

Does daily multivitamin supplementation improve memory in older adults?

According to results of a randomized cognitive ancillary trial involving 3,562 men and women (67%) with an average age of 71 years, after 1 year of taking multivitamin/mineral supplementation, participants' **performance improved beyond the effect of practice alone on a web-based test of immediate memory recall** (number of words recalled out of 20 presented at 3-second intervals), from 7.1 to 7.81 words versus 7.2 to 7.65 words in the placebo group. No improvement occurred in tests of novel object recognition, memory recall at 15 minutes, or in a test of executive function.

FAST TRACK

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EXPERT COMMENTARY

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Preservation of function, both physical and cognitive, is key to long-term health and well-being. Age-related loss of function drives millions of people to spend an enormous amount of money each year on unregulated therapies—vitamins, supplements, infusions, hormones, and

“natural” products—all toward the promise of improvement or preservation of physical strength, sexual function, and maintenance of lean body mass and cognitive abilities. Yeung and colleagues set out to determine whether the daily use of a multivitamin/mineral supplement (Centrum Silver) would impact memory in older adults.¹

Details of the study

The COSMOS-Web study was designed to test the authors' primary hypothesis that daily dietary flavanols would improve memory over 1 year.¹ This study was embedded within the larger COSMOS (COcoa Supplement and Multivitamin Outcomes Study) trial, in which 21,442 people were recruited to assess the impact of flavanols and multivitamin supplements on cardiovascular and cancer outcomes.

Results of another ancillary study, the COSMOS-Mind trial (n = 2,262, average age 73, 60% female), reported no improvement

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with flavanols compared with placebo on a battery of tests of cognitive function administered by phone. In COSMOS-Mind, however, it was concluded that a daily multivitamin/mineral supplement improved the composite score of cognitive tests compared with placebo, particularly in participants with a history of cardiovascular disease.²

The COSMOS-Web trial recruited an additional cohort within the larger COSMOS trial from 2016–2017 (n = 3,562, average age 71, 67% female) to participate in this study specifically geared to assess memory, using the web-based ModRey test (a test of memory validated for use in a non-impaired population). To qualify for enrollment, participants had to have access to an internet-connected computer. They were randomly assigned in a 2 x 2 study design to receive a daily multivitamin supplement or placebo; each of these cohorts was further divided into a flavanol supplementation or a placebo group. Analysis of the data showed no association between flavanol use and performance on any of the measures of memory or cognitive function.³

The COSMOS-Web trial assessed episodic recall, a function of hippocampus-mediated cognition that is particularly vulnerable to the effects of aging as demonstrated previously by neuroimaging and neuropsychological studies. The authors deployed a battery of 3 tests via a web platform for patients to complete online and independently.

The prespecified primary outcome was performance on episodic recall as measured by the ModRey test after 1 year of supplementation with multivitamins versus placebo. The ModRey test presents a series of 20 words at 3-second intervals to participants. At the conclusion of the last word, participants were asked to recall as many words as they could; after completing the 2 additional tasks, participants were asked again to recall the words. A secondary outcome of this test is the ratio of delayed to immediate recall.

Two additional tests were administered to assess cognitive performance related to different brain regions, the ModBent test



(assessing novel object recognition) and the Flanker task (a measure of executive function). There was a placebo run-in phase during which participants' adherence to daily supplement intake was ascertained. Participants were excluded if they demonstrated less than 75% adherence to study pills during the run-in placebo phase. The cognitive tasks were presented at study initiation and at yearly intervals for 3 years. The authors chose to use the results at 1 year as their primary outcome to assess the impact of supplementation during the period when adherence would be highest.

Results. At baseline, the placebo cohort recalled 7.2 words of 20 compared with 7.1 in the supplement group. In both groups there was a practice effect, with improvement in scores in the placebo group to 7.65 words and in the multivitamin group to 7.81 words. The improvement from baseline was statistically significantly better (0.71 words) in the multivitamin cohort than in the placebo group (0.45 words). There was no improvement in either group in the ModRey memory retention test (ability to recall the words after 15 minutes) or in the ModBent or Flanker tests. At 3 years of treatment, the placebo

group improved by 0.92 words (SD, 3.22) whereas the multivitamin group improved by 1.13 words (SD, 3.39). These changes remained statistically significant.

The group with cardiovascular disease had lower baseline performance on the ModRey test. With supplementation, however, the improvement in this cohort was significantly greater than in those without cardiovascular disease at 1 year. The authors acknowledged that the changes were small and may not have been noticeable to the individuals, but they argued that even small changes as demonstrated in this study can have large health benefits at a population level.

The results of the COSMOS-Web trial corroborate the findings of the COSMOS-Mind study with respect to the benefits of multivitamin/mineral supplementation on cognitive test performance, particularly in a population with preexisting cardiovascular disease. The tests used across the 2 studies were different, which lends greater reliability to the findings.

Study strengths and limitations

A major strength of this study is its careful, rigorous design as a double-blind, placebo-controlled trial in a large patient population. Great care was devoted to ensuring study medication adherence. Another strength is that the cognitive tests chosen for the COSMOS-Web trial have been validated in cognitively normal populations, not those already impaired.

A limitation, however, is in the demographics of the study. The patient population was overwhelmingly White (93%), 67% were female, and they were well educated (94.8% having completed some college or beyond). Their baseline health was good; only 4.7% had a history of cardiovascular disease. Although generalizability of the study results from this population may be concerning, relative benefits of supplementation in this healthy, generally well-nourished and educated group may be lower than might be expected in a more nutritionally and educationally challenged population.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

In this well-designed, randomized controlled trial by Yeung and colleagues, multivitamin/mineral supplementation improved performance on a test of immediate episodic memory at 1, 2, and 3 years compared with placebo. Given the simplicity and safety of this intervention, even with a small effect size, it makes sense to advise older patients that daily multivitamin use provides micronutrients and vitamins that may be absent in the diet or poorly absorbed by older adults. Whether this highly specific improvement in a test of hippocampal function translates into overall cognitive performance with aging remains a question.

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Finally, the difference between the placebo and active supplementation groups was small. Whether this less-than-1-word difference in immediate memory recall is noticeable by a patient is questionable. Both groups improved in their test performance over time—a consequence of serial cognitive tests of any kind. Although the authors calculated that the difference in recall translates to a 3-year reduction in age-related memory decline, it is hard to reconcile that with the fact that both groups actually improved over the 3 years of the study. ●

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