No. 14
Fall 2019

VITAL Signs

News and information for participants in the *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL)

VITAL results contribute to pooled analyses of randomized clinical trials of vitamin D and omega-3 fatty acids for cancer and cardiovascular disease prevention

VITAL is the largest and longest randomized trial of daily high-dose vitamin D (vitamin D3 [cholecalciferol], 2000 IU) and omega-3 fatty acid supplementation (Omacor® fish oil, 1 gram) for the prevention of cancer and cardiovascular disease in generally healthy men and women without these conditions at baseline. The trial has made major contributions to science. In the year since VITAL's key findings were published (see the November 2018 issue of this newsletter), we have collaborated with colleagues at Harvard and other institutions to combine, or pool, the results of VITAL with the results of other clinical trials to summarize the available trial evidence on the effectiveness of vitamin D for prevention of cancer and cardiovascular disease, and of omega-3 fatty acids for prevention of cardiovascular disease. The technical term for an analysis that pools data across studies is a meta-analysis. Here we briefly recap VITAL's key findings and describe the results of our three recent meta-analyses.

■ Vitamin D and cancer. In VITAL, vitamin D supplementation did not reduce the risk of developing cancer but appeared to reduce the risk

— continued on page 3 —

From the VITAL Study Directors

Dear VITAL participant,

Thank you for your many years of extraordinary dedication to VITAL. We would like to update you on the progress of the study since announcing the primary findings on cancer and cardiovascular disease in November 2018. Working with colleagues, we combined, or pooled, the results of VITAL with those from previous randomized trials to summarize the available trial findings on the effect of vitamin D and omega-3 fatty acid supplementation on cancer and cardiovascular disease. The pooled results are described on pages 1 and 3 of this newsletter. We have also been analyzing the data collected in VITAL ancillary studies of other outcomes. Read about these studies on page 2—and stay tuned for additional findings in the coming year.

Please note that we will be sending you a follow-up health questionnaire in January 2020. This questionnaire will be similar to the ones that you have completed in prior years. Even if there are no changes in your health since the previous questionnaire, your response is still very important to us. The information that you provide will allow us to build upon the wealth of data already collected to examine the longer-term effects of vitamin D and omega-3 fatty acid supplements and to explore other health-related topics.

We also want to share that we have submitted a grant proposal to the National Institutes of Health asking for funding to continue following the VITAL study population. If our proposal is approved and we receive the requested funding, we will continue to send you annual study questionnaires for a few more years. (You will ***not*** be asked to restart study pills.) Long-term follow-up is important in analyzing data from trials of dietary supplements and cancer and/or cardiovascular disease because effects of nutritional factors on risk of these slow-developing diseases, particularly cancer, typically become clear only after several years. We also hope to look further at which individuals, based on various blood-based markers, are most likely to derive benefit from vitamin D or omega-3 fatty acid supplements. As always, we will continue to send you newsletters and other communications to keep you informed about the study's progress and additional findings.

If you have study-related questions or comments, please contact us at vitalstudy@partners.org or 1-800-388-3963, or by postal mail at the address on page 3. Thank you again for making VITAL a success!

JoAnn Manson, MD
Professor of Medicine
Harvard Medical School
Brigham and Women's Hospital

Julie Buring, ScD
Professor of Medicine
Harvard Medical School
Brigham and Women's Hospital

VITAL researchers announce findings from initial ancillary studies

Although VITAL was designed to test whether vitamin D and omega-3 fatty acid supplements reduce the risk of cancer and cardiovascular disease, ancillary studies are examining many other outcomes, including bone health, colorectal polyps, inflammation, diabetes, atrial fibrillation, heart failure, cognition, autoimmune disorders, respiratory disease, and depression. Results are now—or will soon be—available to provide a more complete picture of the balance of benefits and risks of supplementation. Recently published results are summarized here, and forthcoming results will be provided in future newsletters.

■ Vitamin D and bone health.

Although many people take vitamin D supplements to promote bone health, data from earlier trials have shown inconsistent effects on this outcome in those at average risk of osteoporosis. We partnered with Harvard colleague Dr. Meryl LeBoff to examine the effect of supplemental vitamin D on changes in bone mineral density and bone structure. Bone mineral density at the spine, hip, and whole body was measured by dual-energy X-ray absorptiometry (DEXA) scan at the start of the study and again two years later in 771 Boston-area VITAL participants who were not taking bone-health medications. Supplemental vitamin D did not affect bone density or structure. "Vitamin D did not improve bone health in generally healthy individuals not preselected for low vitamin D levels," said Dr. LeBoff. "Participants may already have had vitamin D levels necessary for bone health. The findings do not apply to patients with extremely low vitamin D levels or with osteoporosis." *Reference:* LeBoff M., et al. American Society for Bone and Mineral Research Annual Meeting 2019; Abstract 1046.

■ Omega-3 fatty acids and colorectal polyps.

Omega-3 fatty acid supplementation did not reduce the risk of colorectal cancer in VITAL. However, because effects of nutritional factors on risk of cancer, a slow-developing disease, typically emerge only after several years, it may be useful to study the effect of supplementation on cancer precursors such as colorectal polyps. Colorectal polyps are small growths on the lining of the colon or rectum. Most polyps are harmless, but some can become cancerous. We partnered with Harvard colleagues Drs. Mingyang Song and Edward Giovannucci to test whether supplemental omega-3 fatty acids reduce the risk of developing colorectal polyps. Study physicians reviewed pathology records of participants who reported a diagnosis of colorectal polyps to confirm the diagnosis and extract clinical information. Omega-3 supplementation did not reduce the risk of developing colorectal polyps in the overall study sample. However, in subgroup analyses, supplementation was associated with a lower risk of the main type of colorectal polyps among those with low blood levels of omega-3 fatty acids at study entry and among African Americans. "The potential benefit of omega-3 supplementation for reducing colorectal polyps in these groups requires confirmation in future studies," noted Dr. Song. *Reference:* Song M., et al. American Association for Cancer Research Annual Meeting 2019; Abstract LB-249.

■ Vitamin D, omega-3 fatty acids, and inflammation.

Chronic systemic inflammation has serious health consequences, raising the risk of diseases such as cardiovascular disease, cancer, and osteoporosis. We partnered with Harvard colleague Dr. Karen Costenbader to examine whether supplemental vitamin D and omega-3 fatty acids reduce inflammation. Changes in blood levels of three inflammatory biomarkers—high-sensitivity C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-receptor 2—were measured among 1,561 VITAL participants who provided blood samples at the start of the study and again one year later. Neither intervention reduced levels of these markers. However, in subgroup analyses, omega-3 supplementation appeared to reduce CRP in those with low fish intake (less than 1½ servings per week) but not in those with higher fish intake. This result is consistent with the main-trial finding that those with low fish intake were more likely than those with high fish intake to experience a reduction in major cardiovascular disease events with omega-3 supplementation. "The findings suggest that neither vitamin D nor omega-3 fatty acids have generalized anti-inflammatory effects," said Dr. Costenbader. "However, omega-3 fatty acids may reduce selective markers of inflammation in those with low fish intake." *Reference:* Costenbader K., et al. *Clinical Chemistry,* November 2019.

— POOLED ANALYSES cont'd from page 1 —

of cancer-related death. Earlier vitamin D trials in initially healthy participants had also hinted at stronger benefits for cancer death than for cancer incidence. We reviewed 10 trials of vitamin D and cancer risk, 5 of which also considered cancer-related death, including VITAL. These trials included 83,353 and 75,239 participants, respectively. We found that, overall, vitamin D was associated with a significant 13% reduction in cancer death but had no effect on cancer risk. The encouraging findings for cancer death are supported by laboratory research suggesting that vitamin D may decrease tumor invasiveness and the likelihood of metastasis, and by observational studies of cancer patients showing that higher vitamin D blood levels at diagnosis predict longer survival. Some (though not all) observational studies of initially healthy individuals also suggest that higher vitamin D blood levels measured months or years prior to a cancer diagnosis are associated with a reduced risk of cancer death. The results of our meta-analysis, which was led by Harvard colleague Dr. NaNa Keum, were published in *Annals of Oncology* in February 2019.

■ Vitamin D and cardiovascular disease.

In VITAL, vitamin D supplementation did not reduce risk of major cardiovascular events (heart attack, stroke, and cardiovascular death) considered together, nor did it reduce each type of cardiovascular event considered separately. We reviewed 21 trials with a total of 83,291 participants, including VITAL, and found that vitamin D was not effective for prevention of these outcomes. The results of this meta-analysis, which was led by Dr. Mahmoud Barbarawi at Michigan State University, were published online in June 2019 in the *Journal of the American Medical Association (JAMA) Cardiology.*

■ Omega-3 fatty acids and cardiovascular disease.

In VITAL, omega-3 fatty acid supplementation did not reduce the risk of major cardiovascular events in the overall study population but did reduce risk of these events by 19% in people with low fish intake (less than 1½ servings per week). In addition, omega-3 fatty acid supplementation reduced the risk of heart attack by 28% when considered separately from other cardiovascular events; this benefit appeared strongest in African Americans. We reviewed 13 omega-3 fatty acid trials with a total of 127,477 participants, including VITAL, and found that heart disease, but not stroke, was reduced by omega-3 fatty acid supplementation (stroke was reduced in only one trial that tested a very high dose). Omega-3 supplements were associated with a significant 8% reduction in risk of heart attack in analyses that excluded the high-dose trial and a 12% reduction in analyses that included all 13 trials. Of note, a so-called "dose-response" relationship was observed; the higher the daily dose of omega-3 fatty acids, the greater the protection against heart disease. Caveat: With the exception of VITAL, omega-3 fatty acid trials to date have been conducted in patients with a history of, or at high risk for, cardiovascular disease. Thus, additional research on omega-3s in general or "usual risk" populations is still needed. VITAL's promising findings for African Americans also warrant further study. The results of our meta-analysis, which was led by Harvard colleague Dr. Yang Hu, were published in the *Journal of the American Heart Association* in October 2019.

Many participants complete their annual study questionnaires online!

Although we continue to welcome paper-and-pencil questionnaires submitted by postal mail, please remember that VITAL participants may instead choose to fill out and submit their annual questionnaires online. We use a well-established, privacy-protected web-based system for the online collection of questionnaire data. The next annual questionnaire will be sent to you in January 2020. If you have already provided your e-mail address to us, we will send you an e-mail with a personalized link to a secure website where you can complete and submit this questionnaire. If you have not yet provided your e-mail address and would prefer the e-form option, please contact us at vitalstudy@partners.org or 1-800-388-3963. Most participants now complete their questionnaires online. Of those who completed the last annual questionnaire (which was sent in January 2019), 60% submitted the questionnaire electronically and 40% submitted it by postal mail.

***VIT*amin D and Omeg*A*-3 Tria*L* (VITAL Study)**

900 Commonwealth Avenue, Floor 3
Boston, Massachusetts 02215
Telephone: 1-800-388-3963
E-mail: vitalstudy@partners.org
Website: www.vitalstudy.org

VITAL on the Go

Joel S., of California, writes, "I've had two months of sailing adventures in Madagascar and along the coast of East Africa. Here I'm enjoying the company of a family of lemurs on the island of Nosy Komba just off the Madagascar coast!"

Maria S., of Georgia, celebrating her 80th birthday with her daughters Ciara and Karen at the border of Togolese Republic, West Africa, in April 2018.

Elden L., of Minnesota, writes, "This photo was taken ... in Sendafa, Ethiopia, where my church operates a school for children who might not otherwise receive an education because of their extreme poverty. .... Our team of 7 spent one week working in the 320-student kindergarten through grade 5 classrooms with skill-building games and art work."

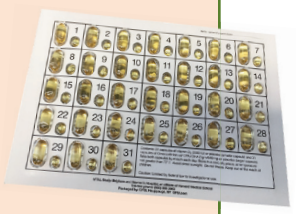
Ray W., of Washington, celebrated his 80th birthday with running friends. He writes, "My 'runs' lately are usually walks, but all of us have finished the Boston Marathon. I'm one of the few in this group of Columbia Basin (Eastern Washington State) runners that has only run Boston once (in 2009)."

Please write to us!

We would love to hear your thoughts about participating in the VITAL study and contributing to scientific knowledge about the role of vitamin D and omega-3 fatty acid supplementation in human health. We also continue to welcome your photos and stories—travel and otherwise. We will feature a sampling of responses in future newsletters. Please write to us at vitalstudy@partners.org or the postal address in the box on page 3.

FUN FACT:

What percentage of participants correctly guessed the type of study capsules they were assigned to during the study pill-taking period?



The VITAL study questionnaire that you filled out in early 2018, shortly after the study pill-taking period ended, included the following: "At the beginning of the trial, you were randomly assigned (like the flip of a coin) to either active or placebo for each study pill. If you had to guess, for each, what do you think you were assigned to? Active/placebo/no idea". For vitamin D, about 59% of participants said that they had no idea; 23% guessed their treatment assignment correctly; and 18% guessed incorrectly. For omega-3 fatty acids, 55% of study participants said they had no idea; 26% guessed correctly; and 19% guessed incorrectly. We are pleased with these numbers, as they indicate that, in general, study participants did not know whether they had been assigned to active or placebo study pills. This "blinding" of study participants is important in helping to ensure the validity of findings from randomized clinical trials such as VITAL.