Systematic Review

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

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Abstract

Poor vitamin B₁₂ status may lead to the development of cognitive decline and dementia but there is a large variation in the quality, design of and results reported from these investigations. We have undertaken a systematic review of the evidence for the association between vitamin B₁₂ status and cognitive decline in older adults. A database search of the literature to 2011 was undertaken, using keywords related to vitamin B₁₂ and cognition. All prospective cohort studies assessing the association of serum vitamin B₁₂ or biomarkers were included. Quality assessment and extraction of the data were undertaken by two researchers. The quality assessment tool assigns a positive, neutral or negative rating. Of 3772 published articles, thirty-five cohort studies (n=14325 subjects) were identified and evaluated. No association between serum vitamin B₁₂ concentrations and cognitive decline or dementia was found. However, four studies that used newer biomarkers of vitamin B₁₂ status (methylmalonic acid and holotranscobalamin (holoTC)) showed associations between poor vitamin B₁₂ status and the increased risk of cognitive decline or dementia diagnosis. In general, the studies were of reasonable quality (twenty-one positive, ten neutral and four negative quality) but of short duration and inadequate subject numbers to determine whether an effect exists. Future studies should be of adequate duration (at least 6 years), recruit subjects from the seventh decade, choose markers of vitamin B₁₂ status with adequate specificity such as holoTC and/or methylmalonic acid and employ standardised neurocognitive assessment tools and not screening tests in order to ascertain any relationship between vitamin B₁₂ status and cognitive decline.

Key words: Vitamin B₁₂; Cognition; Dementia; Systematic reviews

Cognitive decline and dementia have a significant impact on the independence and quality of life of sufferers and carers, and research into modifiable risk factors is paramount.

The most prevalent form of dementia is Alzheimer's disease (AD) which accounts for up to 70% of cases(1), with other common forms including dementia with Lewy bodies, frontotemporal dementia and vascular dementia(2). Risk factors for dementia include advanced age, genetics, low educational level as well as CVD, and its component vascular risk factors(1,2). The most important known genetic risk factor for the development of dementia is possession of the apoE4 allele which substantially increases the risk of AD by two to three times(3).

Poor vitamin B₁₂ status has been linked to cognitive decline for at least 50 years(4) but the role of vitamin B₁₂ in this process is not clear. Vitamin B₁₂ deficiency causes neurological degeneration with demyelination of the spinal cord and some initial studies have described a reversible dementia related to vitamin B₁₂ deficiency(5–10).

A link between vitamin B₁₂ status and cognitive decline is biologically plausible. Vitamin B₁₂ is required for DNA and myelin synthesis, and it is a cofactor for the methylation of total homocysteine (tHcy) to methionine and for the conversion of methylmalonyl-CoA to succinyl-CoA(11). Both tHcy and methylmalonic acid (MMA) accumulate while holotranscobalamin (holoTC), the active transport protein carrying vitamin B₁₂, decreases with inadequate vitamin B₁₂ status.

The suggested aetiologies behind any association between cognitive decline related to low vitamin B₁₂ status include inadequate methylation in the central nervous system(12), the accumulation of tHcy and/or MMA(13), the effects on the cerebral vasculature and brain atrophy and white matter damage(1).
Recent reviews have linked high tHcy concentrations with an increased risk of cognitive decline and dementia(14–18), however, it is not known whether tHcy is a marker of disease or a causative factor in the dementing process. A large number of studies have investigated the association between vitamin B12 status and cognition, but there is no consistency in outcomes and the independent role of vitamin B12 status in the development of neurocognitive decline is uncertain.

Cross-sectional studies showed positive associations between serum vitamin B12 and scores on cognitive tests, but cohort studies did not(19,20). Balk et al.(19) assessed seven cohort studies, with only two showing associations of improved cognition with higher serum vitamin B12 concentrations. In three recent reviews, it was found that seven of fifteen, one of six and three of cohort studies showed associations between low serum vitamin B12 status and increased rates of cognitive decline(20–22). These reviews, although finding no association between vitamin B12 and cognitive decline, have highlighted the methodological limitations of studies(15,19–21).

The most recent systematic reviews include studies published before 2007(19,21) and only include studies assessing vitamin B12 concentrations. Other studies that utilise sensitive biomarkers of vitamin B12 status, holoTC and MMA, have since been published. The aim of the present systematic literature review was to provide an up-to-date identification and critical appraisal of published studies of the longitudinal association between vitamin B12 status and the spectrum of cognitive decline and dementias in older adults.

Methods
A review protocol including library search strategy, inclusion and exclusion criteria, use of data extraction and quality tool templates was determined before the review.

Search strategy
A literature search was undertaken on 6 June 2010 and an update was performed on 12 August 2011. Database searches included Medline (1950–present), Pre-medline, Psyc INFO (1806–present), all EBM Reviews (ACP Journal Club, DARE and CCTR (1991–present), and Cochrane DSR (2005–present)), Cinahl (1982–present) and Embase (1980–present). Both medical subject headings and text words were used for dietary supplement terms, vitamin B12 and biomarkers (e.g. homocysteine, methylmalonic acid and holotranscobalamin) and common terms for cognition and dementia (e.g. cognition, dementia, memory and Alzheimer’s disease) with appropriate truncation. The full search terms for the Medline database can be seen in the Appendix. Filters to limit publications to English language and to middle- and older-aged human subjects were applied at the end of each database search if available.

Study selection
Citations from each literature database search were downloaded into referencing software Endnote X1. Titles and abstracts were assessed for inclusion criteria. Inclusion criteria were prospective cohort studies assessing the association of serum vitamin B12, MMA or holoTC and cognition or dementia in older adults. Studies that measured vitamin B12 status but only reported a lack of association in the text of the results were also included. All other studies were excluded. The reference lists of included studies and reviews identified in the literature search were checked for relevant articles. Studies with more than one publication from the same subject sample were reported as one study and studies reporting more than one outcome, e.g. dementia and AD, were reported separately.

Data extraction and synthesis
The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2009 statement was used to guide the conduct and reporting of the present systematic review(23). Data were extracted by two reviewers using the American Dietetic Association’s Evidence Analysis data extraction template(24), with adjudication by a third reviewer if required. For each study, the following information was extracted: study description; participant selection and characteristics (including age, disease characteristics, baseline cognitive status and method of diagnosis); inclusion and exclusion criteria; subject numbers and withdrawals; statistical methods used; ascertainment and length of exposure; outcome measure characteristics; funding arrangements. No attempt was made to contact authors of included studies as only published data were included. A meta-analysis was deemed inappropriate due to the variability of baseline populations, cognitive and vitamin B12 status tests and reported outcome statistics.

Study quality
The quality of the studies was assessed by two reviewers using the American Dietetic Association Study Quality criteria guidelines(24), with a third reviewer resolving any disagreements. The quality assessment tool comprises ten questions related to the soundness and reporting of study design, methods and results and returns one of three scores of ‘positive’, ‘neutral’ or ‘negative’. An overall positive score requires that the majority of the questions be answered ‘yes’ and that four essential validity questions be answered ‘yes’. These questions assess bias in subject selection, comparability of subject groups, intensity and duration of exposure and the validity and reliability of the outcome measurements. For the present review, two of these questions were not able to be answered as the information is not known, so the questions were designated as ‘not applicable’ as outlined in the National Institute for Health and Clinical Excellence (NICE) guideline development manual(25). These questions (numbers 6 and 7) relate to the ‘intensity and duration of exposure’ to low vitamin B12 status required to show an effect and the ‘validity and reliability of outcome measures’, i.e. of cognitive assessment tools. A neutral score is given if the answers to the four essential validity questions do not indicate that the study is exceptionally strong and a negative is awarded if most (six or more) of the answers to the validity questions are ‘No’.
Results
A total of 3772 citations were downloaded for review with thirty-five cohort studies fulfilling the selection criteria. Fig. 1 illustrates the study selection process.

Summary of included studies
The studies were from ten countries encompassing the areas of North America (11), Europe (16), the UK (3), Asia (4) and Israel (1), and assessed a total of 14,325 subjects. Subject ages ranged from 47 to 101 years with a mean sample size of 409 subjects (median 271; range 24–1405), followed for a mean of 5·4 years (median 4·4 years; range 0·5–35 years).

Vitamin B₁₂ status was determined predominantly by serum vitamin B₁₂ concentrations alone (thirty-one studies). However, four studies used MMA²⁶,²⁷ and/or holoTC²⁶,²⁸,²⁹ and one study used MMA in combination with serum vitamin B₁₂²⁷. The majority of studies used multiple regression to assess the association of serum vitamin B₁₂ and cognition with three studies applying cut-points of 110–251 pmol/l³⁰–³². Moreover, seven studies reported only unadjusted data³⁰,³³–³⁸.

Cognitive decline was assessed in seventeen studies²⁶,²⁷,³⁵,³⁷,³⁹–⁵¹, the development of dementia or AD was determined in thirteen studies²⁸–⁵⁴,³⁴,⁵²–⁵⁶ and five studies assessed cognitive deterioration in subjects with diagnosed dementia or AD³⁶,³⁸,⁵⁷–⁵⁹. Furthermore, five studies reported two outcomes, one for dementia and one for AD²⁹–³²,⁵⁴.

Quality assessment and outcome
Quality assessment found that twenty-one studies were positive, ten were neutral and four were negative. Of the twenty-one positive studies with a low risk of bias, seven studies found positive associations between vitamin B₁₂ status and cognitive decline²⁶,²⁷,⁴²,⁴⁷, dementia²⁹,³¹ or AD²⁸,²⁹,³¹ and fourteen studies did not³²,³⁴,³⁹,⁴¹,⁴³–⁴⁶,⁵⁰,⁵²–⁵⁴,⁵⁷,⁶⁰.

In addition, nineteen²⁶,²⁷,³¹,³²,³⁴,³⁹,⁴¹–⁴⁷,⁵⁰,⁵²–⁵⁴,⁵⁷,⁶⁰ of the twenty-one studies of positive quality used serum vitamin B₁₂ with three finding significant associations with cognitive decline²⁷,⁴²,⁴⁷. All four studies using the markers holoTC and/or MMA were of positive quality and all showed significant associations with cognitive decline, dementia or AD²⁶–²⁹.

Neuropsychological assessment was performed using standardised tools. Dementia and AD diagnosis were defined by the Diagnostic and Statistical Manual of Mental Disorders (third and fourth edition), the Mattis Dementia Rating Scale.

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Fig. 1. Flow chart of literature search and study selection.
Table 1. Relationship between vitamin B₁₂ and cognitive decline in non-demented subjects
(Mean values, ranges and medians)

<table>
<thead>
<tr>
<th>Study</th>
<th>Age* and sex</th>
<th>Follow-up years, n</th>
<th>Exclusion criteria</th>
<th>Adjustments</th>
<th>Vitamin B₁₂ biomarkers and cognitive outcome</th>
<th>Outcome summary</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. (39), South Korea</td>
<td>71·9 years M</td>
<td>2·4 years 607</td>
<td>Dementia</td>
<td>Age, sex, education</td>
<td>No association of the change in MMSE-K with ascending baseline serum vitamin B₁₂ quintiles</td>
<td>No effect</td>
<td>P</td>
</tr>
<tr>
<td>Haan et al. (40), USA</td>
<td>60–101 years M</td>
<td>4·5 years 1405</td>
<td>Dementia, CIND, subjects without blood results</td>
<td>Age, education, tHcy, excluding baseline stroke</td>
<td>U-shaped association between vitamin B₁₂ and dementia/CIND (HR 1·07, 95 % CI 1·02, 1·11). Vitamin B₁₂ modified the positive association between tHcy and outcome. Rates of dementia or CIND associated with tHcy for those in the lowest and highest tertiles of vitamin B₁₂ were higher (HR 1·61, P for interaction = 0·04) and lower (HR 0·94, P = 0·02) v. those in the middle tertile, respectively.</td>
<td>Increased risk. Interaction effect of tHcy and serum vitamin B₁₂</td>
<td>O</td>
</tr>
<tr>
<td>Kado et al. (41) and Brown et al. (74), USA</td>
<td>74 years M</td>
<td>7 years 370</td>
<td>Based on physical activity, activities of daily living and cognitive functions</td>
<td>Age, sex, education, baseline cognitive and physical function, smoking, vitamin B₆, folate, tHcy</td>
<td>No association of quartiles of serum vitamin B₁₂ and composite score of five tests (confrontation naming test, delayed recognition span test, test to assess geometric figure copying, similarities subtest of WAIS-R and a test to assess abstract concept formation). Reanalysis of data in 2011: no interaction of low vitamin B₁₂ (&lt;294·1 pg/ml) with apoE4 status in predicting cognitive decline (cognitive tests as above)</td>
<td>No effect</td>
<td>P</td>
</tr>
<tr>
<td>Elias et al. (42), USA</td>
<td>60–82 years M</td>
<td>7·6 years 705</td>
<td>Stroke, dementia, tHcy &gt; 90 μmol/l</td>
<td>Age, sex, education, plasma B₆ and folate, stroke, renal and CVD risk factors, apoE4, smoking, alcohol, coffee</td>
<td>Serum vitamin B₁₂ significantly associated with improved global composite score, visual reproductions – immediate and delayed recall, visual reproductions – delayed recognition, logical memory – immediate and delayed recall (β = 0·021, 0·0356, 0·041, 0·0413, 0·033 and 0·043, respectively, all at least P = 0·05)</td>
<td>Yes, reduced risk</td>
<td>P</td>
</tr>
<tr>
<td>Teunissen et al. (43), The Netherlands</td>
<td>57 years M</td>
<td>6 years 92</td>
<td>CVD, stroke, PD, dementia, epilepsy, mental disability, psychotropic drug use</td>
<td>Age, sex, education</td>
<td>No association of baseline serum vitamin B₁₂ with Stroop test, Letter-Digit Coding Test, Word Learning Test or Delayed Recall</td>
<td>No effect</td>
<td>P</td>
</tr>
<tr>
<td>McCaddon et al. (44), UK</td>
<td>74 years† M</td>
<td>5 years 32</td>
<td>Dementia, MMSE ≤ 25, pernicious anaemia, gastric surgery, hepato–renal disease, cancer, malabsorption, vegetarian, taking medications affecting tHcy</td>
<td>Age, HT, smoking, education, folate, tHcy, creatinine</td>
<td>No independent association between serum vitamin B₁₂ and MMSE</td>
<td>No effect</td>
<td>P</td>
</tr>
</tbody>
</table>

M, male; MMSE-K, Mini Mental State Examination – Korean; P, positive; CIND, cognitive impairment no dementia; tHcy, total homocysteine; HR, hazard ratio; O, neutral; WAIS-R, Wechsler Adult Intelligence Scale-Revised; PD, Parkinson’s disease; MMSE, Mini Mental State Examination Score; HT, hypertension.

* Mean or range (years).
† Median.
and the Mental Deterioration Battery of the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke criteria. Studies assessing cognitive decline used a variety of neuropsychological tool sets or individual tests, singly or in combination, and included the Mini Mental State Examination (MMSE) score, the Wechsler Adult Intelligence Scale subsets, the Boston Naming Test, the Stroop Colour Word Test and the Wechsler Memory Scale.

Cognitive decline and vitamin B12 status in non-demented subjects

The association of cognitive decline with vitamin B12 status in non-demented subjects was assessed in six studies (Table 1). Haan et al. found that vitamin B12 was associated with an increased hazard ratio for the development of dementia or cognitive impairment (hazard ratio 1-07, 95 % CI 1-02, 1-11). Interactions between vitamin B12 and tHcy were also found, with vitamin B12 modifying the association between tHcy and the development of dementia or cognitive impairment. For those in the first tertile of serum vitamin B12 (<340 pg/ml), the rates of dementia or cognitive impairment associated with tHcy were higher, and for those in the third tertile of vitamin B12 (≥498 pg/ml), the rates of dementia or cognitive impairment were lower compared with the second tertile. Elias et al. found a small significant association of serum vitamin B12 with the Wechsler Memory Scale composite score and its subsets. However, four studies showed no associations of cognitive decline and serum vitamin B12 after a mean follow-up period of 5-1 years.

Cognitive decline and vitamin B12 status in subjects with unspecified cognition

The association of cognitive decline in subjects with normal or unspecified cognition was assessed in eleven studies using multiple tests of cognition. Of these eleven studies, four found an association of vitamin B12 status and at least one test of cognition (Table 2). Tucker et al. studied male subjects for 3 years and found a positive association of serum vitamin B12 and construction praxis (a neuropsychological assessment tool), but no other cognitive measures. Further, two studies followed subjects for 6 years, with Nurk et al. finding a trend for increasing risk of memory deficit with decreasing quintiles of baseline vitamin B12 and the Kendrick Object Learning Test, and Tangney et al. found associations between higher serum vitamin B12 and a slower decline in memory, and a faster decline in memory with higher MMA concentrations. Clarke et al. followed 472 subjects for 10 years and reported no association of cognitive decline (MMSE score) with serum vitamin B12 concentrations, but found that a doubling of holoTC or MMA was associated with a slower and faster cognitive decline, respectively. Moreover, seven studies found no associations between serum vitamin B12 and individual or composite cognition scores or the MMSE after a follow-up ranging between 2-3 and 6-0 years.

Development of dementia in subjects with mild cognitive impairment

The development of dementia or AD in subjects with cognitive impairment was assessed in three studies. Of these, one study from Sweden analysed unadjusted data and found that females who developed AD had lower baseline vitamin B12 concentrations compared with those without AD, but no effect was found in the other two studies assessing subjects with cognitive impairment (34,60) (Table 3).

Development of dementia in subjects with no dementia at baseline

A further eight studies assessed non-demented subjects and the development of dementia (Table 4). Of these, three studies found associations between serum vitamin B12 or holoTC and the development of dementia (29,31), and found five and four associations with AD and serum vitamin B12 alone or in combination with low serum folate concentrations (28,29,31) (Table 5). Wang et al. detected no association between serum vitamin B12 or folate and AD alone but found a doubling of risk of AD with serum vitamin B12 ≤150 pmol/l or serum folate ≤10 nmol/l compared with normal concentrations. A 7-fold additional risk was found for subjects with a MMSE ≥26 and serum vitamin B12 ≤250 pmol/l or folate ≤12 nmol/l v. normal (31). Kivipelto et al. found that subjects with baseline holoTC concentrations in the third, compared with the first, quartile had a reduced relative risk for the development of AD after nearly 7 years (relative risk 0.38, 95 % CI 0.15, 0.94). However, no difference between the fourth and first quartiles was found. Hooshmand et al. also found that subjects with lower holoTC had a reduced OR of 0.977 for each 1 pmol/l increase in holoTC.

Cognitive decline in subjects with existing dementia

The association of baseline vitamin B12 and cognitive deterioration was assessed in five studies of subjects with dementia (Table 6). No associations between vitamin B12 and cognition were observed (36,38,57–59).

Discussion

The present review finds that there is insufficient evidence to determine whether vitamin B12 status is associated with cognitive decline or dementia. The assessment of the thirty-five cohort studies or, more particularly, of the twenty-one studies of positive quality, does not support a role for the association of serum vitamin B12 concentrations in the aetiology of cognitive impairment or dementia. Of the twenty-one studies of positive quality, seven found significant associations between vitamin B12 status and cognitive decline (26,27,42,47) dementia (29,31) or AD (28,29,31). An interesting finding of the review is that the markers of vitamin B12 status with greater specificity, i.e. holoTC and MMA, showed consistent results with all four
Table 2. Relationship between vitamin B\textsubscript{12} and cognitive decline in subjects with unspecified cognition

(Mean values and ranges)

<table>
<thead>
<tr>
<th>Study</th>
<th>Age* and sex</th>
<th>Follow-up years, n</th>
<th>Exclusion criteria</th>
<th>Adjustments</th>
<th>Vitamin B\textsubscript{12} biomarkers and cognitive outcome</th>
<th>Outcome summary</th>
<th>Quality score</th>
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</thead>
<tbody>
<tr>
<td>van den Kommer \textit{et al.} \textsuperscript{(45)}, The Netherlands</td>
<td>75-4 years 48-5 % M</td>
<td>6 years n 895</td>
<td>Subjects with high serum vitamin B\textsubscript{12} or Cr, blood results</td>
<td>Age, sex, education, time, Cr, HDL, HT, TAG, ACT</td>
<td>Association of tHcy and cognition confounded by vitamin B\textsubscript{12} for immediate recall, information processing speed, fluid intelligence, but not for MMSE or retention. No data on the independent effect of serum vitamin B\textsubscript{12} concentrations</td>
<td>No effect</td>
<td>P</td>
</tr>
<tr>
<td>Tangney \textit{et al.} \textsuperscript{(27)}, USA</td>
<td>80 years 61 % M</td>
<td>6 years n 498</td>
<td>Not reported</td>
<td>Age, sex, education, race, frequent cognitive activities, serum Cr, smoking, alcohol, SFA (g/d), diet, vitamin E, niacin, total vitamin C, serves fish/week</td>
<td>Higher serum vitamin B\textsubscript{12} associated with a slower decline and higher MMA associated with a faster decline in cognition based on a composite score of the East Boston Test of immediate and delayed recall. MMSE and Symbol Digit Modalities Test ($\beta = 0.00013$ and $0.00016$, $P &lt; 0.005$, respectively)</td>
<td>Yes, reduced risk</td>
<td>P</td>
</tr>
<tr>
<td>Clarke \textit{et al.} \textsuperscript{(26)}, UK</td>
<td>71-9 years 38 % M</td>
<td>10 years n 472</td>
<td>Serum vitamin B\textsubscript{12} &gt; 1000 pmol/l or holoTC &gt; 400 pmol/l or vitamin B\textsubscript{12} injections or supplement use</td>
<td>Sex, education, smoking, history of vascular disease, MMSE, systolic BP, apoe, tHcy, holoTC, MMA</td>
<td>Using the MMSE score, a doubling of holoTC from 50 to 100 pmol/l was associated with a 30 % slower cognitive decline; an increase of MMA from 0.25 to 0.5 pmol/l was associated with a &gt;50 % more rapid cognitive decline. No association with serum vitamin B\textsubscript{12}</td>
<td>Yes, reduced risk</td>
<td>P</td>
</tr>
<tr>
<td>Kang \textit{et al.} \textsuperscript{(46)}, USA</td>
<td>&gt;70 years 100 % F</td>
<td>4 years n 389†</td>
<td>History of stroke, CHD, breast or colon cancer, subjects without blood results</td>
<td>Assay batch, time between blood and cognitive test, age, education, DM, BP, TC, HRT use, menopause age, BMI, smoking, mental health, antidepressant use, aspirin use, alcohol, PA, vitamin E supplement use</td>
<td>No association between serum B\textsubscript{12} and mean difference in the rate of cognitive decline assessed by the global score, telephone interview for cognitive status or verbal score</td>
<td>No effect</td>
<td>P</td>
</tr>
<tr>
<td>Tucker \textit{et al.} \textsuperscript{(47)}, USA</td>
<td>67 years 100 % M</td>
<td>3 years n 280–284‡</td>
<td>Subjects with less than two cycles of cognitive testing</td>
<td>Time from cognitive measure, baseline score, age, education, BMI, smoking, alcohol, Cr, systolic BP, DM, FA fortification introduction, tHcy, serum folate concentrations</td>
<td>Positive association of serum vitamin B\textsubscript{12} and construction praxis (spatial copying, sum of drawings, $\beta^2 = 0.59$, $P &lt; 0.05$) but no association of serum vitamin B\textsubscript{12} with language (verbal fluency), working memory (backward digit span, longest span recalled), recall memory (word lists) or MMSE</td>
<td>Yes, reduced risk</td>
<td>P</td>
</tr>
<tr>
<td>Mooijaart \textit{et al.} \textsuperscript{(48)}, The Netherlands</td>
<td>&gt;85 years 34 % M</td>
<td>4 years n 341</td>
<td>&lt;85 years</td>
<td>Sex, education, depression, B\textsubscript{12} and FA supplements, living arrangements, tHcy, folate concentrations</td>
<td>No association between serum vitamin B\textsubscript{12} and decrease in MMSE, global score, Stroop test, Letter-Digit Coding Test or 2-Word-Learning Test</td>
<td>No effect</td>
<td>O</td>
</tr>
<tr>
<td>Nurk \textit{et al.} \textsuperscript{(49)}, Norway</td>
<td>65–67 years 45 % M</td>
<td>6 years n 235</td>
<td>Baseline tHcy &gt; 40 (\mu)mol/l</td>
<td>Sex, apoE genotype, education, CVD, HT, depression score</td>
<td>Trend for increasing risk of memory deficit (using the Kendrick Object Learning Test) with lower vitamin B\textsubscript{12} quintiles ($P$ for trend=0.042, Q1 v. Q5: OR 1.63, 95 % CI 1.0–2.7)</td>
<td>Yes, reduced risk</td>
<td>O</td>
</tr>
<tr>
<td>Garcia \textit{et al.} \textsuperscript{(50)}, Canada</td>
<td>72-9 years 28 % M</td>
<td>2-3 years n 104</td>
<td>Vitamin B\textsubscript{12} supplement use, gastric/ileal surgery, Cr &gt; 130 (\mu)mol/l, neurological disease, MMSE &lt; 24, depression, institutional living</td>
<td>Age, sex, education, time between visits, erythrocyte folate, DM, HT</td>
<td>In subjects with more than 40 % increase in tHcy from baseline, tHcy associated with declining Stroop scores ($P = 0.001$) but no association with serum vitamin B\textsubscript{12}. Rate of change of the Stroop score not related to serum vitamin B\textsubscript{12}</td>
<td>No effect</td>
<td>P</td>
</tr>
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</table>
### Table 2. Continued

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<tr>
<th>Study</th>
<th>Age and sex</th>
<th>Follow-up, years</th>
<th>Exclusion criteria</th>
<th>Adjustments</th>
<th>Vitamin B12 biomarkers and cognitive outcome</th>
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</thead>
<tbody>
<tr>
<td>Dufouil et al. (35)</td>
<td>75–80 years</td>
<td>5 years</td>
<td>Subjects living in psychiatric institutions, unable to answer questions, wheelchair</td>
<td>No adjustments</td>
<td>No association of baseline serum vitamin B12 concentrations with cognitive outcome and MMSE.</td>
</tr>
<tr>
<td>Et al. (36)</td>
<td>67 years</td>
<td>4 years</td>
<td>Not reported</td>
<td>No adjustments</td>
<td>No association of serum vitamin B12 with Trail-Making Test scores or Digit-Making Test scores.</td>
</tr>
<tr>
<td>Eussen et al. (37)</td>
<td>41.4±4.9 M</td>
<td>n=262</td>
<td></td>
<td>No adjustments</td>
<td>No association between serum vitamin B12 and Shipley-Hartford Intelligence Test scores.</td>
</tr>
<tr>
<td>Gagné et al. (38)</td>
<td>280–284</td>
<td>6 years</td>
<td></td>
<td>No adjustments</td>
<td>No association of baseline serum vitamin B12 with Shipley-Hartford Intelligence Test scores.</td>
</tr>
<tr>
<td>La Rue et al. (39)</td>
<td>77 years</td>
<td>6 years</td>
<td>No data</td>
<td>No adjustments</td>
<td>No association of baseline serum vitamin B12 with Shipley-Hartford Intelligence Test scores.</td>
</tr>
<tr>
<td>Ma et al. (26)</td>
<td>239–243</td>
<td>6 years</td>
<td></td>
<td>No adjustments</td>
<td>No association of baseline serum vitamin B12 with Shipley-Hartford Intelligence Test scores.</td>
</tr>
<tr>
<td>Mialhe et al. (40)</td>
<td>45% M</td>
<td>n=137</td>
<td></td>
<td>No adjustments</td>
<td>No association of baseline serum vitamin B12 with Shipley-Hartford Intelligence Test scores.</td>
</tr>
<tr>
<td>Tangney et al. (27)</td>
<td>235–239</td>
<td>6 years</td>
<td></td>
<td>No adjustments</td>
<td>No association of baseline serum vitamin B12 with Shipley-Hartford Intelligence Test scores.</td>
</tr>
<tr>
<td>Vargas et al. (41)</td>
<td>391</td>
<td>6 years</td>
<td></td>
<td>No adjustments</td>
<td>No association of baseline serum vitamin B12 with Shipley-Hartford Intelligence Test scores.</td>
</tr>
<tr>
<td>Whiting et al. (42)</td>
<td>389</td>
<td>6 years</td>
<td></td>
<td>No adjustments</td>
<td>No association of baseline serum vitamin B12 with Shipley-Hartford Intelligence Test scores.</td>
</tr>
<tr>
<td>Zandi et al. (43)</td>
<td>391</td>
<td>6 years</td>
<td></td>
<td>No adjustments</td>
<td>No association of baseline serum vitamin B12 with Shipley-Hartford Intelligence Test scores.</td>
</tr>
</tbody>
</table>

**Outcome summary**

<table>
<thead>
<tr>
<th>Quality score</th>
<th>Outcome summary</th>
<th>Quality score</th>
<th>Outcome summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>No effect</td>
<td>N</td>
<td>No effect</td>
</tr>
<tr>
<td>N</td>
<td>No effect</td>
<td>N</td>
<td>No effect</td>
</tr>
<tr>
<td>N</td>
<td>No effect</td>
<td>N</td>
<td>No effect</td>
</tr>
<tr>
<td>N</td>
<td>No effect</td>
<td>N</td>
<td>No effect</td>
</tr>
</tbody>
</table>

**Quality score notes**

- **O**: Outcome reached
- **N**: Outcome not reached
- **M**: Methodology reached

---

**Studies finding associations with cognitive decline**

Studies finding associations with cognitive decline include Tangney et al. (27), Kivipelto et al. (29), and AD (28,29). However, the study by Kivipelto et al. (29) found associations of holo TC and dementia development only for the third quartile.

The subject’s age at recruitment and the length of time of exposure to a low vitamin B12 status for a change (if any) in cognition to be noted are not known; however, cognitive impairment and dementia generally develop over many years and studies of inadequate duration may not show any effect. The median duration of studies was 4 years, with only seven of the thirty-five studies assessing cognition for more than 6 years. The majority of studies recruited subjects aged greater than 75 years at baseline, with only two studies recruiting subjects from a midlife stage, with a follow-up of 35 and 6 years, respectively; however, neither showed any association with serum vitamin B12 and cognition (45,52).

Of the nine studies recruiting subjects from the seventh decade or earlier, five (33,40,42,47,49) found associations between cognitive decline and vitamin B12 status, while only five (40–29,31) of the twenty-five studies commencing in later life found associations. The effect of vitamin B12 status is likely to commence in midlife with a long period for disease development, hence the baseline age of subjects needs consideration (1).

In order to ascertain whether any effect exists, the correct diagnosis of vitamin B12 status must be made; however, there is no ‘gold standard’ for the determination of vitamin B12 status and each diagnostic assay has limitations. High vitamin B12 concentrations generally indicate sufficiency, but the interpretation of the lower concentrations of vitamin B12 concentrations is unclear (61,62). Vitamin B12 is carried by two proteins, with the active form of holotranscobalamin making up only 20–30% of the total serum vitamin B12 measured. Studies have shown that the determination of the active form of vitamin B12, holotranscobalamin and/or MMA, an indicator of tissue stores, improves the prediction of low vitamin B12 status (62), and a recent review has found the use of serum vitamin B12 concentrations alone unreliable in diagnosing a vitamin B12 deficiency (63). Of the thirty-two studies that assessed serum vitamin B12, ten showed associations with cognition, while four of four studies assessing the newer and more specific markers of vitamin B12 status showed an effect. Of the two studies that assessed holoTC or MMA in addition to serum vitamin B12, only the study by Tangney et al. (27) showed an association with serum vitamin B12, and this was in a folate-fortified population using neuropsychological assessment tools and after a follow-up of 6 years. Furthermore, one cohort study published after the literature evaluation for the present review was completed has been located. This study assessed non-demented subjects from the Cardiovascular Risk Factors, Aging and Dementia study (64) and supports the association of low holoTC concentrations with a decline in cognition.

The present review of papers indicates that the direction of any likely effect is consistent, with low vitamin B12 status being associated with increased rates of dementia or cognitive impairment. There was one study showing that both low and high serum vitamin B12 concentrations were associated with an increased risk of dementia or cognitive impairment. However, this result was confounded by an interaction effect.
### Table 3. Relationship between vitamin B₁₂ and dementia or Alzheimer’s disease (AD) in subjects with mild cognitive impairment

(Mean values and ranges)

<table>
<thead>
<tr>
<th>Study</th>
<th>Age and sex</th>
<th>Follow-up years, n</th>
<th>Exclusion criteria</th>
<th>Quality score</th>
<th>Outcome summary</th>
<th>Vitamin B₁₂ biomarkers and cognitive outcome</th>
<th>Adjustments</th>
<th>Outcome in case of reduction of vitamin B₁₂</th>
<th>Follow-up</th>
<th>Quality score</th>
<th>Outcome in case of reduction of vitamin B₁₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annerbo et al. (34), Sweden</td>
<td>65·1 years, 65·1 years</td>
<td>6 years, n = 93</td>
<td>Non-MCI subjects</td>
<td>48 % M</td>
<td>No effect</td>
<td>No difference in serum vitamin B₁₂ concentrations between subjects who converted to AD and those who did not</td>
<td>No adjustments</td>
<td>Higher tHcy not related to conversion to dementia (HR 0·6, 95% CI 0·26, 1·39, P = 0·234).</td>
<td>6 years</td>
<td>46</td>
<td>Yes, reduced risk in females</td>
</tr>
<tr>
<td>Ravaglia et al. (50), Italy</td>
<td>76·0 years, 68·1 years</td>
<td>6 years</td>
<td>Non-MCI subjects, MMSE &lt; 24, poor ADL function, cancer, neurological, metabolic, haematological, psychiatric disorders, depression, normal routine blood tests</td>
<td>49 % M</td>
<td>No effect</td>
<td>No difference in serum vitamin B₁₂ concentrations between subjects who converted to AD and those who did not</td>
<td>No adjustments</td>
<td>No difference in serum vitamin B₁₂ concentrations between subjects who converted to AD and those who did not</td>
<td>6 years</td>
<td>46</td>
<td>No differences in any analysis assessing the role of vitamin B₁₂ status.</td>
</tr>
<tr>
<td>Anero et al. (33), Sweden</td>
<td>64·5 years, 64·5 years</td>
<td>6 years</td>
<td>Subjects taking B₁₂ supplements, diagnosis of concussion (mild trauma cerebri)</td>
<td>42 % M</td>
<td>No effect</td>
<td>No difference in serum vitamin B₁₂ concentrations between subjects who converted to AD and those who did not</td>
<td>No adjustments</td>
<td>No difference in serum vitamin B₁₂ concentrations between subjects who converted to AD and those who did not</td>
<td>6 years</td>
<td>46</td>
<td>No differences in any analysis assessing the role of vitamin B₁₂ status.</td>
</tr>
<tr>
<td>Anero et al. (32), Italy</td>
<td>64·5 years, 64·5 years</td>
<td>6 years</td>
<td>Subjects taking B₁₂ supplements, diagnosis of concussion (mild trauma cerebri)</td>
<td>42 % M</td>
<td>No effect</td>
<td>No difference in serum vitamin B₁₂ concentrations between subjects who converted to AD and those who did not</td>
<td>No adjustments</td>
<td>No difference in serum vitamin B₁₂ concentrations between subjects who converted to AD and those who did not</td>
<td>6 years</td>
<td>46</td>
<td>No differences in any analysis assessing the role of vitamin B₁₂ status.</td>
</tr>
</tbody>
</table>

Vitamin B₁₂ status and cognitive decline (27,40,42,47) compared with approximately one-third of studies overall (20, 29, 31, 33, 40, 42, 47). This is consistent with the postulated detrimental effect of high levels of cognitive decline, chronic disease profiles and folate fortification strategies. Some studies excluded subjects with dementia or cognitive impairment while others included all subjects without assessment of cognition. Baseline vitamin B₁₂ concentrations were not always described as a number of studies were primarily assessing the effect of tHcy on cognition. All measures of vitamin B₁₂ status are confounded by diseases such as renal and liver disease, and the adjustment for confounders based on the chronic disease profile, e.g. stroke and renal diseases, is required to ensure that the true effect of vitamin B₁₂ status can be seen.

Numerous genes have been implicated in the development of cognitive decline and dementia (70), with the most common genetic polymorphism being the apoE4 genotype which doubles the risk of AD development (71). Low vitamin B₁₂ concentrations have been found to increase the risk of cognitive decline in apoE4 carriers in some (72,73) but not all studies (51,74). Of the studies reviewed, eight (26,28,29,42,49,54,55,59) controlled for apoE4 in statistical analysis, with five (26,28,29,42,49) showing associations of vitamin B₁₂ status and cognitive decline after adjustment for confounders. Due to the potential impact of genotype on the risk of disease, known genetic traits must be controlled for in any analysis assessing the role of vitamin B₁₂ status.

Higher folate status has been associated with improved cognition (1), but in subjects with low vitamin B₁₂ status, high serum folate concentrations have been associated with increased concentrations of MMA and tHcy (70) and increased cognitive decline (76). In the present review, half (four out of seven) of the studies performed in folate-fortified subjects found negative associations between vitamin B₁₂ status and cognitive decline (27,40,42,47) compared with approximately one-third of studies overall (20, 29, 31, 33, 40, 42, 47). This is consistent with the postulated detrimental effect of high between vitamin B₁₂ and tHcy that was not included in the reported statistical model (40).
Table 4. Relationship between vitamin B\textsubscript{12} and development of dementia in subjects without dementia at baseline
(Mean values, medians and ranges)

<table>
<thead>
<tr>
<th>Study</th>
<th>Age* and sex</th>
<th>Follow up years, n</th>
<th>Exclusion criteria</th>
<th>Adjustments</th>
<th>Vitamin B\textsubscript{12} biomarkers and dementia outcome</th>
<th>Outcome summary</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zylberstein et al.\textsuperscript{(52)}</td>
<td>47 years 100% F</td>
<td>35 years n 1368</td>
<td>Not reported</td>
<td>Age, creatinine, education, BMI, TC, TAG, BP, smoking</td>
<td>Vitamin B\textsubscript{12} not associated with dementia diagnosed using the DSM III-R (either alone or in the full model)</td>
<td>No effect</td>
<td>P</td>
</tr>
<tr>
<td>Knuttila et al.\textsuperscript{(53)}</td>
<td>Sweden</td>
<td>81-0 years 25% M</td>
<td>6-7 years n 83</td>
<td>Dementia, aged &lt;75 years, without tHcy, holoTC, folate or vitamin B\textsubscript{12} supplement use</td>
<td>Subjects with holoTC in the third v. first quartile had a reduced risk of dementia using the DSM III criteria (RR 0.47, 95% CI 0.23, 0.96). No risk reduction for the fourth quartile and no association of holoTC and dementia as a continuous variable</td>
<td>Yes, reduced risk with Q3 holoTC</td>
<td>P</td>
</tr>
<tr>
<td>Kim et al.\textsuperscript{(54)}</td>
<td>South Korea</td>
<td>71-8 years 43% M</td>
<td>2-4 years n 518</td>
<td>Dementia</td>
<td>No association between baseline serum vitamin B\textsubscript{12} and MMSE-K. Subjects who developed dementia had smaller increases in serum vitamin B\textsubscript{12} over the 2-4-year follow-up (0.3 v. 56 pmol/l, P=0.01)</td>
<td>No effect</td>
<td>P</td>
</tr>
<tr>
<td>Haan et al.\textsuperscript{(45)}</td>
<td>USA</td>
<td>60–101 years 42% M</td>
<td>4-5 years n 1405</td>
<td>Dementia, CIND, no blood tests</td>
<td>U-shaped association between vitamin B\textsubscript{12} and dementia/CIND (HR 1.07, 95% CI 1.02, 1.11). Vitamin B\textsubscript{12} modified the positive association between tHcy and outcome. Rates of dementia or CIND associated with tHcy for those in the lowest and highest tertiles of vitamin B\textsubscript{12} were higher (HR 1.61, P=0.04) and lower (HR 0.94, P=0.02) v. those in the middle tertile, respectively</td>
<td>Increased risk. Interaction effect of tHcy and serum vitamin B\textsubscript{12}</td>
<td>O</td>
</tr>
<tr>
<td>Ravalgia et al.\textsuperscript{(46)}</td>
<td>Italy</td>
<td>73-6 years 47% M</td>
<td>3-8 years n 816</td>
<td>Dementia, no blood tests</td>
<td>No difference in dementia rates for subjects with serum vitamin B\textsubscript{12} ≤ 251 v. &gt;251 pmol/l using the NINCDS–ADRDA criteria</td>
<td>No effect</td>
<td>P</td>
</tr>
<tr>
<td>Seshadri et al.\textsuperscript{(46)}</td>
<td>USA</td>
<td>76 years 38.9% M</td>
<td>8 years\†, range 1–13 years n 932</td>
<td>Dementia</td>
<td>Serum vitamin B\textsubscript{12} not independently related to the risk of dementia</td>
<td>No effect</td>
<td>P</td>
</tr>
<tr>
<td>Wang et al.\textsuperscript{(47)}</td>
<td>Sweden</td>
<td>75–101 years 19% M</td>
<td>3 years n 370</td>
<td>Dementia, subjects who refused blood tests, vitamin B\textsubscript{12} or FA supplements</td>
<td>No difference in the risk of dementia (using the DSM III criteria) for vitamin B\textsubscript{12} ≤ 150 v. &gt;150 pmol/l. Subjects with vitamin B\textsubscript{12} ≤ 150 pmol/l or folate ≤ 10 pmol/l v. normal had an increased risk of dementia (RR 1.8, 95% CI 1.1, 2.8)</td>
<td>Yes, reduced risk</td>
<td>P</td>
</tr>
<tr>
<td>Crystal et al.\textsuperscript{(48)}</td>
<td>USA</td>
<td>75–85 years No data</td>
<td>5 years n 410</td>
<td>Not reported</td>
<td>No difference in dementia incidence using the DSM III criteria in subjects with vitamin B\textsubscript{12} &lt; 110 pmol/l v. &gt;110 pmol/l</td>
<td>No effect</td>
<td>N</td>
</tr>
</tbody>
</table>

\(\text{M, male; MMSE, Mini Mental State Examination; TC, total cholesterol; BP, blood pressure; DSM III-R, Diagnostic and Statistical Manual of Mental Disorders (third edition revised); P, positive; tHcy, total homocysteine; holoTC, holo-transcobalamin; Alb, albumin; Cr, creatinine; RR, relative risk; Q, quartile; PA, physical activity; MMSE-K, Mini Mental State Examination – Korea; CIND, cognitive impairment no dementia; HR, hazard ratio; O, neutral; NINCDS–ADRDA, National Institute of Neurological and Communicative Disease and Stroke–Alzheimer's Disease and Related Disorders Association; FA, folic acid; N, negative.}\)

* Mean or range (years).
\† Median.
### Table 5. Relationship between vitamin B₁₂ and the development of Alzheimer’s disease (AD) in subjects with no dementia

(Mean values, medians and ranges)

<table>
<thead>
<tr>
<th>Study</th>
<th>Age* and sex</th>
<th>Follow-up years, n</th>
<th>Exclusion criteria</th>
<th>Adjustments</th>
<th>Vitamin B₁₂ biomarkers and AD outcome</th>
<th>Outcome summary</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hooshmand et al. (28), Sweden</td>
<td>70-7 years 38 % M</td>
<td>7-4 years n 271</td>
<td>Dementia</td>
<td>Age, sex, BMI, education, apoE4 allele, BP, tHcy, folate, MMSE, smoking, stroke, renal disease, follow-up time</td>
<td>Subjects with lower holoTC had an increased risk of AD using the NINCDS–ADRDA criteria. OR for the risk of AD for a 1 pmol/l increase in holoTC was 0.977 (95 % CI 0.958, 0.997). Adjusting for holoTC attenuated the tHcy–AD link, with an OR decrease from 1.16 to 1.10 (95 % CI 0.96, 1.25)</td>
<td>Yes, reduced risk</td>
<td>P</td>
</tr>
<tr>
<td>Crystal et al. (30), USA</td>
<td>75–85 years no data</td>
<td>5 years n 410</td>
<td>Not reported</td>
<td>No adjustments</td>
<td>No difference in AD incidence using the DSM III criteria in subjects with serum vitamin B₁₂ ≤110 pmol/l</td>
<td>No effect</td>
<td>N</td>
</tr>
<tr>
<td>Wang et al. (31), Sweden</td>
<td>75–101 years 19 % M</td>
<td>3 years n 370</td>
<td>Not reported</td>
<td>Age, sex, education</td>
<td>No difference in AD risk using the DSM III-R criteria for vitamin B₁₂ cut-point of 150 pmol/l. Doubling of the risk of AD for vitamin B₁₂ ≥150 pmol/l or serum folate = 10 nmol/l (RR 2.1, 95 % CI 1.2, 3.1); seven times increased risk of AD for MMSE &gt; 26 and vitamin B₁₂ ≥250 pmol/l or serum folate = 12 nmol/l v. normal (RR 7.0, 95 % CI 1.2, 31.6); no increased risk for MMSE ≤26; three times increased risk of AD for MMSE &gt; 26 and vitamin B₁₂ ≤150 pmol/l or folate = 10 nmol/l v. normal (RR 3.1, 95 % CI 1.1, 8.4) but no association for those with MMSE &lt; 26</td>
<td>Yes, no effect of vitamin B₁₂ alone, but increased risk with low vitamin B₁₂ or folate</td>
<td>P</td>
</tr>
<tr>
<td>Luchsinger et al. (55), USA</td>
<td>76-2 years 28-3 % M</td>
<td>4-7 years n 679</td>
<td>Aged &lt; 65 years, dementia</td>
<td>Ethnicity; apoE genotype, smoking, DM, HT, CHD, Cr</td>
<td>No association between serum vitamin B₁₂ and the risk of AD using the NINCDS–ADRDA criteria</td>
<td>No effect</td>
<td>O</td>
</tr>
<tr>
<td>Ravaliga et al. (32), Italy</td>
<td>73-6 (so 6-3) years</td>
<td>3-8 years n 816</td>
<td>Dementia</td>
<td>Age, sex, education, apoE genotype, vascular risk factors, tHcy, serum folate</td>
<td>No difference in AD incidence using the NINCDS–ADRDA criteria for serum vitamin B₁₂ ≤251 v. &gt; 251 pmol/l</td>
<td>No effect</td>
<td>P</td>
</tr>
<tr>
<td>Kivipelto et al. (33), Sweden</td>
<td>81-0 years 25 % M</td>
<td>6-7 years n 61</td>
<td>Dementia, aged &lt; 75 years, no blood results, vitamin B₁₂ or folate supplement use</td>
<td>Age, sex, education, baseline BMI, Alb, Hb, Cr, MMSE, holoTC, tHcy, serum folate</td>
<td>Subjects with holoTC in the third v. first quartile had a reduced risk of AD using the DSM III criteria (RR 0.38, 95 % CI 0.15, 0.94). No risk reduction for the fourth quartile and no association of holoTC and AD as a continuous variable</td>
<td>Yes, reduced risk with Q3 holoTC</td>
<td>P</td>
</tr>
<tr>
<td>Seshadri et al. (54), USA</td>
<td>76 years 38-9 % M</td>
<td>8 years †, n 932</td>
<td>Dementia</td>
<td>Age, sex, apoE genotype</td>
<td>Serum vitamin B₁₂ not independently related to the risk of AD using the DSM IV and NINCDS–ADRDA criteria</td>
<td>No effect</td>
<td>P</td>
</tr>
<tr>
<td>Bowirrat et al. (56), Israeli Arabs</td>
<td>No data</td>
<td>20 months, n 158</td>
<td>Not reported</td>
<td>Birth year, sex</td>
<td>In the lowest vitamin B₁₂ tertile did not have a greater risk of developing AD</td>
<td>No effect</td>
<td>N</td>
</tr>
</tbody>
</table>

M, male; MMSE, Mini Mental State Examination; BP, blood pressure; tHcy, total homocysteine; holoTC, holotranscobalamin; NINCDS–ADRDA, National Institute of Neurological and Communicative Disease and Stroke–Alzheimer’s Disease and Related Disorders Association; P, positive; DSM III and DSM IV, Diagnostic and Statistical Manual of Mental Disorders (third and fourth edition); N, negative; DSM III-R, Diagnostic and Statistical Manual of Mental Disorders (third edition Revised); RR, relative risk; DM, diabetes; HT, hypertension; Cr, creatinine; O, neutral; Alb, albumin.

* Mean or range (years).
† Median.
Table 6. Relationship of vitamin B₁₂ and cognitive decline in subjects with dementia or Alzheimer’s disease (AD) (Mean values and ranges)

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)*, sex</th>
<th>Follow-up years, n</th>
<th>Exclusion criteria</th>
<th>Adjustments</th>
<th>Vitamin B₁₂ biomarkers and AD outcome</th>
<th>Outcome summary</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oulhaj et al. (57), UK</td>
<td>71·9 years 44 % M</td>
<td>4 years n 97</td>
<td>Subjects with no CAMCOG scores or baseline score ( \leq 35 )</td>
<td>Age at baseline, stroke, education, treatment with centrally acting drugs, tHcy and interaction terms</td>
<td>No effect of serum vitamin B₁₂ on the decline in CAMCOG score from baseline</td>
<td>No effect</td>
<td>P</td>
</tr>
<tr>
<td>Small et al. (58), Sweden</td>
<td>83·5 years 23 % M</td>
<td>2·5 years n 24</td>
<td>Not reported</td>
<td>Age, sex, education, AD or vascular dementia</td>
<td>No effect of serum vitamin B₁₂ on the decline in memory, visuospatial or verbal decline scores</td>
<td>No effect</td>
<td>O</td>
</tr>
<tr>
<td>Small et al. (59), Sweden</td>
<td>85·9 years 22 % M</td>
<td>2·6 years n 27</td>
<td>Not reported</td>
<td>Baseline MMSE, dementia diagnosis, years between testing, age, sex, education</td>
<td>Serum vitamin B₁₂ did not predict the MMSE decline</td>
<td>No effect</td>
<td>O</td>
</tr>
<tr>
<td>Tu et al. (38), Taiwan</td>
<td>73·8 years 33 % M</td>
<td>0-5 years n 92</td>
<td>Cr &gt; 15 mg/l, stroke, modified Hachinski ischaemia score &gt; 4, abnormal LFT, FA or vitamin B₁₂ supplements</td>
<td>No adjustments</td>
<td>No correlation between Cognitive Ability Screening score or between the Cognitive Ability Screening ratio (time 1:time 2) and serum vitamin B₁₂</td>
<td>No effect</td>
<td>O</td>
</tr>
<tr>
<td>Huang et al. (36), Taiwan</td>
<td>72·8 years 41 % M</td>
<td>2 years n 133</td>
<td>Cr &gt; 15 mg/l, stroke, modified Hachinski ischaemia score &gt; 4, abnormal LFT, FA or vitamin B₁₂ supplements</td>
<td>No adjustments</td>
<td>No difference in serum vitamin B₁₂ concentrations between AD subjects who had a decline in MMSE by &lt; 3 v. ( \geq 3 )</td>
<td>No effect</td>
<td>O</td>
</tr>
</tbody>
</table>

M, male; CAMCOG, Cambridge Cognitive Assessment; P, positive; O, neutral; MMSE, Mini Mental State Examination; Cr, creatinine; LFT, liver function tests; FA, folic acid.

* Mean or range (years).
folate concentrations on the progression of cognitive impairment[77].

The studies may have been underpowered to show an effect of vitamin B12 with only ten studies having sample sizes of more than 500. Power calculations were generally not performed or reported; however, many studies cited inadequate power as a possible explanation for the lack of effect seen. The population standard deviation for serum vitamin B12 biomarkers can be large and any effect is only likely to be seen in subjects with a low vitamin B12 status which is found in 10–20% of older people[78], indicating that the number of study subjects may need to be larger.

The present systematic review has limitations, as it assessed only cohort studies and did not attempt to locate unpublished results or include publications not in English. A meta-analysis only cohort studies and did not attempt to locate unpublished studies. The choice of cognitive outcome measure. The biomarkers of vitamin B12 status and outcome measures used. The strengths of the study include the inclusion of multiple database and hand searches. The present review included all located studies, including those primarily interested in tHcy, with any reported associations between vitamin B12 and cognition, and included studies with only in-text associations of no effect between vitamin B12 and cognition. This increased the number of included studies and thus reduced reporting bias. The use of a quality tool strengthened the study, but the lack of knowledge of the time frame of cognitive decline or dementia development and the inability to determine vitamin B12 adequacy limited its application.

Future studies should aim to use MMA and/or holoTC as well as serum vitamin B12 and describe the analysis fully, including both significant and non-significant outcome results for any tested cut-points and continuous measures of vitamin B12 status. Studies should be of adequate duration (more than 6 years) and choose sensitive cognitive assessment rather than screening tools. Further research into the sensitivity and specificity of these tests is needed. Where possible, studies should aim to include the assessment and adjustment for confounders of age, sex, smoking, physical activity, socio-economic status, vitamin and genetic factors, and others known to be associated with the increased risk of cognitive decline, e.g. CVD, diabetes and chronic kidney disease.

In summary, current studies examined in the present review do not show a clear link between serum vitamin B12 concentrations and cognitive decline, but these studies were limited by recruitment age, inadequate subject numbers, lack of adjustment for confounders, study duration and, in some studies, the choice of cognitive outcome measure. The biomarkers of vitamin B12 status showed consistent significant associations between lower vitamin B12 status and increased rates of cognitive decline or dementia diagnosis, and these biomarkers deserve more study.

Acknowledgements

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References


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Appendix: Medline search protocol

1. vitamin b12.mp. or exp Vitamin B 12/
2. vitamin b12 deficiency.mp. or exp Vitamin B 12 Deficiency/
3. transcobalamin.mp. or exp Transcobalamins/
4. exp homocystine/ or exp s-adenosylhomocysteine/
5. homocysteine.mp.
6. homocysteine.mp.
7. homocysteine.mp.
8. exp Hyperhomocysteineemia/
9. hyperhomocysteineemia.mp.
10. hyperhomocysteinaemia.mp.
11. methylmalonic acid.mp.
12. methylmalonate.mp.
13. holotranscobalamin.mp.
14. cognition/ or exp awareness/ or exp comprehension/
15. cognition.mp.
16. cognit*.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier]
17. dementia.mp. or exp Dementia/
18. exp Dementia, Vascular/ or exp Dementia, Multi-Infarct/ or Dementia/ or exp Frontotemporal Dementia/
19. memory/ or memory, short-term/ or mental recall/or “recognition (psychology)”/ or “retention (psychology)”/
20. memory.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier]
21. alzheimer’s disease.mp. or exp Alzheimers Disease/
22. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
23. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
24. dietary supplements.mp. or Dietary Supplements/
25. 22 or 24
26. 23 and 25
27. limit 22 to “middle aged (45 plus years)”