



From the COSMOS Trial Directors

Dear COSMOS participant,

Thank you for your dedication to COSMOS. We will continue to send you annual health questionnaires to learn more about health effects of the COSMOS interventions and healthy aging in general! Please be on the lookout for your next annual questionnaire, to be sent at the beginning of January 2025. **Your response is important, regardless of which study pills you received in the trial and whether or not your health has changed since the previous questionnaire.** The information that you provide will allow us to examine the long-term effects of the cocoa extract and multivitamin supplements compared with the placebos. This is critical because the effects of nutritional factors on risks of cancer and other slow-developing conditions often become clearer only after many years (see lead story, which provides several examples, on pages 1-2).

As always, you may submit your annual questionnaire online or by postal mail. We encourage you to consider the online option. If you have given us your e-mail address, we will e-mail you with a link to a secure website where you can complete your questionnaire. If you have not provided your e-mail address and would prefer the e-form option, please e-mail us at COSMOStrial@partners.org or call us at 1-800-633-6913 at your earliest convenience.

Thank you again for being part of the COSMOS community and helping to ensure the long-term success of the study!



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The importance of long-term follow-up of study participants in clinical trials

Long-term follow-up of clinical trial participants is critical to assess fully the effect of study treatments on cancer and other slow-developing conditions. It may take years or decades for important benefits or risks of treatment to emerge or strengthen, and such effects may occur even after the intervention is stopped. Conversely, treatment effects seen during the intervention phase of the trial may dissipate or weaken over time. Here we present a small sampling of such findings from clinical trials of nutritional interventions reported in the medical literature over the last 20 years.

Multivitamins and cancer

The first example highlights the importance of long-term follow-up in trials of multivitamins for cancer prevention, such as COSMOS. In the

Physicians' Health Study II (PHS II), which tested the effects of a daily multivitamin supplement in more than 14,000 US men, participants in the multivitamin group had a modest but significant 8 percent reduction in cancer incidence compared with their counterparts in the placebo group at 11 years [1]. Moreover, multivitamin use was associated with an 18 percent reduction in cancer among those aged 70 years and older, as well as a 27 percent reduction in new cancers among those who started the trial with a history of cancer.

"These results show that possible cancer prevention effects of multivitamins may take many years to manifest," said COSMOS Trial Co-Director Dr. Howard Sesso, who also led PHS II. "Thus, the importance of long-term follow-up of study participants cannot be overstated."

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Multivitamins, cocoa extract, and cognition: more findings from COSMOS

Preserving cognitive function is one of the top health priorities for older adults. Vitamins, minerals, bioactive compounds, and other nutrients are necessary for maintaining normal brain function, and deficiencies in these may increase risk for cognitive decline. As reported in previous newsletters, two COSMOS substudies tested whether daily use of a multivitamin or cocoa extract reduced the risk of age-related memory loss or cognitive decline. COSMOS-Web, which enrolled 3,562 participants who completed annual online questionnaires to assess memory, and COSMOS-Mind, which enrolled 2,262 participants who completed annual telephone interviews to assess cognitive function, found beneficial effects for daily multivitamin use on these outcomes. COSMOS-Web also found cognitive benefit for cocoa extract in individuals with a less healthy diet at study entry.



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Vitamin D, omega-3 fatty acids, and autoimmune disease

Examples from other nutrition trials demonstrate the need for long-term follow-up to evaluate the persistence of treatment effects after the intervention phase ends. In the Vitamin D and Omega-3 Trial (VITAL), which tested the effects of supplemental vitamin D and omega-3 fatty acids in nearly 26,000 US adults, vitamin D reduced the risk of developing autoimmune disease by 22 percent during the 5-year pill-taking phase of the study, with the protective effect strengthening to a 39 percent reduction in the second half of this phase. In addition, omega-3 fatty acids were associated with a 15 percent reduction in risk of autoimmune disease, although the association was not statistically significant.

In analyses that incorporated data from participants who were followed for an additional two years after the study pill-taking phase ended, the protective effect of vitamin D waned, whereas the protective effect of omega-3 fatty acids strengthened to a statistically significant 17 percent reduction [2].

“The protection against autoimmune disease offered by supplemental vitamin

D does not last after discontinuation of use,” noted COSMOS Trial Co-Director Dr. JoAnn Manson, who also leads VITAL. “On the other hand, the protection conferred by supplemental omega-3 fatty acids persists for at least 2 years after stopping these supplements.”

Diet and breast cancer

In the Women’s Health Initiative Dietary Modification Trial, which tested the effects of a low-fat diet with increased fruit, vegetable, and grain consumption in nearly 49,000 US women, no significant effect on breast cancer death was observed during the 8.5-year intervention period. However, a statistically significant 21 percent reduction in breast cancer death emerged more than a decade after the intervention ended [3].

Calcium and colorectal polyps

In the Calcium Polyp Prevention Trial, which tested 4 years of supplemental calcium for the prevention of recurrent colorectal polyps in 930 US adults with a history of such polyps, there was a significant 15 percent reduction in this outcome during the intervention phase, which strengthened to a 37 percent reduction during the first 5 years of post-intervention follow-up [4].

Vitamin E and prostate cancer

In the SELECT trial, which tested 5.5 years of vitamin E supplementation for prevention of prostate cancer in 35,000 US and Canadian men, there was a borderline significant increase in this outcome during the intervention phase that strengthened and became statistically significant with 7 to 12 years of cumulative follow-up [5].

We hope that the above examples have given you a new perspective on the importance of continuing to complete the annual COSMOS questionnaires and, if applicable, to respond to written requests allowing us to review relevant medical records about health changes of interest, such as new diagnoses of cancer or cardiovascular disease. Such information is essential to determine the long-term health effects of multivitamin and cocoa extract supplements compared with the placebos. Thank you for your continuing commitment to COSMOS!

References:

- [1] Gaziano J.M., et al. *JAMA* 2012; 308:1871-1880.
- [2] Costenbader K.H., et al. *Arthritis & Rheumatology* 2024; 76:973-83.
- [3] Chlebowski R.T., et al. *Journal of Clinical Oncology* 2020; 38:1419-1428
- [4] Grau M.V., et al. *Journal of the National Cancer Institute* 2007;99:129-136.
- [5] Klein E.A., et al. *JAMA* 2011; 306:1549-1556.

COSMOS: a rich resource to advance knowledge on healthy aging

Your participation in COSMOS continues to help advance scientific knowledge about cocoa extract and multivitamin use! Most recently, we have been looking at the effect of the study supplements on wellness and healthy aging. For example, we are currently investigating the effects of the study interventions on:

- eye health, including macular degeneration and cataract
- falls, fracture, physical function, and frailty
- other components of healthy aging, including self-perceived health, quality of life, mood, stress, and sleep.

The results of this research are expected to shed light on the role of the study supplements in promoting healthy aging. Future newsletters will summarize the findings after they are published in the medical literature.

Interested in participating in new clinical trials?

We are extremely grateful for your participation in COSMOS and encourage you to extend your contributions to research beyond COSMOS by joining other clinical trials. Please be on the lookout for invitations to participate in new studies! Based on your responses to previous COSMOS questionnaires, you may receive an invitation to participate in a study about the effects of pistachio consumption on cognitive function and other health outcomes. Stay tuned for more details!

New findings

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Now, a third COSMOS substudy—COSMOS-Clinic—has also reported cognitive benefits from multivitamins. COSMOS-Clinic enrolled 573 COSMOS participants who resided within driving distance to the study’s clinic at Brigham and Women’s Hospital in Boston, Massachusetts, where they completed in-person cognitive assessments at the start of COSMOS and again 2 years later. There was a modest benefit for multivitamins on overall cognitive function, with a significant benefit on memory, although there was no benefit on attention or executive function (skills needed to make plans, solve problems, and adapt to changing situations). Moreover, an analysis that combined the data from all three COSMOS substudies showed clear evidence of multivitamin benefits on overall cognitive function and memory in particular; the magnitude of the effect on overall cognitive function was equivalent to slowing cognitive aging by 2 years. “The combined COSMOS results powerfully support a potential role for the use of multivitamins for healthy cognitive aging,” said COSMOS collaborator Dr. Chirag Vyas of Harvard Medical School.

COSMOS-Clinic also examined the effect of the cocoa extract supplement on cognitive function. Although there was no benefit in the total group of COSMOS-

Clinic participants, such supplementation appeared to favorably affect cognitive function, particularly executive function, in individuals with a less healthy diet at baseline. “The promising cognitive benefits of cocoa extract in those with poorer diet quality seen in both COSMOS-Clinic and COSMOS-Web warrant further study,” said Dr. Vyas.

To read the published papers on these and other COSMOS findings, please visit the COSMOS website at cosmostrial.org.

References:

Vyas C.M., et al. *American Journal of Clinical Nutrition* 2024; 119:692–701; Vyas C.M., et al. *American Journal of Clinical Nutrition* 2024; 119:39–48.

A call for photos and reflections

We welcome photos—of you with your pets, on your travels, or engaged in your hobbies, for example—and stories or short reflections about participating in COSMOS. For example, we would be happy to receive a one-sentence summary of what COSMOS means to you. Please send these materials to COSMOStrial@partners.org or the postal address at the bottom of this page. A sampling of responses will be published in future newsletters.



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Participant challenge: a guessing game

How many COSMOS questionnaires have been returned from all 21,442 COSMOS participants since the start of the trial?

Please submit your guess by December 6th via the following link:

https://redcap.link/guess_cosmos_surveys.

The winner (person who guesses closest without going over) will be announced when the 2025 questionnaire is sent in January!

