BY LOGAN BRONWELL

The Overlooked Importance of VITAMIN D RECEPTORS

Just a few years ago, vitamin D was simply known as the "bone vitamin." Thanks to the hard work of many scientists, especially Michael Holick, MD, a pioneer in vitamin D research, the data show that nearly every tissue and cell type in the body has receptors for vitamin D.[1] As a result of this discovery, much higher doses are required for optimal functioning. This discovery has radically changed how we understand the role of vitamin D in the body.

Unless your body is at optimal levels, you are opening the door to a host of disorders, ranging from heart disease and Alzheimer's to weak bones and diabetes.[2,3]

In fact, even if you have normal blood sugar today, a vitamin D deficiency makes you **91%** more likely to progress to insulin resistance, or "pre-diabetes," and it more than doubles your risk for progressing to active, type II diabetes.[4]

Unfortunately, vitamin D deficiency is a global epidemic. An estimated **1 billion people** do not have adequate vitamin D levels.[5] And **64%** of Americans don't have enough vitamin D to keep all of their tissues operating at peak capacity.[6]

The results of this deficiency are catastrophic. Studies have now shown that vitamin D deficiency is associated with increased risk of a long list of diseases that span all systems in the body. In fact, low levels of vitamin D increase the risk of non-Alzheimer's dementia *almost 20 times*![7]

While checking for vitamin D levels is still not standard of care for many physicians, you will realize from reading this article that assessing **vitamin D status** is one of the most important health-protecting steps you can take. Fortunately, achieving optimal levels of vitamin D is easy, inexpensive, and highly protective against a range of lethal diseases. >

Why Vitamin D is so Vital

While humans can make some vitamin D in their bodies, most of us require additional amounts from our diet, the sun, or from supplements in order to maintain adequate levels.

Once vitamin D has been ingested in the diet or produced in the skin, the liver and kidneys convert it to its active form, called 1,25-dihydroxyvitamin D, or **vitamin D3**.[8,9]

Virtually every tissue type in your body has receptors for vitamin D, meaning that they all require vitamin D for adequate functioning.[8,9] The very presence of specific receptors define vitamin D as a **hormone**, rather than a vitamin.[8] It interacts with receptors throughout the body and has a number of different effects.

It's becoming evident that higher doses of vitamin D are required to support its other activities in tissues such as heart muscle, brain cells, and fat tissue, to name just a few. Additionally, vitamin D regulates genes that control cell growth and development, immune function, and metabolic control.[5,8]

Studies have now shown that vitamin D deficiency is associated with increased risk of numerous chronic disorders, including type II diabetes, cancer, infections, and cardiovascular, autoimmune, and neurological diseases (See the table on page 45 for greater detail).[8,9]

The Global Vitamin D Deficiency

The problem is that most of us are simply not getting enough vitamin D to allow our bodies to work optimally at all of the functions that vitamin D supports. An estimated **1 billion people** (that's about a seventh of the global population) have inadequate vitamin D supplies in their bodies.[5]

According to mainstream medical standards, there are three levels of vitamin D status: sufficient, insufficient, and deficient.

- People who are considered vitamin D "sufficient" have blood levels of at least **30 ng/mL**. However, optimal vitamin D status is achieved with a minimum of **50 ng/mL**.
- Those considered "insufficient" (meaning their bodies aren't at optimal vitamin D capacity) have levels between **21 and 29 ng/mL**.
- And those who are "deficient" are defined as having levels at or below **20 ng/mL**.[8]

By those criteria, **25%** of Americans are *insufficient*, and **39%** are outright *deficient*.[6] In other words, fully **64%** of Americans don't have enough vitamin D to keep all of their tissues operating at peak capacity. It's hardly any wonder we are plagued with so many chronic diseases.

Vitamin D Supports Cardiovascular Health

Vitamin D deficiency is common in people with cardiovascular disease; almost all people with heart failure have reduced levels.[10] It is now recognized as an independent predictor for diseases of the heart and blood vessels, including heart attacks and strokes.[11]

One study published this year found that women with vitamin D levels in the top one-third of the population had **68%** lower risk of heart attacks compared with those in the lowest third; men in the top third had a **44%** lower risk.[12]

Conversely, if your vitamin D level is in that lower range, you have a **42%** increased risk of dying of cardiovascular disease and a **49** to **64%** increased risk of a stroke.[13,14] The risk of having clogged coronary arteries (the precursor of a heart attack) is more than **doubled** for people with vitamin D deficiency (less than **20 ng/mL**).[15]

Why does vitamin D deficiency lead to such a dramatic increase in the risk for having America's #1 killer disease?

It's because the heart muscle, blood vessels, and other circulatory system components are rich in **vitamin D receptors**, which means they depend heavily on vitamin D for optimum function.[16]

Animals bred to have no vitamin D receptors have cardiovascular disease at an early age and end up with enlarged, dysfunctional hearts.[10,17,18] These effects are likely due to vitamin D's role in increasing protective signaling pathways in those tissues, while preventing harmful ones.[19] In addition, vitamin D is required to prevent the excessive buildup of collagen and other fibrotic proteins that stiffen heart muscle and artery walls, reducing blood flow and raising blood pressure.[11]

Human Studies Verify D's Heart Benefits

There's no shortage of compelling human studies of vitamin D and cardiovascular risk. One study found that a daily supplement of **3,320 IU** reduced triglycerides by **13.5%** (vs. a **3%** increase with a standard weight-loss program) and also reduced ***tumor necrosis factor-alpha***, a major marker of inflammation that

contributes to atherosclerosis.[20] Supplementation has also been shown to relax blood vessels, helping to reduce blood pressure and improve blood flow.[19]

In a study of African-American teens (a group at very high risk for hypertension and cardiovascular disease), vitamin D supplements of **2,000 IU/day** boosted blood levels into the sufficient range. The supplemented group also saw a significant and beneficial decrease in **aortic stiffness**, a measure of cardiovascular risk.[21]

In another study of African-American adults (also at high risk for cardiovascular disease), **60,000 IU/month** for 4 months (about **2,000 IU/day**) improved ***endothelial function***, an essential property of blood vessels that allows them to provide adequate blood flow at safe pressures.[22] Similar effects have been shown in stroke survivors, who really need to optimize their endothelial function.[23]

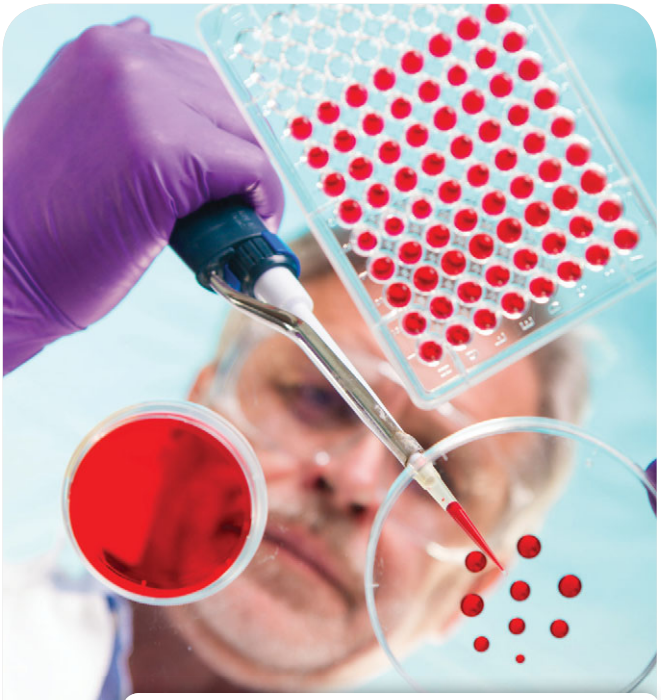
In a study of vitamin D supplementation in obese and overweight women (with an average age of 38 years), supplementing with **1,000 IU/day** significantly raised protective HDL-cholesterol levels and significantly lowered body fat mass after 12 weeks.[24]

Vitamin D deficiency is also implicated in **peripheral arterial disease**, in which hardened, narrowed arteries fail to provide enough blood to the extremities, especially the legs.[25] People with lower vitamin D levels are more likely to develop peripheral artery disease, in direct proportion to how low their levels are. And in fact, amputation, the worst consequence of this condition, is much more likely among those with the lowest levels.[25]

It's clearer than ever that you need vitamin D to maintain your cardiovascular health—but it's important to make sure you're taking the proper dose. Studies of cardiovascular patients who use only **400 to 600 IU/day** in general show no benefits, whereas those using **2,000 IU or more** do.[20,21,26] One study demonstrated that **2,000 IU/day** is the minimum needed to ensure that people reach the minimum target of **30 ng/mL** of vitamin D in their blood.[27]

Vitamin D Lowers Diabetes Risk

Vitamin D can also play a critical role in diabetes. People with diabetes (both types I and II) have even lower levels of vitamin D than the general population.[28,29] A vitamin D deficiency makes you **91%** more likely to progress to **insulin resistance**, or "prediabetes" (even for those with normal blood sugar). Additionally, a vitamin D deficiency more than ***doubles your risk*** for progressing to full-blown **type II diabetes**.[4]



What You Need to Know

Vitamin D: Essential Hormone

- **Most people think of vitamin D as the "bone vitamin," but recent discoveries show that vitamin D is essential for a tremendous number of normal body processes.**
- **Virtually every tissue type in the body possesses receptors for the activated vitamin D molecule, defining it as a true hormone.**
- **Low vitamin D levels are associated with increased risks of cardiovascular and neurological disease, cancer, diabetes, and autoimmune disorders.**
- **The majority of Americans have vitamin D levels below the minimum recommended concentration of 50 ng/mL, explaining in part the high prevalence of these diseases.**
- **Fortunately, supplementation with vitamin D3 has been shown to be protective for all of these conditions, when taken at the dose of at least 2,000 IU/day. (Most people need 5,000 to 7,000 IU/day of vitamin D3 to achieve optimal blood levels.)**

This close connection between vitamin D and diabetes is due to **vitamin D receptors**, which are found in the pancreas's insulin-producing cells and in liver, fat, and muscle tissue, all of which influence the fate of glucose in your blood.[28]

For example, white blood cells called **macrophages** have vitamin D receptors. When macrophages are taken from diabetics, they display a high level of fat content, which contributes to diabetics' increased cardiovascular risk. However, when those cells are treated in the lab with vitamin D, they stop their pathological fat uptake—ultimately helping reduce cardiovascular risk.[30]

Similarly, compared to healthy controls, diabetic lab animals have decreased numbers of insulin and vitamin D receptors in their brains; they have more body fat and higher levels of inflammation and DNA damage; and they perform poorly on tests of memory and cognition (remember that Alzheimer's disease has been called "diabetes of the brain").[31,32] But vitamin D supplementation **restored** all of those functions to near-normal levels—including improved cognitive performance.[31,33] This is an especially important finding, since it shows the potential of vitamin D to help reverse the process of diabetes.

The inflammatory changes in diabetic animals, as in humans, lead to increased fat in the liver, a condition known as **non-alcoholic fatty liver disease** (NAFLD). This condition further degenerates due to a vitamin D deficiency.[34] But when human diabetics with similar elevated inflammatory markers are supplemented with **1,000 IU/day** of vitamin D, the inflammation is substantially reduced.[35]

Perhaps the most remarkable news about vitamin D in this context, however, is that *it slows the progression from pre-diabetes to diabetes*. When obese, non-diabetic adults supplemented with **2,000 IU/day** of vitamin D or placebo for 16 weeks, the vitamin D group had significantly improved glucose clearance from their blood, improved insulin secretion from the pancreas, and a trend to lower levels of hemoglobin A1c (the marker of long-term glucose exposure). Control subjects instead saw a worsening of all those parameters.[36]

Vitamin D supplementation also benefits those who already have diabetes. Diabetics receiving **1,000 IU/day** of vitamin D in yogurt saw significant decreases in fasting blood sugar, hemoglobin A1c, insulin resistance, waist circumference, and body mass index, compared with controls receiving no vitamin D.[37]

Studies show that supplementation with vitamin D3 can reduce blood pressure, total cholesterol, and LDL-cholesterol—all risk factors for the heart and kidney diseases for which diabetics are at increased risk.[38] Treatment with active vitamin D3 also significantly reduces protein levels in urine, a marker of kidney disease.[39]

With few exceptions, doses of vitamin D of less than **1,200 IU/day** have not been shown to be as effective as doses of **2,000 IU/day** at lowering blood sugar, hemoglobin A1c, lipid levels, and other disease markers in diabetic patients.[40,41]

Vitamin D Protects Brain Cells

Vitamin D is especially powerful against neurodegenerative diseases such as Alzheimer's and Parkinson's. Long-term studies show that low vitamin D levels increase the risk of cognitive decline of any kind by **41 to 60%**; increase the risk of Alzheimer's dementia by **77%**; and increase the risk of non-Alzheimer's dementia by *nearly 20-fold*.[7,42,43] And higher vitamin D concentrations are correlated with lower severity in Parkinson's disease.[44]

Even though existing treatments for neurodegenerative diseases can only treat symptoms and temporarily slow their progression,[45] vitamin D has been found to *reverse neurodegenerative decline*. A recent study showed that adding vitamin D to a standard memory drug, memantine, for 6 months in newly diagnosed Alzheimer's patients produced significant *gains* in cognition, suggesting a synergism between vitamin D and the drug.[46]

Supplementation with vitamin D has such potent benefits for the brain because the brain relies on **vitamin D receptors** for protection against a variety of destructive processes.[47] Vitamin D has been shown to have a critical role in nerve cell growth and differentiation, nerve transmission, and the "plasticity" of connections that's so essential for normal learning and memory.[48] Without adequate vitamin D, all of those functions suffer, and some fail.

In Alzheimer's disease, that failure is manifested as increased amounts of the abnormal, inflammatory protein called ***amyloid beta*** (or Abeta). Studies show that when vitamin D is added to cultures of cells from Alzheimer's patients, it speeds the clearance of Abeta.[49]

When laboratory animals bred to spontaneously develop Abeta plaques are supplemented with vitamin D, they show a decrease in brain inflammation, an increase in protective nerve growth factor, and they develop fewer Abeta plaques compared to control animals.[50]

Even normal elderly lab rats (those without Alzheimer's) can experience cognitive benefits from vitamin D supplementation. Older rats have significant difficulty with cognitive testing, along with elevated levels of pro-inflammatory cytokines, decreased levels of anti-inflammatory cytokines, and higher levels of Abeta proteins in their brains.[51] But supplementing with vitamin D for as little as 21 days significantly *reversed* the inflammatory changes and *improved* clearance of Abeta.[51] This shows the potential of vitamin D to prevent the onset of age-related cognitive decline—even when it's not associated with Alzheimer's disease.

Vitamin D can benefit people with Parkinson's disease as well. In humans, it's already known that vitamin D supplementation reduces falls and improves balance in healthy older adults—two problems often faced by patients with Parkinson's.[44] A randomized, placebo-controlled clinical trial has shown that **1,200 IU/day** of vitamin D3 prevents deterioration in Parkinson's disease patients over a 12-month period.[52] Intriguingly, this effect depended on the patients' type of vitamin D receptors in brain tissue.

Vitamin D Blocks Cancer

Low levels of vitamin D in the blood are strongly associated with elevated cancer risk. Compared to people with higher vitamin D levels, those with low levels have an **83** to **150%** increased risk of developing cancer.[53-55]

This strong correlation is due to **vitamin D receptors**, which regulate a number of signaling pathways involved in inflammation, tumor growth, and immune system surveillance for cancer—especially in the epithelial cells of the skin, breast, prostate, and colon (tissues that are prone to cancer development).[56-58]

The problem is that in cancer cells, the vitamin D receptor is dramatically decreased, leaving cells unregulated and prone to reproduce in an out-of-control fashion.[57] Treating cancer cells in culture with vitamin D, however, produces a number of actions that help fight against cancer: it decreases tumor cell proliferation, quells inflammation, reduces invasiveness, and increases tumor cell death (apoptosis).[57,59,60]

The benefits of these actions are especially seen in cancers of the breast, prostate, and colon.

Breast Cancer

In animals with experimentally induced breast cancer, for example, these effects of vitamin D reduced the incidence, number, and size of tumors, particularly when vitamin D was combined with EPA and DHA from fish oil.[59,61]

In vivo studies have shown that activated vitamin D3 has some benefits specific to estrogen-dependent breast cancer. It reduces overall tumor-promoting estrogen effects by decreasing the expression of the *aromatase* enzyme that makes estrogen in breast tissue and by decreasing the expression of the alpha form of estrogen receptor that aggravates certain malignancies.[60]

Human studies are now pointing in a similar direction. In the large Women's Health Initiative study, even a low dose of **400 IU/day** of vitamin D combined with calcium was associated with an up to **20%** decrease in breast cancer in women who had not taken supplements previously.[62,63]

Prostate Cancer

Cancers of the prostate also respond to vitamin D supplementation, as shown by a study in which men with early prostate cancer received **4,000 IU/day** for a year.[64] Fifty-five percent of supplemented subjects showed a decrease in tumor-positive biopsies or a decrease in the **Gleason** tumor score, while an additional **11%** showed no change (meaning the cancer had not progressed). Since prostate cancer is often such a slow-growing malignancy, it is ideal for prevention with vitamin D.[65]

Colorectal Cancer

Cancers of the colon and rectum usually start as benign polyps (or *adenomas*), which progress to malignancy as a result of chronic inflammation. Colorectal adenoma patients who took **800 IU/day** of vitamin D3 experienced a significant **77%** decrease in

Increased Disease Risk With Low Vitamin D Levels

CONDITION	RISK INCREASE WITH LOW VITAMIN D LEVELS*
Autoimmune: Multiple Sclerosis[78]	61%
Autoimmune: Psoriasis[79]	189%
Autoimmune: Rheumatoid Arthritis[80]	24% (Patients taking vitamin D supplements had 24% lower risk.)
Cancer, Bladder[54]	83% overall; 494% for invasive tumors
Cancer, Breast[53]	150%
Cancer, Thyroid[55]	100%
Cognitive Decline[7]	41 to 60%
Cardiovascular: (Risk of Heart Attack)[12,13,15]	38 to 192%
Dementia, Alzheimer's[43]	77% increase for lowest vitamin D intake
Dementia, Non-Alzheimer's[7]	Almost 20-fold increase
Infection, Respiratory[81]	36%
Metabolic: Diabetes[4,82]	91% for insulin resistance, 38 to 106% for type II diabetes
Metabolic: Risk of progression from normal blood glucose to diabetes[83]	77%
Stroke[13,84]	22 to 64%

* Defined either as serum levels less than **30 ng/mL** (**75 nmol/L**), or as lowest percentiles vs. highest; risk expressed as percent increased for those with normal or highest levels.

inflammatory markers that can promote cancer development.[56] In a similar group of patients, **800 IU/day** of vitamin D3 produced marked decreases in levels of the tumor promoter *beta-catenin*, with an increase in the tumor suppressor known as *APC*.[66]

Vitamin D and Autoimmune Disease

Vitamin D is essential for maintaining a balanced immune system. Immune system cells are well-supplied with vitamin D receptors, which along with vitamin D itself, help the system modulate its response: from "attack mode" in the face of pressing threats to "cleanup and wind-down" mode once the threat is past and tissue damage becomes a concern.[67-69]

Vitamin D plays a role in the onset and progression of autoimmune diseases, including type I diabetes, lupus, rheumatoid arthritis, psoriasis, and multiple sclerosis.[68,70-72]

Fortunately, studies show that restoring vitamin D levels to the healthy range through supplementation can help patients with autoimmune diseases. Supplementation has been shown to increase the number of regulatory **T-cells** that restore immune system activity to its normal state, preventing the overactive response characteristic of autoimmune diseases.[73]

The increase in vitamin D levels through supplementation has a number of disease-specific benefits:

- It causes a decline in the disease activity in **rheumatoid arthritis** and **lupus**.[71,72]
- It reduces the risk of developing **type I diabetes** and preserves insulin-producing pancreatic cells once the disease has started. [74]
- It suppresses the development of **multiple sclerosis** in animal models of the disease, and a large human trial has shown that supplementation was associated with a **40%** reduction in the risk of developing multiple sclerosis.[70,75]

The Vitamin D Solution

With over 1 billion people worldwide faced with insufficient levels of vitamin D, it's easy to see why so many of these life-threatening diseases are skyrocketing to epidemic proportions.

Fortunately, the solution is straightforward. Start by taking a high quality vitamin D3 supplement of at least **2,000 IU** daily (small children need at least **400 to 1,000 IU**).[8,9] Next, get your vitamin D level checked as soon as possible. Be sure the lab tests for "***25-hydroxyvitamin D***," which is the best measure of vitamin D status.[8] To get your blood concentration up to the sufficient level, you'll need to take **100 IU** of additional D3 for each **1 ng/mL** you need to raise it.[8]

So if your level comes in at a low **20 ng/mL**, you'll need to take an additional **3,000 IU** (**100 IU** x **30 ng/mL**) to get yourself up to **50 ng/mL**. Recheck the level in 2 to 3 months. Once you are in the sufficient range, you might be able to maintain that level by taking **2,000 IU** daily, though most people nowadays are taking doses of **5,000 IU** and higher to get their levels closer to high optimal range of **80 ng/mL**. Confirm this with repeat testing at least once a year.[76] Many people, especially those with pre-existing chronic illness, find they need more to boost their levels adequately.[76,77]

Summary

Despite reams of evidence to the contrary, mainstream medicine continues to mainly regard vitamin D as essential only for healthy bone maintenance. But the discovery that the vitamin D receptor is found in virtually all human tissues has suggested to many that the vitamin (actually a hormone) is vital for most human functions.

Frighteningly, though, the majority of Americans have insufficient vitamin D levels to support good health, resulting in an increase in a host of chronic diseases.

Supplementing with **2,000-8,000 IU/day** of vitamin D3 is the best way to get your levels back to normal and to promote your body's maintenance—not just of bone health, but of robust cardiovascular, metabolic, neurologic, and immune function, while also preventing cancers of the breast, prostate, and colon, and likely many others.

Remember to take your vitamin D with the meal of the day that contains the most fat, as this greatly enhances vitamin D absorption.

You owe it to yourself to get your vitamin D level tested now—but don't wait for the results. Odds are that you haven't got enough vitamin D in your body for optimal health, so you should begin a vitamin D3 supplement today.

On page 49 is a description of a special offer for a **blood test panel** that includes 25-hydroxyvitamin D, glucose, cholesterol, LDL, HDL, triglycerides, and a host of other health markers. The cost of this panel is only **$56** for ***Life Extension*** members. ●

If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.

References

1. Available at: http://www.sciencenews.org/view/generic/id/64101/description/Vitamin_D_is_essential_to_the_modern__indoor_lifestyle. Accessed May 21, 2013.
2. Available at: http://www.scientificamerican.com/article.cfm?id=vitamin-d-deficiency-united-states. Accessed May 21, 2013.
3. Annweiler C, Llewellyn DJ, Beauchet O. Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis*. 2013;33(3):659-74.
4. Huang Y, Li X, Wang M, et al. Lipoprotein lipase links vitamin D, insulin resistance, and type 2 diabetes: a cross-sectional epidemiological study. *Cardiovasc Diabetol.* 2013;12:17.
5. Wacker M, Holick MF. Vitamin D - effects on skeletal and extraskeletal health and the need for supplementation. *Nutrients*. 2013 Jan 10;5(1):111-48.
6. Mitchell DM, Henao MP, Finkelstein JS, Burnett-Bowie SA. Prevalence and predictors of vitamin D deficiency in healthy adults. *Endocr Pract*. 2012 Nov-Dec;18(6):914-23.
7. Annweiler C, Rolland Y, Schott AM, Blain H, Vellas B, Beauchet O. Serum vitamin D deficiency as a predictor of incident non-Alzheimer dementias: a 7-year longitudinal study. *Dement Geriatr Cogn Disord*. 2011;32(4):273-8.
8. Holick MF. Vitamin D: evolutionary, physiological and health perspectives. *Curr Drug Targets.* 2011 Jan;12(1):4-18.
9. Holick MF. Vitamin D: a d-lightful solution for health. *J Investig Med.* 2011 Aug;59(6):872-80.
10. Pilz S, Tomaschitz A, Drechsler C, Dekker JM, Marz W. Vitamin D deficiency and myocardial diseases. *Mol Nutr Food Res.* 2010 Aug;54(8):1103-13.
11. Artaza JN, Norris KC. Vitamin D reduces the expression of collagen and key profibrotic factors by inducing an antifibrotic phenotype in mesenchymal multipotent cells. *J Endocrinol.* 2009 Feb;200(2):207-21.
12. Karakas M, Thorand B, Zierer A, et al. Low levels of serum 25-hydroxyvitamin D are associated with increased risk of myocardial infarction, especially in women: results from the MONICA/KORA Augsburg case-cohort study. *J Clin Endocrinol Metab.* 2013 Jan;98(1):272-80.
13. Wang L, Song Y, Manson JE, et al. Circulating 25-hydroxyvitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes.* 2012 Nov;5(6):819-29.
14. Sun Q, Pan A, Hu FB, Manson JE, Rexrode KM. 25-Hydroxyvitamin D levels and the risk of stroke: a prospective study and meta-analysis. *Stroke.* 2012 Jun;43(6):1470-7.
15. Shor R, Tirosh A, Shemesh L, et al. 25 hydroxyvitamin D levels in patients undergoing coronary artery catheterization. *Eur J Intern Med.* 2012 Jul;23(5):470-3.
16. Pilz S, Tomaschitz A, Marz W, et al. Vitamin D, cardiovascular disease and mortality. *Clin Endocrinol (Oxf).* 2011 Nov;75(5):575-84.
17. Pilz S, Kienreich K, Tomaschitz A, et al. Vitamin D and cardiovascular disease: update and outlook. *Scand J Clin Lab Invest Suppl.* 2012 Apr;243:83-91.
18. Zittermann A, Gummert JF. Sun, vitamin D, and cardiovascular disease. *J Photochem Photobiol B.* 2010 Nov 3;101(2):124-9.

19. Available at: http://www.health.harvard.edu/newsweek/vitamin-d-and-your-health.htm. Accessed May 21, 2013.
20. Zittermann A, Frisch S, Berthold HK, et al. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *Am J Clin Nutr.* 2009 May;89(5):1321-7.
21. Dong Y, Stallmann-Jorgensen IS, Pollock NK, et al. A 16-week randomized clinical trial of 2000 international units daily vitamin D3 supplementation in black youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness. *J Clin Endocrinol Metab.* 2010 Oct;95(10):4584-91.
22. Harris RA, Pedersen-White J, Guo DH, et al. Vitamin D3 supplementation for 16 weeks improves flow-mediated dilation in overweight African-American adults. *Am J Hypertens.* 2011 May;24(5):557-62.
23. Witham MD, Dove FJ, Sugden JA, Doney AS, Struthers AD. The effect of vitamin D replacement on markers of vascular health in stroke patients - a randomised controlled trial. *Nutr Metab Cardiovasc Dis.* 2012 Oct;22(10):864-70.
24. Salehpour A, Shidfar F, Hosseinpanah F, et al. Vitamin D3 and the risk of CVD in overweight and obese women: a randomised controlled trial. *Br J Nutr.* 2012 Nov 28;108(10):1866-73.
25. Chua GT, Chan YC, Cheng SW. Vitamin D status and peripheral arterial disease: evidence so far. *Vasc Health Risk Manag.* 2011;7:671-5.
26. Wood AD, Secombes KR, Thies F, et al. Vitamin D3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT. *J Clin Endocrinol Metab.* 2012 Oct;97(10):3557-68.
27. Tran B, Armstrong BK, Carlin JB, et al. Recruitment and results of a pilot trial of vitamin D supplementation in the general population of Australia. *J Clin Endocrinol Metab.* 2012 Dec;97(12):4473-80.
28. Takiishi T, Gysemans C, Bouillon R, Mathieu C. Vitamin D and diabetes. *Endocrinol Metab Clin North Am.* 2010 Jun;39(2):419-46, table of contents.
29. Wolden-Kirk H, Overbergh L, Christesen HT, Brusgaard K, Mathieu C. Vitamin D and diabetes: its importance for beta cell and immune function. *Mol Cell Endocrinol.* 2011 Dec 5;347(1-2):106-20.
30. Oh J, Weng S, Felton SK, et al. 1,25(OH)2 vitamin d inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. *Circulation.* 2009 Aug 25;120(8):687-98.
31. Kumar PT, Antony S, Nandhu MS, Sadanandan J, Naijil G, Paulose CS. Vitamin D3 restores altered cholinergic and insulin receptor expression in the cerebral cortex and muscarinic M3 receptor expression in pancreatic islets of streptozotocin induced diabetic rats. *J Nutr Biochem.* 2011 May;22(5):418-25.
32. Meerza D, Naseem I, Ahmed J. Effect of 1, 25(OH)(2) vitamin D(3) on glucose homeostasis and DNA damage in type 2 diabetic mice. *J Diabetes Complications.* 2012 Sep-Oct;26(5):363-8.
33. Siddiqui SM, Chang E, Li J, et al. Dietary intervention with vitamin D, calcium, and whey protein reduced fat mass and increased lean mass in rats. *Nutr Res.* 2008 Nov;28(11):783-90.
34. Roth CL, Elfers CT, Figlewicz DP, et al. Vitamin D deficiency in obese rats exacerbates nonalcoholic fatty liver disease and increases hepatic resistin and Toll-like receptor activation. *Hepatology.* 2012 Apr;55(4):1103-11.
35. Shab-Bidar S, Neyestani TR, Djazayery A, et al. Improvement of vitamin D status resulted in amelioration of biomarkers of systemic inflammation in the subjects with type 2 diabetes. *Diabetes Metab Res Rev.* 2012 Jul;28(5):424-30.
36. Mitri J, Dawson-Hughes B, Hu FB, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J Clin Nutr.* 2011 Aug;94(2):486-94.
37. Nikooyeh B, Neyestani TR, Farvid M, et al. Daily consumption of vitamin D- or vitamin D + calcium-fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial. *Am J Clin Nutr.* 2011 Apr;93(4):764-71.
38. Bonakdaran S, Hami M, Hatefi A. The effects of calcitriol on albuminuria in patients with type-2 diabetes mellitus. *Saudi J Kidney Dis Transpl.* 2012 Nov;23(6):1215-20.
39. Krairittichai U, Mahannopkul R, Bunnag S. An open label, randomized controlled study of oral calcitriol for the treatment of proteinuria in patients with diabetic kidney disease. *J Med Assoc Thai.* 2012 Mar;95 Suppl 3:S41-7.
40. Patel P, Poretsky L, Liao E. Lack of effect of subtherapeutic vitamin D treatment on glycemic and lipid parameters in Type 2 diabetes: A pilot prospective randomized trial. *J Diabetes.* 2010 Mar;2(1):36-40.
41. Eftekhari MH, Akbarzadeh M, Dabbaghmanesh MH, Hasanzadeh J. Impact of treatment with oral calcitriol on glucose indices in type 2 diabetes mellitus patients. *Asia Pac J Clin Nutr.* 2011;20(4):521-6.
42. Dickens AP, Lang IA, Langa KM, Kos K, Llewellyn DJ. Vitamin D, cognitive dysfunction and dementia in older adults. *CNS Drugs.* 2011 Aug;25(8):629-39.
43. Annweiler C, Rolland Y, Schott AM, et al. Higher vitamin D dietary intake is associated with lower risk of alzheimer's disease: a 7-year follow-up. *J Gerontol A Biol Sci Med Sci.* 2012 Nov;67(11):1205-11.
44. Peterson AL, Mancini M, Horak FB. The relationship between balance control and vitamin D in Parkinson's disease-a pilot study. *Mov Disord.* 2013 Apr 2.
45. Annweiler C, Fantino B, Parot-Schinkel E, Thiery S, Gautier J, Beauchet O. Alzheimer's disease--input of vitamin D with mEmantine assay (AD-IDEA trial): study protocol for a randomized controlled trial. *Trials.* 2011;12:230.
46. Annweiler C, Herrmann FR, Fantino B, Brugg B, Beauchet O. Effectiveness of the combination of memantine plus vitamin D on cognition in patients with Alzheimer disease: a pre-post pilot study. *Cogn Behav Neurol.* 2012 Sep;25(3):121-7.
47. Soni M, Kos K, Lang IA, Jones K, Melzer D, Llewellyn DJ. Vitamin D and cognitive function. *Scand J Clin Lab Invest Suppl.* 2012 Apr;243:79-82.

48. Deluca GC, Kimball SM, Kolasinski J, Ramagopalan SV, Ebers GC. The Role of Vitamin D in Nervous System Health and Disease. *Neuropathol Appl Neurobiol.* 2013 Jan 21.
49. Masoumi A, Goldenson B, Ghirmai S, et al. 1alpha,25-dihydroxyvitamin D3 interacts with curcuminoids to stimulate amyloid-beta clearance by macrophages of Alzheimer's disease patients. *J Alzheimers Dis.* 2009;17(3):703-17.
50. Yu J, Gattoni-Celli M, Zhu H, et al. Vitamin D3-enriched diet correlates with a decrease of amyloid plaques in the brain of AbetaPP transgenic mice. *J Alzheimers Dis.* 2011;25(2):295-307.
51. Briones TL, Darwish H. Vitamin D mitigates age-related cognitive decline through the modulation of pro-inflammatory state and decrease in amyloid burden. *J Neuroinflammation.* 2012;9:244.
52. Suzuki M, Yoshioka M, Hashimoto M, et al. Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson disease. *Am J Clin Nutr.* 2013 May;97(5):1004-13.
53. Bilinski K, Boyages J. Association between 25-hydroxyvitamin D concentration and breast cancer risk in an Australian population: an observational case-control study. *Breast Cancer Res Treat.* 2013 Jan;137(2):599-607.
54. Amaral AF, Mendez-Pertuz M, Munoz A, et al. Plasma 25-hydroxyvitamin D(3) and bladder cancer risk according to tumor stage and FGFR3 status: a mechanism-based epidemiological study. *J Natl Cancer Inst.* 2012 Dec 19;104(24):1897-904.
55. Roskies M, Dolev Y, Caglar D, et al. Vitamin D deficiency as a potentially modifiable risk factor for thyroid cancer. *J Otolaryngol Head Neck Surg.* 2012 Jun 1;41(3):160-3.
56. Hopkins MH, Owen J, Ahearn T, et al. Effects of supplemental vitamin D and calcium on biomarkers of inflammation in colorectal adenoma patients: a randomized, controlled clinical trial. *Cancer Prev Res (Phila).* 2011 Oct;4(10):1645-54.
57. Dormoy V, Beraud C, Lindner V, et al. Vitamin D3 triggers antitumor activity through targeting hedgehog signaling in human renal cell carcinoma. *Carcinogenesis.* 2012 Nov;33(11):2084-93.
58. Welsh J. Cellular and molecular effects of vitamin D on carcinogenesis. *Arch Biochem Biophys.* 2012 Jul 1;523(1):107-14.
59. Krishnan AV, Swami S, Feldman D. Equivalent anticancer activities of dietary vitamin D and calcitriol in an animal model of breast cancer: Importance of mammary CYP27B1 for treatment and prevention. *J Steroid Biochem Mol Biol.* 2012 Aug 23.
60. Krishnan AV, Swami S, Feldman D. The potential therapeutic benefits of vitamin D in the treatment of estrogen receptor positive breast cancer. *Steroids.* 2012 Sep;77(11):1107-12.
61. Chatterjee M, Janarthan M, Manivannan R, Rana A. Combinatorial effect of fish oil (Maxepa) and 1alpha,25-dihydroxyvitamin D(3) in the chemoprevention of DMBA-induced mammary carcinogenesis in rats. *Chem Biol Interact.* 2010 Oct 6;188(1):102-10.
62. Bolland MJ, Grey A, Gamble GD, Reid IR. Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. *Am J Clin Nutr.* 2011 Oct;94(4):1144-9.
63. Brunner RL, Wactawski-Wende J, Caan BJ, et al. The effect of calcium plus vitamin D on risk for invasive cancer: results of the Women's Health Initiative (WHI) calcium plus vitamin D randomized clinical trial. *Nutr Cancer.* 2011;63(6):827-41.
64. Marshall DT, Savage SJ, Garrett-Mayer E, et al. Vitamin D3 supplementation at 4000 international units per day for one year results in a decrease of positive cores at repeat biopsy in subjects with low-risk prostate cancer under active surveillance. *J Clin Endocrinol Metab.* 2012 Jul;97(7):2315-24.
65. Swami S, Krishnan AV, Wang JY, et al. Dietary vitamin D(3) and 1,25-dihydroxyvitamin D(3) (calcitriol) exhibit equivalent anticancer activity in mouse xenograft models of breast and prostate cancer. *Endocrinology.* 2012 Jun;153(6):2576-87.
66. Ahearn TU, Shaukat A, Flanders WD, Rutherford RE, Bostick RM. A randomized clinical trial of the effects of supplemental calcium and vitamin D3 on the APC/beta-catenin pathway in the normal mucosa of colorectal adenoma patients. *Cancer Prev Res (Phila).* 2012 Oct;5(10):1247-56.
67. Bouillon R, Carmeliet G, Verlinden L, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev.* 2008 Oct;29(6):726-76.
68. Vitamin D supplement in early childhood and risk for Type I (insulin-dependent) diabetes mellitus. The EURODIAB Substudy 2 Study Group. *Diabetologia.* 1999 Jan;42(1):51-4.
69. Littorin B, Blom P, Scholin A, et al. Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS). *Diabetologia.* 2006 Dec;49(12):2847-52.
70. Brown SJ. The role of vitamin D in multiple sclerosis. *Ann Pharmacother.* 2006 Jun;40(6):1158-61.
71. Amital H, Szekanecz Z, Szucs G, et al. Serum concentrations of 25-OH vitamin D in patients with systemic lupus erythematosus (SLE) are inversely related to disease activity: is it time to routinely supplement patients with SLE with vitamin D? *Ann Rheum Dis.* 2010 Jun;69(6):1155-7.
72. Andjelkovic Z, Vojinovic J, Pejnovic N, et al. Disease modifying and immunomodulatory effects of high dose 1 alpha (OH) D3 in rheumatoid arthritis patients. *Clin Exp Rheumatol.* 1999 Jul-Aug;17(4):453-6.
73. Bock G, Prietl B, Mader JK, et al. The effect of vitamin D supplementation on peripheral regulatory T cells and beta cell function in healthy humans: a randomized controlled trial. *Diabetes Metab Res Rev.* 2011 Nov;27(8):942-5.
74. Li X, Liao L, Yan X, et al. Protective effects of 1-alpha-hydroxyvitamin D3 on residual beta-cell function in patients with adult-onset latent autoimmune diabetes (LADA). *Diabetes Metab Res Rev.* 2009 Jul;25(5):411-6.
75. Cantorna MT, Zhao J, Yang L. Vitamin D, invariant natural killer T-cells and experimental autoimmune disease. *Proc Nutr Soc.* 2012 Feb;71(1):62-6.
76. Tokmak F, Quack I, Schieren G, et al. High-dose cholecalciferol to correct vitamin D deficiency in haemodialysis patients. *Nephrol Dial Transplant.* 2008 Dec;23(12):4016-20.
77. Maki KC, Rubin MR, Wong LG, McManus JF, Jensen CD, Lawless A. Effects of vitamin D supplementation on 25-hydroxyvitamin D, high-density lipoprotein cholesterol, and other cardiovascular disease risk markers in subjects with elevated waist circumference. *Int J Food Sci Nutr.* 2011 Jun;62(4):318-27.
78. Salzer J, Hallmans G, Nystrom M, Stenlund H, Wadell G, Sundstrom P. Vitamin D as a protective factor in multiple sclerosis. *Neurology.* 2012 Nov 20;79(21):2140-5.
79. Orgaz-Molina J, Buendia-Eisman A, Arrabal-Polo MA, Ruiz JC, Arias-Santiago S. Deficiency of serum concentration of 25-hydroxyvitamin D in psoriatic patients: a case-control study. *J Am Acad Dermatol.* 2012 Nov;67(5):931-8.
80. Song GG, Bae SC, Lee YH. Association between vitamin D intake and the risk of rheumatoid arthritis: a meta-analysis. *Clin Rheumatol.* 2012 Dec;31(12):1733-9.
81. Ginde AA, Mansbach JM, Camargo CA, Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med.* 2009 Feb 23;169(4):384-90.
82. Song Y, Wang L, Pittas AG, et al. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: A meta-analysis of prospective studies. *Diabetes Care.* 2013 May;36(5):1422-8.
83. Tsur A, Feldman BS, Feldhammer I, Hoshen MB, Leibowitz G, Balicer RD. Decreased serum concentrations of 25-hydroxycholecalciferol are associated with increased risk of progression to impaired fasting glucose and diabetes. *Diabetes Care.* 2013 May;36(5):1361-7.
84. Kojima G, Bell C, Abbott RD, et al. Low dietary vitamin D predicts 34-year incident stroke: the Honolulu Heart Program. *Stroke.* 2012 Aug;43(8):2163-7.

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References

1. *Curr Drug Targets*. 2011 Jan;12(1):4-18.
2. *J Investig Med*. 2011 Aug;59(6):872-80.