



News and information for participants in the **VITamin D and Omega-3 Trial (VITAL)**

From the VITAL Study Directors

Dear VITAL participant,

Now that the **VITamin D and Omega-3 Trial (VITAL)** is well underway, we again wish to thank you for your commitment to this important research study. We are grateful that you have chosen to



JoAnn Manson, MD

enroll in this landmark study—and to take your study pills faithfully—to help us obtain much needed information about the health effects of vitamin D and marine omega-3 fatty acid (fish oil) supplements.

Your participation, along with that of 20,000 other men and women throughout the country, will allow us to determine whether these supplements lower the risk for cancer, heart disease, and stroke among people without these conditions at the trial's start. Because the jury is still out on these questions, many patients,



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healthcare providers, and professional medical organizations are eagerly awaiting the results of this trial, which is the largest of its kind.

Thank you again!

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Health benefits of marine omega-3 fatty acids (fish oil): the jury is still out

Omega-3 fatty acids—EPA (eicosapentaenoic acid), DHA (docosahexaenoic acid), and ALA (alpha-linolenic acid)—are all the rage. Sales of omega-3 supplements have risen markedly in recent years; these pills are now among the top five best-selling dietary supplements. EPA and DHA are found primarily in fish and hence are often called “marine omega-3s,” whereas ALA is found in plant sources such as flaxseed, walnuts, and canola and soybean oils. To date, the scientific evidence for health benefits is more promising—though still inconclusive—for the marine omega-3s than for ALA. Marine omega-3s have been shown to keep inflammation and triglycerides in check; prevent blood clotting; and possibly slow atherosclerosis, all of which may reduce the risk for heart disease and stroke. They may also limit the body's production of substances that promote unchecked cell growth, a process necessary for cancer development.

Researchers have observed that people who choose to eat fish frequently are less likely to develop cardiovascular disease (heart attack or stroke) than those who choose not to eat fish, but

this may be because fish eaters start out healthier and lead healthier lifestyles. Large randomized clinical trials such as VITAL avoid this potential bias because participants are assigned at random (as by a coin toss) to the treatment of interest (such as fish oil) or to a control group, so their results are considered more reliable. In two large trials of patients with heart disease or at high risk for it, fish oil offered a cardiovascular benefit. Among 11,000 heart-attack patients in Italy, fish oil (EPA+DHA, 850 milligrams [mg]/

day) lowered the risk for a subsequent cardiovascular event by 20% over 3½ years. Among 18,000 patients taking cholesterol-lowering drugs in Japan, fish oil (EPA, 1.8 grams/day) cut the risk for heart disease by 19% over 4½ years. The control groups in these studies, however, were not given placebos, so some researchers do not consider the findings conclusive. Moreover, two other trials—one followed 4800

heart-attack patients in the Netherlands for 3 years and the other followed 2500 patients with cardiovascular disease in France for 4½ years—found that fish oil (EPA+DHA, 400 mg/day in

“To date, the scientific evidence for health benefits is ... promising—though still inconclusive ...”

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VITAL Q&A

Q. What is the reason for collecting blood samples from study participants?

As an optional part of VITAL, we are requesting blood samples from willing participants at the start of the study so that we can make the best use of VITAL data on health outcomes. These samples will allow us to study whether baseline blood levels of vitamin D and omega-3s, as well as other blood markers, affect (a) an individual's risk for developing a particular disease and (b) the usefulness of vitamin D or omega-3 fatty acid supplements in preventing that disease. Study participants will receive a blood kit, including collection instructions, in the postal mail. We know that some participants will be able to have their blood drawn by their local healthcare providers, whereas others will require assistance in locating someone to draw their blood. After you receive your blood kit, please call us toll-free at 1-877-517-2555 if you need assistance in arranging the blood draw.

Q. May I have a copy of my blood test results? If not, why?

A. Unfortunately, we do not release the results of blood tests to study participants. There are four reasons for this policy. First, we will not analyze the blood samples until the end of the study (several years from now), so the results will not be an accurate measure of vitamin D and omega-3 blood levels at that time. Second, some lab tests will be done on only a sample of participants (not on everyone). Third, the labs we will use to analyze the blood samples are certified as research labs rather than clinical labs—this

means that they apply different standards for analysis and their results cannot be directly compared with results from clinical labs. Fourth, informing participants of blood test results could bias the study's findings if a large percentage of participants start to take vitamin D supplements on their own to achieve a blood level that they think is best (VITAL is designed to test this very question—i.e., does a higher blood level of vitamin D actually provide health benefits compared with an “average” blood level?).

Q. VITAL participants are not allowed to take (a) nonstudy vitamin D supplements of more than 800 international units (IU) per day, (b) calcium supplements of more than 1200 mg per day, or (c) nonstudy fish oil supplements of any dose while they are in the study. What are the reasons for these restrictions?

A. These restrictions are in place so that the VITAL study will be able to determine whether vitamin D and omega-3 fatty acid supplements prevent cancer, heart attack, and stroke while also ensuring the safety of participants, whether they are assigned to take placebo, study pills containing vitamin D at a dose of 2000 IU/day, and/or study pills containing fish oil at a dose of 1 gram/day. People who take large amounts of supplemental vitamin D or fish oil outside the study will weaken the study's ability to detect benefits of these nutrients, should such benefits exist. Moreover, the risks of consuming high doses of supplemental vitamin D (more than 4000 IU/day) or fish oil (more than 3 grams/day) on a long-term basis are not completely known.

In addition, very large amounts of supplemental calcium (above the amount we allow) may combine with even modest amounts of supplemental vitamin D to increase the risk for kidney stones.

Please note that VITAL participants are allowed to take up to 800 IU/day of vitamin D in nonstudy supplements should they choose to do so. Together with intake from food (which averages 200-300 IU/day), most participants can opt to consume at least 1000 IU/day of vitamin D on their own, which is actually more than the “recommended dietary allowances” (RDA) of 600 IU/day for adults up to age 70 and 800 IU/day for those aged 71 and older recently set by the Institute of Medicine (IOM). Thus, no one will become vitamin D deficient due to participation in VITAL, even if assigned to the placebo group. Moreover, no participant assigned to take vitamin D will get too much unless a nonstudy supplement containing more than the 800 IU/day allowed is also taken. In other words, participants in the vitamin D group who follow the study requirements will be consuming at most about 3000 IU/day of vitamin D, which is below the safety limit of 4000 IU/day set by the IOM. Thus, neither group should have safety concerns from participation.

VITAL participants are also allowed to take up to 1200 mg/day of calcium in supplements should they choose to do so. Together with intake from food (which averages about 700 mg/day), most participants can opt to consume almost 2000 mg/day. This is not only higher than the current RDA for calcium—1000 mg/day for men aged

51-70 and 1200 mg/day for women aged 51-70 and adults aged 71 and older—but is also close to the IOM's safety limit of 2000 mg/day. No one will become calcium deficient as a result of participating in VITAL.

Finally, although use of fish oil supplements is not allowed, there are no restrictions on how much fish can be eaten during the study. Participants should feel free to follow current recommendations from the federal government and the American Heart Association to eat fish, particularly fatty fish, at least twice per week.

Q. What should I do if I forget to take my study pills?

A. If you realize before you go to bed that you forgot to take that day's pills, please take them then. However, if you accidentally skip a day, do not "double up" on the pills the next day—just resume taking your pills according to schedule and leave the unused ones in the calendar pack.

Q. Should I take my study pills with food?

A. To aid absorption, it is best to take the pills with a meal or snack. However, it is acceptable to take them on an empty stomach if it is easier to remember to take your pills at other times of the day.

Q. I've recently moved into a new home. How can I ensure that I will continue to receive my study pills and questionnaires in a timely fashion?

A. To ensure that study mailings continue without delay, please notify us of changes in your mailing address, phone number, and/or e-mail as soon as possible.

Ancillary Studies

Although the main goal of VITAL is to test whether vitamin D or omega-3 fatty acid supplements can prevent cancer, heart disease, and stroke, we are closely collaborating with colleagues to examine whether these supplements provide other health benefits, such as lowering the risk for:

- diabetes
- high blood pressure
- memory loss or cognitive decline
- autoimmune conditions such as thyroid disease, rheumatoid arthritis, and lupus
- other conditions, including infections, asthma, depression, chronic knee pain symptoms, and physical disability and falls.

If your responses to our initial questionnaires indicate that you are eligible for one or more ancillary (add-on) studies of these outcomes, you may receive separate mailings about these studies from our colleagues soon after enrolling in VITAL. (Please be assured that such mailings will occur far less often after the first few months of enrollment.) Participation in these add-on studies is optional and will not affect your participation in the main trial. In addition, participants who live within driving distance of Brigham and Women's Hospital in Boston, Massachusetts will be invited to come for optional clinic visits to have more detailed studies, including tests of blood sugar, lung function, physical function, bone density, and heart structure.

Recruit a pal

We will be recruiting participants for VITAL throughout 2012. Please spread the word to friends and family (men aged 50 or older and women aged 55 or older [note the age change] with no history of cancer, heart attack, or stroke) about this important research—you can refer those who are interested to our website, www.vitalstudy.org, or ask them to call us toll-free at 1-800-388-3963.

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the first trial and 600 mg/day in the second) did not protect against future cardiovascular events. (For comparison, VITAL is testing 1 gram of Omacor® fish oil [EPA+DHA, 840 mg/day].) There are fewer large trials of the omega-3s for cancer prevention, although the Japanese study found no link between fish oil use and risk for developing cancer. And, importantly,

there are no large trials of the marine omega-3s in people at usual (rather than high) risk for heart disease. VITAL is the first and only large trial to study the health effects of fish oil in a generally healthy population. Its results are expected to provide a definitive answer to the question of whether fish oil does in fact lower heart disease, stroke, and cancer risk in healthy men and women.

VITAL on the Go

VITAL participant **Harry Shulman**, of Newton, Massachusetts, a licensed social worker and CEO of South Shore Mental Health, recently toted his pill packs on an international trip that included stops in Spain and Israel. Given his family history of high cholesterol and blood pressure, he tries to maintain a healthy lifestyle—for example, he is an avid walker, hiker, and skier—but has to date not taken nutritional supplements, including vitamin D and omega-3 fatty acids, because of the lack of convincing data that they prevent cardiovascular and other diseases. He joined VITAL to help fill this knowledge gap, which will allow

him to make a more informed choice about using these supplements in the future.



Harry Shulman in Barcelona, Spain (top) and at the ruins of a Roman settlement, Zippori National Park, Israel (bottom).

A Call for Photos

We enjoy receiving photos of VITAL participants. If you like, please send us a photo (digital preferred) of you with your calendar pack, along with a note describing where the photo was taken, as well as any reflections about your participation in VITAL. Although we cannot publish all photos, we plan to include as many as possible in future newsletters.



VITamin D and Omega-3 Trial (VITAL Study)

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Screening for cancer: recommendations for midlife and older adults

All adults, especially those at midlife and beyond, should be aware of the importance of cancer screening. Screening can detect tumors at earlier, more treatable stages, thus increasing the likelihood of recovery, and—in the case of colorectal screening—can lead to removal of polyps to prevent cancer from developing. Current screening recommendations from the American Cancer Society* are listed here. It should be noted that these are general guidelines only. Some people may need to follow different screening procedures and schedules. Ask your healthcare provider to recommend the type and timing of screening that is best for you based on your personal and family medical history.

Breast cancer Women aged 40 and older should have yearly mammograms and yearly clinical breast exams. (Another professional organization recommends starting screening at age 50 and continuing every 2 years until age 75.†)

Women with a strong family history or genetic or other factors that increase risk should be screened with magnetic resonance imaging (MRI) in addition to mammograms. (Less than 2% of all US women are in this category.)

Cervical cancer Beginning at age 30, women who have had 3 normal Pap test results in a row should have a Pap test every 2 to 3 years.

Women aged 70 and older who have had 3 or more normal Pap tests in a row and no abnormal Pap test results in the last 10 years may choose to stop having Pap tests.

Colorectal cancer or colorectal polyps Men and women aged 50 and older should be screened for colorectal polyps (some polyps are precancerous) and cancer with one of the following: colonoscopy every 10 years, flexible sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, or CT colonography (a CT scan of the large intestine, often dubbed “virtual colonoscopy”) every 5 years. Alternatively, they should be screened for cancer with a yearly fecal occult blood test (FOBT) or other similar tests.

Endometrial (uterine) cancer At menopause, women should talk with their healthcare providers about the symptoms of endometrial cancer.

Women should report any unexpected bleeding or spotting to their healthcare providers and discuss the need for any special monitoring.

Prostate cancer Men aged 50 and older should talk with their healthcare providers about the pros and cons of testing to decide whether testing is right for them.

Men who are African American or whose father or brother developed prostate cancer before age 65 should have this talk at age 45.

Men who decide to be tested should have the prostate-specific antigen (PSA) blood test with or without a rectal exam.† How often to be tested will depend on the PSA test results and other factors.

*Adapted from American Cancer Society, Guidelines for the Early Detection of Cancer. Available at: <http://www.cancer.org/Healthy/FindCancerEarly/CancerScreeningGuidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer>.

†Screening guidelines are also issued by the U.S. Preventive Services Task Force, which recommends less frequent screening for some cancers than the American Cancer Society. For example, the USPSTF does not recommend screening mammography for healthy women aged 40-49 or aged 75+, nor does it recommend routine screening with the PSA test for men at average risk for prostate cancer. For more information on the USPSTF guidelines, see <http://www.womenshealth.gov/screening-tests-and-vaccines/> or <http://www.uspreventiveservicestaskforce.org/adultrec.htm>.