Vitamin B12 status, cognitive decline and dementia: a systematic review of prospective cohort studies

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CRD summary
This review concluded that there was insufficient evidence to show a clear link between serum vitamin B\textsubscript{12} concentrations and cognitive decline or dementia in older adults. Given the differences between studies and limitations of the evidence, the authors’ cautious conclusions and recommendations for future research seem appropriate.

Authors’ objectives
To assess the association between vitamin B\textsubscript{12} status and cognitive decline and dementias in older adults.

Searching
Eight databases (including MEDLINE, DARE and The Cochrane Library) were searched up to August 2011 for relevant publications in English. Search terms were reported. In addition, reference lists of relevant articles were manually screened.

Study selection
Eligible for inclusion were prospective cohort studies that assessed the association of markers (serum vitamin B\textsubscript{12}, methylmalonic acid, or holotranscobalamin) with cognition or dementia in older adults.

The included studies were conducted in 10 countries including three in the UK. Average participant ages ranged from 47 to older than 85 years; some studies included participants with dementia. Most studies determined vitamin B\textsubscript{12} status using serum vitamin B\textsubscript{12} concentrations (markers) alone. Outcome measures included cognitive decline, development of dementia or Alzheimer’s disease, or cognitive deterioration in participants diagnosed with dementia or Alzheimer’s disease (as defined in the review).

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
Study quality was assessed using the 10-item American Dietetic Association Study Quality tool. Studies were assigned a ‘positive’ overall score (denoting low risk of bias) if most questions and four essential validity questions were reported as a ‘yes’. Studies were considered ‘neutral’ if answers to the four essential validity questions did not indicate that the study is exceptionally strong. Studies were ‘negative’ if most (six or more) answers to the validity questions were ‘no’.

Two reviewers assessed study quality; a third reviewer was involved where discrepancies occurred.

Data extraction
Summary outcome effects were extracted using a previously published template. Most studies used multiple regression to assess the association of serum vitamin B\textsubscript{12} and cognition, while others applied cut-points of 110pmol/L to 251pmol/L, or reported only unadjusted data. No attempt was made to contact primary authors.

Two reviewers extracted data; where discrepancies arose, a third reviewer acted as an adjudicator.

Methods of synthesis
A meta-analysis was not deemed appropriate because of differences in participant populations, vitamin status tests, and outcomes across studies. Therefore, outcome data were presented in tables and as a narrative synthesis, separately for each outcome and separately for participants with and without dementia. Results were also reported separately depending on quality score.

Results of the review
Thirty-five cohort studies (14,325 participants, range 24 to 1,405) were included in the review. Follow-up ranged from
0.5 to 35 years. Twenty-one studies were considered to be of positive quality, 10 neutral quality, and four negative quality.

Of the 21 positive-quality studies, seven reported positive associations between vitamin B$_{12}$ status and cognitive decline, dementia or Alzheimer's disease, and 14 studies did not. Nineteen of the 21 positive-studies used serum vitamin B$_{12}$, of which three studies reported significant associations with cognitive decline. All four studies with positive-quality that used the methylmalonic acid markers and holotranscobalamin markers reported significant associations with cognitive decline, dementia or Alzheimer's disease.

Cognitive decline and vitamin B$_{12}$ status in non-demented participants: Four of six studies reported no association between cognitive decline and serum vitamin B$_{12}$ after a mean follow-up of 5.1 years.

Cognitive decline and vitamin B$_{12}$ status in participants with unspecified cognition: Four of 11 studies reported an association between vitamin B$_{12}$ status and at least one test of cognition. Seven studies found no association between 2.3 and 6.0 years follow-up.

Cognitive decline in participants with existing dementia: All five studies reported no association between vitamin B$_{12}$ and cognition.

Development of dementia in participants with no dementia at baseline: Five of eight studies reported no association between serum vitamin B$_{12}$ and the development of dementia. Five of eight studies reported no association between holotranscobalamin or serum vitamin B$_{12}$ alone or in combination with low serum folate concentrations and the development of Alzheimer's disease.

**Authors’ conclusions**
There was insufficient evidence to show a clear link between serum vitamin B$_{12}$ concentrations and cognitive decline or dementia.

**CRD commentary**
The review question and supporting inclusion criteria were broadly stated. Multiple databases were searched. However, the search was limited to published articles in English (as acknowledged by the authors), which meant that potentially relevant data may have been missed. Data extraction and quality assessment were performed in duplicate, which reduced the potential for reviewer error and bias. However, it was unclear whether this was true for study selection.

Study quality was assessed but only overall scores were reported, and the limitations of a cohort design should also be taken into consideration. Study and population characteristics confirmed the variability across studies. The reporting of outcome data were limited in some studies. The authors highlighted some of the limitations of the evidence, including the use of different neuropsychological tests to detect cognitive change, the differences between studies, and small sample sizes. It was unclear how serum markers were measured and whether the methods were appropriate and comparable across studies. It may also have been useful to assess outcomes at different serum cut-off levels to identify the optimal level.

Given the limitations of the evidence, the authors’ cautious conclusions and recommendations for future research seem appropriate.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that future studies should use methylmalonic acid and holotranscobalamin as well as serum vitamin B$_{12}$, and describe both significant and non-significant results for any tests cut-points and continuous measures of vitamin B$_{12}$ status. Further research should also be of adequate duration (more than six years) and further explore sensitivity and specificity of the markers in question.

**Funding**
None.
Bibliographic details

PubMedID
23084026

DOI
10.1017/S0007114512004175

Original Paper URL
http://journals.cambridge.org/action/displayAbstract?fromPage=online&amp;aid=8783699

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Aged, 80 and over; Biomarkers; Cognition; Cognition Disorders /blood /etiologic /physiopathology; Dementia /blood /etiologic /physiopathology; Disease Progression; Female; Humans; Male; Methylmalonic Acid /blood; Middle Aged; Mild Cognitive Impairment /blood /etiologic /physiopathology; Nutritional Status; Transcobalamin /analysis; Vitamin B 12 /blood; Vitamin B 12 Deficiency /physiopathology

AccessionNumber
12013004353

Date bibliographic record published
05/03/2013

Date abstract record published
01/10/2014

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.