Vitamin B12 and Cognitive Function: An Evidence-Based Analysis

Health Quality Ontario

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Abstract

Background

More than 2.9 million serum vitamin B12 tests were performed in 2010 in Ontario at a cost of $40 million. Vitamin B12 deficiency has been associated with a few neurocognitive disorders.

Objective

To determine the clinical utility of B12 testing in patients with suspected dementia or cognitive decline.

Methods

Three questions were addressed:

- Is there an association between vitamin B12 deficiency and the onset of dementia or cognitive decline?
- Does treatment with vitamin B12 supplementation improve cognitive function in patients with dementia or cognitive decline and vitamin B12 deficiency?
- What is the effectiveness of oral versus parenteral vitamin B12 supplementation in those with confirmed vitamin B12 deficiency?

A literature search was performed using MEDLINE, Embase, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the Centre for Reviews and Dissemination database, from January 2002 until August 2012.

Results

Eighteen studies (7 systematic reviews and 11 observational studies) were identified to address the question of the association between B12 and the onset of dementia. Four systematic reviews were identified to address the question of the treatment of B12 on cognitive function. Finally, 3 randomized controlled trials were identified that compared oral B12 to intramuscular B12.

Conclusions

- Based on very low quality evidence, there does appear to be an association between elevated plasma homocysteine levels (a by-product of B vitamins) and the onset of dementia.
- Based on moderate quality evidence, but with less than optimal duration of follow-up, treatment with B12 supplementation does not appreciably change cognitive function.
- Based on low to moderate quality of evidence, treatment with vitamin B12 and folate in patients with mild cognitive impairment seems to slow the rate of brain atrophy.
- Based on moderate quality evidence, oral vitamin B12 is as effective as parenteral vitamin B12 in patients with confirmed B12 deficiency.

Plain Language Summary

Low levels of vitamin B12 have been associated with neurocognitive disorders. This evidence-based analysis assessed the usefulness of serum vitamin B12 testing as it relates to brain function. This review found very low quality evidence that suggests a connection between high plasma homocysteine levels (a by-product of B vitamin metabolism in the body) and the onset of dementia. Moderate quality of evidence indicates treatment with vitamin B12 does not improve brain function. Moderate quality of evidence also indicates treatment using oral vitamin B12 supplements is as effective as injections of vitamin B12.

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List of Abbreviations

AD	Alzheimer disease
CADTH	Canadian Agency for Drugs and Technologies in Health
CCCDTD	Canadian Consensus Conference on the Diagnosis and Treatment of Dementia
CI	Confidence interval
CINAHL	EBSCO Cumulative Index to Nursing & Allied Health Literature
CRD	Centre for Reviews and Dissemination
EBA	Evidence-based analysis
Hcy	Homocysteine
HQO	Health Quality Ontario
MCV	Mean corpuscular volume
MMA	Methylmalonic acid
NHANES	National Health and Nutritional Examination Survey
RCT	Randomized controlled trial
SIGN	Scottish Intercollegiate Guidelines Network

Background

Objective of Analysis

This evidence-based analysis (EBA) aims to establish the clinical utility of testing serum vitamin B12 in patients with suspected dementia or cognitive decline. This EBA attempts to answer the following 3 questions:

- Is there an association between vitamin B12 deficiency and the onset of dementia or cognitive decline?
- Does treatment with vitamin B12 supplementation improve cognitive function in patients with dementia or cognitive decline and vitamin B12 deficiency?
- What is the effectiveness of oral versus parenteral vitamin B12 supplementation in those with confirmed vitamin B12 deficiency?

Clinical Need and Target Population

Vitamin B12 is a water-soluble, essential vitamin. A deficiency in vitamin B12 can lead to a specific set of neurologic disorders (subacute combined degeneration of the spinal cord, cognitive impairment) and one hematologic disorder (megaloblastic anemia) disorders.

There are 4 main reasons a person becomes vitamin B12 deficient: (1)

- Inadequate dietary intake of vitamin B12, as in strict vegetarianism (over the long term)
- Malabsorption of vitamin B12
    - Autoimmune pernicious anemia
    - Age-related atrophic gastritis
    - Gastrectomy or gastric bypass
- Ileal disease (e.g., Crohn disease) or ileal resection
- Drug use (e.g., metformin and, possibly, proton pump inhibitors)

On the basis of results from a 5-year observational study of Australians in general practice, the rate of macrocytosis (mean corpuscular volume [MCV] > 100 fL) is about 2% to 3%. (2;3) Important causes of macrocytosis include alcohol overuse, B vitamin deficiency, medications, and bone marrow disorders. (2;4) Based on a summary of studies, Kaferle and Strzoda (4) estimated that vitamin B12 deficiency was the cause of macrocytosis in 6% to 28% of the cases. However, not all cases of vitamin B12 deficiency are associated with macrocytosis or anemia. The 1988 studies by Carmel (5) and by Lindenbaum et al (6) noted that about 15% of patients can have low vitamin B12 levels without laboratory findings consistent with anemia or macrocytosis: so-called subclinical B12 (cobalamin) deficiency.

Prevalence of Vitamin B12 Deficiency

In 1996, Carmel (7) reported that the prevalence of undiagnosed pernicious anemia among 729 older adults (age $\geq$ 60 years) was 1.9%. Then in 2004, Guralnik et al (8) reported that 10.6% of the population age 65 years or older in the National Health and Nutritional Examination Survey (NHANES) had anemia and that 11.3% of the anemia cases were B12-related. In Ontario, this translates to between 22,668 and

50,473 people older than 60 years who might have B12-related anemia. In fiscal year 2010/2011, there were 1.2 million B12 tests in people aged 60 years or older in Ontario.

Vitamin B12 and Cognitive Function

The Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD) was held in 2007. Delegates at that meeting recommended that serum cobalamin (vitamin B12) levels be determined for all older adults suspected of dementia or cognitive decline (Grade B, Level 2). (9) "Grade B" implies that there was fair evidence to support vitamin B12 testing, and "Level 2" suggests that the evidence was obtained from observational studies. (10) This recommendation was added to the consensus guidelines in 2007. (11)

The process for developing CCCDTD recommendations is quite rigorous. (10) Vitamin B12 testing was just one of several domains that were part of the consensus conference. Each domain was assigned a working group with representation from the College of Family Physicians of Canada, in addition to other experts with particular interests in certain domains. Each working group performed literature searches, summarized the data, and drafted recommendations. The summary reports and recommendations were posted on a website for feedback from all conference participants. All recommendations achieved consensus of 80% or greater.

In 2007 and 2008, 2 articles were published providing more background on the vitamin B12 recommendation for diagnosis of suspected dementia or cognitive decline in older adults. (11;12) Neither article clearly identified the studies on which the CCCDTD recommendation was based, nor how the recommendation was determined to be Grade B, Level 2. Feldman et al stated that "the primary role of laboratory investigations … is to rule out the rare presence of a treatable disorder presenting as memory loss." (11)

Feldman et al (11) could have been referring to reversible dementia. Given that vitamin B12 deficiency can cause neurologic deficits, a dementia caused by B12 deficiency is thought to be reversible. Other causes of possibly reversible dementias include normal-pressure hydroencephalus and brain tumours. In 2003, Clarfield (13) published a systematic review of 39 studies (N = 7,042) examining reversible dementia. He reported that approximately 9% of the cases were potentially reversible dementia and that 0.6% of cases actually reversed.

In 2007, the Guidelines and Protocols Advisory Committee of British Columbia released guidelines on the diagnosis of cognitive impairment in the elderly. (14) The committee recommended that vitamin B12 be performed in the initial work-up for those with suspected mild cognitive impairment or dementia, but added the caveat, "Current data from systematic reviews of randomized double blind trials, however, do not provide evidence of improvement in cognition or dementia with B12 treatment."

Ontario Context

In fiscal year 2010/2011, more than 2.9 million serum vitamin B12 laboratory tests were billed to the province at a cost of approximately $40 million. The number of vitamin B12 tests performed has increased since fiscal year 2005/2006, particularly in the community setting (Table 1, Figure 1). In 2007 the vitamin B12 test was added to the laboratory requisition form that physicians use to request lab tests; as noted previously, the recommendations of the CCCDTD published in 2007 stated that older adults with suspected dementia or cognitive decline should have their vitamin B12 levels assessed. (9) Laboratory tests for vitamin B12 increased by nearly 1 million between 2007/2008 and 2008/2009. The serum vitamin B12 test was removed from the laboratory requisition form in November 2012.

Table 1. Volume of Vitamin B12 Laboratory Tests in Ontario for Fiscal Years 2005/2006 to 2010/2011

Fiscal Year	Hospital	Community	Total
2005/2006	173,284	1,083,219	1,256,503
2006/2007	199,412	1,188,066	1,387,478
2007/2008	206,917	1,509,800	1,716,717
2008/2009	222,136	2,436,765	2,658,901
2009/2010	247,746	2,865,684	3,113,430
2010/2011	255,620	2,651,992	2,907,612
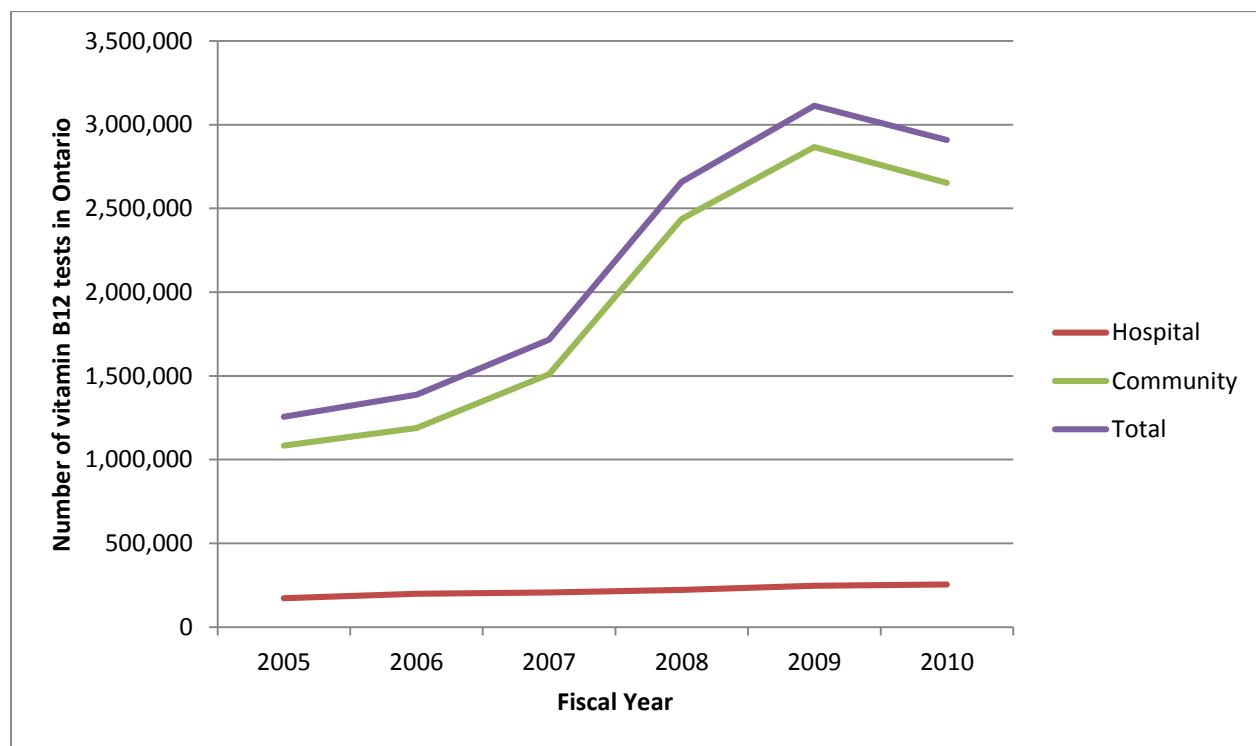
Figure 1. Number of Vitamin B12 Tests in Ontario for Fiscal Years 2005/2006 to 2010/2011

Diagnostic Accuracy of Serum Vitamin B12 Testing

In 2011, Willis et al (15) published a systematic review and meta-analysis of the diagnostic accuracy of serum tests for assessing vitamin B12 (or cobalamin). They searched the literature from 1990 to 2009 and identified 54 studies for inclusion. They reported that no consistent reference standard is used to measure the accuracy of the serum vitamin B12 test, thus making it difficult to establish the accuracy of the test. They reported a range of variability for sensitivity and specificity across the studies. Sensitivity ranged from 13% to 75%, and specificity ranged from 45% to 100%. Willis et al (15) attributed the wide ranges of sensitivity and specificity to the inconsistent use of a reference standard.

Hvas and Nexo (16) also published an article regarding the diagnostic accuracy for serum vitamin B12 testing. Although their review was not systematic, they described the strengths and weaknesses of each of

the serum tests for assessing vitamin B12. A summary of the tests based on the review of Hvas and Nexo (16) is listed in Table 2.

The National Health and Nutrition Examination Survey measures the health status of Americans. Part of the survey includes assessments of vitamin B12 biomarkers including cobalamin, methylmalonic acid (MMA), and total homocysteine (Hcy). They established that, because of the challenges in sensitivity and specificity of tests, 2 tests (preferably cobalamin and MMA) should be performed when assessing vitamin B12 levels. They recommended MMA over total Hcy because Hcy also increases in the absence of other vitamins (folate and B6). (17;18)

Table 2. Summary of Laboratory Tests to Assess Vitamin B12 Deficiency

Laboratory Test	Rationale for Test	Advantages	Disadvantages
Cobalamin	Decreases in vitamin B12 deficiency	Easily accessible test $10–$15 per test (in Ontario) Most commonly used test with the most literature about abnormal cut-offs	Sensitivity and specificity is unclear
Methymalonic acid[a]	Increases with vitamin B12 deficiency	High sensitivity	Questionable specificity ~$105 per test in Ontario (uninsured)
Total homocysteine[a]	Increases with vitamin B12 deficiency	High sensitivity	Low specificity influenced by lifestyle factors (smoking, alcohol consumption, coffee consumption) ~$65 per test in Ontario (uninsured)
Holotranscobalamin[a]	Decreases with vitamin B12 deficiency Newer test, clinical utility unclear	High sensitivity	Specificity unclear

[a]These laboratory tests are uninsured in community laboratories in Ontario.
Source: Hvas and Nexo. (16)

Existing Guidelines

In addition to the British Columbia recommendations mentioned above (14), two other guidelines on the diagnosis of vitamin B12 deficiency were identified. The 3 guidelines (19-21) were assessed using the Appraisal of Guidelines for Research and Evaluation tool. (22) All 3 guidelines scored poorly on the linkages provided between the evidence and recommendations.

The recommendations from each of the guidelines are listed in Table 3. The systematic review by Andres et al (21) used a flow chart or care pathway to describe their recommendations, rather than text. A notable difference in the guideline by Andres et al (21) was that they recommended screening all patients in institutions or psychiatric hospitals for vitamin B12 deficiency. This was not a factor in either of the other guidelines. Andres et al (21) reported that the prevalence of vitamin B12 deficiency was much higher (30% to 40%) in patients who were sick or institutionalized. As mentioned previously, in all guidelines the relationship between the recommendations and the evidence presented was very weak.

The Scottish Intercollegiate Guidelines Network (SIGN) also issued guidelines in 2006 on the management of patients with dementia. On the basis of their evidence review, they stated that "[t]here is

no evidence that routine batteries of laboratory tests improve the accuracy of the clinical diagnosis of dementia." (23) According to SIGN, this statement was based on high-quality case-control or cohort studies.

Table 3. Guidelines for Assessment of Vitamin B12 Levels

Guideline	Whom to Test?	How Frequently?	Overall Recommendation
BC Guidelines and Protocols Advisory Committee, 2012 (19)	Patients with unexplained neurologic symptoms (paresthesia, numbness, poor motor coordination, memory lapses) Patients with acrocytic anemia or macrocytosis	Not reported	Routine screening for vitamin B12 deficiency is not recommended
Smellie et al, 2005 (20)	Patients with acrocytic anemia Patients with acrocytosis Patients with specific neurocognitive abnormalities	"There is no obvious merit in repeating vitamin B12 measurements unless lack of compliance is suspected or anemia recurs"	Not reported
Andres et al, 2004 (21)	Elderly patients with malnutrition All patients in institutions and psychiatric hospitals All patients with hematologic or neurocognitive manifestations of vitamin B12 deficiency	Not reported	Not reported

Evidence-Based Analysis

Research Questions

- Is there an association between vitamin B12 deficiency and the onset of dementia or cognitive decline?
- Does treatment with vitamin B12 supplementation improve cognitive function in patients with dementia or cognitive decline and vitamin B12 deficiency?
- What is the effectiveness of oral versus parenteral vitamin B12 supplementation in those with confirmed vitamin B12 deficiency?

Research Methods

Literature Search

Search Strategy

A literature search was performed on August 26, 2012, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2002, until August 26, 2012. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion and Exclusion Criteria and Outcomes of Interest

Question 1. Is there an association between vitamin B12 deficiency and the onset of dementia or cognitive decline?

Inclusion criteria
- Systematic reviews, meta-analyses, randomized controlled trials (RCTs), longitudinal observational studies
- No clinical signs or symptoms of dementia at onset of study
- Study must report onset of dementia, Alzheimer disease (AD), or cognitive decline as an outcome measure
- $N \geq 100$
- Observational period 2 years or longer

Exclusion criteria
- Cross-sectional studies, case series, case reports
- Non-English studies
- Institutionalized subjects (inpatients)

Outcomes of interest
- Onset of dementia or Alzheimer disease
- Change in cognitive function

Question 2. Does treatment with vitamin B12 supplementation improve cognitive function in patients with dementia or cognitive decline and vitamin B12 deficiency?

Inclusion criteria
- Systematic reviews, meta-analyses, RCTs
- Supplementation with vitamin B12 alone
- Any dosage or method (oral or parenteral) of vitamin B12 included
- 12 months or more of follow-up
- Patients with confirmed vitamin B12 deficiency (for the purpose of this review B12 < 200 pmol/L)
- Results reported for patients with cognitive impairment, any type of dementia, or AD separately from the results of healthy subjects

Exclusion criteria
- Observational studies, case series, case reports
- Non-English studies
- Studies looking at multivitamin supplementation

Outcomes of interest
- Change in cognitive function
- Change in vitamin B12 levels

Question 3. What is the effectiveness of oral versus parenteral vitamin B12 supplementation in those with confirmed vitamin B12 deficiency?

Inclusion criteria
- Systematic reviews, meta-analyses, RCTs
- Studies comparing oral versus parenteral vitamin B12 of any dose
- No limitation on duration of supplementation or follow-up
- Patients with demonstrated vitamin B12 deficiency (as defined by the study)

Exclusion criteria
- Observational studies, case series, case reports
- Non-English studies

Outcomes of interest
- Serum vitamin B12 measurements
- Adverse events
- Acceptability and compliance

Statistical Analysis

Because the outcomes reported were heterogeneous, the studies were not pooled.

Expert Panel

In the fall of 2012, a Clinical Expert Advisory Panel on Appropriate Utilization of Vitamin B12 Testing for Neurocognitive-Based Indications was appointed to place the evidence produced by HQO in context and to provide advice on the clinical utility of vitamin B12 in older adults with suspected dementia or

cognitive impairment within the Ontario health care system. The panel was comprised of physicians, personnel from the Ministry of Health and Long-Term Care, and representatives from the community.

The statements, conclusions, and views expressed in this report do not necessarily represent the views of Advisory Panel members.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (24) The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials (RCTs) are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose response gradient, and accounting for all residual confounding factors. (24) For more detailed information, please refer to the latest series of GRADE articles. (24)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High   High confidence in the effect estimate—the true effect lies close to the estimate of the effect

Moderate   Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different

Low   Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect

Very Low   Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Evidence-Based Analysis

The database search yielded 1,360 citations published between January 1, 2002, and August 26, 2012 (with duplicates removed). Articles were excluded on the basis of information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. (Figure 2)
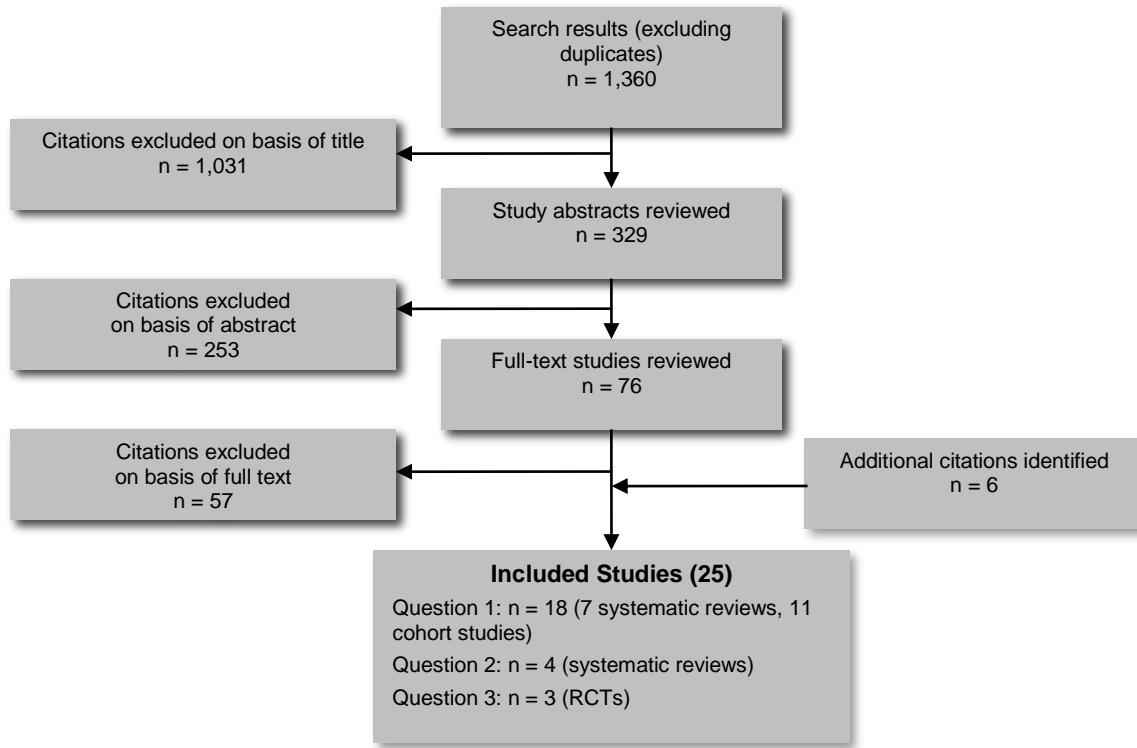

Figure 2. Citation Flow Chart
Abbreviation: RCT, randomized controlled trial.

For each included study, the study design was identified and is summarized in Table 4, which is a modified version of a hierarchy of study design by Goodman. (25)

Table 4. Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies		
	Question 1	Question 2	Question 3
RCT studies			
Systematic review of RCTs	-	4	-
Large RCT (N > 100)	-	-	-
Small RCT (N < 100)	-	-	3
Observational studies			
Systematic review of non-RCTs with contemporaneous controls	7	-	-
Non-RCT with non-contemporaneous controls	-	-	-
Systematic review of non-RCTs with historical controls	-	-	-
Non-RCT with historical controls	-	-	-
Longitudinal cohort study	11		
Database, registry, or cross-sectional study	-	-	-
Case series	-	-	-
Retrospective review, modelling	-	-	-
Studies presented at an international conference	-	-	-
Expert opinion	-	-	-
Total	**18**	**4**	**3**

Abbreviation: RCT, randomized controlled trial.

Question 1: Is there an association between vitamin B12 deficiency and the onset of dementia or cognitive decline?

Seven systematic reviews examined the relationship between vitamin B12 and cognitive function. (26-32) Table 5 summarizes the systematic reviews.

Some of the systematic reviews were searching for studies of B vitamins; others were looking for the relationship between cognitive function and Hcy levels. B vitamins (folate, B6, and B12) convert Hcy into methionine (an amino acid) into protein. High levels of Hcy are associated with low levels of B vitamins. Thus, levels of serum Hcy are an indirect measure of serum vitamin B12 levels, but Hcy is also elevated in the presence of renal impairment, a common abnormality in older adults, whose decline in renal function worsens with advancing age.

Overall, the systematic reviews concluded that there may be an association between high Hcy levels and the onset of dementia, but that, at this time, there was insufficient evidence to confidently make this statement. Moreover, the relation between elevated plasma Hcy and cognitive impairment can be confounded by the presence of renal impairment, possibly caused by a combination of chronic hypertension and diabetes mellitus, compounded by increasing age.

Table 5. Summary of Systematic Reviews Examining the Association Between Vitamin B12 (or Hyperhomocysteinemia) and the Onset of Dementia

Author, Year	Question	Sources/Dates Searched	No. of Studies Included	Conclusion
Moore et al, 2012 (26)	What is the association between low vitamin B12 levels, neurodegenerative disease, and cognitive impairment?	MEDLINE, PsychINFO, PubMed/to 2011	Unclear	Low serum vitamin B12 levels are associated with neurodegenerative disease and cognitive impairment.
Ho et al, 2011 (27)	What is the role of Hcy as a risk factor for dementia, cognitive decline, and cognitive impairment?	PubMed, Embase, PsychINFO, Biosis, Cochrane Library/to 2008	17	Individuals with AD have higher Hcy levels than controls; however, a causal relationship between high Hcy level and risk of developing dementia is not supported.
Wald et al, 2011 (28)	What is the relationship between serum Hcy and dementia?	MEDLINE, PsychINFO/to 2009	8 (cohort)	There is a positive association between serum Hcy and dementia.
Dangour et al, 2010 (29)	What is the strength of the available evidence that serum nutrient levels, dietary consumption, or nutrient supplementation were associated with primary prevention or treatment of dementia?	PubMed, Embase, Cochrane Library/to 2007	33	Available evidence is insufficient to draw definitive conclusions on the association of B vitamins with cognitive decline or dementia.
Van Dam and Van Gool, 2009 (30)	What is the association between Hcy levels and AD?	PubMed, Embase, PsychINFO/to 2007	18	Increased serum levels of Hcy predispose to AD; more studies are needed.
Raman et al, 2007 (31)	What is the association between blood levels or dietary intake of B vitamins and the risk and progression of neurocognitive deficit?	MEDLINE, Commonwealth Agricultural Bureau/to 2006	24 (cohort)	Data supporting the association (of B vitamins and cognitive function) were limited because of the heterogeneity in cognition-assessment methodology and due to scarcity of good quality studies and standardized threshold levels for categorizing low B-vitamin status.
Ellinson et al, 2004 (32)	What is the evidence of an association between low serum vitamin B12 and cognitive impairment in subjects older than 60 years?	Medline, PsychINFO, CINAHL, Embase, Food and Nutrition in AGRIS, Biosis/to 2003	6	The evidence does not support a correlation between serum vitamin B12 and cognitive impairment in people older than 60 years.

Abbreviations: AD, Alzheimer disease, AGRIS, International System for Agricultural Science and Technology; CINAHL, EBSCO Cumulative Index to Nursing & Allied Health Literature; Hcy, homocysteine; No., number.

These systematic reviews included a series of different studies. For this EBA, all of the studies in each of the systematic reviews were reviewed, in addition to searching for additional studies through the aforementioned literature search.

Overall, 11 longitudinal observational studies were included in this study. (33-43) The studies are described in Table 6. The most recent study by Zylberstein et al (33) reported the longest follow-up at 30 years. This Swedish study recruited women in 1968 and 1969 who were between the ages of 38 and 60 years at the time. Researchers measured their Hcy levels at baseline, and then followed the women for 30 years in the longitudinal study. The researchers found that higher levels of Hcy in mid-life were significantly associated with the onset of dementia and AD in later life.

An interesting trend was observed among the studies assessing the association between Hcy levels and the onset of dementia. The studies that followed patients for less than 3 years were much less likely to report a significant association between high Hcy levels and the onset of dementia than studies with longer follow-up.

All studies assessed Hcy levels as a surrogate for vitamin B12 levels, except for the study by Wang et al, (40) which measured vitamin B12 levels. After 3 years of follow-up, Wang et al did not report a significant difference in the onset of dementia or AD between those with low B12 levels versus those with normal B12 levels. Again, these results could be misleading, in that elevated Hcy and the onset of dementia can be confounded by renal impairment, chronic hypertension, and diabetes mellitus, all of which are known risk factors for vascular dementia.

The observational studies were assessed for quality using GRADE. There was risk of bias in some studies due to incomplete follow-up and lack of adjustment for confounding. Also, because Hcy is a surrogate measure of vitamin B12, directness in these studies was limited, as the intent was to find the association between vitamin B12 and the onset of dementia, not the association of Hcy and the onset of dementia. More details on the assessment of quality can be found in Appendix 3. Therefore, very low quality evidence indicates an association between Hcy levels and the onset of dementia, but it is impossible to make a conclusion about the specific association between vitamin B12 and the onset of dementia.

Table 6. Studies Included in Highest-Scoring Systematic Reviews, Sorted by Length of Observation Period

Author, Year (Location)	No. of Subjects (Dementia Cases)	Mean Age (Years) at Baseline (SD)	Mean Baseline B12 (SD)	Mean Baseline Hcy (SD)	Hcy as a Predictor for Dementia (Adjusted) (95% CI)	Hcy as a Predictor for AD (Adjusted) (95% CI)	Adjustment Factors	Obs. Period (Years)
Zylberstein et al, 2011 (33) (Sweden)	1,368 (151)	46.8 (no SD) (all women)	397 pmol/L (138)	11.8 µmol/L (4.6)	Highest vs lowest Hcy quintile: HR, 1.7 (1.1–2.6)	Highest vs lowest Hcy quintile: HR, 2.13 (1.22–3.73)	Age, creatinine, vitamin B12, education, and other risk factors	30
Seshadri et al, 2002 (34) (USA)	1,092 (111)	Men 76 (5) Women 77 (6)	416 pg/mL (209)	13.1 µmol/L (6.3)	Hcy as a continuous variable: RR, 1.3 (1.1–1.5)	Hcy as a continuous variable: RR 1.4 (1.1–1.7)	Age, sex	8
Kivipelto et al, 2009 (35) (Sweden)	228 (83)	81.0 (4.6)	317 pmol/L (138)	18.6 µmol/L (10.7)	Hcy as a continuous variable: RR, 1.01 (1.00–1.02)	Hcy as a continuous variable: RR, 1.01 (1.00–1.03)	Age, sex, education	6.7
Nurk et al, 2005 (36) (Norway)	2,189 (235)	72.0 (no SD) at follow-up, all patients were eligible between 65–67 years	347 pmol/L (341–354)	11.5 µmol/L (11.3–11.6)	Highest vs lowest Hcy quintile: OR, 2.34 (1.39–3.91)	NR	Sex, APOE genotype, education, CVD, HBP, depression score	6
Luchsinger et al, 2004 (37) (USA)	679 (109)	76.2 (5.7)	NR	Cut-off value: > 15.6 µmol/L	NR	Highest vs lowest Hcy quartile: HR, 1.4 (0.8–2.4)	Age, sex, education, APOE genotype	4.7
Haan et al, 2007 (38) (USA)	1,779 (62)	60–101 years (mean NR)	334 pmol/L (150)	10.8 µmol/L (6.5)	Highest vs lowest Hcy tertile: HR, 2.39 (1.11–5.16)	NR	Vitamin B12, education	4.5
Ravaglia et al, 2005 (39) (Italy)	816 (112)	73.6 (6.3)	NR	259 pmol/L (95% CI, 94–708)	Hcy >15 µmol/L: HR, 2.08 (1.31–3.30)	Hcy >15 µmol/L: HR, 2.11 (1.19–3.76)	Age, sex, education, APOE genotype, stroke, creatinine, folate, B12	4
Wang et al, 2001 (40) (Sweden)	370 (78)	>75 (mean NR)	Cut-off value: B12 < 150 pmol/L	NR	Vitamin B12: RR, 1.3 (0.7–2.3)	Vitamin B12: RR, 1.6 (0.9–2.8)	Age, sex, education	3
Kalmijn et al, 1999 (41) (Nether-lands)	702 (110)	67.7 (7.1)	NR	15.6 µmol/L (SE, 0.35)	Highest vs lowest Hcy tertile: OR, 1.30 (0.50–3.38)	NR	Age, sex, education	2.6
Kim et al, 2008 (42) (South Korea)	518 (45)	71.6 (4.9)	382 pmol/L (148)	12.3 µmol/L (5.2)	Highest vs lowest Hcy quintile: OR, 1.10 (0.86–1.40)	NR	Age, sex, education	2.4
Rowan et al, 2007 (43) (UK)	126 (26)	79.4 (IQR, 77.3–82.8) post-stroke	264 pmol/L (169)	16.0 µmol/L (5.1)	Unclear if it was adjusted Hcy as a continuous variable: OR, 1.04 (0.96–1.14)	NR	N/A	2

Abbreviations: APOE, apolipoprotein E; CI, confidence interval; CVD, cardiovascular disease; Hcy, homocysteine; HBP, high blood pressure; HR, hazard ratio; IQR, interquartiile range; N/A, not applicable; No., number; NR, not reported; Obs, observation; OR, odds ratio; RR, relative risk; SD, standard deviation; SE, standard error; vs, versus.

Question 2: Does treatment with vitamin B12 supplementation improve cognitive function in patients with dementia or cognitive decline and vitamin B12 deficiency?

Four systematic reviews investigated the effect of treatment of vitamin B12 in patients with cognitive impairment or dementia. (44-47) No additional RCTs were identified that were not included in at least one of the systematic reviews. All 4 systematic reviews came to the same conclusion, which was that treatment with vitamin B12 supplementation did not improve cognitive function. With the exception of the systematic review by the Cochrane Collaboration (47), systematic reviews included heterogeneous study populations. The systematic reviews included studies of patients with varying degrees of cognitive impairment, and vitamin B12 deficiency was not part of the eligibility criteria for any of the systematic reviews (including the Cochrane review).

None of the 17 RCTs included in the systematic reviews met the inclusion criteria for this evidence-based analysis. (48-64) (Table 7) The criteria for this analysis state that studies needed to include patients with vitamin B12 deficiency and with cognitive impairment or dementia. Also, the minimum follow-up duration was 12 months. None of the 17 RCTs identified were able to meet all 3 of these criteria. The RCTs all used various measures for assessing cognitive function, and none of the studies demonstrated a change in cognitive function between the vitamin B12 treatment and placebo arms regardless of what combination of cognitive function tests were used.

The studies assessing cognitive function had to be at least 12 months in duration. Experts believe it can take up to 18 months for cognitive function assessments to measure a change. According to experts, results from cognitive tests can vary from day to day in the same person, and the overall variance is large in populations. (Confidential personal communication, October 30, 2012) Most studies that measured the effect of vitamin B12 on cognitive function were less than 6 months in duration.

One small RCT aimed to answer whether treatment with vitamin B12 in patients with dementia (or cognitive impairment) and vitamin B12 deficiency improved cognitive function. (63) Only 11 patients were enrolled in the study, and the duration of follow-up was not reported. Researchers did not find any improvement in cognitive function with vitamin B12 treatment, but the study was not powered to detect a difference. All of the other studies either included a combination of "healthy" and cognitively impaired older adults with vitamin B12 deficiency, or cognitively impaired adults without vitamin B12 deficiency.

One study did not use cognitive function as the primary outcome; rather, researchers looked at the effect of B vitamins on the rate of brain atrophy, as a surrogate measure of functioning. The article by Smith et al (65) described the results of the VITACOG study. Patients (N = 168) were randomized to receive supplementation with vitamins B12, B6, and folate or placebo for 2 years. All patients underwent magnetic resonance imaging to assess brain atrophy at the start of the trial and again at 2 years. The results of the intent-to-treat analysis indicated a significant difference in the rate of atrophy per year in the group receiving the B vitamin supplements (0.76%; 95% CI, 0.63%–0.90%) versus the group receiving the placebo (1.08%; 95% CI, 0.94%–1.22%; $P = 0.001$). According to the authors of this RCT, this is also a clinically significant difference. They stated that, in normal aging, one expects 0.5% atrophy per year and 2.5% atrophy per year in AD. (66)

Thus, none of the studies assessing cognitive function were able to identify a difference in cognitive performance between vitamin B12 supplementation versus placebo; however, a study of the rate of brain atrophy did demonstrate that B vitamins slowed the rate of brain atrophy in patients with mild cognitive impairment. The quality of the evidence was assessed using GRADE. For the outcome of cognitive function, the GRADE is moderate. This is based on RCTs with the primary limitation being that none of these trials were performed in the population of interest (i.e., patients with cognitive impairment or dementia and vitamin B12 deficiency). Evidence for the outcome of rate of brain atrophy per year was

graded to be low to moderate because only 1 study assessed brain atrophy, which is an indirect measure of disease progression and cognitive function. More details on the quality assessment of the evidence using GRADE can be found in Appendix 3.

Therefore, moderate quality evidence indicates treatment with vitamin B12 supplementation does not change cognitive function in patients with or without dementia or cognitive impairment and with or without vitamin B12 deficiency. Low to moderate quality of evidence indicates treatment with vitamin B12 and folate for patients with mild cognitive impairment slows the rate of brain atrophy compared with those who receive a placebo.

Table 7. Studies Included in Systematic Reviews of the Effectiveness of Vitamin B12 on Cognitive Function

Author, Year[a]	Vitamin B12 Deficient?	Cognitive Impairment or Dementia?	Duration of Follow-up (months)
De Jager et al, 2012 (48)	No	Yes (mild cognitive impairment)	24
Kwok et al, 2011 (49)	No	Yes (mild to moderate AD or vascular dementia)	24
Ford et al, 2010 (50)	Not reported	Unclear	24
Aisen et al, 2008 (51)	No	Yes (mild to moderate AD)	18
Kang et al, 2008 (52)	Not reported	Not reported at baseline	60
Eussen et al, 2006 (53)	Yes (100–200 pmol/L)	Mixed (40% mild to moderate cognitive impairment); results not stratified for patients with cognitive impairment	6
McMahon et al, 2006 (54)	Likely (high Hcy implies low B12)	No	24
Lewerin et al, 2005 (55)	No	Unclear	4
Stott et al, 2005 (56)	No	Mixed (mild or moderate cognitive impairment included)	12
Garcia et al, 2004 (57)	No	No	6
Hvas et al, 2004 (58)	Likely (increased MMA implies low B12)	Mixed (1/3 cognitive impairment)	3
Clarke et al, 2003 (59)	No	Yes (mild to moderate dementia)	3
Bryan et al, 2002 (60)	Not reported	No	1
Seal et al, 2002 (61)	Yes (100–150 pmol/L)	Mixed (1/3 cognitive impairment); results not stratified for patients with cognitive impairment	1
Kwok et al, 1998 (62)	Yes (< 120 pmol/L)	Mixed (20% with dementia); results not stratified for patients with dementia	4
De la Fourniere et al, 1997 (63)	Yes (< 178 pmol/L)	Yes (all AD)	Not reported
Kral et al, 1970 (64)	N/A	N/A	N/A

[a]Studies where B12 was part of the treatment arm.
Abbreviations: AD, Alzheimer disease; Hcy, homocysteine; MMA, methylmaloninc acid; N/A, not applicable.

Question 3: What is the effectiveness of oral versus parenteral vitamin B12 supplementation in those with confirmed vitamin B12 deficiency?

In 2005, Vidal-Alaball et al published a Cochrane systematic review comparing oral vitamin B12 to intramuscular vitamin B12 for patients with vitamin B12 deficiency. (67) They identified 2 RCTs that met their inclusion criteria. (68;69) They found that the limited evidence provided in the 2 RCTs indicated oral vitamin B12 was as effective as intramuscular vitamin B12.

The Canadian Agency for Drugs and Technologies in Health (CADTH) published a health technology assessment in 2007 comparing oral versus injectable vitamin B12. (70) They used the Vidal-Alaball et al (67) review as the basis for their rapid review and concluded that oral supplementation was as effective as parenteral vitamin B12, but more research was needed to confirm long-term efficacy.

In addition to the 2 RCTs identified in the review by Vidal-Alaball et al, Castelli et al published a study in 2011, which was funded by the manufacturer of an oral B12 supplement. The study compared oral B12 to intramuscular B12 in patients with mild B12 deficiency (< 258 pmol/L). (71) The authors state that none of the patients had symptoms of vitamin B12 deficiency. The cut-off for vitamin B12 deficiency of 258 pmol/L was higher than most other studies (< 150–200 pmol/L). However, there is some evidence to support increasing the threshold for deficiency to 300 pmol/L. (72) The authors randomized 50 patients to receive either oral B12 or intramuscular B12 for 90 days. They included patients who were older than 60 years of age and also patients who were younger than 60 years of age who had gastrointestinal abnormalities or were on a restricted diet (vegan). After 90 days, all of the patients had vitamin B12 levels higher than 258 pmol/L. It was unclear why the study was designed as a superiority trial and not a noninferiority trial, given that the hypothesis was to establish whether oral B12 is an appropriate alternative to intramuscular B12.

Bolaman et al conducted their RCT in Turkey. (69) At the time their study was being conducted, oral B12 in tablet form was unavailable, so they suspended the 1,000 µg of vitamin B12 in 20 mL of fruit juice for participants to consume. The primary end points for this study were change in hemoglobin levels from baseline to 90 days and signs and symptoms of anemia. The authors did not describe specifically which signs and symptoms of anemia they were measuring. Unlike the Castelli et al RCT, this study does not appear to have been funded by the manufacturer of the B12 supplement.

The study by Kuzminski et al randomized 38 patients to receive either oral or intramuscular vitamin B12. (68) Unlike the other studies, participants receiving oral B12 had 2,000 µg daily, instead of 1,000 µg daily. The group receiving intramuscular B12 in this study received 1,000 µg, like the intramuscular group in other studies. It is unsurprising that, at the final measurement of B12 levels on day 120, participants in the oral B12 group had substantially higher B12 values than participants in the intramuscular B12 group (742 pmol/L versus 240 pmol/L), given that the oral group was receiving twice the amount of B12 that the intramuscular group was receiving and that the oral group was taking the vitamin B12 supplement daily, while the intramuscular group had not had an injection since day 90. Nonetheless, both groups reported mean values well above the cut-off threshold for vitamin B12 deficiency defined in this study (118 pmol/L).

Patients with pernicious anemia are characterized by a lack of intrinsic factor in the gastrointestinal tract, limiting the ability to absorb vitamin B12. One of the reasons for injecting vitamin B12 intramuscularly is to avoid relying on the absorption of vitamin B12 through the gastrointestinal tract. The study by Kuzminski et al reported results for each patient and listed which patients had pernicious anemia. All 5 patients in the oral B12 group with pernicious anemia achieved serum B12 levels greater than 232 pmol/L (range, 232 pmol/L to 1,550 pmol/L) after 4 months of oral therapy.

None of the RCTs reported any severe adverse events associated with taking oral or intramuscular B12 supplementation. The RCTs are summarized in Table 8.

In January 2012, the British Columbia Guidelines and Protocols Advisory Committee released guidelines on the diagnosis and management of vitamin B12 deficiency. The Committee recommended oral vitamin B12 supplementation because it is as effective as parenteral vitamin B12. (19)

The GRADE quality of evidence for these 3 RCTs was assessed as moderate. The quality was downgraded because of the risk of bias in each of the RCTs. Some limitations include the impossibility of blinding in any of the studies, the failure to report a primary outcome in the study by Bolaman et al, (69) the funding and conduct of the study by Castelli et al (71) by the manufacturer of the oral vitamin B12 supplement, and the imbalance between the treatment courses received in the study by Kuzminski et al (68). More details of the GRADE assessment are listed in Appendix 3.

It is also important to note that these studies were all short term; the long-term effects of taking oral B12 instead of intramuscular injections are unknown.

Table 8. Randomized Controlled Trials Comparing Oral Vitamin B12 to Intramuscular Vitamin B12 in Patients with Vitamin B12 Deficiency

Author, Year	Number of Patients	Population	Cut-off for B12 Deficiency	Interventions	Primary Outcome	Intent-to-Treat Analysis	Outcomes
Castelli et al, 2011 (71)	50 (48 completed the study, both drop-outs from the oral group)	Vitamin B12-deficient patients ≥60 years or ≥18 years with GI abnormalities or receiving a restricted diet	< 258 pmol/L	Oral (n = 22): 1,000 µg taken daily for 90 days IM (n = 26): 1,000 µg given on days 1, 3, 7, 10, 14, 21, 30, 60, and 90	Proportion of patients in each treatment arm with normalized vitamin B12 levels (≥ 258 pmol/L)	Yes	All patients had vitamin B12 levels > 258 pmol/L on days 61 and 91
Bolaman et al, 2003[a] (69)	70 (10 dropped out after < 10 days of treatment)	Patients with megaloblastic anemia (including 11 patients with suspected pernicious anemia) ≥16 years	< 118 pmol/L	Oral (n = 26): 1,000 µg taken daily for 10 days, then weekly for 4 weeks, then monthly IM (n = 34): 1,000 µg given daily for 10 days, then weekly for 4 weeks, then monthly	Hemoglobin level and signs or symptoms of anemia	No; drop-outs excluded from analysis	Significant improvement in hemoglobin levels in both groups from baseline to 90 days, approaching normal value ($P < .01$)
Kuzminski et al, 1998[a] (68)	38 (5 excluded from analysis because of folate deficiency, not B12 deficiency)	Vitamin B12 deficient (including 7 with confirmed pernicious anemia)	< 118 pmol/L	Oral (n = 18): 2,000 µg daily for 120 days IM (n = 15): 1,000 µg given on days 1, 3, 7, 10, 14, 21, 30, 60, and 90	Not specified	No; 5 patients with folate deficiency excluded from analysis	The mean vitamin B12 level in both the oral and intramuscular group was > 240 pmol/L

Abbreviations: GI, gastrointestinal; IM, intramuscular.
[a] These randomized controlled trials were included in the Cochrane systematic review by Vidal-Aaball et al, 2005. (67)

Discussion

The clinical utility of serum vitamin B12 testing is a complicated issue. To begin with, the accuracy of the serum B12 test is not great. (15) In 2011, Willis et al conducted a systematic review and meta-analysis of serum B12 testing and found that the sensitivity ranged from 13% to 75%, and the specificity ranged from 45% to 100%. (15) This variation in sensitivity and specificity is likely due to the lack of a consistent reference standard to assess serum B12 levels. Thus, widespread screening using the serum B12 test would be ill-advised because many inaccurate results would lead to inappropriate treatment and unnecessary repeat testing.

The cut-off point to establish vitamin B12 deficiency also varies across studies and across community laboratories in Ontario. One laboratory in Ontario sets the cut-off for B12 deficiency at 107 pmol/L, while another sets the cut-off at 148 pmol/L. This variation is likely due to the methods of analysis used by each of the laboratories. In the literature, thresholds range from 150 to 350 pmol/L. Without a consistent definition of B12 deficiency, it is challenging to even comment on the prevalence of the condition. Studies estimate the rate of deficiency from less than 2% to more than 30%. (21;73-76) This variation is likely due to the differences in cut-off values for deficiency and the inaccuracy of the B12 test. Probably a cut-off of 150 pmol/L is the preferred value to define vitamin B12 deficiency.

Given the limitations of the diagnostic accuracy of serum B12 testing and the inconsistency of cut-off values, one could conclude that the clinical utility of vitamin B12 testing is limited because the test itself is unreliable. However, the widely cited study by Lindenbaum et al from 1988 (6) stated that "neuropsychiatric disorders due to cobalamin deficiency occur commonly in the absence of anemia," thus creating utility in measuring serum B12 levels in addition to complete blood count, because vitamin B12 deficiency could exist without anemia. There were some limitations of this study, including some inconsistencies in the results reported. For instance, Lindenbaum et al list the laboratory findings of patients with neurocognitive abnormalities but without anemia. Even though they state these patients do not have anemia, 15 of 40 patients have abnormally high mean corpuscular volumes (based on the cut-off criteria Lindenbaum et al used), and 6 additional patients have abnormal hematocrit levels. These results lead to a suspicion of anemia. This evidence suggests that some patients have vitamin B12 deficiency without anemia, but the prevalence is lower than reported. Dr Carmel reported similar findings in 1988. (5)

Another possible reason raised for assessing serum vitamin B12 levels was to identify cases of reversible dementia. Because vitamin B12 deficiency can cause neurologic deficits, there is some thought that a dementia caused by vitamin B12 deficiency can be reversed. However, in 2003, Clarfield (13) published a systematic review of 39 studies (N = 7042) examining reversible dementia. He reported that approximately 9% of the cases were potentially reversible and that 0.6% of cases actually reversed. Thus, he demonstrated that truly reversible dementias are quite rare.

It is important to note that the Clinical Expert Advisory Panel on Appropriate Utilization of Vitamin B12 Testing for Neurocognitive-Based Indications, convened by Health Quality Ontario to place the evidence for this analysis into context, believed strongly that testing serum B12 levels has a place in clinical practice. Panel members were also certain that oral B12 supplementation should not be recommended for a general population of older adults because it is unclear what the risks of taking vitamin B12 supplements might be. In 2012 CADTH reported in a rapid review that "[v]itamin B12 supplementation was not found to slow cognitive decline or improve cognitive function in participants with or without cognitive impairment." (77)

Another challenge with the body of evidence on the association between vitamin B12 deficiency and cognitive function is the measure of cognitive function. Several tests are designed to assess cognitive function, and all of the studies in this evidence-based analysis used a different battery of tests to measure cognitive function, limiting the possibility of pooling the results. There is no standard for assessing change in cognitive function. (78-80) Changes in cognitive function can occur slowly over time, so studies of short duration (less than 6 months) are unlikely to be able to demonstrate a change in cognitive function. As it turned out, none of the 17 RCTs identified that compared treatment with B vitamins to placebo demonstrated a difference in cognitive function, regardless of the duration of follow-up or the battery of cognitive function tests used.

Finally, a recent commentary by Dr Stabler in the *New England Journal of Medicine* (81) reiterated some of the findings of this evidence based analysis: 1) The sensitivity and specificity of the vitamin B12 test is questionable, and 2) high-dose oral vitamin B12 supplementation is as effective as intramuscular B12. Dr Stabler stated that vitamin B12 deficiency should be determined on the basis of both vitamin B12 test results and clinical symptoms of deficiency (including paresthesias). She also endorsed the vitamin B12 supplementation in adults older than 50 years recommended by the Institute of Medicine's Food and Nutrition Board, which states that "It is advisable for most of [the recommended daily intake of vitamin B12 to] be obtained by consuming foods fortified with B12 or a B12-containing supplement." (82)

Conclusions

Question 1: Is there an association between vitamin B12 deficiency and the onset of dementia or cognitive decline?

- Based on very low quality evidence, there does appear to be an association between homocysteine levels (a by-product of B vitamins) and the onset of dementia.

Question 2: Does treatment with vitamin B12 supplementation improve cognitive function in patients with dementia or cognitive decline and vitamin B12 deficiency?

- Based on moderate quality evidence, treatment with vitamin B12 supplementation does not change cognitive function in patients with or without dementia or cognitive impairment and with or without vitamin B12 deficiency.
- Based on low to moderate quality of evidence, treatment with vitamin B12 and folate in patients who have mild cognitive impairment seems to slow the rate of brain atrophy compared with patients who have mild cognitive impairment receiving a placebo. Whether this translates into clinical benefit is unknown.

Question 3: What is the effectiveness of oral versus parenteral vitamin B12 supplementation in those with confirmed vitamin B12 deficiency?

- Based on moderate quality evidence, oral vitamin B12 is as effective as parenteral vitamin B12 in patients with confirmed B12 deficiency in the short term.

Acknowledgements

Appendices

Appendix 1: Literature Search Strategy

Search date: August 26, 2012
Databases searched: Ovid MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, Embase; Wiley; Cochrane; Centre for Reviews and Dissemination (CRD) database
Limits: 2002-present; Human; English; NOT case reports, comments, editorials, letters
Filters: RCTS & MAs/SRs/HTAs for administration route question (#3)

1   exp Vitamin B 12 Deficiency/ use mesz

2   exp Vitamin B 12/df use mesz

3   Transcobalamins/df use mesz

4   exp Cyanocobalamin Deficiency/ use emez

5   ((b12 or b 12 or cyanocobalamin or cobalamin* or transcobalamin* or cobamide? or hydroxocobalamin or hydroxo-cobalamin or hydroxycobalamin) adj3 (deficien* or inadequa* or insufficien* or low blood level* or low serum level* or low plasma level* or suboptimal or sub-optimal or subnormal or sub-normal)).ti,ab.

6   (an?emia* adj2 (addison* or pernicious* or megaloblastic)).ti,ab.

7   or/1-6

8   exp Vitamin B 12/ use mesz

9   Transcobalamins/ use mesz

10 Transcobalamin/ use emez

11 Cyanocobalamin/ use emez

12 (b12 or b 12 or cyanocobalamin or cobalamin* or transcobalamin* or cobamide? or hydroxocobalamin or hydroxo-cobalamin or hydroxycobalamin).ti,ab.

13 or/8-12

14 exp Dementia/

15 exp Cognition Disorders/ use mesz

16 (alzheimer* or amentia? or dementia* or demention or senile or senility or (cognit* adj (decline or disorder? or impair*))).ti,ab.

17 or/14-16

18 (7 or 13) and 17

19 Case Reports/ or Comment.pt. or Editorial.pt. or Letter.pt.

20 Case Report/ or Comment/ or Editorial/ or Letter/

21 or/19-20

22 18 not 21

23 limit 22 to english language

24 limit 23 to yr="2002 -Current"

25 exp animals/

26 exp animal experimentation/

27 exp models animal/

28 exp animal experiment/

29 nonhuman/

30 exp vertebrate/

31 or/25-30

32 exp humans/

33 exp human experiment/

34 or/32-33

35 31 not 34

36 24 not 35

37 remove duplicates from 36

38 7 and 13

39 38 not 21

40 limit 39 to (controlled clinical trial or meta analysis or randomized controlled trial)

41 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ use mesz

42 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ use emez

43 (health technology adj2 assess$).ti,ab.

44 exp Random Allocation/ or exp Double-Blind Method/ or exp Control Groups/ or exp Placebos/ use mesz

45 Randomized Controlled Trial/ or exp Randomization/ or exp RANDOM SAMPLE/ or Double Blind Procedure/ or exp Triple Blind Procedure/ or exp Control Group/ or exp PLACEBO/ use emez

46 (random* or RCT).ti,ab.

47 (placebo* or sham*).ti,ab.

48 (control* adj2 clinical trial*).ti,ab.

49 meta analysis/ use emez

50 (meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.

51 or/41-50

52 (39 and 51) or 40

53 limit 52 to english language

54 limit 53 to yr="2002 -Current"

55 remove duplicates from 54

Appendix 2: Systematic Reviews of Treatment with B12 for Cognitive Function

Table A1. Systematic Reviews of Treatment with B12 for Cognitive Function

Author, Year	Question (Sources Searched/Dates)	Studies Where B12 was Part of Treatment Arm	Study Included in this EBA?	Vitamin B12 Deficient?	Cognitive Impairment or Dementia?	Duration of Study (Months)	Overall Conclusion
Ford and Almeida, 2012 (44)	What is the efficacy of treatment with vitamins B12, B6, or folate in slowing cognitive decline among older adults with and without cognitive impairment? (PubMed, PsychINFO, Embase, Cochrane/to 2011)	Aisen et al, 2008 (51)	No	No	Yes (mild to moderate AD)	18	No difference in cognitive function whether receiving vitamin B12 supplementation or not
		Clarke et al, 2003 (59)	No	No	Yes (mild to moderate dementia)	3	
		De Jager et al, 2012 (48)	No	No	Yes (mild cognitive impairment)	24	
		Kwok et al, 2011 (49)	No	No	Yes (mild to moderate AD or vascular dementia)	24	
		Garcia et al, 2004 (57)	No	No	No	6	
		Hvas et al, 2004 (58)	No	Likely (increased MMA implies low B12)	Mixed (1/3 cognitive impairment)	3	
		Eussen et al, 2006 (53)	No	Yes (100–200 pmol/L)	Mixed (40% mild-moderate cognitive impairment); results not stratified for patients with cognitive impairment	6	
		Ford et al, 2010 (50)	No	Not reported	Unclear	24	
		Kang et al, 2008 (52)	No	Not reported	Not reported at baseline	60	
		Seal et al, 2002 (61)	No	Yes (100–150 pmol/L)	Mixed (1/3 cognitive impairment); results not stratified for patients with cognitive impairment	1	
		Lewerin et al, 2005 (55)	No	No	Unclear	4	
		McMahon et al, 2006 (54)	No	Likely (high Hcy implies low B12)	No	24	
		Stott et al, 2005 (56)	No	No	Mixed (mild or moderate cognitive impairment included)	12	

Author, Year	Question (Sources Searched/Dates)	Studies Where B12 was Part of Treatment Arm	Study Included in this EBA?	Vitamin B12 Deficient?	Cognitive Impairment or Dementia?	Duration of Study (Months)	Overall Conclusion
Jia et al, 2008 (45)	What is effect of nutrient supplementation on cognitive function in people aged ≥ 65 years? (MEDLINE, Embase/ to 2006)	De la Fourniere et al, 1997 (63)	No (full study in French, N = 11)	Yes (< 178 pmol/L)	Yes (all AD)	Not reported	No difference in cognitive function whether receiving vitamin B12 supplementation or not
		Kwok et al, 1998 (62)	No	Yes (< 120 pmol/L)	Mixed (20% with dementia); results not stratified for patients with dementia	4	
		Bryan et al, 2002 (60)	No	Not reported	No	1	
		Seal et al, 2002 (61)	No	Yes (100–150 pmol/L)	Mixed (1/3 cognitive impairment); results not stratified for patients with cognitive impairment	1	
		Clarke et al, 2003 (59)	No	No	Yes (mild to moderate dementia)	3	
		Lewerin et al, 2005 (55)	No	No	Unclear	4	
		Stott et al, 2005 (56)	No	No	Mixed (mild or moderate cognitive impairment included)	12	
		Eussen et al, 2006 (53)	No	Yes (100–200 pmol/L)	Mixed (40% mild to moderate cognitive impairment); results not stratified for patients with cognitive impairment	6	
		McMahon et al, 2006 (54)	No	Likely (high Hcy implies low B12)	No	24	
Balk et al, 2007 (46)	Does supplementation with vitamins B6, B12, and folic acid prevent or decrease progression of neurologic changes associated with dementia? (MEDLINE, Commonwealth Agricultural Bureau/to 2005)	Hvas et al, 2004 (58)	No	Likely (increased MMA implies low B12)	Mixed (1/3 cognitive impairment)	3	No difference in cognitive function whether receiving vitamin B12 supplementation or not
		Eussen et al, 2006 (53)	No	Yes (100–200 pmol/L)	Mixed (40% mild-moderate cognitive impairment); results not stratified for patients with cognitive impairment	6	
		Bryan et al, 2002 (60)	No	Not reported	No	1	
		Seal et al, 2002 (61)	No	Yes (100–150 pmol/L)	Mixed (1/3 cognitive impairment); results not stratified for patients with	1	

Author, Year	Question (Sources Searched/Dates)	Studies Where B12 was Part of Treatment Arm	Study Included in this EBA?	Vitamin B12 Deficient?	Cognitive Impairment or Dementia?	Duration of Study (Months)	Overall Conclusion
					cognitive impairment		
		Kwok et al, 1998 (62)	No	Yes (< 120 pmol/L)	Mixed (20% with dementia); results not stratified for patients with dementia	3	
		Kral et al, 1970 (64)	No (outdated)	N/A	N/A	N/A	
Malouf and Areosa, 2003 (Cochrane Review) (47)	What is effect of vitamin B12 supplementation on cognitive function of demented and elderly healthy people in terms of preventing the onset or progression of cognitive impairment? (MEDLINE, Embase, Cochrane/to 2006)	Hvas et al, 2004 (58)	No	Likely (increased MMA implies low B12)	Mixed (1/3 cognitive impairment)	3	No difference in cognitive function whether receiving vitamin B12 supplementation or not
		Seal et al, 2002 (61)	No	Yes (100–150 pmol/L)	Mixed (1/3 cognitive impairment); results not stratified for patients with cognitive impairment	1	
		De la Fourniere et al, 1997 (63)	No (full study in French, N = 11)	Yes (< 178 pmol/L)	Yes (all AD)	Not reported	

Abbreviations: AD, Alzheimer disease; EBA, evidence-based analysis; Hcy, homocysteine; MMA, methylmalonic acid.

Appendix 3: Evidence Quality Assessment

Table A2. GRADE Evidence Profile for the Association Between Homocysteine and the Onset of Dementia

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Homocysteine as a predictor of dementia							
11 longitudinal observational studies	Some limitations[a]	No serious limitations[b]	Serious limitations (-1)[c]	No serious limitations	Undetected	None	⊕⊕ Low

[a] There were some limitations in studies used to answer this question. Limitations included incomplete follow-up, insufficient control for confounding, and inappropriate measure of outcomes—but overall studies were well reported.
[b] When studies are stratified by years of follow-up, there is consistency in the outcomes—the longer the follow-up period, the more likely an association between homocysteine levels and the onset of dementia.
[c] Homocysteine is an indirect measure of serum vitamin B12.

Table A3. Risk of Bias Among Observational Trials for the Association Between Homocysteine and the Onset of Dementia

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Zylberstein et al, 2011 (33)	No limitations	No limitations	No limitations	No limitations	No limitations
Seshadri et al, 2002 (34)	No limitations	No limitations	No limitations	No limitations	No limitations
Kivipelto et al, 2009 (35)	No limitations	No limitations	No limitations	No limitations	No limitations
Nurk et al, 2005 (36)	No limitations	No limitations	No limitations	No limitations	Limitations[a]
Luchsinger et al, 2004 (37)	No limitations	No limitations	No limitations	No limitations	No limitations
Haan et al, 2007 (38)	No limitations	No limitations	Limitations[b]	Limitations[c]	No limitations
Ravaglia et al, 2005 (39)	No limitations	No limitations	No limitations	No limitations	No limitations
Wang et al, 2001 (40)	No limitations	No limitations	Limitations[d]	No limitations	No limitations
Kalmijn et al, 1999 (41)	No limitations	No limitations	Limitations[b]	No limitations	No limitations
Kim et al, 2008 (42)	No limitations	No limitations	No limitations	No limitations	No limitations
Rowan et al, 2007 (43)	No limitations	No limitations	No limitations	Limitations[e]	No limitations

[a] It is unclear how many patients completed full 6 years of follow-up.
[b] Studies reported wide confidence intervals.
[c] This analysis was not adjusted for age or sex.
[d] This study measured vitamin B12 levels, while all other studies measured homocysteine.
[e] It is unclear whether the analysis was adjusted.

Table A4. GRADE Evidence Profile for Comparison of B Vitamins Versus Placebo

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Cognitive function							
4 systematic reviews (including 17 RCTs)	No serious limitations	No serious limitations	Serious limitations (-1)[a]	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Rate of brain atrophy per year							
1 RCT (VITACOG)	No serious limitations	Consistency unknown (single study)	Serious limitations (-1)[b]	No serious limitations	Undetected	None	⊕⊕ Low-Moderate

[a] None of the RCTs identified included the population of interest (i.e., patients with dementia or cognitive impairment and vitamin B12 deficiency).
[b] Rate of brain atrophy is an indirect measure of disease progression and cognitive function.
Abbreviation: RCT, randomized controlled trial.

Table A5. Risk of Bias Among Randomized Controlled Trials for Comparison of B Vitamins Versus Placebo

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Smith et al VITACOG, 2010 (65)	No limitations	No limitations	No limitations	No limitations	No limitations

Table A6. GRADE Evidence Profile for Comparison of Oral Vitamin B12 and Parenteral Vitamin B12

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Mean vitamin B12 level above cut-off at end of study							
3 (RCTs)	Serious limitations (-1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate

[a] The risk of bias assessment identified limitations with each of the randomized controlled trials (see Table A7).
Abbreviation: RCT, randomized controlled trial.

Table A7. Risk of Bias Among Randomized Controlled Trials for Comparison of Oral Vitamin B12 and Parenteral Vitamin B12

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Castelli et al, 2011 (71)	No limitations	Limitations[a]	No limitations	No limitations	Limitations[b]
Bolaman et al, 2003 (69)	No limitations	Limitations[a]	Limitations[c]	Limitations[d]	No limitations
Kuzminski et al, 1998 (68)	Limitations[e]	Limitations[a]	Limitations[c]	No limitations	No limitations

[a]It is impossible to blind this randomized controlled trial because participants were randomized to oral or injected vitamin B12; thus it is impossible to disguise or hide the intervention.
[b]This study was funded and conducted by the manufacturer of the oral vitamin B12 supplement.
[c]An intent-to-treat analysis was not reported.
[d]The primary end point was reported to be signs and symptoms of anemia; however, no detail was given to describe the signs and symptoms of anemia in the results.
[e]The randomization process was not described.

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