analyses by trial, participant, and intervention.

Assessment of reporting biases
If we can identify a sufficient number of trials (at least 10), we will use funnel plots with appropriate statistics to explore reporting biases and other biases related to small-study effects (see also Data synthesis).

Data synthesis
Whenever possible, we will use standard inverse-variance random-effects meta-analysis to combine outcome data across the trials (DerSimonian 1986) at end of trial and, if possible, at least one additional time point (see Primary outcomes and Data extraction and management for definitions of time points). We will visually inspect forest plots for the presence of heterogeneity and will calculate the variance estimate tau^2 as a measure of between-trial heterogeneity (DerSimonian 1986). We prespecify a tau^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). The I^2 statistic and the corresponding Chi^2 test will be depicted in addition (Higgins 2003), to facilitate readers more familiar with this statistic. I^2 describes the percentage of variation across trials attributable to heterogeneity rather than chance, with values of 25%, 50%, and 75% typically being interpreted as low, moderate, and high between-trial heterogeneity. Tau^2 will be preferred over I^2 in the interpretation of between-trial heterogeneity, as the interpretation of I^2 can be largely affected by the precision of trials included in the meta-analysis (Rücker 2008). If sufficient trials (around 10) can be identified that contribute to the analyses of primary outcomes, we will explore the association between trial size and treatment effects using funnel plots, where we plot effect sizes on the x-axis against their standard errors (SEs) on the y-axis (Moreno 2009; Sterne 2001). We will assess funnel plot asymmetry with the appropriate statistics for the metrics analysed (Higgins 2011). All P values are two-sided. We will probably conduct statistical analyses in Review Manager 5 and in STATA, release 13 (StataCorp, College Station, Texas), but this may vary across reviews depending on the statisticians involved.

Subgroup analysis and investigation of heterogeneity
If we identify 10 or more trials that contribute to the analyses of primary outcomes, we aim to perform stratified analyses of the primary effectiveness outcome, according to the following trial characteristics: concealment of allocation, blinding of participants, blinded outcome assessment, intention-to-treat analysis, trial size, type of control intervention, duration of treatment, and length of follow-up from randomisation. We will use univariable random-effects meta-regression models (Thompson 1999) as tests of interaction between treatment effect and these characteristics. We will determine the cut-off for trial size for each review topic separately, based on a sample size calculation for the primary effectiveness outcome. We will define cut-offs for treatment duration and follow-up duration specifically for each review topic. In both cases, we will define the cut-offs before the start of data extraction.

Sensitivity analysis
For each review, we will perform one sensitivity analysis for the primary effectiveness outcome, including high-quality trials only. We will define high quality by the results of the stratified analyses, based on the statistically significant (P < 0.05) interaction terms for methodological characteristics. If possible, we will also perform sensitivity analyses according to the definitions used for MCI or dementia, namely including only those trials that used internationally accepted definitions.

GRADE and 'Summary of findings' table:
We will use GRADE to describe the quality of the overall body of evidence (Guyatt 2008; Higgins 2011) for each outcome in the 'Summary of findings' table. We define quality as the degree of confidence which we can place in the estimates of treatment benefits and harms. There are 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 which do not have serious limitations as ‘high quality’. However, several factors can lead to the downgrading of the evidence to moderate, low, or very low. The degree of downgrading is
determined by the seriousness of these factors: study limitations (risk of bias); inconsistency; indirectness of evidence; imprecision, and publication bias (Guyatt 2008; Higgins 2011).

**Results**

**ACKNOWLEDGEMENTS**

This protocol is largely based on a general template constructed for the development of a larger series of protocols and reviews covered by a National Institute for Health Research (NIHR Systematic Reviews Programme Grant). The common protocol covered four types of intervention, for which some evidence exists, that may modify the risk of developing cognitive impairments or dementia. These include nutritional supplements, exercise, cognition, and dietary interventions. These interventions will each be evaluated in three distinct populations: healthy mid life, healthy elderly, and those with mild cognitive impairment (MCI).
Additional references

Abbott 2004

Adlard 2005

Ainslie 2008

Albert 2011

Barrientos 2011

Bjelakovic 2012

Blondell 2014

Brigelius-Flohe 2007

Bugg 2011

Cassilhas 2007

Cheng 2003

Chodzko-Zajko 2009

Christa Maree Stephan 2013

Christensen 2013

Churchill 2002

Cosvas 2002

Crane 2013

Da Costa 2012
Da Costa 2014

DerSimonian 1986

Dik 2003

Duara 2011

Dubois 2014

Ehninger 2003
Ehninger D, Kempermann G. Regional effects of wheel running and environmental enrichment on cell genesis and microglia proliferation in the adult murine neocortex. Cerebral Cortex 2003;13(8):845-51. [PUBMED: 12853371]

Elwood 2013

Ericksen 2012

Ericksen 2014

Farris 2003

Fleg 2012

Forbes 2015a

Forbes 2015b

Forbes 2015c

Gauthier 2015

Ghisi 2010

Guyatt 2008

Higgins 2003

Higgins 2011

Intlekofer 2013

Jellinger 2006
Kim 2014

Klein 2002

Kohman 2013

Larson 2006

Lautenschlager 2010

Lavie 2011

Liang 2010

Liu-Ambrose 2010

Liu-Ambrose 2012

Matthews 2007

Matthews 2008

Matthews 2013

Middleton 2009

Mitchell 2009

Moreno 2009

Murugesan 2012

Petersen 1999

Petersen 2004

Phillips 2014

Podewils 2005
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Rücker 2008

Radak 2014

Rao 1992

Reichenbach 2010

Rogers 1990

Rutjes 2009a

Rutjes 2009b

Rutjes 2010

Rutjes 2012

Ryan 2000

Rückert 2008

Savva 2009

Sofi 2011

Spiegelhalter 2004

Stephan 2007

Sterne 2001

Taafe 2008

Talbot 2012

Thompson 1999

Vaynm 2004

Voss 2013

Wareham 2000
Appendix 1. Biological plausibility of effects of exercise intervention on cognitive outcomes

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Biological plausibility</th>
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<tbody>
<tr>
<td><strong>Aerobic</strong></td>
<td></td>
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<tr>
<td>Inflammation (CRP, pro-inflammatory cytokines)</td>
<td>Inflammation may impair growth factor signalling and aerobic exercise may reduce systemic inflammation (Cotman 2007).</td>
</tr>
<tr>
<td>Antioxidant Capacity / oxidative stress</td>
<td>Excessive reactive oxygen species may lead to neurodegeneration. Antioxidant capacity and oxidative stress may be reduced with aerobic exercise (Radak 2014).</td>
</tr>
<tr>
<td>Growth Factors (BDNF, IGF-1, VEGF)</td>
<td>BDNF, IGF-1, and VEGF are growth factors associated with neurogenesis (Voss 2013) and angiogenesis, and are increased with aerobic exercise.</td>
</tr>
<tr>
<td>Neurogenesis/dendritic branching</td>
<td>Relationship between fitness and hippocampal volume has been observed in humans, and moderate-intensity walking for 1 year increased the size of the anterior hippocampus (Erickson 2014). Also, greater medial temporal lobe volumes have been observed in those that exercise (Bugg 2011).</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Improved brain insulin signalling. Insulin is also a vasodilator and may improve cerebral blood flow (Talbot 2012).</td>
</tr>
<tr>
<td>Cerebral Blood flow and angiogenesis</td>
<td>Relationship between cerebral blood flow and fitness (Ainslie 2008). Exercise increases hippocampal capillary density and branching (Murugesan 2012).</td>
</tr>
<tr>
<td>Amyloid-β plaque</td>
<td>Exercise decreases extracellular amyloid-β in various regions of the brain (Adlard 2005) and is inversely related to the amount of exercise regularly performed (Liang 2010).</td>
</tr>
<tr>
<td>Microglia</td>
<td>Aerobic exercise reduces aging-related microglial priming and activation, which could reduce brain inflammation (Barrientos 2011; Kohman 2013). Exercise also increases microglia cells, which if protective, could aid in neuro-protection (Ehninger 2003).</td>
</tr>
</tbody>
</table>
### Resistance

<table>
<thead>
<tr>
<th>Inflammation (CRP, pro-inflammatory cytokines)</th>
<th>Associated in the maintenance of cerebral perfusion and may impair growth factor signalling (Cotman 2007).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Factors (BDNF, IGF-1, VEGF)</td>
<td>BDNF, IGF-1, and VEGF are growth factors associated with neurogenesis (Voss 2013) and are increased with resistance exercise.</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Improved brain insulin signalling. Insulin is a vasodilator and may improve cerebral blood flow (Talbot 2012).</td>
</tr>
</tbody>
</table>

#### Combinations of one or more exercise interventions

See above

See above

**FOOTNOTES:** Abbreviations: CRP, C-reactive protein; BDNF, Brain-derived neurotrophic factor; IGF-1, Insulin-like growth factor 1; VEGF, Vascular endothelial growth factor.

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### Appendix 2. MEDLINE search strategy

1. Exercise/
2. Cool-down Exercise/
3. Muscle Stretching Exercises/
4. Physical Conditioning, human/
5. Plyometric Exercise/
6. Resistance Training/
7. Running/
8. Jogging/
9. Swimming/
10. Walking/
11. Warm-up Exercise/
12. Physical Fitness/
13. Exercise Movement Techniques/
14. Physical Endurance/
15. Physical Exertion/
16. Exercise Therapy/
17. Tai Ji/
18. Dancing/
19. Dance Therapy/
20. "physical activit*".ti,ab.
21. "physical exercis*".ti,ab.
22. ((exercis* adj3 train*) OR exercising).ti,ab.
23. exercis* adj 3 prog*.ti,ab.
24. (resistance adj2 train*).ti,ab.
25. aerobic*.ti,ab.
26. (stretch adj4 (muscle* OR exercis*)).ti,ab.
27. walking.ti,ab.
28. running.ti,ab.
29. cycling.ti,ab.
30. "exercise bike*".ti,ab.
31. swim*.ti,ab.
32. fitness.ti,ab.
33. "physical endurance".ti,ab.
34. "physical performance".ti,ab.
35. jogging.ti,ab.
36. yoga.ti,ab.
37. handball.ti,ab.
38. "tai ji" OR "tai chi".ti,ab.
39. (dance OR dancing).ti,ab.
40. (cardiovascular adj3 exercis*).ti,ab.
41. or/1-40
42. "aging/
43. Aged/
44. "Aged, 80 and over"/
45. Middle Aged
46. Age Factors
47. Mild Cognitive Impairment/
48. MCI.ti,ab.
49. AAMI.ti,ab.
50. ACMI.ti,ab.
51. ARCD.ti,ab.
52. CIND.ti,ab.
53. (nMCI OR aMCI OR mMCI OR MCIa).ti,ab.
54. "old* age*".ti,ab.
55. elderly.ti,ab.
56. "middle age*".ti,ab.
57. "old*adults".ti,ab.
58. seniors.ti,ab.
59. "senior citizens".ti,ab.
60. "community dwelling".ti,ab.
61. pensioners.ti,ab.
62. or/42-61
63. "Cognition/
64. "Cognition Disorders/
65. Memory/
66. Memory Disorders/
67. Brain/
68. Executive Function/
69. (cognit* ADj3 (func* OR declin* OR impair* OR impor* OR improv* OR deficit* OR progress* OR perform* OR abilit*)).ti,ab.
70. "mental perform*".ti,ab.
71. memory.ti,ab.
72. "executive function".ti,ab.
73. Dementia/
74. Alzheimer Disease/
75. demen*.ti,ab.
76. alzheimer*.ti,ab.
77. or/63-76
78. randomized controlled trial.pt.
79. controlled clinical trial.pt.
80. randomized.ab.
81. placebo.ab.
82. drug therapy.fs.
83. randomly.ab.
84. trial.ab.
85. groups.ab.
86. or/78-85
87. exp animals/ not humans.sh.
88. 86 not 87
89. 88 AND 77 AND 62 AND 41 [all results]
90. "Exercise/
91. "Cognition/
92. "Aging/
Appendix 3. Characteristics to be used in the stratified analyses to explore between-trial variations in intervention effects

<table>
<thead>
<tr>
<th>Item</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bias-related characteristics</strong>*</td>
<td></td>
</tr>
<tr>
<td>Concealment of allocation (avoiding selection bias)</td>
<td>We will use the guidance from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) to judge bias related to sequence generation and concealment of allocation, using the two Cochrane ‘Risk of bias’ items. From these, the statistician will derive a single variable to be used in the stratified analysis: we will judge allocation concealment to be at low risk of bias if the investigators responsible for participant selection were unable to suspect before allocation which treatment was next. We will downgrade concealment to a high risk of bias if there is evidence of inadequate sequence generation.</td>
</tr>
</tbody>
</table>
| Blinding of participants and personnel (avoiding performance bias) | We will judge this to be at low risk of bias if:  
- a credible sham procedure was used; or if a placebo supplement or pill was used that was reported to be identical in appearance to the experimental intervention and the specific outcome or group of outcomes is/are likely to be influenced by lack of blinding.  
- 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) | **For self-reported/partner-reported outcomes:**  
We will judge this to be at low risk of bias if:  
- we consider self-reported outcomes AND blinding of participants 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 participants was reported.  
**For other outcomes:**  
We will consider outcome assessment to be blinded if it was reported to be blinded. |
| Statistical Analyses (avoiding attrition bias) | **For continuous outcomes**  
We will judge this to be at low risk of bias if:  
- at least 90% of the participants randomised were analysed AND the difference in percentage of participants not analysed was 5% or lower across trial arms,  
- for trials using imputations to handle missing data: the percentage of participants with missing data did not exceed 20% AND the difference in percentage of participants with imputed data was 5% or lower across trial arms AND we judge applied imputation methods to be appropriate. We will consider multiple imputation techniques appropriate, but we will judge simple methods such as ‘last observation carried forward’ or ‘baseline carried forward’ as inappropriate.  
**For binary outcomes of rare events**  
We will judge this to be at low risk of bias if:  
- the event rate is low (e.g. incidence of dementia) AND at least 95% of the participants randomised were analysed AND there is no evidence of differential reasons for missing data that may alter the estimate AND the rate of missing data does not exceed the expected event rates.  
**For binary outcomes of non-rare events**  
We will judge this to be at low risk of bias if:  
- at least 90% of the participants randomised were analysed AND the difference in percentage of participants not analysed was 5% or lower across trial arms AND there is no evidence of differential
reasons for missing data that may alter the estimate AND the rate of missing data does not exceed the expected event rates.

**Trial Size**
We will determine the cut-off to distinguish small from larger trials by a sample size calculation on the primary outcome.

**Follow-up duration**
As no literature is yet available on follow-up duration as a possible effect modifier, we will use the median follow-up duration to categorise in short-term and long-term follow-up durations.

**Treatment related characteristics**

**Treatment duration**
As no literature is yet available on treatment duration as a possible effect modifier, we will use the median follow-up duration to categorise in short-term and long-term treatment durations.

* The descriptions depicted in this Table are in addition to the guidance provided by Cochrane (Higgins 2011).

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Completion of the protocol: Scott Forbes, Dorothy Forbes, Sean Forbes, Catherine Blake, Lee Yee Chong, Emily Thiessen, Anne Rutjes, Jonathan Little
Completion of the searches: Anna Noel-Storr
Screening of references:
Acquisition of data:
Risk of bias Assessments and GRADING:
Statistical analysis:
Overall interpretation of data:
Manuscript preparation:

**DECLARATIONS OF INTEREST**

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  Intramural Support

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