



From the COSMOS Trial Directors

Dear COSMOS participant,

Thank you! We would like to express our gratitude for your dedication to COSMOS and send you our best wishes for 2020! With your help, the study is getting closer to achieving its goal of determining whether taking daily supplements of cocoa flavanols (600 mg/day) or a common multivitamin reduces the risk of developing heart disease, stroke, and cancer. As described in the article on page 1 of this newsletter, COSMOS is the only large randomized trial of cocoa flavanols and one of only two large trials of multivitamins in the world. As such, its results are expected to shape medical and public health guidelines regarding the use of these supplements for prevention of heart disease, stroke, and cancer. Please help COSMOS achieve its goals by continuing to take your study pills and continuing to complete the study questionnaires.

And an appeal . . . We also have a request for those of you who have stopped taking the study pills. If you are medically able to do so, we would very much like for you to consider restarting the study pills at this time. Higher pill-taking rates will help to ensure that COSMOS achieves its scientific goals. If you wish to resume taking the study pills and need calendar packs, please contact us at 1-800-633-6913, COSMOStrial@partners.org, or the postal address on page 4.

Thank you again for being part of the COSMOS community!

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We Can't Do It Without You!

The continued participation of each member of the COSMOS study population is essential to answer the question of whether older adults should consider taking cocoa flavanol or multivitamin supplements to lower their risk for heart disease, stroke, and cancer. Some studies suggest that this may be the case, but available results are not definitive. It is unclear whether taking these supplements can prevent these diseases—and whether any benefits outweigh any risks.

To date, COSMOS is the only large, long-term randomized clinical trial designed to test whether cocoa flavanols can prevent heart disease and stroke. Many small, short-term trials have shown that consuming high doses of these compounds relaxes blood vessels and stimulates blood flow; reduces blood pressure and inflammation; and improves blood sugar control and the lipid profile—changes expected to lower risk for developing heart disease and stroke. However, it is not known whether cocoa flavanols actually protect against these two outcomes. Many times in the past, hypotheses based on promising preliminary data have not held up when rigorously tested in large, long-term trials. With your continued dedication, COSMOS is expected to provide a clear answer as to whether cocoa flavanols are effective for cardiovascular disease prevention. (As an aside, studies of chocolate generally do not show the same promising signals as do studies of cocoa flavanols. Chocolate contains only a small amount of cocoa flavanols, and it is difficult to get a significant “dose” of flavanols from chocolate without also consuming excessive sugar, fat, and calories.)

COSMOS is also one of only two large, long-term randomized trials to test a multivitamin (Centrum Silver[®]) that contains a comprehensive array of vitamins and minerals to help meet recommended daily intakes, and the only such study to include both female and male participants. In the Physicians' Health Study,¹ a long-term randomized trial conducted among 14,641 U.S. male physicians aged 50 and older, men assigned to take a multivitamin (an earlier formulation of Centrum Silver[®]) had a modest but significant 8 percent reduction in cancer risk compared with their counterparts assigned to placebo. Moreover, multivitamin use was associated with an 18 percent reduction in cancer risk among those aged 70 and older, as well as a 27 percent reduction in new cancers among those who began the trial with a history of cancer. With your continued collaboration, we expect the COSMOS findings to clarify the value of multivitamins for preventing cancer and cardiovascular disease in a general population of U.S. women and men.

Of note, it is important to consider participants' baseline nutritional status when evaluating the health effects of dietary supplements such as multivitamins and cocoa flavanols. It is possible, for example, that multivitamins offer greater disease protection to people who consume a nutrient-poor diet or who have low blood levels of certain nutrients. COSMOS is well positioned to examine this question. At the start of the study, participants completed a detailed questionnaire about their diet, and a subgroup also provided a blood sample that will be analyzed for biomarkers such as vitamin, mineral, and flavanol levels.

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Sleep and heart health

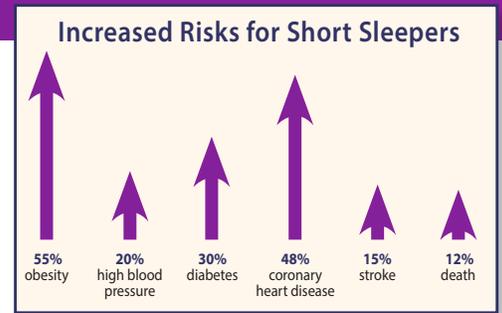
How much sleep do you need? Although physiologic sleep requirements vary from person to person, many authorities recommend that midlife and older adults get 7 to 8 hours of sleep per night for optimal health and functioning. The percentage of Americans failing to meet this guideline has been climbing in recent decades, rising from about 22 percent in 1977 to 35 percent in 2014.^{1,2} This is concerning, because not getting enough sleep can negatively affect cardiovascular health, according to the American Heart Association’s (AHA) first-ever scientific statement on sleep, which was released in 2016.¹ The AHA concluded that, compared with those who habitually sleep 7 to 8 hours per night, adults who sleep fewer than 7 hours per night are at increased risk for obesity, high blood pressure, diabetes, coronary heart disease (the association may be strongest in those who use tranquilizers or other sleep-inducing medications), and stroke. What accounts for these relationships? Short sleepers are more likely to overeat and to consume an unhealthy diet, with less food variety, more calories from snacks and fewer from main meals, and greater intakes of sugar, caffeine, and alcohol. Though the data are not entirely consistent, experimental studies show that sleep restriction unfavorably affects

appetite-regulating hormones, blood sugar processing, heart rate variability, and blood vessel dilation, and increases inflammation and stress hormone levels.

The AHA also found evidence linking two specific sleep disorders—insomnia and obstructive sleep apnea—to an increased risk for diabetes and cardiovascular disease. About 30 to 45% of adults—and an even higher percentage of those aged 65 and older—report symptoms of insomnia, and 17% of men and 9% of women aged 50 and older have sleep apnea (repeated pauses in breathing during sleep because of a narrowed airway).

In addition to cardiovascular consequences, insufficient sleep has also been linked to impaired learning and memory formation, decreased attention span, and impaired decision-making ability; irritability and depression; greater susceptibility to infection; motor-vehicle and other accidental injuries; and, possibly, survival after a cancer diagnosis. A 2010 analysis of 16 studies involving 1.4 million participants followed from 3 to 25 years concluded that short sleepers have a 12% higher risk of premature death.³

On the flip side, too much sleep may also be bad for your health. Studies show



that sleeping 9 or more hours per night is associated with an increased risk for obesity, diabetes, and heart disease, as well as a 30% higher risk of death.³ However, as noted above, people do differ in the amount of sleep they need, and genes have been found to influence an individual’s sleep requirement.

For more information, including tips on getting a good night’s sleep, you may wish to check out the following online resources: the National Sleep Foundation’s website at sleepfoundation.org; the Sleep Education website of the American Academy of Sleep Medicine at sleepeducation.org; and the Healthy Sleep website produced by the Division of Sleep Medicine at Harvard Medical School and the WGBH Educational Foundation at healthysleep.med.harvard.edu.

Sources: 1. *Circulation* 2016; 134:e367-e386.; 2. https://www.cdc.gov/sleep/data_statistics.html (Accessed 2019 Nov 12); 3. *Sleep* 2010; 33:585-592.

COSMOS TEAM PHOTOS



COSMOS team members at the entrance to the COSMOS office and on a tour of Fenway Park in Boston.

Q&A

Q. I recently had surgery and stopped taking my study pills. Can I start taking them again, or am I out of the study?

A. Yes, you can restart, and, no, you are not out of the study! We realize that certain events may change your level of participation in COSMOS. Maybe you've moved, or started a new job or relationship, or become ill, or have begun caring for a sick family member. If such changes mean you cannot take the study pills for a while, you have to do what you have to do. If circumstances change and you can restart the study pills, we would very much like for you to do so. Resuming your study pills as soon as possible will help COSMOS to determine whether cocoa flavanols and multivitamins can prevent heart disease, stroke, and cancer. If you would like to restart your study pills, please contact us (1-800-633-6913 or COSMOStrial@partners.org).

Q. Will participants be told which type of study pills they were taking? If so, when?

A. Yes, after completing and returning the questionnaire that will be sent when the study pill-taking period ends, participants will be told whether they were assigned to active or placebo cocoa flavanols, and to active or placebo multivitamins. The exact date on which study pill-taking will end has yet to be determined; stay tuned for an announcement later this year.

Q. I know that the main outcomes of interest in COSMOS are heart disease, stroke, and cancer, and that ancillary studies are examining cognitive function and eye health. Why do study questionnaires also ask about other ailments—for example, peripheral artery disease (leg pain), fatigue, and shortness of breath?

A. In addition to the main and ancillary outcomes, we will be examining whether the study treatments reduce risk of other conditions. The goal is to provide a more complete picture of the balance of benefits and risks of cocoa flavanol and multivitamin supplementation.

Q. I am taking a supplement for eye health. Can I still take the COSMOS study pills?

A. There are a number of popular eye-health supplements on the market today. Some but not all of these supplements contain high amounts of lutein, which is also present in the multivitamin tested in COSMOS. To avoid the possibility of consuming too much lutein, you should not take eye-health supplements with high amounts of this nutrient in conjunction with the study multivitamins (gray pills). Please contact us at 1-800-633-6913 or COSMOStrial@partners.org for guidance on which specific eye-health supplements are and are not acceptable to use while taking the study multivitamins.

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Recent findings from another large trial—the VITamin D and Omega-3 Trial (VITAL),² which randomized 25,871 U.S. adults to 5 years of supplemental omega-3 fatty acids (fish oil) or to placebo—highlight the value of such considerations. In participants who entered the trial with low fish consumption (less than 1½ servings per week), omega-3 fatty acid supplementation led to a 19% reduction in major cardiovascular events, including a 40% reduction in heart attack, as well as a trend toward a reduction in death from any cause. In contrast, for participants with higher fish consumption (1½ servings or more per week), omega-3 supplementation did not affect rates of these conditions.

Each COSMOS participant who continues to take his or her study pills strengthens the study's ability to detect beneficial and/or harmful effects of cocoa flavanols and multivitamins (if such effects exist), both in the overall study population and within subgroups defined by baseline nutritional status. The continued dedication of participants assigned to placebo is equally critical to that of participants assigned to active supplements. It is only by comparing the health outcomes of people on active supplements to the health outcomes of people on placebo that COSMOS will be able to determine if differences between these groups are attributable to the supplements.

It may be reassuring to know that the health outcomes of COSMOS participants are closely monitored by a panel of independent medical and statistical experts. If the panel were to find that one of the treatment groups was doing much better or worse than the others, participants would be notified as soon as possible so that they could change their supplement regimen should they wish to do so.

Sources: 1. Gaziano JM, et al. *Journal of the American Medical Association* 2012; 308:1871-80.
2. Manson JE, et al. *New England Journal of Medicine* 2019; 380:23-32.

Reminder: Study questionnaires can be completed online!

Although we continue to welcome paper-and-pencil questionnaires submitted by postal mail, we also offer the option for you to fill out and submit your study questionnaires online. We use a well-established, secure web-based system to collect data online. If you have not yet provided your e-mail address and would prefer to receive an e-mail invitation to complete the questionnaires online, please contact us at COSMOStrial@partners.org or 1-800-633-6913. The majority of COSMOS participants now complete their questionnaires online!



Weldon E., of Texas, writes, "Wherever I go, COSMOS goes with me, even in Paris. I'm hopeful that my participation will lead to longer and healthier lives for African American men."



Linda K., of California, writes, "I am taking part in the COSMOS Trial... to do my part in helping me and others to stay healthy as long as possible. With my 70th birthday approaching this year, I can honestly say I've never felt better!"



Margaret (Peggy) M., of California, writes, "I am happy to participate in the COSMOS Study. I lost my sister to heart disease and Alzheimer's two years ago and will do anything I can to help prevent these diseases."



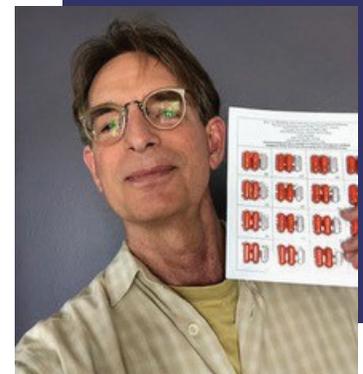
Barbara F., of Louisiana, writes, "I actually had to wait 3 months before I could join the study because of a knee replacement surgery. I was very excited when I was told it was ok to delay my start! In 2004 I discovered two blockages in my heart and had stents put in my heart. I was so close to having a heart attack. ... I don't know which meds I'm getting, but I hope [that] whatever data is gathered, it will be helpful in preventing heart attacks."



Justina L., of California, writes, "The reason [I joined] the COSMOS trial is [that] I always wanted to do something for human health, and I am very happy [with] what I am doing now."



Mark R., of Washington, pictured at Deception Pass in that state, writes, "I joined COSMOS in New Hampshire to play a part in this study. My mother died from cancer and my father died from heart failure. I wanted to help as many people as possible, including myself."



David P.-S., of California, writes, "I'm so excited to be a part of this study. I too am glad to play a small role in better understanding how to prevent heart disease, stroke and cancer. In a world with so much chaos and challenge, it is fulfilling to be a part of a possible solution. All I do is take the pills, answer questions, and then of course there's that humbling online cognitive test!"

WHY DID YOU JOIN COSMOS?

Please let us know by writing to COSMOStrial@partners.org or the postal address listed in the box to the right (and feel free to include a photo of you with your pill pack!). We will include a sampling of responses in future newsletters.

COcoa Supplement and **M**ultivitamin **O**utcomes **S**tudy (COSMOS)



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