

GB

„Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial.“

DE

Die Wirkung einer Folsäure-Supplementierung über drei Jahre auf die kognitive Funktion bei älteren Erwachsenen in der FACIT-Studie: eine randomisierte, doppelblinde, kontrollierte Studie.

GR

„Αποτέλεσμα 3-ετούς χορήγησης φολικού οξέος στη γνωστική λειτουργία ενηλίκων μεγαλύτερης ηλικίας στη δοκιμή FACIT: μια τυχαιοποιημένη, διπλή τυφλή, ελεγχόμενη δοκιμή.“

FR

Effet d'une supplémentation en acide folique sur 3 ans sur la fonction cognitive chez les adultes âgés de l'étude FACIT : étude randomisée, contrôlée, réalisée en double aveugle.

CZ

„Účinek 3leté suplementace kyseliny listovou na kognitivní funkci u starších dospělých ve studii FACIT: randomizovaná, dvojité zaslepená, kontrolovaná studie.“

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[Lancet](#). 2007 Jan 20;369(9557):208-16.

**Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial.**

[Durga J](#), [van Boxtel MP](#), [Schouten EG](#), [Kok FJ](#), [Jolles J](#), [Katan MB](#), [Verhoef P](#).

Source Division of Human Nutrition, Wageningen University, 6700 EV Wageningen, Netherlands. jane.durga@rdls.nestle.com

**BACKGROUND:** Low folate and raised homocysteine concentrations in blood are associated with poor cognitive performance in the general population. As part of the FACIT trial to assess the effect of folic acid on markers of atherosclerosis in men and women aged 50-70 years with raised plasma total homocysteine and normal serum vitamin B12 at screening, we report here the findings for the secondary endpoint: the effect of folic acid supplementation on cognitive performance.

**METHODS:** Our randomised, double blind, placebo controlled study took place between November, 1999, and December, 2004, in the Netherlands. We randomly assigned 818 participants 800 mug daily oral folic acid or placebo for 3 years. The effect on cognitive performance was measured as the difference between the two groups in the 3-year change in performance for memory, sensorimotor speed, complex speed, information processing speed, and word fluency. Analysis was by intention-to-treat. This trial is registered with clinicaltrials.gov with trial number NCT00110604.

**FINDINGS:** Serum folate concentrations increased by 576% (95% CI 539 to 614) and plasma total homocysteine concentrations decreased by 26% (24 to 28) in participants taking folic acid compared with those taking placebo. The 3-year change in memory (difference in Z scores 0.132, 95% CI 0.032 to 0.233), information processing speed (0.087, 0.016 to 0.158) and sensorimotor speed (0.064, -0.001 to 0.129) were significantly better in the folic acid group than in the placebo group.

**INTERPRETATION:** Folic acid supplementation for 3 years significantly improved domains of cognitive function that tend to decline with age.

PMID: 17240287

GB

Folate and brain function in the elderly.

DE

Folat und Hirnfunktion bei älteren Menschen.

GR

Φολικό οξύ και εγκεφαλική λειτουργία σε ηλικιωμένους.

FR

Le folate et le fonctionnement cérébral chez les personnes âgées.

CZ

Folát a mozková funkce u starších jedinců.

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[Curr Opin Clin Nutr Metab Care.](#) 2004 Nov;7(6):659-64.

## **Folate and brain function in the elderly.**

[D'Anci KE](#), [Rosenberg IH](#).

**Source** Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts, USA.

**PURPOSE OF REVIEW:** Over the past several decades, folate has emerged as an important nutrient in several key conditions of concern to the elderly. Subclinical levels of folate inadequacy can have significant negative impacts on health in older individuals.

**RECENT FINDINGS:** Serum and red blood cell folate levels are associated with depression in younger individuals, but the relationship is less clear in older people. However, folate status does predict response to antidepressant treatment in older individuals. Cognitive decline and some forms of dementia, including Alzheimer's disease, are associated with lower folate levels. Supplementation with folic acid can provide cognitive benefits in some circumstances. Folic acid supplementation is generally regarded as safe; however, there remains some concern that high levels of folic acid may exacerbate the neurological consequences of a vitamin B12 deficiency.

**SUMMARY:** Evidence for the role of folate in depression and dementia in the aged is increasing, although there remains much about mechanisms to be determined.

PMID: 15534434

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„Intake and status of folate and related B-vitamins: considerations and challenges in achieving optimal status.“

Ⓓ

Aufnahme und Status von Folat und verwandter B-Vitamine: Erwägungen und Schwierigkeiten beim Erreichen des optimalen Status.

Ⓖ

Πρόσληψη και επίπεδα φολικού οξέος και σχετικών βιταμινών ομάδας Β: σκέψεις και προκλήσεις για την επίτευξη της ιδανικής κατάστασης.

Ⓕ

Prise et statut du folate et des vitamines B apparentées : considérations et défis dans la recherche d'un état optimal.

Ⓒ

„Příjem a hladina folátu a související vitamíny skupiny B: úvahy a výzvy v dosahování optimální hladiny.“

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[Br J Nutr.](#) 2008 Jun;99 Suppl 3:S48-54. doi: 10.1017/S0007114508006855.

## **Intake and status of folate and related B-vitamins: considerations and challenges in achieving optimal status.**

[McNulty H](#), [Scott JM](#).

**Source** The Northern Ireland Centre for Food and Health (NICHE), School of Biomedical Sciences, University of Ulster, Coleraine BT52 1SA, Northern Ireland.

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### **Abstract**

Folate and the metabolically related B-vitamins, vitamin B12 and riboflavin, have attracted much scientific and public health interest in recent years. Apart from a well established role in preventing neural tube defects (NTDs), evidence is emerging to support other potential roles for folate and/or related B-vitamins in protecting against cardiovascular disease (especially stroke), certain cancers, cognitive impairment and osteoporosis. However, typical folate intakes are sub-optimal, in that although adequate in preventing clinical folate deficiency (i.e. megaloblastic anaemia) in most people, they are generally insufficient to achieve a folate status associated with the lowest risk of NTDs. Natural food folates have a limited ability to enhance folate status as a result of their poor stability under typical cooking conditions and incomplete bioavailability when compared with the synthetic vitamin, folic acid (as found in supplements and fortified foods). Current folate recommendations to prevent NTDs (based primarily on folic acid supplementation) have been found to be ineffective in several European countries. In contrast, in North America and Chile, the policy of mandatory folic acid-fortification has proven itself in terms of lowering the prevalence of NTD, but remains controversial because of concerns regarding potential risks of chronic exposure to high-dose folic acid. In the case of vitamin B12, the achievement of an optimal status is particularly difficult for many older people because of the common problem of food-bound B12 malabsorption. Finally, there is evidence that riboflavin status is generally low in the UK population, and particularly so in younger women; this warrants further investigation.

PMID: 18598588

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„Beneficial effects of folic acid on enhancement of memory and antioxidant status in aged rat brain.“

Ⓓ

Günstige Wirkung von Folsäure auf die Gedächtnisstärkung und den antioxidativen Status im alten Rattenhirn.

Ⓔ

Ευεργετικά αποτελέσματα του φολικού οξέος στη βελτίωση της μνήμης και της αντιοξειδωτικής κατάστασης στον εγκέφαλο γηραιών ποντικών.

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Effets bénéfiques de l'acide folique sur l'amélioration de la mémoire et statut des anti-oxydants dans le cerveau du rat âgé.

Ⓖ

Příznivé účinky listové kyseliny na zlepšení paměti a hladiny antioxidantů v mozku starých potkanů.

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[Cell Mol Neurobiol.](#) 2011 Jan;31(1):83-91. doi: 10.1007/s10571-010-9557-1. Epub 2010 Dec 18.

**Beneficial effects of folic acid on enhancement of memory and antioxidant status in aged rat brain.**

[Singh R](#), [Kanwar SS](#), [Sood PK](#), [Nehru B](#).

#### **Source**

Department of Biophysics, Panjab University, Chandigarh, India.

#### **Abstract**

As our population ages, diseases affecting memory and daily functioning will affect an increasing number of individuals, their families and the healthcare system. Therefore, there is a need to study and evaluate effects of certain conditions for anti-aging of the brain. Nutrient supplementation can modify the brain function. The chemistry and function of both the developing and the mature brain are influenced by diet (Fernstrom, *Am J Clinical Nutrition* 71:1669S-1673S, 2000). Clinical, biochemical, and pathological aspects have shown a correlation between mental symptoms, especially depression and cognitive decline, with high incidence of folate deficiency (Bottiglieri et al., *J Neurol Neurosurg Psychiatry* 69:562, 2000). In the present study, consequences of folic acid supplementation on brain dysfunction as a result of aging were studied in cerebral cortex, mid brain, and cerebellar regions of rat brain. This study was carried out on 6-, 11-, and 16-month-old rats, which received folic acid at a dose of 5 mg/kg body weight/day for a period of 8 weeks. Respective control groups of the same age groups were also taken. At the end of the treatment duration, behavioral studies were performed and later the animals were killed for various biochemical and histological investigations. Results indicated significant improvement in memory as assessed by active avoidance, passive avoidance, and plus maze tests in the folic acid supplemented aged animals. Significant improvement was also seen in the cellular protective mechanisms where by the activity of superoxide dismutase and catalase enzymes increased in folic acid supplemented group and so was the glutathione content. Increased lipid peroxidation content, a marker of aging, was also found to be decreased during folic acid supplementation in all the three regions of brain in

our study. Thus, it can be concluded that folic acid helps in improving the memory status by reducing oxidative stress and maintaining the integrity of neurons during aging.

PMID: 21170581

Ⓒ

„Folic acid, neurodegenerative and neuropsychiatric disease.“

Ⓓ

Folsäure, neurodegenerative und neuropsychiatrische Erkrankung.

Ⓔ

„Φολικό οξύ, νευροεκφυλιστική και νευροψυχιατρική νόσος.“

Ⓕ

Acide folique, maladie neurodégénérative et neuropsychiatrique.

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Listová kyselina, neurodegenerativní a neuropsychiatrické poruchy.

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[Curr Mol Med.](#) 2009 Apr;9(3):315-23.

## **Folic acid, neurodegenerative and neuropsychiatric disease.**

[Kronenberg G](#), [Colla M](#), [Endres M](#).

**Source** Klinik und Poliklinik für Neurologie, Charité-Universitätsmedizin Berlin, Campus Mitte, Charitéplatz 1, D-10117 Berlin, Germany.

### **Abstract**

Folic acid plays an important role in neuroplasticity and in the maintenance of neuronal integrity. Folate is a co-factor in one-carbon metabolism during which it promotes the regeneration of methionine from homocysteine, a highly reactive sulfur-containing amino acid. Methionine may then be converted to S-adenosylmethionine (SAM), the principal methyl donor in most biosynthetic methylation reactions. On the cellular level, folate deficiency and hyperhomocysteinemia exert multiple detrimental effects. These include induction of DNA damage, uracil misincorporation into DNA and altered patterns of DNA methylation. Low folate status and elevated homocysteine increase the generation of reactive oxygen species and contribute to excitotoxicity and mitochondrial dysfunction which may lead to apoptosis. Strong epidemiological and experimental evidence links derangements of one-carbon metabolism to vascular, neurodegenerative and neuropsychiatric disease, including most prominently cerebral ischemia, Alzheimer's dementia and depression. Although firm evidence from controlled clinical trials is largely lacking, B-vitamin supplementation and homocysteine reduction may have a role especially in the primary prevention of stroke and dementia as well as as an adjunct to antidepressant pharmacotherapy.

PMID: 19355913

GB

„Dietary supplementation with apple juice decreases endogenous amyloid-beta levels in murine brain.“

DE

Dietätische Supplementierung mit Apfelsaft senkt den endogenen Amyloid-beta-Spiegel im Mäusehirn.

GR

„Διατροφικά συμπληρώματα με χυμό μήλου μειώνουν τα ενδογενή επίπεδα βήτα-αμυλοειδούς πρωτεΐνης στον εγκέφαλο ποντικών.“

FR

Une supplémentation du régime alimentaire avec du jus de pomme réduit les niveaux de bêta-amyloïde endogènes dans le cerveau des murins.

CZ

Potravinová suplementace jablečným džusem snižuje hladiny endogenního beta-amyloidu v myším mozku.

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[J Alzheimers Dis.](#) 2009;16(1):167-71. doi: 10.3233/JAD-2009-0959.

## **Dietary supplementation with apple juice decreases endogenous amyloid-beta levels in murine brain.**

[Chan A](#), [Shea TB](#).

**Source** Department of Biological Sciences, University of Massachusetts-Lowell, Lowell, MA, USA.

### **Abstract**

Folate deficiency has been associated with age-related neurodegeneration. We demonstrate herein that dietary deficiency in folate and vitamin E, coupled pro-oxidant stress induced by dietary iron, increased amyloid-beta (A $\beta$ ) levels in normal adult mice. This increase was potentiated by apolipoprotein E (ApoE) deficiency as shown by treatment of transgenic mice homozygously lacking murine ApoE. Dietary supplementation with apple juice concentrate in drinking water alleviated the increase in A $\beta$  for both mouse genotypes. These findings provide further evidence linking nutritional and genetic risk factors for age-related neurodegeneration, and underscore that dietary supplementation may be useful to augment therapeutic approaches.

PMID: 19158432