



Update on marine omega-3 fatty acid (fish oil) research

Fish oil supplements rank among the best-selling dietary supplements in the United States. A recent national survey found that 1 in 10 U.S. adults take omega-3 supplements. (Only multivitamin-mineral formulations and calcium, which are taken by 32% and 11% of adults, respectively, are more widely used.) The popularity of omega-3 supplements highlights the need for rigorous scientific research to clarify the balance of health benefits and risks associated with these products.

The evidence for health benefits of marine omega-3s is promising though still inconclusive. Marine omega-3s tamp down inflammation, lower the blood fats known as triglycerides, prevent blood clotting, and possibly slow atherosclerosis—effects that would be expected to reduce the risk for cardiovascular disease (heart disease and stroke). However, whether marine omega-3s actually do lower the risk for developing heart disease or stroke is uncertain. The only sure way to determine this is to carry out a large, long-term randomized clinical trial such as VITAL.

We last reported on the state of omega-3 research in our second newsletter. Since then, three research teams have combined the results of previous clinical trials (the technical term is a *meta-analysis*) in an attempt to determine whether fish oil can help prevent cardiovascular disease.

In the May 14, 2012 issue of *Archives of Internal Medicine*, South Korean researchers analyzed data from 14 trials of patients with a history of cardiovascular disease (or at high risk for it) and concluded that fish oil did not prevent additional cardiovascular events. However, healthy people without prior cardiovascular disease (or at “average” risk for it) were not studied, so we don’t know the effects of fish oil in such individuals. In addition, many participants were taking medications for their heart disease that may have

obscured the effects of the omega-3s. Most of the trials were small or of short duration, limiting their ability to detect possible benefits.

Two additional meta-analyses of clinical trials of marine omega-3s—again, mostly in patients at elevated heart disease risk and on heart medications—were subsequently published. These meta-analyses yielded inconsistent results, despite a large overlap in the studies reviewed. One meta-analysis, published in the June

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From the VITAL Study Directors

Dear VITAL participant,

We wish to thank each of you for your continuing dedication to the **VITamin D and Omega-3 Trial (VITAL)**. We are grateful for your collaboration in this landmark clinical trial, which is expected to provide important information about the health effects of vitamin D and marine omega-3 fatty acid (fish oil) supplements. Your participation in the study, along with that of more than 24,000 other men and women throughout the country, will allow us to determine whether these supplements lower the risk for cancer, heart disease, and stroke. In addition, more than a dozen substudies are testing the effect of vitamin D and fish oil on other health



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outcomes. Two of these substudies are highlighted on page 3 of this newsletter.

Thank you again for your commitment to VITAL!

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VITAL Q&A

Q. I recently had hip surgery. I was a bit overwhelmed during my recovery and stopped taking my study pills. Can I start taking them again, or am I out of the study?

A. Absolutely, yes, you can restart, and absolutely no, you are not out of the study! We realize that certain events may change your level of participation in VITAL. Maybe you've moved, or started a new job or relationship, or become ill, or have begun caring for a sick family member. If such changes mean you cannot take the study pills for a while, you have to do what you have to do. If circumstances change and you can restart the study pills, we would very much like for you to do so. Resuming your study pills as soon as possible will help VITAL to determine whether vitamin D and fish oil can prevent cancer, heart disease, and stroke. If you cannot restart the study pills, we hope you will keep filling out the study questionnaires. We are grateful for whatever level of participation you can give us. Even if your participation drops to zero—something we very much hope won't happen—you aren't out of the study. By design, everyone who joined the study at the beginning must be included in the analysis at the end. You cannot be replaced! So, as you see, we need you, and we are most grateful for whatever contribution you can make between now and the end of the study.

If you haven't taken your study pills in a while and would like to start taking them again, please contact

us (1-800-388-3963 or vitalstudy@partners.org) for a new supply.

Q. I heard a recent report that the actual amount of vitamin D in some vitamin D supplements may be different from the amount stated on the label. Is this true for the vitamin D supplements in VITAL?

A. This is not the case for VITAL supplements, which have undergone extensive quality-control testing. A report in the April 8, 2013 issue of *JAMA Internal Medicine* did find dose inaccuracies in an investigation of several brands of over-the-counter (OTC) vitamin D supplements. The brands that were examined were not specified. However, VITAL's vitamin D supplement, which is made by the California-based company Pharmavite (and sold commercially under the Nature Made label), has been rigorously tested to ensure that its dose (2000 IU) and potency are accurate.

A general tip: when choosing OTC dietary supplements such as vitamin D, look for the USP (U.S. Pharmacopeial Convention) Verified Mark on the label, which indicates that the product "contains the ingredients listed on the label, in the declared potency and amounts; does not contain harmful levels of specified contaminants; will break down and release into the body within a specified amount of time; and has been made according to FDA current good manufacturing practices using sanitary and well-controlled procedures."*

Q. Lately I've read discouraging news about the effectiveness of vitamin D supplements. What's the story?

A. Recent clinical trials of vitamin D have found a benefit for lowering blood pressure but no effect on chronic knee pain symptoms, respiratory disease symptoms, infections, and depression. However, the data from these studies are far from conclusive, either because they enrolled few participants, were of short duration, or—in the case of the depression study—tested vitamin D doses now considered too low to be effective. VITAL substudies are expected to provide more definitive data on the effect of vitamin D on these and other outcomes.

Q. Why do you ask for the name and telephone number of a contact person?

A. In a long-term study such as VITAL, we occasionally lose touch with study participants when they move or have other changes in their status. We will write or telephone your contact person to ask for your current address or phone number only if we cannot reach you after multiple attempts.

*U.S. Pharmacopeial Convention, *USP Verified Dietary Supplements*. Available at: <http://www.usp.org/usp-verification-services/usp-verified-dietary-supplements>

Spotlight on VITAL substudies

Although the primary goal of the VITAL trial is to determine whether supplemental vitamin D and fish oil prevent heart disease, stroke, and cancer, several substudies are testing the effect of these nutrients on other health outcomes. Two such substudies are highlighted here; others will be featured in future newsletters. Participation in these substudies is *optional* and will not affect your participation in the main trial.

Cognitive function

As we age, many of us are concerned with keeping our minds sharp and avoiding memory loss. Vitamin D and omega-3 fatty acids have promising but unproven roles in this area. There are no large, long-term randomized clinical trials designed to test the effect of these nutrients on thinking and memory.

The VITAL team is partnering with Harvard colleagues Drs. Jae Hee Kang and Francine Grodstein to test whether vitamin D and fish oil supplements can prevent cognitive decline. The goal is to enroll 3,000 VITAL participants aged 65 years or older to be interviewed by phone three times during the trial. Each interview will last 25 minutes and will briefly assess memory and thinking ability. (This short assessment cannot be used alone to diagnose dementia or specific neurologic disorders; such diagnoses would require a comprehensive in-person medical evaluation.) The substudy, funded by the National Institute on Aging, is an exciting opportunity for VITAL

participants to help advance scientific understanding of nutrition and brain health.

Diabetes-related kidney disease

More than one third of people with diabetes develop kidney disease, which can be detected as high levels of protein in the urine or high levels of creatinine in the blood. Kidney disease, in turn, confers a higher risk for heart disease and other health problems. Therefore, preventing kidney disease can have a powerful impact on the health of people with diabetes.

Experiments in animals suggest that vitamin D and omega-3 fatty acids prevent kidney damage. Whether these supplements also improve kidney health

in people is not known. To answer this question, the VITAL team has partnered with kidney specialist Dr. Ian de Boer at the University of Washington. The Diabetic Kidney Disease (DKD) substudy will test whether vitamin D and fish oil favorably affect urine protein levels and blood creatinine levels in people with diabetes. To date, more than 1,300 VITAL participants with diabetes have agreed to participate. These individuals are answering detailed questionnaires about diabetes and kidney disease and are providing blood and urine samples by mail. The substudy is funded by the National Institute for Diabetes and Digestive and Kidney Diseases. Results are expected to help doctors decide how to prevent this major complication of diabetes.

Certificate of Confidentiality

The VITAL study team is committed to protecting your privacy. Data from completed questionnaires, medical records, and other information in our computer files are identified by study number only, and only a few staff members have access to the file that links study numbers with participants' names. In addition, we have been granted a Certificate of Confidentiality from the federal government. This certificate protects the privacy of participants in health research projects. VITAL researchers cannot be forced to disclose your identity, or other information collected about you in VITAL, in any legal proceedings at the federal, state, or local level. If needed, you can ask us to disclose some of this information to your health care provider or insurance company without violating this Certificate of Confidentiality. In addition, federal agencies may review our records under limited circumstances, such as a request from the Department of Health and Human Services for an audit or program evaluation, or a request from the Food and Drug Agency under the Food, Drug and Cosmetic Act. These agencies are also required to protect your privacy, however. Your trust is essential to the success of the study, and we would never do anything to risk losing your faith in us. Thank you for your commitment to VITAL.

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2012 issue of the *British Journal of Nutrition*, reviewed 21 trials and found that fish oil supplements reduced the risk of cardiovascular events, whereas the other meta-analysis, published in the September 12, 2012 issue of *Journal of the American Medical Association (JAMA)*, reviewed 20 trials and concluded that fish oil was not effective for this purpose. The opposite conclusions of these meta-analyses highlight the continuing scientific uncertainty regarding the potential cardiovascular benefits of fish oil in high-risk patients. And the fact that so few studies of people without heart problems were available for inclusion in these meta-analyses underscores the knowledge gap that VITAL was designed to fill—what are the health effects of fish oil in a generally healthy population?

Because it is a randomized clinical trial with many thousands of participants (more than 24,000 people have enrolled to date) who have committed to taking their study pills for the long haul (the study is planned to last 5 years), VITAL is expected to provide a definitive answer to whether fish oil (and vitamin D) prevent first occurrences of heart attack, stroke, or cancer in initially healthy men and women. Thank you to each and every one of you for your continuing commitment to answering these important questions in VITAL!



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VITAL on the Go



Joe E., RPh, of Tennessee, at the Dead Sea, Israel, in November 2012. He writes, "It is a pleasure to participate in the study and be a part of guiding the nation's health care needs."



Gwendolyn J., of Maryland, gave a presentation to a group of health students at Prince George's Community College in Largo, Maryland. She briefed the students on research studies that she has participated in over the past 18 years, including VITAL.



Jerry L., a retired Navy and commercial airline pilot, of California, at Dodge Ridge Ski Resort in the Northern Sierra Mountains, California.



Hilkka B., of Connecticut, at the Great Wall of China, in September 2012.



Husband and wife participants **Charles (Art) and Victoria W.**, of Georgia, vacationing in Costa Rica.



Patricia W., of Nevada, writes, "Just wanted to let you know my pill pack made it to the southernmost city in the southern hemisphere—Ushuaia, Argentina."

Thank you for the photos! Because we received such an enthusiastic response to our previous photo request, we regret that we cannot publish all photos received. However, we very much enjoy your snapshots and stories, so please keep them coming! We'll continue to print as many as possible in future newsletters. Photos (digital preferred) can be sent to vitalstudy@partners.org or our postal address (see box to the left). No participant photo will be published without the participant's express written consent.