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Why governments are selling Vitamin D short

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Reinhold Vieth is frustrated. A thin, bald professor at the University of Toronto's Department of Laboratory Medicine and Patho-biology, Vieth is among the most knowledgeable people in the world on the subject of vitamin D. He began studying it as a graduate student in 1974 and hasn't changed his focus since. "I stick with vitamin D and follow it where it goes," he says.

In recent years, vitamin D has been going to some exciting places. Reports of new and promising studies seem to emerge almost weekly. A 2007 analysis of vitamin D studies found that individuals with higher vitamin D levels are significantly – as much as 50 per cent – less likely to develop colorectal cancer. Another 2007 study found that women who took 1,100 International Units (IU) of vitamin D per day together with a calcium supplement reduced their overall cancer risk by 60 per cent. And the excitement is not only about cancer prevention. Low vitamin D levels have been linked to an increased risk of osteoporosis, heart disease, multiple sclerosis, type 1 diabetes, depression and rheumatoid arthritis, among other diseases. Perhaps not surprisingly, in light of the other studies, one recent review of the health records of more than 13,000 Americans found that individuals with the lowest vitamin D levels were 26 per cent more likely, in an eight-year period, to die than those with the highest levels.

Sunlight
10,000 IU from 15-20 minutes of midday summer sun
Oysters
270 International Units (IU) of vitamin D per half-dozen
Dried shiitake mushrooms
172 IU per 100g

So why is Dr Vieth so frustrated? You might think he'd have cause for celebration. But for him and other vitamin D researchers around the world, the good news comes with a bitter aftertaste. They believe they can prove vitamin D could help millions live longer and be healthier and yet they have not been able to convince their own governments.

In the US and Canada, official vitamin D policy is set by the Institute of Medicine. And in the opinion of Vieth, the current recommendations – 200 International Units per day for people under 50, 400 for people aged 51-70, and 600 for those 71 and older – are outrageously low. Bruce Hollis, professor of paediatrics at the Medical University of South Carolina, calls 400 IU a day "a joke". That's because the best research suggests that to achieve the higher vitamin D blood levels associated with disease prevention, most adults in the US would need to take 1,000-2,000 IU a day: five to 10 times more than the current official recommendation for adults.

In the UK, the government's Committee on Medical Aspects of Food and Nutrition Policy has declined to set a "Reference Nutrient Intake" value for people "leading a normal lifestyle", arguing that you can get the vitamin D you need from food and sunlight. But they fall in line with the Americans where they do make recommendations: for people confined indoors, the elderly and pregnant women, they suggest a daily intake of 10 micrograms a day. That's equal to 400 IU.

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Vitamin D was discovered in the early 20th century as scientists searched for a cure for rickets, a disease that softens the bones of children, leaving them bowlegged and deformed. It had been known for some time that children in cities were more likely to suffer from rickets than those in the countryside. But it wasn't until the 1920s that scientists in the US and UK realised rickets was caused by a vitamin D deficiency, caused in city kids by lack of sunlight. We obtain our other vitamins from our food; but while it's possible to get vitamin D from oily fish and some other foods, most of the vitamin D in our bodies doesn't come from diet at all but from a chemical process that takes place when the sun's ultraviolet light strikes our skin.

In the 1950s and 1960s, when American and other dietary guidelines first specified vitamin D intakes of up to 400 IU for adults, nobody understood that vitamin D could do anything other than regulate calcium. And since 200 IU is enough to prevent rickets in children – assuming they have at least a moderate amount of calcium in their diet – it was assumed that 200 IU was sufficient. It was only in the following decades, as scientists came to understand how vitamin D works in our bodies, that the picture changed.

After it forms in our skin, vitamin D undergoes two critical transformations. First our liver metabolises it, turning it into calcidiol. If you have your vitamin D blood levels checked, it's the amount of calcidiol in your blood that will be tested. From the liver, calcidiol makes its way to the kidneys, where it is turned into calcitriol, arguably the most potent steroid hormone in the body. In other words, while vitamin D is lumped together with other vitamins, by the time our bodies are done with it, it has more in common with testosterone or oestrogen than with vitamins A or C.

Mackerel
643 IU per 100g. Halibut gives you 230 IU per 100g, pickled herring 113 IU per 100
Tinned sardines
23 IU per 12g fish. Tinned salmon gives you 550 IU per 100g, tinned tuna 270 IU per 100g

If you have only a small amount of D in your body, it will all be used by the kidneys to produce calcitriol and maintain blood calcium levels. But when there is more vitamin D available, something very different happens. As scientists have discovered in recent decades, it's not only the kidneys that can make calcitriol from the calcidiol produced in the liver. Many tissues throughout the body can as well. These tissues use the hormone locally, within the cells, to regulate their behaviour.

"Calcidiol is like a blank piece of paper," Vieth explains. "And calcitriol is like the message written on to it. Calcitriol is needed by our bodies to convey many kinds of messages, and virtually every cell in our body has a receptor that can read and respond to it."

The first real evidence for the cancer-fighting properties of vitamin D emerged in the early 1980s, when researchers found that if they added calcitriol to immature malignant leukaemia cells, the cells would stop growing. They could only guess why this was, but scientists have since shown that vitamin D interacts with an unusually large number of genes and has the apparent ability to turn them on and off.

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This new understanding of how vitamin D works in our bodies, together with a large quantity of evidence of the benefits of higher vitamin D levels, might make it seem like an obvious move for the world's governments to adjust their recommendations for daily intake. But Vieth and other vitamin D advocates have good reason to think there will be minimal changes made to dietary guidelines. Last December, the World Health Organisation's International Agency for Research on Cancer issued a 465-page report that concluded there was no need to raise vitamin D recommendations.

The reason is not a lack of research but a lack of the right kind of research, say vitamin D sceptics. Most evidence for vitamin D and health is based on epidemiological surveys. Many of these studies, particularly early ones, were based on geography. Epidemiologists have found, for example, that multiple sclerosis – a disease of the central nervous system – and a number of cancers become more common the farther you move away from the equator. In the US, you are four times more likely to develop MS if you live in a state that borders Canada than if you live in the south. The theory is that as you move away from the equator, you receive less "UVB" ultraviolet sunlight (UVB is a subtype of UV light and the most important for vitamin D production), and thus fewer opportunities to make vitamin D in your skin.

Hard-boiled eggs
26 IU per egg; 25 IU per egg yolk
Fortified cows' milk
250 IU per pint
Fortified orange juice
270 IU per pint

This may sound like persuasive research to lay readers, but for scientists, such correlations aren't generally convincing, as there could be plenty of other possible reasons why people living at higher latitudes are more likely to suffer from MS.

The more compelling evidence for the connection between vitamin D and disease onset comes from the wide range of studies in recent years that have actually measured vitamin D levels in blood. But even these studies only show correlations. They can demonstrate, as one Harvard School of Public Health study did in 2006, that the vitamin D status of healthy young adults can predict their future risk of developing MS, but they can't definitively demonstrate that higher vitamin D levels prevent MS. It's possible, for example, that there is another mechanism at work in the early stage of MS that causes vitamin D levels to drop during the first stage of a progressive disease *(see box below for more on MS)*.

Few mainstream researchers would disagree that a single correlation study should not be given much weight in determining public policy. It's only when looked at in aggregate that these survey studies – together with the many small clinical trials and our new knowledge of how vitamin D works at the cellular level – begin to make a powerful case for increasing the current vitamin D recommendations.

And yet, if the WHO report of 2008 is any indicator, such a case isn't always strong enough to sway a sceptical committee. All the recent research notwithstanding, vitamin D is still missing the gold standard of evidence-based medicine: large, randomised controlled trials which can demonstrate its ability to

The link to MS

Multiple sclerosis is thought to be caused by a mix of environmental and genetic factors. And while scientists are still trying to unravel how these interact, a growing body of research points to vitamin D as a key environmental factor.

In people with MS, the immune system malfunctions and attacks

prevent major diseases. The WHO report concludes that "we should wait for the results of new randomised trials" before changing vitamin D recommendations.

It's a position echoed in the UK by the National Institute of Clinical Excellence (Nice), which advises the government on whether drugs should be paid for by the state. After reviewing the vitamin D literature, in 2003 Nice pointed to the absence of randomised clinical trials and suggested that there was no need even to recommend vitamin D to pregnant women – a conclusion that was overruled by the government's chief medical officer after paediatricians objected.

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For Britons, the most alarming aspect of these government responses is that people living in the UK have so much to lose. For much of the year, it is impossible in this country to obtain vitamin D from the sun – for the same reason it is impossible to suffer sunburn. There is simply not enough UVB ultraviolet radiation in our winter and autumn sunlight. And unless you happen to consume a lot of oily fish, it's very hard to get much vitamin D from your diet. (In addition to oily fish, eggs and fortified foods have small amounts of vitamin D.) It's no surprise, then, that a 2007 study of middle-aged British adults found that 90 per cent had less-than-optimal levels of vitamin D during winter and spring. In the US, by comparison, three-quarters of teenagers and adults are estimated to be deficient in vitamin D.

Advocates of changes to the vitamin D recommendations in the UK and elsewhere don't disagree that large, randomised control trials are important. The trouble is, trials that could convince policymakers to advise an across-the-board increase to vitamin D recommendations for all children and adults might never take place.

There are a number of obstacles to the research, but the simplest, and biggest, is money. Vitamin D is not a proprietary compound. It's cheap and easy to produce. A bottle of 180 1,000-IU capsules can be purchased online for about £9. No pharmaceutical company is going to put up the many millions of dollars necessary to conduct the trials.

the protective coating around nerve cells known as myelin sheaths. The disease can affect sight, balance, continence, speech and more, and reduces life expectancy. Vitamin D's influence on MS – and other autoimmune diseases such as type 1 diabetes – is thought to be related to the vitamin's ability to suppress autoimmune responses.

The link between vitamin D and MS was for many years thought to be wild speculation. Now more and more studies point in the same direction: people who have higher levels of vitamin D in their blood early in life are less likely to get MS later in life. Also, MS patients have been found to have low levels of vitamin D in their blood– and the levels appear to be even lower during relapses.

One small study published this year found that MS patients who took high doses of vitamin D – an average of 14,000 IU a day for a year – had significantly fewer relapses than those MS patients who took an average of 1,000 IU a day. Studies have also shown that vitamin D prevents experimental autoimmune encephalomyelitis (EAE), the mouse model of human MS.

Michael Gleimer, a research fellow at Harvard Medical School who has no connection to the vitamin D controversy, notes that it is easy for a medical research fellow to do a small-scale study on something like vitamin D. "It is non-controversial, easy to get approval for, and popular-sciency enough that it may land you in the science section of BBC news," Gleimer says. "But to do a large, definitive, long-term study, one needs cash. This is something a pharmaceutical company could do. But why would they want to push vitamin D? It's cheap and there is no patent for it."

Vitamin D also has to overcome the baggage of other vitamins. Asked for his thoughts on the US and Canada's current daily vitamin D recommendations, Len Lichtenfeld, deputy chief medical officer of the American Cancer Society, said that "similar 'signals' regarding other vitamins and nutritional supplements – suggesting that they decreased the incidence of certain cancers – have not been borne out in subsequent randomised clinical trials."

The main culprit here is vitamin E, which caused a great deal of excitement in the early 1990s. The enthusiasm for vitamin E at the time was great enough to convince the US government to invest millions in just the sort of large clinical trials that have yet to be conducted for vitamin D. But E turned out to be a disappointment, showing no benefits whatsoever in preventing cancer.

There's a third obstacle in the way of large clinical trials with vitamin D. Like other nutrients, it faces a systemic problem. A typical clinical trial follows what Vieth calls a "pharmaceutical drug company model", where a group of sick people are given a carefully selected dose of a drug to see if it makes a difference to their condition, compared with a second group of sick people who receive a placebo.

The drawback of this model is that it doesn't work nearly as well if the goal of the study is not to determine if a person gets better but to determine if the substance can prevent you from becoming ill at all. "It takes a great deal of time and huge population to look at healthy people and see what develops," says Mariela Glandt, an endocrinologist and the former director of the Diabetes Clinical Trials Center at Hadassah Hospital in Jerusalem. "It's just much more expensive and time-consuming."

Not even the recent announcement of a $20m study by Harvard Medical School and the Brigham and Women's Hospital in Boston is enough to make Vieth optimistic. Funded by National Institutes of Health and other institutions, the research will look at vitamin D and omega-3 fatty acids (which have also shown disease-fighting promise) in the primary prevention of chronic disease in adults ages 60 and over. If the results are good, they could help make the case for raising vitamin D recommendations for older adults. But Vieth believes it would still be difficult to persuade policy-makers of the need to raise vitamin D levels for everyone. "'If you start with people older than age 65 and do clinical trials with them', policy-makers say, 'Why should we impose this drug on everyone in society?'"

Fortified tofu
120 IU per 80g
Vitamin D capsules
100-5,000 IU; most multivitamin pills contain 400 IU of vitamin D
Cod liver oil
450 IU per teaspoon; capsule amounts vary

And if it remains challenging to raise enough money to study prevention in older adults, it's nearly impossible to find the money to study younger people; a younger population is less susceptible to disease, so any convincing study would require an enormous number of participants.

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Then there is a problem that is more specific to vitamin D. The latest research suggests that it takes 1,000 IU a day or more to achieve vitamin D's anti-cancer benefits. But often when a smaller vitamin D trial does receive funding, it is conducted with the current lower vitamin D recommendation – and then fails to prove effective.

These failures, such as a highly publicised Lancet study in 2005 that found 800 IU of vitamin D and calcium given in prevention trials (trials in which many participants did not take the supplements regularly) did not prevent bone fractures, are then used by review committees as grounds for leaving the current vitamin D recommendations in place.

It was precisely such studies that convinced the authors of the WHO report that there was no need for action on vitamin D. The report concluded that vitamin D recommendations did not need to be raised because there was not yet evidence that supplementing with 400-840 IU of vitamin D could prevent cancer. What the conclusion left out, as though the authors couldn't imagine anyone taking more than 840 IU, was a randomised clinical trial which found that 1,110 IU taken daily is effective in preventing cancer in women.

With so many factors weighing against a large vitamin D trial for anyone who is not old or sick with cancer or another serious disease, the best hope for advocates of higher vitamin D recommendations may be convincing the medical authorities and the public to take the epidemiology survey studies more seriously. (Even if a large trial did get off the ground, it would probably be at least a decade before there were results.)

It's not an impossible task. In other instances, the medical community has been ready to recognise survey evidence: "The evidence favouring vitamin D is probably as good as the evidence that shows smoking is bad for you," Vieth says, explaining that just as smoking is correlated with certain cancers, so are low vitamin D levels. "But when these government officials see the same kind of evidence that deals with vitamin D as they see with smoking they go, 'Oh wait a minute. We can't really trust this.'"

Vieth pauses, as though he can barely stand to talk about such a miserable state of affairs. "It's easy to say 'don't do something – don't smoke'. It's very hard to say 'take this. Take vitamin D.'"

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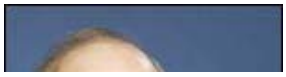
Can we overdose?

One of the debates surrounding vitamin D is whether too much can be toxic. The US's Institute of Medicine's recommendations – unchanged since 1997 – were influenced in part by a 1984 study concluding that 3,800 IU of vitamin D per day could cause hypercalcemia, or too much calcium in the blood. Symptoms include kidney stones, vomiting and muscle atrophy.

But the 1984 study was flawed: it failed to measure the amount of vitamin D administered; based on the findings of other studies, it now looks as though subjects



were given 100 times more vitamin D than intended.Moreover, how could it be that 3,800 IU was toxic, when 20 minutes of midday sunbathing in the summer makes at least 10,000 IU of vitamin D in our bodies?

In 1999, Reinhold Vieth *(pictured right)* published a review of vitamin D research in response to the IOM conclusions. In it, he argued that there was no evidence that amounts lower than 20,000 IU a day could be toxic. “Throughout my preparation of this review, I was amazed at the lack of evidence supporting statements about the toxicity of moderate doses of vitamin D,” Vieth wrote.

Studies have since shown 10,000 IU a day of vitamin D to be safe. While any substance will become toxic in excess, vitamin D researchers today accept that the current vitamin D recommendations could be more than quadrupled with no fear of toxicity.