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Design and baseline characteristics of participants in the COcoa Supplement and Multivitamin Outcomes Study (COSMOS)

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abstract

Background: Cocoa extract and multivitamins have been proposed to reduce the risk of cardiovascular disease (CVD) and cancer, respectively. However, few randomized clinical trials have tested their long-term effects on these outcomes.

Methods: The COcoa Supplement and Multivitamin Outcomes Study (COSMOS) is a randomized, double-blind, placebo-controlled, 2×2 factorial trial of a cocoa extract supplement and a multivitamin supplement to reduce the risk of CVD and cancer. Here we describe the pragmatic, hybrid design of the trial and baseline characteristics of the trial participants.

Results: The nationwide study population includes 21,442 U.S. women aged ≥65 years and men aged ≥60 years without baseline myocardial infarction (MI), stroke, or a recent (within the past 2 years) cancer diagnosis. Participants were randomized in a 2×2 factorial design to one of four groups: (1) cocoa extract (containing 500 mg/d flavanols, including 80 mg (−)-epicatechins) and a multivitamin (Centrum Silver©); (2) cocoa extract and multivitamin placebo; (3) multivitamin and cocoa extract placebo; or (4) both placebos. Randomization successfully distributed baseline demographic, clinical, behavioral, and dietary characteristics across treatment groups. Baseline biospecimens were collected from 6867 participants, with at least one follow-up biospecimen from 2142 participants. The primary outcome for the cocoa extract intervention is total CVD (a composite of MI, stroke, cardiovascular mortality, coronary revascularization, unstable angina requiring hospitalization, carotid artery surgery, and peripheral artery surgery); the primary outcome for the multivitamin intervention is total invasive cancer.

Conclusion: COSMOS will provide important information on the health effects of cocoa extract and multivitamin supplementation in older U.S. adults.

Introduction

Cocoa is made from the bean of the cacao tree, *Theobroma cacao*, and has a long history of medicinal use[1] and potential health benefits based upon its flavanol and procyanidin

content,[2] along with other flavanol-containing foods and beverages such as grapes, wine, tea, and others. Several smaller-scale, shorter-term clinical dietary intervention studies have investigated various flavanol-containing foods, beverages, and purified flavanols and procyanidins in the context of vascular function and cardiovascular health.[3–5] Within this body of literature, studies based on cocoa and cocoa products are prominent and often use chemically and nutritionally well-characterized test materials that have been consistently linked with cardiovascular[6,7] and cardiometabolic[8] health with beneficial effects on endothelium-dependent vasodilation,[9–12] blood pressure (BP),[9,13–15] inflammation,[16,17] and platelet activation.[18,19] These data have also provided important insights into the absorption, distribution, metabolism, and excretion of flavanols in humans[20–22] and the potential vascular effects due to intake of the flavanol (−)-epicatechin.[12,23] However, there have been no large-scale trials testing cocoa extract for prevention of clinical cardiovascular disease (CVD) events.

Multivitamins, which typically contain a broad range of essential vitamins and minerals, are the most common dietary supplement taken by at least one-third of US adults[24,25] and an even larger percentage of older adults.[26,27] Studies have reported that adults take multivitamins to promote general health and well-being[28] or to reduce chronic diseases.[29] Yet findings from longitudinal studies of long-term multivitamin use and total and site-specific cancer[30–36] and CVD[33,37–40] are inconsistent. In the Physicians' Health Study (PHS) II, a randomized trial testing a multivitamin in 14,641 men aged ≥50 years, there was a modest but statistically significant 8% reduction in total incident cancer[41] and no effect on CVD.[42] Notably, among 1,312 men with a baseline history of cancer in PHS II, a daily multivitamin significantly reduced cancer by 27%. With no corresponding randomized trial data in women, a confirmatory large-scale randomized trial was warranted given the potential clinical and public health impact of any benefits associated with multivitamin use.

We therefore initiated the COcoa Supplement and Multivitamin Outcomes Study (COSMOS), a pragmatic, large-scale, 2×2 factorial randomized trial testing a cocoa extract supplement and a standard multivitamin in the prevention of CVD and cancer events among older women and men. COSMOS also represents an important collaboration among academic, government, and industry partners as a cost-effective clinical trial that leverages existing cohort infrastructure including that of the Women's Health Initiative (WHI) and the VITamin D and OmegA-3 TriaL (VITAL).[43] We describe the overall methodology of COSMOS and present baseline characteristics of the COSMOS trial cohort.

Methods

The COcoa Supplement and Multivitamin Outcomes Study (COSMOS) [clinicaltrials.gov NCT02422745] is a randomized, double-blind, placebo-controlled, 2×2 factorial trial testing a cocoa extract supplement (containing 500 mg/d cocoa flavanols, including 80 mg (−)-epicatechins) and a multivitamin supplement (Centrum Silver®) to reduce the risk of cardiovascular disease (CVD) and cancer in 21,442 U.S. adults, including 12,666 women aged ≥65 years and 8,776 men aged ≥60 years who are free of self-reported myocardial infarction, stroke, and recently diagnosed cancer within the past 2 years. Figure 1 summarizes the overall recruitment and 2×2 factorial design for the COSMOS trial.

Integration of WHI and VITAL cohorts as part of recruitment

We enhanced recruitment for COSMOS by inviting potential participants with available data from existing cohorts ("embedded" recruitment). We initially mailed to 71,521 active participants from the Women's Health Initiative (WHI) Extension Study[44] and then to 237,736 participants (including 140,454 women and 97,282 men) contacted for, but not randomized into, the VITamin D and OmegA-3 TriaL (VITAL) at Brigham and Women's Hospital (BWH).[45] To ultimately reach our recruitment targets, BWH sent mass mailings with recruitment invitations using commercially available mailing tapes to 2,616,343 U.S. men and women plus 3,380 volunteers who heard about the study through multiple sources, including advertisements and word of mouth.

Additional Recruitment Efforts

The nationwide trial recruitment process for COSMOS began in June 2015 and was completed by March 2018. The overall process of recruitment and determining eligibility had 4 steps, including (1) a brief initial screening questionnaire completed by 191,796 participants; (2) for those expressing interest and having initial eligibility, a baseline questionnaire and informed consent were sent; (3) for those eligible, willing, and consenting, a placebo run-in of at least 2 months was begun by 35,669 participants; and (4) for all run-in participants, final compliance, eligibility, expanded baseline characteristics, and semi-quantitative food frequency questionnaires were completed.[46] All CSMOS subjects read and remotely signed an informed consent. When deciding whether to sign the consent form, potential participants were given multiple opportunities to speak with study staff about the risks and benefits of study participation. All trial activities were overseen by the Human Subjects Committee at BWH/Mass General Brigham.

Eligibility criteria

Eligible participants did not report a history of MI or stroke and were not diagnosed with invasive cancer (except non-melanoma skin cancer) in the last 2 years. Participants had to agree to forgo supplements of cocoa extract and multivitamins during the trial (chocolate intake was not restricted), and limit vitamin D to ≤1000 IU/day and calcium to ≤1200 mg/day from all supplemental sources during the trial, and complete at least a 2-month placebo run-in phase in which they missed ≤8 days of pills per month (equivalent to taking ~75% of study pills). Safety exclusions included renal failure or dialysis or other serious conditions that would preclude participation. We also excluded participants with extreme sensitivity to caffeine given the modest theobromine (50 mg/day) and caffeine (15 mg/day) content of the cocoa extract supplement.

Interventions and calendar packs

Active cocoa extract and matching inert placebo was provided by Mars Edge. The cocoa extract intervention was selected based on extensive prior testing of similar products for quality, patient safety, and vascular and cardiometabolic outcomes in small mechanistic trials. Participants were asked to take two capsules per day. Upon initiation of the COSMOS trial, the cocoa flavanol content totaled 600 mg/day, including 80 mg/d (−)-epicatechin. After the COSMOS trial began, an advanced method to analyze cocoa flavanols was

accredited by AOAC International as a First Action Official Method of Analysis.[47] This updated method relied on a reference material (RM8403) recently standardized and made commercially available by the U.S. National Institute of Standards and Technology. Although the actual cocoa flavanol content of the COSMOS intervention remained unchanged throughout the trial, the application of this new analytical method led to expected changes in how the total cocoa flavanol content is now reported. Applying AOAC 2020.05/RM8403 to the COSMOS intervention, the total cocoa flavanol content of the COSMOS intervention is now determined to be 500 mg/day. Reporting of (−)-epicatechin content remained unaffected.

Active multivitamin (currently marketed as Centrum Silver®) and matching inert placebo was provided by Pfizer Inc (Pfizer Consumer Healthcare is now part of GSK Consumer Healthcare). We selected the multivitamin intervention for greater generalizability as a commonly used formulation, along with prior safety and consistency with that tested in PHS II, despite minor formulation differences (See Supplemental Table 1 for the composition of the cocoa extract supplement and Supplemental Table 2 for the composition of the multivitamin.) Participants took one active or placebo multivitamin tablet per day. Participants were provided with blinded calendar packs containing all study pills.

Run-in and randomization

A total of 35,669 potential participants who remained eligible and interested after the second mailing were asked to complete at least a 2-month single-blind placebo run-in to eliminate poor compliers prior to randomization, increase study power, and improve the internal validity of a trial.[48] Eliminating non-compliers prior to randomization through the use of a placebo run-in mitigates the impact of noncompliance on exposure misclassification and the dilution of the intervention's effects. In addition, by using an inert placebo during the run-in period, we avoided excluding non-compliant participants due to adverse intervention effects that can occur from giving active pills during the run-in phase.

We excluded 14,227 (39.9%) of 35,669 participants after the run-in due to noncompliance (defined as not taking study pills on >8 days per month during the run-in) or becoming unwilling or ineligible to participate in COSMOS. Among those randomized, median run-in was 4.6 (4.1–5.5) months. From April 2016 to March 2018, 21,442 participants meeting all eligibility requirements were randomized via a 2×2 factorial design to one of four treatment groups with equal probabilities: (1) active cocoa extract (containing 500 mg/d flavanols, including 80 mg (−)-epicatechins) and an active daily multivitamin (Centrum Silver®) (n=5,360); (2) active cocoa extract and multivitamin placebo (n=5,359); (3) active multivitamin and cocoa extract placebo (n=5,360); or (4) both placebos (n=5,363). Randomization was computer generated using a permuted block approach and stratified by sex (women, men), age (for women, 65-<70, 70-<75, 75-<80, 80-<85, and ≥85 years; for men, 60-<65, 65-<70, 70-<75, 75-<80, and ≥80 years), and recruitment source (WHI or BWH) in blocks of twelve. Double-blinded calendar packs containing their assigned pills were centrally mailed to all randomized COSMOS participants, with resupplies of their blinded calendar packs mailed as needed and typically coinciding with the receipt of follow-up questionnaires.

Follow-up

Approximately 6 and 12 months following randomization and semi-annually thereafter, COSMOS participants were sent follow-up questionnaires via REDCap or mail to assess compliance with randomized treatments, use of non-trial cocoa supplements and/or multivitamins, potential side effects of the interventions, updated medical history including study outcomes (confirmed by medical records, as described below), and other relevant lifestyle, clinical, and dietary risk factors. A second food frequency questionnaire was sent at 2 years follow-up. COSMOS participants from the WHI received separate annual mailings from the WHI to update medical history and outcome follow-up. The COSMOS randomized treatments continued through December 31, 2020, ending as scheduled, and with a median (IQR) treatment period of 3.6 (3.2 – 4.2) years.

Primary Outcomes

The primary outcome for the cocoa extract intervention when COSMOS was initiated was a composite total cardiovascular outcome including incident myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular mortality. However, during the active COSMOS intervention period, we observed that the overall rates of CVD were less than originally projected due to (a) the impact of COVID-19 on 2020 reported CVD event rates; (b) WHI women comprising 21.5%, versus the original plan for 66.7%, of the COSMOS trial cohort, resulting in younger non-WHI women with lower CVD event rates; and (c) lower CVD rates due to increasing use of statins and other preventive treatments. As a result, in November 2020 we obtained approval from the COSMOS Data and Safety Monitoring Board (DSMB) to expand the primary total CVD outcome to add carotid artery surgery, peripheral artery surgery, and unstable angina requiring hospitalization, consistent with the atherosclerotic mechanisms underlying the intervention hypotheses, especially for the cocoa flavanols. This expansion of the total CVD outcome would provide us with a similar number of outcomes as used in our initial power calculations. However, this mix of cardiovascular outcomes may be less rigorous and biologically relevant than a stricter composite cardiovascular outcome limited to MI, stroke, and CVD death. For the multivitamin intervention, the primary outcome was invasive cancer, excluding non-melanoma skin cancer.

Sample Size and Power Calculations

Power calculations for the primary outcomes were initially based upon a 2×2 factorial trial in 18,000 participants, including 12,000 women aged ≥65 years and 6,000 men aged ≥60 years, and then were revised upward to 22,000 participants, including 13,000 women and 9,000 men, based on initial WHI and BWH recruitment patterns. Each primary outcome comparison (cocoa extract versus placebo and multivitamins versus placebo) was based on an independent, marginal test at α=0.05. Estimates of study power using the log-rank tables by Freedman[49] and the expected numbers of confirmed events were based on the following assumptions: (1) independent and equal allocation of participants to each treatment; (2) an age distribution based on that observed among WHI women ≥65 years and men aged ≥60 years responding to the VITAL mailings; (3) annualized age-specific event rates based on observed rates during WHI and VITAL follow-up, adjusted for aging; (4) equivalent

event rates for men and women given that women are approximately 5 years older than men; (5) expected mean trial follow-up of 4 years, with minimal loss to follow-up as seen previously in WHI and VITAL; and (6) an average of 80% compliance with study pills. These assumptions remained identical for our power calculations for 18,000, then 22,000, participants. For 22,000 randomized participants, we had at least 80% power to detect an 11% relative hazard reduction in total CVD with the expected number of events. Similarly, there would be at least 90% power to detect a 14% reduction in total cancer.

Secondary outcomes

For the cocoa extract intervention, secondary outcomes included the original composite CVD outcome of MI, stroke, cardiovascular mortality and coronary revascularization; a combined outcome of CVD events and all-cause mortality; individual cardiovascular events comprising the expanded composite outcome; invasive cancer (excluding non-melanoma skin cancer); and key site-specific cancers, including breast, colorectal, and lung cancer. For the multivitamin intervention, secondary outcomes again included key site-specific cancers in older individuals, including breast, colorectal, and lung cancer; the risk of total cancer among those with a baseline history of cancer (given previous evidence for a significant 27% reduction in total cancer among men aged 50 years or older in PHS II[41]); the expanded total CVD outcome; a combined outcome of CVD and all-cause mortality; and individual cardiovascular events comprising the expanded composite total cardiovascular outcome.

Medical record collection

COSMOS participants reporting a primary or secondary study outcome signed a medical record release form allowing WHI and BWH to request related medical records that were evaluated and processed according to standardized procedures.[50] COSMOS participants from the WHI Medical Records Cohort (MRC) had medical record retrieval and outcome adjudication using established WHI procedures; events reported by other WHI participants enrolled in COSMOS were identified and adjudicated using the same procedures as the WHI MRC participants. COSMOS participants from BWH followed the same medical record retrieval and adjudication procedures, which were conducted by BWH staff.

Outcome adjudication

Self-reported primary and secondary outcomes were confirmed or disconfirmed through medical record review by a committee of physicians and investigators blinded to treatment assignment. To adjudicate CVD events, discharge summaries, electrocardiograms (ECGs), laboratory values, and test reports were sought. MI was defined by standardized criteria including cardiac pain, cardiac enzymes including troponin levels, and ECG findings. Coronary revascularization included documented coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI), coronary stent, or artherectomy.[50] Unstable angina requiring hospitalization included reports of increased pain, use of medications to alleviate pain, no evidence of MI, plus other related factors. Because unstable angina requiring hospitalization had not previously been adjudicated for WHI participants in COSMOS, these medical records were obtained by BWH staff and self-reports adjudicated by BWH adjudicators. Carotid artery surgery and peripheral artery surgery included review and identification from surgical and radiology reports. Stroke was classified according to

the Trial of Org 10172 in Acute Stroke Therapy (TOAST)[51] and Oxfordshire subtype.[52] Coronary heart disease and stroke deaths included deaths consistent with either outcome as an underlying cause. For incident cancers, discharge summaries, pathology reports, operative reports, and diagnostic or treatment procedure reports, including both inpatient and outpatient diagnoses, were requested. Invasive cancer was confirmed by a biopsy or surgical pathology report that substantiated a malignant invasive cancer at any location other than non-melanoma skin cancer.[50] All histologic types and anatomic subsites were included. Noncancerous colorectal polyps, atypical benign breast disease, in situ cancers, and other premalignant benign conditions were excluded. Finally, second primaries at a site and recurrences of cancer were also ascertained. For participants determined to be deceased, BWH or WHI Regional Center staff, as appropriate, reached out to the family requesting permission to obtain medical records and a copy of the death certificate. Death certificates were alternatively requested from the participant's next of kin and periodic National Death Index Plus searches were also performed.

Biospecimen collection and clinic subcohort

COSMOS is a hybrid trial that combines large-scale remote interventions with in-person biospecimen collections and clinic-based assessments for in-depth mechanistic studies on how the proposed interventions may lead to study outcomes.[53] COSMOS participants were asked to provide optional baseline biospecimens, and we invited an equal number of women and men to provide sufficient power to evaluate effect modification by sex. A total of 6,867 randomized participants returned blood and spot urine samples collected either (a) on their own through mailed biospecimen kits that were returned by the participant or (b) by home-based visits by Examination Management Services, Inc. that also included seated BP and anthropometrics measurements. A third option of visiting a Quest clinic for a biospecimen collection was added during the study to assist with follow-up biospecimen collection and shipments. At least one follow-up biospecimen was collected at 1-, 2-, and/or 3-, year follow-up in 2,155 participants using similar procedures.

The COSMOS clinic subcohort consisted of 603 participants in the greater Boston area willing to complete a baseline in-person clinic visit toward the end of the run-in phase and just before their final eligibility assessment and randomization. The clinic visits consisted of in-depth phenotyping with measurements of anthropometrics, seated BP, 24-hour ambulatory BP, physical performance, biospecimen collection, dual-energy x-ray absorptiometry testing for spine and hip bone mineral density, pulse wave analysis and velocity, and structured cognitive assessments.[45] A total of 535 (89% of those completing a baseline assessment) participants had repeated follow-up clinic assessments at 2 years follow-up.

Cognitive ancillary studies

Two separately funded COSMOS substudies were integrated into the initial COSMOS trial design to examine cognitive outcomes. First, COSMOS Mind [clinicaltrials.gov NCT03035201] examined a global composite measure of cognitive function across 3 years of telephone-based assessments in 2,142 non-demented participants aged ≥65 years.[54] Second, COSMOS Web [clinicaltrials.gov NCT04582617] examined the interventions on

a range of aging-related cognitive measures using a novel online-administered test battery initially in nearly 4,000 COSMOS participants with 3 years of follow-up assessments. COSMOS Web was built upon earlier[55] and more recent findings[56] on the effect of cocoa flavanol supplementation over 12 weeks on changes in cognition in healthy older adults. The primary outcome for COSMOS Web will be change in ModRey immediate recall performance[56,57] over 1 year.

Data analyses

The primary analyses of this 2×2 factorial trial will be based on the intention-to-treat principle[58] and use Cox proportional hazards models for time-to event data[59] to estimate the hazard ratio for each intervention using indicators for the specific treatment and stratifying the baseline hazard function by the second intervention, sex, age group, and recruitment center. Kaplan-Meier cumulative incidence curves, interactions between randomization groups with time, and analyses that exclude the first 1 and 2 years of follow-up will assess whether treatment effects vary over time.[60] In secondary analyses, we will examine effect modification by the other randomized intervention, age, sex, other key risk factors, concomitant medications, baseline dietary intake of chocolate (for the cocoa extract analyses) or fruit and vegetable intake (for the multivitamin analyses), and baseline history of disease (CVD or cancer). Interactions will be interpreted cautiously as hypothesis generating. We will also examine compliance analyses that estimate the effects on our outcomes when weighted by the inverse probability of dependent-censoring for non-compliance with study procedures, with compliance defined as missing ≤8 days of study pills per month and abstaining from use of non-study cocoa extract or multivitamins.[61] Main results from the trial are expected to be published in 2022.

For the present study, to ascertain the comparability of treatment groups at baseline, we calculated the mean or median values of continuous variables and percentages in each category of discrete variables. Differences for continuous variables were tested by two-sample t-test or analysis of variance for more than two groups for normally distributed data and the nonparametric two-sample Wilcoxon rank–sum or Kruskal–Wallis test comparing multiple groups for data that were not normally distributed. Percentages were compared by chi-square tests. Statistical significance was assessed with two-sided p-values.

Results

Table 1 presents the baseline characteristics of the COSMOS trial cohort overall and stratified by randomized treatment assignment. Of the 21,442 randomized participants, 59.1% are women and 40.9% are men. The mean age of the cohort is 72.1 years (range 60–102.7 years). The majority of the cohort reported their race as white (90.0%) while 5.3% are Black 2.3% are Asian/Pacific Islander, and 0.3% are American Indian/Alaskan Native. 2.6% of the cohort reported their ethnicity as Hispanic/Latino. All four geographic regions of the United States are well-represented. There were no clinically important or statistically significant differences between treatment groups comparing these demographic factors. For major cancer and/or CVD risk factors, 27.2% of participants were obese (body mass index ≥30 kg/m^2), 58.1% were hypertensive, 13.4% had diabetes, 44.2% current use

cholesterol-lowering medication, and 4.0% were current smokers. Of the 3,550 individuals (16.6% of the entire COSMOS trial cohort) who reported a diagnosis of cancer more than two years prior to study enrollment, 679 (3.2%) reported melanoma and 2,740 (12.8%) reported non-skin cancer. Of those reporting a non-skin cancer, 32.0% had a history of breast cancer and 21.0% had a history of prostate cancer. There were no clinically important or statistically significant differences between the treatment groups for these factors or for any other health history or behavioral characteristics listed below. At the initial screening, 0.4% of the cohort reported using cocoa flavanol supplements and 41.0% of individuals reported using multivitamins. However, these individuals agreed to stop taking cocoa flavanol or multivitamin supplements for the trial duration and thus were randomized into COSMOS.

Table 2 provides the baseline demographic, health, and behavioral characteristics of study participants stratified by sex. As expected given the sex-specific age cut points for trial entry (age ≥60 years for men and age ≥65 years for women), the average age of female participants was older than male participants (mean age 74.2 versus 69.0 years; $P < 0.001$). There were significant differences between men and women in nearly all baseline characteristics examined. For example, men were more likely to report a lower prevalence of obesity, parental history of MI, personal history of non-skin cancer, family history of colorectal or lung cancer, multivitamin use, vitamin D or calcium supplement use at initial screening; had higher levels of physical activity; and had a higher prevalence of cholesterol-lowering medication use, diabetes and antidiabetic medications, personal history of a revascularization procedure, personal history of melanoma only, current smoking, aspirin use, consumption of alcohol daily or more often, and colonoscopy/sigmoidoscopy in the past 10 years.

Table 3 provides the baseline characteristics of the 6,867 participants who provided an optional blood sample (with nearly all additionally providing a spot urine) at baseline (the “blood subcohort”), the 603 individuals who had a baseline health examination at the Center for Clinical Investigation (CCI) at BWH (the “clinic subcohort”), and the 3,550 individuals who reported a history of cancer at study enrollment. Overall, the blood subcohorts was similar to the overall COSMOS cohort, although there was a higher percentage of non-Hispanic white individuals and of men. This difference in sex distribution is expected given the design decision to enroll equal numbers of men and women into the blood subcohort. Due to the higher percentage of men and the lower age eligibility in men compared to women, we also observed a slightly higher percentage of individuals in the youngest age group (60 to 69 years) in the blood subcohort than in the total cohort. To participate in the clinic subcohort, individuals had to be willing to travel to the CCI clinic and complete a 5- to 7-hour assessment. As a result, the clinic subcohort is younger and somewhat healthier than the overall cohort, with a lower prevalence of hypertension, cholesterol-lowering medication use, diabetes, and obesity, a higher level of physical activity, and a higher prevalence of compliance with cancer screening recommendations (colonoscopy/sigmoidoscopy and mammography). Further, the majority of COSMOS clinic subcohort participants were non-Hispanic white. Of the 603 individuals in the clinic subcohort, 236 individuals also participated in the blood subcohort and provided remotely collected blood and urine samples. Finally, those with a history of cancer at study enrollment were slightly

older than the overall cohort (mean age 73.9 years) and were slightly more likely to report a family history of cancer in their first-degree relatives.

Discussion

We observed balance in the distribution of demographic, health history, and behavioral characteristics across the four randomized treatments groups in COSMOS. This implies that unknown or unmeasured confounders are also likely to be equally distributed across the treatment groups. As a result, we expect that any observed differences in our outcomes will be attributable to the interventions themselves rather than to uncontrolled confounding.

For efficiency, COSMOS recruited participants from the WHI and non-randomized participants in VITAL. Among WHI and VITAL participants invited to participate in COSMOS, randomization rates were 6.4% and 2.9%, respectively, figures which are substantially higher than the randomization rate of 0.36% which we observed from our nationwide mass mailings to age-eligible adults.[53] This demonstrates that leveraging other ongoing epidemiologic studies may help to improve and expedite recruitment in clinical trials, which typically involves major logistical, budgetary, and time challenges. In addition, this approach successfully recruited an older population of individuals for a trial that will be conducted almost entirely through remote assessments. Notably, over the course of the trial to date, more than 75% of the study population was willing to complete questionnaires through REDCap (electronic data capture). Although men aged ≥60 years and women aged ≥65 years were eligible to participate in the trial, the average age of the trial cohort was 72.1 years. The ability to collect not only baseline questionnaire data, but also biospecimens, demonstrates the feasibility of using pragmatic and cost-effective recruitment and data collection methods in older adults.

Another important feature of COSMOS is the hybrid design, which combines a large-scale remotely-conducted trial to complement primary and secondary clinical outcomes with detailed phenotyping on a subset of individuals to answer mechanistic questions as well as address additional clinically meaningful outcomes such as cognitive function. As described earlier, the COSMOS blood subcohort was designed to have equal numbers of men and women. As a result, the blood subcohort has a higher percentage of males than the overall cohort, but is otherwise similar to the overall COSMOS study population. This suggests that analyses utilizing the data from the blood subcohort will be generalizable to the full trial population. Further, the availability of multiple follow-up biospecimen collections will allow us to examine changes in compliance-based biomarkers of both interventions, as well as changes in other markers related to the study outcomes. Although the clinic subcohort was slightly younger and healthier than the total cohort, the results from the clinic subcohort will be internally valid and should provide important in-depth, in-person phenotyping of participants in the context of the results from the main trial. However, generalizability may be limited given the modest racial and ethnic diversity of the cohort as well as the potential for healthy volunteer bias for participants willing and eligible to enroll in a largely mail-based clinical trial.

In summary, COSMOS is a large-scale, innovative, and pragmatic randomized trial that will provide important and relevant information about the balance of benefits and risks of a cocoa extract supplement for the prevention of CVD and of a multivitamin for the prevention of cancer among older adults. The unique hybrid design of COSMOS, which includes biospecimen collections and clinic-based assessments, will also allow for in-depth mechanistic studies on how the proposed interventions may lead to study outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

COSMOS has been approved and overseen by the Institutional Review Board of Brigham and Women's Hospital/Mass General Brigham. COSMOS is registered at clinicaltrials.gov (NCT02422745). The COSMOS website is www.cosmostrial.org. We are deeply indebted to the 21,442 COSMOS participants for their steadfast and conscientious collaboration and to our COSMOS Research Group of trial investigators and staff for their commitment and perseverance to the trial despite the challenges of the COVID-19 pandemic. We would like to specifically acknowledge the following individuals from the COSMOS Research Group for their scientific (Brigham and Women's Hospital [BWH]), Fred Hutchinson Cancer Research Center [FHCRC], Women's Health Initiative [WHI], Data Safety and Monitoring Board [DSMB], Mars Edge) and logistical (BWH, FHCRC, DSMB, Mars Edge, Contract Pharmacal Corp, Pfizer Consumer Healthcare [now GSK Consumer Healthcare]) contributions:

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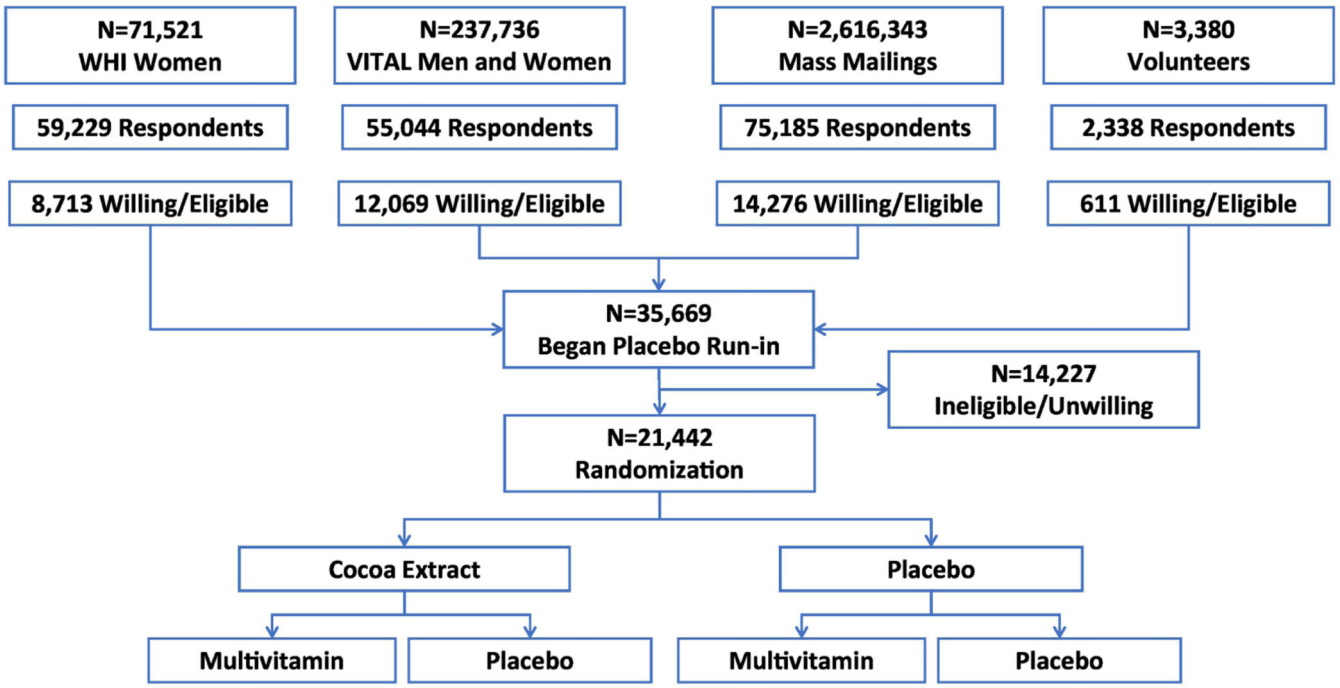

Figure 1.

Recruitment and 2×2 factorial design for the COcoa Supplement and Multivitamin Outcomes Study (COSMOS)

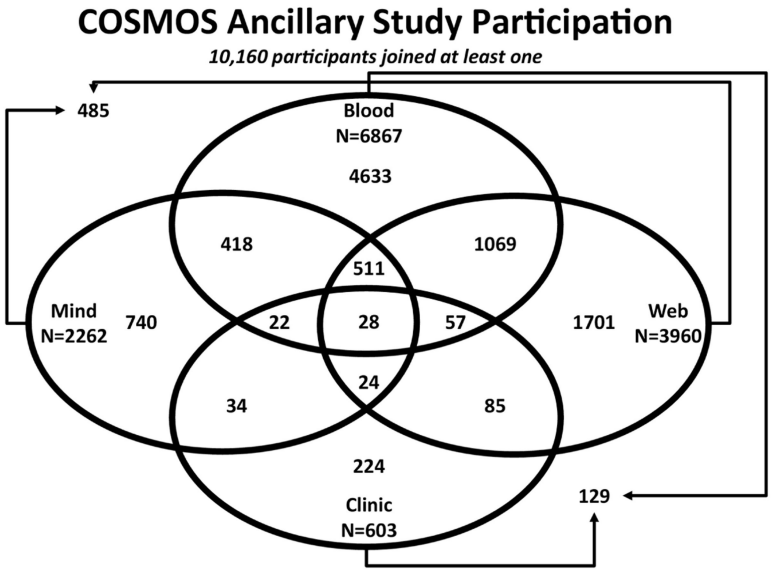

Figure 2.
Summary of COSMOS ancillary study participation.

Table 1.

Baseline demographic, health, and behavioral characteristics among 21,442 COSMOS participants, according to randomized treatment assignment.

Baseline Characteristic	Total cohort[a] (N=21,442)	Cocoa extract active and Multivitamin active (N=5360)	Cocoa extract active and Multivitamin placebo (N=5359)	Cocoa extract placebo and Multivitamin active (N=5360)	Cocoa extract placebo and Multivitamin placebo (N=5363)
Sex, % Male Female	 8776 (40.9) 12666 (59.1)	 2189 (40.8) 3171 (59.2)	 2193 (40.9) 3166 (59.1)	 2193 (40.9) 3167 (59.1)	 2201 (41.0) 3162 (59.0)
Mean age (SD), years	72.1 (6.6)	72.1 (6.6)	72.1 (6.6)	72.1 (6.5)	72.1 (6.6)
Age group, years, % 60–69 70–74 75–79 80–84 ≥85	 9224 (43.0) 5774 (26.9) 3751 (17.5) 1761 (8.2) 932 (4.4)	 2305 (43.0) 1443 (26.9) 938 (17.5) 441 (8.2) 233 (4.4)	 2305 (43.0) 1443 (26.9) 938 (17.5) 441 (8.2) 232 (4.3)	 2306 (43.0) 1443 (26.9) 937 (17.5) 448 (8.4) 226 (4.2)	 2308 (43.0) 1445 (26.9) 938 (17.5) 431 (8.0) 241 (4.5)
Hispanic/Latino, %	544 (2.6)	134 (2.6)	118 (2.3)	150 (2.9)	142 (2.8)
Race, % White Black Asian/Pacific Islander American Indian/Alaskan Native Multiracial/other/unknown or not reported	 19294 (90.0) 1131 (5.3) 499 (2.3) 59 (0.3) 459 (2.1)	 4796 (89.5) 290 (5.4) 138 (2.6) 17 (0.3) 119 (2.2)	 4828 (90.1) 268 (5.0) 136 (2.5) 14 (0.3) 113 (2.1)	 4832 (90.1) 278 (5.2) 120 (2.2) 20 (0.4) 110 (2.1)	 4838 (90.2) 295 (5.5) 105 (2.0) 8 (0.1) 117 (2.2)
Geographic region, % Northeast[b] Midwest/Mountain South West/Southwest	 5941 (27.7) 5071 (23.6) 6151 (28.7) 4279 (20.0)	 1495(27.9) 1295 (24.2) 1497 (27.9) 1073 (20.0)	 1450 (27.1) 1241 (23.2) 1567 (29.2) 1101 (20.5)	 1504 (28.1) 1266 (23.6) 1547 (28.9) 1043 (19.5)	 1492 (27.8) 1269 (23.7) 1540 (28.7) 1062 (19.8)
Education, % High school diploma/GED or less Attended or graduated from college Post-college	 2296 (10.8) 8685 (40.9) 10241 (48.3)	 588 (11.1) 2117 (39.9) 2596 (49.0)	 553 (10.4) 2211 (41.6) 2551 (48.0)	 592 (11.2) 2198 (41.5) 2508 (47.3)	 563 (10.6) 2159 (40.7) 2586 (48.7)
Health History					
Mean body mass index (SD), kg/m^2	27.7 (5.4)	27.6 (5.3)	27.7 (5.4)	27.7 (5.4)	27.8 (5.5)
Obesity[c], %	5718 (27.2)	1402 (26.7)	1457 (27.7)	1398 (26.6)	1461 (27.8)
Hypertension, %	12423 (58.1)	3048 (57.0)	3142 (58.8)	3105 (58.1)	3128 (58.5)
Ever use of anti-hypertensive medication, %	11217 (53.0)	2758 (52.3)	2817 (53.1)	2814 (53.2)	2828 (53.3)
Current use of cholesterol-lowering medication, %	9405 (44.2)	2366 (44.4)	2346 (44.0)	2348 (44.2)	2345 (44.0)
Diabetes, %	2864 (13.4)	702 (13.1)	715 (13.3)	713 (13.3)	734 (13.7)
Current use of antidiabetic medication, %	2233 (10.4)	541 (10.1)	558 (10.4)	557 (10.4)	577 (10.8)
Parental history of premature myocardial infarction[d], %	4112 (21.6)	1044 (22.1)	1027 (21.5)	1054 (22.1)	987 (20.7)
Personal history of revascularization procedure, %	862 (4.0)	225 (4.2)	205 (3.8)	201 (3.8)	231 (4.3)
Personal history of cancer, % Only melanoma Melanoma plus non-skin	 3550 (16.6) 679 (3.2)	 917 (17.1) 168 (3.1)	 858 (16.0) 163 (3.0)	 896 (16.7) 183 (3.4)	 879 (16.4) 165 (3.1)

Baseline Characteristic	Total cohort[a] (N=21,442)	Cocoa extract active and Multivitamin active (N=5360)	Cocoa extract active and Multivitamin placebo (N=5359)	Cocoa extract placebo and Multivitamin active (N=5360)	Cocoa extract placebo and Multivitamin placebo (N=5363)
cancer Only non-skin cancer	131 (0.6) 2740 (12.8)	36 (0.7) 713 (13.3)	34 (0.6) 661 (12.3)	25 (0.5) 688 (12.8)	36 (0.7) 678 (12.6)
Family history of cancer in first degree relative Colorectal, % Breast (women only, %) Prostate (men only, %) Lung, %	3748 (18.5) 2522 (21.1) 1548 (18.7) 3569 (17.7)	929 (18.3) 648 (21.5) 389 (18.9) 873 (17.3)	920 (18.2) 605 (20.2) 385 (18.4) 911 (18.0)	938 (18.6) 638 (21.6) 390 (18.8) 896 (18.0)	961 (19.0) 631 (21.2) 384 (18.5) 889 (17.6)
Behavioral characteristics and medication use					
Smoking, % Current Past Never	835 (4.0) 8731 (41.3) 11565 (54.7)	199 (3.8) 2173 (41.2) 2904 (55.0)	199 (3.8) 2223 (42.1) 2862 (54.2)	218 (4.1) 2172 (41.0) 2904 (54.9)	219 (4.2) 2163 (41.0) 2895 (54.9)
Leisure-time physical activity and stair climbing, total MET-hours/week, median (IQR)	17.6 (5.7–33.5)	18.0 (5.7–34.1)	17.3 (5.5–33.5)	17.8 (6.0–33.5)	17.1 (5.6–33.4)
Aspirin use in past month, %	10379 (48.9)	2617 (49.3)	2594 (48.9)	2551 (48.1)	2617 (49.3)
Postmenopausal hormone use, % (women only) Current Past Never	1021 (8.2) 6158 (49.7) 5199 (42.0)	256 (8.3) 1548 (49.9) 1298 (41.8)	246 (7.9) 1561 (50.4) 1290 (41.7)	247 (8.0) 1521 (49.0) 1333 (43.0)	272 (8.8) 1528 (49.6) 1278 (41.5)
Screening behaviors in past 10 years Colonoscopy/sigmoidoscopy, % Prostate-specific antigen test, % (men only) Mammogram, % (women only)	17572 (83.4) 6958 (81.3) 11650 (93.4)	4393 (83.3) 1715(80.4) 2906 (93.0)	4373 (83.0) 1764 (82.2) 2918 (93.6)	4422 (83.8) 1718 (80.5) 2919 (93.7)	4384 (83.4) 1761 (82.0) 2907 (93.4)
Dietary factors at initial screening					
Calcium intake from supplements[e], % None ≤1200 mg/day >1200 mg/day	10917 (51.5) 9200 (43.4) 1066 (5.0)	2708 (51.0) 2342 (44.1) 255 (4.8)	2731 (51.7) 2279 (43.1) 273 (5.2)	2775 (52.5) 2254 (42.6) 261 (4.9)	2703 (51.0) 2325 (43.8) 277 (5.2)
Vitamin D intake from supplements[e], % None ≤1000 IU/day >1000 IU/day	7960 (37.6) 8670 (41.0) 4536 (21.4)	1971 (37.2) 2218 (41.9) 1109 (20.9)	1962 (37.1) 2133 (40.3) 1193 (22.6)	2041 (38.6) 2113 (40.0) 1129 (21.4)	1986 (37.5) 2206 (41.6) 1105 (20.9)
Current use of multivitamins[f], %	8795 (41.2)	2237 (41.9)	2201 (41.2)	2176 (40.8)	2181 (40.8)
Current use of cocoa extract supplements[f], %	91 (0.4)	22 (0.4)	23 (0.4)	20 (0.4)	26 (0.5)
Chocolate intake[g], % Rarely Monthly Weekly Daily or more often	3352 (17.0) 2923 (14.8) 11129 (56.4) 2317 (11.8)	850 (17.2) 716 (14.5) 2800 (56.8) 568 (11.5)	790 (16.1) 739 (15.1) 2806 (57.3) 566 (11.5)	850 (17.1) 751 (15.1) 2775 (55.9) 586 (11.8)	862 (17.5) 717 (14.6) 2748 (55.8) 597 (12.1)
Alcohol use[g], % Rarely Monthly	5867 (29.7) 1462 (7.4)	1408 (28.5) 376 (7.6)	1489 (30.4) 349 (7.1)	1483 (29.9) 375 (7.6)	1487 (30.1) 362 (7.3)

Baseline Characteristic	Total cohort[a] (N=21,442)	Cocoa extract active and Multivitamin active (N=5360)	Cocoa extract active and Multivitamin placebo (N=5359)	Cocoa extract placebo and Multivitamin active (N=5360)	Cocoa extract placebo and Multivitamin placebo (N=5363)
Weekly	7136 (36.2)	1821 (36.9)	1779 (36.3)	1736 (35.0)	1800 (36.4)
Daily or more often	5276 (26.7)	1331 (27.0)	1289 (26.3)	1366 (27.5)	1290 (26.1)

[a] For categorical variables, this column contains # participants in category/% of nonmissing responses. For continuous variables, this column contains mean (standard deviation) or median (interquartile range) for nonmissing responses. The prevalence of missing responses for all variables ranged from 0 to <5%, except for the following: parental history of premature myocardial infarction (11.2%), history of cancer in first-degree relative (colorectal, 5.6%; prostate, 5.5%; lung, 6.0%; breast 5.7%), chocolate intake (8.0%), alcohol consumption (7.9%),

[b] Includes one individual living on a US Army Base in Europe.

[c] Height and weight were self-reported

[d] Defined as a heart attack prior to 65 years of age

[e] Participants had to agree to limit vitamin D to ≤1000 IU/day and calcium to ≤1200 mg/day from all supplemental sources during the trial

[f] Participants had to agree to forgo supplements of cocoa extract and multivitamins (chocolate intake was not restricted) during the trial.

[g] Includes consumption of milk chocolate, dark chocolate, white chocolate and candy bars

[h] Includes beer, liquor, red wine, and white wine.

Table 2.

Baseline demographic, health, and behavioral characteristics among 21,442 COSMOS participants, according to sex.

Baseline Characteristic[a]	**Men (N=8776)**[b]	**Women (N=12666)**[b]
Mean age (SD), years	69.0 (6.1)	74.2 (6.0)
Age group, years, % 60–69 70–74 75–79 80–84 ≥85	 5580 (63.6) 1753 (20.0) 898 (10.2) 382 (4.4) 163 (1.9)	 3644 (28.8) 4021 (31.7) 2853 (22.5) 1379 (10.9) 769 (6.1)
Hispanic/Latino, %	233 (2.8)	311 (2.6)
Race, % White Black Asian/Pacific Islander American Indian/Alaskan Native Multiracial/other/unknown or not reported	 7940 (90.5) 392 (4.5) 254 (2.9) 19 (0.2) 171 (1.9)	 11354 (89.6) 739 (5.8) 245 (1.9) 40 (0.3) 288 (2.3)
Geographic region, % Northeast Midwest/Mountain South West/Southwest	 2721 (31.0) 2063 (23.5) 2596 (29.6) 1396 (15.9)	 3220 (25.4) 3008 (23.7) 3555 (28.1) 2883 (22.8)
Education, % High school diploma/GED or less Attended or graduated from college Post-college	 540 (6.2) 3348 (38.5) 4808 (55.3)	 1756 (14.0) 5337 (42.6) 5433 (43.4)
Health History		
Mean body mass index (SD), kg/m^2	27.9 (4.7)	27.5 (5.8)
Obesity, %	2291 (26.3)	3427 (27.8)
Hypertension, %	5074 (57.9)	7349 (58.2)
Ever use of anti-hypertensive medication, %	4530 (52.3)	6687 (53.4)
Current use of cholesterol-lowering medication, %	4302 (49.2)	5103 (40.7)
Diabetes, %	1273 (14.5)	1591 (12.6)
Current use of antidiabetic medication, %	1014 (11.6)	1219 (9.6)
Parental history of premature myocardial infarction, %	1625 (20.4)	2487 (22.4)
Personal history of revascularization procedure, %	564 (6.4)	298 (2.4)
Personal history of cancer, % Only melanoma Melanoma plus non-skin cancer Only non-skin cancer	 1346 (15.3) 342 (3.9) 59 (0.7) 945 (10.8)	 2204 (17.4) 337 (2.7) 72 (0.6) 1795 (14.2)
Family history of cancer in first degree relative Colorectal, % Breast (women only, %) Prostate (men only, %) Lung, %	 1384 (16.7) NA 1548 (18.7) 1378 (16.7)	 2364 (19.7) 2522 (21.1) NA 2191 (18.4)
Behavioral characteristics and medication use		
Smoking, % Current Past Never	 415 (4.8) 3622 (41.8) 4620 (53.4)	 420 (3.4) 5109 (41.0) 6945 (55.7)

Baseline Characteristic[a]	Men (N=8776)[b]	Women (N=12666)[b]
Leisure-time physical activity and stair climbing, total MET hours/week, median (IQR)	20.3 (7.5, 36.9)	15.9 (4.7, 31.3)
Aspirin use in past month, %	4700 (53.8)	5679 (45.4)
Postmenopausal hormone use, % (women only) Current Past Never	 NA NA NA	 1021 (8.2) 6158 (49.7) 5199 (42.0)
Screening behaviors in past 10 years Colonoscopy/sigmoidoscopy, % Prostate-specific antigen test, % (men only) Mammogram, % (women only)	 7441 (85.8) 6958 (81.3) NA	 10131 (81.7) NA 11650 (93.4)
Dietary factors at initial screening		
Calcium intake from supplements, % None ≤1200 mg/day >1200 mg/day	 5920 (67.9) 2668 (30.6) 126 (1.5)	 4997 (40.1) 6532 (52.4) 940 (7.5)
Vitamin D intake from supplements, % None ≤1000 IU/day >1000 IU/day	 4519 (52.0) 3008 (34.6) 1166 (13.4)	 3441 (27.6) 5662 (45.4) 3370 (27.0)
Current use of multivitamins, %	3208 (36.7)	5587 (44.3)
Current use of cocoa extract supplements, %	28 (0.3)	63 (0.5)
Chocolate intake Rarely Monthly Weekly Daily or more often	 1442 (18.5) 1108 (14.2) 4378 (56.2) 862 (11.1)	 1910 (16.0) 1815 (15.2) 6751 (56.6) 1455 (12.2)
Alcohol use, % Rarely Monthly Weekly Daily or more often	 7810 (89.0) 1814 (23.2) 441 (5.6) 2762 (35.4) 2793 (35.8)	 11931 (94.2) 4053 (34.0) 1021 (8.6) 4374 (36.7) 2483 (20.8)

[a] Variable definitions are provided in footnotes to Table 1.

[b] For categorical variables, this column contains # participants in category/% of nonmissing responses. For continuous variables, this column contains mean (standard deviation) or median (interquartile range) for nonmissing responses.

Table 3.

Baseline demographic, health, and behavioral characteristics among 21,442 COSMOS participants, in the overall cohort and according to participation in (a) the baseline blood subcohort, (b) the baseline clinic subcohort, and (c) those with a baseline history of cancer.

Baseline Characteristic[a]	**Total cohort**[b] **(N=21,442)**	**Blood subcohort (N=6867)**	**Clinic subcohort**[c] **(N=603)**	**Baseline History of Cancer (N=3550)**
Sex, % Male Female	 8776 (40.9) 12666 (59.1)	 3369 (49.1) 3498 (50.9)	 306 (50.7) 297 (49.3)	 1346 (37.9) 2204 (62.1)
Mean age (SD), years	72.1 (6.6)	71.1 (6.3)	69.7 (5.5)	73.9 (6.5)
Age group, years, % 60–69 70–74 75–79 80–84 ≥85	 9224 (43.0) 5774 (26.9) 3751 (17.5) 1761 (8.2) 932 (4.4)	 3363 (49.0) 1785 (26.0) 1078 (15.7) 421 (6.1) 220 (3.2)	 347 (57.5) 165 (27.4) 63 (10.4) 25 (4.1) 3 (0.5)	 1043 (29.4) 1110 (31.3) 776 (21.9) 398 (11.2) 223 (6.3)
Hispanic/Latino, %	544 (2.6)	160 (2.4)	6 (1.0)	65 (1.9)
White race, %	19294 (90.0)	6427 (93.6)	586 (97.2)	3246 (91.4)
Geographic region, % Northeast Midwest/Mountain South West/Southwest	 5941 (27.7) 5071 (23.7) 6151 (28.7) 4279 (20.0)	 1969 (28.7) 1696 (24.7) 1887 (27.5) 1315 (19.1)	 603 (100)	 955 (26.9) 876 (24.7) 961 (27.1) 758 (21.4)
Education, % High school diploma/GED or less Attended or graduated from college Post-college	 2296 (10.8) 8685 (40.9) 10241 (48.3)	 588 (8.7) 2773 (40.9) 3426 (50.5)	 37 (6.2) 236 (39.8) 320 (54.0)	 363 (10.4) 1405 (40.2) 1731 (49.5)
Health History				
Mean body mass index (SD), kg/m^2	27.7 (5.4)	27.6 (5.3)	27.1 (4.9)	27.6 (5.4)
Obesity, %	5718 (27.2)	1753 (25.9)	136 (22.8)	923 (26.5)
Hypertension, %	12423 (58.1)	3865 (56.4)	301 (49.9)	2190 (61.9)
Ever use of anti-hypertensive medication, %	11217 (53.0)	3499 (51.6)	261 (44.0)	1989 (56.8)
Current use of cholesterol-lowering medication, %	9405 (44.2)	3118 (45.6)	254 (42.2)	1672 (47.5)
Diabetes, %	2864 (13.4)	871 (12.7)	66 (11.0)	484 (13.6)
Current use of antidiabetic medication, %	2233 (10.4)	660 (9.6)	53 (8.8)	377 (10.6)
Parental history of premature myocardial infarction, %	4112 (21.6)	1386 (22.3)	124 (22.8)	692 (22.1)
Personal history of revascularization procedure, %	862 (4.0)	291 (4.2)	23 (3.8)	159 (4.5)
Personal history of cancer, % Only melanoma Melanoma plus non-skin cancer Only non-skin cancer	 3550 (16.6) 679 (3.2) 131 (0.6) 2740 (12.8)	 1149 (16.7) 205 (3.0) 43 (0.6) 901 (13.1)	 94 (15.6) 20 (3.3) 1 (0.2) 73 (12.1)	 3550 (100.0) 679 (19.1) 131 (3.7) 2740 (77.2)
Family history of cancer in first degree relative Colorectal, % Breast (women only, %) Prostate (men only, %) Lung, %	 3748 (18.5) 2522 (21.1) 1547 (18.7) 3569 (17.7)	 1220 (18.7) 717 (21.5) 602 (18.8) 1160 (17.8)	 98 (17.2) 56 (19.6) 54 (19.1) 107 (18.9)	 677 (20.3) 509 (24.6) 321 (25.3) 629 (18.9)

Baseline Characteristic[a]	Total cohort[b] (N=21,442)	Blood subcohort (N=6867)	Clinic subcohort[c] (N=603)	Baseline History of Cancer (N=3550)
Behavioral characteristics and medication use				
Smoking, % Current Past Never	 835 (4.0) 8731 (41.3) 11565 (54.7)	 254 (3.7) 2829 (41.7) 3701(54.6)	 14 (2.3) 260 (43.6) 323 (54.1)	 117 (3.3) 1562 (44.7) 1817 (52.0)
Leisure-time physical activity and stair climbing, total METhours/week, median (IQR)	17.6 (5.7–33.5)	20.0 (7.3, 35.3)	20.0 (8.1, 36.6)	16.6 (5.4, 31.4)
Aspirin use in past month, %	10379 (48.9)	3383 (49.6)	274 (45.8)	1681 (47.9)
Postmenopausal hormone use, % (women only) Current Past Never	 1021 (8.2) 6158 (49.7) 5199 (42.0)	 337 (9.8) 1717 (50.2) 1368 (40.0)	 29 (9.8) 121 (41.0) 145 (49.2)	 128 (6.0) 1096 (51.1) 921 (42.9)
Screening behaviors in past 10 years Colonoscopy/sigmoidoscopy, % Prostate-specific antigen test, % (men only) Mammogram, % (women only)	 17572 (83.4) 6958 (81.3) 11650 (93.4)	 5862 (86.5) 2748 (83.2) 3280 (94.9)	 557 (93.5) 234 (78.3) 290 (98.3)	 3047 (87.3) 1159 (88.1) 2007 (92.8)
Dietary factors at initial screening				
Calcium intake from supplements, % None ≤1200 mg/day >1200 mg/day	 10917 (51.5) 9200 (43.4) 1066 (5.0)	 3511 (51.7) 2938 (43.3) 343 (5.1)	 328 (54.9) 246 (41.2) 23 (3.9)	 1639 (46.8) 1663 (47.5) 202 (5.8)
Vitamin D intake from supplements, % None ≤1000 IU/day >1000 IU/day	 7960 (37.6) 8670 (41.0) 4536 (21.4)	 2535 (37.3) 2718 (40.0) 1545 (22.7)	 239 (40.0) 249 (41.7) 109 (18.3)	 1123 (32.0) 1524 (43.4) 863 (24.6)
Current use of multivitamins, %	8795 (41.2)	2904 (42.4)	231 (38.4)	1594 (45.1)
Current use of cocoa extract supplements, %	91 (0.4)	19 (0.3)	2 (0.3)	17 (0.5)
Chocolate intake Rarely Monthly Weekly Daily or more often	 3352 (17.0) 2923 (14.8) 11129 (56.4) 2317 (11.8)	 1054 (16.2) 967 (14.9) 3712 (57.2) 757 (11.7)	 96 (16.7) 82 (14.2) 330 (57.5) 66 (11.5)	 562 (17.3) 462 (14.2) 1846 (56.8) 382 (11.7)
Alcohol use, % Rarely Monthly Weekly Daily or more often	 5867 (29.7) 1462 (7.4) 7136 (36.2) 5276 (26.7)	 1745 (26.9) 431 (6.6) 2387 (36.7) 1936 (29.8)	 131 (22.9) 33 (5.8) 226 (39.6) 181 (31.7)	 970 (29.8) 238 (7.3) 1167 (35.9) 877 (27.0)

[a] Variable definitions are provided in footnotes to Table 1.

[b] For categorical variables, this column contains # participants in category/% of nonmissing responses. For continuous variables, this column contains mean (standard deviation) or median (interquartile range) for nonmissing responses.

[c] Participants in the greater Boston area willing to complete a baseline clinic visit toward the end of the run-in phase and just before their final eligibility assessment and randomization