REVIEW

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Over-the-Counter Supplement Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia

A Systematic Review

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Background: Optimal interventions to prevent or delay cognitive decline, mild cognitive impairment (MCI), or dementia are uncertain.

Purpose: To summarize the evidence on efficacy and harms of over-the-counter (OTC) supplements to prevent or delay cognitive decline, MCI, or clinical Alzheimer-type dementia in adults with normal cognition or MCI but no dementia diagnosis.

Data Sources: Multiple electronic databases from 2009 to July 2017 and bibliographies of systematic reviews.

Study Selection: English-language trials of at least 6 months' duration that enrolled adults without dementia and compared cognitive outcomes with an OTC supplement versus placebo or active controls.

Data Extraction: Extraction performed by a single reviewer and confirmed by a second reviewer; dual-reviewer assessment of risk of bias; consensus determination of strength of evidence.

Data Synthesis: Thirty-eight trials with low to medium risk of bias compared ω-3 fatty acids, soy, ginkgo biloba, B vitamins, vitamin D plus calcium, vitamin C or β-carotene, multi-ingredient supplements, or other OTC interventions with placebo or other supplements. Few studies examined effects on clinical Alzheimer-type dementia or MCI, and those that did suggested no benefit. Daily folic acid plus vitamin B_{12} was associated with improvements in performance on some objectively measured memory tests that were statistically significant but of questionable clinical significance. Moderate-strength evidence showed that vitamin E had no benefit on cognition. Evidence about effects of ω-3 fatty acids, soy, ginkgo biloba, folic acid alone or with other B vitamins, β-carotene, vitamin C, vitamin D plus calcium, and multivitamins or multi-ingredient supplements was either insufficient or low-strength, suggesting that these supplements did not reduce risk for cognitive decline. Adverse events were rarely reported.

Limitation: Studies had high attrition and short follow-up and used a highly variable set of cognitive outcome measures.

Conclusion: Evidence is insufficient to recommend any OTC supplement for cognitive protection in adults with normal cognition or MCI.

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Fear of losing cognitive ability to Alzheimer disease and related dementias drives a growing industry of over-the-counter (OTC) supplements intended to boost brain health and prevent or slow cognitive decline. The Alzheimer's Research and Prevention Foundation recommends that people "be sure to take [their] vitamins and memory-specific nutrients" and suggests optimal dosages for an array of vitamins and nutrients (1). An estimated 63% of older adults use OTC supplements (2). In 2015, Americans spent $37 billion on OTC supplements and $91 million on ginkgo biloba–just one of a growing number of supplements marketed to boost memory (3).

See also:

Related articles. 30, 39, 63
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Web-Only
Supplement
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Whether any dietary or herbal supplement or specific food can prevent or delay cognitive decline is unclear. This review summarizes the evidence on efficacy and harms of OTC supplements to prevent or delay cognitive decline, mild cognitive impairment (MCI), or clinical Alzheimer-type dementia.

METHODS

We developed and followed a standard protocol (https://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2202).

Data Sources and Searches

We searched Ovid MEDLINE, PsycINFO, EMBASE, and the Cochrane Central Register of Controlled Trials for relevant literature published between 2009 and July 2017 (see Part A of the **Supplement**, available at Annals.org, for search strategies). We identified studies published before 2009 by searching citations in systematic reviews and pertinent studies (4–8).

Table 1. Number of Studies With Low or Moderate Risk of Bias, by Intervention Type and Population

Intervention	Studies in Adults With Normal Cognition, *k*		Studies in Adults With MCI, *k*	
	Versus Placebo	Versus Active Control	Versus Placebo	Versus Active Control
ω-3 fatty acids	7	1 (vs. B vitamins)	1	0
Soy	5	0	1	0
Ginkgo biloba	3	0	2	0
B vitamins	Folic acid: 1 Folic acid plus B_{12}: 2 Folate plus B_6 plus B_{12}: 2	1 (vs. different B vitamin groups)	Folic acid plus B_6 plus B_{12}: 2	0
Vitamin D plus calcium	1	0	0	0
Vitamin E	3	0	1	0
Vitamin C/β-carotene	1	0	0	0
Multi-ingredient supplements	6	0	1	0
Other OTC interventions	4	0	0	0
Total*	35	2	7	0

MCI = mild cognitive impairment; OTC = over-the-counter.
* Total is >38 because some studies had multiple groups.

Study Selection

Two investigators independently reviewed titles and abstracts and screened the full text of potentially eligible references. We included randomized and nonrandomized controlled trials of any OTC supplements that enrolled adults with normal cognition or MCI. Because the review focused on prevention, we excluded studies of adults with dementia. We included only studies that followed participants for at least 6 months, reported incident MCI or dementia (our main outcome of interest) or cognitive performance outcomes, and were published in English. There were no restrictions on sample size or comparator type. Disagreements about eligibility were resolved by consensus.

Data Extraction and Quality Assessment

One reviewer extracted information on study design, population, intervention, comparator, setting, and funding source from eligible studies. For each study, 2 reviewers read the full text and independently rated risk of bias for the overall study and for each outcome and time point as low, medium, or high according to Agency for Healthcare Research and Quality (AHRQ) guidance (9). Outcomes and adverse events were extracted from studies with low to medium risk of bias. A second reviewer checked the quality of all data.

Data Synthesis and Analysis

We summarized results for studies with low to medium risk of bias by intervention, baseline cognitive status (presumed normal cognition or MCI), and outcome. Because studies used highly variable outcome measures, neuropsychological tests were categorized according to the following 4 specific cognitive domains to facilitate analysis: executive function, attention, and processing speed; memory; language; and visuospatial abilities (see **Supplement Table A1** for the list of cognitive outcomes that were used and **Supplement Table A2** for measurement properties, including change indices, of neuropsychological tests that were used). We grouped executive function, attention, and processing speed because a large number of cognitive tests frequently measure all 3 of these related domains. Our preliminary work found that studies analyzed and reported cognitive test results in widely varying ways, frequently making it impossible to determine effect size or assess whether between-group differences in scores or subscores were clinically meaningful. We instead analyzed and report cognitive test results by direction of effect and statistical significance.

When there were at least 2 studies or 1 large study (>500 participants) for a treatment comparison, 2 reviewers graded strength of evidence for each outcome on the basis of study limitations, directness, consistency, and precision; otherwise, strength of evidence was graded as insufficient (10). Assessments were confirmed by consensus.

Role of the Funding Source

This review was funded by the National Institute on Aging and the AHRQ. These agencies and members of the National Academies Committee on Preventing Dementia and Cognitive Impairment helped refine the scope and reviewed a draft report of findings. The authors are solely responsible for the content, preparation, and writing of the manuscript and the decision to submit it for publication.

RESULTS

We identified 63 publications of 56 unique studies covering 13 categories of OTC treatments (**Appendix Figure**, available at Annals.org). A third of the studies were at least partially funded by industry. Eighteen were assessed as having high risk of bias and were not further analyzed. **Table 1** depicts the interventions and populations of the 38 studies judged as having low or medium risk of bias. Detailed evidence tables and risk-of-bias assessments are presented for studies involving adults with normal cognition in Part B of the **Supplement** and for studies involving adults with MCI in Part C of the **Supplement**; these tables are also available in the parent technical report (11). **Table 2** summarizes the strength of evidence for the findings.

Table 2. Effect of OTC Supplement Interventions Versus Control on Cognitive Outcomes in Adults With Normal Cognition and MCI*

Outcome	Normal Cognition		MCI	
	Conclusion	Strength of Evidence (Justification)	Conclusion	Strength of Evidence (Justification)
ω-3 fatty acids vs. placebo (*k* = 7; *n* = 21 027)				
Dementia	No benefit (*k* = 1; *n* = 12 536; 6 y; adults with diabetes or glucose intolerance)	Low (high study limitations, unknown consistency, not precise)	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No benefit (*k* = 4; *n* = 16 431; 6 y)	Low (medium study limitations, not direct, not precise)	Limited data	Insufficient (*k* = 1; *n* < 500)
Multidomain tests	No benefit (*k* = 1; *n* = 744; 2 y)	Low (medium study limitations, not direct, unknown consistency, not precise)	Limited data	Insufficient (*k* = 1; *n* < 500)
Executive function/attention/ processing speed	No benefit (*k* = 5; *n* = 5079; 6 y)	Low (medium study limitations, not direct, not precise)	Limited data	Insufficient (*k* = 1; *n* < 500)
Memory	No benefit (*k* = 1; *n* = 3428; 4 y)	Low (medium study limitations, not direct, not precise)	Limited data	Insufficient (*k* = 1; *n* < 500)
ω-3 fatty acids vs. B vitamins (folate, B_6, and B_{12}) (*k* = 1; *n* = 885)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No benefit (*k* = 1; *n* = 885; 4 y)	Low (medium study limitations, not direct, not precise, unknown consistency)	No data	Insufficient
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/ processing speed	No data	Insufficient	No data	Insufficient
Memory	No benefit (*k* = 1; *n* = 885; 4 y)	Low (medium study limitations, not direct, not precise, unknown consistency)	No data	Insufficient
ω-3 fatty acids plus B vitamins (folate, B_6, and B_{12}) vs. B vitamins alone (folate, B_6, and B_{12}) (*k* = 1; *n* = 884)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No benefit (*k* = 1; *n* = 884; 4 y)	Low (not direct, not precise, unknown consistency)	No data	Insufficient
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/ processing speed	No data	Insufficient	No data	Insufficient
Memory	No benefit (*k* = 1; *n* = 884; 4 y)	Low (not direct, not precise, unknown consistency)	No data	Insufficient
Soy vs. placebo (*k* = 5; *n* = 829)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	Unable to draw conclusion	Insufficient (medium study limitations, not direct, not precise)	Limited data	Insufficient (*k* = 1; *n* < 500)
Multidomain tests	Unable to draw conclusion	Insufficient (medium study limitations, not direct, not precise)	No data	Insufficient
Executive function/attention/ processing speed	No benefit (*k* = 5; *n* = 829; 2.5 y)	Low (medium study limitations, not precise)	No data	Insufficient
Memory	No benefit (*k* = 5; *n* = 829; 2.5 y)	Low (medium study limitations, not precise)	Limited data	Insufficient (*k* = 1; *n* < 500)

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Table 2–Continued

Outcome	Normal Cognition		MCI	
	Conclusion	Strength of Evidence (Justification)	Conclusion	Strength of Evidence (Justification)
Ginkgo biloba vs. placebo (*k* = 3; *n* = 6041)				
Dementia	No benefit (*k* = 3; *n* = 5407; 6 y; adults aged >70 y)	Low (medium study limitations, not precise)	Limited data	Insufficient (*k* = 1; *n* < 500)
MCI	Limited data	Insufficient (*k* = 1; *n* < 500)	Not applicable	Not applicable
Brief cognitive test	No data	Insufficient	No data	Insufficient
Multidomain tests	No benefit (*k* = 1; *n* = 3069; 6 y; adults aged >70 y)	Low (medium study limitations, not direct, unknown consistency, not precise)	No data	Insufficient
Executive function/attention/ processing speed	No benefit (*k* = 1; *n* = 5079; 6 y; adults aged >70 y)	Low (medium study limitations, not direct, not precise)	Limited data	Insufficient (*k* = 1; *n* < 500)
Memory	No benefit (*k* = 1; *n* = 3187; 6 y; adults aged >70 y)	Low (medium study limitations, not direct, not precise)	No data	Insufficient
B vitamin: folic acid vs. placebo (*k* = 1; *n* = 818)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No data	Insufficient	No data	Insufficient
Multidomain tests	Unable to draw conclusion	Insufficient (not direct, unknown consistency, not precise)	No data	Insufficient
Executive function/attention/ processing speed	Unable to draw conclusion	Insufficient (not direct, unknown consistency, not precise)	No data	Insufficient
Memory	Unable to draw conclusion	Insufficient (not direct, unknown consistency, not precise)	No data	Insufficient
B vitamin: folic acid plus B_{12} vs. placebo (*k* = 2; *n* = 3819)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	Unable to draw conclusion	Insufficient (not direct, unknown consistency, not precise)	No data	Insufficient
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/ processing speed	No benefit (*k* = 2; *n* = 3456; 2 y)	Moderate (not direct, unclear precision)	No data	Insufficient
Memory	Improved (*k* = 2; *n* = 3456; 2 y)	Low (not direct, not precise)	No data	Insufficient
B vitamin: folate plus B_6 plus B_{12} vs. placebo (*k* = 2; *n* = 1524)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No benefit (*k* = 2; *n* = 1124; 4 y)	Low (not direct, not precise)	Limited data	Insufficient (*k* = 1; *n* < 500)
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/ processing speed	Unable to draw conclusion	Insufficient (not direct, not consistent, not precise)	No data	Insufficient
Memory	No benefit (*k* = 2; *n* = 1538; 3.3 y)	Low (medium study limitations, not precise)	Limited data	Insufficient (*k* = 1; *n* < 500)
Vitamin D plus calcium vs. placebo (*k* = 1; *n* = 4143)				
Dementia or MCI	No benefit (*k* = 1; *n* = 4122; 7 y)	Low (medium study limitations, unknown consistency)	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	Unable to draw conclusion	Insufficient (medium study limitations, not direct, not precise, unknown consistency)	No data	Insufficient
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/ processing speed	No benefit (*k* = 1; *n* = 4122; 7 y)	Low (medium study limitations, not direct, unknown consistency)	No data	Insufficient
Memory	No benefit (*k* = 1; *n* = 4122; 7 y)	Low (medium study limitations, not direct, unknown consistency)	No data	Insufficient

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Table 2–Continued

Outcome	Normal Cognition		MCI	
	Conclusion	Strength of Evidence (Justification)	Conclusion	Strength of Evidence (Justification)
Vitamin E vs. placebo (*k* = 3; *n* = 12 830)				
Dementia	No data	Insufficient	No benefit (*k* = 1; *n* = 516; 3 y)	Low (medium study limitations, not direct, unknown consistency)
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No benefit (*k* = 2; *n* = 7497; 4 y; for women)	Moderate (medium study limitations, not direct)	Unable to draw conclusion	Insufficient (medium study limitations, not direct, unknown consistency, unclear precision)
Multidomain tests	No benefit (*k* = 2; *n* = 7497; 4 y; for women)	Moderate (medium study limitations, not direct)	Unable to draw conclusion	Insufficient (medium study limitations, not direct, unknown consistency, not precise)
Executive function/attention/ processing speed	No data	Insufficient	Unable to draw conclusion	Insufficient (medium study limitations, not direct, unknown consistency, not precise)
Memory	No benefit (*k* = 2; *n* = 7497; 4 y; for women)	Moderate (medium study limitations, not direct)	Unable to draw conclusion	Insufficient (medium study limitations, not direct, unknown consistency, not precise)
Vitamin C vs. placebo (*k* = 1; *n* = 2471)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No benefit (*k* = 1; *n* = 2271; 4 y; for women)	Low (not direct, unknown consistency, not precise)	No data	Insufficient
Multidomain tests	No benefit (*k* = 1; *n* = 2271; 4 y; for women)	Low (not direct, unknown consistency, not precise)	No data	Insufficient
Executive function/attention/ processing speed	No data	Insufficient	No data	Insufficient
Memory	No benefit (*k* = 1; *n* = 2271; 4 y; for women)	Low (not direct, unknown consistency, not precise)	No data	Insufficient
β-Carotene vs. placebo (*k* = 1; *n* = 2471)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No benefit (*k* = 1; *n* = 2271; 4 y; for women)	Low (not direct, unknown consistency, not precise)	No data	Insufficient
Multidomain tests	No benefit (*k* = 1; *n* = 2271; 4 y; for women)	Low (not direct, unknown consistency, not precise)	No data	Insufficient
Executive function/attention/ processing speed	No data	Insufficient	No data	Insufficient
Memory	No benefit (*k* = 1; *n* = 2271; 4 y; for women)	Low (not direct, unknown consistency, not precise)	No data	Insufficient
Multivitamin vs. placebo (*k* = 4; *n* = 27 613)				
Dementia	No benefit (*k* = 1; *n* = 20 469; 5 y)	Low (medium study limitations, unknown consistency, not precise)	No data	Insufficient
MCI	No benefit (*k* = 1; *n* = 20 469; 5 y)	Low (medium study limitations, unknown consistency, not precise)	Not applicable	Not applicable
Brief cognitive test	Unable to draw conclusion	Insufficient (medium study limitations, not direct, not precise)	Limited data	Insufficient (*k* = 1; *n* < 500)
Multidomain tests	No benefit (*k* = 1; *n* = 5296; unclear timing)	Low (medium study limitations, not direct, unknown consistency)	No data	Insufficient
Executive function/attention/ processing speed	No benefit (*k* = 2; *n* = 992; 1 y)	Low (medium study limitations, not direct, unclear precision)	No data	Insufficient
Memory	No benefit (*k* = 2; *n* = 5516; unclear timing)	Low (medium study limitations, not direct, not precise)	No data	Insufficient

MCI = mild cognitive impairment; OTC = over-the-counter.
* Evidence based on trials with low to moderate risk of bias; trials with high risk of bias were not included in the analyses.

ω-3 Fatty Acids

Normal Cognition

Seven randomized trials with low to medium risk of bias (n = 21 027) that enrolled adults with presumed normal cognition compared ω-3 fatty acids with placebo (12–18). Interventions lasted from 6 months to more than 6 years. Five trials reported cognitive exclusion criteria, including a Mini-Mental State Examination (MMSE) score less than 22 (14, 15), less than 24 (13), or less than 26 (16, 17) out of a possible 30 points. One study used only docosahexaenoic acid (DHA) (17); all others used some combination of eicosapentaenoic acid (EPA) plus DHA. The largest study (n = 15 077) allowed participation of adults who were already using ω-3 supplementation (18). Populations varied in baseline health and risk for cognitive decline. Participants included patients with diabetes or impaired glucose tolerance (18), patients with a history of ischemic heart disease (12) or coronary artery disease (14), and healthy adults (13, 15–17).

None of the studies reported on incident Alzheimer-type dementia or MCI. A large multinational study of adults with diabetes or impaired glucose tolerance (n = 15 077) used a combination of clinical diagnosis or an MMSE score less than 24 and found no difference in probable dementia incidence between the EPA/DHA group and the placebo group at a median follow-up of 6.2 years (hazard ratio [HR], 0.93 [95% CI, 0.86 to 1.0]) (18).

Overall, studies provided low-strength evidence suggesting that ω-3 fatty acids do not improve cognitive performance in adults with normal cognition compared with placebo. Of 67 reported cognitive tests—including 9 brief cognitive tests (12, 14, 17, 18); 1 test of multidomain neuropsychological performance (13); 32 tests of executive function, attention, and processing speed (13, 15–18); and 25 memory tests (13, 15–17)—only 5 showed scores that were statistically significantly better in ω-3–treated groups than in control groups. These 5 tests were administered in 2 studies that had relatively short follow-up (6 months) and included fewer than 5% of the total participants in the 7 studies (16, 17).

Four studies did not report adverse events, and no studies reported statistically significant differences in adverse events between the ω-3 and placebo groups. The parent technical report provides details on adverse events (11).

Subgroups were examined in 4 studies. No statistically significant differences in effect were found by age (12, 14, 15, 18), sex (14, 15, 18), time since myocardial infarction (14), or diabetes status (18).

One study (n = 884) with 4-year follow-up examined the comparative effectiveness of ω-3 fatty acids and B vitamins on cognition (12). No between-group differences were found for any cognitive outcome between ω-3 fatty acids (alone or in combination with B vitamins) and B vitamins alone. Adverse events were not reported.

MCI

Evidence was insufficient for benefits of ω-3 fatty acids on cognitive outcomes compared with placebo after 1 year in the single small study of adults with MCI that we identified (n = 36) (19). No serious adverse events were reported.

Soy

Normal Cognition

Five randomized trials with low to medium risk of bias that enrolled 35 to 350 participants (n = 829) and lasted 6 months to 2.5 years compared soy supplementation with placebo (20–25). Populations included older adults without dementia (20) and generally healthy postmenopausal women (21, 23–25). Baseline testing excluded persons with cognitive impairment in 2 of the studies (20, 21). Mean reported baseline MMSE scores ranged from 28 to 29 (20–23).

None of the trials reported MCI or Alzheimer-type dementia outcomes. Evidence was deemed insufficient to determine soy's effect on brief cognitive test performance (21, 25) and multidomain neuropsychological test performance (21, 24) and low-strength for soy having no effect on executive function, attention, and processing speed (20, 21, 23–25) or memory (20–25) for up to 2.5 years.

Two studies reported no serious adverse events and no statistically significant differences in adverse events between the soy and placebo groups (21, 25).

MCI

Evidence was insufficient to determine any beneficial effect on cognitive outcomes from soybean-derived phosphatidylserine at 2 doses (100 and 300 mg daily) compared with placebo after 9 months in a single small study of adults with MCI (n = 78) (22). No serious adverse events were reported.

Ginkgo biloba

Normal Cognition

Three randomized trials (n = 5559) with low to medium risk of bias that enrolled older adults with presumed normal cognition compared ginkgo biloba (240 mg/d) versus placebo for up to 6 years (26–29). Sample sizes ranged from 118 to 3069 participants. All assessed cognition at baseline and excluded persons with dementia (26, 28) or MCI (27, 29). The GEM (Ginkgo Evaluation of Memory) study (26, 28) enrolled a subsample of persons with MCI (approximately 16% of the total study sample). Age inclusion criteria were older than 70 years (29), older than 75 years (26, 28), and older than 85 years (27).

Two of the trials provided low-strength evidence on Alzheimer-type dementia incidence (26, 28, 29); neither showed protective benefits of ginkgo biloba versus placebo (26, 28, 29). Similarly, low-strength evidence suggested that ginkgo biloba does not improve multidomain neuropsychological test performance (28); executive function, attention, and processing speed (28); or memory (27, 28).

All 3 studies reported adverse events, including stroke and cardiac events. Neither the GEM study (26, 28) nor the study by Vellas and colleagues (29) (n = 5437) found statistically significant differences in adverse events, such as stroke or cardiac events, between the ginkgo biloba and placebo groups. In the small study of adults aged 85 years or older (n = 122), Dodge and colleagues reported a larger number of strokes and transient ischemic attacks in the ginkgo biloba group than the placebo group over 3.5 years (7 vs. 0; P = 0.01) (27).

Vellas and colleagues assessed 13 planned subgroups and found cognitive benefits with ginkgo biloba in men, persons who consumed alcohol at baseline, and adults who continued the intervention for at least 4 years (29). Results were not adjusted for multiple testing (all differences would have been nonsignificant with a Bonferroni correction) (29). The GEM study reported no effect modification for sex, age, race, APOE status, education, or MCI at baseline and a significant treatment-by-group interaction (P = 0.02) favoring placebo for participants with baseline cardiovascular disease (28).

MCI

Evidence was insufficient to determine any effects of ginkgo biloba versus placebo on cognitive outcomes in adults with MCI. A 6-month study (n = 160) showed a small benefit with ginkgo biloba compared with placebo in 2 measures of executive function, attention, and processing speed (30). However, cognitive benefits were not observed in the GEM study (n = 482), which found no difference in rates of Alzheimer-type dementia between the ginkgo biloba and placebo groups after a median follow-up of more than 6 years (26).

B Vitamins

Folic Acid

One study (n = 818) in adults with presumed normal cognition (mean MMSE score of 29) provided insufficient evidence for benefits of daily folic acid (0.8 mg) compared with placebo over 3 years (31). Investigators recruited persons with high homocysteine levels that were likely due to suboptimal folate concentrations. Diagnostic outcomes (MCI and Alzheimer-type dementia), brief cognitive test performance, and adverse events were not reported. Three of 5 cognitive tests related to multidomain neuropsychological test performance, executive function, and memory showed favorable results with folic acid versus placebo.

Folic Acid and B_{12}

Two trials (n = 3819) in adults with presumed normal cognition (mean MMSE score of 28 or modified Telephone Interview for Cognitive Status [TICS-m] score of 27 out of 50]) compared daily folic acid (0.4 mg) plus B_{12} (0.1 to 0.5 mg) versus placebo for 2 years (32, 33). One trial (n = 2919) recruited persons with presumed B_{12} deficiency (elevated homocysteine levels ≥12 μmol/L) (32). Neither study reported MCI or Alzheimer-type dementia outcomes. Medium-strength evidence showed no difference between treatment groups for executive function, attention, and processing speed, and low-strength evidence showed benefit with folic acid and B_{12} for memory (32, 33). Evidence was insufficient for brief cognitive test performance because of inconsistency of effect direction between trials. Adverse events were not reported. Post hoc subgroup analyses found a slight benefit for memory with folic acid and B_{12} compared with placebo in participants with low baseline levels of holotranscobalamin (another biomarker associated with vitamin B deficiency) (33).

Folate or Folic Acid, B_6, and B_{12}

Normal Cognition. Two trials (n = 1524) in adults with presumed normal cognition (mean MMSE score of 29 and Isaac Set Test score of 36 out of 40]) compared the combination of daily folate (0.56 to 1.0 mg), B_6 (3 to 10 mg), and B_{12} (0.2 to 0.5 mg) versus placebo for 2 to 4 years (12, 34). One recruited adults with homocysteine levels of at least 13 μmol/L (34). Low-strength evidence showed no difference between the treatment and placebo groups in brief cognitive test performance or memory (12, 34). Evidence was insufficient to conclude a possible effect of treatment on executive function, attention, and processing speed (34). Adverse events were not reported.

Subgroup analysis findings were mixed in 1 study. Andreeva and colleagues reported that participants with a history of myocardial infarction or unstable angina who received folate, B_6, and B_{12} performed worse on 1 of 8 cognitive tests at 4 years than participants of the same age who received placebo. Participants aged 65 years or older receiving folate, B_6, and B_{12} had lower brief cognitive test scores and performed worse on 1 memory test than participants of the same age who received placebo (12).

MCI. Evidence was insufficient for no benefit for brief cognitive test performance or memory from 1 study of folic acid, B_6, and B_{12} in adults with MCI (n = 217) because of limited data (single study with <500 participants) (35–38). Serious adverse events were not reported.

Vitamin D Plus Calcium

One trial (n = 4143) compared daily vitamin D_3 (0.01 mg) plus calcium (1000 mg) versus placebo for a mean of 7.8 years (39). Participants in the intervention group were also allowed an additional supplement (600 mg of vitamin D and 1000 mg of calcium daily) if desired. Participants included women aged 65 years or older with normal cognition confirmed through cognitive testing at baseline. Low-strength evidence showed no benefit of vitamin D plus calcium compared with placebo for MCI or Alzheimer-type dementia (pooled as a single outcome; HR, 0.94 [CI, 0.72 to 1.24]; P = 0.68); executive function, attention, and processing speed; or memory. Evidence on brief cognitive test performance was insufficient. No adverse events were reported.

Vitamin E

Normal Cognition

Three trials (n = 12 830) in women (40, 41) and men (42) with presumed normal cognition compared daily vitamin E (270 to 400 mg) with placebo for 9 to 10 years. Baseline cognition was not reported in 1 study (40), but a mean TICS score of 34 out of 41 and a mean Memory Impairment Screen score of 7.6 out of 8 were reported in the others (41, 42). One study reported diagnostic outcomes. The study of men reported no difference in incidence of dementia at 10 years (low-strength evidence) (42) but reported no other cognitive outcomes. Results were extracted at 4 years for both studies in women because of higher attrition at later time points (40, 41). Moderate-strength evidence showed no difference between vitamin E and placebo in brief cognitive test performance, multidomain neuropsychological test performance, or memory. Executive function, attention, and processing speed and adverse events were not reported, and subgroup analyses did not differ by any of the participant characteristics examined.

MCI

One trial (n = 516) in adults with amnestic MCI compared vitamin E (2000 IU/d) with placebo for 3 years (43). Low-strength evidence showed no benefit with vitamin E for incident Alzheimer-type dementia (probability of progression to Alzheimer disease: HR, 1.02 [CI, 0.74 to 1.41]; P = 0.91; Z score for Clinical Dementia Rating Sum of Boxes, 0.03 [CI not reported]). Evidence was insufficient to draw conclusions for any other cognitive test outcomes, including brief cognitive test performance; multidomain neuropsychological test performance; executive function, attention, and processing speed; or memory. No between-group differences in adverse events were reported.

Vitamin C or β-Carotene

One trial (n = 2824) randomly assigned women to daily vitamin C (500 mg), β-carotene (50 mg), or placebo for 9 years (results for the vitamin E group were discussed earlier) (40). Women were presumed to have normal cognition, although baseline cognition was not reported. Results were extracted at 4 years because of high attrition at later time points. Diagnostic outcomes were not reported. Low-strength evidence showed no difference for either vitamin C or β-carotene versus placebo for brief cognitive test performance, multidomain neuropsychological test performance, or memory. Adverse events were not reported. Subgroup analyses of cognitive results reported benefit with β-carotene for participants with low dietary intake of β-carotene at baseline (P = 0.02). Among participants with cardiovascular events during follow-up, vitamin C was associated with better brief cognitive test performance.

Multivitamins and Multi-ingredient Supplements

Normal Cognition

Four studies (total n = 27 613) of adults with presumed normal cognition compared multivitamins with placebo (44–47). Only 1 reported baseline cognition (mean TICS score of 34) (46). Multivitamin interventions included varying doses and combinations of vitamins A, B, C, D, and E; β-carotene; biotin; cobalamin; copper; folic acid; iodine; iron; magnesium; manganese; niacin; pantothenic acid; pyridoxine; riboflavin; selenium; thiamine; and zinc (44–47). Study participants included physicians aged 65 years or older (46), adults older than 65 years (47), women older than 60 years (44), and adults aged 40 to 80 years who were at serious risk for death (45, 47). Study samples were large, ranging from 1130 to 20 536 participants, and study durations ranged from 6 months to 8.5 years.

Low-strength evidence from 1 trial (n = 20 536) showed no difference in diagnosis of MCI or Alzheimer-type dementia over 5 years (45). For cognitive test results, low-strength evidence showed no differences between multivitamins and placebo in multidomain neuropsychological test performance (46); executive function, attention, and processing speed (44, 47); or memory (44, 46). No statistically significant difference was found between groups in brief cognitive test performance. Adverse events were not reported.

Overall, no differences were found in subgroup analyses of these multivitamin supplement studies. In 3 trials, cognitive results did not differ by lifestyle factors, including smoking history, alcohol use, fruit and vegetable intake, or nutritional deficiency (not defined) (44, 46, 47). Two trials assessed the effect of baseline cognition, education, prior supplement use, and comorbidities on cognitive outcomes (46, 48). Final cognitive and diagnostic results did not differ by cognitive performance at baseline; academic degree attained; job training; body mass index; diabetes; hypertension; hyperlipidemia; depression; or prior use of folates, hormone replacement therapy, or vitamin deficiency.

Two additional studies involving persons with normal cognition examined treatment effects on cognitive outcomes for other multivitamin or multi-ingredient interventions, but evidence was not assessed because of the small size of the studies (48, 49).

MCI

Evidence was insufficient to determine any benefit of combined daily vitamin E (300 mg) and vitamin C (400 mg) on cognitive outcomes compared with placebo after 1 year in a single study of adults with MCI (n = 256) (50). No serious adverse events were reported.

Other OTC Interventions

Evidence was insufficient to draw conclusions for dehydroepiandrosterone (n = 227) (51), red clover (n = 30) (52), resveratrol (n = 46) (53), and plant sterols or stanols (n = 57) (54) for adults with presumed normal cognition because of the small size of the single studies for each of these interventions.

DISCUSSION

Our review found that only a small number of OTC supplements on the market have been evaluated for potential effects on cognition and dementia. Available evidence from trials with low to medium risk of bias showed that most of the OTC interventions studied have no proven benefit in preventing or delaying cognitive decline, MCI, or dementia in older adults. Moderate-strength evidence showed that vitamin E has no benefit on cognition. Evidence about effects of ω-3 fatty acids, soy, ginkgo biloba, folic acid alone or with other B vitamins, β-carotene, vitamin C, vitamin D plus calcium, and multivitamins or multi-ingredient supplements was either insufficient or low-strength, suggesting that the supplements did not reduce risk for MCI, Alzheimer-type dementia, or cognitive decline. Other OTC interventions, such as dehydroepiandrosterone and resveratrol, also had insufficient evidence from which to draw conclusions.

The few available data for vitamin B_{12} showed mixed findings. There was moderate-strength evidence that vitamin B_{12} plus folic acid had no effects on executive function, attention, and processing speed compared with placebo and low-strength evidence that it provided benefit (of questionable clinical significance) for brief cognitive test performance and memory. When vitamin B_6 was added to the combined therapies, benefits for brief cognitive test performance and memory were no longer observed.

Most OTC supplements are based on doses that could be derived from dietary intake and that are hypothesized to be less likely to have adverse effects than "therapeutic" doses. These supplements may work better in persons who have insufficient intake or levels of the nutrient or vitamin. Generally, baseline deficiencies were reported only in studies of B vitamins. Interactions with metabolic, environmental, and other nutrition intake factors could overwhelm possible small effects related to nutritional doses.

Our literature searches identified several other relevant systematic reviews (7, 55–57). Unlike prior reviews, which typically focused on older adults with cognitive decline or dementia, our review focused on older adults without preexisting dementia, with most trials targeting those with no evidence of impairment. Also, we did not analyze trials with high risk of bias. Nonetheless, our findings of little evidence of clinically important benefits of OTC supplements on cognition and prevention of cognitive decline are consistent with the findings of the other reviews.

The available evidence is scant and has several limitations. We frequently judged evidence to be insufficient and were not able to draw clear conclusions because of methodological inadequacies, including high attrition and short follow-up. When multiple studies examined the effects of the same supplements on similar cognitive outcomes, the results could not be pooled because of substantial differences in the outcome measures used. Most studies focused on cognitive performance test outcomes rather than clinical diagnostic outcomes or global function. Few studies enrolled persons with MCI or included the incident MCI or Alzheimer-type dementia outcomes. Many studies did not report baseline cognitive inclusion or exclusion criteria, and in other studies, definitions of "normal" cognition were applied inconsistently. There were few reports of serious adverse events. In most cases, adverse events were not assessed; in the few studies where serious adverse events were reported, sample sizes were inadequate to assess whether they differed from those in the placebo groups.

Overall, this review showed little to no benefit of OTC supplement use in preventing cognitive decline, MCI, or Alzheimer-type dementia. Evidence is insufficient for health care providers to recommend any of the wide variety of OTC dietary supplements to patients with normal cognition or MCI. More and larger trials that test effects of supplements and use clinically important outcomes are urgently needed. Unfortunately, searches of ClinicalTrials.gov show only 2 trials that are ongoing (NCT02750293 and NCT01669915) and several that are past their anticipated end date but have not been reported or updated in 2 years.

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Appendix Figure. Evidence search and selection.