



**Ounce of prevention.** Cod-liver oil has been given as preventative medicine for decades (*left*, British children in 1938 are presumably getting their spoonful). Now scientists are amassing tens of thousands of volunteers to test the preventative power of one of its ingredients: vitamin D.

trials of other vitamins have shown. Even a believer like Julian Peto, an epidemiologist at the London School of Hygiene and Tropical Medicine, cautions, “You have got to be very certain. Mass medication is not something you embark on lightly.” He adds: “What we know comes mainly from observational studies.”

In the next few years, however, the long-standing vitamin D debate may finally be put to rest. In a number of large clinical trials, tens of thousands of people around the world will take a supplement or placebo pills in an effort to pin down the health benefits of the sunshine vitamin.

**A body of evidence**

Vitamin D was first recognized for its role in bone health. It helps the body absorb calcium, and children who do not get enough of it can develop rickets, a bone-softening disease. But low vitamin D levels have also been implicated in infectious diseases. For instance, patients with TB tend to have lower vitamin D levels, and Martineau points to studies showing that the compound helps immune cells called macrophages kill the mycobacterium responsible for TB, as well as suppress the secretion of enzymes the pathogen uses to degrade lung tissue.

In 2010, a randomized trial in 334 Japanese schoolchildren found that those taking vitamin D supplements were less likely to suffer from an influenza infection. And in August, scientists from Harvard Medical School in Boston reported in *Pediatrics* that Mongolian schoolchildren whose milk was fortified with vitamin D had half the risk of catching a cold compared to those drinking unfortified milk. It is perfectly plausible that lower vitamin D levels in winter might be the reason colds predominately circulate then, Peto says.

Proponents of the sunshine vitamin have also amassed a variety of data suggesting it wards off asthma, diabetes, stroke, multiple sclerosis, and cognitive decline. And a body of evidence indicates vitamin D could cut the risk of cancer and cardiovascular disease dramatically, they argue. For colorectal and breast cancer alone, raising vitamin D levels on a population level could pre-

# Uncertain Verdict as Vitamin D Goes On Trial

Boosting levels of vitamin D with supplements has been touted to prevent diseases, but many scientists say only clinical trials now in the works can confirm such hopes

**IN 1848, DOCTORS AT THE HOSPITAL FOR Consumption and Diseases of the Chest in London** undertook one of the world’s first clinical trials. More than 1000 patients with tuberculosis (TB) were either just cared for, as no effective treatment was known, or were also given a spoonful of cod-liver oil three times a day. Nineteen percent of patients on cod-liver oil deteriorated or died, compared to 33% in the control group.


Before antibiotics became available in the mid-20th century, many TB patients were also sent to sanatoriums in Switzerland or other countries. Lying in their beds, they were wheeled out into the sun for phototherapy. Looking back, says Adrian Martineau, an immunologist at Barts and The London School of Medicine and Dentistry in London, the two experimental therapies had something in common: vitamin D, which wasn’t discovered until 1922.

Unlike other vitamins, the human body produces most of its vitamin D itself—with the help of sunshine. In the skin, a precursor molecule called 7-dehydrocholesterol is turned into vitamin D<sub>3</sub> by UV light. Ninety percent of vitamin D circulating in the human body is produced that way. Only 10% comes from food, in the United States and Canada mostly from milk, which is fortified with the vitamin in those countries. It is also naturally abundant in some foods including fatty fish, sun-dried mushrooms—and cod-liver oil.

Martineau has studied the connection between TB and vitamin D for years and has become convinced that the compound can not only help treat TB but also prevent it. He is part of a vocal camp of scientists who praise the powers of vitamin D and see it as something of a cure-all—or rather a prevent-all. In addition to its well-established benefits for bone health, they say vitamin D may—with little or no side effects—be able to ward off colds and other infections and cut the risk of asthma, diabetes, cancer, heart disease, and a slew of other chronic diseases.

Some of these scientists, such as Michael Holick, an endocrinologist at Boston University School of Medicine and a veteran of vitamin D studies, advocate fortifying more foods with the vitamin and advising people to take supplements and get more sun exposure. “Even if only one of these diseases turns out to be prevented by vitamin D, it is worth it,” he says. The public certainly seems to buy that argument. In the United States, sales of vitamin D supplements have increased from \$50 million in 2005 to \$600 million in 2011, according to the *Nutrition Business Journal*. Ninety years after it was discovered, vitamin D seems to be enjoying its moment in the sun.

But other researchers warn that the benefits of vitamin D are far from proven. They also caution that its widespread use as a supplement could do more harm than good, as

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vent more than 100,000 cases each year and cut deaths from these diseases by three-fourths in the United States and Canada, a paper published in the *Annals of Epidemiology* in 2009 calculated.

One comprehensive review of the vitamin D literature, a meta-analysis published in 2011 by the Cochrane Collaboration, concluded that vitamin D<sub>3</sub> supplementation (but not other forms of the vitamin) reduced overall mortality by about 6% among the more than 90,000 people in the 50 studies examined. “That is not overwhelming, but it is borderline significant,” says Robert Scragg, a vitamin D researcher at the University of Auckland in New Zealand.

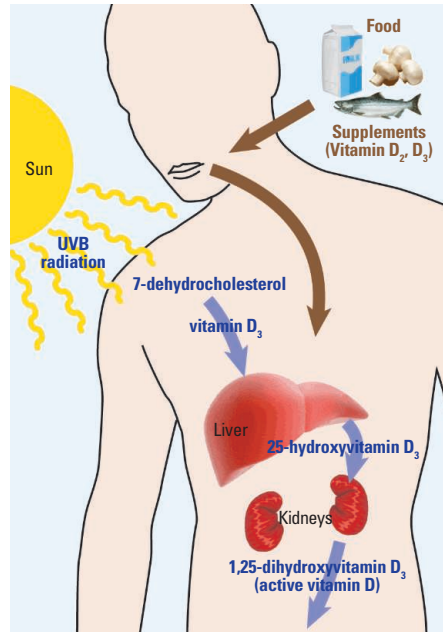
Many vitamin D enthusiasts point to evolution to bolster their case. Dark skin protects skin cells from UV damage, but it also reduces the amount of vitamin D that is produced; African-Americans in the United States generally have lower levels of vitamin D in the blood than the rest of the population. “The strongest single bit of evidence [that more vitamin D is good for a person] is that humans turned white when they moved north,” Peto says. “That suggests low vitamin D levels must have had [a negative] effect on survival.”

### Mass medication

However, some veteran vitamin researchers caution that other vitamins have been linked to a broad range of health benefits, only to have the evidence crumble upon closer examination. In the 1990s, for example, observational studies suggested that antioxidants such as beta carotene (a precursor of vitamin A) could shield the body from the cancer-causing compounds in tobacco and other harmful substances. But in 1994, a prospective clinical trial with nearly 30,000 smokers in Finland concluded that those who had taken beta carotene supplements were actually 18% more likely to develop lung cancer and 8% more likely to die during the trial. Two years later, a U.S. study examining vitamin A supplements in smokers and asbestos workers was stopped early because there were 28% more lung cancers and 17% more deaths in the group receiving



**Vital sunshine.** UV rays striking the skin convert the molecule 7-dehydrocholesterol to an inactive form of vitamin D<sub>3</sub>. It is then converted first in the liver and then the kidneys to 1,25-dihydroxyvitamin D<sub>3</sub>, the active form of the vitamin.



vitamin A than among the untreated.

Another antioxidant, vitamin E, was also touted as a cancer killer. But in 2008, a cancer-prevention trial evaluating vitamin E and selenium supplementation was stopped because participants taking vitamin E had become more likely to get prostate cancer. The risk difference then was not statistically significant, but follow-up data published late last year showed a significant increase of 17% compared with the control group.

Some predict that history is about to repeat itself. “I think vitamin D is going the way of these other treatments,” says Andrew Grey, a researcher at the University of Auckland. Low levels of vitamin D might simply be a marker of bad health rather than the cause of it, he suggests: “Almost always the levels are lower in patients who are sicker, but that could be because they exercise less and do not go outside so much.” Another confounding factor: Vitamin D is fat-soluble, so obese patients also tend to have lower levels of circulating vitamin D.

JoAnn Manson, an endocrinologist at Harvard Medical School, agrees that once again enthusiasm for a vitamin is outpacing the evidence: “There are many reasons that low vitamin D levels might be linked to these chronic diseases. Correlation does not prove causation.”

Other groups reviewing vitamin D data haven’t been as impressed as the Cochrane group. After sifting through hundreds of studies, a panel convened by the Institute of Medicine (IOM) concluded in 2010 that vitamin D was important for bone health, but that evidence did not support other benefits from vitamin D intake.

### Difficult dosing

Tackling another contentious issue at the heart of the vitamin D debate, the IOM report also recommended an adequate blood level of the vitamin: 50 nmol/l. “Some people with malabsorption may need higher levels, but for the healthy population 50 nmol per liter is certainly enough,” says Clifford Rosen, a bone-health expert at Maine Medical Center Research Institute in Scarborough, who was on the panel. The report also pointed out that most people in the United States reach that level through diet and sun exposure alone.

The strong vitamin D proponents, as well as other scientists, say the IOM threshold is too low and hark back to prehistoric times to make their point. They argue that as humans started wearing clothes, developed sunscreens, and began spending many hours indoors, they cut themselves off from the level of vitamin D they used to have. Dutch scientists published a study earlier this year examining vitamin D levels in two tribes in Tanzania. Living close to the equator, following a hunter-gatherer-like lifestyle, and not using sunscreen, the Maasai and Hazabe peoples had a mean serum concentration of 115 nmol/l. “That is probably where we all should be,” says Holick, who takes supplement pills to keep his vitamin D level between 100 and 150 nmol per liter.

Others don’t aim as high, at least for keeping the skeleton strong—the best studied aspect of vitamin D prevention science. “To ensure good bone health in everyone, you need to aim for a level of 75 nmol per liter,” says Michael Amling of the University Medical Center Hamburg-Eppendorf in Germany.

In a 2010 paper, Amling examined the bones and vitamin D levels of 675 people who had died in car accidents or of other unnatural causes. Seven of 82 people with a level above 50 nmol/l had weak bones. “That means almost 10% of the people with a serum level above this threshold have weak bones,” Amling says.

But the IOM panel, which had set itself the goal of allowing no more than 2.5% of the population to be at risk of brittle bones, used a different number: It divided the seven bodies with high vitamin D but low bone health by the total number of bodies: 675. “That was a grave mathematical mistake,”

Amling says.

Rosen warns that having higher blood levels of vitamin D could be harmful. "I can actually live with 75 nmol per liter, but above that I am a little concerned," he says.

He and others cite a 2010 Australian study in which women aged 70 years or older were given a megadose of 500,000 international units (IUs) once a year. Vitamin D levels in their blood shot up to an average of 120 nmol/l, but these participants also fell and fractured their bones more often than those in the placebo group, the scientists reported.

Proponents of vitamin D argue that such a megadose is unphysiological and that the study is a special case that should not be weighed too heavily in any risk-benefit anal-

### Proving prevention

With the intent of resolving the usefulness of vitamin D, several investigators are launching large-scale trials to examine the benefits of vitamin D in a number of chronic diseases. In the VITAL study Harvard's Manson leads, for example, 20,000 healthy people in the United States will receive either 2000 IUs of vitamin D a day or a placebo for 5 years. That should be enough to raise blood levels of vitamin D to 75 nmol/l or more in nearly all participants, she says. The trial will look at health outcomes as diverse as stroke, diabetes, cardiovascular disease, and cancer. The first participants are already taking their pills, and the last ones should be recruited by the end of the year, Manson says. Similar studies are starting in Finland, New Zealand, and Switzerland;

the volunteers will be mailed 400 pills once a year. If many people forget to take their pills, that would make it harder to detect a difference between the treatment and control groups.

There is another respect in which the vitamin D trials differ from most other randomized clinical trials: Normally, the placebo group receives none of the compound being investigated, but participants in the placebo group of a vitamin D trial will still produce the vitamin in their skin and consume it with their food. That narrows the gap between the two groups. In addition, in all the ongoing trials, participants will be allowed to take low-dosed vitamin D supplements if they were already taking them. Holick sees that as a fatal flaw in the VITAL study and others: "They are essentially comparing 800 IUs

a day with 2000 IUs." The trial should have given the treatment group 4000-IU supplements to see a clear difference between it and the "control" group, he argues. But Manson points out that participants in both groups are allowed to take supplements. "The difference remains 2000 IUs," she says.

The double-blind Finnish study, which will start in a few months, will divide participants into three groups of 6000 that will take either a 1600-IU vitamin D supplement daily, 3200 IUs, or a placebo. And in the study in New Zealand, which in 2017 could be the first to report results, participants will take 100,000 IUs or a placebo once a month.

Even these large studies may not be definitive enough on their own to settle the vitamin D issue, says Scragg, who heads the New Zealand study. He cites recent evidence suggesting that vitamin D may only be beneficial in those with low initial levels of the vitamin. That means proof of the effectiveness of supplementation may only come from pooling the various studies, he says: "Then you could segment people into various vitamin D ranges based on baseline levels and see whether it has an effect or not."

Until those data are in, and maybe even afterward, scientists will likely keep on arguing, Rosen says. Evidence does not matter to many people when it comes to vitamin D, he maintains: "It is a religion. People really believe this stuff works."

—KAI KUPFERSCHMIDT

### Vitamin D on Trial

NAME	PLACE	PARTICIPANTS	DOSE	MAIN OUTCOMES	CURRENT STATE	RESULTS EXPECTED
VITAL	U.S.	20,000, men: 50+ women: 55+	2000 IU D <sub>3</sub> daily	Cancer, Cardiovascular disease	Recruitment to finish end of 2012	2017
FIND	Finland	18,000 men: 60+, women: 65+	1600 IU D <sub>3</sub> daily or 3200 IU D <sub>3</sub> daily	Cancer, Cardiovascular disease, Diabetes	Recruitment started in spring, supplementation to start in autumn	2020
ViDA	New Zealand	5100, 50+	100,000 IU D <sub>3</sub> a month (200,000 IU in June)	Cardiovascular disease, Respiratory disease, Fractures	Recruitment to finish this year	2017
DOHealth	8 European cities	2150, 70+	2000 IU D <sub>3</sub> daily	Infections, Fractures, Blood pressure, Cognitive function, Lower extremity function	Recruiting	2017
VIDAL	U.K.	20,000, 65–84	60,000 IU monthly	Longevity and others	Planned 2-year feasibility study on 1600 patients is recruiting	2020 (if main study gets go-ahead)

ysis. Rosen disagrees: "There is very little randomized clinical trial data that gets up to these levels, and there is just no evidence that it actually protects against skeletal problems or other diseases."

Interjecting another note of caution, a paper published in the *American Journal of Cardiology* in January 2012 showed that vitamin D in the blood reduces inflammation, measured by a protein called C-reactive protein (CRP)—until the vitamin's level reaches 50 nmol/l. Above that mark, the relationship reverses and more vitamin D increases CRP levels again. The authors concluded that supplementation with vitamin D to reduce inflammation may be beneficial only in those with low serum concentrations of the vitamin.

another one in the United Kingdom is in the pipeline (see table).

Such prevention trials are challenging—and may not ultimately satisfy everyone. They must have large numbers of subjects and run for a long time, because enough participants need to develop a disease to see a difference between the two groups. That makes them very costly; the VITAL study, funded by the U.S. National Institutes of Health, will cost about \$30 million. Compliance is also an issue, because healthy people taking part in a trial of vitamin D may be more likely to forget to take the pills than sick patients in a drug trial—especially because there is no doctor administering the treatment in a clinic. In the VITAL study, participants will receive their pills in the mail once a month; in the Finnish study,