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From Sun & Sea

NEW STUDY PUTS VITAMIN D & OMEGA-3S TO THE TEST

BY BONNIE LIEBMAN

"They're two of the most promising nutrients available for the prevention of cardiovascular disease and cancer," says JoAnn E. Manson, professor of medicine at the Harvard Medical School and chief of the Division of Preventive Medicine at Brigham and Women's Hospital in Boston. That's an understatement.

Manson is a principal investigator for the new VITAL trial (***VIT***amin D and Omeg***A***-3 Tria***L***), which will test vitamin D and omega-3 fats from fish oil on heart disease, stroke, and cancers, especially of the colon, breast, and prostate. But the trial will also look at the supplements' effect on other illnesses.

"We're also interested in studying diabetes, high blood pressure, bone density, vision, memory loss, depression, autoimmune diseases, and other health outcomes," says Manson.

And *you* may be eligible to participate.

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From Sun & Sea

NEW STUDY PUTS VITAMIN D & OMEGA-3S TO THE TEST

Why launch a brand new trial to test high doses of vitamin D and omega-3 fats from fish? Don't we already know they're worth taking?

"Some people believe the evidence is already strong enough to recommend much higher intakes," notes Harvard's JoAnn Manson. "But we tend to forget the lessons of other nutrients—like vitamin E, vitamin C, B vitamins, folic acid, selenium, and beta-carotene.

"Large-scale trials didn't confirm their benefits and even found some risks when they were consumed at high levels. So let's not just jump on the bandwagon until we have clinical trials."

Here's what we know—and don't know—about vitamin D and omega-3s from fish.

VITAMIN D

CANCER

The results were unexpected.

When researchers at Creighton University in Omaha, Nebraska, decided to give roughly 1,200 healthy postmenopausal women either a placebo or calcium (1,500 mg) plus vitamin D (1,000 IU) every day, they wanted to know if the two nutrients would keep bones from breaking.

Instead, they found that the women who were given both vitamin D and calcium were 77 percent less likely to be diagnosed with cancer—mostly of the breast—over the next four years.[1]

It didn't take long for supplement makers to spring into action. "Emerging science suggests that vitamin D supports breast health," boasts Centrum Ultra Women's and other multivitamins. (Supplement makers love vitamin D because you can't get much from food. See "How the Body Makes Vitamin D," p. 4.)

But the story isn't so simple.

"The study showed a significant reduction in total cancer, but it was too small to look at types of cancer," cautions Manson. Only seven women who took a placebo—versus four who took vitamin D and calcium—were diagnosed with breast cancer. And even for total cancers, "the results need to be replicated."

A much bigger trial—the Women's Health Initiative—tested vitamin D (and calcium) or a placebo on 36,000 healthy women for an average of seven years. Vitamin D takers had no lower risk of breast cancer than placebo takers.[2]

"The Women's Health Initiative was large scale, but it tested only 400 IU a day, which many believe is too low to prevent cancer or heart disease," says Manson.

Clinical trials like the Creighton study and the Women's Health Initiative randomly assigned people to take a vitamin or a placebo. In theory, trials can offer the clearest answers because vitamin takers and placebo takers are chosen at random from the same pool of subjects.

But researchers also weigh studies that investigate whether people with higher blood levels of vitamin D have a lower risk of cancer years later. Some of those studies find a lower risk, but others don't.[3]

"In the Nurses' Health Study, we saw an association between higher blood levels of vitamin D and a lower risk of breast cancer in women over 60," says Elizabeth Bertone-Johnson of the University of Massachusetts. "That hasn't always been replicated in other studies.

"In a nutshell, the evidence that vitamin D protects against breast cancer is suggestive but inconclusive," says Bertone-Johnson.

The same could be said for the link between vitamin D and colorectal cancer. For example, in a study of 535 male health professionals and female nurses, those with high blood levels of vitamin D were only half as likely to be diagnosed with colon cancer as those with low levels.[4] And in other studies, colon cancer patients with higher vitamin D levels are less likely to die of the disease.[5]

"The evidence is stronger for colorectal than for breast cancer," says Manson. "In several studies, blood levels of vitamin D predict the risk of colorectal cancer, but not breast cancer." But some studies find no link with colorectal cancer at all.[3]

In contrast, animal and test-tube studies offer a surplus of evidence that vitamin D protects against cancer.

"It's plausible because vitamin D decreases cell proliferation and increases cell differentiation," explains Manson. "It also curbs the growth of new blood vessels, which could stop cancers from growing. And it has powerful anti-inflammatory effects."

But without clinical trials, those findings aren't enough to act on. And some human evidence has caused some worry.

A 2006 study of Finnish male smokers found a higher risk of pancreatic cancer among those with higher blood levels of vitamin D.[6]

A 2009 study of (mostly nonsmoking) U.S. men and women found no link overall. However, in people from states with low sun exposure (in this study, Michigan, Minnesota, and Wisconsin), high blood vitamin D levels again were linked with a higher risk of pancreatic cancer.[7]

Another U.S. study found a lower risk of aggressive prostate cancer among those with the lowest vitamin D blood levels, but the risk didn't rise with higher vitamin D levels.[8]

"It's hard to know what to make of

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Illustration: The Page Group, Inc.

these findings without further research," says Manson. "But it's reassuring that most other studies haven't shown these elevated risks."

HEART ATTACK & STROKE

If you look at animal and laboratory studies, there's no shortage of evidence that vitamin D might protect the heart.

"In animal models, when the vitamin D pathway is disrupted, it overactivates the renin-angiotensin hormone system," says Thomas Wang, an assistant professor of medicine at the Harvard Medical School and a cardiologist at Massachusetts General Hospital in Boston.

Over time, too much of those hormones can harm the heart.

"The system revs up when the body is under stress, which is a good thing in the short term," Wang explains. "But over the long term, it's not good to have sustained increased levels of these hormones. In fact, ACE inhibitors and many other therapies for cardiovascular disease are aimed at blocking the renin-angiotensin system."

Vitamin D may act in other ways. "It seems to suppress inflammation, which plays a role in the progression of cardiovascular disease," says Wang. "And it may act directly on the heart cells and cells in the walls of blood vessels."

What about evidence in people?

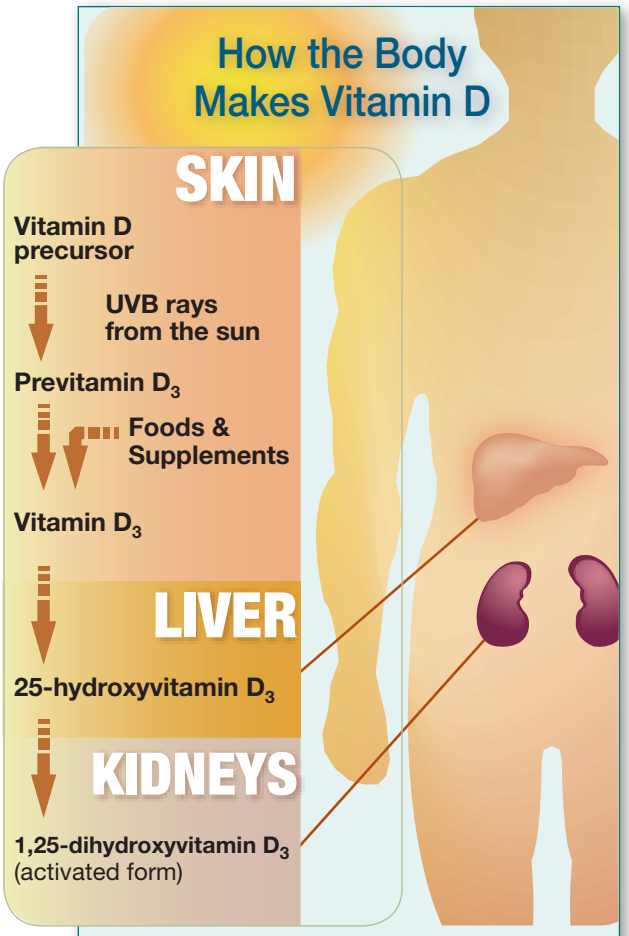
When Wang and his colleagues tracked roughly 1,700 people in the Framingham Heart Study for five years, those with low vitamin D blood levels (below 15 ng/mL) had a 60 percent higher risk of heart disease than those with higher levels.[9] And in a study of male health professionals, men with low blood levels of vitamin D were twice as likely to have a heart attack as men with high levels (above 30 ng/mL).[10]

"These studies show an association between low vitamin D levels and a higher risk of heart attacks, strokes, and other cardiovascular events, but they don't prove that one causes the other," says Wang.

Other research suggests that vitamin D may keep blood pressure from rising. In a study of roughly 600 men and 1,200 women, those with low vitamin D levels were three times more likely to be diagnosed with high blood pressure over the next four years than those with high vitamin D levels.[11]

"A fair amount of epidemiological data and a little data from small trials suggest that vitamin D may lower blood pressure," says Wang. And that fits with the renin hypothesis because renin boosts blood pressure.

"One can imagine how the story fits together nicely," says Wang. "But other hypotheses haven't been borne out when trials are done, so we have to take it with a grain of salt until we have more data."



Where's the D? Only a few foods (like fatty fish) have more than 200 IU of vitamin D per serving. Ultraviolet rays from the sun can prompt your skin, liver, and kidneys to make vitamin D, but UV rays are too weak in the winter (unless you live as far south as Los Angeles or Atlanta). That's why it may be simpler to get vitamin D from a supplement.

OTHER OUTCOMES

The VITAL study was designed to see if vitamin D and omega-3s in fish oil can lower the risk of cancer, heart attacks, and strokes, but the study will also look at other problems. Among them:

Falls & fractures. Vitamin D can prevent falls and bone fractures in older people, but it only works if they take enough, says Bess Dawson-Hughes of the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University in Boston.

She and her colleagues looked at the best trials that tested vitamin D or a placebo on falls. "There was no reduced risk of falling in trials where the dose was 200 to 600 International Units," she explained at a recent meeting of the Institute of Medicine in Washington, D.C. (Her analysis has not yet been published.)

"When trials used doses of 700 to 1,000 units, we saw a significant 20 percent risk reduction of falls," she added. "We concluded that fall risk reduction begins at 700 IU and increases progressively with higher doses."

The picture was similar when Dawson-Hughes looked at studies that tested vitamin D on bones.[12] "With lower-dose trials, we see no risk reduction for fracture, but for the higher-dose trials, we see a risk reduction of 20 percent," she explained.

Vitamin D helps the body absorb calcium, so it's no surprise that the nutrient would curb the risk of broken bones. And researchers now think they know how vitamin D keeps people from falling.

"We have identified vitamin D receptors on the fast-twitch fibers in muscles that are the first responders when you are about to fall," noted Dawson-Hughes. "So it's biologically plausible that vitamin D will affect muscle, and we certainly know that [weaker] lower extremity muscles are a risk factor for falls."

Her bottom line: "The results support the use of a higher dose of vitamin D—defined as somewhat north of 700 International Units—to prevent falls and fractures."

Type 2 diabetes. When researchers gave roughly 300 people without diabetes either vitamin D (700 IU) plus calcium (500 mg) or a placebo every day, their goal was to look primarily at bone, not blood sugar levels.

However, among people who started the study with impaired fasting blood sugar (higher than normal but not high enough to be classified as diabetes), those who got vitamin D and calcium had a smaller rise in blood sugar levels over three years than those who got a placebo.[13]

These and other findings suggest that vitamin D may lower the risk of diabetes, but "they need to be replicated in clinical trials," concludes Dawson-Hughes.

Depression. "Lay publications were saying that vitamin D was good for mood, but I was surprised that there was very little in the literature," says University of Massachusetts researcher Elizabeth Bertone-Johnson, who recently reviewed the evidence.[14]

The best evidence so far, she says, comes from a trial on roughly 350 overweight people in Norway.[15]

"Individuals randomized to a fairly high dose of vitamin D—40,000 IU a week—had lower scores on a depressive symptoms scale after one year than those randomized to placebo."

However, the trial had limitations, notes Bertone-Johnson. "We need additional studies to know if vitamin D plays a role in depression."

Autoimmune disease. "Vitamin D has powerful anti-inflammatory effects, and there's preliminary evidence that it may lower the risk of multiple sclerosis, rheumatoid arthritis, lupus, and autoimmune thyroid disease," says Manson. "But we need much more data to reach firm conclusions."

FISH OILS

HEART DISEASE

It started in the early 1970s, when Hans Olaf Bang and Jørn Dyerberg suggested that the Eskimos of Greenland had a lower rate of heart disease than residents of Denmark because they ate a diet consisting largely of whale blubber and seal meat.[16]

Nearly 40 years later, the VITAL study hopes to determine if the major omega-3 fats found in fish—EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) can protect the heart.

"Some people believe that the evidence is already strong enough to recommend much higher intakes," says Harvard's JoAnn Manson. "But prevention trials have tended to be in high-risk populations who are either post-heart-attack or who have multiple risk factors for coronary heart disease."

For example, an Italian trial called the GISSI Prevention study tested fish oil on roughly 11,000 men and women who had already suffered a heart attack.[17] They were randomly assigned to take EPA and DHA (850 milligrams total) or vitamin E (300 mg) or both every day or no pills at all. (There was no placebo, and the participants knew which pills they were taking, but researchers still consider the results important.)

After 3½ years, the risk of dying of a sudden death heart attack was 45 percent lower in those taking EPA and DHA than in those who took no pills. (Vitamin E had no impact on heart attacks.)

How would fish oil matter?

"Anti-arrhythmia is the main mechanism on the table," explains William Harris of the Sanford School of Medicine at the University of South Dakota.

In other words, EPA and DHA may curb the risk of an irregular heartbeat, which can be lethal if it strikes the lower chambers of the heart called the ventricles.

"Ventricular fibrillation can kill you because it's really no heartbeat at all," says Harris. "It's just a quiver."

Another possibility: "Fish oils could have an anti-inflammatory effect, which could reduce the risk for a coronary plaque rupture," Harris explains. Plaque is the buildup of cholesterol, calcium, smooth muscle cells, and cell debris in artery walls.

Inflammatory cells sent by the immune system break down the cap that forms on the plaque. When the cap ruptures, a clot forms around it, blocking the flow of blood. That's a heart attack. (See cover story, Jan./Feb. 2009.)

"Anti-arrhythmic and plaque stabilization are the most logical explanations, but neither is a slam-dunk case at this point," says Harris.

Among the question marks: in three trials, when researchers gave fish oil to people with abnormal heart rhythms, their heartbeats were no less likely to set off the defibrillators that had been implanted in their chests.[18-20]

"The trials were disappointing," says Harris. But they don't mean that fish oil is useless or harmful.

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Omegas by the Mouthful

Shoot for two servings of fatty fish per week, which would supply about 500 mg a day of DHA plus EPA. Most foods with added fish oil have much lower levels. "Omega-3" foods that contain only ALA (alpha-linolenic acid) are not listed. *Brand-name foods are in italics.*

Food *(6 oz. cooked for fish, unless noted)*	DHA + EPA *(mg)*
Atlantic salmon, farmed	3,650
Atlantic salmon, wild	3,130
Coho salmon, farmed	2,180
Rainbow trout, farmed	1,960
Coho salmon, wild	1,800
Rainbow trout, wild	1,680
Swordfish	1,390
Bumble Bee Salmon—Red, Pink, or Blueback (3 oz.)	1,200
Sardines, in tomato sauce *(3 oz.)*	1,190
Pacific oysters *(3 oz.)*	1,170
Flounder or Sole	850
Sardines, in vegetable oil, drained *(3 oz.)*	840
Halibut	790
Rockfish	750
Ocean perch	640
Scallops	620
Skipjack tuna, fresh	560
Pacific cod or Yellowfin tuna, fresh	470

Food *(6 oz. cooked for fish, unless noted)*	DHA + EPA *(mg)*
Blue crab *(3 oz.)*	400
Catfish, wild, or Haddock	400
Chicken of the Sea Skinless Boneless Pink Salmon (3 oz.)	350
Catfish, farmed	300
Shrimp *(3 oz.)* or Atlantic cod	270
Clams *(3 oz.)*	240
StarKist or Chicken of the Sea Solid White Albacore Tuna, in water (3 oz.)[1]	230
StarKist Very Low Sodium Chunk White Albacore Tuna, in water (3 oz.)	220
Land O Lakes Omega-3 Eggs (1)	150
StarKist or Chicken of the Sea Chunk Light Tuna, in water (3 oz.)[1]	140
Eggland's Best Grade A Large Eggs (1)	50
Silk Plus Omega-3 DHA Soy Milk (1 cup)	30
Smart Balance HeartRight spread (1 Tbs.)	30
Egg *(1 large)*	20

[1]Average.

Sources: manufacturers, USDA, and independent lab analyses. Chart compiled by Melissa Pryputniewicz.

"Going to a fast heartbeat, which sets off the device, is not the same mechanism as developing an electrical disturbance that throws you into ventricular fibrillation," he notes. "So what we learned is that the defibrillating device is not a good model for testing the question of whether DHA and EPA prevent ventricular fibrillation."

Other evidence in favor of fish oils: "They decrease blood clotting and they lower triglycerides," notes Manson. (Doctors often prescribe high doses—about 4,000 mg a day—for people with high triglycerides.) But VITAL will use a more modest dose.

"You're going up to the Japanese intake, which is about 1,000 milligrams a day," says Harris. "It's not a lifetime of omega-3s like the Japanese have, but it's the biggest and best shot we've got."

What to do in the meantime? "The American Heart Association's recommendations are still great," says Harris, who co-authored them in 2002.[21]

"People without heart disease should eat two servings of fatty fish a week, which would give them 400 to 500 milligrams of EPA plus DHA a day." (Fatty fish include salmon, herring, mackerel, trout, and sardines.) "People with coronary heart disease should get 1,000 milligrams a day, either from fish or a pill," says Harris.

D + DHA + EPA. Farmed salmon has a quarter of the vitamin D of wild salmon. All salmon is rich in EPA and DHA.

If you're looking for fish oil, don't get confused by foods that boast about their omega-3s. Most contain ALA (alpha-linolenic acid), which is a shorter-chain omega-3 fat. So far, there isn't good evidence that it works like EPA and DHA.

"We need to eliminate ALA as a surrogate omega-3," says Harris. Our bodies convert very little ALA to EPA and none to DHA. Why? The body can't take the first step, which is to change ALA to an intermediate fat called stearidonic acid (SDA).

"Making that jump is the biggest hurdle," says Harris. "That's why there's so little conversion to EPA."

Monsanto is working on a soybean oil with stearidonic acid, he points out. "Unlike ALA, about 15 to 20 percent of SDA is converted to EPA. So the new oil will have a more bioavailable precursor that goes to EPA. Then you won't have to kill any fish."

And vegetarians can already buy foods or pills with DHA made by algae. (Most foods with added DHA from algae contain only 32 mg per serving, but pills can hit 100 or 200 mg.) Soon that may change, says Harris. "I would bet in 10 years, we'll have microbial sources of EPA and DHA."

But without a study like VITAL, we won't know if EPA and DHA really matter.

"The question keeps coming up: With all of the promising observations, why do we need a trial?" asks Manson. "But we've never had large-scale clinical trials in healthy people to see if omega-3s from fish oil can lower the risk of first cardiac events."

CANCER

"Some observational studies suggest that higher fish intake is associated with a lower risk of colon cancers," says Manson.

For example, when researcher tracked 22,000 male physicians for 22 years, fish eaters had a 25 percent lower risk of colorectal cancer.[22] But other studies find little or no link.[23] And a meta-analysis that looked at omega-3 fats (rather than fish) found no impact on any cancer.[24]

"Omega-3s look more promising for cardiovascular disease," says Manson. "They have anti-inflammatory and anti-angiogenesis effects, but they're not as well studied for cancer as for heart disease."

Angiogenesis is the growth of new blood vessels. The body needs new blood vessels, for example, to heal wounds, but tumors also need them in order to spread.

Finding Fish Oil

Fish oil labels can trip you up. Here's a guide to take to the store:

Two softgels have 2,400 mg of fish oil, but only 720 mg of EPA + DHA.

- **Most fish oil is only 30 percent EPA and DHA.** So a fish oil bottle that says "1,000 mg" on the front may contain only 300 mg of EPA and DHA. Check the bottle's Supplement Facts for the amount of EPA and DHA.
- **"Double strength" may just mean you take two pills.** Some brands *are* more concentrated, others aren't. Check the Supplement Facts to find out how many pills you'll have to take to get the EPA and DHA you want.
- **Ignore other omegas.** You don't need other omega-3s (like ALA) or omega-6 fats.
- **Major brands are all mercury-free.** *Consumer Reports* and ConsumerLab.com have found no mercury in any big brands, whether or not the label says they're mercury-free.
- **You can buy DHA made from algae.** But so far, there is no vegetarian source of EPA.

Photos: © senicphoto/fotolia.com (salmon), Stephen Schmidt (label).

OTHER OUTCOMES

Memory. So far, EPA and DHA haven't boosted memory in short-term experiments. For example, when Dutch researchers gave roughly 300 healthy men and women aged 65 or older EPA and DHA in a higher dose (1,800 milligrams a day total) or a lower dose (400 mg a day) for six months, they did no better on memory and other tests than those who took a placebo.[25]

But six months may not be long enough to matter. "We're now measuring omega-3 levels in the blood of 7,500 women who were followed for about 10 years," says Harris. "Our hypothesis is that those who started with the highest levels will lose cognitive function the slowest.

"That's based on about 10 to 15 European and American population studies in which higher fish eaters had better cognitive function," he adds. "Some studies don't show a relationship, but the majority do."[26,27]

Depression. The brain is rich in DHA, and some small studies have reported that fish oil improved symptoms in people with major depression.[28]

But when researchers gave EPA and DHA to 300 independently living older people and 200 older people with mild to moderate depression, they saw no difference in mood or depression scores after 12 to 26 weeks.[29,30]

"With 20,000 participants, our trial should have more power to see if omega-3s can alleviate depression," says Manson.

Vision. Degeneration of the macula—the center of the retina—is the most common cause of blindness in older people. Some studies show a lower risk of macular degeneration in fish eaters.[31] And early macular degeneration was about 25 percent less likely to get worse in people who reported eating the most EPA and DHA.[32]

"Our photoreceptors—the cells we see with—are rich in EPA and DHA," explains Emily Chew, deputy director of the Division of Epidemiology and Clinical Research at the National Eye Institute in Bethesda, Maryland.

A large trial called AREDS2 (Age-Related Eye Disease Study 2) is testing EPA and DHA (1,000 mg a day total) on people who already have early macular degeneration. "But so far, no trial has tested EPA and DHA on vision in people who don't already have eye disease," says Manson.

Autoimmune disease. "Omega-3 fats are anti-inflammatory," says Manson. "The VITAL study should tell us more about whether they lower the risk of rheumatoid arthritis and other autoimmune diseases."

Is VITAL for You?

JoAnn E. Manson, MD

In January 2010, researchers at Harvard University and elsewhere will launch the ***VIT***amin D and Omeg***A***-3 Tria***L*** (VITAL). The goal: to find out if vitamin D_3 (2,000 IU a day) and EPA plus DHA (1,000 mg a day total) can lower the risk of cancer, heart disease, stroke, and other illnesses.

"It's an opportunity to make an enormous contribution and to get important answers," says lead investigator JoAnn Manson of the Harvard Medical School.

Who is eligible? You must be at least 65 (if you're a woman) or 60 (if you're a man) and have no history of heart attack, stroke, or cancer (except non-melanoma skin cancer). You will get pills and forms by mail, so you don't need to visit Boston to participate.

If you qualify, you will be assigned to take vitamin D, fish oil, both, or a placebo, but you won't know which you are getting.

You'll still be able to take some vitamins on your own. "We will ask people to limit vitamin D supplements to about 800 IU a day," says Manson. "But you wouldn't be able to take fish oil on your own since that would dilute our results."

Are the supplements safe?

"We will be doing extensive safety monitoring—checking hospitalizations, clinic visits, symptoms, bleeding problems, and other adverse event outcomes," says Manson. "But we don't expect any safety concerns with these doses." The Institute of Medicine considers 2,000 IU of vitamin D safe, and the American Heart Association recommends 1,000 mg a day of EPA and DHA for people with heart disease.

To learn more, go to www.vitalstudy.org or call 1-800-388-3963.

The Bottom Line

- Shoot for 700 to 1,000 IU of vitamin D a day. (Most multivitamins have 400 IU.)
- Expect only 40 to 150 IU of vitamin D in most foods that are fortified with D.
- Shoot for two servings of fatty fish (like salmon, trout, or sardines) per week. That supplies about 400 to 500 mg of EPA + DHA per day.
- If you have heart disease, take 1,000 mg of EPA + DHA a day. You need about 3,000 mg of fish oil to get 1,000 mg of EPA + DHA (see "Finding Fish Oil").

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