

## Folic Acid Supplementation Improved Cognitive Function in Older Adults

Durga J, van Boxtel MPJ, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. *Lancet* 2007;369:208–16.

### Study Overview

**Objective.** To determine if folic acid supplementation affects age-related cognitive decline in older adults.

**Design.** Randomized, double-blind, placebo-controlled study with an intent-to-treat analysis.

**Setting and participants.** Men and postmenopausal women aged 50 to 70 years from the Netherlands were enrolled. This was a substudy of the Folic Acid and Carotid Intima-media Thickness (FACIT) trial, a study evaluating folic acid supplementation on progression of atherosclerosis. Participants were excluded if they had dementia; plasma homocysteine concentration  $< 13 \mu\text{mol/L}$  or  $> 26 \mu\text{mol/L}$ ; serum vitamin B<sub>12</sub> concentration  $< 200 \text{ pmol/L}$ ; renal, intestinal, or thyroid disease; or if they used any medication that might impact folate metabolism or used vitamin B supplements.

**Intervention.** Participants were randomized to 800  $\mu\text{g}$  folic acid daily or matching placebo for 3 years.

**Main outcome measures.** The primary outcome measures were change in cognitive function from baseline to the end of the study, as measured by tests of memory, sensorimotor speed, complex speed, information processing speed, and word fluency; and change in global cognitive function (average of the 5 tests). Variations of the tests used at baseline were used at the end of the study. Although not an outcome measure, participants were screened for dementia using the Mini-Mental State Examination.

**Main results.** 406 participants were randomized to folic acid and 413 were randomized to placebo. Participant characteristics and scores on cognitive tests were similar between the 2 groups at baseline. After 3 years, serum folate levels were significantly greater in the folic acid group compared with the placebo group (76 nmol/L versus 13 nmol/L;  $P < 0.001$ ), and plasma total homocysteine levels were significantly lower (10.1  $\mu\text{mol/L}$  versus 13.4  $\mu\text{mol/L}$ ;  $P < 0.001$ ). After 3 years, there was a significant difference in mean memory scores (0.13 [95% confidence interval {CI}, 0.03–0.23];

$P = 0.01$ ) and mean scores in information processing speed (0.087 [95% CI, 0.02–0.16];  $P = 0.02$ ) between the folic acid and placebo groups. There was also a borderline statistically significant difference in mean scores in sensorimotor speed between the folic acid and placebo groups (0.06 [95% CI, –0.001 to 0.13];  $P = 0.055$ ).

**Conclusion.** Supplementation with folic acid over a 3-year period appears to reduce the rate of cognitive decline in older adults.

### Commentary

Cognitive decline is associated with normal aging but can also be associated with progression to dementia. Although potential risk factors associated with cognitive decline have been suggested in observational studies [1], few interventions have been evaluated. Low serum folic acid is believed to be related to memory loss; however, prior randomized trials have been inconsistent with regard to the effect of folate supplementation on cognitive function [2]. Much of this discrepancy may stem from small sample sizes, the chosen dose of folic acid, duration of therapy, and method for assessing cognitive decline. To address these limitations, Durga et al performed a well-designed randomized trial of folate supplementation, one of the largest interventional trials of folic acid and cognitive function to date. Patients were evaluated over 3 years, and the dose of folic acid was relatively modest. Additionally, rather than relying on relatively insensitive instruments to detect global cognitive decline (eg, the Mini-Mental State Examination), domain-specific instruments were used to assess cognitive function.

Some limitations should be noted. The investigators included only participants who would be expected to benefit most from folic acid supplementation—patients who had moderately elevated homocysteine levels (a risk factor for vascular events). However, this group represents only 22% of the original population (3044 of 4200 participants were excluded due to low plasma total homocysteine). Although this restriction produced a relatively homogeneous sample and helps support the validity of the findings, the generalizability of the study to a larger population is limited. An

additional limitation of the study, as with any study evaluating cognitive function, is the difficulty extrapolating the clinical significance of a change of a few points on a memory test. Despite these limitations, the study suggests that folic acid supplementation can reduce the rate of cognitive decline within some domains in older adults with moderately elevated homocysteine levels.

### Applications for Clinical Practice

In addition to its chemoprotective role in colorectal and breast cancer, folic acid supplementation may delay cognitive decline in older adults, although the population included in this study may not be representative of the general population.

While it is likely premature to recommend folic acid supplementation to all patients specifically to reduce cognitive decline associated with aging, this study adds to the growing evidence in favor of dietary supplementation with folic acid.

—Review by Harvey J. Murff, MD, MPH

### References

1. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. *Neurology* 1998;51:728–33.
2. Malouf M, Grimley EJ, Areosa SA. Folic acid with or without vitamin B12 for cognition and dementia. *Cochrane Database Syst Rev* 2003;(4):CD004514.

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