Title: Can supplements maintain cognition in mid to later life? COMMENTARY ON… COCHRANE CORNER   
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Declaration of interest: None  
Funding: Nil to declare  
Acknowledgements: The author would like to thank Dr Riccardo De Giorgi, Wellcome Trust Doctoral Training Fellow, at Oxford University Department of Psychiatry, for his comments and suggestions. The views expressed are those of the authors and not necessarily those of the NHS or the Department of Health.  
Author contributions: Alexander Smith is the sole author of this publication

# Introduction

Dementia poses a large burden on healthcare systems around the world, in 2015 it was estimated to cost US$818 billion (1.1% of global gross domestic product), with 50 million diagnosed with the syndrome and 10 million new cases a year. This is forecast to rise to 152 million cases in 2050 (World Health Organisation, 2019). A1-year delay in onset would forecast 12 million fewer cases worldwide in 2050 (Winblad, et al., 2016) and with a case requiring residential care costing approximately £2,500 per month in the UK (Gustavsson, et al., 2011), the societal and healthcare costs would be significant.

There is currently no cure for dementia and limited progress in therapeutics for the condition, subsequently an interest in modifiable risk factors throughout the lifespan has developed (Hussenoeder & Riedel-Heller, 2018). Some of this focus has involved vascular and dietary risk factors (Hill, et al., 2019). There is a growing body of literature linking the nutrition and the development of dementia, in particular lower levels of vitamins, such as folate and Vitamins B12, C and E, in the cognitively impaired (Gustafson, et al., 2015).

In terms of current guidance in the UK it is advised not to offer ginseng, vitamin E or herbal supplements to those already diagnosed with dementia (National Institute for Health and Care excellence, 2018), the NHS advising a healthy diet as a modifiable risk factor for dementia (NHS, 2017). There is little guidance relating to supplements in maintaining cognitive health in those not diagnosed with dementia although the Scientific Advisory Committee Network concluded that overall there was insufficient evidence ‘that higher intakes of individual nutrients protect against cognitive decline, MCI or dementias AD’ (Scientific Advisory Committee on Nutrition, 2018). The World Health Organisation strongly recommend that ‘Vitamins B and E, Poly Unsaturated Fatty Acids and multi-complex supplementation should not be recommended to reduce the risk of cognitive decline and/or dementia’ (World Health Organisation, 2019).

# Definition of the clinical question

The Cochrane review by Rutjes et al. (Rutjes, et al., 2018) aimed to evaluate the effects of vitamin and mineral supplements on cognitive function (i.e. their “efficacy”) in cognitively healthy people aged 40 years or older.

Specifically, the primary outcome was maintenance of mean overall cognitive functioning in cognitively healthy individuals in mid and late life assessed using recognised measures of cognitive function (Box 1). The authors acknowledged that the degree of change (or not) in scores that qualifies as maintenance is unknown and opted for maintenance being no statistical difference between intervention and control groups with a significance value of p<0.05.

The authors also measured nine secondary outcomes covering validated measures of specific cognitive functioning subdomains (e.g. executive function, speed of processing, and episodic memory), incidence of Mild Cognitive Impairment or all-cause dementia, quality of life, mortality, functional performance, number of participants experiencing an adverse event and clinical global impression. Whilst clinically important these will not be the focus of this commentary owing firstly to the incomplete data available for each measure in each supplement category and secondly the proportionate educational value added by included in examining these measures.

# Methods

The authors included randomised and quasi-randomised controlled studies in any language. They did not specify the time frame of their search. Trials ranged from 3 months to up to 20 years in duration, with cognitively-healthy (or at least 80% sample deemed cognitively-healthy) participants aged 40 years and over. Interventions were pooled into six groups according to supplement/s: antioxidants; B vitamins; vitamin D & calcium; zinc & copper; selenium, and finally complex multivitamins. Control comparisons were interventions that were not expected to impact on cognition (placebo or usual care). It could not be ascertained what usual care entailed specifically, as many individuals in mid- to later-life use multivitamins, some trials did not use placebo as a comparator. In the context of the exact mechanism between vitamins and cognition yet to be elucidated, we cannot be reliably confident that comparator interventions have no impact on cognition. This could affect results by minimising any difference seen between intervention and control groups.

The authors searched electronic databases and trial registries monthly and performed six monthly searches of a number of sources for grey literature including searches of conference proceedings, screened the reference lists of trials & recent systematic reviews, subject-specific guidelines as well as contacting companies and experts in the field in an effort to obtain grey literature. This is relevant to the review’s results, contributing to a wider evidence base and thus more precise results as well as reducing publication bias.

Measures of treatment effect used mean difference for continuous data sets using the same scales and standardised mean difference for continuous data using different scales (Box 2). Risk ratios were used for dichotomous data.

Risk of bias was assessed by using the Cochrane’s ‘Risk of bias’ tool. Of the twenty-eight studies included, eight were at high risk of attrition bias and six at high risk of reporting bias, the latter largely attributable to the variable primary outcomes of the studies included, in some cases adding cognitive assessment at a later stage in the study. This is important as it could represent possible outcome reporting bias and whilst *post hoc* analysis is acceptable when accounted for in design and analysis, inclusion of a test mid-way through a trial, not designed appropriately for said test, could lead to conclusions that are either inaccurate or have low strength.

The authors acknowledged the heterogeneity in the field and two of the measures to measure it were I2 and tau2.

No subgroup analyses (i.e. examining if effect if different in different subgroups) were performed due to the small number of trials included and no sensitivity analyses (i.e. restricting analysis to one subgroup) were performed. Possible sensitivity analysis that could be valuable would be those with only cognitively healthy samples, or those who measured cognitive function from the outset. These may have led more precise results with higher certainty in the results.

# Results

Twenty-seven studies were included totalling a population of over 83,000 participants aged 40 years

and over who were deemed cognitively healthy (i.e. without a dementia diagnosis or cognitive

impairment) at baseline. The definition was made by each trial separately e.g. not having a formal dementia diagnosis, not scoring positive on a Telephone Interview for Cognitive Status (TICS), scoring above a certain threshold on Mini Mental State Exam (MMSE). This variation in definition could have resulted in those with cognitive impairment not yet qualifying for a diagnosis of dementia being included. Despite wanting to examine cognitively healthy people, the authors included studies with 80% of the sample deemed cognitively healthy – it was not clear why this percentage was chosen but could it influence the outcome e.g. by attenuating a small difference seen between cognitively impaired and healthy people. For example, for the hypothetical 20% cognitively impaired in mid-life, it can be presumed other stronger risk factors may be present for cognitive impairment (e.g. genetic risks) and as such the efficacy of supplements in primary prevention could be underestimated. The authors comment that it is ‘possible some participants may not have been cognitively healthy at baseline’.

No benefit in overall cognitive function with B vitamin supplementation was observed at any time point. The quality of the evidence ranged from low to moderate. This finding is in agreement with the other previous systematic review and meta-analysis in this area (Clarke et al. 2014).

Antioxidant studies included three supplements (vitamin E, C and beta carotene). One study on

vitamin E supplementation found a significative improvement in MMSE for the intervention group at

3-12 months (Mean Difference [MD] 1.4, 95% CI 1.18 to 1.62, n = 74). However, this finding is burdened by the very low quality of the evidence due to imprecision and indirectness (Box 3). Moreover, the clinical value of an improvement of 1.4 on the MMSE seems minimal in the context of advising an individual to take supplements for the rest of their life. It is possible the MMSE is not sensitive enough to identify the cognitive changes examined here, although Tsoi et al. (Tsoi, et al., 2015) found it to be of comparable sensitivity and specificity to alternative cognitive tests.

One study could be used to examine the effect vitamin C supplementation on overall cognitive

functioning and suggested there may be a small beneficial effect after 5 to 10 years (MD 0.46 (95% CI 0.14 to 0.78, n = not reported, P = 0.006). Beta-carotene showed small benefits in overall cognitive function (TICS) after an average of 18 years of treatment.

Two trials involving vitamin D supplementation were included although not pooled due to the fivefold differences in equivalent dosage used between studies. Additionally, one trial included calcium supplementation whilst the other smaller trial did not. The smaller trial of 60 participants found no significant differences in Montreal Cognitive Assessment (MoCA) scores between control and intervention groups (MD 0.76 points, CI not reported, P = 0.186), with a moderate degree of certainty. The larger study found no significant differences between placebo and control groups in terms of incidence of dementia or probable Mild Cognitive Impairment over the 7.8 year follow up (Hazard Ratio 0.94, 95% CI 0.72 to 1.24, P = 0.68).

Only one RCT of 1072 participants used zinc and copper supplementation and found no statistically

significant effect on overall cognitive function (measured with MMSE) after 5-10 years of supplementation (MD 0.6, 95% CI -0.19 to 1.39, n =1072).

No significant difference was identified between placebo and selenium supplementation from a single arm of an RCT study assessing incidence of dementia over 12-year period (HR 0.83, 95% CI 0.61 to 1.13, P = 0.23, n = 7388).

In terms of complex multivitamins (containing B vitamins and antioxidants +/- minerals) no significant differences for overall cognitive functioning by Telephone Interview of Cognitive Status (TICS) were identified at either 2.5 years (MD 0.04, 95% CI -0.09 to 0.18; n = 5947) or 8.5 years (MD 0.12, 95% CI -0.14 to 0.38; n = 2324).

The quality of the evidence was ranged from “very low” to “moderate” using the GRADE criteria.

This is largely based upon restriction of participants enrolled (e.g. samples restricted by gender,

comorbidity), leading to indirect conclusions and uncertainty around the risk of selection and attrition bias (see Box 3). Additionally, the trials included were very heterogenous in terms of design, duration, and primary outcomes, therefore many issues can be identified such as the possibility of including participants which were not cognitively healthy at baseline or with no baseline cognition scores.

In terms of efficacy, the results were consistent in reporting no benefit of any supplement over the

different time points. The confidence intervals were relatively small, which could indicate precise

results, though more likely reflects the limited number of studies included in each review component.

The duration of studies also varied considerably, with the authors having to create arbitrary categories for classification of results/effects, which the authors acknowledged limited the pooling of studies for analysis (as evidenced by forest plots with one study per category). Although acknowledged the value of this approach in terms of drawing confident clinical conclusions is questionable. However, it should also be acknowledged the efforts of the authors to bring some clarity and categorisation to a heterogenous field.

# Discussion

In summary, this review found insufficient evidence that giving supplements to cognitively healthy middle- or old-age adults, had any effect on maintaining cognitive function or preventing dementia.

Whilst acknowledging the effect sizes are small, their clinical relevance is also questionable. Results

for Vitamin C could only be drawn from one study only, with small effect sizes and confidence intervals approaching zero. In line with the authors conclusion that this is low certainty evidence,

supplementation with Vitamin C is unlikely to have meaningful clinical impact on the prevention of

cognitive decline based on the available evidence.

The authors highlight that the evidence only indirectly addresses the review question with regards to

doses and study duration. The lack of understanding of the relationship between cognition and

vitamin/mineral supplementation possibly contributed to the wide variety of doses and duration of

studies, which weakens the evidence of the field. However, the authors also suggest that grouping of

such heterogenous samples and interventions, especially with B vitamins studies, may disguise any

subtle effects on cognition.

It is noteworthy that, whilst many studies did not examine cognitive status as a primary outcome,

there were no comments on the feasibility and acceptability or taking supplements every day for

several years, if not decades. Although the safety of over the counter supplements could be assumed in the short term, side effects or adverse effects of any intervention/supplementation would warrant comment.

A figure for the cost-benefit for supplementation e.g. for Vitamin C or beta-carotene and comparing

to other interventions, would be interesting. National formulary list indicates for a month’s supply of

a Vitamin B compound tablets will cost £2.82, likewise for Vitamin C a month’s supply at a dose for

prophylaxis of scurvy (typical indication) is £3.29 (Treatments summary, Vitamins, 2018). When

crudely compared to other long-term medication such as simvastatin (52p for months’ supply) or

ramipril (81p for months’ supply), vitamin supplementation can appear relatively expensive.

Several issues impact the confidence one can have in the result of the review. Firstly, most studies did not include cognition as a primary outcome. As such no baseline cognitive assessments were

performed or only included at a later stage. The authors noted that when used, the cognitive

assessment often lacked the sensitivity to detect changes in cognition. Secondly, samples were often

restricted in ways which limit applicability to older, clinical populations (e.g. gender, co-morbidity).

Thirdly, incidence of dementia was assessed in only three studies used, showing indirect implications

for dementia prevention. It was also raised that most studies assessing cognition were short-term

studies (<2 years), which is felt to be too short time period when evaluating the use of mineral/vitamin supplementation for the long-term prevention of Mild Cognitive Impairment (MCI) or dementia. It is thought that 5-20% of over 65yo have MCI. The annual conversion rate MCI to dementia is approximately 5-10%, with the majority of those diagnosed with MCI not progressing to dementia at 10yrs. In this context studies less than two years in duration are unlikely to identify cognitive deterioration and thus any impact vitamin supplementation would have on it.

*Implications for clinical practice and research*

With a hypothetical patient in clinic we can state that, based on current available evidence, there is no indication that using vitamins or supplements can maintain cognitive function or prevent dementia in the middle- and old-age population. Additionally, costs can become a burden, especially if bought ‘over the counter’ and there is some evidence suggesting supplementation is not without risk. For instance, the risk of stomach cramp or diarrhoea with excessive Vitamin C consumption, or the elevated risk of lung cancer in smokers who consume more than the recommended daily allowance per day (Wooltorton, 2003).

The implications for research include the questions that remain regarding doses, supplement

combinations, characteristics of a suitable population and the duration of studies required to find any effects on cognition, in particular the long-term effects of supplements started in mid-life. Key to this will be the understanding of the pathology of cognitive decline and dementia and the role of

vitamins/supplements in modifying it. The authors suggest using smaller studies of highly sensitive

cognitive assessments, akin to a phase II trial, to elucidate mechanisms and identify any subtle effects that supplementation may have.

As long-term studies involving Vitamin C and beta carotene demonstrated potential effects, future

research could focus on antioxidant vitamins (vitamin C and beta carotene) for maintaining cognitive

health and/or as a modifiable risk factor for dementia.

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