Recent Findings from VITAL

The main 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. However, VITAL researchers are also studying the effect of these supplements on many other outcomes. Here is a summary of recently published results. For the complete list of VITAL publications, please visit the VITAL website at www.vitalstudy.org.

- **Autoimmune disease.**

Autoimmune diseases occur when the body’s immune system misidentifies its own healthy tissues as foreign and attacks them. The resulting inflammation affects various parts of the body and can cause fatigue; muscle aches; joint pain, stiffness, and swelling; skin issues; abdominal pain; and digestion difficulties. Autoimmune diseases generally increase with age, occur more commonly in women, and can run in families. In observational studies, vitamin D blood levels have been shown to be lower both among people with and those who later develop autoimmune diseases. In small trials of patients with diagnosed autoimmune disease, supplemental omega-3 fatty acids improved disease outcomes. However, trials of supplemental vitamin D or omega-3 fatty acids for prevention of autoimmune disease in initially healthy individuals are lacking. VITAL researchers partnered with Harvard colleague Dr. Karen Costenbader to fill this knowledge gap. During the trial, study participants answered questions about new diagnoses of rheumatoid arthritis, polymyalgia rheumatica, autoimmune thyroid disease, psoriasis, and inflammatory bowel disease, and were also asked to report all other new-onset autoimmune diseases. With participants’ permission, study physicians then reviewed participants’ medical records to confirm reported diagnoses. Vitamin D reduced the risk of developing confirmed autoimmune disease by 22%, with...

-continued on page 2

**Dear VITAL participant,**

Thank you for your commitment to VITAL and your continued completion of the study’s health questionnaires. Please be on the lookout for the next annual questionnaire, to be sent in mid- to late January 2023. Your response is important, regardless of which study pills you received in the trial and whether or not you have had changes in your health since the previous questionnaire. The information that you provide will enhance the value of the data already collected and allow us to examine the longer-term effects of vitamin D and omega-3 fatty acid supplements compared with the placebos and to explore other health-related topics.

Although you may continue to submit your annual questionnaires by postal mail, you now have the option of completing these questionnaires online. 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 fill out and submit your 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 at your earliest convenience.

As always, we welcome your current photos (without pill packs!), stories (travel or otherwise), and thoughts about participating in VITAL. Please send these to us at vitalstudy@partners.org or the postal address in the box on page 4 of this newsletter. Also, we are excited to announce the debut of the “Participant Profile” feature (see page 3), which we hope will be a recurring feature of the newsletter. If you are interested in contributing a longer submission for this purpose, please send a letter of inquiry to vitalstudy@partners.org or our postal address to explore this possibility.

Thank you again for being part of the VITAL community and helping to ensure the study’s success!

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the protective effect strengthening to a 39% reduction after two years of supplementation. Omega-3 fatty acids were associated with a 15% reduction in risk of confirmed autoimmune disease, although this was not statistically significant. However, among participants with a family history of autoimmune disease, omega-3 fatty acids lowered the risk of developing confirmed autoimmune disease by 34%. Moreover, when investigators considered not only confirmed autoimmune disease but also probable autoimmune disease diagnoses, omega-3 fatty acids were associated with an 18% reduction in risk in the total study population. “This is the first direct evidence that daily supplementation may reduce autoimmune disease incidence,” said Dr. Costenbader. “We look forward to honing and expanding our findings and encourage professional societies to consider these results when developing future guidelines for the prevention of autoimmune diseases in midlife and older adults.” Reference: Hahn J, et al. British Medical Journal 2022 Jan 26; 376:e066452.

Fracture. Although many people take vitamin D supplements to promote bone health, data from previous randomized trials have shown inconsistent effects on fracture risk in generally healthy populations. VITAL researchers, led by Harvard colleague Dr. Meryl S. LeBoff, tested whether supplemental vitamin D and omega-3 fatty acids reduced risk of fracture and found that neither supplement was effective for this purpose. “Vitamin D did not reduce fracture risk in generally healthy midlife and older individuals not preselected for low vitamin D levels, low bone mass, or osteoporosis,” said Dr. LeBoff. “Participants may already have had vitamin D levels necessary for fracture protection. The findings do not apply to patients with extremely low vitamin D levels or with osteoporosis.” “More vitamin D is not necessarily better,” added VITAL Principal Investigator Dr. JoAnn Manson. “The findings suggest that only small to moderate amounts of vitamin D are needed to maintain bone health.” Future studies in VITAL will investigate whether new blood markers of vitamin D levels or genetic variation in vitamin D absorption or metabolism help to identify individuals who may benefit from supplemental vitamin D for bone health. References: LeBoff MS, et al. New England Journal of Medicine 2022 Jul 28; 387:299-309; LeBoff MS, et al. American Society for Bone and Mineral Research Annual Meeting, Abstract # SUN-738, Sept. 12, 2022.

Cognitive decline. Animal and laboratory studies suggest that low blood levels of vitamin D or omega-3 fatty acids are linked to impaired brain development and function. In humans, some though not all observational studies have implicated low intakes of vitamin D or omega-3 fatty acids in cognitive impairment. Previous trials have not found benefit for supplemental vitamin D or omega-3 fatty acids in reducing cognitive decline, but the vitamin D trials tested lower doses than did VITAL, and most omega-3 fatty acid trials had small sample sizes and short durations. The VITAL team, together with Harvard colleagues Drs. Jae Hee Kang and Francine Grodstein, examined whether vitamin D and omega-3 fatty acid supplements reduce cognitive decline. Investigators asked 4,218 VITAL participants aged 60 years or older to complete a series of telephone or in-person interviews to assess memory and thinking ability over a 2- to 3-year period. Neither study supplement prevented cognitive decline in the overall group. However, Black individuals assigned to vitamin D experienced less cognitive decline than their counterparts assigned to placebo. “Supplemental vitamin D appears to provide cognitive benefits in Black individuals,” said Dr. Kang. “This promising finding requires confirmation in future studies.” Reference: Kang JH, et al. Scientific Reports 2021 Dec 1; 11:23253; Kang JH, et al. Alzheimer’s & Dementia 2022 Apr 5; 8:e12288.

Heart failure. Heart failure is a progressive condition in which the heart does not pump enough blood to meet the body’s oxygen needs. VITAL researchers partnered with Harvard colleague Dr. Luc Djoussé to examine whether supplemental vitamin D and omega-3 fatty acids protect against being hospitalized for heart failure. As previously reported (see issue 15 of the newsletter), the findings for omega-3 fatty acids, though not for vitamin D, suggest benefit. Although the omega-3 fatty acid intervention did not reduce the risk of a first hospitalization for heart failure, it did reduce the risk of a subsequent hospitalization for this condition by 14% during the pill-taking phase of the study. These results were promising, so investigators followed up with a more detailed investigation, which showed that the effect of supplemental omega-3 fatty acids on risk of heart failure hospitalization differed according to type 2 diabetes status and race. Among participants who entered VITAL with diabetes, omega-3 fatty acid supplementation reduced the risk of first and subsequent hospitalizations for heart failure by 31% and 47%, respectively. On the other hand, among participants without diabetes at study entry, supplementation offered no such benefit. With respect to race, omega-3 fatty acid supplementation did not reduce the risk of first heart failure hospitalization in either Black or –continued on page 4
I was born in 1938 amid the Great Depression; growing up in a tiny Alabama town, I discovered that I could draw long before I could write and surprisingly that I could capture uncanny likenesses of people. I used that God-given talent infrequently during college, two years of military service and in law school, although I sometimes put a sketch in a publication.

During my 44 years of trial practice—nearly always defending corporate or institutional clients—I created an occasional small sculpture for one of our children, using an impermanent medium.

In 1996 my wife Robbie discovered a local bronze foundry in Birmingham, and I began accepting commissions to sculpt portraits in bronze. Over the next 26 years and especially since my retirement in 2008, my bronze portrait busts have been placed in the U.S. Supreme Court, the Supreme Court of British Columbia, the Supreme Court of Alabama, the Supreme Court Historical Society headquarters, the Alabama State House, the O’Neal Comprehensive Cancer Center, the High Hampton History Museum, and in various private collections around the country.

Through the years I devoted considerable effort to physical and mental conditioning, to that point that even at present I walk three miles and work many crossword puzzles every day and play duplicate bridge several times a week. Aware since 2006 that I have a partial blockage of a coronary artery, I was delighted to learn of and participate in the VITAL study and have followed its reports with great interest after the end of the study pill-taking period. I have even continued with 2000 IUs daily of vitamin D3, being absolutely convinced that it has profound benefits for my body and mind (and don’t mind more frequently trimming nails and hair).

I think all of us VITAL study subjects (together with the public) owe a huge debt of gratitude to the magnificent VITAL team. I don’t believe I would have made it to age 84 without them.
non-Hispanic White participants. However, supplementation reduced the risk of subsequent heart failure hospitalization in Black participants by 35%, whereas White participants derived only modest benefit. “These findings echo the greater reductions in heart attack with omega-3 fatty acid supplementation in Black than in White participants,” noted Dr. Djoussé. “Further study of the potential heart benefits of omega-3s in Blacks and other minority populations is needed.” Reference: Djoussé L, et al. JACC Heart Failure 2020 Apr; 10:227-234.

**Physical function following stroke.** Studies of stroke patients show lower blood levels of vitamin D at hospital admission are associated with greater stroke severity and worse physical function after discharge. Animal studies suggest that omega-3 fatty acid supplementation may reduce brain damage after stroke, potentially resulting in better stroke outcomes. However, whether supplemental vitamin D or omega-3 fatty acids taken prior to stroke can improve stroke outcomes is not known. To examine this question, VITAL researchers asked approximately 200 VITAL participants who experienced a stroke during the trial to complete questionnaires about their day-to-day functioning after their stroke. Vitamin D had no effect on stroke outcomes, whereas participants who had been randomized to omega-3 fatty acids were less likely to report post-stroke limitations in physical function or physical disability than those randomized to placebo. “Stroke is a leading cause of disability, so these results, if replicated in additional studies, may have major public health implications,” said VITAL collaborator Dr. Pamela Rist. Reference: Rist PM, et al. European Journal of Neurology 2021 Mar; 28:809-815.

**Urinary issues.** Observational studies suggest that women with higher dietary intakes or blood levels of vitamin D may have lower rates of urinary incontinence (unintentional release of urine), but data from randomized trials are limited. VITAL researchers collaborated with Dr. Alayne Markland at the University of Alabama at Birmingham to examine whether supplemental vitamin D protects against the development of or worsening of urinary incontinence. In the overall study population of women, vitamin D did not affect the risk of the development or progression of urinary incontinence. VITAL investigators also examined whether vitamin D reduced the risk of overactive bladder (a frequent and sudden urge to urinate that may be difficult to control) and urinary incontinence in men. In the overall study population of men, vitamin D did not affect the risk of either condition. However, among men who entered the trial with low vitamin D blood levels (25-hydroxyvitamin D below 20 ng/mL), vitamin D supplementation halved the risk of overactive bladder but also slightly raised the risk of urinary incontinence. “Despite these paradoxical findings, additional evaluation of supplemental vitamin D for overactive bladder in men with low vitamin D status is warranted,” said Dr. Markland. References: Markland AD, et al. American Journal of Obstetrics and Gynecology 2022 Apr; 226:535.e1-535.e12; Markland AD, et al. Journal of Urology [e-published 2022 Sept 6]

**Other conditions.** In VITAL, neither supplemental vitamin D nor omega-3 fatty acids reduced migraine frequency or severity among participants with a history of migraine, nor did these supplements prevent the onset of frailty or slow the rate of frailty progression over time.

Additionally, no benefits were found for omega-3 fatty acids in relation to depression or dry eye disease. References: Please see the VITAL publications list at www.vitalstudy.org.