



News and information for participants in the *VITamin D and Omega-3 Trial (VITAL)*

The Importance of Long-Term Follow-Up of Study Participants in Clinical Trials

Long-term observational follow-up of clinical trial participants after the intervention phase ends is critical to assess fully the effects of study treatments on cancer and other slow-developing conditions. Important benefits or risks of treatment may emerge or strengthen in the years or even decades after the intervention is stopped. Alternatively, treatment effects seen during the intervention phase may dissipate or weaken during this time. Here we present a small sampling of such findings from clinical trials of nutritional interventions reported in the medical literature over the last 15 years.

The first and most recent example is, fittingly enough, from VITAL. As reported in the 2022 issue of the newsletter, supplemental vitamin D reduced the

risk of developing autoimmune disease by 22% during the pill-taking phase of the study, with the protective effect strengthening to a 39% reduction in the second half of this phase. In addition, supplemental omega-3 fatty acids were associated with a 15% reduction in risk of autoimmune disease, although the association was not statistically significant. Now, a new report by the VITAL team, led by Dr. Karen Costenbader at Harvard Medical School, presents findings that incorporate data from participants who were followed for an additional two years after the study pill-taking phase ended. In this analysis, which considered a cumulative total of 7.3 years of follow-up (5.3 years of pill-taking plus 2 years of post-intervention follow-up), the protective

effect of vitamin D waned, whereas the protective effect for omega-3 fatty acids strengthened to a statistically significant 17% reduction [1].

“These results show that protection against autoimmune disease offered by supplemental vitamin D does not last after discontinuation of use,” said Dr. Costenbader. “On the other hand, the protection conferred by supplemental omega-3 fatty acids persists for at least 2 years after stopping these supplements.”

Examples from other nutrition trials also demonstrate the need for long-term follow-up to capture treatment effects. In the Women’s Health Initiative Dietary Modification Trial, which tested the effects of a low-fat diet with increased fruit, vegetable, and

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From the VITAL Study Directors

Dear VITAL participant,

Thank you for your dedication to VITAL and your continued completion of the study’s health questionnaires. The next annual questionnaire will be sent in February 2025. Your response is important, regardless of which study pills you received in the trial and whether your health has changed since the previous questionnaire. The information that you provide will allow us to study the long-term health effects of supplemental vitamin D and omega-3 fatty acids 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, at the top of this page).

As always, you may submit your annual questionnaire online or by postal mail. 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 contact us at vitalstudy@partners.org or 1-800-388-3963 at your earliest convenience.

We continue to welcome your photos, stories (travel or otherwise), and reflections about your VITAL participation. Please send these to vitalstudy@partners.org or the postal address on page 4 of this newsletter. If you wish to contribute a longer submission for consideration as a “Participant Profile” (see page 3), please send an e-mail or letter of inquiry to explore this possibility.

Thank you again for being part of the VITAL community!

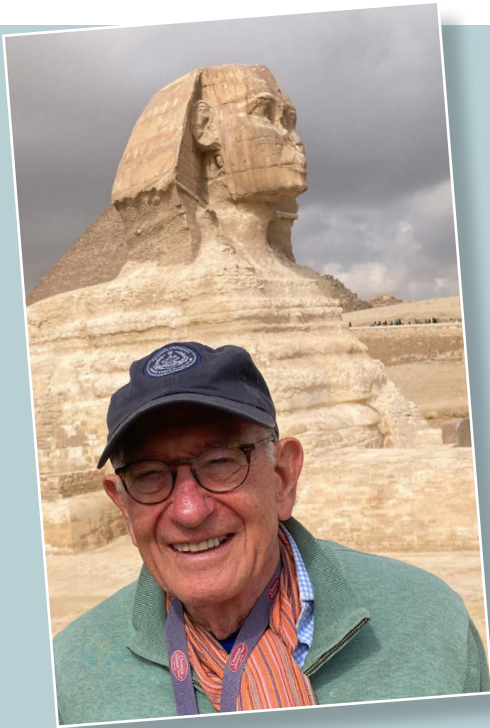


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Dr. Lee, an investigator on VITAL since its inception, joined Dr. Manson as the study’s Co-Director earlier this year. Dr. Lee replaces former Co-Director Dr. Julie Buring, who is now enjoying her retirement!



Jay R., of Ohio, in Cairo, Egypt



Virginia J., of New York, in Battambang, Cambodia

Recent Findings from VITAL

The primary aims of VITAL were to test whether supplemental vitamin D (2000 IU per day) and omega-3 fatty acids (1 gram per day) reduce the risk of cancer and cardiovascular disease. VITAL researchers are also studying the effect of these supplements on other outcomes. Here is a summary of selected recent findings. For the complete list of VITAL publications, please visit vitalstudy.org.

■ Vitamin D dosing frequency and cancer death

Findings from VITAL and other vitamin D trials indicate that supplemental vitamin D appears to reduce the risk of advanced cancer or cancer-related death, with the protective effect strongest among people with a healthy body weight (as reflected by body mass index [BMI] below 25 [calculated as weight in kilograms divided by height in meters squared]).

Whether vitamin D supplementation is effective in preventing cancer death appears to depend on dosing strategy.

Some trials (such as VITAL) have tested daily administration of vitamin D, whereas others have tested weekly or less frequent administration of large “bolus” doses. In 2022, VITAL researchers analyzed data from six vitamin D trials and found a significant 13% reduction in cancer death in the three daily-dose trials but no reduction in the three bolus-dose trials. Now, a newer report that included a larger number of trials has confirmed these results. In an analysis of 14 vitamin D trials (104,727 participants) that tested either daily (10 trials) or infrequent bolus (4 trials) dosing, VITAL Principal Investigator Dr. JoAnn Manson and international colleagues found that vitamin D was associated with a significant 12% reduction in cancer death in the daily-dose trials, whereas there was no benefit on this outcome in the bolus-dose trials.

“These analyses support a beneficial effect of daily—but not infrequent bolus—dosing of vitamin D on cancer mortality,” stated Dr. Manson. “Infrequent bolus doses produce large,

nonphysiologic fluctuations in vitamin D blood levels, which may eliminate some beneficial effects of supplementation.”

Reference: Kuznia S., et al. Ageing Research Reviews 2023 Jun; 87:101923.

■ Other conditions

Neither vitamin D nor omega-3 fatty acid supplementation was related to 2-year changes in measures of physical performance (such as grip strength and walking speed) in a subgroup of 1,054 Boston-area participants who received in-person assessments at Brigham and Women’s Hospital at baseline and again 2 years later. These supplements also did not reduce the prevalence or severity of chronic pain in the overall VITAL cohort. In addition, supplemental vitamin D was unrelated to the risk of upper respiratory infection.

References: Chou S.H., et al. Journal of Clinical Endocrinology and Metabolism [e-published 2024 Mar 15]; Soens M.A., et al. Pain 2024 Mar 1; 165(3):635-643; Camargo C.A., Jr., et al. Clinical Infectious Diseases 2024 May 15; 78(5):1162-1169.

Engineer, Antique Auto Enthusiast, Science Fiction Writer, and Volunteer: A Short Autobiography

by Richard Cutler

I was born in 1946, making me an early Baby Boomer, the generation noted by many as the “doers.” My education led me to becoming an engineer, and that led to a wide variety of professional activities over the years, culminating as the Director of Facilities at the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts. Though I am not a scientist, the scientific process that needed support proved fascinating.

I have always been one that would jump in rather than complain. I’m not especially fond of volunteering, but believing “someone has to do it” has had me involved with perhaps too many committees and boards, including my town’s Zoning Board of Appeals since 1978 and the Select Board for six years.

Over the years, my fascination with machines, desire to travel, and history led me to antique automobiles and the Horseless Carriage Club of America. I was asked to run and was elected as the Club’s national president. The Club is a driving club, so the cars currently in our stable are driven, and my wife Gini and I have been to, and seen some, fascinating parts of the world because of the hobby. We currently have four cars that we restored and registered for driving on public roads, with another being put together. They range from a 1911 Maxwell [red car in photo] to a 1929 Ford [green car in photo].

I’ve always had a mindset of “what if,” which was enhanced while working at the MBL. Combining that with some historical facts and projecting into a future scenario found me writing my first science fiction novel after official retirement. To me, writing books is something like eating potato chips (“you can’t stop with just one”); two more novels have been



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published, and a fourth is in the editing phase. Lately I have been giving talks on “the misunderstanding of science fiction.” Both the books and talks have been well received, but I learned that you write because you want to, not with any expectation you’ll get rich. As an old saying goes, “If you have a business that

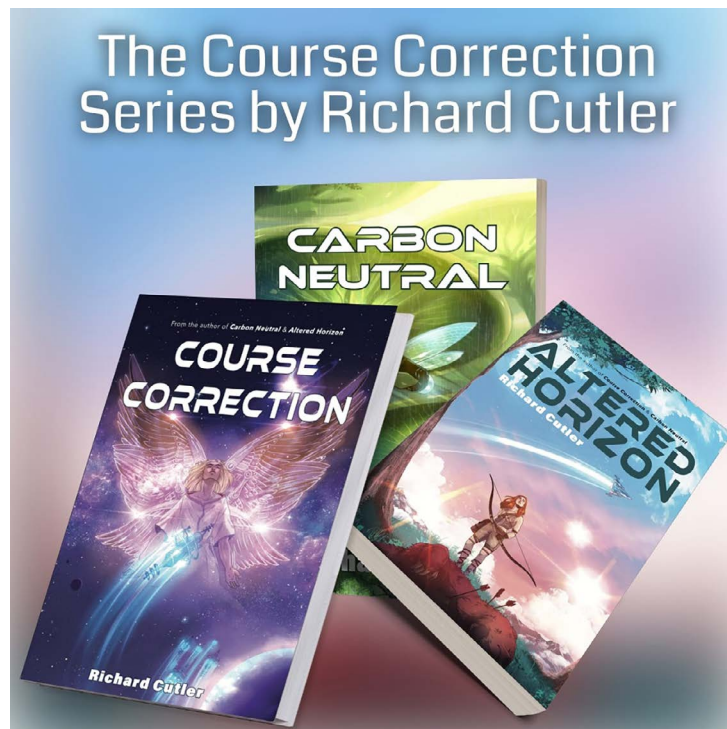


doesn’t make money, it’s a hobby.” Writing has become another hobby.

My mind won’t let me stay idle, and, as long as the body is able, I keep busy with whatever comes along and is interesting. I garden, go fishing, volunteer for environmental needs, watch grandkids grow, and have even harvested cranberries.

When the VITAL study was announced, my aforementioned scientific curiosity and belief that “someone has to do it” motivated me to participate. I have followed closely everything related to the study that comes my way.

I was out of commission for some time after being diagnosed with bladder cancer. It seems fitting that it was treatments and surgery at Brigham and Women’s Hospital—VITAL’s home base—that would take care of that little problem. I am cancer free and remain ready for the next chapter in life’s adventure.



VITAL in One Word



In the last newsletter, we challenged participants to describe VITAL in only ONE word. A big thank you to all who responded! The artwork here includes a sampling of the responses. The font size of each word reflects the number of participants who used that word.

The Importance of Long-Term Follow-Up of Study Participants in Clinical Trials

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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% reduction in breast cancer death emerged more than a decade after the intervention ended [2]. 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% reduction in this outcome during the intervention phase, which strengthened to a 37% reduction during the first 5 years of post-intervention follow-up [3]. In the Linxian Nutrition Intervention Trial, which tested 5 years of supplemental vitamin C and molybdenum in nearly 30,000 adults in China, a significant 7% reduction in stroke death was seen after 30 years of cumulative follow-up [4]. 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 (we could list even more!) have convinced you of the importance of continuing to participate in VITAL by completing the study's annual questionnaires and, if applicable, responding to written requests allowing us to review relevant medical records about health changes of interest, including new diagnoses of cancer or cardiovascular disease. Such information is essential to determine the long-term health effects of supplemental vitamin D and omega-3 fatty acids compared with the placebos. Thank you for your continuing commitment to VITAL!

References:

- [1] Costenbader K.H., et al. *Arthritis & Rheumatology* 2024; 76:973-83.
- [2] Chlebowski, R.T., et al. *Journal of Clinical Oncology* 2020; 38:1419-1428
- [3] Grau M.V., et al. *Journal of the National Cancer Institute* 2007;99:129-136.
- [4] Wang S.M., et al. *Journal of the National Cancer Institute* 2018; 110:1229-1238.
- [5] Klein E.A., et al. *JAMA* 2011; 306:1549-1556.



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(VITAL Study)

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