Received: 12 April 2022 | Revised: 8 July 2022 | Accepted: 10 July 2022

DOI: 10.1002/alz.12767

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Effects of cocoa extract and a multivitamin on cognitive function: A randomized clinical trial

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Abstract

Introduction: Dietary supplements are touted for cognitive protection, but supporting evidence is mixed. COSMOS-Mind tested whether daily administration of cocoa extract (containing 500 mg/day flavanols) versus placebo and a commercial multivitamin-mineral (MVM) versus placebo improved cognition in older women and men.

Methods: COSMOS-Mind, a large randomized two-by-two factorial 3-year trial, assessed cognition by telephone at baseline and annually. The primary outcome was a global cognition composite formed from mean standardized (z) scores (relative to baseline) from individual tests, including the Telephone Interview of Cognitive Status, Word List and Story Recall, Oral Trail-Making, Verbal Fluency, Number Span, and Digit Ordering. Using intention-to-treat, the primary endpoint was change in this composite with 3 years of cocoa extract use. The pre-specified secondary endpoint was change in the composite with 3 years of MVM supplementation. Treatment effects were also examined for executive function and memory composite scores, and in pre-specified subgroups at higher risk for cognitive decline.

Results: A total of 2262 participants were enrolled (mean age = 73y; 60% women; 89% non-Hispanic White), and 92% completed the baseline and at least one annual assessment. Cocoa extract had no effect on global cognition (mean z-score = 0.03, 95% CI: -0.02 to 0.08; $P = .28$). Daily MVM supplementation, relative to placebo, resulted in a statistically significant benefit on global cognition (mean z = 0.07, 95% CI 0.02 to 0.12; $P = .007$), and this effect was most pronounced in participants with a history of cardiovascular disease (*no history*: 0.06, 95% CI 0.01 to 0.11; *history*: 0.14, 95% CI -0.02 to 0.31; interaction, nominal $P = .01$). Multivitamin-mineral benefits were also observed for memory and executive function. The cocoa extract by MVM group interaction was not significant for any of the cognitive composites.

Discussion: Cocoa extract did not benefit cognition. However, COSMOS-Mind provides the first evidence from a large, long-term, pragmatic trial to support the potential efficacy of a MVM to improve cognition in older adults. Additional work is needed to

confirm these findings in a more diverse cohort and to identify mechanisms to account for MVM effects.

KEYWORDS
aging, clinical trial, cocoa extract, cognition, cognitive function, flavanols, multivitamin, older adults

Highlights

- COSMOS-Mind was a large simple pragmatic randomized clinical trial in older adults conducted by mail and telephone.
- The trial used a two-by-two factorial design to assess treatment effects of two different interventions within a single large study.
- We found no cognitive benefit of daily cocoa extract administration (containing 500 mg flavanols) for 3 years.
- Daily multivitamin-mineral (MVM) supplementation for 3 years improved global cognition, episodic memory, and executive function in older adults.
- The MVM benefit appeared to be greater for adults with cardiovascular disease.

1 | BACKGROUND

There is an urgent need to identify effective strategies to preserve cognitive function to mitigate the heavy societal burden associated with Alzheimer's disease (AD) and related dementia, which affect more than 46 million people worldwide.[1] No interventions to prevent cognitive decline in asymptomatic older adults have been approved by the United States Food and Drug Administration (FDA), and to date, there is insufficient evidence to support a clinical benefit of any pharmacologic treatment for adults with mild cognitive impairment due to AD.[2,3] Identifying a safe, affordable, and accessible intervention to protect cognitive function against decline in older adults is a pressing public health priority.[4]

Cocoa, in its unprocessed form, contains high quantities of catechins and epicatechins, members of a subclass of flavonoids known as flavanols,[5,6] and modest amounts of theobromine (an alkaloid of the cacao bean) and caffeine. Dietary consumption of cocoa flavanols may slow cognitive decline through improved cerebral vasodilation,[7] blood flow, perfusion and angiogenesis.[8,9] Epicatechin, the most common flavanol in cocoa, is rapidly absorbed, readily crosses the blood-brain barrier, can be detected in the brain,[10] and may have accumulating physiological effects at higher levels.[11,12] Much of the support for cognition-enhancing effects of flavonoids in healthy older adults comes from epidemiological studies,[13,14] and a few small clinical trials.[15–17] Memory and executive function appear to benefit the most, particularly with higher amounts of cocoa flavanols (500–750 mg/day), according to a recent review.[18]

Individual micronutrients and minerals target multiple biologic pathways that support normal body and brain function,[19] and deficiencies in older adults may increase risk for cognitive decline and dementia.[20] Trials of single nutrients such as folic acid with or without other B vitamins,[21–24] omega-3 fatty acids,[25,26] and vitamin D[20,27,28] on cognition have yielded mixed results, which could reflect either no benefit or study design issues that impede cross-study comparisons. Some of these issues relate to the specific micronutrients tested (alone or in combination), the specific cognitive tests administered, the outcome measure (single test vs. composite score), and participant demographics and nutritional status.[29,30] Although not without controversy, particularly with respect to potential cognition-enhancing effects of B vitamins,[21,22] the conclusion of meta-analytic reviews is that the evidence is insufficient to encourage care providers to recommend use of individual nutrient supplements for brain health.[31,32]

Longer-term daily intake (>12 months) of a multivitamin-mineral (MVM) alone or with other dietary supplements to enhance global cognitive function in older adults (≥65 years) has been examined in just one large randomized controlled trial (RCT), which included only male physicians.[33] Further study is needed given their widespread use in the general population.[34] Here we tested whether daily treatment with cocoa extract (CE) and/or a MVM for 3 years protected cognitive function in older adults.

2 | METHODS

2.1 | Study design

COSMOS-Mind (COcoa Supplement and Multivitamin Outcomes Study of the Mind) was an ancillary study to a large pragmatic, placebo-controlled, 2 × 2 factorial clinical trial testing the effects of daily supplementation with cocoa extract (CE) and/or a MVM on cardiovascular and cancer outcomes.[35–37] Given that no additive or synergistic effects were expected with CE and MVM supplementation, the 2 × 2 factorial design provided an efficient strategy to examine treatment effects of two different agents within a single trial. The CE (Mars Edge,

of Mars, Inc.) contained 500 mg of cocoa flavanols, including 80 mg (-)-epicatechins and modest amounts of theobromine (~50 mg/day) and caffeine (~15 mg/day) that likely enhance flavanols' central and vascular effects.[38,39] The 500 mg/day of cocoa flavanols exceeds mean reported intake[40] and is consistent with amounts tested in short-term cardiovascular trials.[41] The essential nutrients contained in the MVM (Centrum Silver; Pfizer Consumer Healthcare, now Haleon) are listed in Table S6. COSMOS-Mind examined the effects of these supplements on cognitive function, and the details of study design, participant demographics, and baseline characteristics are published.[42] The study was conducted in accordance with The Code of Ethics of the World Medical Association, and was approved by the Institutional Review Board of Wake Forest University School of Medicine.

2.2 | Participants

Enrollment of two thousand parent trial participants was targeted for COSMOS-Mind. Parent trial eligibility criteria included: (1) no history of myocardial infarction (MI) or stroke (history of other cardiovascular events including transient ischemic attack, congestive heart failure, coronary artery bypass graft, angioplasty, and stent was permitted); (2) no history of cancer within the past 2 years (excluding non-melanoma skin cancer); (3) no serious illness precluding participation; (4) not taking cocoa or vitamin/mineral supplements, or, willing to forego use during the trial; (5) no reported extreme sensitivity to cocoa products or caffeine; (6) successful completion of ≥2-month placebo run-in with ≥75% study pill adherence; and (7) not currently participating in another clinical trial. Additional COSMOS-Mind eligibility criteria included: (1) ≥65 years of age; (2) not taking insulin for diabetes; and (3) able to complete the telephone cognitive assessment (to screen out participants with significant impairment). Participants provided informed consent and received a $15 gift card upon completion of each assessment.

2.3 | Randomization and masking

Randomization was controlled by the parent trial using a computer-generated sequential list of random allocations for the four treatment combinations.[36,37] The random allocation sequence was created using SAS statistical software (version 9.4) and was stratified by sex, age (5-year bins), and recruitment source (Brigham and Women's Hospital, Women's Health Initiative). All trial investigators, examiners, and participants were masked to treatment group assignment.

2.4 | Procedures

As previously described,[42] parent trial participants were recruited through mailings to Women's Health Initiative Extension Study participants and by Brigham and Women's Hospital to participants contacted for, but not randomized into, the vitamin D and OmegA-3 TriaL, and through commercial mailing lists and media campaigns. As a result, 35,669 adults began a placebo run-in, of which 21,442 (60%) were ultimately randomized into COSMOS. During the placebo run-in, eligible candidates received an invitation to also participate in COSMOS-Mind. Interested individuals were contacted to: (1) provide more information about the ancillary study, (2) test for hearing acuity, and (3) schedule the baseline telephone cognitive assessment. Individuals from traditionally underrepresented groups in research (self-identified as American Indian/Alaska Native, Asian/Pacific Islander, Black/African American, Hispanic; completing 12 years or less of education) were prioritized in the COSMOS-Mind initial contact queue (pre-randomization) to increase their representation in the sample. Demographics and baseline anthropometrics (height, weight) and medical history were provided by participants via questionnaires.

RESEARCH IN CONTEXT

1. **Systematic review**: The literature was reviewed using PubMed and MEDLINE. Much of the support for potential cognitive benefits of cocoa flavanols in older adults is based on observational studies. Only a few controlled trials have examined the effects of a multivitamin-mineral (MVM) supplement on cognition for older adults.
2. **Interpretation**: There was no cognitive improvement with daily intake for 3 years of cocoa extract containing 500 mg/day cocoa flavanols. However, we provide the first evidence in a long-term, randomized controlled trial of older women and men that daily use of a safe, readily accessible, and low-cost MVM can improve cognition. This finding could have important public health implications for brain health and resilience against future cognitive decline.
3. **Future directions**: Our results challenge the current status quo regarding the efficacy of MVM supplementation to improve cognitive function and set the stage for new avenues of research to identify mechanisms and alternate approaches involving combination therapy.

2.5 | Outcomes

A standardized telephone cognitive battery was administered at baseline and annually for 3 years to assess general cognitive status, episodic memory and executive function. Tests included the 50-point modified Telephone Interview for Cognitive Status (TICSm with 10-minute short delay word list recall), an additional 40-minute Long Delay Word List Recall,[43] immediate and delayed Story Recall (SRI & II),[44] Oral Trail-Making Test Part B (OTMT-B, log transformed; Part A was administered for practice only),[45] Verbal Fluency by category (VF-C) and letter (VF-L),[46] Number Span (NS),[47] and Digit Ordering Test (DOT).[48]

Details about testing procedures, including hearing acuity screening, and administration and scoring are published.[42]

The primary outcome was a global cognition composite (reported as a z-score based on baseline data from the study cohort) formed from mean standardized (z) scores of pre-specified individual test metrics, with higher scores reflecting better performance. Key secondary outcomes included an episodic memory composite (Long Delay Word List Recall, SRI, SRII) and an executive function composite (OTMT-B, VF-C, VF-L, NST, DOT) that were also formed using mean standardized (z) scores.

Tertiary outcomes included the Cognitive Change Index (CCI),[49] a self-report measure of cognitive concerns, and the short 15-item version of the Geriatric Depression Scale (GDS-SF) to permit subgroup analyses for individuals scoring low and high on these scales. Adverse events were recorded by the parent trial, and events reported during a cognitive assessment were relayed to the COSMOS team for tracking and follow-up.

2.6 | Statistical analyses

The primary and secondary endpoints have been previously described[42] and were pre-specified in the protocol (provided as a supplement). We followed the intention-to-treat approach: all participants were grouped as originally randomly assigned and scores from all cognitive assessments (baseline and Years 1, 2 and 3) for all participants were included in analyses. Scores were used as dependent variables in linear mixed effects models. Time was a categorical factor. No covariates were included in models for the primary comparisons. As specified in the protocol, inference was based on the mean difference of scores obtained across follow-up assessments relative to the baseline score for participants assigned to receive CE versus CE-placebo (primary endpoint), and for participants assigned to receive MVM versus MVM-placebo (key secondary endpoint). That is, for means at Years 0, 1, 2, and 3 represented by μ_0, μ_1, μ_2, and μ_3, this can be expressed as $(\mu_1 + \mu_2 + \mu_3)/3 - \mu_0$. Separate linear contrasts were used to compare active and placebo arms by CE and by MVM group assignment. For example, the contrast for CE effects is described by $[(\mu_{CE1} + \mu_{CE2} + \mu_{CE3})/3 - \mu_{CE0}] - [(\mu_{CE\text{-}PL1} + \mu_{CE\text{-}PL2} + \mu_{CD\text{-}PL3})/3 - \mu_{CE\text{-}PL0}]$, where μ_{CE} and $\mu_{CE\text{-}PL}$ represent the marginal means for CE and CE-placebo at each time point, respectively. This corresponds to an intention-to-treat approach in which all data are included in analyses irrespective of follow-up. We chose to parameterize our primary and secondary endpoints as mean differences from baseline across follow-up to avoid making specific assumptions about the nature of intervention effects (for example, we did not assume that intervention effects accumulated linearly and base comparisons on differences between slopes) and to treat any differences at each of the time points equally. We explored interactions between the CE and MVM treatments and the consistency of CE and MVM treatment effects among subgroups (using forest plots[50]) based on sex, and baseline age (<70 or ≥70 years), body mass index (BMI; < 25, 25-29, ≥30 kg/m^2), general cognitive function (TICSm tertiles), subjective cognitive concerns (CCI median split), depressive symptoms (GDS-SF median split), type 2 diabetes, history of hypertension, and history of CVD (based on self-report of transient ischemic attack, congestive heart failure, coronary artery bypass graft, angioplasty, or stent). Subgroups were pre-specified given their possible associations with cognitive and/or cardiovascular response to the interventions.[51–53] Multiple imputation by fully conditional specification was used to examine the influence of missing data.[54] No adjustments were made for multiple comparisons. The targeted 2000-person sample was projected to provide >90% power to detect an effect size of 0.10 standard deviations (see Statistical Power supplement for more information. Analyses were performed using SAS v9.4.

3 | RESULTS

COSMOS-Mind participants were enrolled from August 2, 2016 to August 17, 2017. A total of 5342 individuals screening for the parent trial were approached for ancillary study enrollment. Phone calls were attempted for 3223 individuals (60%) and of these, 2262 (70%) were enrolled in COSMOS-Mind (Figure 1). Baseline characteristics and baseline cognitive test scores were well balanced across treatment groups (Table 1 and Table S1). Of enrolled participants, 2082 (92%) completed the cognitive assessment at Year 1, 1906 (84%) at Year 2, 1790 (79%) at Year 3, and 1732 (77%) in all 3 years of follow-up. Relative to participants who completed all assessments, those missing at least one assessment were more likely to be from underrepresented racial or ethnic groups, reported less physical activity and chocolate intake and more smoking, tended to have lower education and baseline TICSm scores, and higher prevalence of type 2 diabetes (Table S2). Characteristics of participants with no follow-up data (N = 180) are provided in Table S3. Self-reported compliance (pill count) was comparable across treatment groups (% taking ≥75% study pills in Years 1, 2, and 3: 92%, 88%, and 84%).

Figure 2A shows change in global cognition, relative to baseline, for participants assigned to CE (Figure 1, Groups 2 & 4) versus CE-placebo (Figure 1, Groups 1 & 3). Mean scores in both CE groups increased through the first 2 years (likely due to retest practice effects[55]) and then plateaued but did not differ significantly from one another. The mean change (CE minus CE-placebo) z-score for global cognition was 0.03 (95% CI: -0.02 to 0.08; P = .28). In contrast, Figure 2B shows a significant treatment effect of MVM (Figure 1, Groups 3 & 4) versus MVM-placebo (Figure 1, Groups 1 & 2) on global cognition (secondary endpoint), with a mean change (MVM minus MVM-placebo) z-score of 0.07 (95% CI: 0.02 to 0.12; P = .007). Baseline MVM use was not associated with MVM treatment response (*no prior use*: 0.062, 95% CI: -0.002 to 0.13; *prior use*: 0.077, 95% CI: 0.003 to 0.15; interaction, nominal P = .88).

In pre-specified subgroup analyses of the primary outcome (global cognition composite), forest plots of CE effects (Figure 2C) suggest that response may vary with baseline BMI. Figure 2D forest plots show a relative benefit of MVM versus MVM-placebo for participants with a

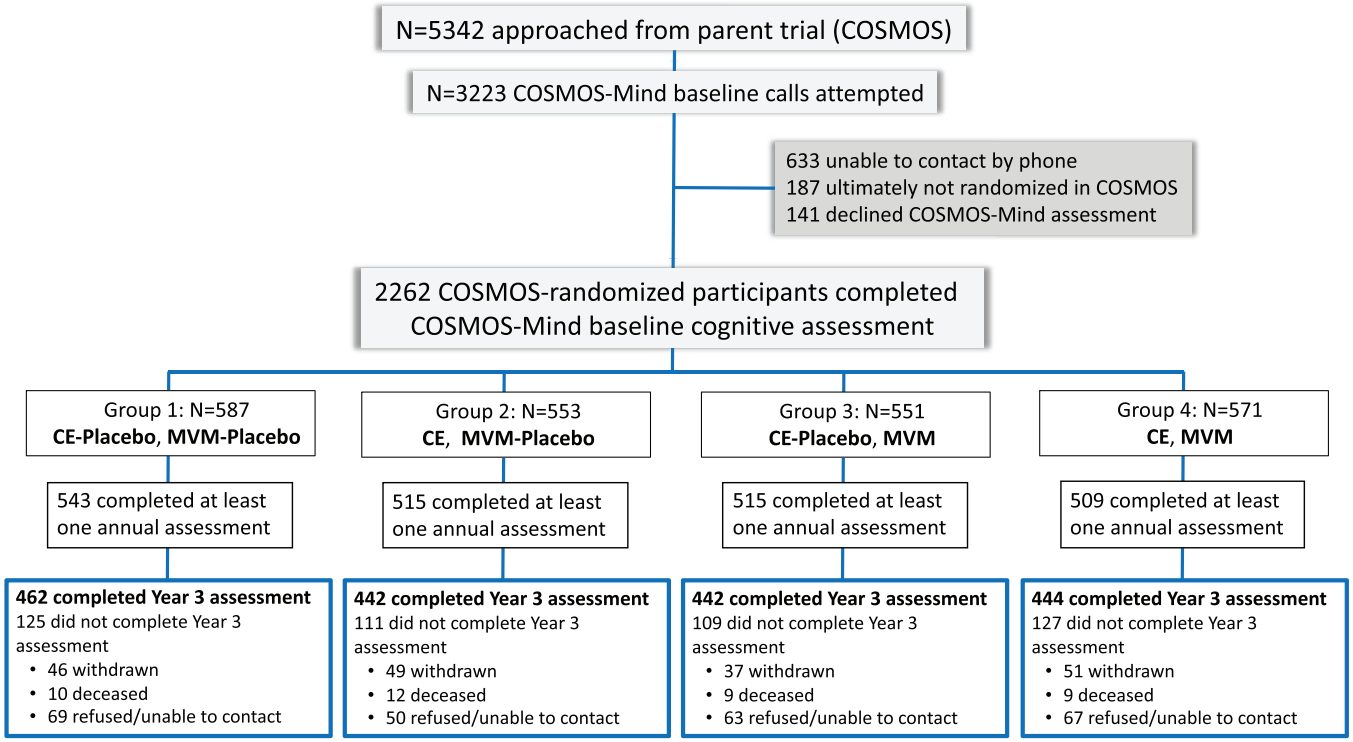

FIGURE 1 Consort diagram showing flow of participants from first approach through randomization to each of the four treatment combinations in the two-by-two factorial design. Abbreviations: CE, cocoa extract; MVM, multivitamin-mineral

CVD history (*no history*: 0.06, 95% CI: 0.01 to 0.11; *history*: 0.14, 95% CI: -0.02 to 0.31; interaction, nominal $P = .01$). As seen in Figure 3, at baseline, participants without CVD history outperformed those with CVD history on the global cognition composite (mean difference = 0.22, 95% CI: 0.08 to 0.37; $P = .003$); after Year 1, the MVM-placebo declined while the MVM group showed relative improvement (or protection against decline). There was no evidence of disproportionate loss of Year 3 data by CVD history (Table S4). The CVD history subgroup (compared to subgroup without CVD history) included more men, and tended to be older, have higher BMI, more hypertension, more statin use, more depression, less physical activity, and lower scores on the TICSm. When participants with CVD history were excluded in a sensitivity test from the overall analysis of MVM effects on the global cognition composite, the main MVM finding remained unchanged (mean change z-score = 0.06, 95% CI: 0.01 to 0.11; $P = .02$). That is, even though the pattern of results differed for subgroups with and without CVD at baseline, 3 years of MVM treatment improved global cognition for all participants, not just those with CVD history.

CE had no effect on the episodic memory composite (mean change z-score = 0.03, 95% CI: -0.04 to 0.09; $P = .40$) or on the executive function composite (mean change z-score = 0.03, 95% CI: -0.02 to 0.08; $P = .23$) (Figure S1). In contrast, but consistent with the positive MVM effect described above, MVM supplementation led to relative improvements both for memory (mean change z-score = 0.06, 95% CI: 0.002 to 0.13; $P = .04$) and for executive function (mean change z-score = 0.06, 95% CI: 0.01 to 0.11; $P = .02$) (Figure 4).

There was no evidence for an interaction between CE and MVM supplementation for the primary outcome (mean change z-score [95% CI]; CE-placebo/MVM-placebo: 0.15 [0.10 to 0.20]; CE/MVM-placebo: 0.15 [0.11 to 0.20]; CE-placebo/MVM: 0.20[0.15 to 0.24]; CE/MVM: 0.24 [0.19 to 0.29]; interaction, $P = .40$) or for the memory and executive function composites. That is, adding CE did not alter the benefit of MVM on cognition.

Multiple imputation provided no evidence that differential attrition biased the results (Table S5), and there were no safety concerns of supplement use during the trial.

4 | DISCUSSION

COSMOS-Mind is the first large-scale, long-term RCT to assess the effects of cocoa extract and a MVM supplement on global cognition in older women and men from the general population. Although our findings did not support a positive effect of CE (primary endpoint), cognition significantly benefited from 3 years of daily MVM use (secondary endpoint). Moreover, the results of pre-planned subgroup analyses indicated that participants with baseline history of CVD may show a more pronounced MVM benefit, suggesting either greater relative improvement or more protection from CVD-related cognitive decline.

Daily CE supplementation for 3 years did not affect cognitive function in our trial. Only a handful of controlled, shorter-term trials have examined the potential benefits of cocoa flavanols on cognition in older adults. While some studies showed cognitive benefits,[16,17,56] others

TABLE 1 Distribution of baseline characteristics for COSMOS-Mind participants by cocoa extract (CE) and multivitamin-mineral (MVM) treatment assignment

Characteristic[a]	Overall (*N* = 2262)	CE-Placebo, MVM-Placebo (*N* = 587)	CE, MVM-Placebo (*N* = 553)	CE-Placebo, MVM (*N* = 551)	CE, MVM (*N* = 571)
Age, mean (SD), years	72.97 (5.63)	73.10 (5.72)	73.21 (5.62)	72.86 (5.64)	72.70 (5.52)
Sex, *N* (%)					
Male	914 (40.4)	227 (38.7)	223 (40.3)	232 (42.1)	232 (40.6)
Female	1348 (59.6)	360 (61.3)	330 (59.7)	319 (57.9)	339 (59.4)
Race and ethnicity, *N* (%)					
American Indian/Alaska native	13 (0.6)	2 (0.3)	1 (0.2)	8 (1.5)	2 (0.4)
Asian/Pacific Islander	39 (1.7)	8 (1.4)	12 (2.2)	10 (1.8)	9 (1.6)
Black/African American	131 (5.8)	34 (5.8)	23 (4.2)	34 (6.2)	40 (7.0)
Hispanic	67 (3.0)	21 (3.6)	18 (3.3)	15 (2.7)	13 (2.3)
Multiracial/unknown/not reported	6 (0.3)	2 (0.3)	1 (0.2)	2 (0.4)	1 (0.2)
Non-Hispanic White	2006 (88.7)	520 (88.6)	498 (90.1)	482 (87.5)	506 (88.6)
Education, *N* (%)					
Did not complete high school	11 (0.5)	4 (0.7)	1 (0.2)	4 (0.7)	2 (0.4)
High school diploma or G.E.D.	258 (11.4)	69 (11.8)	68 (12.3)	58 (10.5)	63 (11.0)
Attended or graduated college	880 (38.9)	230 (39.2)	207 (37.4)	220 (39.9)	223 (39.1)
Post-college	1113 (49.2)	284 (48.4)	277 (50.1)	269 (48.8)	283 (49.6)
Body mass index, mean (SD), kg/m^2	27.64 (5.16)	27.48 (5.08)	27.86 (5.40)	27.57 (5.15)	27.65 (5.01)
Diabetes, *N* (%)	255 (11.3)	74 (12.6)	60 (10.9)	61 (11.1)	60 (10.5)
CVD history, *N* (%)[b]	197 (8.7)	59 (10.1)	36 (6.5)	44 (8.0)	58 (10.2)
Hypertension, *N* (%)	1333 (59.2)	358 (61.3)	321 (58.3)	318 (57.7)	336 (59.3)
Medication use, *N* (%)					
Antihypertensive	1013 (54.3)	327 (56.2)	292 (53.5)	296 (54.0)	314 (55.5)
Non-steroidal anti-inflammatory drug (NSAID)	627 (28.0)	168 (28.9)	152 (27.7)	137 (25.3)	170 (30.0)
Statin	976 (43.5)	262 (45.0)	240 (43.8)	224 (41.0)	250 (44.1)
Total metabolic equivalent (MET) hours of exercise per week, mean (SD)	22.41 (23.47)	21.51 (22.65)	22.55 (23.83)	23.57 (25.78)	22.07 (21.51)
Depression, *N* (%)	469 (20.9)	123 (21.2)	105 (19.1)	124 (22.8)	117 (20.6)
Smoking status, *N* (%)					
Never	1153 (51.8)	308 (53.4)	271 (49.5)	276 (51.2)	298 (53.1)
Past	1004 (45.1)	247 (42.8)	267 (48.7)	245 (45.5)	245 (43.7)
Current	68 (3.0)	22 (3.8)	10 (1.8)	18 (3.3)	18 (3.2)
Alcohol intake, *N* (%)					
Rarely/never	646 (29.4)	193 (33.6)	140 (25.9)	152 (28.4)	161 (29.4)
Monthly	152 (6.9)	37 (6.5)	42 (7.8)	38 (7.1)	35 (6.4)
Weekly	812 (36.9)	196 (34.2)	219 (40.5)	192 (35.8)	205 (37.5)
Daily	588 (26.8)	148 (25.8)	140 (25.9)	154 (28.7)	146 (26.7)
Baseline chocolate intake, *N* (%)					
Rarely/never	361 (16.5)	88 (15.4)	90 (16.7)	91 (17.0)	92 (16.8)
Monthly	307 (14.0)	77 (13.5)	74 (13.8)	70 (13.1)	86 (15.7)
Weekly	1274 (58.2)	337 (59.0)	319 (59.3)	312 (58.3)	306 (55.9)
Daily	249 (11.4)	69 (12.1)	55 (10.2)	62 (11.6)	63 (11.5)

(Continues)

TABLE 1 (Continued)

Characteristic[a]	Overall (*N* = 2262)	CE-Placebo, MVM-Placebo (*N* = 587)	CE, MVM-Placebo (*N* = 553)	CE-Placebo, MVM (*N* = 551)	CE, MVM (*N* = 571)
Baseline multivitamin-mineral use, *N* (%)	956 (42.5)	242 (41.7)	232 (42.3)	238 (43.4)	244 (42.7)
Baseline cognitive function, mean (SD)					
Global cognition composite	0.00 (1.00)	-0.05 (0.99)	0.02 (1.00)	0.05 (1.02)	-0.01 (0.99)
Executive function composite	0.00 (1.00)	-0.05 (0.99)	-0.03 (0.97)	0.08 (1.04)	0.01 (1.00)
Episodic memory composite	0.00 (1.00)	-0.03 (1.01)	0.07 (0.99)	0.01 (1.00)	-0.04 (1.01)
TICSm[c]	36.60 (3.89)	36.45 (3.88)	36.66 (3.96)	36.63 (3.84)	36.68 (3.87)
Long Delay Word List Recall[d]	3.02 (1.83)	2.95 (1.78)	3.05 (1.83)	3.09 (1.86)	2.99 (1.85)
Story Recall[e]					
Immediate	12.00 (3.85)	11.91 (3.91)	12.26 (3.77)	11.95 (3.79)	11.89 (3.91)
Delayed	10.77 (3.94)	10.77 (3.95)	10.98 (3.88)	10.75 (3.86)	10.57 (4.06)
Oral Trail-Making Test, median (IQR)[f]					
Part A	9 (8, 11)	9 (8, 11)	9 (8, 11)	9 (8, 11)	9 (8, 11)
Part B	30 (24, 46)	30 (23, 44)	30 (24, 46)	30 (24, 46)	31 (24, 48)
Verbal Fluency[g]					
Category	35.02 (8.24)	34.80 (7.88)	34.89 (8.26)	35.32 (8.33)	35.07 (8.51)
Letter	25.54 (8.12)	25.34 (7.82)	25.40 (7.67)	26.01 (8.29)	25.42 (8.65)
Number Span[h]					
Forward	8.19 (2.39)	8.10 (2.32)	8.06 (2.43)	8.39 (2.51)	8.22 (2.29)
Backward	6.87 (2.32)	6.85 (2.32)	6.86 (2.17)	6.97 (2.53)	6.80 (2.25)
Digit Ordering Test[i]	6.27 (2.19)	6.16 (2.22)	6.25 (2.08)	6.39 (2.27)	6.27 (2.19)

[a]There were no significant group differences for any baseline characteristic (i.e., $P > .05$).
[b]Based on self-report of transient ischemic attack, congestive heart failure, coronary artery bypass graft, angioplasty, or stent.
[c]Telephone Interview for Cognitive Status-modified (TICSm; maximum score = 50) is a measure of global cognition and includes short delay word list recall (10-minute delay).
[d]Long Delay Word List Recall (40-minute delay; maximum score = 10) measures verbal memory.
[e]Immediate and Delayed Story Recall (SRI & II) measures verbal memory (maximum score per test = 25).
[f]Oral Trail-Making Test is a modified version of the original paper and pencil version that measures simple attention (Part A; not included in analyses) and executive function (Part B); times to complete Part B were log transformed prior to analysis.
[g]Verbal Fluency is a measure of language accessibility and includes fluency by category (animals, vegetables) and by letter (F, L).
[h]Number Span measures simple attention and working memory.
[i]Digit Ordering Test is a task of working memory that is similar to but more difficult than Number Span Backward.

did not.[8,57–59] In the CoCoA study, a double-blind, 8-week RCT that examined cocoa flavanol effects on cognition, 90 cognitively healthy older adults[17] and 90 individuals with amnestic MCI[16] received a daily drink containing low (45 mg/day), medium (520 mg/day), or high (993 mg/day) amounts of cocoa flavanols. Performance on the Trail-Making Test, verbal fluency, and the cognitive composite that combined these test scores improved for high- and medium-dose groups relative to the low-dose group, regardless of participant cognitive status. In a smaller ($n = 37$) 3-month RCT comparing 900 mg/day versus 45 mg/day of cocoa flavanols, blood flow increased in the dentate gyrus of the hippocampus, which was associated with a treatment-related improvement on a hippocampal-dependent memory task in adults (50–69 years old).[56] In a 12-week RCT of 260, 510, or 770 mg/day of cocoa flavanols in 211 adults (50–75 years old), although there was no effect on the primary endpoint (computer-administered object-recognition task), secondary analyses indicated a dose-dependent improvement on list-learning in adults with a poor quality baseline diet.[60] These trials all included short treatment durations showing acute effects of cocoa flavanols on cognition. In COSMOS-Mind, acute cognitive effects of cocoa flavanols (less than 3 months) that were not sustained would have been missed as our assessments were completed only once per year. COSMOS-Mind also differed from these studies as the active supplement included not only cocoa flavanols, but also theobromine and caffeine. Furthermore, it is possible that the COSMOS-Mind cocoa flavanol dose was too low to provide cognitive benefit within the study observation period, particularly in light of previous dose-dependent findings.[60]

In contrast to the negative CE findings, we found that assignment to 3 years of MVM improved global cognition, episodic memory, and executive function. Previous RCTs of MVM supplements on cognition have

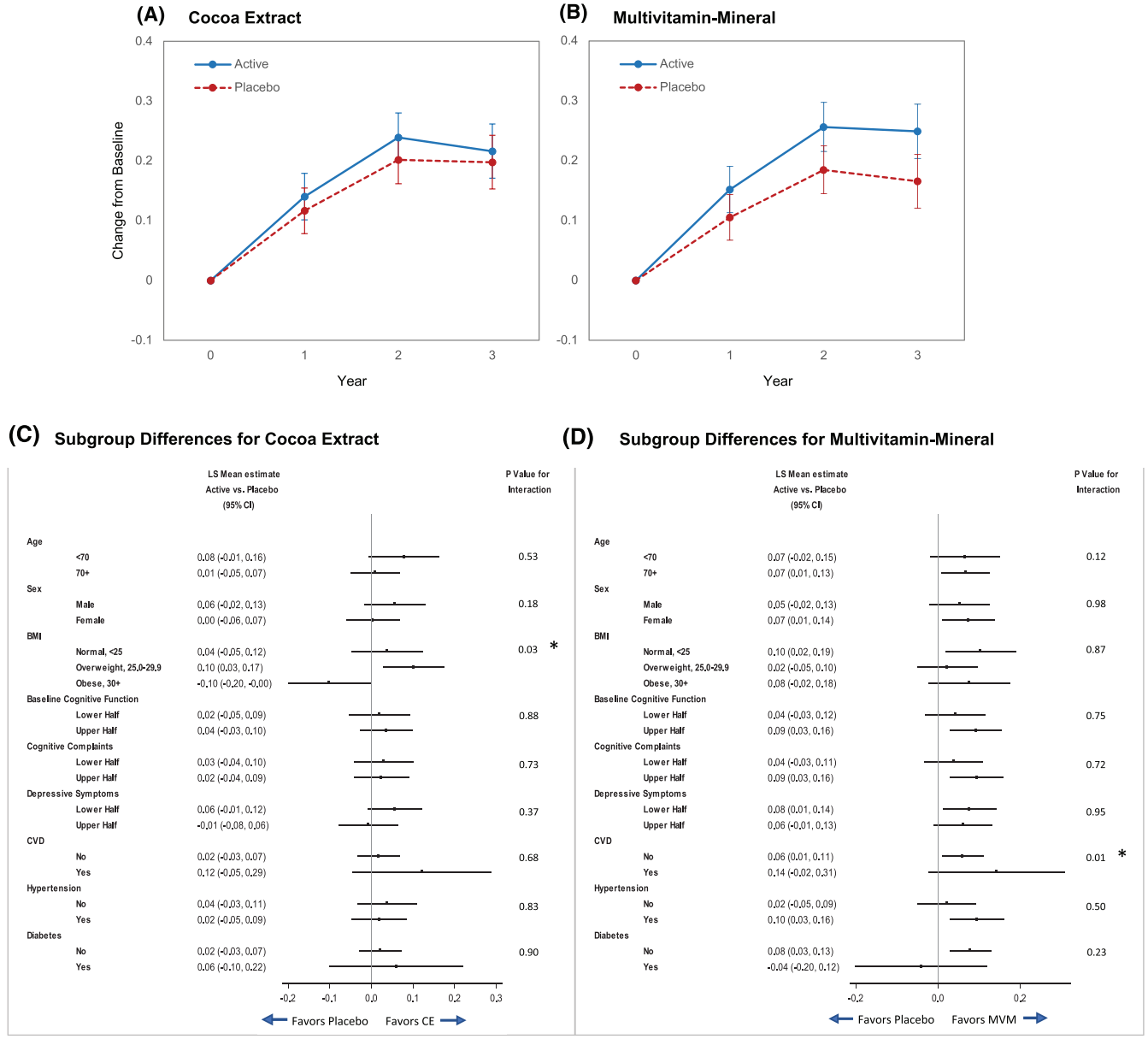

FIGURE 2 Three-year change in global cognition composite by assignment to (A) daily cocoa extract supplementation, and (B) daily multivitamin-mineral supplementation (plotted values: mean standardized (z) scores (relative to baseline) and 95% confidence intervals). Forest plot marginal differences by baseline subgroups for (C) cocoa extract and (D) multivitamin-mineral treatment groups

reported inconsistent effects. The majority were short in duration (up to 12 months) and relied on individual test scores to assess cognitive effects rather than a composite, which may provide greater statistical power to detect a difference across multiple tests and cognitive domains (if effect sizes are similar across its components).[61]

The only long-term MVM RCT prior to our study was the 12-year Physician's Health Study II (PHS II) of older U.S. male physicians that tested whether a daily MVM supplement prevented risk of major CVD[62] and cancer.[63] A PHS II cognitive substudy of 5947 healthy, highly educated men (aged ≥65 years) reported no MVM effects on a global cognition composite.[33] There are several differences between COSMOS-Mind and PHS II worth highlighting. The COSMOS-Mind and PHS II cohorts differed on key baseline characteristics: PHS II participants were restricted to male physicians who were predominantly White and non-Hispanic, whereas COSMOS-Mind included a relatively more diverse cohort. Although baseline cognitive scores were comparable for participants across studies (i.e., TICSm; VF-C for animals), COSMOS-Mind administered additional tests of executive function (i.e., OTMT-B, VF-L, NS, DOT) and more challenging episodic memory tests (i.e., Long Delay Word List Recall, and a longer version of Story Recall with 55% more components to remember) that may have increased sensitivity to detect effects. In PHS II, the initial cognitive testing began an average of 2.5 years (range: 0.18–5.3 years) after randomization to MVM or placebo, nearly at the point in time when the final follow-up assessment was completed in COSMOS-Mind. Our data suggest that MVM treatment effects increased from baseline in

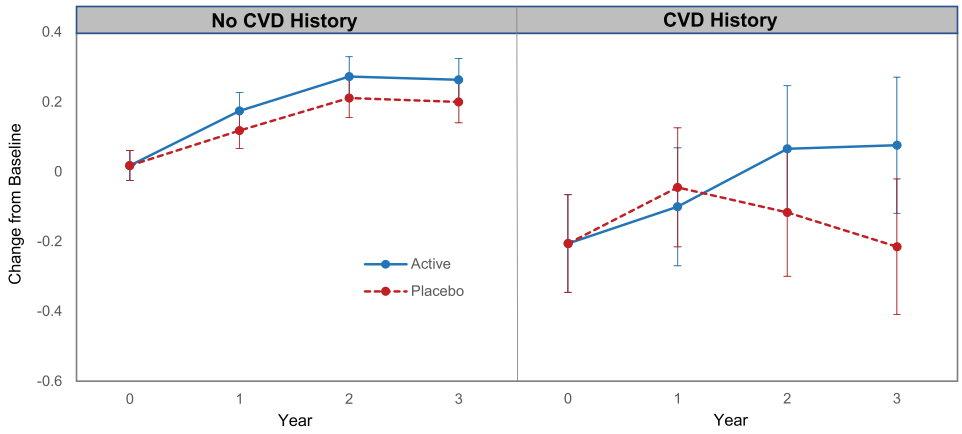

FIGURE 3 Three-year change in global cognition composite for the active and placebo multivitamin-mineral groups by history of cardiovascular disease, which was based on self-report of transient ischemic attack, congestive heart failure, coronary artery bypass graft, angioplasty, or stent (plotted values: mean standardized (z) scores and 95% confidence intervals).

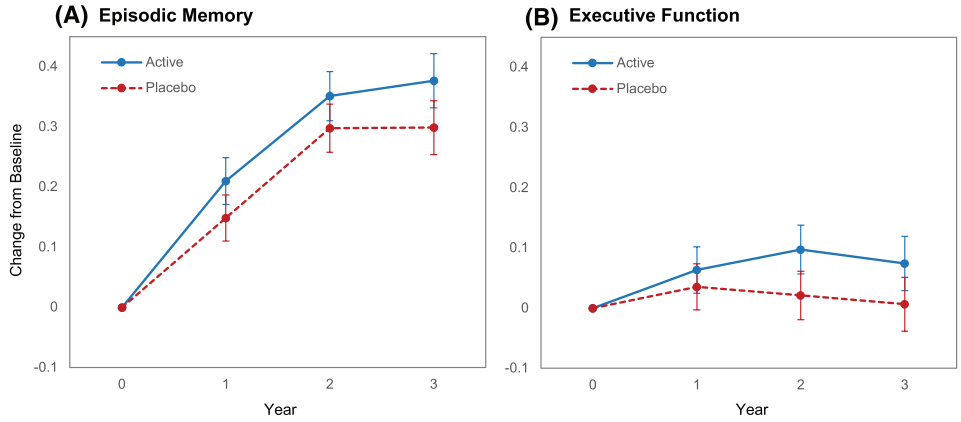

FIGURE 4 Three-year change in the episodic memory composite (A) and executive function composite (B) for the active and placebo multivitamin-mineral groups (plotted values: mean standardized (z) scores and 95% confidence intervals).

the first 2 years and then remained stable between Years 2 and 3 (Figure 2). As a result, any early cognitive benefits of MVM in PHS II would likely have been missed because of their assessment schedule given the COSMOS-Mind cognitive trajectory showing benefit within 2 years. Also, the specific components of the MVM supplements administered in the two studies differed (Table S6); in COSMOS (parent study), lutein and lycopene were added, amounts of vitamins D and K were 150%–300% higher, and amounts of vitamin A and minerals such as iron, magnesium, and copper were lower. Although some reports suggest cognition-protecting benefits of components that were at higher levels in the COSMOS MVM,[64–67] no consensus has been reached about the role of specific supplement quantities for brain health.

Our results suggest that MVM cognitive benefits may be more pronounced among older adults with CVD. At baseline, global cognitive function was lower for adults with versus without CVD history, which is consistent with other reports.[68] The MVM-treated CVD history subgroup had sustained increases in cognitive function after 2 years (Figure 3), while the placebo-treated CVD history subgroup showed cognitive decline after Year 1. One account for this finding relates to the potential treatment-related improvement in micronutrient levels in CVD-compromised individuals, which could, in turn, have beneficial consequences for brain health. The results of observational studies[69] suggest that micronutrient levels are typically lower in patients with CVD versus those without CVD (e.g., heart failure), and may be susceptible to drug interactions.[52] In CVD patients, for example, vitamin D deficiency is highly prevalent and predicts disease severity; vitamin K deficiency is linked to coronary artery calcification and increased CVD-related mortality; circulating levels of thiamine, vitamin C and selenium are relatively low (suboptimal, not necessarily deficient)[69]; and certain medications can reduce vitamin B12 absorption and bioavailability.[70] In PHS II, there was no evidence that MVM supplementation affected cardiovascular health status.[62] Nonetheless, additional investigation of treatment-related micronutrient status in a more diverse cohort of participants is warranted to confirm COSMOS-Mind findings and to explore mechanisms that might account for the observed benefit.

To estimate clinical significance of our findings, we used COSMOS-Mind data to model treatment-related protection against cognitive

aging. At baseline, slope of the global cognition composite scores by participant age (ranging from 64 to 100 years) was -0.045 SD/year (standard error = 0.004). The treatment effect of MVM relative to MVM-placebo was 0.083 SDs (95% CI: 0.020 to 0.146) at Year 3. This corresponds to baseline composite scores for individuals who were 1.8 years apart in age. By this albeit imprecise yardstick, 3 years of MVM supplementation appeared to have slowed aging by 1.8 years, or by 60%. Further speculation regarding the clinical significance of our MVM findings is difficult at this time given the relatively short duration of follow-up and the likely impact of practice effects commonly observed in trials with repeat cognitive testing that distort estimates of treatment-related change on metrics such as 'cognitive age.' Another trial is needed in a diverse cohort to confirm our findings and further assess the clinical significance of MVM supplementation on cognitive health in older women and men.

COSMOS-Mind had several strengths. The 2 × 2 factorial design allowed us to efficiently examine the effects of two different interventions within a single study, under the assumption of no additive effects when interventions are combined. The pragmatic approach (using mail and telephone only) facilitated recruitment of over 2000 older adults in less than 15 months, minimized participant burden (no travel needed), and provided an opportunity for research participation to individuals who may not have had ready access to an academic institution.

Study limitations included: (1) race and ethnicity of the cohort was not representative of older Americans, which affects generalizability of our results; (2) adherence to study pills and health history (e.g., CVD) were tracked using self-report; (3) inability to assess whether specific components of the COSMOS MVM were responsible for the observed cognitive benefits; (4) data were not collected to permit analyses of biomarkers or potential effect modifiers (e.g., apolipoprotein E genotype); and (5) type 1 error was not controlled across secondary and tertiary analyses in COSMOS-Mind and for outcomes measured in the parent COSMOS trial and its other ancillary studies.

In conclusion, daily intake of cocoa extract for 3 years had no effect on cognition. However, COSMOS-Mind provides the first evidence from a large-scale, long-term, pragmatic RCT to suggest that daily use of a safe, readily accessible, and relatively low-cost MVM supplement has the potential to improve or protect cognitive function for older women and men. An additional trial is needed to confirm these findings in a more representative cohort and to explore potential mechanisms for cognitive benefit. This work may ultimately have important public health implications for standard of care to improve or protect cognitive function in older adults.

AUTHOR CONTRIBUTIONS

Concept and design: Laura D. Baker, Mark A. Espeland, Sally A. Shumaker, Stephen R. Rapp, JoAnn E. Manson, and Howard D. Sesso. Acquisition, analysis, or interpretation of data: Laura D. Baker, Mark A. Espeland, Sarah A. Gaussoin, Sally A. Shumaker, Stephen R. Rapp, JoAnn E. Manson, and Howard D. Sesso. Statistical analysis: Mark A. Espeland and Sarah A. Gaussoin. Manuscript development: Laura D. Baker, Mark A. Espeland, Sarah A. Gaussoin, Sally A. Shumaker, Stephen R. Rapp, JoAnn E. Manson, and Howard D. Sesso. Obtained funding: Laura D. Baker, Mark A. Espeland, Sally A. Shumaker, Stephen R. Rapp, JoAnn E. Manson, and Howard D. Sesso.

OTHER CONTRIBUTIONS

We thank and acknowledge the contributions of all COSMOS-Mind participants for their time and commitment to the study. We also thank the COSMOS-Mind study team members who provided their expertise to meaningfully connect to participants, keep them engaged, and collect and manage the cognitive data for over 8000 assessments. Wake Forest University School of Medicine (Winston-Salem NC) Team members included Brad Caudle, Debbie Pleasants M.ED., Cheryl Summerville, Alecia Jenkins, Ashley Lentz, Charlene Hunt, Debbie Booth, Deborah Kampman, Dylan Jarrell, Heather Dailey, Leonard Jordan, Marcelle Clavette, Margaret Pierce, Sharnita Duran, Sonya Ashburn, Darrin Harris, Julia Spell, Mary Barr, and Leslie Gordineer. We are especially grateful to the parent trial investigators (Manson, Sesso, and Garnet Anderson, PhD, of the Fred Hutchinson Cancer Research Center, Seattle WA) and the study team at Brigham and Women's Hospital (Boston, MA) for their partnership from study inception.

ACKNOWLEDGMENTS

The COSMOS-Mind study and investigators were supported through an award provided by the National Institute on Aging, of the National Institutes of Health (R01AG050657). Drs. Manson and Sesso also received support for the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) through an investigator-initiated grant from Mars Edge, a segment of Mars, Inc. dedicated to nutrition research, which included infrastructure support and the donation of study pills and packaging. Pfizer Consumer Healthcare (now Haleon) provided support through the partial provision of study pills and packaging.

CONFLICT OF INTERESTS

Research reported in this publication was supported by the National Institute on Aging of the National Institutes of Health and the content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Neither the National Institutes on Health, Mars, nor Pfizer contributed to any aspect of the trial including design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. The authors have no competing interests to report. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Baker LD, Manson JE, Rapp SR, et al. Effects of cocoa extract and a multivitamin on cognitive function: A randomized clinical trial. *Alzheimer's Dement*. 2023;19:1308–1319. https://doi.org/10.1002/alz.12767