No. 18
Fall 2023

VITAL Signs

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

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. Additionally, VITAL researchers are investigating the effect of these supplements on other outcomes and are studying health issues that do not directly relate to the study supplements. Here is a summary of selected recently published results that may be of particular interest to you. For the complete list of VITAL publications, please visit the VITAL website at vitalstudy.org.

Vitamin D dosing frequency, body mass index, and cancer

As reported in previous newsletters, the results of VITAL and other vitamin D trials, considered in aggregate, indicate that vitamin D supplementation does not lower the risk of developing cancer but does appear to reduce the risk of advanced cancer or cancer-related death. In VITAL, supplemental vitamin D reduced the risk of metastatic or fatal cancer by a significant 17% during the pill-taking phase of the study, with the protective effect most pronounced among individuals with a healthy body weight (body mass index [BMI] below 25 [calculated as weight in kilograms divided by height in meters squared]).

Whether or not the effectiveness of vitamin D for cancer prevention depends on dosing strategy (daily vs. weekly or less frequent dosing) is unclear. To address this question, VITAL researchers, led by Harvard colleague Dr. NaNa Keum, analyzed available data from 12 trials of supplemental vitamin D and cancer risk, six of which also considered cancer-related death. Some of these trials, including VITAL, tested daily administration of vitamin D (doses ranged from 400 to 4000 IU per day), whereas others tested less frequent administration of large "bolus" doses (20,000 IU per week to 500,000 IU per year). The researchers found that, overall, vitamin D supplementation did not affect the risk of developing cancer, regardless of whether vitamin D was taken daily or less frequently. However, in the three trials of daily supplementation that reported results according to the BMI of study participants (one of these trials was VITAL), individuals with healthy weight experienced a significant 24% treatment-associated reduction in cancer

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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. Please keep an eye out for the next annual questionnaire, which will be sent in mid-to-late January 2024. 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 study the longer-term health effects of supplemental vitamin D and omega-3 fatty acids compared with the placebos and to investigate other health-related topics in the overall cohort.

You may submit your annual questionnaire online or by postal mail. If you have given us your email address, we will send you an email with a personalized link to a secure website where you can fill out and submit your questionnaire. If you have not provided your email 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 (without pill packs!), stories (travel or otherwise), and reflections 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. If you would like to contribute a longer submission for consideration as a "Participant Profile" (see page 3), please send an email or letter of inquiry to explore this possibility.

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

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risk, whereas those with overweight or obesity did not derive a treatment benefit. (For more on the effect of BMI on participants' response to vitamin D supplementation, please see the next section.) The researchers also found that supplemental vitamin D was associated with a small but nonsignificant 8% reduction in cancer death across all trials. Upon closer examination, a significant 13% reduction in cancer death was seen in trials of daily dosing, whereas there was no benefit in trials of infrequent bolus dosing. VITAL was the only daily-dosing trial that reported results for cancer death according to BMI, finding a significant 42% treatment-associated reduction in individuals with healthy weight but no benefit in their counterparts with overweight or obesity.

"The results of this analysis support an effect of daily—but not infrequent bolus—dosing of vitamin D for reducing cancer mortality, and, among individuals with healthy weights, cancer incidence," noted VITAL Principal Investigator Dr. JoAnn Manson. "Infrequent bolus doses lead to large, nonphysiologic fluctuations in vitamin D blood levels, which may undercut some of the beneficial effects of supplementation."

Reference: Keum N., et al. *British Journal of Cancer* 2022 Sep; 127(5): 872-878.

Body mass index and response to vitamin D supplementation

As described in the previous section, data from VITAL and other randomized trials indicate that daily vitamin D supplementation reduces cancer risk in individuals with healthy weight but not in those with overweight or obesity, and data from VITAL show similar findings for cancer death. Comparable results have also been found for autoimmune disease in VITAL and for type 2 diabetes in other vitamin D trials, with significant treatment-associated reductions in these outcomes in participants with healthy weight but not in those with obesity. (Analyses of VITAL data on vitamin D in relation to risk of type 2 diabetes are underway; results will be provided in a future newsletter.) To begin to understand the physiology underlying these findings, VITAL investigators, led by Dr. Deirdre Tobias, examined data from 16,515 VITAL participants who provided a blood sample at the beginning of the trial, 2742 of whom also provided a second sample two years later. Compared with their counterparts with healthy weight, study participants with elevated body weight had lower baseline blood levels of vitamin D as well as a less robust response to supplementation—i.e., their vitamin D blood levels (total 25-hydroxyvitamin D, free vitamin D, and bioavailable vitamin D) increased by a smaller amount in response to a given dose of vitamin D. (*Technical note:* Total 25-hydroxyvitamin D, the marker most commonly measured by labs used by healthcare providers, has long been viewed as the best single indicator of vitamin D status. However, newer biomarkers give more information about the biological availability of the vitamin D.)

"These findings suggest that BMI is associated with a modified response to vitamin D supplementation and may in part explain the observed lack of benefit of vitamin D for certain health outcomes among people with higher body weight" noted Dr. Tobias. "It may be that a greater amount of vitamin D, a fat-soluble vitamin, is sequestered in fat tissue, leaving lower amounts circulating in the blood. Obesity may also suppress conversion of supplemental vitamin D to 25-hydroxyvitamin D in the liver, thereby reducing bioactivity."

Reference: Tobias D.K., et al. *JAMA Network Open* 2023 Jan 3; 6(1):e2250681.

Vitamin D and statin-associated muscle symptoms

Statins are commonly prescribed medications for the treatment of high cholesterol. Side effects of statins include muscle aches or discomfort, which are collectively referred to as statin-associated muscle symptoms (SAMS). SAMS are common and can often lead to discontinuation of statins. Indeed, 648 (31%) of the 2083 VITAL participants who started taking a statin during the trial reported SAMS, and 270 (13%) stopped their statin because of such symptoms. Previous studies of patient characteristics associated with SAMS have yielded conflicting results. In VITAL, women were more likely to report SAMS than men (women vs. men: 35% vs. 27%), and participants aged 50 to 64 years were more likely to report SAMS (35%) than those aged 65-74 years (29%) or 75 years and older (27%). Individuals with higher body mass index were also more likely to report SAMS than leaner individuals, but the association weakened after statistically adjusting for other factors. Race/ethnicity, physical activity level, smoking history, and the presence or absence of hypertension and diabetes were unrelated to the likelihood of experiencing SAMS.

Observational studies have found that low blood levels of vitamin D are associated with the development of SAMS. Studies have also reported that many patients who stopped taking a statin because of SAMS and were then treated with vitamin D were able to resume taking a statin. However, these studies were not randomized trials and did not have placebo control groups. Randomized, placebo-controlled trials of supplemental vitamin D to prevent or treat SAMS are lacking. To fill this gap, VITAL investigators, in collaboration with Dr. Mark Hlatky at Stanford and Drs. Pedro Gonzalez and Neil Stone at Northwestern, studied the aforementioned 2083 participants who started a statin after enrolling in the trial. Of these participants, 1033 had been assigned to vitamin D and 1050 to placebo. The researchers found that vitamin D did not affect the likelihood of reporting muscle symptoms or of stopping a statin because of such symptoms, even among those who entered the trial with low vitamin D blood levels.

"Vitamin D supplementation did not prevent statin-associated muscle symptoms or reduce statin discontinuation, which suggests that it lacks a clinically important effect in this regard," said Dr. Stone.

References: Gonzalez P.E., et al. *American Heart Journal* 2022 Oct; 252:39-41; Hlatky M.A., et al. *JAMA Cardiology* 2023 Jan 1; 8(1):74-80.

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Teacher, Minister, Writer, and Volunteer

Making VITAL Part of My Busy Life

by Jane Myers Perrine

Jane Myers Perrine is the name I use informally and as my pen name.

I've always enjoyed volunteering. I was named an honorary citizen of Louisville for my volunteer work there and nominated for Volunteer of the Year in Savannah.

Because my blood type is rare, I was often called on to contribute in emergencies, an easy way to help others. Also, I participated in clinical trials for my own chronic illness.

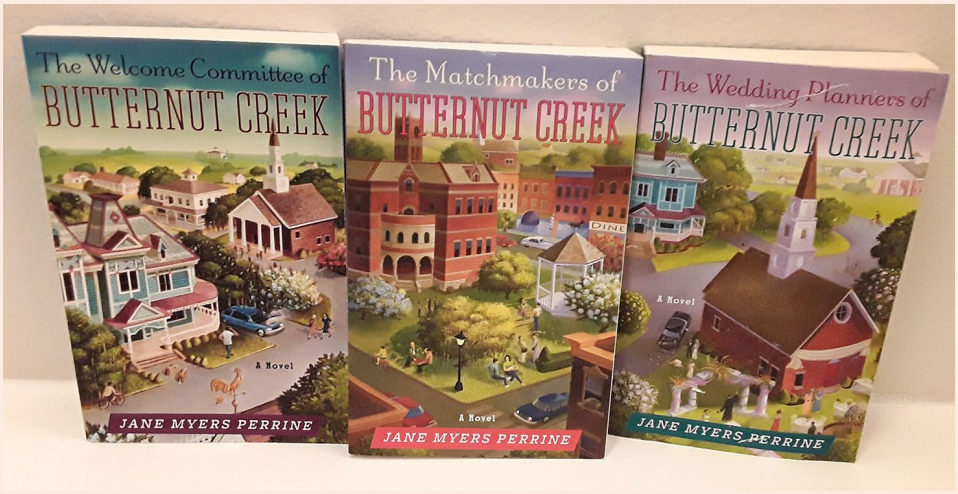
For those reasons, when I read about the VITAL study at Brigham and Women's Hospital in Boston, I responded quickly. I'd heard of Brigham and Women's for years so was pleased to be included in this trial, to help expand medical knowledge. It was even easier than giving blood.

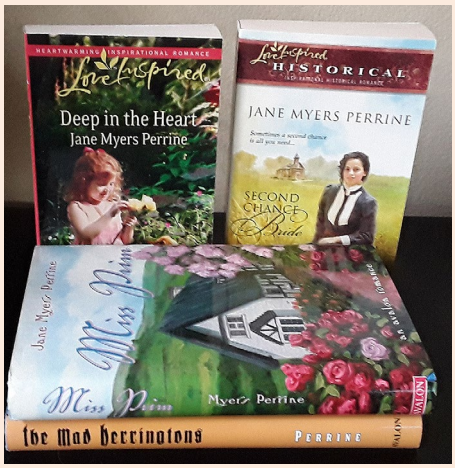
My life has been varied and full. I love teenagers and the Spanish language—I was a Spanish literature major at Kansas State University. These loves led me to teaching Spanish in high school and college for thirty years as well as participating in volunteer opportunities because I speak Spanish.

"The most popular of [my published books] is the three-book *Butternut Creek* series about a young minister called to a small-town church. These novels are sprinkled with experiences my husband and I had in ministry."

I'm an ordained minister, too. As well as following my minister husband from parish to parish, I served three churches and often filled pulpits because I love to preach.

And I'm an award-winning, multi-published writer. My third-grade teacher said I'd be an author. In fifth grade, I wrote a play about archaeologists in Egypt that we presented for my class. In college, I co-wrote an award-winning one-act play. Because life interfered, it took many years before I began to write seriously.





My first love was novels written during the Regency period in England, 1811-1820. Then I began to write about my adopted state, Texas—both women's fiction and Western historicals. Several were set in the beautiful Hill Country where I now live with my calico cat, Tammy Wynette.

Ten of my books have been published traditionally, which means I write the manuscript and the publisher buys the novel and pays me an advance and royalties. The most popular of these is the three-book *Butternut Creek* series about a young minister called to a small-town church. These novels are sprinkled with experiences my husband and I had in ministry. Also, I've e-published two mysteries.

From the VITAL study, I learned the importance of doing randomized trials to test the benefits and risks of taking dietary supplements or other treatments. And every time I read one of the VITAL study newsletters, I'm so very proud that Brigham and Women's allowed me to take part in it.

Vitamin D, omega-3 fatty acids, and depression in high-risk individuals

As reported in previous newsletters, no benefits were found for either vitamin D or omega-3 fatty acid supplementation in preventing depression or improving mood in the overall VITAL study population. In a new report, VITAL investigators collaborated with Harvard colleagues Drs. Chirag Vyas and Olivia Okereke to investigate the effect of these supplements in 720 participants at elevated risk for clinical depression because of the presence of depressive symptoms or risk factors for depression at baseline, such as anxiety, physical or functional limitations, certain medical conditions, caregiving burden, problem drinking, or low psychosocial support. These participants completed detailed in-person evaluations at the start of VITAL and again 2 years later. (The evaluations were conducted at Brigham and Women's Hospital in Boston.) The researchers found that neither supplement reduced the risk of new-onset depression or improved mood scores.

"Neither vitamin D nor omega-3 fatty acid supplementation showed benefits for prevention of depression in older adults, even in those individuals at highest risk for developing the condition," said Dr. Vyas.

Reference: Vyas C.M., et al. *Journal of Clinical Psychiatry* 2023 Jun 26; 84(4):22m14629.

Sex differences in atrial fibrillation risk

Atrial fibrillation (AFib for short) is an irregular heartbeat known as an arrhythmia. The four chambers of the heart normally beat at a steady rate. However, in AFib, the upper chambers of the heart (the atria) quiver or contract in a rapid, disorganized manner (fibrillation), creating an irregular rhythm. If left untreated, AFib can increase risks of stroke and heart failure. AFib is the most common heart rhythm problem in adults aged 65 and older. VITAL investigators, led by Dr. Christine Albert at Cedars Sinai Medical Center, examined whether women and men without prior cardiovascular disease had similar or different risks of developing AFib. They found that women were at lower risk of AFib after statistical adjustment for the effects of age, body mass index, and other risk factors. However, greater height is a risk factor for AFib, and, after accounting for height differences between women and men, women no longer had a lower risk of AFib than men.

"These data suggest that sex differences in body size account for much of the previously reported protective association between female sex and AFib," Dr. Albert noted. "These data also underscore the importance of AFib prevention in women."

Reference: Siddiqi H.K., et al. *JAMA Cardiol* 2022 Oct 1; 7(10):1027-1035.

New VITAL Ancillary Study on Breast Cancer and Depression

VITAL investigators, together with Harvard colleagues Drs. Aditi Hazra and Olivia Okereke, are excited to announce the recent receipt of funding from the National Institutes of Health to study whether the effects of a breast cancer diagnosis and resulting treatment on mood and depression risk differ by race or ethnicity. Depression after breast cancer has most commonly been studied in White rather than Black women or those of other racial and/or ethnic backgrounds. However, post-diagnosis concerns may differ by race or ethnicity, particularly for Black women, who are more likely than non-Hispanic White women to be diagnosed with more aggressive cancer subtypes, to report worse health-related quality of life, and to experience greater breast cancer mortality. "An improved understanding of the effects of a breast cancer diagnosis on mood, as well as the factors that increase depression risk following a diagnosis, is a crucial first step in designing well-informed approaches to depression prevention and overall mental health promotion for Black women affected by breast cancer," said Dr. Okereke.

Participant Challenge

Describe VITAL in only one word! Please send your word to vitalstudy@partners.org or the postal address in the box below. We'll share the responses in a future newsletter.

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