



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

From the VITAL Study Directors

Dear VITAL participant,

As the **VITamin D and Omega-3 Trial (VITAL)** gets underway, we wish to thank each of you for your commitment to this important research study. Your participation, along with that of 20,000 other men and women throughout the country, will allow us to determine whether a daily dietary supplement of vitamin D3 (2000 IU) or omega-3 fatty acids (Omacor® fish



JoAnn Manson, MD

oil, 1 gram) reduces the risk for developing cancer, heart disease, and stroke among people without these conditions at the trial's start. During the course of the study, we will send you periodic newsletters to keep you informed about the study's progress, as well as health topics that we hope will be of interest.



Julie Buring, ScD

We will also answer frequently asked questions from participants in our newsletters and on our study website, www.vitalstudy.org.

Thank you again, and welcome to the VITAL study!

JoAnn Manson, MD
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New national guidelines for vitamin D intake highlight the need for the VITAL study

You may have heard about a new report from the respected Institute of Medicine (IOM), released in late 2010, that made recommendations about the amount of vitamin D that most Americans should consume. The IOM recommended 600 international units (IU) per day for people aged 1 to 70 and 800 IU per day for those aged 71 and older (an increase from the 400–600 IU/day previously recommended for adults at midlife and older).

To develop its recommendation, the IOM reviewed nearly 1000 scientific studies of vitamin D in relation to not only bone health but also many other health outcomes. It concluded that there is clear evidence that vitamin D has bone benefits but that current research is inconclusive as to whether higher vitamin D intake can cut the risk for cancer, heart disease, stroke, or other chronic diseases. We simply don't know whether vitamin D supplements are beneficial in preventing diseases beyond osteoporosis or other bone disorders—nor do we know the amount of vitamin D that might be necessary to do so.

Because of this uncertainty, the IOM called for more research to determine (a) whether higher doses of vitamin D can lower the risk for cancer, heart disease, stroke, and other chronic illnesses and (b) whether such doses pose any health risks. The only sure way to identify the health

benefits and risks of doses of vitamin D above the currently recommended amount is to carry out a large randomized clinical trial such as VITAL—that is, randomly assign one group of people to take a vitamin D supplement and assign another similar group of people to take a placebo and then track health outcomes in both groups for several years. Indeed, large trials of other widely used supplements have sometimes found benefits, but in other cases—such as with high doses of beta carotene, vitamin E, selenium, and even calcium—have debunked some health claims for these supplements and uncovered health risks that may not have otherwise been detected.

Given the current lack of evidence for non-bone benefits of vitamin D, the IOM based its vitamin D recommendation on the amount required for bone health only. The new guidelines call for a daily intake—or “recommended dietary allowance” (RDA)—that will meet the vitamin D needs of at least 97.5 percent of U.S. and Canadian residents. As noted earlier, these RDAs for adults are 600 to 800 IU per day. Although the sun activates vitamin D production in our skin, the IOM assumed little or no sun exposure because of differences in people's ability to produce vitamin D—resulting from differences in skin color, as well as season

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The VITAL research team: Brigham and Women's Hospital, Harvard Medical School

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of the year, location of residence, and use of sunscreen—and concerns about skin cancer. This means that the guidelines are adequate for everyone, including those living in the northern United States during the winter when the sun's rays are weak.

The IOM's report challenges the notion that many Americans are vitamin D deficient and cautions against the need for widespread blood tests for vitamin D. Many laboratories consider a vitamin D blood level of 30 or 40 nanograms per milliliter (ng/ml) to be best, but little research supports this claim. The IOM's recommended intakes correspond to a vitamin D blood level of 20 ng/ml—again, sufficient to maintain strong bones for at least 97.5 percent of the U.S. and Canadian population. Most people meeting the intake guidelines do not need a vitamin D blood test.

The IOM also carefully reviewed available safety data on high-dose vitamin D supplements before raising the acceptable upper limit of daily intake to 4000 IU for adults, from the 2000 IU set previously. Extremely high intakes of vitamin D can lead to too much calcium in the blood and damage the kidney and heart, but whether moderately high doses of vitamin D have side effects is not yet clear.

Given the new IOM report (by the way, one of the study directors, Dr. JoAnn Manson, served on the IOM panel), we want to assure you that VITAL has been designed to ensure the safety of its participants, whether they are assigned to take placebo or pills containing vitamin D at a dose of 2000 IU per day. VITAL allows participants to take up to 800 IU of vitamin D per day in nonstudy supplements should they choose to do so.

Together with intake from food (which averages 200 to 300 IU/day*), most participants will be able to consume at least 1000 IU of vitamin D daily, which is more than the new RDA. Thus, no participant should become vitamin D deficient due to participation in the trial, even if he or she is in the placebo group. Moreover, no participant who is assigned to take vitamin D will get too much unless he or she also takes a non-study vitamin D supplement containing more than the 800 IU per day allowed. In other words, participants in the vitamin D group who follow the study's requirements will be consuming at most about 3000 IU of vitamin D per day, which is well within the IOM's safety range.

VITAL is designed to answer the scientific questions regarding vitamin D that are considered important by the IOM: do vitamin D doses above the new RDA prevent cancer, heart disease, stroke, and other non-bone diseases? We are grateful that you have chosen to enroll in this landmark trial—and to take your study pills faithfully—to help us obtain much needed information about the health effects of vitamin D and omega-3 fatty acids (fish oil). Although the omega-3s haven't made headlines as often as vitamin D lately, scientific research regarding their health benefits remains promising though inconclusive. VITAL is the first and only large trial to study the health effects of omega-3 supplements in people who are generally healthy.

**Natural food sources of vitamin D include fatty fish (such as salmon, sardines, and mackerel) and eggs. Vitamin D is also added to milk and some other dairy products, cereals, and orange juice (check product labels).*

Ancillary studies

Although the main goal of VITAL is to test whether vitamin D or omega-3 fatty acids can prevent cancer, heart disease, and stroke, we will also assess whether these supplements confer 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, fractures, chronic knee pain symptoms, and physical disability and falls).

You will hear more about these studies later. In addition, a small subgroup of participants will be invited to come for optional clinic visits to have more detailed studies.

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 or women aged 55 or older 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.

Numbers to know for your heart's health

Many factors are known to increase the risk for coronary heart disease. The more risk factors a person has, the greater the likelihood that he or she will develop heart disease and suffer a heart attack. Some risk factors are beyond your control, including increasing age and a family history of heart disease. However, most risk factors, including an unfavorable cholesterol profile, high blood pressure, and high blood sugar, can be modified by making relatively simple lifestyle changes—quitting smoking, increasing physical activity, losing excess weight, and improving your diet—and, if necessary, taking certain medicines.

Some years ago, the American Heart

Association adopted the slogan “Know your numbers” to boost the public’s awareness of heart health. Let’s review 11 numbers that are worth knowing.

The fats in your blood are collectively known as lipids, the most important of which are **LDL (bad) cholesterol** and **HDL (good) cholesterol**. The lower your LDL and the higher your HDL, the lower your odds of having a heart attack. **Total cholesterol** is a useful general measure. High **triglycerides** also increase risk, especially in combination with excess weight, high blood sugar, and low HDL cholesterol.

Your blood pressure has two components: **systolic pressure**

(the top number of a blood pressure reading, or your pressure when your heart contracts) and **diastolic pressure** (the bottom number, or your pressure when your heart relaxes). The higher each reading is, the greater your chance of experiencing a heart attack or stroke.

Excess weight—especially at the waist—adversely affects heart health. **Body mass index (BMI)** indicates weight in relation to height. To calculate your BMI, multiply your weight in pounds by 703, divide the resulting number by your height in inches, and then divide again by your height in inches. Individuals with a BMI of 18.5 to 24.9 are considered to be at

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Do you know your numbers?

Indicator	Ideal	When to worry ^a	How often should it be measured? ^b	Write your number here
Lipids			Every 5 years	
Total cholesterol	Under 200 mg/dL	240 mg/dL or higher		
HDL cholesterol	Over 50 mg/dL	40 mg/dL or lower		
LDL cholesterol	Under 100 mg/dL ^c	160 mg/dL or higher ^d		
Triglycerides	Under 150 mg/dL	200 mg/dL or higher		
Blood pressure			Every year	
Systolic	Under 120 mm Hg	140 mm Hg or higher ^e		
Diastolic	Under 80 mm Hg	90 mm Hg or higher ^f		
Body measurements			At every physical exam	
Body mass index	Under 25 kg/m ²	30 kg/m ² or higher		
Waist circumference				
Men	Under 35 inches	40 inches or higher		
Women	Under 30 inches	35 inches or higher		
Fasting blood sugar ^g	Under 100 mg/dL	Over 125 mg/dL	Every 3 years	
Hemoglobin A1c ^h	Under 7% ^h	Over 8% ^h	Every 3 to 6 months ^h	
C-reactive protein (CRP) ⁱ	Under 1 mg/L	3 mg/L or higher	Not determined	

a. When to take action beyond lifestyle changes. These numbers may be different for people with heart disease, stroke, diabetes, or other medical issues.

b. More often for people with abnormal values or at increased risk for heart disease.

c. For people who have an LDL cholesterol level below 100 mg/dL but are at high risk for heart disease because of other risk factors, a goal of below 70 mg/dL is recommended.

d. This depends on how many other risk factors are present. For people with many risk factors, an LDL over 100 or 130 suggests the need for treatment with cholesterol-lowering medications; for others, an LDL of 160 or more, or 190 or more, does so.

e. 130 mm Hg or higher for people with heart disease, diabetes, or kidney disease.

f. 80 mm Hg or higher for people with heart disease, diabetes, or kidney disease.

g. People with blood sugar levels of 100 to 125 mg/dL have prediabetes, and those with blood sugar levels of 126 mg/dL or higher have full-blown diabetes.

h. For people with diabetes. Goal may vary depending on other risk factors.

i. CRP levels may vary by race/ethnicity. Some guidelines recommend CRP screening (using a high-sensitivity or cardio CRP test) for people at moderate risk for heart disease by virtue of other risk factors.

VITAL Q&A

Q. In a randomized clinical trial such as VITAL, participants are assigned at random—via a figurative flip of the coin—to an active treatment or an inactive placebo. Why?

A. If the trial is large enough, the random assignment process ensures that the treatment group is nearly identical to the placebo group in terms of age, lifestyle, general health, and other factors that might influence future health outcomes. Because the only characteristic that differs between the groups is the treatment under study, it is very likely that any differences in future health outcomes found between the groups will be due to the treatment.

Q. Will my health information be kept confidential?

A. Yes! We are committed to protecting your privacy. Information from completed questionnaires and medical records is identified in our computer files by study number only, and only a few staff members have access to the file that links study numbers with participants' names. Your information will be used only for VITAL, and no personal information will identify participants in published research findings. Your trust is essential to the success of the study, and we would never do anything to risk losing your faith in us.



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a healthy weight, while those with a BMI of 25 to 29.9 are overweight, and those with a BMI of 30 or more are obese. To determine your **waist circumference**, hold a tape measure at the level of your navel and circle your torso with it. Measure below, not at, the narrowest part of your abdomen.

Diabetes, or high blood sugar, is harmful to the heart. **Fasting blood sugar** provides a snapshot of your blood sugar at one point in time, while **hemoglobin A1c** gives a time-lapse look over several weeks. Although doctors typically order the latter test only for patients with diagnosed diabetes, some are now also recommending it for individuals at higher-than-usual risk for diabetes and heart disease.

Other substances in the blood, including **C-reactive protein** (CRP), homocysteine, lipoprotein(a), and fibrinogen, have recently been linked to an increased risk for heart disease. Of these, CRP has received the most publicity. An elevated CRP level indicates low-grade inflammation, a process implicated in heart disease. However, it is unclear exactly what level of CRP increases your risk and whether controlling CRP will help lower that risk.

Having more than one risk factor for heart disease is especially worrisome, because risk factors tend to “gang up” to worsen each other’s effects. One potent cluster—an increased waist circumference, high triglycerides, low HDL cholesterol, high blood pressure, and high blood sugar—is known as the **metabolic syndrome**. About 1 in 4 U.S. adults

have this syndrome, which is associated with an increased risk for diabetes, heart disease, and stroke.

Estimating your heart disease risk

There are tools that use your numbers to estimate your likelihood of having a first heart attack or being diagnosed with heart disease in the next 10 years. One widely used tool is the Framingham risk score. Go to <http://hin.nhlbi.nih.gov/atp/iii/calculator.asp>, or ask your healthcare provider to calculate your score. Two web-based tools—www.reynoldsriskscore.org

All of us can benefit from adopting healthy lifestyle choices...

and www.yourdiseaserisk.harvard.edu—developed by researchers at Harvard Medical School and Harvard School of Public Health, respectively, give alternate estimates of

your heart disease risk. The Harvard tools incorporate a wider array of potential risk factors than does the Framingham tool. The latter Harvard website also offers personalized tips for prevention, as well as tools for estimating your risk for stroke, diabetes, certain cancers, and osteoporosis.

Being aware of your heart disease risk may motivate you to make healthy lifestyle changes and will help your doctor determine whether to prescribe certain medicines to lower your risk. Drugs that lower blood pressure or favorably affect cholesterol levels can prevent heart attacks and increase survival in people at above-average cardiovascular risk. All of us can benefit from adopting healthy lifestyle choices and, when warranted, taking medications. Indeed, the greater your cardiovascular risk is, the greater the payoff from prevention efforts is likely to be.