

# Daily folic acid supplementation for 3 years improved cognitive function in older persons

Durga J, van Boxtel MP, 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.

**Clinical impact ratings:** Mental Health ★★★★★☆☆ GIM/FP/GP ★★★★★☆☆ Genetics ★★★★★☆☆ Geriatrics ★★★★★☆☆  
Neurology ★★★★★☆☆

## QUESTION

In older persons, does daily folic acid supplementation for 3 years improve cognitive function?

## METHODS

**Design:** Randomized placebo-controlled trial (Folic Acid and Carotid Intima-media Thickness [FACIT] trial).

**Allocation:** Concealed.\*

**Blinding:** Blinded {clinicians, participants, data collectors, outcome assessors, data safety and monitoring committee, manuscript writers, and data analysts/statisticians}†.\*

**Follow-up period:** 3 years.

**Setting:** Gelderland province, the Netherlands.

**Participants:** 818 men and postmenopausal women 50 to 70 years of age (mean age 60 y, 72% men) recruited from municipal and blood bank registries who reported ≥ 80% compliance during a 6-week placebo run-in period. 51 participants had 1 household member who was also enrolled and received the same treatment. Exclusion criteria included plasma total homocysteine level at screening < 13 μmol/L or > 26 μmol/L if possibly caused by serum vitamin B<sub>12</sub> level < 200 pmol/L, renal or thyroid disease, or use of drugs that affect folate metabolism; intestinal disease; and use of vitamin B supplements or drugs that affect atherosclerotic progression.

**Intervention:** Folic acid, 800 μg/d (*n* = 405), or matching placebo (*n* = 413).

**Outcomes:** 3-year change in performance for 5 tests of cognitive function (memory, sensory-motor speed, complex speed, information-processing speed, and word fluency) and global cognitive function (mean of the 5 domains).

**Patient follow-up:** 98% (intention-to-treat analysis).

## MAIN RESULTS

At 3 years, the folic acid group improved more than the placebo group for global cognitive function and memory and declined less for information-processing speed (Table).

Groups did not differ for change in sensory-motor speed, complex speed, and word fluency (Table).

## CONCLUSION

Daily folic acid supplementation for 3 years improved some aspects of cognitive function in older persons.

*Sources of funding:* Netherlands Organisation for Health Research and Development.

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\*See Glossary.

†Information provided by author.

## Daily folic acid vs placebo for cognitive function in older persons at 3 years‡

Outcomes	Mean change from baseline <sup>§</sup>		Difference in change between groups (95% CI)
	Folic acid	Placebo	
Global cognitive function	0.07	0.02	0.05 (0.004 to 0.10)
Memory	0.48	0.35	0.13 (0.03 to 0.23)
Sensory-motor speed	-0.04	-0.11	0.06 (-0.001 to 0.13)
Complex speed	-0.03	-0.06	0.04 (-0.05 to 0.12)
Information-processing speed	-0.07	-0.16	0.09 (0.02 to 0.16)
Word fluency	-0.002	0.07	-0.07 (-0.19 to 0.05)

‡CI defined in Glossary.

§Mean Z scores.

## COMMENTARY

Despite suggestive epidemiologic associations, trials of supplementation with folate, vitamin B<sub>12</sub>, or both to reduce homocysteine levels have shown little effect on cognitive performance in older persons (1, 2). In the FACIT trial by Durga and colleagues, participants 50 to 70 years of age with elevated homocysteine levels were randomized to treatment with folate or placebo for a longer time than in previous studies. Those in the folate group showed better results for speed of information processing and memory. Several factors, including the small effect size and strict inclusion criteria, limit the clinical relevance and generalizability of results.

That some participants were functionally deficient in folate was shown by the decline in homocysteine levels following folate supplementation. Post hoc subgroup analyses showed that the effects of folate were greater in participants who had vitamin B<sub>12</sub> levels < 250 pmol/L. These levels are often associated with occult vitamin B<sub>12</sub> deficiency, and consequently, high homocysteine levels. Without measuring the level of methylmalonic acid, it is unclear whether this subgroup was also functionally deficient in vitamin B<sub>12</sub>.

The results of the FACIT trial may not apply to persons in the United States and Canada, where food is fortified with folic acid. 27%

of all participants screened for this trial had homocysteine levels ≥ 13 μmol/L. For U.S. women of similar age, 13.2 μmol/L is the 95th percentile of homocysteine levels, whereas 10.74 μmol/L is the 75th percentile and 14.99 μmol/L is the 95th percentile for men (3). The results of the FACIT trial require replication with further elucidation of the populations who might benefit from folic acid supplementation.

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## References

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