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Original Research Article

Effect of cocoa extract supplementation on cognitive function: results from the clinic subcohort of the COSMOS trial

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A B S T R A C T

Background: Some prior randomized clinical trials (RCTs) that tested the effects of cocoa extract (CE), a source of flavanols, on late-life cognition have yielded promising findings. A long-term RCT using in-person neuropsychological tests covering multiple cognitive domains may clarify the cognitive effects of CE.

Objectives: To test whether daily supplementation with CE, compared with placebo, produces better cognitive change over 2 y.

Methods: The COcoa Supplement and Multivitamin Outcomes Study (COSMOS) is a 2 × 2 factorial RCT of CE [500 mg flavanols/d, including 80 mg (–)-epicatechin] and/or a daily multivitamin-mineral supplement for cardiovascular disease and cancer prevention among 21,442 United States adults aged ≥60 y. There were 573 participants in the clinic subcohort of COSMOS (that is, COSMOS-Clinic) who completed all cognitive tests at baseline; of these, 492 completed 2-y follow-up assessments. The primary outcome was global cognition (averaging z-scores across 11 tests). Secondary outcomes were episodic memory and executive function/attention. Repeated measures models were used to compare randomized groups.

Results: Participants' mean age (standard deviation) was 69.6 (5.3); 49.2% were females. Daily supplementation with CE, compared with placebo, had no significant effect on 2-y change in global cognition {mean difference [95% confidence interval (CI)]: −0.01 (−0.08, 0.05) standard deviation units (SU)}. CE, compared with placebo, had no significant effects on 2-y change in episodic memory [mean difference (95% CI): −0.01 (−0.13, 0.10) SU] or executive function/attention [mean difference (95% CI): 0.003 (−0.07, 0.08) SU]. Subgroup analyses uncorrected for multiple-testing suggested cognitive benefits of CE supplementation, compared with placebo among those with poorer baseline diet quality.

Conclusions: Among 573 older adults who underwent repeat in-person, detailed neuropsychological assessments over 2 y, daily CE supplementation, compared with placebo, showed no overall benefits for global or domain-specific cognitive function. Possible cognitive benefits of CE among those with poorer diet quality warrant further study.

Trial registration: This trial was registered at clinicaltrials.gov with identifier – NCT02422745.

Keywords: cocoa extract, flavanols, cognition, randomized clinical trial, geriatric

Introduction

Adults aged 65 y and older, a group at high risk for developing Alzheimer disease and related dementias (ADRD), constitute the fastest growing age segment in the United States [1]. Subtle decrements in cognitive function during aging strongly predict worsened cognitive decline and an increased risk of ADRD many years later [2,3]. Thus, interventions that target the earliest signs of age-related cognitive decline may help to preserve cognitive function. Cocoa extract (CE) represents a promising example of nutrient supplementation to benefit late-life cognition.

CE contains flavanols, a subclass of flavonoids, and modest amounts of theobromine and caffeine [4]. Cocoa flavanols, including (–)-epicatechin, have been postulated to affect cognitive function by

Abbreviation: 3MS, Modified Mini-Mental State; ADRD, Alzheimer disease and related dementias; aMCI, amnestic mild cognitive impairment; CE, cocoa extract; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval; CN, cognitively normal; COSMOS, COcoa Supplement and Multivitamin Outcomes Study; CVD, cardiovascular disease; EBMT, East Boston Memory Test; HHIE-S, Hearing Handicap Inventory for the Elderly—Screening; IRB, Institutional Review Board; MVM, multivitamin-mineral; RCT, randomized clinical trial; SU, standard deviation units; TMT, Trail Making Test.

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interacting with intracellular signaling pathways that mediate neuroinflammation and neurodegeneration and by improving cerebral vasodilation and perfusion [5,6]. Epidemiological studies showed positive associations between the consumption of cocoa products and various health outcomes, including cognition [4,7,8]. However, evidence from randomized clinical trials (RCTs) has not consistently shown the benefits of CE supplementation for cognitive change in older adults [9–13].

To the best of our knowledge, 9 smaller (n ~200; treatment duration: ≤6 mo) [9–11] and 2 larger (n > 2000; treatment duration: >12 mo) [12,13] RCTs have investigated the effects of CE supplementation on cognitive change during mid- or late life. Whereas the smaller scale RCTs have been mostly favorable, the 2 larger scale RCTs suggested no overall effects on prespecified primary cognitive endpoints [12]. Both larger scale RCTs were separately conducted ancillary cognitive substudies of the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) trial: COSMOS-Mind (annual telephone-based cognitive assessments for 3 y) [12] and COSMOS-Web (annual web-based cognitive assessments for 3 y) [13]. Of note, the COSMOS-Web study reported significantly better change in hippocampal-dependent memory with CE supplementation, compared with placebo, among participants in the lowest tertile of habitual diet quality or flavanol consumption at baseline. Thus, an RCT that administers in-person neuropsychological assessments, measuring subtle changes across multiple cognitive domains, could provide further clarity on the potential cognitive benefits of CE supplementation in older adults.

In this study, we tested the effects of daily CE supplementation on cognitive change over 2 y among 573 older adults from the clinic subcohort of the COSMOS trial (COSMOS-Clinic), who underwent in-person, detailed neuropsychological assessments [14]. We hypothesized that daily supplementation with CE, compared with placebo, would result in better change over 2 y in our primary outcome of global cognition, summarized by 11 different cognitive tests. Second, we tested whether CE, compared with placebo, would result in better change over 2 y in the domains of episodic memory and executive function/attention. We also explored potential modifying roles of baseline factors, including diet and flavanol status, on the effects of CE supplementation compared with placebo on cognition.

Methods

Study design

COSMOS is a recently completed RCT of 21,442 United States participants (including 8776 males ≥60 y and 12,666 females ≥65 y) that tested daily supplementation of CE (2 capsules/d containing 500 mg cocoa flavanols/d, including 80 mg (–)-epicatechin; supplied by Mars Edge], a commercial multivitamin-mineral (MVM) (Centrum Silver®; supplied by Pfizer Consumer Healthcare, now Haleon) and/or matching placebos in a 2 × 2 factorial design for prevention of cardiovascular disease (CVD) and cancer (enrollment period: April 2016–March 2018, with the end of the intervention: December 31, 2020); the detailed protocol and main findings were published elsewhere [14–16].

The exclusion criteria for the COSMOS trial were history of myocardial infarction or stroke (history of other cardiovascular events, including transient ischemic attack, congestive heart failure, coronary artery bypass grafting, angioplasty, and stenting, was permitted); diagnosis of cancer except for non-melanoma skin cancer within the past 2 y; other serious illnesses precluding participation; unwillingness to stop CE, multivitamin, and vitamin D (>1000 international unit/d), or high-dose calcium (>1200 mg/d) supplementation during the trial; extreme sensitivity to caffeine; <75% compliance to study pills during at least a 2-mo placebo run-in period; and inability to communicate in English. During the trial, participants answered study pill adherence questions (that is, number of d/mo taking study pills from their monthly calendar packs) in questionnaires every 6 mo [14]. Participants reported demographics, physical, behavioral, and other health-related characteristics on COSMOS baseline questionnaires. In addition, participants completed a semi-quantitative food frequency questionnaire at baseline and 2 y.

COSMOS used a pragmatic, hybrid design that included a nationwide cohort of 21,442 United States participants and a subcohort of 603 COSMOS-Clinic participants who lived in the greater Boston area to attend the NIH-sponsored Center for Clinical Investigation at Brigham and Women's Hospital for detailed, in-person health evaluations and biospecimen (blood and spot urine) collections at baseline and 2 y. COSMOS-Clinic participants were eligible for the COSMOS-Clinic cognitive substudy if they had no indication of substantial hearing impairment and completed a 45-min battery of neuropsychological assessments. All participants provided written informed consent, and study approvals were obtained by the Institutional Review Board (IRB) at Mass General Brigham. COSMOS-Clinic cognitive substudy analyses were pre-specified under tertiary aims on the ClinicalTrials.gov registration page of COSMOS (NCT02422745).

Procedures

Study procedures followed a protocol that was developed and IRB-approved before COSMOS-Clinic enrollment and randomization (see details in Supplementary Methods A–C). Of 603 COSMOS-Clinic participants, 602 were interested in neuropsychological evaluations. First, we administered the Hearing Handicap Inventory for the Elderly—Screening (HHIE-S) Version [17] and the Clock-in-the-Box (range = 0–8 points) [18], a rapid (1–2 min) cognitive screening test. Participants who scored >24 points on HHIE-S (that is, having >50% likelihood of substantial hearing impairment) [19] were only administered the Modified Mini-Mental State (3MS; range = 0–100 points), a measure of general cognition [20,21]. Participants without substantial hearing impairment (HHIE-S ≤24 points) were administered the detailed neuropsychological assessment, which included the 3MS and the following measures: tests from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (that is, immediate total learning, range = 0–30 words; delayed recall, range = 0–10 words; and recognition, maximum score = 10 points) [22–24]; immediate and delayed recall trials of the East Boston Memory Test (EBMT, range = 0–12 points) [25]; 2 tests of category fluency (naming animals and vegetables) [22]; Trail Making Test (TMT) Part A (range = 0–150 s) and Part B (range = 0–300 s) [26]; and Digit Span Backward test (maximum score = 8 points) [27]. COSMOS-Clinic neuropsychological assessments were conducted at baseline and an average of 2 y later; details of test administration and scoring are provided in the Supplement.

Ascertainment of primary and secondary cognitive outcomes

The primary outcome was the global cognition composite that averaged z-scores of 11 tests: 3MS; CERAD immediate total learning, delayed recall, and recognition; immediate and delayed EBMT recall trials; 2 category fluency tests; TMT-A and TMT-B; and Digit Span Backwards.

Secondary outcomes included composites of *1*) episodic memory (averaging z-scores of 4 tests: EBMT immediate and delayed recall trials and CERAD immediate total learning and delayed recall); *2*) executive function/attention composite (averaging z-scores of 5 tests: 2 category fluency, TMT-A, TMT-B, and Digit Span Backwards). We calculated the composite scores for global cognition, episodic memory, and executive function/attention using mean standardized (z) scores of the relevant component tests; higher z-scores reflected better performance. The baseline means and SD of component cognitive tests were used to compute the z-scores at baseline and follow-up.

Statistical analyses

Main analyses

Basing assumptions on prior data (SD = 0.6, correlation coefficient = 0.75) [28,29], we calculated that this study had >80% power to detect effect sizes of 0.12 standard deviation units (SU) or greater in the global cognition score, comparing CE and placebo groups, with a planned sample size of 500 and an assumed 10% loss to follow-up (see details in Supplementary Methods D).

The analysis for the effect of CE supplementation, compared with placebo, included all randomly assigned participants regardless of pill compliance, participation in the 2-y follow-up, and scores from all cognitive assessments (baseline or year 2); 573 participants who completed all neuropsychological tests at baseline made up the analytical sample (see CONSORT diagram, Figure 1). Descriptive characteristics were compared between CE and placebo groups. To examine mean differences in change in global cognition between the CE and placebo groups, we used repeated measures models over a 2-y follow-up time with an unstructured covariance matrix to incorporate the within-participant correlation. Models were adjusted for prespecified design variables such as age, sex, randomization to the MVM group, and MVM effect over time (that is, time-×-MVM). We estimated the mean change in global cognition over follow-up using a time-×-CE interaction; as the repeated measures models can handle missing data, all participants contributed to the analysis at 1 or both time points. Models were fitted by maximum likelihood, and we used Wald tests for statistical testing [30]. For secondary outcomes, we constructed repeated measures models with the above-mentioned model specifications and covariates adjustment.

Subgroup analyses

We addressed whether the effect of CE supplementation, compared with placebo, on change in the primary outcome of global cognition over 2 y was modified by design variables or subgroups selected a priori based on importance in cognitive decline and ADRD risk [31,32]: age (<70 or ≥70 y); sex; self-reported race and ethnicity (non--Hispanic White or other racial and/or ethnic groups); randomization to the MVM group; baseline general cognitive score (3MS tertiles); presence of subjective cognitive complaints [0 or ≥1 points on Structured Telephone Interview for Dementia Assessment questions] [33]; body mass index (<25, 25–29, ≥30 kg/m^2); self-reported history of CVD (transient ischemic attack, congestive heart failure, coronary artery bypass graft, angioplasty, or stent), hypertension, type 2 diabetes, and depression.

In a separate web-based cognition substudy within COSMOS (that is, COSMOS-Web) [13], CE supplementation, compared with placebo, led to better cognitive function, especially episodic memory, among participants with lower diet quality or flavanol consumption at baseline. To confirm this in the COSMOS-Clinic sample, we stratified our main analyses by habitual diet quality (tertiles of the Alternative Healthy Eating Index—2010) [34] or habitual flavanol consumption [tertiles of urinary concentrations of 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone metabolite] [35].

Posthoc analysis

We reran the main analyses examining treatment effects on global and domain-specific cognitive function scores after adjustments for baseline values of additional potential confounders that significantly differed between the CE and placebo groups in this sample (such as frequency of alcohol use and history of diabetes).

All tests were 2 sided, and $P < 0.05$ was used to indicate statistical significance. Analyses regarding secondary cognitive outcomes and subgroups were considered hypothesis-generating and were not

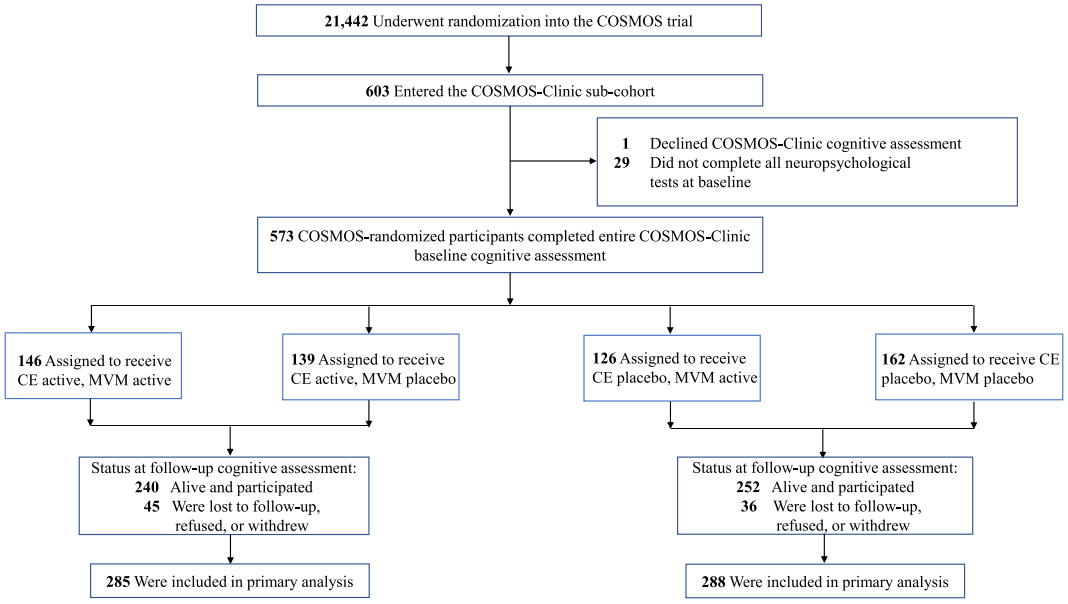

FIGURE 1. Flowchart of participants in the COSMOS-Clinic subcohort study. CE, cocoa extract; COSMOS, COcoa Supplement and Multivitamin Outcomes Study [14–16]; MVM, multivitamin-mineral.

TABLE 1
Participant characteristics by intervention group ($n = 573$)

Characteristic	No. (%) of participants[1]	
	CE group ($n = 285$)	Placebo group ($n = 288$)
Age at first cognitive assessment, mean (SD)	69.8 (5.5)	69.4 (5.2)
Sex, *n* (%)		
Male	151 (53.0)	140 (48.6)
Female	134 (47.0)	148 (51.4)
Randomization to MVM supplement		
Active group	146 (51.2)	126 (43.8)
Placebo group	139 (48.8)	162 (56.2)
Self-reported race/ethnicity, *n* (%)		
Non-Hispanic White	278 (97.5)	275 (95.5)
Other[2]	7 (2.5)	13 (4.5)
Education, *n* (%)	($n = 281$)	($n = 284$)
College or lower	124 (44.1)	134 (47.2)
Postcollege	157 (55.8)	150 (52.8)
BMI, median (IQR) (kg/m^2)	27.6 (24.8–30.8)	27.0 (24.1–30.4)
Leisure-time physical activity, median (IQR), MET-(h/wk)	19.4 (7.2–36.5)	20.9 (8.4–36.6)
Habitual diet quality, AHEI-2010, mean (SD)	43.8 (10.6)	43.4 (10.2)
Urine gVLM, mean (SD) (μM)	9.3 (15.5)	8.7 (14.0)
Smoking status, *n* (%)	($n = 281$)	($n = 286$)
Never	156 (55.5)	155 (54.2)
Past or current	125 (44.5)	131 (45.9)
Frequency of alcohol use, *n* (%)	($n = 266$)	($n = 276$)
Never or rarely	72 (27.1)	51 (18.5)
Monthly	20 (7.5)	13 (4.7)
Weekly	99 (37.2)	114 (41.3)
Daily	75 (28.2)	98 (35.5)
Prerandomization use of chocolate intake, *n* (%)	($n = 267$)	($n = 278$)
Rarely/never	41 (15.4)	46 (16.6)
Monthly	35 (13.1)	45 (16.2)
Weekly	159 (59.6)	156 (56.1)
Daily	32 (12.0)	31 (11.2)
History of hypertension, *n* (%)	147 (51.6)	135 (46.9)
History of CVD,[3] *n* (%)	21 (7.5)	14 (5.0)
History of diabetes, *n* (%)	41 (14.4)	22 (7.7)
History of high-cholesterol medication, *n* (%)	119 (41.8)	106 (37.1)
History of depression, *n* (%)	74 (26.2)	83 (28.9)
Baseline cognitive outcomes, mean (SD)		
Primary outcome		
Global cognition composite[4]	–0.02 (0.56)	0.02 (0.56)
Secondary outcomes		
Episodic memory composite[5]	–0.03 (0.75)	0.03 (0.71)
Executive attention/function composite[6]	0.00 (0.66)	0.00 (0.65)
Presence of subjective cognitive complaints,[7] *n* (%)		
Yes	91 (31.9)	93 (32.3)
No	194 (68.1)	195 (67.7)

Abbreviations: 3MS, Modified Mini-Mental State [20,21]; AHEI, alternative healthy eating index [34]; CE, cocoa extract; CERAD, Consortium to Establish a Registry for Alzheimer's Disease [22,23]; CVD, cardiovascular disease; gVLM, 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone metabolite [35]; IQR, interquartile range; MET, metabolic equivalent of task; MVM, multivitamin-mineral.

[1] Unless otherwise indicated. The percentages may not sum to 100 because of rounding.

[2] Other racial/ethnic groups included African American/Black, Hispanic (not African American), Asian, Native Hawaiian or other Pacific Islander, multiple race or unknown race or unknown ethnicity.

[3] On the basis of the self-report of transient ischemic attack, congestive heart failure, coronary artery bypass graft, angioplasty, or stent.

[4] Global cognition composite was obtained by averaging z-scores of 11 tests: 3MS [20,21], tests from the CERAD (immediate total learning, delayed recall, and recognition) [22,23], immediate and delayed recall trials of the East Boston Memory Test [25], and category fluency tests (naming animals and vegetables) [22], Trail Making Tests A and B [26], and Digit Span Backwards [27].

[5] Episodic memory composite was obtained by averaging z-scores of 4 tests: immediate and delayed recall trials of the East Boston Memory Test [25], CERAD immediate total learning and delayed recall tests [22,23].

[6] Executive function/attention composite was obtained by averaging z-scores of 5 tests: category fluency tests (naming animals and vegetables) [22], Trail Making Tests A and B [26], and Digit Span Backwards [27].

[7] Subjective cognitive complaints were ascertained using the Structured Telephone Interview for Dementia Assessment [33].

controlled for multiple hypothesis testing or adaptive adjustments to raw *P*-values; thus, these results should be interpreted with caution. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and R.

Results

Figure 1 summarizes the recruitment and disposition of COSMOS-Clinic participants. Of the 603 COSMOS-Clinic participants, 573 completed all cognitive tests at baseline. Among these 573 participants, 81 (14.1%) were lost-to-follow-up, refused follow-up cognitive assessment, or withdrew from the COSMOS-Clinic substudy before the follow-up cognitive assessment; 492/573 (85.9%) completed all neuropsychological tests at baseline and 2 y. The median (interquartile range) testing interval = 2.0 (1.9–2.0) y. Among participants who provided answers on the study pill compliance questionnaires (98% of this sample), 96.4% in the CE group, and 92.6% in the placebo group reported adequate adherence to study pills (that is, taking ≥75% study pills/mo) at year 1. At 2 y, 91.4% of the CE group and 90.9% of the placebo group reported adequate study pill adherence. This report includes results regarding the CE effects on cognitive change in the COSMOS-Clinic cognitive substudy; results regarding MVM effects on cognitive change will be reported in a separate article.

Baseline characteristics

There were 285 participants randomized to CE, and 288 were randomized to placebo. The mean (SD) age was 69.6 (5.3) y; females comprised 49.2%; 53.6% had postbaccalaureate education, and 11% reported prerandomization daily chocolate intake. Descriptive characteristics were comparable across treatment groups (Table 1).

Main analyses

Primary outcome

Participants randomized to CE, compared with placebo, had no statistically significant benefit on global cognition over 2 y (Table 2); the mean difference in change in global cognition score was not statistically different from 0 over an average follow-up of 2 y [–0.01 SU; 95% confidence interval (CI): –0.08, 0.05]. The least-squares means of global cognition scores increased between baseline and follow-up in both treatment groups, likely reflecting practice effects [36].

Secondary outcomes

Participants randomized to CE, compared with placebo, had no statistically significant benefits on secondary cognitive outcomes over 2 y (Table 2); the mean difference in change was –0.01 SU (95% CI: –0.13, 0.10) for episodic memory score and 0.003 SU (95% CI: –0.07, 0.08) for executive function/attention score. The least-squares means of cognitive scores increased between baseline and follow-up in both treatment groups for episodic memory but not executive function/attention.

Subgroup analyses

There were no significant interactions by the selected subgroups for the effect of CE, compared with placebo, on change in global cognition (Figure 2). There was no significant interaction between the CE and MVM interventions for global cognition (*P*-interaction = 0.46).

There were borderline interactions by habitual diet quality for the effect of CE supplementation on global cognition (*P*-interaction = 0.08) and executive function (*P*-interaction = 0.04), but not on episodic memory scores (*P*-interaction = 0.54) (Figure 3). Among participants in the lowest tertile of habitual diet quality at baseline, CE supplementation,

TABLE 2
Adjusted mean difference in change in cognitive outcomes over a 2-y follow-up, comparing CE and placebo groups[1]

	CE group		Placebo group		Adjusted mean difference (95% CI) for change over a 2-y follow-up, SU
	N	Mean (SE)[2]	*N*	Mean (SE)[2]	
Primary outcome					
Global cognition[3]					
Baseline	285	–0.006 (0.03)	288	0.01 (0.03)	—
Year 2	240	0.13 (0.03)	252	0.16 (0.03)	–0.01 (–0.08, 0.05)
Secondary outcomes					
Episodic memory[4]					
Baseline	285	–0.02 (0.04)	288	0.02 (0.04)	—
Year 2	240	0.27 (0.04)	252	0.32 (0.04)	-0.01 (-0.13, 0.10)
Executive function/attention[5]					
Baseline	285	0.007 (0.04)	288	0.00 (0.04)	—
Year 2	240	0.007 (0.04)	252	–0.003 (0.04)	0.003 (–0.07, 0.08)

Abbreviations: 3MS, Modified Mini-Mental State [20,21]; CE, cocoa extract; CERAD, Consortium to Establish a Registry for Alzheimer's Disease [22,23]; CI, confidence interval; MVM, multivitamin-mineral; SU, standard deviation units.

[1] Results are from repeated measures models to measure the means over time; all participants contributed to the repeated measure analysis at one and/or both time points. Models were controlled for age, sex, randomization to the MVM group, and MVM effect over time (MVM × time). Analyses regarding secondary outcomes were not adjusted for multiple comparisons; therefore, results should be interpreted with caution.

[2] Mean and SEs are calculated from a multivariable model that adjusted for age, sex, randomization to the MVM group, and MVM effect over time (MVM × time).

[3] Global cognition composite was obtained by averaging z-scores of 11 tests: 3MS [20,21], tests from the CERAD (immediate total learning, delayed recall, and recognition) [22,23], immediate and delayed recall trials of the East Boston Memory Test [25], category fluency tests (naming animals and vegetables) [22], Trail Making Tests A and B [26], and Digit Span Backwards [27].

[4] Episodic memory composite was obtained by averaging z-scores of 4 tests: immediate and delayed recall trials of the East Boston Memory Test [25], CERAD immediate total learning and delayed recall tests [22,23].

[5] Executive function/attention composite was obtained by averaging z-scores of 5 tests: category fluency tests (naming animals and vegetables) [22], Trail Making Tests A and B [26], and Digit Span Backwards [27].

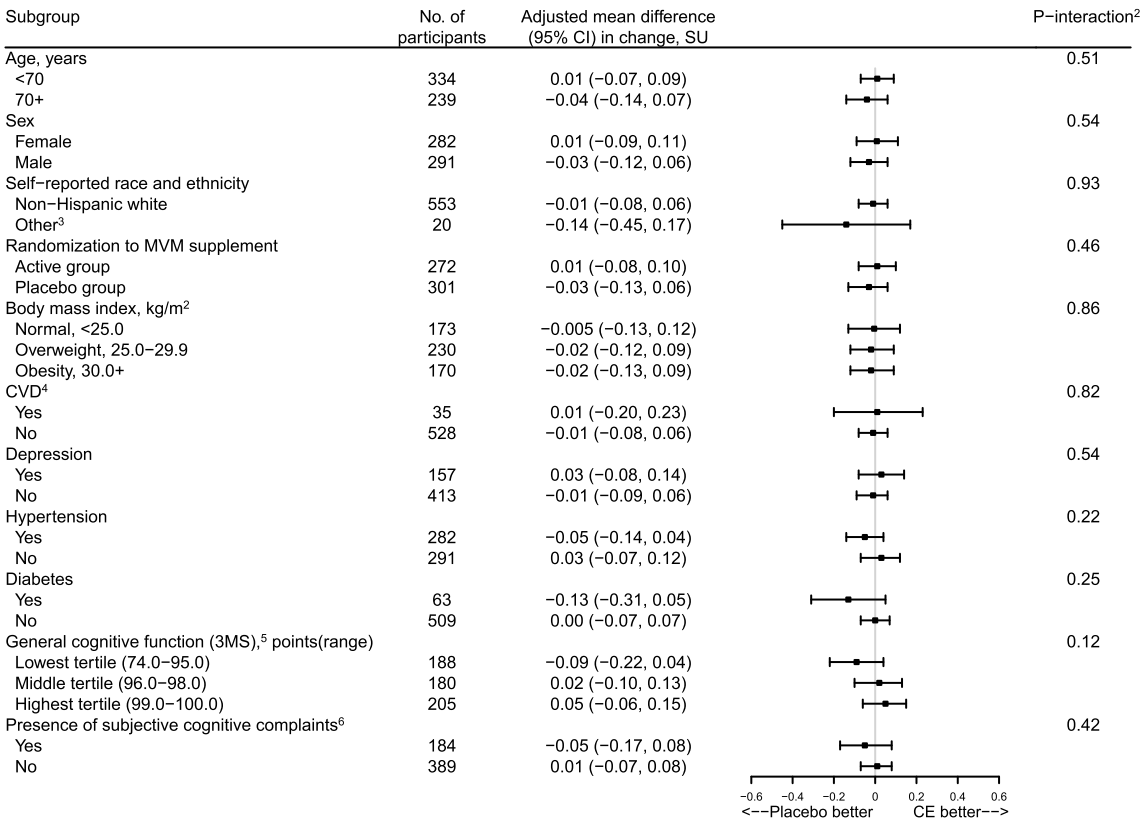

FIGURE 2. Adjusted mean difference in change in global cognition composite over a 2-y follow-up comparing CE and placebo groups, according to prespecified subgroups.[1] 3MS, Modified Mini-Mental State [20,21]; CE, cocoa extract; CI, confidence interval; CVD, cardiovascular disease; MVM, multivitamin-mineral; SU, standard deviation units.

[1]Analyses were from repeated measures models to estimate the means over time; models were controlled for age, sex, randomization to the MVM group, and MVM effect over time (MVM × time). Adjusted mean differences (95% CI) between the CE and placebo groups in global cognition composite scores over a 2-y follow-up period are shown within subgroups. Analyses were not adjusted for multiple comparisons; therefore, results should be interpreted with caution.

[2]*P*-interaction is from the 1-df test with subgroup-×-CE treatment-×-time interaction term in the model.

[3]Other racial/ethnic groups included African American/Black, Hispanic (not African American), Asian, Native Hawaiian, or other Pacific Islander, multiple race or unknown race or unknown ethnicity.

[4]On the basis of the self-report of transient ischemic attack, congestive heart failure, coronary artery bypass graft, angioplasty, or stent.

[5]For this subgroup analysis, we excluded the z-score of the general cognition test from the global cognition composite.

[6]Subjective cognitive complaints were ascertained using the Structured Telephone Interview for Dementia Assessment [33].

compared with placebo, resulted in relatively better 2-y changes in global cognition score [mean difference (95% CI): 0.09 SU (−0.04, 0.23)] and executive function score [mean difference (95% CI): 0.13 SU (−0.006, 0.26)]. However, there were no apparent interactions by habitual flavanol consumption in the effects of CE supplementation on change in global and domain-specific cognition over 2 y.

Posthoc analyses

When we adjusted repeated measures models for potential confounders that significantly differed between the CE and placebo groups (such as frequency of alcohol and history of diabetes) in addition to prespecified designed variables, results of CE supplementation on change in global and domain-specific cognitive function scores remained null, and estimates were identical to those from main analyses (see Supplemental Table 1).

Discussion

In this RCT of 573 older males and females, daily supplementation with CE (containing 500 mg cocoa flavanols, including 80 mg/d (–)-epicatechin), compared with placebo, did not result in significantly better change in global cognition over an average follow-up of 2 y. Treatment effects of CE on change in global cognition did not significantly vary by selected subgroups, but a borderline trend for benefit was observed by habitual diet quality at baseline. In addition, no significant benefits of CE, compared with placebo, were observed for episodic memory or executive function/attention over 2 y in the overall sample; however, a suggestive benefit of CE supplementation for executive function/attention was observed among those with poorer habitual diet quality at baseline.

CE is a rich source of flavanols and procyanidins that are also found in tea, berries, grapes, wine, and other plant-based foods. Cocoa flavanols, including (–)-epicatechin, may exert neuroprotective effects by reducing oxidative stress and inflammation, promoting neurogenesis, and improving cerebral blood flow [5,6]. CE supplements also contain modest amounts of functional ingredients such as methylxanthines (for example, theobromine), which exhibit neuroprotective properties [37]. Thus, on the basis of the strong biological plausibility, we hypothesized that daily supplementation with CE, compared with placebo, would lead to more favorable changes in cognitive function, as measured using an array of detailed cognitive tests conducted in person. However, 2 y of

Outcome; subgroup	No. of participants	Adjusted mean difference (95% CI) in change, SU	P−interaction[2]
Global cognition			
AHEI−2010 (range), points			0.08
Lowest tertile (15.50−38.50)	169	0.09 (−0.04, 0.23)	
Middle tertile (39.50−47.50)	174	−0.01 (−0.13, 0.10)	
Highest tertile (48.50−72.50)	178	−0.06 (−0.16, 0.05)	
gVLM (range), μM			0.40
Lowest tertile (0.02−0.97)	151	−0.005 (−0.14, 0.13)	
Middle tertile (0.99−6.30)	152	−0.04 (−0.16, 0.09)	
Highest tertile (6.35−71.81)	151	0.07 (−0.06, 0.21)	
Episodic memory			
AHEI−2010 (range), points			0.54
Lowest tertile (15.50−38.50)	169	0.08 (−0.17, 0.32)	
Middle tertile (39.50−47.50)	174	−0.02 (−0.21, 0.18)	
Highest tertile (48.50−72.50)	178	−0.02 (−0.20, 0.16)	
gVLM (range), μM			0.95
Lowest tertile (0.02−0.97)	151	0.08 (−0.15, 0.32)	
Middle tertile (0.99−6.30)	152	−0.07 (−0.29, 0.15)	
Highest tertile (6.35−71.81)	151	0.05 (−0.16, 0.26)	
Executive function/attention			
AHEI−2010 (range), points			0.04
Lowest tertile (15.50−38.50)	169	0.13 (−0.006, 0.26)	
Middle tertile (39.50−47.50)	174	−0.001 (−0.14, 0.13)	
Highest tertile (48.50−72.50)	178	−0.08 (−0.21, 0.06)	
gVLM (range), μM			0.55
Lowest tertile (0.02−0.97)	151	−0.01 (−0.16, 0.14)	
Middle tertile (0.99−6.30)	152	0.002 (−0.14, 0.15)	
Highest tertile (6.35−71.81)	151	0.06 (−0.10, 0.22)	

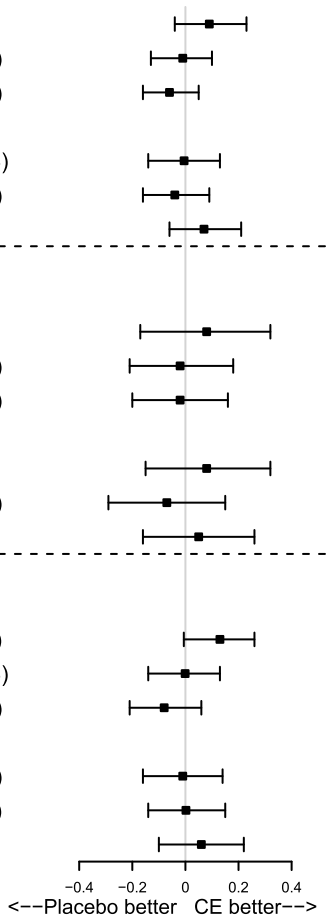

FIGURE 3. Adjusted mean difference in change in global and domain-specific cognition scores over a 2-y follow-up comparing CE and placebo groups, according to habitual diet quality and flavanol consumption at baseline.[1] AHEI, Alternative Healthy Dietary Index [34]; CE, cocoa extract; CI, confidence interval; gVLM, 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone metabolite [35]; MVM, multivitamin-mineral; SU, standard deviation units.
[1]Analyses were from repeated measures models to estimate the means over time; models were controlled for age, sex, randomization to the MVM group, and MVM effect over time (MVM × time). Adjusted mean differences (95% CI) between the CE and placebo groups in cognition composite scores over a 2-y follow-up period are shown within subgroups. Analyses were not adjusted for multiple comparisons; therefore, results should be interpreted with caution.
[2]P-interaction is from the 1-df test with subgroup-×-CE treatment-×-time interaction term in the model.

daily CE supplementation did not affect overall cognition in this sample.

The results from this study contrasted with favorable results from epidemiological studies [7,8] and some smaller scale RCTs [9–11]. For instance, a recent 12-wk RCT by Sloan and colleagues ($n = 211$; mean age = 62 y) [38] randomized participants to 0, 260, 510, or 770 mg of cocoa flavonols per day and found a dose-dependent effect of cocoa flavanols compared with placebo on list-learning memory but not on object recognition and list-sorting performance. In addition, the parallel arm, double-blind CoCoA (Cocoa, Cognition, and Aging) trial included 90 older adults with amnestic mild cognitive impairment (aMCI) [39] and 90 older adults with cognitively normal (CN) [40] status who received a daily drink containing low (45 mg/d), medium (520 mg/d), or high (993 mg/d) amounts of cocoa flavanols over 8 wk. Regardless of baseline cognitive status (aMCI or CN), randomization to both high- and medium-cocoa flavanol intake groups, compared with the low-intake group, showed significant benefits on an overall cognition composite score that included the 3MS, TMT-A, TMT-B, and verbal fluency tests. In contrast to these earlier trials conducted over 8–12 wk, neither COSMOS-Clinic, which had a 2-y testing interval, nor COSMOS-Mind [12], which had annual follow-up over 3 y, were designed to test for acute benefits of CE on global cognition. Any acute benefits of CE supplementation on global cognition, even if present, were not sustained during the longer-term follow-up in COSMOS. Of note, the amount of CE tested in COSMOS was comparable with that used in the aforementioned positive trials; thus, although favorable findings from shorter-term RCTs may reflect the possibility of acute rather than sustained cognitive benefits of cocoa flavanols, the amount of cocoa flavanols was unlikely to be a factor in the differing outcomes.

Our findings appear consistent with the primary findings of 2 recently completed, separate COSMOS cognitive ancillary RCTs, COSMOS-Mind ($n = 2262$; telephone-based annual cognitive assessments for 3 y) and COSMOS-Web ($n = 3524$; web-based annual cognitive assessments for 3 y) [12,13]. Although cognitive testing in our study was

administered in person, and the 11 tests in the assessment were selected to capture subtle changes across multiple cognitive domains among the high-functioning COSMOS-Clinic participants, we found no significant differences in the 2-y changes in global cognition or domain-specific composite scores between the CE and placebo groups. Nonetheless, the possibility remains that CE may benefit specific cognitive functions among risk groups based on baseline diet and nutrient status. For instance, in the large COSMOS-Web study ($n = 3562$) [13], there was evidence of CE benefit on a prespecified measure of episodic memory among those with lower habitual diet quality or flavanol consumption. Our subgroup analyses uncorrected for multiple-testing suggested modest benefits of CE supplementation on global cognition, with stronger point estimates for executive function but not for episodic memory, among participants with lower habitual diet quality at baseline; there were no significant differences in the effects of CE supplementation on global and domain-specific cognition by tertiles of habitual flavanol consumption at baseline. Although both COSMOS-Clinic and COSMOS-Web tested the same CE supplement, these substudies differed in sample size and prespecified cognitive measures used for episodic memory. Results from both COSMOS substudies emphasize the importance of considering baseline diet and nutrient status in future trials that investigate the role of CE on cognitive change in older adults and further clarify mechanisms underlying the cognitive benefits of CE supplementation in key groups.

This study had several strengths, including a well-characterized and deeply phenotyped sample; in-person administration of a detailed neuropsychological assessment comprising 11 tests; ability to investigate CE effects on multiple cognitive domains; high follow-up and compliance rates; and rich covariate data for addressing differences in treatment effects on cognition by subgroups. However, several potential limitations should also be noted. First, because of the 2-y follow-up interval in COSMOS-Clinic, it would not have been possible to detect acute or short-term cognitive effects of CE supplementation. Second, the increases in mean cognitive scores between baseline and 2-y follow-up, in both the CE and placebo groups, were consistent with practice effects in global cognition and episodic memory, but not executive function/attention; alternative testing strategies and/or a longer follow-up period might have mitigated the influence of practice effects on observed outcome scores [36]. Third, the sample had relatively low racial and ethnic diversity, which can limit generalizability. Fourth, the COSMOS CE intervention encompassed all naturally occurring bioactive compounds of the cocoa bean [including 500 mg/d cocoa flavanols, 80 mg/d (–)-epicatechin, and theobromine] tested in a single formulation; thus, we could not test cognitive effects of different CE formulations, the individual components of CE, or different amounts of cocoa flavanols or (–)-epicatechin. For example, we cannot exclude that even higher amounts of cocoa flavanols (up to 1000 mg/d) may be necessary to detect beneficial effects on verbal memory and executive function/attention, including among older adults who are CN at baseline [26]. Finally, we did not control for type-1 error in analyses regarding secondary cognitive outcomes and subgroups; therefore, these results should be interpreted with caution.

In conclusion, in this cognitive substudy of the COSMOS trial, involving 573 older males and females who underwent repeat in-person neuropsychological assessment over 2 y, daily supplementation with CE, compared with placebo, did not result in significantly better changes in global or domain-specific cognitive function scores. However, a subgroup analysis showed suggestive benefits for cognitive function among those with poorer habitual diet quality at baseline. Additional research on the role of CE supplementation in more diverse populations and among those with lower diet quality is warranted.

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Author contributions

The authors' responsibilities were as follows – JEM, HDS, OIO: study design; JEM, HDS: funding; JEM, HDS, AW, OIO: data collection; CMV, NRC, OIO: data analysis; CMV, JEM, NRC, OIO: data interpretation; CMV: Initial drafting of the manuscript; CMV, JEM, HDS, PMR, AW, EK, MVM, NRC, OIO: critical review of manuscript; JEM, HDS, NRC, OIO: supervision; CMV, OIO: had full access to data and attest to the completeness and accuracy of the data and data analyses; and all authors read and approved the final manuscript.

Conflict of interest

CMV has received research support from Nestlé-Purina Petcare Company, Mars Edge, and the American Foundation for Suicide Prevention. HDS has received research support from Mars Edge, Pure Encapsulations, and Pfizer Inc. and honoraria and/or travel for lectures from the Council for Responsible Nutrition, BASF, NIH, and the American Society of Nutrition during the conduct of the study. JEM has received research support from Mars Edge. OIO receives royalties from Springer Publishing for a book on late-life depression prevention. OIO has received honoraria and/or travel support for lectures from the AARP Global Council on Brain Health and research support from the NIH and the Alzheimer's Association. No other authors have disclosures to report.

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GSK Consumer Healthcare) contributions. Voting members of the DSMB for COSMOS and ancillary studies included: Lawrence S. Cohen, MD (Chair); Theodore Colton, ScD; Craig Henderson, MD; Stephen Hulley, MD; Alice H Lichtenstein, ScD; Eugene R Passamani, MD; Rebecca A Silliman, MD, PhD; Nanette Wenger, MD; Shari E Ludlam (NIH Observer). COSMOS is registered at clinicaltrials.gov (NCT02422745). The COSMOS website is www.cosmostrial.org. The NIH, Harvard Catalyst, US FDA, Mars Edge, Contract Pharmacal Corp, and Pfizer Consumer Healthcare (now Haleon) had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request. The data set(s) will be de-identified prior to release for sharing. We will make the data and associated documentation available to users only under a data-sharing agreement. Details on the availability of the study data to other investigators will be on our study website at https://cosmostrial.org/.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.10.031.

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