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[Intervention Protocol]

Exercise interventions for maintaining cognitive function in cognitively healthy people in mid life

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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 on cognitive function in cognitively healthy people in mid life.

We refer to [Forbes 2015b](#) for the review protocol on Exercise interventions for maintaining cognitive function in cognitively healthy people in late life and to [Forbes 2015c](#) for the review protocol on Exercise interventions for prevention of dementia in people with mild cognitive impairment.

BACKGROUND

Description of the condition

Cognitive health, mild cognitive impairment and dementia

Cognitively healthy or successful cognitive aging can be defined as “Not just the absence of cognitive impairment, but the development and preservation of the multi-dimensional cognitive structure that allows the older adult to maintain social connectedness, and ongoing sense of purpose, and the abilities to function independently, to permit functional recovery from illness and injury, and to cope with residual cognitive deficits”, but there is no broad consensus on such definition yet (Depp 2012; Hendrie 2006). Successful cognitive aging is distinct from mild cognitive impairment (MCI) and dementia.

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 judgment 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. Prior to the onset of the disease, there is usually a stage of mild cognitive impairment (MCI) when cognitive deficits beyond those of normal aging are detectable, but ordinary activities are not significantly affected.

Types of MCI and dementia

There are numerous different definitions of MCI, with different focus (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 Alzheimer's disease (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 (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 proportion of cognitive impairment attributable to Alzheimer's reduces with age (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). The influence of physical activity on cognition may vary across age groups (Bielak 2014). Bielak 2014 found that cognition was higher in young physically active adults and this cognitive advantage was maintained over time. 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 function and the incidence of dementia in mid life.

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 and/or glucose intolerance 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; Liu-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 programmes (e.g. frequency, intensity, duration, and modality of exercise) is yet to be evaluated (Forbes 2015a).

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.

For individuals, fear of cognitive decline and dementia may be powerful motivators to seek preventive interventions. Nutritional supplements and cognitive activities (e.g. computerised ‘brain training’ games) in particular are subject to promotion by those with commercial interests. It is important for people to know whether time and money invested to prevent cognitive decline are likely to be well spent. Information about adverse effects is also important. 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).

OBJECTIVES

To evaluate the effects of exercise interventions on cognitive function in cognitively healthy people in mid life.

We refer to [Forbes 2015b](#) for the review protocol on Exercise interventions for maintaining cognitive function in cognitively healthy people in late life and to [Forbes 2015c](#) for the review protocol on Exercise interventions for prevention of dementia in people with mild cognitive impairment.

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 cognitively healthy people in mid life.

The cognitive status of participants will be determined by the study authors' own definitions of 'cognitively healthy', and we will record these definitions.

We will classify trials or subgroup analyses focusing on participants with ages ranging from 40 to 65 years as mid life, and those of 65 years and older as late life. We will cover participants with a mean age of 65 years in a separate review ([Forbes 2015b](#)). Where studies clearly state the age of participants among their inclusion criteria, we will use this as in the classification. If this is not available, we will use the median and range, or mean and standard deviation, to help place studies with a broad age range into the most appropriate review category. For example, we will consider a study with an age range of 40 to 70, with a median of 50 years or less as mid life, whereas we would probably categorise one with a median of 65 years or more as late life.

We will contact authors if we need further clarification to determine health status or age. 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 include these trials in order to give a full picture of the data, although we acknowledge 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 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).

The main time point of interest is *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 will also extract and present outcome data reported at other time points after randomisation.

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
- incidence of MCI or dementia.

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 the biomarker data.

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 the included interventions, in order to acquire additional randomised trial reports that we do not identify by the searches.

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 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/content/modifiable-risk-factors. In brief, teams of volunteers will perform a 'first assess' on the search results. We will recruit the volunteers through the author team'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 cardio-respiratory or strength changes as reported; we expect them to involve an increase 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 reported data at six months, nine months and one year, we will extract and analyse only the one-year data 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 form of 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 τ^2 as a measure of between-trial heterogeneity (DerSimonian 1986). We prespecify a τ^2 of 0.04 to represent low heterogeneity, 0.09 to represent moderate heterogeneity, and 0.16 to represent high heterogeneity between trials (Spiegelhalter 2004). 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. τ^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).

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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).

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

Exercise	Biological plausibility
Aerobic	
Inflammation (CRP, pro-inflammatory cytokines)	Inflammation may impair growth factor signalling and aerobic exercise may reduce systemic inflammation (Cotman 2007).
Antioxidant Capacity / oxidative stress	Excessive reactive oxygen species may lead to neurodegeneration. Antioxidant capacity and oxidative stress may be reduced with aerobic exercise (Radak 2014).
Growth Factors (BDNF, IGF-1, VEGF)	BDNF, IGF-1, and VEGF are growth factors associated with neurogenesis (Voss 2013) and angiogenesis, and are increased with aerobic exercise.
Neurogenesis/dendritic branching	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).
Insulin sensitivity	Improved brain insulin signalling. Insulin is also a vasodilator and may improve cerebral blood flow (Talbot 2012).
Cerebral Blood flow and angiogenesis	Relationship between cerebral blood flow and fitness (Ainslie 2008). Exercise increases hippocampal capillary density and branching (Murugesan 2012).
Amyloid- β plaque	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).
Microglia	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).
Resistance	
Inflammation (CRP, pro-inflammatory cytokines)	Associated in the maintenance of cerebral perfusion and may impair growth factor signalling (Cotman 2007).
Growth Factors (BDNF, IGF-1, VEGF)	BDNF, IGF-1, and VEGF are growth factors associated with neurogenesis (Voss 2013) and are increased with resistance exercise.

(Continued)

Insulin sensitivity	Improved brain insulin signalling. Insulin is a vasodilator and may improve cerebral blood flow (Talbot 2012).
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Combinations of one or more exercise interventions

See above	See above
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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 reduc* OR impair* OR improve* 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. dement*.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/
93. *Mild Cognitive Impairment/
94. "Aged, 80 and over"/ or Aged/ or Middle Aged/
95. 92 or 93 or 94
96. 90 and 91
97. 78 or 79
98. 95 and 96 and 97 ['high relevancy' results - directly sent to core author team]
99. 89 not 98 [results minus those sent directly to the author team. These will be screen by a team of citation screeners]

Appendix 3. Characteristics to be used in the stratified analyses to explore between-trial variations in intervention effects

Item	Definition
<i>Bias-related characteristics*</i>	
Concealment of allocation (avoiding selection bias)	We will use the guidance from the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> (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.
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)	<i>For self-reported/partner-reported outcomes:</i> 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. <i>For other outcomes:</i> We will consider outcome assessment to be blinded if it was reported to be blinded.
Statistical Analyses (avoiding attrition bias)	<i>For continuous outcomes</i> 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. <i>For binary outcomes of rare events</i> 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. <i>For binary outcomes of non-rare events</i> 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.

(Continued)

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

CONTRIBUTIONS OF AUTHORS

Completion of the protocol: Scott Forbes, Dorothy Forbes, Sean Forbes, Catherine Blake, Lee Yee Chong, Emily Thiessen, Anne Rutjes, Jonathan Little

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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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