



From the COSMOS Trial Directors

Dear COSMOS participant,

Now that the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) is well underway, we wish to thank each of you for your commitment to this important research study. We are grateful that you have chosen to enroll in this landmark study—and to take your study pills faithfully—to determine whether taking daily supplements of cocoa extract (which contain 600 mg per day of cocoa flavanols, as well as other natural compounds in the cocoa bean) or a common multivitamin (Centrum Silver) reduces the risk for developing heart disease, stroke, or cancer. We are pleased to report that we have met, and even exceeded, our recruitment goal—more than 18,000 participants throughout the United States have joined the study!

COSMOS is being conducted by researchers at Brigham and Women's Hospital in collaboration with Dr. Garnet Anderson and colleagues at the Fred Hutchinson Cancer Research Center in Seattle (see photo on page 3).

Thank you for being part of the COSMOS community!

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COSMOS: Testing the health benefits of cocoa flavanols and multivitamins

Although many small, short-term clinical trials have shown that consumption of high amounts of cocoa flavanols favorably affects the cardiovascular system by relaxing blood vessels and stimulating blood flow, improving control of blood sugar and blood lipid profile, reducing blood pressure, and tamping down inflammation, it remains unknown whether long-term use of cocoa flavanol supplements protects against the development of heart disease and stroke. COSMOS is the first and only large randomized clinical trial designed to test whether long-term daily consumption of a flavanol-rich cocoa extract can prevent heart disease and stroke, as well as cancer, in generally healthy adults.

COSMOS is also testing whether a daily multivitamin (Centrum Silver) can prevent these diseases. Because COSMOS is the first large randomized trial of multivitamins to include both women and men as participants, its eventual results are expected to shape guidelines regarding multivitamin use for prevention of cancer and cardiovascular disease in the general population.

In addition, several optional COSMOS substudies are examining whether the supplements confer other health benefits. Eye- and cognition-related substudies are described below, and other substudies will be featured in future newsletters.

Eye substudy. Cataract and age-related macular degeneration (AMD) are leading causes of vision loss in middle-aged and

older U.S. adults. Cataract is a clouding of the lens of the eye, and AMD is a degeneration of the central part of the retina responsible for fine-detail vision. In **COSMOS-Eye**, the COSMOS team is partnering with Harvard colleague Dr. William Christen to determine if a daily multivitamin and a cocoa extract supplement can prevent cataract and AMD. COSMOS participants are asked on questionnaires whether they have been diagnosed with either of these conditions or have had cataract surgery. Participants who report these outcomes are asked to sign a medical record release form to allow us to obtain the relevant medical record information from their eye doctor. This research is funded by the National Eye Institute at the National Institutes of Health.

Cognitive substudies. Laboratory studies show that cocoa flavanols not only dilate blood vessels and improve blood flow in the brain but also may promote brain cell connections and survival and protect brain cells from harmful inflammation. Higher flavanol intake is associated with lower risk for cognitive decline and Alzheimer's disease in some observational studies, and two small, short-term randomized trials have found cognition-enhancing effects of cocoa flavanols. These results, together with the above data showing favorable effects of cocoa flavanols on heart risk factors and accumulating evidence linking heart and brain health (see related story on page 2), suggest that cocoa extract supplementation may be of benefit for cognitive function.

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Preventing Memory Loss

Memory loss is such a frightening and frustrating aspect of aging that of course we want to do what we can to keep our minds sharp. Although genetic factors—which we cannot control—affect a person’s susceptibility to cognitive decline, scientific research conducted over the last three decades has begun to identify strategies that may help to reduce our risk. That said, it is important to recognize that cognitive research is still in a state of relative infancy—there are many small studies with non-rigorous study designs but fewer large, long-term observational studies and even fewer large clinical trials. (With respect to the nutritional supplements being tested in COSMOS, cocoa flavanols have shown promise in observational studies and in small randomized trials but have not been tested in large trials. Data from large trials of multivitamins are also sparse. To help fill these knowledge gaps, COSMOS substudies are testing whether cocoa flavanol supplements and/or a multivitamin can prevent cognitive decline in a subset of participants [see page 1].)

Although large clinical trials are necessary to confirm some of these recommendations, here are some strategies currently endorsed by the Alzheimer’s Association¹ that may help to lower the risk of cognitive decline and dementia. As you look through the list, you may notice that many of the recommendations echo those for good heart health—and that’s no coincidence. The concept of “what’s good for the heart is also good for the brain” emerged early on and has been consistently supported by cognitive research.

☀️ Make moderate-intensity physical activity such as walking, biking, swimming, and gardening, or more vigorous activity such as jogging and hiking, a habit. Aim for 150 minutes per week of moderate activity or 75 minutes per week of vigorous activity. In one long-term study of 18,000 female nurses

aged 70-81 years, women who were the most physically active appeared to shave 3 years off their cognitive age compared with physically inactive women.

☀️ Eat a healthy diet that *emphasizes* vegetables, fruits, and whole grains; *includes* fish, beans, nuts, poultry, low-fat dairy products, and oils rich in unsaturated fats (such as canola or olive oil); and *limits* sweets, sugary beverages, and red meats. Well-known examples of this dietary pattern are the Mediterranean and the Dietary Approaches to Stop Hypertension (DASH) diets.

☀️ Engage in cognitively stimulating or challenging activities such as reading; playing strategy games such as bridge, chess, or Scrabble; memorizing poetry, geographical facts (for example, state capitals), or the like; solving crossword or jigsaw puzzles; learning a foreign language; practicing a musical instrument; trying new recipes; or taking classes at a local college or community center. In an eye-opening randomized trial among 2,832 older adults, those who received as few as ten 60- to 75-minute sessions of mental training not only experienced immediate improvement in their cognitive functioning in daily activities but also continued to show benefits 10 years later, compared with control subjects.

☀️ Avoid head injuries. Wear a seat belt when in the car, use a helmet when on a bike, and take precautions to prevent falls, such as doing balance and coordination exercises (for example, yoga or tai chi) and making sure that your home is well lit and free of stumble-inducing obstacles. Nightlights or bedside flashlights are useful for middle-of-the-night trips to the bathroom.

☀️ Take care of your mental health. Seek treatment for symptoms of depression or anxiety, and try to reduce stress. Stress triggers our adrenal glands to release cortisol, a stress hormone that, at chronically high levels, negatively affects the brain.

☀️ Get a good night’s sleep. Seek treatment for conditions that interfere with quality sleep, such as insomnia or sleep apnea.

☀️ Don’t smoke. People who have never smoked or who have quit smoking appear to be 30% less likely to experience cognitive decline than current smokers.

☀️ Avoid or manage medical conditions that raise risk of cardiovascular disease, including hypertension, diabetes, high LDL (“bad”) cholesterol, and the metabolic syndrome, a cluster of symptoms that includes abdominal obesity (belly fat), high triglycerides, high blood pressure, high blood sugar, and low HDL (“good”) cholesterol. Recently, investigators with the Atherosclerosis Risk in Communities (ARIC) study, which followed 15,744 adults aged 45-64 for 25 years, found that those with cardiovascular risk factors during middle age were more likely to develop dementia later in life.² The researchers also analyzed brain scans from a subgroup of ARIC participants and found that the presence of one or more cardiovascular risk factors at midlife was associated with higher levels of beta amyloid, a protein that often accumulates in the brains of Alzheimer’s patients.³

☀️ Maintain strong social connections to family and friends. Although cognitive researchers disagree on the importance of this strategy, some data suggest that people who are socially engaged may be less likely to experience cognitive decline than those who are socially isolated. This may be in part because isolated individuals have fewer opportunities for cognitively stimulating conversations or activities.

1. Alzheimer’s Association. Lifestyle changes help reduce risk of cognitive decline, June 1, 2015. Available at http://www.alz.org/news_and_events_lifestyle_changes_help_reduce_risk.asp
 2. *JAMA Neurology* 2017; 74:1246-1254.
 3. *JAMA* 2017; 317:1443-1450.

Q&A

Q. My doctor wants to know what study pills I am taking as part of COSMOS. What should I tell him or her?

A. Please tell your doctor that you are taking part in a 4-year randomized clinical trial of a cocoa extract supplement and a multivitamin for the prevention of cardiovascular disease and cancer. Your orange study capsules contain *either* cocoa extract (two capsules contain 600 mg of cocoa flavanols) or placebo, and your grey study tablets contain *either* a multivitamin (Centrum Silver) or placebo. At the end of the trial, you will be told which type of study pills you have been taking. Although it may be helpful for your doctor to be aware of your participation in COSMOS, neither you nor your doctor should assume that the study pills can replace any of your prescribed medications.

Q. Why is it important to complete the annual study questionnaires?

A. For the validity of the study, it is essential that we account for the health status of every person who was assigned to a treatment or placebo group at the beginning of the study. Therefore, even if you are not currently taking the study capsules, it is very important for us to receive your completed health questionnaires. Please know that all information is treated confidentially.

Q. Why do you ask for the name and telephone number of a contact person?

A. In a long-term study such as COSMOS, we occasionally lose touch with study participants when they move or have other changes in their status. We will write or telephone your contact person to ask for your current address or phone number only if we cannot reach you after multiple attempts.

Q. Why do you ask for date of birth on every questionnaire?

A. In a study as large as COSMOS, there are often one or more participants with the same name. In addition to your name and study ID number, your date of birth serves as a unique identifier.

Additional Q&As can be found on the COSMOS website at www.cosmostrial.org.



COSMOS colleagues at the Fred Hutchinson Cancer Research Center in Seattle, Washington.

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Two substudies will examine whether cocoa extract and multivitamins can prevent cognitive decline in COSMOS participants. In **COSMOS-Mind**, approximately 2,000 participants are being interviewed by telephone on a yearly basis during the study. Each interview will last about 45 minutes and will assess memory and thinking ability. This substudy is funded by the National Institute on Aging and is being carried out by the COSMOS team in collaboration with Drs. Laura Baker and Mark Espeland at the Wake Forest School of Medicine in North Carolina. In **COSMOS-Web**, approximately 4,000 participants are completing a 30-minute internet-based computerized assessment at the beginning of the trial and each year thereafter. In addition, a subset of 500 COSMOS participants who live close to Brigham and Women's Hospital in Boston, Massachusetts are completing these assessments in person at the beginning of the trial and again 2 years later. This substudy is funded by Mars Symbioscience and is being carried out by the COSMOS team in collaboration with Drs. Adam Brickman and Scott Small at the Columbia University Medical Center in New York City. (Please note that the cognitive assessments in COSMOS cannot be used alone to diagnose clinical dementia or specific neurologic disorders; such diagnoses require a more comprehensive medical evaluation.) These cognitive substudies offer exciting opportunities for COSMOS participants to contribute to groundbreaking research on cocoa extract supplements, multivitamins, and brain health.

Thank you for participating in COSMOS and taking your study pills faithfully, which will provide critically needed information to resolve uncertainties about the health effects of cocoa flavanols and multivitamins.



DONALD B., of Ohio, at the total solar eclipse in Hopkinsville, Kentucky, August 21, 2017.



JUDITH M., of California, pictured at a tram stop in Lisbon, Portugal, writes, "I have been a participant in the WHI [Women's Health Initiative] for over 20 years. I joined the COSMOS ... study because I am healthy and enjoying my life and would like to contribute so that other[s] ... may similarly live healthy lives."



In August 2017, **ESTHER B.**, of Wisconsin, wrote, "I am very happy to have been chosen to be a participant in the COSMOS test program—I may be 87 but I completely believe in preventive measures of all kinds. Sadly, I lost all my paternal aunties, plus my dearest mother and grandmother to heart problems. If ... COSMOS ... can possibly save even one person—HOORAY FOR COSMOS."



NOMI T., of California, wrote, "I joined COSMOS to do my part in helping to beat cardiovascular disease and cancer and to make sure Hispanic women benefit from the results."

WHAT MOTIVATED YOU TO JOIN COSMOS?



For a chance to be featured in our next newsletter, please let us know what motivated you to join the study by sending an e-mail to COSMOStrial@partners.org or mailing a short note to the postal address in the box to the right—and consider including a photo of yourself with your study pill pack (high-quality digital photos in JPG format are preferred)!

COcoa Supplement and
Multivitamin **O**utcomes **S**tudy
(COSMOS)



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