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Dietary interventions for maintaining cognitive function in cognitively healthy people in mid life (Protocol)

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[Intervention Protocol]

Dietary 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:

In this review we will set out to evaluate the effects of dietary interventions for maintaining cognitive function in cognitively healthy people in mid-life and preventing cognitive decline in late life.

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, an 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 a 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 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 affect 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 MCI when cognitive deficits beyond those of normal ageing are detectable, but ordinary activities are not significantly affected.

Types of MCI and dementia

There are numerous 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 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 their underlying pathology. The four most common subtypes are Alzheimer's disease dementia (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 proportion of dementia attributable to Alzheimer’s disease reduces with age (Savva 2009).

Prevalence of MCI and dementia

In the population-based UK Medical Research Council 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: according to a World Health Organization (WHO) report, only 2% to 10% of cases start before the age of 65 (WHO 2012). The same report estimated 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 (World Health Organization 2012). However, there is a degree of uncertainty about the expected increase in prevalence of dementia. Recent CFAS research by Matthews 2013, and by Christensen 2013 on work in Denmark suggests that age-specific prevalence of dementia may be reducing in developed countries which supports the possibility that there may be modifiable risk factors. Nevertheless, because of population ageing, the overall prevalence continues to rise.

Cognitive function across the lifecourse

There is wide variation between individuals with regards to timing of the onset of cognitive decline or cognitive impairment and the exact age of onset for cognitive decline remains unknown. Until recently cognitive decline was thought to only begin at the age of 60, and a comprehensive literature review in 2004 concluded that there was little evidence of cognitive decline occurring in cognitively healthy people before this age (Hedden 2004). However, a more recent longitudinal study examined whether cognitive decline began before the age of 60 and showed that cognitive decline was evident in younger age groups, for different cognitive measures including reasoning, memory, phonemic and semantic fluency, and cognitive decline was found across all age groups including among those aged 45 to 49 at baseline (Singh-Manoux 2012). Further, cross-sectional studies have suggested that cognitive decline may start as young as 20 to 30 years old for cognitively healthy adults (Salthouse 2009). Many interventions to reduce the risk of cognitive decline currently target those aged 60 years and older; however, if cognitive decline begins at an earlier stage of life then this may be too late for the interventions to be effective as a substantial amount of cognitive decline may have already occurred. Therefore, research into the usefulness of implementing interventions to protect and maintain cognitive function in younger midlife age groups may be more beneficial.

Risk factors for cognitive decline across the lifecourse

Age is the strongest risk factor for cognitive decline; however, it is not the only risk factor. Early and midlife influences of various lifecourse factors (e.g. socioeconomic status and dietary patterns) towards cognitive function have been shown in many studies. A higher socioeconomic status and higher levels of education in younger life have been associated with absolute level of cognitive function in later life; however, there is still debate as to whether this protects against cognitive decline in older life (Everson-Rose 2003). Further, a lower socioeconomic status at midlife has also been shown to have a strong influence on cognitive decline in this age group. To further complicate matters, the relationship between different risk factors throughout the lifecourse and cognitive decline in later life is also largely dependent on the age at which they are measured and may also differ by gender. Current epidemiological evidence () suggests that

known risk factors for vascular disease, including diabetes, midlife obesity, midlife hypertension, smoking and physical inactivity may also be risk factors for cognitive decline and dementia (WHO 2012; World Alzheimer Report 2014). For instance, cardiovascular conditions such as metabolic syndrome have been associated with an increased risk of chronic cardiovascular and neurodegenerative diseases including stroke, coronary heart diseases and dementia (Grundy 2012; Panza 2011). The mechanisms linking the metabolic syndrome to an increased risk of cognitive decline are still poorly understood, but recent hypotheses have proposed that dementia may be the results of metabolic and vascular impairment involving the deregulation of insulin and nitric oxide (NO) signalling pathways (Bourdel-Marchasson 2010; Paul 2011; Siervo 2014).

The cognitive reserve hypothesis suggests different factors across the lifespan, such as education, occupation and regular participation in mentally stimulating activities, can build up a reserve which increases an individual's resistance to cognitive decline and dementia. Neuropathological studies have shown that cognitively healthy individuals can present with advanced Alzheimer's disease pathology at autopsy. The cognitive reserve hypothesis attempts to explain these findings by suggesting these individuals have built up a cognitive resilience throughout their lives which has protected them from the classic hallmarks of Alzheimer's disease, such as amyloid-beta plaques. However, the exact components of the cognitive reserve model are yet to be clarified (Harrison 2015). Dietary habits is also one component which has been suggested to supply the cognitive reserve. Avoidance of obesity and cardiovascular disease by adopting a diet low in saturated fat has been suggested to be part of the cognitive reserve hypothesis. Further, adoption of certain dietary components such as vitamins B12, B6 and resveratrol may be protective, but current evidence of this is lacking. Yet this may be due to applying them to trials too late, when disease is already too advanced; therefore, using them as a primary prevention strategy for cognitive decline may be more useful, but this has not been the focus of research (Esiri 2012). These associations show the importance of investigating protective factors against cognitive decline at an earlier stage of life and that factors affecting cognitive decline do not just begin in later stages of life. Primary prevention strategies to target modifiable risk factors in this younger age group may be more appropriate to focus research towards as there are few available treatment options for cognitive decline in later life.

Description of the intervention

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

This review focusses on randomised control trials (RCTs) investigating the effect of dietary interventions for maintaining cognitive function in healthy subjects during mid-life. Appendix 1 provides an overview of the dietary interventions that will be considered. These vary from foods rich in specific micronutrients, to fatty acids, flavonoids and other non-vitamin nutrients and non-nutrients, to more complex diets such as the Mediterranean diet or Dietary Approach to Stop Hypertension (DASH) diet. The specific effects of vitamin supplements are covered in three other reviews in this programme (Abraham 2015; Al-Assaf 2015; Denton 2015).

How the intervention might work

The interventions which fall within the scope of this review are varied and are based on the largely still poorly understood pathophysiology of dementia. Putative biological mechanisms for each are summarised briefly in Appendix 1.

Dietary risk factors for dementia often overlap and act synergistically with those for cardiovascular and metabolic diseases. Cardiovascular risk factors such as high blood pressure and excess adiposity have been negatively associated with cognitive decline and dementia (Elias 2012; Qiu 2005). Hypertension is known to increase the probability of arterial blockage, which can prevent adequate blood flow to the brain and may lead to adverse effects upon cognition (Barnard 2014; Solomon 2009). Hypertension in midlife has consistently been found to be associated with AD and dementia in later life (Qiu 2005); whereas in later life, risk of AD and dementia are more likely to be associated with hypotension (Kennelly 2009). Hyperglycaemia and insulin resistance are the key clinical features of type 2 diabetes. The association of diabetes with impaired cognitive function and dementia has been confirmed in several longitudinal studies. The Rotterdam study showed that diabetes doubled the risk of developing dementia which was directly associated with diabetes severity (i.e. patients treated with insulin). The association between diabetes and dementia was confirmed in a twin-cohort study which also showed that compared with late-life diabetes (onset age 65 years and over), the risk effect of mid-life diabetes (onset age less than 65 years) on dementia was stronger. These cardiovascular risk factors are incorporated within the concept of metabolic syndrome which has insulin resistance and endothelial dysfunction as key pathogenetic characteristics (Grundy 2012). Targeted dietary interventions can improve either or both pathogenetic components and therefore have downstream effects on cardiovascular risk as well as modify the prospective risk for cognitive decline.

Both animal models and clinical studies have been used to try to explore the possible mechanisms underlying the effects of certain foods and diets towards cognitive functioning. Other proposed mechanisms include anti-oxidant, improved insulin sensitivity, and anti-inflammatory processes (Hughes 2009). Supplementation of nutrients with anti-oxidant properties (i.e. vitamin E, vitamin C) has been proposed and the body of evidence is particularly focused on vitamin E. Total tocopherols levels may have neuro-protective properties, which seems to be supported by a significant association between low levels of total tocopherols and cognitive decline. The role of vitamin C has also been investigated but the evidence from cohort studies is inconclusive (Crichton 2013). The protective role of fruit and vegetables on health outcomes could be also related to the high content of minerals (i.e. potassium, magnesium) or other substances such as flavonoids or inorganic nitrate (Hord 2009; Slavin 2012). Calcium intake may also play a protective role as suggested by recent epidemiological findings suggesting a direct association of dairy products with cardiovascular outcomes (Huth 2012). However, the evidence of the effects of these nutritional factors on cognitive function remain largely unknown and more research is needed to elucidate mechanisms as well as confirm effects in cognitively impaired populations.

Foods containing flavonoids such as red wine, fruits and vegetables have been found to interact with specific neural

pathways and promote the maintenance of synapses (Williams 2012). Flavonoids may enhance cognitive function by enhancing neuronal function and stimulating neurogenesis. They interact with neuronal signalling pathways mediating neurodegeneration and neuroinflammation via the modulation of signalling pathways such as mitogen-activated protein-kinase pathway (MAPK), phosphoinositide 3-kinase (PI3 kinase/Akt) or NO pathways (Spencer 2010). The role played by dietary fat intake is more complex to disentangle and requires a sub-categorisation into the different types of fat (i.e. saturated, mono- and poly-unsaturated) to understand the effects on cognitive function and brain morphology. Saturated fat, for instance, has been found to be a risk factor for cognitive decline during mid-life but no such association has been demonstrated in older populations (Roberts 2012). Poly-unsaturated fatty acids are essential components of the brain and the function of the neuronal plasma membrane is influenced by the fatty acid composition. Poly-unsaturated fatty acids have anti-thrombotic and anti-inflammatory properties and are implicated in neurogenesis and synaptic growth (Denis 2013).

The translation from the epidemiological evidence into clinical trials has been mostly focussed on single interventions testing a specific mechanistic pathway involved in the dementia pathogenesis such as oxidative stress, vascular impairment or inflammation. The advantage of these approaches is the ability to test specific hypotheses but often they have reported negative findings. A more comprehensive approach is to focus on nutritious dietary patterns known to have beneficial effects on human health such as the Mediterrean diet or, more recently, the Dietary Approach to Stop Hypertension (DASH). The epidemiological evidence from the former is largely in support of a preventative role for cognitive decline and dementia while the evidence from the latter is still preliminary. The ENCORE trial showed that an 8-week DASH diet intervention improved psychomotor speed compared to the control group (Smith 2010). The PREDIMED is the first large trial testing the effects of a Mediterrean-like dietary interventions in participants at high vascular risk on several health outcomes including cognitive function. Specifically, participants allocated to the Mediterrenean diet arm showed higher mean Mini Mental State Examination (MMSE) and Clock Drawing Test (CDT) scores after a follow-up of about 6 years (Martinez-Lapiscina 2013).

The effects of the dietary interventions were tested in conditions of energy balance to rule out the confounding beneficial effects of caloric restriction on cognitive function (Fusco 2013). Siervo 2011 conducted a meta-analysis to estimate the effectiveness of intentional weight loss on cognitive function in overweight and obese adults and showed that intentional weight loss appears to be associated with low-order improvements in executive/attention functioning and memory in obese, but not in overweight, individuals.

In summary, dietary interventions in mid-life populations have the potential to promote and maintain healthy cognitive function. It is hoped that in this particular age group ways to treat and, more importantly, to prevent MCI and dementia may become evident.

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 they might invest to prevent cognitive decline is 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 may increase overall mortality compared with placebo (Bjelakovic 2012; Brigelius-Flohe 2007).

This review will provide an opportunity to summarise and appraise the current literature regarding the different types of dietary interventions that have been evaluated in relation to cognitive function in mid-life populations. This is important as it is yet unclear which dietary interventions are potentially most beneficial to maintain healthy cognitive function. This will have important implications for nutrition and dementia research by identifying research gaps as well as potentially beneficial interventions or mechanistic pathways that may lead to the development of new clinical trials and experimental human and animal investigations, respectively. The public health resonance of the results will clearly depend on the robustness of the evidence; however, while the results may not be translated into nutritional and dietary recommendations, they may inform public health bodies and research funders on the urgent need for research investment in this area to mitigate the projected alarming dementia trend over the future decades. In particular, the results will be of high importance to develop public health strategies in developing countries as they contribute to a large proportion of the worldwide dementia trends as a consequence of the nutrition and epidemiological transitions characterised by the adoption of westernised dietary and lifestyle patterns.

OBJECTIVES

In this review we will set out to evaluate the effects of dietary interventions for maintaining cognitive function in cognitively healthy people in mid-life and preventing cognitive decline in late life.

METHODS

Criteria for considering studies for this review

Types of studies

We will include in the review 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 crossover studies, but we will extract and analyse data from the first treatment period only. Trials will be included irrespective of the length of follow-up after the intervention has finished.

Types of participants

We will include the following population: cognitively healthy people in mid-life.

The cognitive status of participants will be determined by the trialists' own definitions of 'cognitively healthy'. These definitions will be recorded.

We will classify trials or subgroup analyses focusing on participants with ages ranging from 40 to 60 years as 'mid life', those of 60 years and older will be classified as 'late life'. The latter will be covered in a separate review (Siervo 2015). Where studies clearly state the age of participants among their inclusion criteria, this will be used 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, a study with an age range of 40 to 70, with a median of 50 years or less will be considered mid-life, whereas one with a median of 60 years or more would likely be categorised as late life.

Trialists will be contacted if further clarification is needed to determine health status or age. If there is no response, then clinical experts in our author team will classify the trials, or these will be listed as 'studies awaiting classification'.

Types of interventions

We will include studies comparing the effects of the described interventions with control interventions that are not expected to have specific risk-modifying effects. The control arms would typically involve placebo or no intervention/usual care. The minimum treatment duration is set at 12 weeks. There is no minimum duration of follow-up. However, all included trials will report outcomes at 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. These trials are included in order to give a full picture of the data, although it is recognised that the relationship between short-term cognitive enhancement and maintenance of cognitive function over longer periods of time is unclear.

Examples of the types of experimental dietary interventions are described in Appendix 1. Dietary interventions will consist of adjustments to diet using components normally regarded as foods, and will also include dietary patterns such as Mediterranean diet or DASH diet. Licensed medical foods, food for special medical purposes and vitamin supplements will not be included. For whole diet interventions, dietary intake information will be extracted.

Types of outcome measures

Primary outcomes

The primary outcome will be overall cognitive functioning measured with any validated measure, for example: Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog); 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 extraction and management).

Outcome data reported at other time points after randomisation will be extracted and presented.

Secondary outcomes

Secondary outcomes are any validated measures of:

- overall cognitive functioning measured with, for example, ADAS-cog; MMSE; RBANS; CAMCOG

- specific cognitive functioning subdomain: episodic memory,

- specific cognitive functioning subdomain: executive functioning,

- specific cognitive functioning subdomain: speed of processing,

- specific cognitive functioning subdomain: semantic memory,

- specific cognitive functioning subdomain: verbal fluency,

- quality of life, either generic or disease-specific,

- clinical global impression,

- functional performance

- mortality

- number of participants experiencing one or more serious adverse events

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

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 CDCIG, 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 search of *The Cochrane Library*'s 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 to ensure that the searches for each suite of reviews is as comprehensive and as up to date as possible to identify published, unpublished and ongoing trials. The search strategy that will be used 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. The search will be restricted to those guidelines meeting NGC's 2013 inclusion criteria published in this year or later.

Experts in the field and companies marketing included interventions will be contacted, 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; Nüesch 2009a; Nüesch 2009b; Reichenbach 2010; Rutjes 2009a; Rutjes 2009b; Rutjes 2010; Rutjes 2012).

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 in detail here http://www.medicine.ox.ac.uk/alois/content/modifiable-risk-factors. In brief, teams of volunteers will perform a 'first assess' on the search results. The crowd will be recruited through the network called Students For Best Evidence: http://www.students4bestevidence.net. They will screen the results using an online tool developed for 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. It is estimated that this will remove 75% to 90% of results retrieved. The remaining results will then be screened by the author team.

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. Discrepancies will be resolved by discussion, or by the involvement of a third reviewer. Where possible, we will extract the following information related to characteristics of participants, intervention and study design:

Participant characteristics

- gender
- baseline age (range, median, mean)
- education (level and years of education)
- baseline cognitive function
- cognitive diagnostic status
- duration of cognitive symptoms, if any
- body mass index (clinical cut-offs, from WHO: below 18.5 (underweight), 18.5-24.9 (normal weight), 25.0-29.9 (pre-obesity), 30.0-34.9 (obesity class I), 35.0-39.9 (obesity class II), above 40 (obesity class III))
- ethnicity
- Apo-E genotype
- diabetes mellitus (yes/no)
- physical activity (as defined by the trialists)
- smoking (ever/never)

Intervention characteristics

- nature of the dietary intervention/name of intervention
- description of the control intervention
- dosage of the interventions
- duration of the dietary and control interventions
- any concomitant treatments

Methodological characteristics

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

If primary and secondary outcome data will be available at multiple time-points within a given trial, we will group with cut-offs to describe immediate results (up to 12 weeks), short term (up to 1 year), medium term (1 to 2 years) and longer term results (more than 2 years). Within these time periods, the longest available data reported by the study will be extracted (for example, if study reported data at 6 months, 9 months and 1 year, only the 1-year data will be extracted and analysed for the 1-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 change-from-baseline data are not available, we will extract the mean value at each time point. When necessary, means and measures of dispersion will be approximated from figures in the reports. For crossover trials, we will extract data on the first treatment period only. Whenever possible, we will extract intention-to-treat data i.e. analysing all patients according to the group randomisation; if this is not available, then we will extract and report data from *available case analyses.* If these data are both not available, we will consider data from per protocol analyses. We will contact the trialists 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 AR, the risk of bias in each of the included trials will be assessed independently by one member of the author team and one experienced reviewer provided by the editorial team, using the Cochrane's 'Risk of bias' tool (Higgins 2011). Disagreements will be resolved 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 care-givers, 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 will be used 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). The treatment effect for dichotomous outcomes will be expressed as a relative risk (RR).

Unit of analysis issues

If cluster randomised trials are included, 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 for Systematic Reviews of Interventions* (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 trialists with a request to provide missing information nor will we impute missing data ourselves.

Assessment of heterogeneity

Heterogeneity will be examined in stratified analyses by trial, participant and intervention characteristics, as outlined in the section Data Analyses and Appendix 3.

Assessment of reporting biases

If a sufficient number of trials (at least 10) can be identified, 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

Experimental interventions which use different dietary interventions with the aim of increasing the same vitamin or substance will be grouped together (e.g., studies which use different naturally occurring foods with the aim of increasing the same vitamin). 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, 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). Funnel plot asymmetry will be assessed with the appropriate statistics for the metrics analysed (Higgins 2011). All P values are 2-sided. Statistical analyses will likely be done in Review Manager 5 (RevMan) and in STATA, release 13 (StataCorp, College Station, Texas), but this may vary depending on the statisticians involved.

Subgroup analysis and investigation of heterogeneity

If around 10 or more trials are identified 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 patients, 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. The cut-off for trial size will be determined for each review topic separately, based on a sample size calculation for the primary effectiveness outcome. Cut-offs for treatment duration and follow-up duration will be defined specifically for each review

topic. In both cases, cut-offs will be defined 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. High quality will be defined by the results of the stratified analyses, based on the statistically significant ($P < 0.05$) interaction terms for methodological characteristics.

GRADE and 'Summary of findings' table:

We will use GRADE to describe the quality of the overall body of evidence for each outcome in the 'Summary of findings' table (Guyatt 2008; Higgins 2011). Quality is defined as the degree of confidence which can be placed in the estimates of treatment benefits and harms. There are four possible ratings: "high", "moderate", "low" and "very low". Rating evidence "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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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 these may modify the risk of developing cognitive impairments or dementia. These include nutritional supplements (Abraham 2015; Al-Assaf 2015; Denton 2015), exercise (Forbes 2015a; Forbes 2015b; Forbes 2015c), cognition (Gates 2015a; Gates 2015b; Karim 2005), and dietary interventions (Tang 2015; Siervo 2015; Stephan 2015). These interventions will be evaluated each 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 dietary interventions for cognitive function at mid-life

Dietary intervention	Biological plausibility	'Dose' range considered in this review
*Foods***		
Foods containing high levels of vitamin B6	Vitamin B6 is involved in fat and carbohydrate metabolism. Vitamin B6 deficiency has been shown to have detrimental effects on brain function in animal studies (Wei 1999).	Any*, but dose should be adequately reported.
Foods containing high levels of vitamin B12	Elevated levels of homocysteine have been associated with Alzheimer's disease, but it is unclear whether this may be due to present cardiovascular disease or insufficient vitamin B12 or folates (Seshadri 2006).	Any*, but dose should be adequately reported.

(Continued)

Foods containing high levels of vitamin C	Vitamin C has anti-oxidant properties which may help to preserve cognitive function (Crichton 2013).	Any*, but dose should be adequately reported.
Foods containing high levels of vitamin D	There are many vitamin D receptors in the brain, and vitamin D has demonstrated effects, referred to as neuroprotective effects, by clearing Alzheimer's disease related products e.g., amyloid-β plaques (Dursun 2011).	Any*, but dose should be adequately reported.
Foods containing high levels of vitamin E	Vitamin E also has anti-oxidant properties which may help preserve cognitive function (Crichton 2013).	Any*, but dose should be adequately reported.
Foods containing high levels of carotenoids	Carotenoids are fat-soluble antioxidants that may protect polyunsaturated fatty acids, such as n-3 fatty acids from oxidation, and are potentially important for Alzheimer's disease (AD) prevention and treatment (Johnson 2013). Examples of food with high carotenoid content are carrots, dark leafy greens, tomatoes or sweet potatoes.	Any*, but dose should be adequately reported.
Foods containing high levels of flavonoids	Berries, dark chocolate or soy beans have high levels of flavonoids which can have anti-inflammatory and anti-oxidant properties which may help decrease oxidative stress and inflammation thought to be involved in cognitive impairment (Devore 2012).	Any*, but dose should be adequately reported.
Foods containing high levels of inorganic nitrate	Green leafy vegetables are particularly rich in dietary nitrate which can be converted into nitric oxide via a non-enzymatic pathway. Nitric oxide has pleiotropic actions on several organs and has direct effects on memory formation and post-synaptic potentiation (Hord 2009). Effects on cognitive function could also be achieved via improvement in endothelial and metabolic functions.	Any*, but dose should be adequately reported.
Food rich in Fatty acids, amino acids and other non-vitamin nutrients and non-nutrients		
Foods rich in mono- and poly-unsaturated fatty acids such as fish oil, olive oil, nuts	Neurotransmission is very energy dependent and the fatty-acids have been shown to improve glucose utilization in this process (Freemantle 2006). Poly-unsaturated fatty acids have anti-inflammatory and anti-atherogenic properties that reduced cardiovascular risk. They are also an essential part of neuronal membranes and involved in neurogenesis and synaptic growth.	Any*, but dose should be adequately reported.
Food rich in Caffeine	Caffeine is a brain stimulant and increases energy metabolism (Snel 2011).	Any*, but dose should be adequately reported.
Food rich in Flavonoids	Flavonoids can have anti-inflammatory and anti-oxidant properties which may help decrease oxidative stress and inflammation thought to be involved in cognitive impairment (Devore 2012).	Any*, but dose should be adequately reported.
Food rich in Glucose	Glucose is an energy source for the brain and plays an important role in neurological function (Arnaiz 2001).	Any*, but dose should be adequately reported.
Nutraceuticals	This class of compounds involves by definition any product derived from food sources with extra health benefits in addition to the basic nutritional value found in foods. The classification of nutraceutical depends on their source and their health effects merely depends on their chemical composition and biological activity. Examples of nutraceuticals that may have an effect on neurocognitive function are Ginkgo biloba, phosphadtidylserine and phosphatidylcholine or huperzine (McDougall 2005).	Any*, but dose should be adequately reported.
Whole diets		

(Continued)

Mediterranean diet	Combination of several foods and nutrients which have already separately been suggested to have beneficial effects towards cognition. It has been proposed that the combination of these foods may have an increased effect (Singh 2014).	Not applicable
Ketogenic diet	The ketogenic diet consists of high-fat, medium-protein, and low-carbohydrate foods. Animal studies have shown that this diet has neuroprotective effects e.g., rats following the ketogenic diet have been shown to have weakened production and accumulation of Alzheimer's disease related products such as amyloid-β (Krikorian 2012).	Not applicable
Low-fat diet	May improve cognitive function via reduction of cardiovascular risk (Hu 2012).	To be defined by the trialists
High-protein diet	May increase availability of certain amino acids. The rate of synthesis and release of certain neurotransmitters are modified by the concentrations of their amino acid precursors in the brain, which is determined by the amount of amino acids available in the blood (Jakobsen 2011).	To be defined by the trialists
Low Glycaemic Index (GI) Diet	The Glycaemic Index (GI) is a ranking of carbohydrate-containing foods based on the overall effect on blood glucose levels. Slowly absorbed foods have a low GI rating, while foods that are more quickly absorbed have a higher rating (Philippou 2014). The influence of carbohydrate's GI on cognitive function is poorly understood.	A GI rating less than 55 will be classified as low.
Dietary Approach to Stop Hypertension (DASH Diet)	Dietary pattern characterised by increased consumption of fruit and vegetables consumption, nuts, low-fat dairy products and whole grains. Proved beneficial effects on cardio-metabolic functions and emerging evidence of protective effects on cognition (Smith 2010,Tangney 2014).	To be defined by the trialists

This table contains examples of dietary interventions; however, others may be found in the literature search and this is not a definitive list. The interventions are based on an equal caloric intake to rule out the confounding effect of energy restriction on cognitive outcomes.

* We will exclude trials where dose is NOT (or is inadequately) reported.

** All vitamin supplements are covered in (Abraham 2015; Al-Assaf 2015; Denton 2015). Here, we will focus on naturally occurring vitamins as part of a dietary intervention.

Appendix 2. MEDLINE search strategy

1. *Diet/
2. Diet, Fat-Restricted/
3. Diet, Protein-Restricted/
4. Diet, Carbohydrate-Restricted/
5. Diet, Gluten-Free/
6. Diet, Macrobiotic/
7. Diet, Atherogenic/
8. Diet, Vegetarian/
9. Diet, Sodium-Restricted/
10. Diet, High-Fat/
11. Diet, Cariogenic/
12. Ketogenic Diet/
13. Diet, Mediterranean/
14. Diet, Reducing/
15. Caloric Restriction/
16. Dietary Fats/
17. Antioxidants/
18. exp Fatty Acids/

19. Fruit/
20. Vegetables/
21. Nutritional Status/
22. Malnutrition/co
23. Energy Intake/
24. Food Habits/
25. Plant Oils/
26. diet*.ti,ab.
27. "whole-diet".ti,ab.
28. mediterranean*.ti,ab.
29. nutrition*.ti,ab.
30. food.ti,ab.
31. "olive oil*".ti,ab.
32. nuts.ti,ab.
33. nutritional.ti,ab.
34. nutrient*.ti,ab.
35. fruit*.ti,ab.
36. vegetable*.ti,ab.
37. calorie*.ti,ab.
38. "omega 3".ti,ab.
39. "omega 6".ti,ab.
40. "fatty acid*".ti,ab.
41. "docosahexaenoic acid".ti,ab.
42. DHA.ti,ab.
43. "eicosapentaenoic acid".ti,ab.
44. EPA.ti,ab.
45. "polyunsaturated fatty acid*".ti,ab.
46. PUFA*.ti,ab.
47. "fish oil*".ti,ab.
48. macronutrient.ti,ab.
49. micronutrient.ti,ab.
50. "energy intake".ti,ab.
51. or/1-50
52. *Aging/
53. Aged/
54. "Aged, 80 and over"/
55. Middle Aged/
56. Age Factors/
57. Mild Cognitive Impairment/
58. MCI.ti,ab.
59. AAMI.ti,ab.
60. ACMI.ti,ab.
61. ARCD.ti,ab.
62. CIND.ti,ab.
63. (nMCI or aMCI or mMCI or MCIa).ti,ab.
64. "old* age*".ti,ab.
65. elderly.ti,ab.
66. "middle age*".ti,ab.
67. "old*adults".ti,ab.
68. seniors.ti,ab.
69. "senior citizens".ti,ab.
70. "community dwelling".ti,ab.
71. pensioners.ti,ab.
72. or/52-71
73. 51 and 72
74. Cognition/
75. Memory/
76. Executive Function/
77. (cognit* adj3 (func* or declin* or reduc* or impair* or improve* or deficit* or progress* or perform* or abilit*)).ti,ab.
78. "mental perform*".ti,ab.
79. (memory or attention or processing).ti,ab.
80. "executive function*".ti,ab.

81. Dementia/
82. Alzheimer Disease/
83. dement*.ti,ab.
84. alzheimer*.ti,ab.
85. Cognition Disorders/
86. or/74-85
87. 73 and 86
88. randomized controlled trial.pt.
89. controlled clinical trial.pt.
90. randomized.ab.
91. placebo.ab.
92. drug therapy.fs.
93. randomly.ab.
94. trial.ab.
95. groups.ab.
96. or/88-95
97. exp Animals/ not humans.sh.
98. 96 not 97
99. 87 and 98 [all results]
100. *Diet/
101. *Cognition/
102. Aging/
103. elderly.ti,ab.
104. "Aged, 80 and over"/
105. Middle Aged/
106. Mild Cognitive Impairment/
107. "mild cognitive impairment".ti.
108. or/102-107
109. 100 and 101 and 108
110. 88 or 89
111. 109 and 110 [results to be sent directly to the author team for assessment]
112. 99 not 111 [results to be screened by the 'crowd']

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

Item	Definition
*Bias related characteristics**	
Concealment of allocation (avoiding selection bias)	The guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) will be used 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: allocation concealment will be judged at low risk of bias if the investigators responsible for patient selection were unable to suspect before allocation which treatment was next. Concealment will downgraded to high risk of bias, if there is evidence of inadequate sequence generation.
Blinding of patients and personnel (avoiding performance bias)	Low risk of bias will be judged if: - a credible sham procedure was used; or if a placebo supplement or pill was used that was reported to be identical in appearance from 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:* Low risk of bias will be judged if: - self-report outcomes were assessed AND blinding of patients was considered adequate AND there was no information to suggest that there was an investigator involved during the process of

(Continued)

	outcome assessment; OR if blinding of investigators performing the outcome assessment was reported AND an attempt to blind patients was reported. *For other outcomes:* Outcome assessment was considered to be blinded if the outcome assessment was reported to be blinded.
Statistical Analyses (avoiding attrition bias)	*For continuous outcomes* Low risk of bias will be judged if: - at least 90% of the patients randomised were analysed AND the difference in percentage of participants not analysed was 5% or lower across trial arms, - for trials using imputations to handle missing data: the percentage of participants with missing data did not exceed 20% AND the difference in percentage of participants with imputed data was 5% or lower across trial arms AND applied imputation methods were judged to be appropriate. Multiple imputation techniques will be considered appropriate, simple methods such as "last observation carried forward" or "baseline carried forward" will be considered inappropriate. *For binary outcomes of rare events* Low risk of bias will be judged if - the event rate is low (e.g. incidence of dementia) AND at least 95% of the patients randomised were analysed AND there is no evidence of differential reasons for missing data that may alter the estimate AND the rate of missing data does not exceed the expected event rates. *For binary outcomes of non-rare events* Low risk of bias will be judged if: - at least 90% of the patients randomised were analysed AND the difference in percentage of participants not analysed was 5% or lower across trial arms AND there is no evidence of differential reasons for missing data that may alter the estimate AND the rate of missing data does not exceed the expected event rates.
Trial Size	The cut-off to distinguish small from larger trials will be determined by a sample size calculation on the primary outcome
Duration of follow-up	We will group studies according to these follow up cut-offs to describe immediate results (up to 12 weeks), short-term (up to 1 year), medium-term (1 to 2 years) and longer-term results (more than 2 years).
Treatment related characteristics	
Experimental and control interventions	The analyses will be stratified according to control type (no intervention or a placebo)
Treatment durartion	The minimum treatment duration of 3 months is considered short term, 3 to 12 months as medium term, and 12 months for long term.
Participant related characteristics	
Baseline characteristics	Gender; body mass index (depending on the number of trials contributing to a comparison, clinical cut-offs as described at Data extraction and management may be grouped); ApoE-4 (yes/no); diabetes mellitus status (yes/no); baseline age (mid-life versus late-life versus other); education (years); physical activity (by trialist definition, likely active versus other); smoking (ever/never)

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

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Completion of the protocol: SLH, RB, CS, AR

Completion of the searches: Cochrane review team

Screening of references: SLH, RB

Acquisition of data: SLH, CS

Risk of bias Assessments and GRADING: SLH, RB, AR

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