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Vitamin and mineral supplementation for maintaining cognitive function in cognitively healthy people in mid life (Protocol)

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[Intervention Protocol]

Vitamin and mineral supplementation 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 vitamin and mineral supplementation on cognitive function in cognitively healthy people in mid life.

BACKGROUND

Description of the condition

Cognitive health, mild cognitive impairment and dementia

Cognitively healthy or successful cognitive ageing 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 a definition yet (Depp 2012; Hendrie 2006). Successful cognitive ageing 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 impaired.

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 mild cognitive impairment (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 lead 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 the 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; World Health Organization 2012). However, the proportion of dementia attributable to Alzheimer’s disease reduces with age (Savva 2009).

Prevalence of MCI and dementia

In the UK Medical Research Council's population-based 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 (World Health Organization 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.

Risk factors

Many dementia syndromes are known to have a long preclinical phase making it important to identify exposure to putative risk factors in mid life, before neuropathological features of various dementia subtypes start to develop in the brain (Rusanen 2011).

Generally, risk factors of dementia can be divided into modifiable and non-modifiable factors: the non-modifiable risk factors include age, genetic factors, family history, gender (females are at higher risk), and Down syndrome. The modifiable factors include smoking (both current and past smoking), high cholesterol, stroke, hypertension, lack of physical activity, diabetes mellitus, obesity, and low educational level. Among the non-modifiable risk factors, age is found to be the most significant one. It has been indicated that, in people who are older than 65 years, the risk of AD (the most typical cause of dementia) doubles every five years (Launer 1999; McCullagh 2001; van den Berg 2012; van der Flier 2005). A pooled analysis of four prospective studies in Europe has revealed that the incidence rate of AD among people aged 90 and over was 63.5/1000 person-year (Launer 1999).

Although age is the strongest risk factor, other risk factors for AD have been identified. Genetics plays a major role in early onset AD, but a lesser role in the much commoner late onset disease. Epidemiological evidence (World Alzheimer Report 2014) suggests that AD shares many risk factors with vascular disease, including diabetes, midlife obesity, midlife hypertension, smoking and physical inactivity (World Health Organization 2012). The possible mechanism of cognitive decline in late life is thought to be due to decreasing co-ordination between different cortical regions which work for the higher level cognitive functions. Such changes in brain function may have a role in some physiological disorders like hypertension, for instance, which is also a risk factor for cognitive decline (Bishop 2010; O'Sullivan 2001).

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. The World

Alzheimer Report 2014 suggests that good nutrition, education and social and mental stimulation may be protective. There is evidence that vitamins such as vitamin B12 and folate will lower homocysteine which is neurotoxic (see Appendix 1: Vitamins). Also, there is evidence that vitamin D might have protective actions and is being proposed for further investigation in the treatment of AD (Annweiler 2012; Llewellyn 2010). A recent randomised controlled trial (RCT) has shown that Vitamin E might slow down functional decline in people with AD (Dysken 2014). Many minerals might have antioxidant properties and may be beneficial in protecting against oxidative stress and free radical damage (see Appendix 1: Minerals). Hence, an evaluation of the role of vitamins and minerals as protective and preventive agents in cognitive impairment is highly warranted. Consequently, it is necessary to evaluate the potentially effective vitamin or mineral (or vitamin and mineral) supplements in persons at either mid life (this review), late life (Al-Assaf 2015), or with MCI (Abraham 2015).

Description of the intervention

This review focusses on RCTs investigating the effect of vitamins and minerals on cognitive functioning. Vitamins are organic compounds that are essential for the normal physiological process in the body and play important roles in growth and development (Kennedy 2011). Minerals are inorganic elements and are nutrients that are needed by the body to grow and develop normally (Centers for Disease Control and Prevention 2014). Most of these essential nutrients are available naturally through diet. Dietary supplements are any consumed products that aim to supplement the diet and provide additional nutrients to the ones obtained by regular diet.

How the intervention might work

Studies have revealed that vitamins and minerals have important roles in the physiology of the human body at cellular and at tissue levels. Putative biological mechanisms for each are summarised briefly in Appendix 1.

There is a complex array of micronutrients which protect the brain in a variety of ways, from protecting against damaging oxygen free radicals to neurogenesis, gene expression, and enzyme and receptor control (Powell 2000). Failure of these important systems appears to be implicated in the occurrence of neural damage and might be neutralised by antioxidant micronutrients (van der Schaft 2013). Therefore, adequate vitamin and mineral levels in the body might possibly enhance cognitive function.

Oxidative stress has been shown to be a damaging process leading to an imbalance between oxygen free radicals, and the anti-oxidative defences of, and repair of oxidative damage to, proteins, lipids, RNA, and DNA (Halliwell 1992; Halliwell 1999; Tabet 2001; Tabet 2002). In addition the central nervous system (CNS) contains high levels of unsaturated fatty acids that are substrates for peroxidation reactions (Ogawa 1994). An important defence mechanism in the brain involves enzymatic antioxidants which, if mediated through the supplementation of micronutrients, may replenish the brain with synthetic antioxidants providing a therapeutic approach to reduce oxidative stress (Reiter 1995). This may be a useful adjunct in modifying risk factors in the pathogenesis of neurodegenerative disorders (Packer 1997).

Vitamins and minerals are involved in thousands of intracellular and extracellular mechanisms in the CNS. Exact functions differ according to the type of molecules and compounds involved. These activities can be classified into a number of roles that support homeostasis and create an ideal environment for neuronal health. This may help maintain brain and cognitive reserve which in turn may impact the rate of decline of those most at risk of dementia. Brain and cognitive reserve, developed early in life and consolidated in mid life, may buffer the expression of symptoms of dementia in the presence of neurodegenerative disease (Casserly 2004).

Vitamins:

Vitamin A may be involved in the stabilisation of beta amyloid fibrils (Ono 2012). Vitamin D has been implicated as a precursor of hormones required for calcium and phosphorus metabolism and also potentially has a role in cognition in older adults (Przybelski 2007). Vitamin E is an antioxidant and is involved in free radical chain reactions; it provides protection against free radical damage (Farina 2012; Takatsu 2009). B vitamins—notably B12 and folic acid—have a role in energy production and metabolism within the CNS. B vitamins have also been implicated in the production of nucleic acids and production and maintenance of myelin, essential for good neuronal health (Kühnast 2013; Osiezagha 2013; Pawlak 2014; Powers 2003; World Alzheimer Report 2014). Several clinical studies evaluated effect of vitamins on cognition. For example, a double-blind placebo RCT showed that 8 weeks' supplementation of multivitamin enhanced contextual recognition memory (a test of episodic memory) in older age men who are at risk of cognitive decline (Harris 2012). They indicated that contextual recognition memory is usually the first cognitive function to be damaged in the development of cognitive decline, mild cognitive impairment and Alzheimer’s disease (Harris 2012).

Minerals:

There are a number of minerals which are involved in neuronal gene expression and the neuronal secretion of neurotransmitters (Ozawa 2012; Rossom 2012). Selenium was found to have some benefit in improving cognitive-cerebral function in older adults post chromium supplementation (Krikorian 2010; Smorgon 2004). Potassium, calcium, and magnesium were found to be protective in a cohort of Japanese participants (Ozawa 2012). Selenium may induce repair of DNA in damaged cells, and so limit growth of cancer cells. Selenium is a critical component of the enzyme glutathione peroxidase that detoxifies harmful molecules, making it especially important for cancer protection. As an antioxidant, selenium has been shown to protect the CNS and immune system from oxidative damage by harmful free radicals (Berr 2012; Mehdi 2013; Smorgon 2004).

Why it is important to do this review

Braak 1991 and Serrano-Pozo 2011 described changes that occur in mid life that justify interventions at an early stage. Shah 2012 found that "in participants in mid life with a mean age of 58 that β-Amyloid (Aβ), a vasoactive protein, and elevated blood pressure (BP) levels are associated with Alzheimer disease (AD) and possibly vascular dementia". Early interventions ultimately aim at maintaining cognitive functioning, preventing cognitive decline and dementia.

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, effort 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 to be associated with higher rates of side effects than placebo (Bjelakovic 2012; Brigelius-Flohe 2007; Miller 2005).

OBJECTIVES

To evaluate the effects of vitamin and mineral supplementation on cognitive function in cognitively healthy people in mid 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. To be considered, trials need to 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. We will include these trials in order to give a full picture of the data, although it is recognized that the relationship between short-term cognitive enhancement and maintenance of cognitive function over longer periods of time is unclear.

Types of participants

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

Only trials using internationally accepted and validated instruments to assess cognitive function or dementia status at baseline will be included.

We will include trial populations of cognitively healthy people in mid life, i.e. participants aged 40 to 65 without a dementia diagnosis or cognitive impairment at baseline. (Mid life is defined for the purposes of disease classification in DSM IV, 1994, as between 40 and 65; those older than 65 years will be classified as late life and will be covered in a separate review (Al-Assaf 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, the median and range or mean and standard deviation will be used 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 65 years or more would likely be categorised as late life.

Regarding concomitant disease, studies are not required to include blood tests.

We will contact trialists if further clarification is needed 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 these as 'studies awaiting classification'.

Types of interventions

We will include studies comparing the effects of the described vitamin and mineral supplementation 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. Experimental interventions may concern individual or combination treatments with any of the supplements listed in Appendix 1. Trials of vitamins or minerals given in combination with other unrelated compounds (e.g. fatty acids, amino acids or medications) will be excluded, unless the effects of the vitamins and minerals can be isolated. A trial evaluating the effects of vitamin A and C versus methionine would thus be excluded, whereas a trial evaluating vitamin A and C with methionine versus methionine only would be included. Only orally-administered supplements taken at any dose will be included.

Types of outcome measures

Primary outcomes

Mean overall cognitive functioning measured with any internationally accepted and 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 extraction and management). Outcome data reported at other time points after randomisation will be extracted and presented according to time points specified in the Data synthesis section.

Secondary outcomes

Secondary outcomes are any internationally accepted and 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 all-cause dementia,

- number of participants experiencing one or more serious adverse events (SAE),

- mortality.

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, will include all outcomes related to cognitive functioning, quality of life and mortality.

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.

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

Data collection and analysis

We will use this protocol alongside instructions for data extraction, quality assessment and statistical analyses, based on a generic protocol generated by the editorial board of CDCIG, to guide this and another 11 reviews on modifiable risk factors (see Acknowledgements).

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: 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 volunteers will be recruited through the author team's institutions. 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 (as a minimum) 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
- ethnicity
- Apo-E genotype
- diabetes mellitus (yes/no)
- physical activity (as defined by the trialists).
- smoking (never/ever)

Intervention characteristics

- nature of the intervention; generic and trade name of intervention
- description of the control condition
- duration of treatment
- dosage and frequency
- any concomitant treatments
- treatment adherence

Methodological characteristics

- trial design (individual or cluster randomisation; parallel-group, factorial or crossover 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 is 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. For all-cause dementia or MCI, only outcome data at 1 year of follow-up or longer will be considered and therefore will be grouped as short-term (1 year), medium-term (up to 2 years) and long-term (more than 2 years).

For dichotomous outcomes (such as incident dementia or mortality), we will extract from each trial the number of participants with each outcome.

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 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 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 sub-optimal 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 are described in Appendix 3 and 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 authors 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 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

Whenever possible, we will use standard inverse-variance random-effects meta-analysis to combine outcome data across the trials at end of trial (DerSimonian 1986); 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 pre-specify 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. 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 2014); and in STATA, release 13 (StataCorp, College Station, Texas).

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 (Appendix 3). We will use univariable random-effects meta-regression models as tests of interaction between treatment effect and these characteristics (Thompson 1999). The cut-off for trial size, treatment duration and follow-up duration are described in Appendix 3.

We will consider pooling interventions which have been postulated to share a main mechanism of action in preventing development of dementia. For example

- antioxidant properties—affecting superoxide dismutase (vitamin A, C, D, E, selenium)
- regulation/lowering levels of homocysteine: vitamins B12, folate and B6

Knowledge of possible mechanisms of actions is evolving, and we will consider other possible subgroups for data analysis as new information arises during the development of the review.

In addition, we will be investigating other effect modifiers, related to the characteristics of participants. Apart from cognition status and age of patients, we will also subgroup patients into whether they are predisposed to risks of deficiency of the vitamin and mineral supplement investigated (for example, presence of malabsorptive diseases, malnutrition, comorbidities or concomitant medications and ethnicity (Dawson-Hughes 2004).

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 less than 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 (Higgins 2011; Guyatt 2008).

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 (Higgins 2011; Guyatt 2008).

ACKNOWLEDGEMENTS

This protocol is largely based on a general template constructed for the development of a larger series of protocols and reviews covered by a National Institute for Health Research (NIHR) Systematic Reviews Programme Grant. The common protocol covered four types of intervention, for which some evidence exists that these may modify the risk of developing cognitive impairments or dementia. These include vitamin and mineral 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). The general protocol was inspired by a generic protocol approved by the Cochrane Musculoskeletal Group for another series of reviews (da Costa 2012; Nüesch 2009; Reichenbach 2010; Rutjes 2009a; Rutjes 2009b; Rutjes 2010).

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APPENDICES

Appendix 1. Biological Plausibility of Vitamins and Minerals

Supplement*	Route	Biological plausibility
Vitamins		
Vitamin A	anti-oxidant; anti-inflammatory; anti-cholinesterase; beta-amyloid inhibition	Carboxylic form of Vitamin A known as all-trans retinoic acid has been shown to have memory restorative function and it may be attributed to its anti-cholinesterase, anti-oxidative and anti-inflammatory potential (Sodhi 2013). Vitamin A and beta-carotene may also inhibit the formation, extension and destabilising effects of beta-amyloid fibrins. Plasma or cerebrospinal fluid concentrations of vitamin A and beta-carotene have been reported to be lower in AD patients, and increased Vit A/beta carotene concentrations have been clinically shown to slow the progression of dementia (Ono 2012).
Vitamin D	neuronal activity	Vitamin D receptor (VDR) and 1, alpha-hydroxylase, the terminal calcitriol-activating enzyme, are distributed throughout both the foetal and adult brain. This is thought to play a role in brain development and critical brain functions (McCann 2008). Significant correlation between serum 25(OH)D levels and cognitive scores were reported in DeLuca 1975 and Przybelski 2007.
Vitamin E	anti-oxidant; beta-amyloid inhibition	Vitamin E consists of a group of tocopherols and tocotrienols. Apart from lipid antioxidant activity, other functions include membrane stabilisation by forming complexes with the products of lipid hydrolysis (Wang 2000). It has been shown that the antioxidant and free radical scavenging activity of Vitamin E inhibits amyloid beta protein induced neuronal cell death and may have implication in prevention and treatment of Alzheimer’s dementia. (Behl 1992).
Vitamin K	neuronal activity	Vitamin K participates in the synthesis of sphingolipids. Sphingolipids participate in important cellular events such as proliferation, differentiation, senescence and cell-cell interactions. Sphingolipid metabolism has been linked to age-related cognitive decline and neurodegenerative diseases such as Alzheimer's disease (Ferland 2012). A cross-sectional study found correlations between higher serum phylloquinone concentration and better cognitive scores in tests evaluating episodic verbal memory among healthy older adults (Ferland 2013).
Thiamine (Vitamin B1)	neuronal activity	Thiamine is required as a cofactor in the cellular production of energy and enhances normal neuronal activities (Osiezagha 2013). Rats with an episode of induced thiamine deficiency had cognitive, learning and memory impairments (Langlais 1995).
Riboflavin (Vitamin B2)	neuronal activity	Riboflavin (7,8-dimethyl-10-ribityl-isoalloxazine) is water soluble. Symptoms of neurodegeneration and peripheral neuropathy in riboflavin deficiency have been documented in animal studies, but not observed in humans. Subclinical riboflavin deficiency may contribute to increased concentrations of plasma homocysteine and may be associated with increased risk of cardiovascular disease and impaired handling of iron (Powers 2003).
Niacin (Vitamin B3)	vascular: anti-inflammatory	Niacin is a water-soluble precursor cofactor essential for the formation of dozens of enzymes. Niacin decreases atherosclerosis development mainly by reducing LDL cholesterol. It also has modest HDL-cholesterol-raising and anti-inflammatory effects (Kühnast 2013). Niacin deficiency causes pellagra. Its neuropsychiatric symptoms are similar to those in Alzheimer's disease or vascular dementia (Amanullah 2010).
Vitamin B6 (Pyridoxine, pyridoxal, pyridoxamine, Pyridoxal 5' phosphate (PLP) and pyri-	homocysteine; neuronal activity	Vitamin B6 is a group of water-soluble compounds (vitamers). Pyridoxal 5' phosphate (PLP) and pyridoxamine 5' phosphate (PMP) are the active coenzyme forms of vitamin B6 (ODS 2014). Vitamin B6 has many important brain functions such as biosynthesis of neurotransmitters (GABA, dopamine, noradrenaline, serotonin), receptor binding, macronu-

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doxamine 5' phosphate (PMP), Pyridoxine 5'-phosphate (PNP))		trient metabolism, and gene expression. In a study looking at low plasma B6 levels predicting cognitive decline and depression in at-risk individuals, low PLP status was seen as a risk factor for cognitive decline and depression in at-risk populations (Scott 2013).
Folic Acid (Vitamin B9)	anti-oxidant; homocysteine; neuronal activity	Folate is a cofactor and promotes the remethylation of homocysteine -- an amino acid that can induce DNA strand breakage, oxidative stress and apoptosis. Folate is required for normal development of the nervous system, playing important roles regulating neurogenesis and programmed cell death. Folate deficiency and its resultant increase in homocysteine levels has been linked to several neurodegenerative conditions, including stroke, Alzheimer's disease and Parkinson's disease (Mattson 2003).
Vitamin B12 (cobalamins: cyanocobalamin, hydroxocobalamin, methylcobalamin, hydroxocobalamin)	homocysteine; neuronal activity	Vitamin B12 acts as a coenzyme in metabolism of amino acids and fatty acids required for the synthesis of nucleic acids, erythrocytes and in the maintenance of myelin (Pawlak 2014). Lower vitamin B12 status has been associated with increased rates of cognitive decline and dementia (Clarke 2007; O'Leary 2012).
Pantothenic Acid (Vitamin B5)	energy; metabolism	Pantothenic acid (PA) is a component of coenzyme A, an essential cofactor in fatty acid oxidation, lipid elongation, and fatty acid synthesis (Kelly 2011). This may have an indirect effect in cognition.
Biotin (Vitamin H)	energy; metabolism	Biotin is also known as Vitamin H and is part of the B complex group of vitamins. They act as cofactors in carboxylase enzymes, fatty acid, and amino acid metabolism. This may have an indirect effect in cognition.
Vitamin C	anti-oxidant	Vitamin C has antioxidant functions and is required for the synthesis of noradrenaline from dopamine. It has been reported that Vitamin C levels have been lower than controls in patients with senile dementia of Alzheimer’s type (Jeandel 1989). In a longitudinal and cross-sectional study it was found that higher vitamin C levels were associated with better memory performance (Perrig 1997).
Minerals		
Calcium	neuronal activity	Calcium ions regulate a number of physiological processes including neuronal gene expression and the neuronal secretion of neurotransmitters (Dolphin 2012; Delage 2014 (accessed 21 September 2015)). Supplementation with calcium together with vitamin D was found to have no significant association with incident cognitive impairment (Rossom 2012). Ozawa 2012 concluded that, in the general Japanese population, higher self-reported dietary intakes of potassium, calcium, and magnesium reduced the risk of all-cause dementia, especially Vascular Dementia (VaD). The proposed mechanism was through the reduction of vascular risk factors.
Chromium	energy production; metabolism.	Chromium is needed for energy production and has been found to promote the effect of insulin involved in metabolism and storage of protein, carbohydrates and lipids within the CNS (Institute of Medicine, FNB 2001; Ozawa 2012;Anderson 1997). Chromium is involved in metabolism of nucleic acid, which is needed to build DNA, the genetic material in cells; and promotes synthesis of cholesterol and fatty acids needed for brain function. It may lower LDL cholesterol and triglyceride levels, raise HDL cholesterol levels and reduce high blood pressure (Preuss 1997), hence may affect vascular risk factors. Insulin resistance is implicated in the pathophysiological changes associated with Alzheimer's disease, and pharmaceutical treatments that overcome insulin resistance improve memory function in subjects with mild cognitive impairment (MCI)

(Continued)

		and early Alzheimer's disease. Chromium (Cr) supplementation improves glucose disposal in patients with insulin resistance and diabetes. A double blind RCT suggested that supplementation with Chromium picolinate can enhance cognitive inhibitory control and cerebral function in older adults at risk for neurodegeneration (Krikorian 2010). An additional study reported a positive correlation between cognitive function and serum chromium levels (Smorgon 2004).
Copper	antioxidant	Copper is a component of an antioxidant enzyme called superoxide dismutase that protects cells from damage by harmful free radicals. Copper is necessary for a healthy nerve system and taste sensitivity (Institute of Medicine, FNB 2001). Copper may promote non-amyloidogenic processing of amyloid precursor protein (APP) and thereby lower the Aβ production in cell culture systems, and it increases lifetime and decreases soluble amyloid production in APP transgenic mice (Borchardt 1999). In Alzheimer patients, a decline of Aβ levels in CSF is reported in adults in the treatment group. (Kaden 2011).
Iodine	neuronal development and structure.	Iodine is needed for the synthesis of thyroid hormones which, in turn, are needed for the myelination of the central nervous system. Iodine is necessary for the normal development of the brain. A deficiency of this mineral during critical periods of development in gestation can lead to intellectual disability and neurodevelopmental problems (Bath 2013a). Positive association was found between maternal iodine status and child IQ at age 8 years and reading ability at age 9 years (Bath 2013b).
Iron	neuronal activity	Iron is needed for development of oligodendrocytes and numerous enzymes that synthesise neurotransmitters such as noradrenaline, serotonin, and dopamine. It is important for production of the haemoglobin in red blood cells (Delage 2014 (accessed 21 September 2015); Institute of Medicine, FNB 2001). Regression analysis showed that non-anaemic iron-deficient adolescent girls who received iron performed better on a test of verbal learning and memory than girls in the control group (Bruner 1996)
Magnesium	energy, metabolism	Magnesium is involved in hundreds of enzyme reactions, including protein synthesis. It plays a role in energy production; can improve insulin sensitivity in diabetics; helps regulate blood sugar level; and regulates neuro-muscular transmission. Higher self-reported dietary intakes of potassium, calcium, and magnesium have been reported to reduce the risk of all-cause dementia, especially VaD, in the general Japanese population (Ozawa 2012).
Manganese	metabolism	Manganese is needed to synthesise fatty acids and cholesterol, and metabolise carbohydrates and proteins. It is important for energy production. It promotes utilisation of other key nutrients like vitamin B1 (thiamine), biotin, choline, ascorbic acid, and vitamin E (Delage 2014 (accessed 21 September 2015)). Manganese is needed for glucose metabolism, which helps regulate blood glucose. It is needed to make manganese superoxide dismutase (MnSOD), one of the key antioxidants that protects cells from free radical damage, and so helps maintains healthy nerves. It works synergistically with the B-complex vitamins to generate an overall feeling of well-being (Institute of Medicine, FNB 2001).
Molybdenum	metabolism	Molybdenum promotes normal cell function; and functions as a cofactor for three essential enzymes that play a vital role in carbohydrate metabolism, utilisation of iron, sulphite detoxification, and uric acid formation (Delage 2014 (accessed 21 September 2015); Institute of Medicine, FNB 2001).
Phosphorus	metabolism, neuronal structure and function.	Phosphorus is needed for metabolism of carbohydrates and fats to produce energy and is involved in the production of ATP required for growth and repair of cells and tissues; needed to make cell membranes. It helps the body utilise the B-complex vi-

(Continued)

		tamins that support proper muscle and nerve function (Delage 2014 (accessed 21 September 2015); Institute of Medicine, FNB 2001).
Potassium	nerve transmission.	Potassium is involved in regulating nerve transmissions and muscle contractions. It helps the body handle sodium and so reduces the risk of high blood pressure (Berr 2012). It has been found to lower the risk of stroke and ischaemic heart disease. Potassium is needed for synthesis of protein from amino acids (Delage 2014 (accessed 21 September 2015); Institute of Medicine, FNB 2001). Higher self-reported dietary intakes of potassium, calcium, and magnesium reduce the risk of all-cause dementia, especially VaD, in the general Japanese population (Ozawa 2012).
Selenium	antioxidant.	Selenium is an important antioxidant especially in combination with vitamin E, in the central nervous system and other body tissues (Delage 2014 (accessed 21 September 2015); Institute of Medicine, FNB 2001; Mehdi 2013; Rahman 2007). Low selenium levels were found to be associated with poorer cognitive function (Berr 2012; Smorgon 2004). Supplementation with selenium has been associated with improved overall health, reducing oxidative stress and reducing the risk of dementia (Mehdi 2013).
Sodium	neuronal activity	Sodium is essential for regulating muscle contractions, nerve transmissions essential for normal CNS physiological mechanisms and homeostasis (Delage 2014 (accessed 21 September 2015); Institute of Medicine, FNB 2001).
Zinc	anti-oxidant neuronal activity	Zinc is a constituent of the antioxidant enzyme superoxide dismutase that helps reduce the harm from free radicals. Zinc regulates cell division and synthesis of genetic cell DNA. It is essential for reproduction, repair, and normal growth within the CNS (Delage 2014 (accessed 21 September 2015)). Zinc is found in high levels in the brain where it performs catalytic, structural and regulatory roles in cellular metabolism. Zinc is bound to proteins but free zinc is present in synaptic vesicles and performs a role in neurotransmission mediated by glutamate and gamma-aminobutyric acid (GABA). Short-term deficits of zinc have been shown to impair certain measures of mental and neurological function while long-term deficits of zinc, especially during gestation, result in malformation or deficits in attention, learning, memory and neuropsychological behaviour (Institute of Medicine, FNB 2001) Zinc was found to be capable of reducing post-ischaemic injury to a variety of tissues and organs through a mechanism that might involve the antagonism of copper reactivity. Although the evidence for the antioxidant properties of zinc is compelling, the mechanisms are still unclear (Powell 2000).

* Only orally-administered supplements taken at any dose for at least 12 weeks are considered. Supplements that combine vitamins or minerals are eligible as well.

Appendix 2. MEDLINE search strategy

1. exp *Vitamins/
2. exp *Minerals/
3. exp *Dietary Supplements/
4. Calcium Carbonate/
5. vitamin*.ti,ab.
6. cholecalciferol.ti,ab.
7. ergocalciferol.ti,ab.
8. toxiferol.ti,ab.
9. retinol.ti,ab.

10. "retinoic acid".ti,ab.
11. Vitamin A/
12. Vitamin B 12/
13. Vitamin D/
14. Vitamin E/
15. "beta-carotene".ti,ab.
16. "alpha-carotene".ti,ab.
17. "gamma-carotene".ti,ab.
18. "beta-cryptoanthin".ti,ab.
19. thiamine.ti,ab.
20. riboflavin.ti,ab.
21. niacin.ti,ab.
22. nicotinamide.ti,ab.
23. pantothenic.ti,ab.
24. pyridoxine.ti,ab.
25. pyridoxal.ti,ab.
26. pyridoxamine.ti,ab.
27. biotin.ti,ab.
28. "folic acid".ti,ab.
29. Folic Acid/
30. cyanocobalamin.ti,ab.
31. methylcobalamin.ti,ab.
32. "l-ascorbic acid".ti,ab.
33. "ascorbic acid".ti,ab.
34. ascorbate.ti,ab.
35. Ascorbic Acid/
36. phylloquinone.ti,ab.
37. phytomeadione.ti,ab.
38. phytonadine.ti,ab.
39. mineral*.ti,ab.
40. multivitamin*.ti,ab.
41. "diet* supplement*".ti,ab.
42. calcium.ti,ab.
43. Calcium/
44. iron.ti,ab.
45. zinc.ti,ab.
46. sodium.ti,ab.
47. potassium.ti,ab.
48. phosphorus.ti,ab.
49. magnesium.ti,ab.
50. chloride.ti,ab.
51. sulphur.ti,ab.
52. mangansese.ti,ab.
53. cobalt.ti,ab.
54. selenium.ti,ab.
55. copper.ti,ab.
56. iodine.ti,ab.
57. fluoride.ti,ab.
58. or/1-57
59. *Aging/
60. Aged/
61. "Aged, 80 and over"/
62. Middle Aged/
63. Age Factors/
64. "mild cognitive impairment".ti,ab.
65. Mild Cognitive Impairment/
66. MCI.ti,ab.
67. AAMI.ti,ab.
68. ACMI.ti,ab.
69. ARCD.ti,ab.
70. CIND.ti,ab.
71. (nMCI or aMCI or mMCI or MCIa).ti,ab.

72. "old* adults".ti,ab.
73. elderly.ti,ab.
74. "old* age*".ti,ab.
75. "middle age*".ti,ab.
76. seniors.ti,ab.
77. "senior citizens".ti,ab.
78. "community dwelling".ti,ab.
79. pensioners.ti,ab.
80. "aged sample".ti,ab.
81. "aged population".ti,ab.
82. or/59-81
83. 58 and 82
84. *Cognition/
85. *Cognition Disorders/
86. Memory/
87. Memory Disorders/
88. (cognit* adj3 (func* or declin* or reduc* or impair* or improve* or deficit* or progress* or perform* or abilit*)).ti,ab.
89. "mental perform*".ti,ab.
90. memory.ti,ab.
91. "executive function*".ti,ab.
92. Executive Function/
93. Attention/
94. (speed adj2 processing).ti,ab.
95. "episodic memory".ti,ab.
96. Memory, Episodic/
97. or/84-96
98. 83 and 97
99. randomized controlled trial.pt.
100. controlled clinical trial.pt.
101. randomized.ab.
102. placebo.ab.
103. drug therapy.fs.
104. randomly.ab.
105. trial.ab.
106. groups.ab.
107. or/99-106
108. exp Animals/ not humans.sh.
109. 107 not 108
110. 98 and 109 [all results]
111. *Vitamins/
112. *Cognition/
113. "Aged, 80 and over"/ or Aged/ or Middle Aged/
114. Mild Cognitive Impairment/
115. "mild cognitive impairment".ti,ab.
116. 113 or 114 or 115
117. 111 and 112 and 116
118. 99 or 100
119. 117 and 118 [results sent directly to author team]
120. 110 not 119 [results minus those sent directly to author team. These results will be screened by the 'crowd']

Appendix 3. Definitions of design, patient and intervention characteristics as applied in the stratified analyses exploring between trial variations in intervention effect

Item	Definition
*Bias related characteristics**	
Concealment of allocation (avoiding selection bias)	The guidance from the *Cochrane Handbook for Systematic Reviews of*

(Continued)

	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 to the experimental intervention and the specific outcome or group of outcomes is/are likely to be influenced by lack of blinding - blinding is absent or suboptimal and the specific outcome, such as mortality, is not likely to be influenced by lack of blinding
Blinding of outcome assessment (avoiding detection bias)	*For self-reported/partner reported outcomes:* Low risk of bias will be judged if: - self-reported outcomes were assessed AND blinding of patients was considered adequate AND there was no information to suggest that there was an investigator involved during the process of outcome assessment; OR if blinding of investigators performing the outcome assessment was reported AND an attempt to blind patients was reported. *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	A large trial will be defined by a sample size calculation for the primary outcome.
Follow-up duration	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) for cognitive outcomes. For all cause dementia or MCI, the follow up durations will be grouped as short-term (1 year), medium-term (up to 2 years) and long-term (more than 2 years).
Treatment related characteristics	
Treatment duration	The minimum treatment duration of 3 months is considered short term, 3 to 12 months as medium term, and 12 months for long term.

(Continued)

Mechanisms of action of the supplements**	Supplements postulated to share a main mechanism of action in preventing development of dementia, including: • Antioxidant properties - affecting superoxide dismutase (vitamin A, C, D, E, selenium) • Regulation/lowering levels of homocysteine: vitamins B12, folate and B6
Dose of supplements	High dose versus low dose supplements will be analysed according to previously reported cut-offs
Participant-related characteristics	
Cognition-related criteria	No risk of deficiency vs at risk of deficiency for the type of vitamin and mineral supplement(s) investigated (e.g. presence of malabsorptive diseases, malnutrition, comorbidities or concomitant medications, and ethnicity (Vitamin D))

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

** Knowledge of possible mechanisms of actions is evolving, and we will consider other possible subgroups for data analysis as new information arises during the development of the review.

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