No. 13
Fall 2018

# VITAL Signs

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

## VITAL researchers announce landmark trial findings

Thanks to your commitment to taking the study capsules and filling out the health questionnaires, we now have the results of 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 included 25,871 adults—12,786 men aged 50 years and older and 13,085 women aged 55 and older—who were followed for an average of 5.3 years. All participants were monitored for the occurrence of cancer and cardiovascular events.

The results were presented by Dr. JoAnn Manson at the American Heart Association's annual meeting in Chicago, Illinois on November 10, 2018 and were concurrently published online in the *New England Journal of Medicine*.

### From the VITAL Study Directors

**Dear VITAL participant,**

We are thrilled to announce that, at long last, the main findings from the VITAL study are here! This issue of the newsletter summarizes these findings, which can also be found on the VITAL website, www.vitalstudy.org.

We also want you to know how very grateful we are for your many years of extraordinary dedication to VITAL. We hope that you proudly display the enclosed certificate of appreciation for your highly valued contributions to this research endeavor.

Finally, we would like to remind you that we will be sending you a follow-up questionnaire in January 2019 and another in 2020 (see page 3). During this time, we will continue to send you newsletters and other communications to keep you informed about the progress and additional findings of the study.

Thank you very much for helping to make 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

### Vitamin D

***Cancer.*** During the trial, 793 cancers occurred among the 12,927 participants assigned to vitamin D, as compared with 824 cancers among the 12,944 participants assigned to vitamin D placebo, a small but nonsignificant reduction. Supplemental vitamin D also did not reduce the occurrence of breast, prostate, or colorectal cancers. However, there was a suggestive 17% reduction in cancer deaths, which became a 25% reduction in analyses that excluded the first two years of follow-up. Excluding early follow-up is a common practice in analyzing data from trials of dietary supplements and cancer because effects of nutritional factors on risk of cancer, a slow-developing disease, typically become clear only after several years.

Although vitamin D did not significantly lower the risk of developing cancer in the total study population, African Americans assigned to vitamin D did experience a suggestive 23% reduction in cancer risk. However, further research is needed to confirm this finding.

***Cardiovascular disease.*** A total of 396 major cardiovascular events—heart attack, stroke, or death from cardiovascular causes—occurred among participants in

— continued on page 2 —

— FINDINGS continued from page 1 —

the vitamin D group, as compared with 409 in the placebo group, a small but nonsignificant reduction. Supplemental vitamin D also did not reduce the occurrence of heart attack, stroke, or cardiovascular death, considered individually, nor did it reduce the risk of death from any cause.

***Side effects.*** There were few side effects of high-dose vitamin D. No significant increases in risk of hypercalcemia (high blood calcium level), kidney stones, or gastrointestinal symptoms were observed.

***Clinical perspective.*** The findings indicate that high-dose vitamin D does not lower the risk of developing cancer or cardiovascular disease in generally healthy men and women, although it appears to lower the risk of cancer death. "The promising results for cancer mortality need to be confirmed in extended follow-up of the study participants and in future trials," said Dr. Manson. "Although our study shows that a vitamin D dose of 2000 IU per day is well tolerated, with few if any side effects, the results do not strongly support the initiation of high-dose vitamin D for prevention of cancer or cardiovascular disease in healthy patients who already meet vitamin D requirements for bone health." National guidelines for vitamin D intake from food and/or supplements recommend 600 IU per day for adults up to age 70 and 800 IU per day for those aged 71 and older. (See Q&A for additional comments.)

## KEY FINDINGS

### Vitamin D supplementation

- Did not reduce risk of cancer
- Did not reduce risk of major cardiovascular events (heart attack, stroke, or cardiovascular death considered together)
- Appeared to reduce risk of cancer-related death

### Omega-3 fatty acid supplementation

- Did not reduce risk of cancer
- Did not reduce 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
- Reduced risk of heart attack by 28%, when heart attack was considered separately from other cardiovascular events; the benefit appeared strongest in African Americans

## Omega-3 fatty acids

***Cardiovascular disease.*** During the trial, 386 major cardiovascular disease events occurred among the 12,933 participants receiving omega-3 fatty acids, as compared with 419 such events among the 12,938 participants receiving placebo, an 8% reduction that was not significant. Upon closer examination, this result was due almost entirely to a reduction in heart attacks without a reduction in strokes. Specifically, the omega-3 fatty acid intervention lowered the risk of heart attack by 28% and the risk of fatal heart attack by 50% but had no benefit on stroke or cardiovascular deaths not related to heart disease. Additionally, omega-3 fatty acids reduced the rate of angioplasty procedures by 22%.

***Cancer.*** A total of 820 cancers occurred among participants in the omega-3 fatty acid group, as compared with 797 in the placebo group, a small but nonsignificant difference. Omega-3 fatty acid supplementation did not reduce the occurrence of breast, prostate, or colorectal cancers, cancer-related deaths, or deaths from any cause. In analyses excluding early follow-up (see vitamin D discussion above), supplementation was associated with a slight but nonsignificant increase in risk of cancer and had no effect on cancer death.

***Side effects.*** The omega-3 fatty acid intervention was well tolerated, with no increase in bleeding or

gastrointestinal symptoms observed in those assigned to the active supplement.

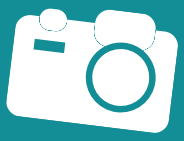
***Subgroup findings.*** The most consistent cardiovascular benefits of supplemental omega-3 fatty acids were found in participants who reported low fish intake at baseline and in African Americans. In participants with low fish consumption (defined as less than 1½ servings per week; one serving is 3-4 ounces), 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, and no indication of increased cancer risk. In contrast, for participants with higher fish consumption (at least 1½ servings per week), omega-3 fatty acids did not protect against cardiovascular events, including heart attacks, or death from any cause, and there was a suggestive increase in cancer risk. Among African Americans, omega-3 fatty acid supplementation led to a 77% reduction in heart attacks, and a benefit was observed regardless of level of fish intake. Some of these findings may have been due to chance and should not be viewed as conclusive.

***Clinical perspective.*** "The results indicate that people with low dietary intake of fish will likely obtain a heart benefit from omega-3 fatty acid supplementation," said Dr. Manson. "On the other hand, those with higher fish consumption do not appear to benefit, perhaps because they are already meeting their omega-3 requirements by eating fish. This pattern of results implies that, while a modest amount of fish oil is desirable, more may not necessarily be better." She added, "Additional research is needed to confirm the strong heart protection seen in African Americans and to determine whether there are other groups who might benefit from omega-3 therapy. People considering the use of omega-3 fatty acids to prevent heart disease must weigh the overall balance of benefits and risks." (See Q&A for additional comments.)

## What's next for VITAL?

Although the main VITAL study was designed to test whether supplemental vitamin D and omega-3 fatty acids affect risk of cancer and cardiovascular disease, ancillary studies are examining diabetes, atrial fibrillation, cognition, autoimmune disorders, lung diseases, depression, and other outcomes. The ancillary results will soon be available to allow a more complete picture of the balance of benefits and risks of supplementation. We will keep you posted as to the results. We will also send you two additional health questionnaires—one in January 2019 and one in 2020. These questionnaires will be similar to the ones that you have previously completed. Your responses will enable 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. Thank you again for your commitment to the study!

## A CALL FOR PHOTOS



We welcome your photos and stories and believe that VITAL participants enjoy learning about each other. For a chance to be featured in a future newsletter, please send a high-quality electronic or film photo of yourself, along with a brief note describing where the photo was taken, to vitalstudy@partners.org or to the address in the box below.


***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 Q&A

**Q. What do the VITAL results mean for me? Should I take vitamin D? Should I take fish oil?**

**A.** Before making a decision about any supplement, it is important to consider your personal health history as well as the overall balance of benefits and risks of supplementation. Discussing these issues with your healthcare provider is optimal, but there is no need to do so on an emergency basis. Stay tuned for ancillary results from VITAL during the next 6 to 12 months—the findings will provide a more complete picture of the benefit-risk balance and may help you and your doctor make a final decision. We anticipate that, over the next year or so, medical and public health authorities will consider whether new recommendations for the use of high-dose vitamin D and omega-3 fatty acid supplements should be made based on the results of VITAL and other key randomized trials.

Our general guidance at this time is that, if you're already taking these supplements in the doses tested by VITAL and you're doing well on them, there's no reason to stop taking them based on the study's findings. On the other hand, if you're not taking these supplements, you may want to wait 6 to 12 months to get a more complete picture of their benefits and risks before making a final choice. For omega-3 supplements specifically, you may want to talk with your healthcare provider over the next several months about taking a supplement if you rarely or never eat fish or if you are African American.

**Q. I eat fish twice per week. Would I have a heart benefit from a fish-oil supplement?**

**A.** The VITAL results suggest that you may not receive a benefit. You should continue to include fish in your diet instead of switching to an omega-3 fatty acid supplement. It is unlikely that all of the health benefits of fish consumption can be achieved with omega-3 supplementation. For example, people who eat fish tend to eat less red meat and less saturated fat, and some of the benefits of fish consumption are likely attributable to avoiding relatively unhealthy foods.

**Q. Are the VITAL results tied to the specific vitamin D and fish-oil products that were tested? Should I expect the same effects with other products?**

**A.** VITAL tested a daily vitamin $D_3$ softgel (2000 IU) manufactured by Pharmavite and marketed in the U.S. under the Nature Made label and a daily fish-oil capsule (1-gram capsule containing 840 mg of omega-3 fatty acids, including eicosapentaenoic acid [EPA, 460 mg] and docosahexaenoic acid [DHA, 380 mg]) manufactured by Pronova/BASF and marketed (albeit at a higher dose [4 grams]) as Omacor in Europe and as Lovaza in the U.S. Although it is unclear whether the VITAL results would apply to other vitamin D or fish-oil supplements that have different doses or lower quality control, we would expect supplements that contain the same doses and produced with the same high quality control as those tested in VITAL to provide similar benefits and risks. (For additional information, see the Q&A column in issue 9 of the newsletter, available at www.vitalstudy.org.)

**Q. Study pill-taking ended on December 31, 2017, and I promptly completed and returned my end-of-pill-taking questionnaire in January 2018. Why did it take so long to report the study results?**

**A.** The large number of VITAL participants—nearly 26,000!—meant that some of the following steps took longer than might otherwise be expected. It took a few months for some participants to complete their questionnaires and for these questionnaires to be processed; several more months to secure participants' permission to obtain medical records regarding reported cancer and cardiovascular disease outcomes and to review such records to confirm and classify diagnoses; and a few more months to analyze the data, prepare manuscripts for submission to a medical journal, and revise the manuscripts to address issues raised by a rigorous review process.

**Q. I have left-over study calendar packs that contain active vitamin D and/or active omega-3 fatty acid supplements. May I still take these study pills?**

**A.** Unfortunately, given the length of time that has elapsed since we mailed these pills to you, the pills have expired and should be discarded. See the third Q&A for information on the study pill ingredients, doses, and options for obtaining the same or similar products.