



From the COSMOS Trial Directors

Dear COSMOS participant,

As the **CO**coa **S**upplement and **M**ultivitamin **O**utcomes **S**tudy (COSMOS) gets underway, we wish to thank each of you for your commitment to this important research study. Your participation, along with that of 18,000 other women and men throughout the country, will allow us 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. During the course of the study, which 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, we will send you periodic newsletters to keep you informed about the study's progress, as well as to discuss health topics that we hope will be of interest. We will also answer frequently asked questions from participants in our newsletters and on our study website, www.cosmostrial.org.

Thank you again, and welcome to the COSMOS community!

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Cocoa flavanols and multivitamins: Promising but still unproven strategies to prevent cardiovascular disease and cancer

Cocoa products are surging in popularity. Sales of chocolate—especially cocoa-rich dark chocolate—are climbing, a trend driven in large part by the growing belief in its health benefits. Indeed, many small, short-term clinical trials have shown that consuming high doses of cocoa flavanols (typically in the form of cocoa beverages or cocoa flavanol supplements) can

relax blood vessels and stimulate blood flow; improve control of blood sugar and blood lipid profile; reduce blood pressure; and tamp down inflammation—changes expected to lower risk for developing cardiovascular disease (see page 2 of this newsletter). However, more definitive evidence is needed to establish whether cocoa flavanols actually protect against heart disease and stroke. COSMOS is the first and only large, long-term randomized clinical trial designed to test whether daily supplementation of flavanol-rich cocoa extract can prevent heart disease and stroke, as well as cancer, in generally healthy women and men.

COSMOS is also testing whether a daily multivitamin (Centrum Silver®) can prevent these diseases. Given that more than one third of all U.S. adults take multivitamin supplements, it is surprising that only one large randomized trial of such a supplement has been completed to date. In the Physicians' Health Study, which randomly assigned 14,641 male

physicians aged 50 and older to take a multivitamin (an earlier Centrum Silver® formulation) or a placebo for 11 years, men in the multivitamin group had a modest but significant 8 percent reduction in cancer incidence compared with their counterparts in the placebo group. Moreover, multivitamin use was associated with an 18 percent reduction in cancer among those aged 70 and older, as well as a 27 percent reduction in new cancers among those who started the trial with a history of cancer. Although these findings are promising, additional large trials in other populations—including both men and women—are needed to confirm (or refute) the value of multivitamins



for cancer or cardiovascular disease prevention. Because COSMOS is the first trial of multivitamins to include women, it is expected to provide results that will help to shape guidelines regarding multivitamin use for prevention of major chronic diseases in the general population.

We are grateful that you have chosen to enroll in this landmark trial and take your study pills faithfully, thus providing critically needed information to resolve continuing uncertainties about the health effects of cocoa flavanols and multivitamins. Thank you for joining the COSMOS community!

Numbers to know for your heart’s health

Many factors are known to increase the risk for coronary heart disease. The more risk factors a person has, the greater the likelihood that he or she will develop heart disease and suffer a heart attack. Some risk factors are beyond one’s control, including increasing age and a family history. However, many risk factors, including high blood pressure, high blood sugar, and unfavorable cholesterol levels, can be modified by increasing physical activity, losing excess weight, quitting smoking, improving your diet, and, when necessary, taking certain medications.

Some years ago, the American Heart Association (AHA) adopted the slogan “Know your numbers” to raise the public’s awareness of heart health. Here are 11 numbers worth knowing.

Your blood pressure has two components: **systolic pressure** (the top

number of a blood pressure reading, or your pressure when your heart contracts) and **diastolic pressure** (the bottom number, or your pressure when your heart relaxes). The higher each reading is, the greater your chance of experiencing a heart attack or stroke.

The fats in your blood are collectively known as lipids, the most important of which are **LDL (bad) cholesterol** and **HDL (good) cholesterol**. The lower your LDL cholesterol and the higher your HDL cholesterol, the lower your odds of having a heart attack. **Total cholesterol** is a useful general measure. High **triglycerides** also increase heart disease risk, especially in combination with excess weight, high blood sugar, and low HDL cholesterol. In recent years, cardiovascular disease prevention guidelines of the American College of Cardiology (ACC) and the

AHA have shifted away from specifying rigid cutpoints for “ideal” and “worrisome” lipid levels to evaluating the need for treatment (such as with statin drugs, which lower LDL cholesterol) in the context of overall cardiovascular risk. Statins are now recommended for the following groups: (1) adults with a history of heart disease or stroke; (2) adults with LDL cholesterol of 190 mg/dL or higher; and (3) adults aged 40 to 75 years with LDL cholesterol of 70 to 189 mg/dL who also have diabetes or a 10-year Atherosclerotic Cardiovascular Disease (ASCVD) risk score of 7.5% or greater (see next page).

Excess weight—especially at the waist or abdomen—negatively affects heart health. **Body mass index (BMI)** is a measure of weight in relation to height. To calculate BMI, multiply your weight in pounds by 703, divide the result by your height in inches, and then divide

Do you know your numbers?

Indicator	Ideal	When to worry ^a	How often should it be measured?	Write your number here
Blood pressure			Every year ^b	
Systolic	Under 120 mm Hg	140 mm Hg or higher ^c		
Diastolic	Under 80 mm Hg	90 mm Hg or higher ^d		
Lipids			Every 5 years ^b	
Total cholesterol	See above text. The specific levels will vary depending on the presence of other risk factors. Ask your healthcare provider about your specific goals.			
HDL cholesterol				
LDL cholesterol				
Triglycerides				
Body measurements			At every physical exam	
Body mass index (BMI)	Under 25 kg/m ²	30 kg/m ² or higher		
Waist circumference				
Men	Under 35 inches	40 inches or higher		
Women	Under 30 inches	35 inches or higher		
Fasting blood sugar ^e	Under 100 mg/dL	Over 125 mg/dL	Every 3 years ^b	
Hemoglobin A1c ^f	Under 7% ^f	Over 8% ^f	Every 3 to 6 months ^f	
C-reactive protein (CRP) ^g	Under 1 mg/L	3 mg/L or higher	Not determined	
ASCVD risk score ^h	Under 5%	7.5% or over	Every 4 to 6 years ⁱ	

a. When to take action beyond lifestyle changes. These numbers may be different for people with heart disease, stroke, diabetes, or other medical issues.

b. More often for people with abnormal values or at increased risk for heart disease.

c. 130 mm Hg or higher for people with heart disease, diabetes, or kidney disease.

d. 80 mm Hg or higher for people with heart disease, diabetes, or kidney disease.

e. People with fasting blood sugar levels of 100 to 125 mg/dL have prediabetes, and those with fasting levels of 126 mg/dL or higher have full-blown diabetes.

f. For people with diabetes.

g. Some (but not all) guidelines recommend CRP screening for people at moderate risk for heart disease by virtue of other risk factors.

h. ASCVD, Atherosclerotic Cardiovascular Disease.

i. For adults aged 40 to 75 years without diabetes and with an LDL cholesterol of 70-189 mg/dL.

again by your height in inches. A BMI of 18.5 to 24.9 is considered a healthy weight; 25 to 29.9 is overweight; and 30 or more is obese. To determine **waist circumference**, hold a tape measure at the level of your navel and circle your torso with it. Measure below, not at, the narrowest part of your abdomen.

Diabetes, or high blood sugar, is harmful to the heart. **Fasting blood sugar** provides a snapshot of your blood sugar at one time point, while **hemoglobin A1c** gives a time-lapse look over several weeks. Although doctors typically order the latter test only for patients with diagnosed diabetes, some now also recommend it for screening and for individuals at higher-than-usual risk for diabetes and heart disease.

Other substances in the blood, including **C-reactive protein** (CRP), homocysteine, lipoprotein(a), and fibrinogen, have also been linked to an increased risk for heart disease. Although these markers may indicate inflammation or increased risk of blood clotting, their measurement is not routinely recommended.

Estimating your heart disease risk

There are many useful tools that use your numbers to estimate your likelihood of having a first heart attack or being

diagnosed with heart disease in the next 10 years. One such tool is the Atherosclerotic Cardiovascular Disease (ASCVD) risk algorithm, released in 2013 by the ACC and the AHA. This tool estimates the 10-year risk of heart attack or stroke for adults aged 20 to 79 years. Go to www.cvriskcalculator.com, or ask your healthcare provider to calculate your score. Two web-based tools—www.reynoldsriskscore.org and www.diseaseriskindex.harvard.edu—developed by researchers at Harvard Medical School and Harvard School of Public Health, respectively, incorporate other potential risk factors and provide alternative estimates of heart disease and stroke risk. The latter website also estimates your risk for diabetes, certain cancers, and osteoporosis, and offers personalized tips for prevention.

Being aware of your heart disease risk may motivate you to make healthy lifestyle changes and will help your doctor decide whether to prescribe certain medicines to lower your risk. Drugs that favorably affect cholesterol levels or lower blood pressure can prevent heart attacks and increase survival. All of us can benefit from adopting healthy lifestyle choices and, when warranted, taking medications. Indeed, the greater your cardiovascular risk is, the greater the payoff from prevention efforts is likely to be.



The COSMOS research team at Brigham and Women's Hospital, Boston, Massachusetts

Ancillary Studies

In addition to testing whether cocoa extract or multivitamin supplements can prevent heart disease, stroke, or cancer, COSMOS will also assess whether these supplements confer other health benefits, such as lowering the risk for:

- memory loss
- cognitive decline
- diabetes
- high blood pressure
- eye diseases

Participants eligible for one or more of these ancillary (add-on) investigations may have already been contacted. In addition, a randomly selected subgroup of participants has been invited to provide blood and urine samples. (Responses to date have been impressively high!) Analyses of these samples will demonstrate how the study supplements may affect the health outcomes of interest. Finally, participants who live close to Brigham and Women's Hospital in Boston, Massachusetts were given the option to have detailed clinic studies, including tests of blood pressure, blood sugar, and cognitive and physical function.

RECRUIT A PAL

We will be recruiting participants for COSMOS throughout 2017. Please spread the word to friends and family about this important research—you can refer those who are interested to our website, www.cosmostrial.org, or ask them to call us toll-free at 1-800-633-6913.

Q&A

Q. Will my health information be kept confidential?

A. Yes! We are committed to protecting your privacy. Information from completed questionnaires and medical records is identified in our computer files by study number only, and only a few authorized staff members have access to the file that can link study numbers with participants' names. Your information will be used only for COSMOS, and no identifying personal information will be included in published research findings. Your trust is essential to the success of the study, and we would never do anything to risk losing your faith in us.

Q. Why was I recruited to participate in COSMOS?

A. You were invited to participate in COSMOS from one of several sources. Participants in the nationwide Women's Health Initiative (WHI), as well as men and women who previously responded to mailings for the VITamin D and Omega-3 Trial (VITAL), received invitations. In addition, population-based mailings using selected mailing lists and invitations to individuals who contacted us after hearing about the study led many more to join.

Q. During the trial, COSMOS participants must agree to: (a) avoid taking nonstudy multivitamin supplements; (b) limit their total intake of vitamin D from nonstudy supplements to 1000 IU or less per day; and (c) limit their total intake of calcium from nonstudy supplements to 1200 mg or less per day. What are the reasons for these restrictions?

A. These restrictions are in place so that COSMOS can clearly determine whether multivitamin supplements prevent heart attack, stroke, and cancer while also ensuring the safety of all participants, whether they are assigned to take a multivitamin or placebo. People who take multivitamins or large amounts of supplemental vitamin D or calcium outside the study will weaken the trial's ability to detect benefits for the multivitamin, should such benefits exist.

The multivitamins being tested in COSMOS contain 1000 IU of vitamin D and 220 mg of calcium. For *vitamin D*, the "recommended dietary allowances" (RDAs) set by the Institute of Medicine (IOM) are 600 IU per day for adults up to age 70 and 800 IU per day for those aged 71 and older, and the safety limit is 4000 IU per day. Because COSMOS participants can choose to take up to 1000 IU per day of supplemental vitamin D outside the study, no one in the placebo group will become vitamin D deficient as a result of study participation. Additionally, no one in the multivitamin group will get too much vitamin D, provided that they follow study guidelines.

For *calcium*, the RDAs set by the IOM are 1000 mg per day for men aged 51-70 and 1200 mg per day for women aged 51-70 and all adults aged 71 and older, and the safety limit is 2000 mg per day. COSMOS participants are allowed to take up to 1200 mg per day of calcium supplements. Together with intake from food (which averages about 700 mg per day), most participants can opt to consume about 2000 mg per day from food and outside calcium supplements. No one will become calcium deficient as a result of study participation.

Q. COSMOS is testing a cocoa extract supplement containing 600 mg of cocoa flavanols. Couldn't I get this amount by snacking on chocolate instead? On a related note, may I still eat chocolate during the study?

A. It is difficult to get a significant amount of cocoa flavanols from chocolate without also consuming excess sugar, milk fat, and calories. The flavanol content of chocolate varies greatly depending on its cocoa percentage and how the cocoa bean is processed. As a rough guide, to get 600 mg of flavanols, you would need to eat about 2 pounds (nearly 5000 calories) of milk chocolate or, more realistically, 4 ounces (600 calories) of dark chocolate—a regimen that, if followed on a regular basis, is sure to lead to weight gain! **That said, there are no restrictions on how much chocolate may be eaten during the trial.** It is extremely unlikely that participants will consume flavanols in amounts high enough to interfere with the study's ability to detect health effects of the cocoa extract supplement.

A call for quotes and photos

Many participants have told COSMOS staff that they are enthusiastic about contributing to research on ways to prevent cardiovascular disease and cancer. What motivated you to join COSMOS? Please let us know by sending an e-mail to COSMOSTrial@partners.org or a short note to the postal address provided in the box to the right—and feel free to include a photo of yourself with your study pill pack! A sampling of photos and responses will be included in future newsletters. (Please note that high-quality digital photos, sent as JPG attachments to e-mails, are preferred and that no photo will be published without the written consent of the participant.)



Cocoa **S**upplement and
Multivitamin **O**utcomes **S**tudy
(COSMOS)

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