Contemporary Clinical Trials 83 (2019) 57–63

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Design and baseline characteristics of the cocoa supplement and multivitamin outcomes study for the Mind: COSMOS-Mind

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ARTICLE INFO

Keywords:
Cocoa flavanols
Multivitamins
Cognitive function
Aging
Alzheimer's disease
Large simple trials

ABSTRACT

Background: Large simple trials are potentially efficient and cost-effective approaches to assess interventions to preserve cognitive function in older adults. High-dose cocoa flavanols supplementation is a promising intervention that warrants additional testing. We describe the design, recruitment success, and baseline characteristics of the Cocoa Supplement and Multivitamin Outcomes Study for the Mind (COSMOS-Mind) trial.

Methods: COSMOS-Mind is an ancillary study to the large-scale and predominantly mail-based COSMOS randomized controlled clinical trial. COSMOS is assessing whether cocoa extract (including 600 mg/d cocoa flavanols) and a multivitamin reduce risks for major cardiovascular events and total invasive cancer. COSMOS-Mind uses telephone-based interviews to assess cognitive function and impairment to determine whether cocoa flavanols benefit cognitive function in adults aged 65 years or older, targeting the enrollment of 2000 participants to provide > 90% statistical power across 3 years of annual follow-up.

Results: Of the 3224 COSMOS screenees who expressed interest in COSMOS-Mind, 2350 (76%) successfully completed baseline cognitive assessments and 2262 (96%) geographically diverse, eligible individuals were ultimately enrolled over one year. At baseline, the primary outcome, a composite of cognitive test scores, was inversely associated with age in a manner consistent with assumptions used in projections of statistical power.

Conclusions: Older adults are willing to enroll in large simple trials that include telephone-based cognitive assessments. Embedding these trials in large studies of other health outcomes is efficient and expands the scientific knowledge gained from the research.

ClinicalTrials.gov Identifiers: NCT03035201 (COSMOS-Mind); NCT102422745 (parent COSMOS).

1. Introduction

With the increasingly large number of people who experience significant cognitive decline, including Alzheimer's disease and related dementias, we are faced with an urgent need to identify effective strategies to preserve cognitive function and mitigate the looming societal burden [1]. There are no FDA-approved interventions to prevent cognitive decline in older adults [2]. Identifying a safe, affordable, and well-tolerated intervention is a high-priority public health care goal [2]. New promising evidence from animal and preliminary clinical studies indicates that high intakes of cocoa flavanols may represent one such potent intervention that warrants testing in a rigorous, sufficiently-powered randomized clinical trial.

Most large multi-center clinical trials of cognitive interventions have been clinic-based, allowing for controlled settings and permitting a range of modes for assessing cognitive function and cognitive

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https://doi.org/10.1016/j.cct.2019.06.019
Received 23 January 2019; Received in revised form 16 June 2019; Accepted 27 June 2019
Available online 02 July 2019

impairment: face-to-face interviews, computer-based assessments, and formal clinical testing (e.g. brain imaging or cerebrospinal fluid collection). This approach is 1) limited in its geographic reach, typically conducted in a few experienced academic medical centers, 2) adds participant burden, and 3) may be costly. These limitations have led to consideration of other models, including networks of trained assessors dispersed across broad geographic regions [3] and computer-based approaches using web-based platforms [4].

Another novel approach is conducting standardized cognitive assessments through telephone interviews [5,6]. We describe the rationale and design of the Cocoa Supplement and Multivitamin Outcomes Study for the Mind (COSMOS-Mind), a large, simple, cost-effective randomized controlled trial to assess the efficacy of cocoa extract (with 600 mg/d cocoa flavonals) to reduce the risk of telephone-based cognitive decline and impairment, including Alzheimer's disease and other related dementias, in a large, older geographically dispersed cohort.

2. Background

Cocoa flavanols and multivitamin supplements hold promise for reducing risks for cardiovascular disease and cancers, which has motivated the large-scale and predominantly mail-based Cocoa Supplement and Multivitamin Outcomes Study (COSMOS) randomized controlled clinical trial to assess the effects of cocoa flavanols and multivitamin supplementation [7].

Cocoa, in its unprocessed form, contains high quantities of a subclass of flavonoids known as flavonals [8], consisting of catechins and epicatechins, along with theobromine, an alkaloid of the cacao bean with vasodilation properties [9]. Epicatechin, the most common flavanol in cocoa, is rapidly absorbed, readily crosses the blood-brain barrier, can be detected in the brain [10,11], and likely has cumulative physiological effects at high intakes [11,12].

Preliminary findings suggest that cocoa flavanols may benefit cognitive function. Several small, relatively short-term clinical trials provide promising but inconsistent findings in support of cognition-enhancing effects [13]. The strongest evidence of cognitive benefit comes from the Cocoa, Cognition, and Aging (CoCoA) Study, a double-blind randomized trial of cocoa flavanols in 90 cognitively healthy older adults [14] and in 90 individuals with mild cognitive impairment (MCI) [15]. CoCoA participants consumed drinks containing high (993 mg), medium (520 mg), or low (45 mg) doses of cocoa flavanols each day for 8 weeks. In both cognitively healthy and MCI individuals, performance on individual tests of attention and processing speed, working memory, and verbal fluency, and on a global cognitive composite score improved for those in the high and medium dose groups relative to the low dose group [14,15].

Cognitive benefits from consuming cocoa flavanols may derive from a number of mechanisms. These include improved vascular function and neurovascular coupling that result in better cerebral blood flow [16,17]; antioxidant actions [17]; interactions with signaling pathways linked to neurogenesis and neuroprotection [18]; reductions in neural inflammation, insulin resistance, and blood pressure [13,14,18]; and favorable effects on beta-amyloid processing [19].

The use of multivitamins to protect cognitive function has been explored in clinical studies in light of evidence to suggest that many of the targeted biologic pathways may support cognitive function [20], and that nutrient deficiencies in older adults increase risk for cognitive decline and dementia [21]. However, as yet there is not consistent evidence to support cognitive benefit with multivitamin supplementation [22,23]. Further study is needed given their widespread use.

Here we describe the design, recruitment, and baseline characteristics of participants in COSMOS-Mind, an ancillary cognitive study to the COSMOS trial conducted to assess whether supplementation with cocoa flavanols and/or multivitamins benefit cognitive function in older adults.

3. Methods

COSMOS is a large simple randomized, double-blind, placebo-controlled, 2 × 2 factorial clinical trial in women (aged ≥65 years) and men (aged ≥60 years). It tests a patented, well-studied cocoa extract supplement (capsules containing 600 mg/d flavanols, including 80 mg (−)-epicatechins, and 50 mg theobromine (Mars Symbioscience)) and a daily multivitamin (Centrum Silver, Pfizer Inc.) in the prevention of cardiovascular disease and cancer. The mean planned treatment and follow-up period in COSMOS is 4 years. Major inclusion criteria are no history of myocardial infarction or stroke; no history of cancer (excluding non-melanoma skin cancer) diagnosed within last 2 years; no other serious illness that would preclude participation; not taking cocoa or multivitamin supplements, or, if taking, willing to forego their use during the trial; willingness to participate, as evidenced by signing an informed consent form; and successful completion (≥75% adherence) in a 3-month placebo run-in.

COSMOS-Mind, as an ancillary study to COSMOS, has adopted its factorial design. It tests the hypothesis that random assignment to daily cocoa extract, compared with placebo has favorable effects on cognitive function over 3 years. Secondary aims of the study include assessing 1) cognitive effects of multivitamin supplementation relative to placebo; 2) effects of cocoa flavanols on incident MCI and Alzheimer's disease and related dementias; and 3) intervention effects on individual cognitive domains of executive function and episodic memory. Tertiary aims are 1) to examine the consistency of treatment responses to cocoa flavanols and the multivitamin across subgroups defined by age, sex, body mass index, baseline global cognitive function (composite score), depressive symptoms, cardiovascular disease and diabetes, and 2) to examine treatment effects on measures of sleep quality, depressive symptoms, and health-related quality of life.

COSMOS-Mind recruited women and men who met COSMOS inclusion criteria and were 1) at least 65 years of age, 2) not using insulin to control diabetes, 3) had not participated in prior research studies using telephone-based cognitive assessments similar to those administered in the current study, and 4) were able to participate in a cognitive assessment by telephone. Participants were asked to identify a reliable informant who would be able to provide additional information about their cognitive and functional abilities. As COSMOS-Mind participants, all would have successfully completed a 3-month placebo run-in adherence evaluation, which likely excluded adults with significant cognitive impairment at enrollment.

3.1. Recruitment and consenting

Invitations to join the parent COSMOS trial were mailed to nearly three million potential volunteers, including women participating in the extension observational phase of the Women's Health Initiative (WHI) [24], non-randomized respondents to recruitment mailings for the VITamin D and OmegA-3 TriaL (VITAL) [25], and individuals identified through commercial mailing lists and media campaigns. COSMOS recruitment of non-randomized VITAL participants and mass mailings was conducted by Brigham and Women's Hospital, while WHI participants were recruited by the WHI Clinical Coordinating Center at Fred Hutchinson Cancer Research Center. As a result, 35,646 participated in the placebo run-in phase and 21,444 (60%) were ultimately enrolled and randomized into COSMOS.

During this enrollment process, COSMOS screenees who met COSMOS-Mind eligibility criteria of at least 65 years of age and no insulin use were also mailed an invitation to enroll in COSMOS-Mind. The COSMOS-Mind study team was provided contact information for those who expressed interest. Telephone calls were then attempted to 1) confirm willingness to participate in COSMOS-Mind, 2) query adherence to the run-in, 3) test for hearing acuity, and 4) schedule a baseline telephone cognitive assessment. To increase sample enrichment by underrepresented groups, which included those with less than

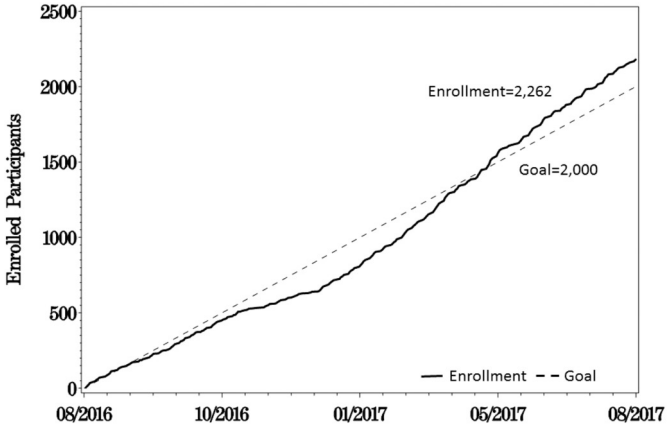

Fig. 1. COSMOS-Mind enrollment: targeted versus achieved over time.

college education, these individuals were prioritized in the COSMOS-Mind initial contact queue to confirm interest in study participation.

COSMOS-Mind enrollment spanned August 2016 to August 2017. Of the 3224 COSMOS screenees who expressed interest, 2350 (76%) successfully completed baseline cognitive assessments, and 2262 (96%) of these were ultimately randomized, a median of 10 days later, in COSMOS and thus became COSMOS-Mind participants, exceeding the recruitment goal of 2000 (Fig. 1).

Participants resided throughout the United States, with geographical representation from all regions and most states (Fig. 2), often many miles from academic medical centers.

3.2. Cognitive function assessment

The standardized cognitive assessment for COSMOS-Mind is administered by trained and certified interviewers masked to treatment assignment in the trial. It consists of the following tests.

- The modified Telephone Interview for Cognitive Status (TICSm) measures global cognitive function [26]. Fourteen items assess orientation, attention, language, learning and memory, and psychomotor skills and abstraction. The modified version of the TICS includes a second free recall trial to assess memory following a short delay for the 10-item word list [27]. In COSMOS-Mind, a third recall trial is administered 15 min after the second trial to quantify memory following a longer delay; this latter score is not included in the total TICSm score.
- Immediate and Delayed Story Recall (SRI & II) measures verbal episodic memory [28]. Participants are read a short story of 25 distinct elements and are asked to recall as many elements as possible immediately after hearing the story (SRI) and again 15–20 min later (SRII). Alternating parallel forms of Story Recall are administered from one annual assessment to the next, in counterbalanced order across participants, to minimize practice effects.
- Oral Trail-Making Test (OTMT) [29] is a modified version of the original Trail-Making Test (TMT) [30] that measures attention (Part A) and executive function (Part B). For Part A, participants are asked to count from 1 to 25 as quickly as possible. For Part B, participants recite numbers and letters in an alternating sequence (1-A-2-B-3-C… 13) as quickly as possible. Time to complete each task (seconds) is recorded. OTMT B errors are corrected immediately with the clock running (time is the score). Once five errors are made the test is stopped and a max score of 300 s is awarded.
- Verbal Fluency is a measure of language accessibility and is assessed using two tasks. Category Fluency requires participants to name as many exemplars of a semantic category as possible in 1 min; two trials are administered (categories: animals, vegetables). Letter Fluency requires participants to name as many words that begin with a specific letter of the alphabet in 1 min; two trials are administered (letters: F, L) [31].
- Number Span Test (NST) measures simple attention and working memory (i.e., ability to manipulate transitory information in short-term memory) [32]. This task requires the participant to repeat a series of single-digit numbers of increasing span length, first in the same order as presented by the examiner (Number Span Forward) and subsequently in the reverse order (Number Span Backward). For each task, 2 trials are administered per span length. The span is increased by 1 number until participants are unable to successfully complete both trials of a given span length. Number of correct responses is recorded.
- Digit Ordering Test (DOT) is also a task of working memory. Participants are read a series of single numerical digits and are asked to recite the numbers in order from lowest to highest (e.g., '2-7-1' would be reordered as '1-2-7') [32]. As with NST, 2 trials are administered per span length, which is increased by 1 until participants fail both trials. Number of correct responses is recorded.

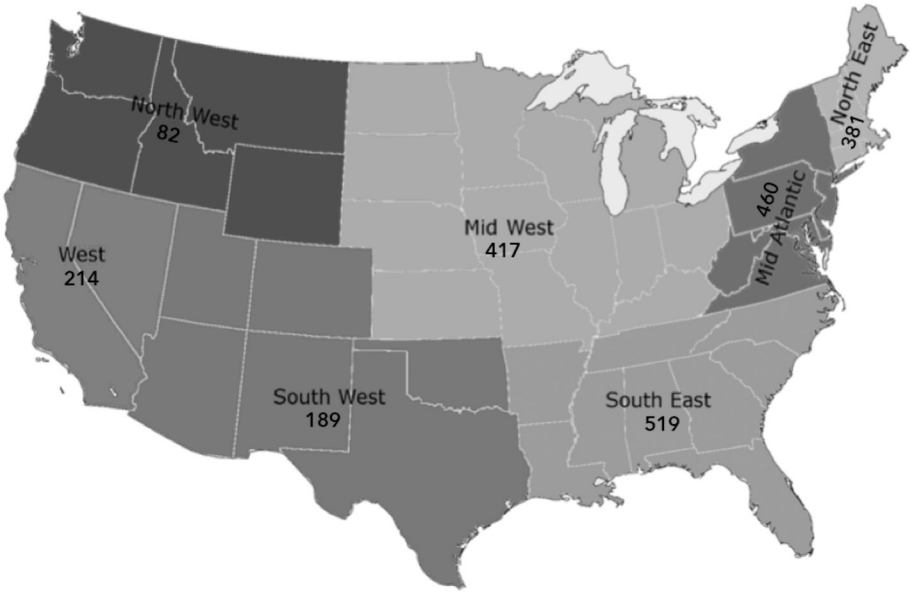

Fig. 2. Geographical distribution of COSMOS-Mind participants: regional sample sizes.

3.3. Additional measures

Additional measurements enrich the COSMOS-Mind trial. The Cognitive Change Index is a self-report questionnaire listing common experiences (e.g., “recalling conversations a few days later”, “remembering names and faces of new people”) and participants indicate amount of perceived change over a specified duration in the past (e.g., 5 years) using a Likert scale [33]. The Geriatric Depression Scale-Short Form measures depressive symptom severity, which is known to affect cognitive function [34]. The Women's Health Initiative Insomnia Rating Scale measures sleep disturbance and insomnia, which are known to impact cognitive function [35]. Finally, the COSMOS trial has richly characterized the cohort at baseline and over time, including self-reported measures related to health and health care, clinical events, and adherence to study pills [7]. These data will be shared with COSMOS-Mind to accomplish its goals and expand its scientific breadth.

3.4. Cognitive adjudication

COSMOS-Mind uses procedures for ascertaining MCI and probable dementia that were developed for the Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health and Outcomes (WHIMS-ECHO) [36] and includes an interview with a reliable informant provided by the participant when TICSm scores fall below 31, or, during follow-up, when TICSm scores drop by 0.5 of a standard deviation relative to age-appropriate normative data. For these participants, the informant is administered a structured telephone interview (Dementia Questionnaire) that includes questions about current cognitive and functional status, and medical events and conditions that could impact cognition (e.g., stroke, psychiatric disorders) [37].

After the planned 3 years of annual evaluations are completed, all available test results and medical information for participants who triggered a Dementia Questionnaire at any time during the study will be provided to dyads of independent dementia experts. The information reviewed will include cognitive data; self-report questionnaires about cognitive concerns, depression, sleep disturbances, and information on hospitalizations, medications and disabilities; informant responses on the Dementia Questionnaire; and relevant health information available through the parent trial (including cardiovascular events and cancers). MCI classifications include amnestic single domain, amnestic multi-domain, non-amnestic single domain, or non-amnestic multi-domain. If the adjudicator dyad agrees on the primary classification (MCI, probable dementia), no further discussion will occur; if the dyad disagrees, the case will be discussed by the entire adjudication panel until consensus is reached. Disagreements regarding MCI sub-classifications will be resolved within dyads and, if not possible, by the entire adjudication panel. For participants who receive a classification of ‘dementia,’ coding will include whether the profile of available results likely reflects an Alzheimer's disease clinical phenotype. For participants who receive a classification of ‘dementia,’ a letter will be sent to notify them that the test results indicated a possible cognitive impairment, and to encourage follow-up with a physician and further evaluation.

3.5. Statistical issues

The primary COSMOS-Mind outcome is a composite measure of cognitive function that combines individual assessments of global cognitive function (TICSm), memory (SR), and executive function (OTMT, Verbal Fluency, NST, DOT). The composite provides a quantifiable measure of cognitive function across multiple domains and greater statistical power than individual measures, even if the intervention effect varies moderately from one individual measure to another. It consolidates type 1 error into a single outcome. Secondary analyses, described below, will examine intervention effects on the constituent measures of the composite score.

The primary hypothesis is that random assignment to cocoa flavanol extract compared to placebo will result in a mean difference over time in the global cognitive composite score. This hypothesis will be tested using 2-tailed type 1 error of 0.05. Inference will be based on the marginal effect estimated from the factorial study design chosen by the parent COSMOS trial, and a mixed effects model for repeated measures (MMRM) with the dependent variable consisting of all measured annual changes from baseline across years of follow-up on every participant, regardless of adherence (i.e. intent-to-treat). Scores from individual tests will be converted to z-scores by dividing their difference from the cohort-wide baseline mean by the cohort-wide baseline standard deviation and ordering these so that greater scores reflect better performance. The composite measure of cognitive function is the average of the individual z-scores. The mean difference in scores from baseline over time will be analyzed with MMRMs. COSMOS-Mind will also assess whether random assignment to a multivitamin compared to placebo affects the global cognitive composite score using parallel analyses to those described above.

We will also assess whether effects of the two interventions interact on the primary outcome, adding a term to the model used in the primary hypothesis. If so, results from the primary marginal comparisons will be qualified. In supporting analyses, individual cognitive test scores and composite scores reflecting episodic memory and executive function will be analyzed, paralleling the strategy used to test the primary hypothesis. Intervention effects on tertiary outcomes including cognitive complaints, sleep quality, and depressive symptoms will be assessed similarly to the analytical approaches for the primary and secondary aims, and further tests will determine whether the interventions interact with respect to tertiary outcomes. Linear contrasts will be used to estimate intervention effects at 3 years. i.e. the marginal mean differences at that time point. Tests of interactions will also assess the potential moderating effect of interventions among subgroups defined by age, sex, body mass index, baseline global cognitive function, cognitive complaints, depressive symptoms, and history and/or current treatment for hypertension and diabetes.

The distribution of follow-up times to MCI and dementia will be assessed with proportional hazards regression. COSMOS-Mind will incorporate cardiovascular and cancer events (from the parent trial) in change-point models to assess their impact on post-event cognitive trajectories. When needed, transformations will be used to improve the symmetry of residual distributions.

No interim monitoring of treatment effects on cognitive outcomes is planned, however monitoring for safety is provided by the COSMOS Data and Safety Monitoring Board. COSMOS-Mind investigators will remain masked to treatment assignment until the parent trial is completed. Routine reports will assess retention, data completeness and quality, and cognitive trajectories over time in the overall COSMOS-Mind cohort.

3.6. Statistical power

Longitudinal sequences of cognitive test scores from the WHIMS-ECHO study [36] ($N = 2878$; 1 to 6 years of annual telephone assessments) were used to calculate the longitudinal covariance of measures by fitting an unstructured MMRM model. Simulations of statistical power were based on 1000 draws of the targeted sample size ($N = 2000$) from a multinormal distribution analyzed with the primary analytical approach described above. While the battery of telephone-based cognitive assessments in the WHIIMS-ECHO trial is not identical to the COSMOS-Mind battery, it was judged to provide a reasonable standard for projections of power. In simulations, random loss-to-follow-up was set to accumulate at 5% per year, as per rates observed in the Women's Health Initiative Memory Study [37]. Based on previous studies of cocoa flavanols on cognition [14,15], the intervention effect was assumed to appear quickly. Calculations were based on 2-sided tests with type 1 error set to 0.05 and 90% power for the primary outcome of a composite score across all cognitive tests. The target of

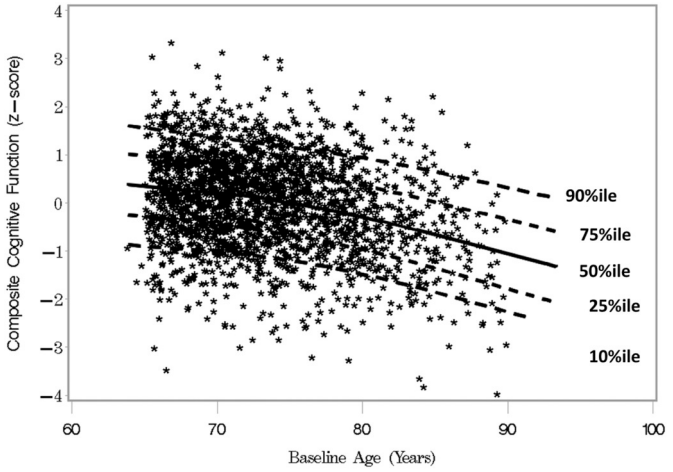

Fig. 3. Distribution of the composite cognitive outcome across age.

enrolling 2000 participants was projected to provide > 90% power to detect a sustained effect size of 0.10 standard deviations and a waning effect size that initially is 0.15 standard deviations. It also provides some leeway should the assumptions made above be not fully realized. Limiting follow-up to 3 years allows a more extended enrollment and analysis period and reduces the number of assessments.

Fig. 3 portrays the distribution of the composite primary outcome for COSMOS-Mind across its age range. The targeted 3-year mean difference between intervention groups for > 90% power was 0.10 standard deviation units, which corresponds approximately to the difference between individuals separated by two years of age in the figure.

3.7. Baseline characteristics

Table 1 describes the 2262 participants who enrolled in COSMOS-Mind and were randomized into the main COSMOS trial. Mean age was 74.4 years and 60% were women. Most had attended college and 10.9% were from traditionally under-represented racial or ethnic minority groups. As noted above, COSMOS-Mind achieved geographical diversity with substantive representation from all regions of the United States. Table 2 describes the scores from the baseline cognitive function assessments.

4. Discussion

Large simple clinical trials that are designed to reduce costs and avoid clinic-based assessments are increasingly advocated [38,39]. These studies target moderate intervention effects and tolerate the potential lack of discrimination that costly clinic-based assessments provide, using randomization and large cohorts to achieve balance and statistical power. Additionally, they allow enrollment to extend far beyond the circumscribed geography of clinical centers, thereby increasing diversity and, potentially, generalizability. COSMOS-Mind demonstrates that such trials designed to assess cognitive outcomes using only telephone- and mail-based participant contact are feasible.

The COSMOS-Mind trial also leverages the opportunity to embed cognitive outcomes as an ancillary study to the primary trial outcomes and leads to efficiency, as recommended by a recent consensus report [2]. In this way, research costs are reduced and the scientific footprint and contributions of studies are magnified.

The timely enrollment seen in COSMOS-Mind, which exceeded the original goals of the study, demonstrates that older adults are willing to enroll in large simple trials and undergo telephone-based cognitive function. This builds on the experience of prior large cohort and trials studies that have demonstrated that high quality cognitive data can be collected through telephone interviews and that these data align well with clinic-based assessments [6,40,41].

Table 1
Distribution of self-reported risk factors for cognitive deficits and dementia at baseline for COSMOS-MIND participants.

Risk factors for cognitive decline	Mean (SD) or frequency (percent) $N = 2262$
Age, years	73.5 (5.7)
Age group	
65–69	715 (31.6)
70–74	778 (34.4)
75–79	467 (20.6)
80–84	211 (19.3)
85+	91 (4.0)
Sex	
Female	1348 (59.6)
Male	914 (40.4)
Education (Missing = 3)	
Less than high school	11 (0.5)
High school or GED	258 (11.4)
Attended college	879 (38.7)
Post-college	1111 (49.2)
Race/Ethnicity, N (%) (Missing = 7)	
African-American/Black	132 (5.9)
American Indian/Alaskan Native	13 (0.6)
Asian	38 (1.7)
Hispanic/Latino	62 (2.8)
Native Hawaiian/Pacific Islander	2 (0.1)
Non-Hispanic White	2008 (89.1)
Body Mass Index, kg/m^2 (Missing = 246)	
< 25	653 (32.4)
25–29	839 (41.6)
≥30	524 (26.0)
Hypertension history, N (%) (Missing = 9)	1333 (59.2)
Aspirin use, N (%) (Missing = 21)	1121 (50.0)
Smoking Status, N (%) (Missing = 37)	
Never	1153 (51.8)
Former	1004 (45.1)
Current	68 (3.1)
Alcohol intake, N (%) (Missing = 70)	
< 1/Day	1607 (73.3)
1/Day	275 (12.6)
2+/day	310 (14.1)

Table 2
Cognitive test scores at baseline for COSMOS-Mind participants.

Cognitive test	Mean	Standard deviation	Interquartile range
TICS-m			
Total score (max = 50)	36.6	3.9	[34, 39]
Long-delay recall (max = 10)	3.02	1.83	[2, 4]
Story recall (max = 25)			
Immediate	12.0	3.8	[10, 15]
Delayed	10.8	3.9	[8, 13]
Oral trail-making test			
Part A	9.6	3.0	[8, 11]
Part B	47.6	56.3	[24, 46]
Verbal fluency			
Category	35.0	8.2	[35, 40]
Letter	25.5	8.1	[25, 31]
Number span test			
Forward	8.19	2.39	[8, 10]
Backward	6.87	2.32	[7, 8]
Digit ordering test	6.26	2.19	[6, 8]

Acknowledgments

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Funding and support

The COcoa Supplement and Multivitamin Outcomes Study for the Mind (COSMOS-Mind) is supported by a grant from the National Institutes of Health: 5R01AG050657-02. Additional support was received from the Wake Forest Alzhiemer's Disease Research Center (P30AG049638-01A1).

The parent COcoa Supplement and Multivitamin Outcomes Study receives support from Mars Symbioscience (infrastructure support, donation of cocoa flavanol capsules and matched placebos, and calendar packaging) and Pfizer Inc. (donation of Centrum Silver multivitamin tablets, matched placebos, and calendar packaging). Recruitment for COSMOS involved a public-private partnership between the Women's Health Initiative (National Institutes of Health; HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C), the VITamin D and OmegA-3 TriaL (National Institutes of Health; CA138962), and Mars Symbioscience.

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators can be found at: http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf [whi.org].

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