Effect of homocysteine lowering treatment on cognitive function: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
This review concluded that vitamins B12, B6, or folic acid supplementation did not improve cognitive function in older adults with or without cognitive impairment. The authors' conclusions reflected the evidence, but there was potential for review bias and considerable differences between small trials, which suggests that the findings should be considered tentative.

Authors' objectives
To assess the efficacy of B-vitamins (B12, B6, or folic acid) in reducing cognitive decline among older adults with and without cognitive impairment.

Searching
PubMed, PsycINFO, EMBASE, and The Cochrane Library were searched from inception up to August 2011 for articles in English. Search terms were reported. Reference lists of relevant articles, clinical trial registration web sites, and conference abstracts were also searched.

Study selection
Eligible for inclusion were randomised placebo controlled trials (RCTs) that assessed the efficacy of vitamin B12, B6 or folic acid in reducing the progression of cognitive decline in older adults (50 years or older), with or without cognitive impairment or dementia. Only trials that reported results for at least 20 participants on one or more cognitive function tests before and after intervention were eligible for inclusion.

Included trials were conducted in the USA, Canada, Europe (including three in England), Hong Kong, New Zealand, and Australia. Participants had cognitive impairments (Alzheimer's disease, dementia, or mild cognitive impairment) or were volunteers without cognitive impairment; some had other health conditions such as hypertension and cerebrovascular disease. Doses of folic acid varied from 0.75mg to 15mg, vitamin B12 varied from 0.05mg to 1mg, and vitamin B6 varied from 3mg to 50mg. The mean duration of trials ranged from four weeks to 5.4 years (taken from table 2). Some trials permitted the use of cholinesterase inhibitors. Sixty-two different cognitive tests were used to measure cognitive function.

The authors also reported the effect of B-vitamins on total homocysteine levels, but it was unclear how this was measured and no other details were provided.

It appeared that both reviewers screened studies for inclusion; discrepancies were resolved through consensus.

Assessment of study quality
Trial quality was assessed for random allocation, allocation concealment, blinding, incomplete outcome data addressed, selective reporting, and other sources of bias.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
One reviewer extracted or calculated mean change from baseline, along with standard deviations. Primary study authors were contacted for clarification of data, where necessary. Cognitive tests were grouped into the following domains: tests of general cognitive functioning; memory; speed of processing and attention tasks; language; executive function; activities of daily living/dementia severity; behaviour; and visuo-spatial tasks.

Methods of synthesis
A random-effects model was used to pool mean changes and standard deviations to calculate standardised mean
differences and 95% confidence intervals. Statistical heterogeneity was assessed using $X^2$ and $I^2$.

Separate analyses were conducted for: all cognitive tests combined and separately for each cognitive domain; separately in patients with and without cognitive impairment; separately for trials that assessed folate supplementation alone and in combination with other B-vitamins.

Separate analyses were performed according to the dietary folate status of patients' country of origin (high or medium/low) using previously published data (as defined in the review). Post-hoc analyses were performed according to length of B-vitamin supplementation (trials of at least six months duration) and study size (trials with at least 100 participants).

Sensitivity analyses were performed in participants with and without cognitive impairment by removing one trial at a time.

Publication bias appears to have been assessed using funnel plots.

Results of the review
Nineteen RCTs (5,398 participants, range 24 to 2,009) were included in the review. Six RCTs met all six quality criteria; the main issues with the remaining trials were on unclear sequence generation and allocation concealment, and incomplete outcome data.

The overall effects of B vitamins across combined cognitive scores and for separate cognitive domains were not statistically different to placebo in participants with cognitive impairment (six RCTs) or without cognitive impairment (13 RCTs). The overall tests for statistical heterogeneity were not significant for participants with cognitive impairment ($I^2=36\%$) or without cognitive impairment ($I^2=0\%$).

Post-hoc analyses, sensitivity analyses, and other analyses did not significantly alter the findings (fully reported in the review).

B-vitamins statistically significantly lowered total homocysteine levels in participants with (SMD -0.74, 95% CI -1.01 to -0.48) and without (SMD -0.88, 95% CI -1.11 to -0.65) cognitive impairment.

There was no evidence of publication bias according to funnel plots (data not shown).

Authors' conclusions
Supplementation with vitamins B12, B6, and folic acid alone or in combination does not improve cognitive function in individuals with or without existing cognitive impairment.

CRD commentary
The review question and inclusion criteria were clearly stated. A satisfactory number of sources were searched for relevant data, but as this was restricted by language, language bias could not be ruled out. Only one reviewer performed the data extraction and it was unclear whether quality assessment was performed in duplicate, which meant that reviewer error and bias could not be ruled out.

Trial quality was assessed and fully reported. There were considerable differences between trials in patient and trial characteristics; the authors went some way to address the differences when pooling the data, and performed various subgroup analyses. The findings were consistent in showing no significant effect on cognitive impairment using B-vitamins, but sample sizes were generally small. The significance of the effects of B-vitamins on total homocysteine levels was unclear and it was unclear how this was measured.

The authors acknowledged some limitations of the evidence, including clinical and methodological heterogeneity between included trials, short treatment durations in some trials, and uncertainties regarding adequate power to detect differences between treatment and placebo groups.

Although the authors' conclusions reflected the evidence, there was some potential for bias in the review, and considerable differences between trials with small sample sizes. As such, the findings should be considered tentative as
their reliability remains unclear.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that it remained to be established whether prolonged treatment with B-vitamins is associated with better cognitive outcomes or if their use could reduce the risk of dementia in later life, particularly in individuals with high total homocysteine or low concentrations of vitamin B12 and folic acid.

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