

Ⓒ

„Vitamin B(12) in neurology and ageing; Clinical and genetic aspects.“

Ⓓ

Vitamin B(12) in der Neurologie und im Alterungsprozess; klinische und genetische Aspekte.

Ⓖ

Η Βιταμίνη Β(12) στη νευρολογία και τη γήρανση: κλινικές και γενετικές διαστάσεις.

Ⓕ

La vitamine B12 en neurologie et dans le vieillissement ; aspects cliniques et génétiques

Ⓒ

Vitamín B(12) v neurologii a při stárnutí; klinické a genetické aspekty.

---

[Biochimie](#). 2012 Dec 7. pii: S0300-9084(12)00476-2. doi:  
10.1016/j.biochi.2012.11.017. [Epub ahead of print]

## **Vitamin B(12) in neurology and ageing; Clinical and genetic aspects.**

[McCaddon A](#).

### **Source**

School of Medicine, Cardiff University, Gwenfro Units 6/7, Wrexham Technology Park, Wrexham LL17 7YP, Wales, United Kingdom. Electronic address:  
mccaddon@sky.com.

### **Abstract**

The classic neurological and psychiatric features associated with vitamin B(12) deficiency have been well described and are the subject of many excellent review articles. The advent of sensitive diagnostic tests, including homocysteine and methylmalonic acid assays, has revealed a surprisingly high prevalence of a more subtle 'subclinical' form of B(12) deficiency, particularly within the elderly. This is often associated with cognitive impairment and dementia, including Alzheimer's disease. Metabolic evidence of B(12) deficiency is also reported in association with other neurodegenerative disorders including vascular dementia, Parkinson's disease and multiple sclerosis. These conditions are all associated with chronic neuro-inflammation and oxidative stress. It is possible that these clinical associations reflect compromised vitamin B(12) metabolism due to such stress. Physicians are also increasingly aware of considerable inter-individual variation in the clinical response to B(12) replacement therapy. Further research is needed to determine to what extent this is attributable to genetic determinants of vitamin B(12) absorption, distribution and cellular uptake.

PMID: 23228515

Ⓒ

„Oral folic acid and vitamin B-12 supplementation to prevent cognitive decline in community-dwelling older adults with depressive symptoms -the Beyond Ageing Project: a randomized controlled trial.“

Ⓓ

Orale Folsäure- und Vitamin-B-12-Supplementierung zur Prävention einer kognitiven Verschlechterung bei selbstständig lebenden älteren Erwachsenen mit depressiven Symptomen - das „Beyond Ageing Project“: eine randomisierte, kontrollierte Studie.

Ⓖ

„Από στόματος χορηγούμενο φολικό οξύ και Βιταμίνη Β-12 για την πρόληψη της διανοητικής κατάπτωσης σε γηραιά άτομα που βρίσκονται σε οίκους ευγηρίας και έχουν συμπτώματα κατάθλιψης - the Beyond Ageing Project: τυχαιοποιημένη ελεγχόμενη δοκιμή.“

Ⓕ

Supplémentation orale en acide folique et en vitamine B12 pour prévenir le déclin cognitif chez les adultes âgés vivant en collectivité et souffrant de symptômes dépressifs - Le projet Au-delà du Vieillissement : étude randomisée et contrôlée.

Ⓒ

Suplementace kyselinou listovou a vitamínem B-12 perorálně jako prevence snižování kognitivních schopností u starších dospělých žijících v komunitě s příznaky deprese – projekt Beyond Ageing: randomizovaná kontrolovaná studie.

---

[Am J Clin Nutr.](#) 2012 Jan;95(1):194-203. doi: 10.3945/ajcn.110.007799. Epub 2011 Dec 14.

**Oral folic acid and vitamin B-12 supplementation to prevent cognitive decline in community-dwelling older adults with depressive symptoms--the Beyond Ageing Project: a randomized controlled trial.**

[Walker JG](#), [Batterham PJ](#), [Mackinnon AJ](#), [Jorm AF](#), [Hickie I](#), [Fenech M](#), [Kljakovic M](#), [Crisp D](#), [Christensen H](#).

Source Centre for Mental Health Research, Australian National University, Canberra, Australia. janine.walker@anu.edu.au

**BACKGROUND:** Evidence remains unclear as to whether folic acid (FA) and vitamin B-12 supplementation is effective in reducing depressive symptoms.

**OBJECTIVES:** The objective was to determine whether oral FA + vitamin B-12 supplementation prevented cognitive decline in a cohort of community-dwelling older adults with elevated psychological distress.

**DESIGN:** A randomized controlled trial (RCT) with a completely crossed  $2 \times 2 \times 2$  factorial design comprising daily oral 400  $\mu\text{g}$  FA + 100  $\mu\text{g}$  vitamin B-12 supplementation (compared with placebo), physical activity promotion, and depression literacy with comparator control interventions for reducing depressive symptoms was conducted in 900 adults aged 60-74 y with elevated psychological distress (Kessler Distress 10-Scale; scores >15). The 2-y intervention was delivered in 10 modules via mail with concurrent telephone tracking calls. Main outcome measures examined change in cognitive functioning at 12 and 24 mo by using the Telephone Interview for Cognitive Status-Modified (TICS-M) and the Brief Test of Adult Cognition by Telephone (processing speed); the Informant Questionnaire on Cognitive Decline in the Elderly was administered at 24 mo.

**RESULTS:** FA + vitamin B-12 improved the TICS-M total ( $P = 0.032$ ; effect size  $d = 0.17$ ), TICS-M immediate ( $P = 0.046$ ;  $d = 0.15$ ), and TICS-M delayed recall ( $P = 0.013$ ; effect size  $d = 0.18$ ) scores at 24 mo in comparison with placebo. No

significant changes were evident in orientation, attention, semantic memory, processing speed, or informant reports.

**CONCLUSION:** Long-term supplementation of daily oral 400 µg FA + 100 µg vitamin B-12 promotes improvement in cognitive functioning after 24 mo, particularly in immediate and delayed memory performance. This trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov) as NCT00214682.

PMID: 22170358

Ⓒ

„Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people.“

Ⓓ

Folsäure mit und ohne Vitamin B12 zur Prävention und Behandlung von gesunden älteren und dementen Menschen.

Ⓖ

„Φολικό οξύ με ή χωρίς Βιταμίνη Β12 για την πρόληψη και θεραπεία υγιών γηραιών ατόμων ή με άνοια.“

Ⓕ

L'acide folique avec ou sans vitamine B12 pour la prévention et le traitement chez les personnes âgées saines et atteintes de démence sénile.

Ⓒ

Listová kyselina s nebo bez vitamínu B12 pro prevenci a léčbu zdravých starších a dementních osob.

---

[Cochrane Database Syst Rev.](#) 2008 Oct 8;(4):CD004514. doi:  
10.1002/14651858.CD004514.pub2.

## **Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people.**

[Malouf R](#), [Grimley Evans J](#).

**Source** Department of Psychiatry, Oxfordshire and Buckinghamshire Mental Health Trust, John Radcliffe Hospital (4th Floor, Room 4401C), Headington, Oxford, UK, OX3 9DU.  
reemmalouf@yahoo.com

**BACKGROUND:** Folate deficiency can result in congenital neural tube defects and megaloblastic anaemia. Low folate levels may be due to insufficient dietary intake or inefficient absorption, but impaired metabolic utilization also occurs. Because B12 deficiency can produce a similar anaemia to folate deficiency, there is a risk that folate supplementation can delay the diagnosis of B12 deficiency, which can cause irreversible neurological damage. Folic acid supplements may sometimes therefore include vitamin B12 supplements with simultaneous administration of vitamin B12. Lesser degrees of folate inadequacy are associated with high blood levels of the amino acid homocysteine which has been linked with the risk of arterial disease, dementia and Alzheimer's disease. There is therefore interest in whether dietary supplementation can improve cognitive function in the elderly. However, any apparent benefit from folic acid which was given in combination with B12 needs to be "corrected" for any effect of vitamin B12 alone. A separate Cochrane review of vitamin B12 and cognitive function has therefore been published.

**OBJECTIVES:** To examine the effects of folic acid supplementation, with or without vitamin B12, on elderly healthy or demented people, in preventing cognitive impairment or retarding its progress.

**SEARCH STRATEGY:** Trials were identified from a search of the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 10 October 2007 using the terms: folic acid, folate, vitamin B9, leucovorin, methyltetrahydrofolate, vitamin B12, cobalamin and cyanocobalamin. This Register contains references from all major health care databases and many ongoing trials databases. In

addition MEDLINE, EMBASE, CINAHL, PsychINFO and LILACS were searched (years 2003-2007) for additional trials of folate with or without vitamin B12 on healthy elderly people.

**SELECTION CRITERIA:** All double-blind, placebo-controlled, randomized trials, in which supplements of folic acid with or without vitamin B12 were compared with placebo for elderly healthy people or people with any type of dementia or cognitive impairment.

**DATA COLLECTION AND ANALYSIS:** The reviewers independently applied the selection criteria and assessed study quality. One reviewer extracted and analysed the data. In comparing intervention with placebo, weighted mean differences and standardized mean difference or odds ratios were estimated.

#### **MAIN RESULTS:**

Eight randomized controlled trials fulfilled the inclusion criteria for this review. Four trials enrolled healthy older people, and four recruited participants with mild to moderate cognitive impairment or dementia with or without diagnosed folate deficiency. Pooling the data was not possible owing to heterogeneity in sample selections, outcomes, trial duration, and dosage. Two studies involved a combination of folic acid and vitamin B12. There is no adequate evidence of benefit from folic acid supplementation with or without vitamin B12 on cognitive function and mood of unselected healthy elderly people. However, in one trial enrolling a selected group of healthy elderly people with high homocysteine levels, 800 mcg/day folic acid supplementation over three years was associated with significant benefit in terms of global functioning (WMD 0.05, 95% CI 0.004 to 0.096,  $P = 0.033$ ); memory storage (WMD 0.14, 95% CI 0.04 to 0.24,  $P = 0.006$ ) and information-processing speed (WMD 0.09, 95% CI 0.02 to 0.16,  $P = 0.016$ ). Four trials involved people with cognitive impairment. In one pilot trial enrolling people with Alzheimer's disease, the overall response to cholinesterase inhibitors significantly improved with folic acid at a dose of 1mg/day (odds ratio: 4.06, 95% CI 1.22 to 13.53;  $P = 0.02$ ) and there was a significant improvement in scores on the Instrumental Activities of Daily Living and the Social Behaviour subscale of the Nurse's Observation Scale for Geriatric Patients (WMD 4.01, 95% CI 0.50 to 7.52,  $P = 0.02$ ). Other trials involving people with cognitive impairment did not show any

benefit in measures of cognitive function from folic acid, with or without vitamin B12. Folic acid plus vitamin B12 was effective in reducing serum homocysteine concentrations (WMD -5.90, 95% CI -8.43 to -3.37,  $P < 0.00001$ ). Folic acid was well tolerated and no adverse effects were reported.

**AUTHORS' CONCLUSIONS:** The small number of studies which have been done provide no consistent evidence either way that folic acid, with or without vitamin B12, has a beneficial effect on cognitive function of unselected healthy or cognitively impaired older people. In a preliminary study, folic acid was associated with improvement in the response of people with Alzheimer's disease to cholinesterase inhibitors. In another, long-term use appeared to improve the cognitive function of healthy older people with high homocysteine levels. More studies are needed on this important issue.

PMID: 18843658

Ⓒ

„The worldwide challenge of the dementias: a role for B vitamins and homocysteine?“

Ⓓ

Die weltweite Herausforderung der Demenzen: eine Rolle für B-Vitamine und Homocystein?

Ⓖ

Η παγκόσμια πρόκληση στις μορφές άνοιας: παίζουν ρόλο οι βιταμίνες Β και η ομοκυστεΐνη;

Ⓕ

Le défi mondial des démences séniles : un rôle pour les vitamines B et l'homocystéine ?

Ⓒ

„Celosvětová výzva demence: úloha vitamínu B a homocysteinu?„

---

[Food Nutr Bull.](#) 2008 Jun;29(2 Suppl):S143-72.

## **The worldwide challenge of the dementias: a role for B vitamins and homocysteine?**

[Smith AD.](#)

**Source** Oxford Project to Investigate Memory and Aging, University of Oxford, UK.  
[david.smith@pharm.ox.ac.uk](mailto:david.smith@pharm.ox.ac.uk)

Dementia has reached epidemic proportions, with an estimated 4.6 million new cases worldwide each year. With an aging world population, the prevalence of dementia will increase dramatically in the next few decades. Of the predicted 114 million who will have dementia in 2050, about three-quarters will live in less developed regions. Although strongly age-related, dementia is not an inevitable part of aging but is a true disease, caused by exposure to several genetic and nongenetic risk factors. Prevention will be possible when the nongenetic risk factors have been identified. Apart from age, more than 20 nongenetic risk factors have been postulated, but very few have been established by randomized intervention studies. Elevated blood concentrations of total homocysteine and low-normal concentrations of B vitamins (folate, vitamin B12, and vitamin B6) are candidate risk factors for both Alzheimer's disease and vascular dementia. Seventy-seven cross-sectional studies on more than 34,000 subjects and 33 prospective studies on more than 12,000 subjects have shown associations between cognitive deficit or dementia and homocysteine and/or B vitamins. Biologically plausible mechanisms have been proposed to account for these associations, including atrophy of the cerebral cortex, but a definite causal pathway has yet to be shown. Raised plasma total homocysteine is a strong prognostic marker of future cognitive decline, and is common in world populations. Low-normal concentrations of the B vitamins, the main determinant of homocysteine concentrations, are also common and occur in particularly vulnerable sections of the population, such as infants and elderly. Large-scale randomized trials of homocysteine-lowering vitamins are needed to see if a proportion of dementia in the world can be prevented.

PMID: 18709889

GB

Prevention of dementia: a role for B vitamins?

DE

Prävention von Demenz: eine Rolle für B-Vitamine?

GR

Πρόληψη της άνοιας: παίζουν ρόλο οι βιταμίνες Β;

FR

Prévention de la démence sénile : un rôle pour les vitamines B ?

CZ

Prevence demence: úloha vitamínů skupiny B?

---

[Nutr Health](#). 2006;18(3):225-6.

## Prevention of dementia: a role for B vitamins?

[Smith AD](#).

Source Oxford Project to Investigate Memory and Aging (OPTIMA), University of Oxford, UK. david.smith@pharm.ox.ac.uk

### Abstract

Dementia has reached epidemic proportions, with an estimated 4.6 million new cases worldwide each year. With an aging world population the prevalence of dementia will increase dramatically in the next few decades. Of the predicted 114 million who will have dementia in 2050 about three-quarters will live in the less-developed regions. Although strongly age-related, dementia is not an inevitable part of aging but is a true disease caused by exposure to several genetic and non-genetic risk factors. Prevention will be possible when the non genetic risk factors have been identified. Apart from age, more than 20 non-genetic risk factors have been postulated but very few have been established by randomised intervention studies. Elevated blood concentrations of total homocysteine and low-normal concentrations of B vitamins (folate, vitamins B-12 and B-6) are candidate risk factors for both Alzheimer's disease and vascular dementia. A review of the literature up to the end of 2005 shows the following. Seventy seven cross-sectional studies on > 34,000 subjects and 33 prospective studies on > 12,000 subjects have shown associations between cognitive deficit or dementia and homocysteine and/or B vitamins. Biologically plausible mechanisms have been proposed to account for these associations, including atrophy of the cerebral cortex, but a definite causal pathway has yet to be shown. Raised plasma total homocysteine is a strong prognostic marker of future cognitive decline, and is common in world populations. Low-normal concentrations of the B vitamins, the main determinant of homocysteine concentrations, are also common and occur in particularly vulnerable sections of the population, such as infants and the elderly. Large-scale randomised trials of homocysteine-lowering B vitamins are needed to see if a proportion of dementia in the world can be prevented.

PMID: 17180867

GB

„Group B vitamins as new variables related to the cardiovascular risk“

DE

Vitamine der B-Gruppe als neue Variable im Hinblick auf das kardiovaskuläre Risiko

GR

Οι βιταμίνες της ομάδας Β ως νέες μεταβλητές που σχετίζονται με τον κίνδυνο καρδιοαγγειακών παθήσεων.

FR

Les vitamines du groupe B en tant que nouvelles variables liées au risque cardiovasculaire.

CZ

Vitamíny skupiny B jako nové proměnné související s kardiovaskulárním rizikem

---

[Ital Heart J Suppl.](#) 2005 Jan;6(1):1-16.

## **Group B vitamins as new variables related to the cardiovascular risk**

[Granieri M](#), [Bellisarii FI](#), [De Caterina R](#).

**Source** Istituto di Cardiologia, Università degli Studi G. d'Annunzio, Chieti.

### **Abstract**

The nutritional status and plasma concentrations of some group B vitamins, namely vitamin B6, vitamin B12 and folic acid, have recently emerged as inverse correlates of cardiovascular risk, and several experimental and clinical studies, these latter mostly retrospective and case-control studies, indicate a defect of such vitamins as capable of promoting the progression of atherosclerosis. Since all these vitamins are implicated in homocysteine metabolism, and since homocysteine has a well-recognized relationship with cardiovascular risk, the simplest hypothesis to explain the relationship of vitamin B6, vitamin B12 and folic acid on the one hand, and cardiovascular risk on the other is that this relationship is mediated by plasma levels of homocysteine. The most convincing literature data for the existence of a relationship with cardiovascular risk are for vitamin B6 and folic acid. These vitamins, however, have also a series of in vitro effects indicating a direct antiatherogenic action, and the results of several clinical studies, especially for vitamin B6, indicate an inverse relationship with cardiovascular risk at least in part independent of homocysteinemia. A further confirmation of these data is important to devise future intervention strategies in primary and secondary prophylaxis of atherosclerotic vascular disease.

PMID: 15776726

Ⓒ

„Does diet affect our mood? The significance of folic acid and homocysteine.“

Ⓓ

Wirkt sich die Ernährung auf unsere Stimmung aus? Die Bedeutung von Folsäure und Homocystein.

Ⓖ

Η διατροφή επηρεάζει τη διάθεσή μας; Η σημασία του φολικού οξέος και της ομοκυστεΐνης.

Ⓕ

Notre nutrition affecte-t-elle notre humeur ? L'importance de l'acide folique et de l'homocystéine.

Ⓒ

Ovlivňuje potrava naši náladu? Význam listové kyseliny a homocysteinu.

---

[Pol Merkur Lekarski](#). 2009 Feb;26(152):136-41.

## **Does diet affect our mood? The significance of folic acid and homocysteine].**

[Karakuła H](#), [Opolska A](#), [Kowal A](#), [Domański M](#), [Płotka A](#), [Perzyński J](#).

Source Medical University of Lublin, The Department of Psychiatry, Poland.

karakulahw@cyberia.pl

In recent years, there has been growing interest in the association between national diet and the possibility of developing various mental disorders, as well as between deficiency of such vitamins as, e.g. folic acid, vitamin B12, B6, and others (e.g., omega-3 fatty acids), elevated serum homocysteine level and the functioning of human brain as well as the occurrence of such disorders as dementia, central nervous system vascular disorders and depression.

### **THE AIM OF THE STUDY:**

was to present the current state of knowledge about the role of folic acid and homocysteine in the human organism as well as the significance of vitamin deficiency, mainly folic acid and hyperhomocysteinemia for the occurrence of mood disorders.

### **METHOD:**

The authors conducted the search of the Internet database Medline ([www.pubmed.com](http://www.pubmed.com)) using as key words: depression, mood, homocysteine, vitamin deficiencies: folic acid, B6 and B12 and time descriptors: 1990-2007.

**RESULTS:** In depression, folate, vitamins B12 and B6, as well as unsaturated omega-3 fatty acids deficiency affects the biochemical processes in the CNS, as folic acid and vitamin B12, participate in the metabolism of S-adenosylmethionine (SAM), a donor of methyl groups, which play a decisive role in the functioning of the nervous system; they are, among others, active in the formation of neurotransmitters (e.g. serotonin), phospholipids that are a component of neuronal myelin sheaths, and cell receptors. The deficiency of the vitamins in question results in hyperhomocysteinemia (the research shows that approximately 45-55% of patients with depression develop significantly elevated serum homocysteine), which causes a decrease in SAM, followed by impaired methylation and, consequently, impaired metabolism of neurotransmitters, phospholipids, myelin, and receptors. Hyperhomocysteinemia also leads to activation of NMDA receptors,

lesions in vascular endothelium, and oxidative stress. All this effects neurotoxicity and promotes the development of various disorders, including depression. Vitamins B12 and B6, folic acid and omega-3 fatty acids supplementation is thus important in patients suffering from their deficiency; national diet as a significant factor in prevention of numerous CNS disorders, including depression, is also worth consideration.

PMID: 19388520

GB

„Cognitive Function in an Elderly Population: Interaction Between Vitamin B12 Status, Depression, and Apolipoprotein E {varepsilon}4: The Hordaland Homocysteine Study.“

DE

„Kognitive Funktion bei der älteren Population: Interaktion zwischen Vitamin B12-Status, Depression und Apolipoprotein E {varepsilon}4: Die Hordaland Homocysteine Study.“

GR

„Γνωστική λειτουργία σε γηράσκοντες πληθυσμούς: αλληλεπίδραση μεταξύ των επιπέδων Βιταμίνης B12, της Κατάθλιψης και της Απολιποπρωτεΐνης E4: The Hordaland Homocysteine Study.“

FR

La fonction cognitive dans une population âgée : interaction entre le statut de la vitamine B12, la dépression et l'apolipoprotéine E {varepsilon}4 : L'étude Hordaland sur l'homocystéine.

CZ

„Kognitivní funkce u starší populace: Interakce mezi hladinou vitamínu B12, depresí a apolipoproteinem E {varepsilon}4: Homocysteinová studie Hordalandu.“

---

[Psychosom Med.](#) 2013 Jan;75(1):20-9. doi: 10.1097/PSY.0b013e3182761b6c. Epub 2012 Dec 4.

## **Cognitive Function in an Elderly Population: Interaction Between Vitamin B12 Status, Depression, and Apolipoprotein E $\epsilon$ 4: The Hordaland Homocysteine Study.**

[Vogiatzoglou A](#), [Smith AD](#), [Nurk E](#), [Drevon CA](#), [Ueland PM](#), [Vollset SE](#), [Nygaard HA](#), [Engedal K](#), [Tell GS](#), [Refsum H](#).

### **Source**

DPhil, Department of Food and Nutritional Sciences, University of Reading, Whiteknights, PO Box 226, Reading RG6 6AP, UK. a.vogiatzoglou@reading.ac.uk.

### **Abstract**

**Objective** To investigate the cross-sectional relation between metabolic markers of vitamin B(12) status and cognitive performance, and possible effect modification by the presence of depression and apolipoprotein E (ApoE)  $\epsilon$ 4. **Methods** This is a population-based study of 1935 participants, aged 71 to 74 years, from Norway. Participants were administered a cognitive test battery, and vitamin B(12) status was assessed by measurements of plasma vitamin B(12), holotranscobalamin (holoTC), methylmalonic acid (MMA), and total homocysteine. **Results** The geometric mean (95% confidence interval) for vitamin B(12) was 348 pM (341-354), whereas 5.9% of participants had vitamin B(12) levels lower than 200 pM. In linear regression analyses, holoTC ( $p = .039$ ) and the holoTC/vitamin B(12) ratio ( $p = .013$ ) were positively related, whereas MMA ( $p = .010$ ) was inversely related, to global cognition, after adjustment for sex, education, ApoE status, plasma creatinine, and history of diabetes, cardiovascular disease, hypertension, and depression. Among those positive for ApoE  $\epsilon$ 4, but not among those without the  $\epsilon$ 4 allele, plasma vitamin B(12) was positively associated with global cognition ( $p = .015$ ), whereas MMA was inversely related to global cognition ( $p = .036$ ) and executive function ( $p = .014$ ). In participants with depression, MMA was inversely associated with global cognition ( $p < .001$ ) and episodic memory ( $p = .001$ ). **Conclusions** Among the well-nourished elderly, low vitamin B(12) status is associated with cognitive deficit, particularly in those with the ApoE  $\epsilon$ 4 allele or with depression.

PMID: 23213264