

Vitamin D: An Under-estimated Ally

Dr Nyjon K Eccles BSc MBBS MRCP PhD



A recent review of the medical literature about vitamin D highlighted some key summary points that I would like to begin this article with:

The enzyme to convert the precursor of vitamin D (1-alpha hydroxylase) is present in kidneys, skin, brain, breast, prostate, colon, vascular smooth muscle, macrophages, endothelium etc suggesting a more general role for vitamin D than maintaining bone health. Furthermore, Vitamin D receptors are found in virtually all tissues and cells. Compared to the 1970's nine times more target organs are recognised for vitamin D. Vitamin D Regulates a variety of genes and gene products. Its role in Programmed cell death suggests it may be required for maintenance of genetic stability. In many Countries there exists unrecognised inadequacy. The amount the skin can produce decreases linearly from age 20's (It will have decreased by 75% by age 70). Vitamin D level predicts performance in older people. Epidemiological studies suggest that it reduces incidence of diabetes, rheumatoid arthritis, multiple sclerosis, viral infection, auto-immune disease and cancer. It leads to a significant reduction in all cause mortality when supplemented. Its reported mechanisms of action include preventing DNA breaks, cell cycle control, decreased proliferation of normal and abnormal cells, encouraging cells to a more differentiated state, enhancing cell communication, being antiinflammatory, antioxidant and immuno-modulatory as well as anti-angiogenic (preventing new blood cell formation). Add to these that it has been found to reduce age-related macular degeneration, enhances production of endogenous antibiotics (defensins) and improves vascular muscle function, controls blood pressure, improves glucose tolerance and we are led to wonder why we are not all testing our blood levels and supplementing Vitamin D if necessary. Such a simple, cheap, natural substance could revolutionize the health of nations!

Vitamin D is one of the fat soluble vitamins (e.g. A, D, E, K). There are two main forms of the vitamin: D2 (ergocalciferol) and D3 (cholecalciferol). Ultraviolet B (UVB 315 nm–280 nm) rays in sunlight will increase D3 levels. A light-skinned person will synthesize 20,000 IU (international units) of vitamin D in 20 minutes sunbathing on a beach. White skin, with less melanin, synthesizes vitamin D in sunlight six times faster than dark skin. This has allowed lighter skinned people to migrate to higher latitudes, populate Europe, Asia, and North America, and be able to make enough vitamin D to survive.

The majority of the world's population now lives above latitude 35° N and is unable to synthesize vitamin D from sunlight for a period of time in winter owing to the angle of the sun.

Rickets, a softening and bending of bones in children, first described in 1651, is another nutritionally specific disease. It reached epidemic proportions following the industrial revolution, which began in the 1750s. In the 19th century, before the importance of exposing children to sunlight was recognized; it is due to vitamin D deficiency. The adult form is called Osteomalacia.

It has been mis-named a vitamin. Vitamin D acts as a steroid hormone. The body makes vitamin D from cholesterol through a process triggered by the action of the sun's ultraviolet B rays on the skin. Vitamin D3 is synthesized from 7-dehydrocholesterol in the skin. The vitamin D binding protein transports the vitamin D3 to the liver where it undergoes hydroxylation to 25(OH)D (the inactive form of vitamin D) and then to the kidneys where it is hydroxylated by the enzyme (Brannon et al, 2008) 1-hydroxylase to 1,25(OH)D, its active form (Brannon et al, 2008). This enzyme is also present in a variety of extra-renal sites, including osteoclasts, skin, colon, brain, and macrophages, which may be the cause of its broad-ranging effects. The half-life of vitamin D in the liver is approximately 3 weeks, which underscores the need for frequent replenishment of the body's supply.

The vitamin D hormone system controls the expression of more than 200 genes and the proteins they produce.

Fatty fish (catfish, salmon, mackerel, sardines, tuna), mushrooms, eggs and meat are rich in D, as well as foods specifically fortified with D. Vitamin D is essential for the proper absorption of calcium and phosphate; explaining vitamin D's critical role in bone health. However, no dietary source for "The Sunshine Vitamin" even comes close to vitamin D levels made naturally from ultraviolet light B exposure.

An estimated 1 billion people worldwide, across all ethnicities and age groups, have a vitamin D deficiency. This is mostly attributable to people getting less sun exposure because of climate, lifestyle, and concerns about skin cancer. The Dietary Reference Intake (DRI) values for vitamin D, established in 1997 were initially established to prevent rickets and osteomalacia, but are now considered too low to prevent chronic disease.

Subtle symptoms of milder deficiency include loss of appetite, diarrhoea, insomnia, vision problems, and a burning sensation in the mouth and throat.

What's important is that 77 percent of Americans, 97 percent of black Americans and 97 percent of Canadians are vitamin D deficient, according to government data. This includes people living in sunny climates and athletes who spend lots of time outside. The vitamin D research community now recommends vitamin D blood levels of 40-60 ng/ml.

Obesity is linked with lower levels of Vitamin D with an inverse correlation between levels and degree of overweight. A study suggests that people who are obese may be less able to convert vitamin D into its hormonally active form (Wortsman et al, 2000). There is a view that vitamin D deficiency may be a primary cause of obesity and that its decline in winter may be an adaptive response to increase fat as protection during the winter months (Foss, 2009).

As the body gets older, the skin loses its ability to convert sunshine into vitamin D. And there is evidence that children aren't getting enough of it. Infants generally aren't sunbathers, and breast milk alone won't provide sufficient levels.

Forty to 75% of the world's population is vitamin D deficient. Vitamin D deficiency puts one at risk for osteomalacia, rickets, falls, tuberculosis, psoriasis, multiple sclerosis, inflammatory bowel disease, type-1 diabetes, high blood pressure, increased heart failure, myopathy, breast and other cancers. It is projected that the incidence of many of these diseases could be reduced by 20% to 50% or more, if the occurrence of vitamin D deficiency and insufficiency were eradicated by increasing vitamin D intakes through increased UVB exposure, fortified foods or supplements.

The Endocrine Society recommends that everyone at risk be screened for vitamin D deficiency. Those especially at risk are infants and children (all ages), pregnant women, those who are over 65 and in community dwellings (without enough sunlight), darker skinned individuals and obese individuals. Their recommendations are for doses of 1,000 to 2,000 IU to achieve appropriate levels, with maximum levels of 10,000 IU per day.

It is recommended that everyone test their vitamin D serum level for a baseline measurement and adjust their intake to reach the desired serum level (See later on Testing).

Many physicians are responding to recent research linking a variety of disease states and general wellness to Vitamin D levels. Vitamin D deficiency (levels measured below 32 ng/ml) does not have obvious symptoms and can increase risk for diseases including flu, cardiovascular disease, osteoporosis and multiple sclerosis. In addition, an increased risk for strokes, diabetes (types 1 and 2), depression, and breast and colon cancer are closely linked to low Vitamin D levels.

The following pages devote some time to looking at the associations of vitamin D to a variety of common diseases.

Link to cancer risk

Both observational studies in humans and animal models support that vitamin D has a beneficial role in cancer prevention and survival. The mechanism of action is probably related to its role in the regulation of cell growth and differentiation. But other mechanism as alluded to above and again referenced below, are possible. (Osborne et al, 2002)

Vitamin D also stops the growth of new blood vessels, and has significant anti-inflammatory effects. In addition it activates genes responsible for programmed cell death (apoptosis). It is also able to activate cell differentiation (keeping cells regulated and well behaved). Any or all of these mechanisms could play a key role the reported cancer-suppressive activity of Vitamin D.

A recent meta-analysis of 63 observational studies looked at the relationship between vitamin D levels and cancer incidence and mortality (Garland et al, 2006). Twenty of the 30 studies looking at vitamin D and colon cancer showed that people with higher vitamin D levels had either a lower incidence of colon cancer or decreased mortality. Similarly, 9 of the 13 studies about breast cancer and 13 of the 26 studies about prostate cancer showed beneficial effects of vitamin D levels on cancer incidence or mortality (some of the studies included more than one type of cancer) (Garland et al, 2006).

A population-based randomized, control trial found that postmenopausal women who were supplemented with calcium and vitamin D had a reduced risk of cancer after the first year of treatment (rate ratio, 0.232; 95% CI, 0.09–0.60).²⁷ There was not a group that was supplemented with vitamin D alone (Lappe et al, 2007).

Colon Cancer

In 18 studies that included more than 10,000 people, colon cancer risk was as much as 33 percent lower in subjects with the highest blood levels of vitamin D compared to those with the lowest levels, researchers report in the *Journal of Clinical Oncology*.

Colon cancer rates are 4 to 6 times higher in North America and Europe, where solar radiation is less intense, particularly during the winter months, compared to the incidence of colon cancer near the equator.

Evidence suggests that to achieve a benefit people may need more than current recommended daily requirements.

Melanoma.

Vitamin D supplementation in modest doses of 400IU a day cut risk by 50% in postmenopausal women. Who had previously had non-melanomatous skin cancers. (Tang et al, June 27 online edition of the *Journal of Clinical Oncology*, 2011).

Breast Cancer.

Breast cancer is more common in women with low vitamin D levels. Low levels of vitamin D were found to be highly indicative of the presence of biological markers typically associated with more aggressive tumors. African-American women and premenopausal women were more likely to have suboptimal vitamin D levels than older, white women (Peppone et al, 2011).

Evidence from a randomized, placebo-controlled, double-blind trial demonstrated vitamin D's ability to prevent breast cancer. A Creighton University study showed that women over age 55 who took a 1,100 IU/day vitamin D supplement, with calcium, and were followed for 4 years had a highly statistically significant ($P < 0.005$) 75% reduction in breast cancer (diagnosed after the first 12 months) compared with women who took a placebo (*Am J Clin Nutr* 2007;85:1568–1591).

In another study on breast cancer, Dr Cedric Garland, professor of family and preventive medicine at the University of California, said: "We found that daily intakes of vitamin D by adults in the range of 4,000-8,000 IU are needed to maintain blood levels of vitamin D metabolites in the range needed to reduce by about half the risk of several diseases [including] breast cancer." He made the bold statement that :**Breast cancer can be virtually "eradicated" by raising vitamin D levels.**

According to research from the newly published study by Cedric F. Garland, Moores Cancer Center of the University of California, San Diego (UCSD), "It is projected that raising the minimum year-around serum 25(OH)D level to 40-60 ng/ml (100-150 nmol/L) would prevent approximately 58,000 new cases of breast cancer and 49,000 new cases of colorectal cancer each year, and three quarters of deaths from these diseases, in the US and Canada." Garland and his colleagues have published epidemiological studies about the potential preventive effects of vitamin D for two decades. As early as 1990, his team showed an association between deficiency in sunlight exposure, low vitamin D and breast cancer. In previous work, they showed associations between increased levels of vitamin D₃ or markers of vitamin D and lower risk for breast, colon, ovarian and kidney cancers

A series of studies on Vitamin D and cancer were published in *Annals of Epidemiology*, Volume 19 2009 (Veith; Mohr; Bertone-Johnson; Garland et al, see references)

Based on observational studies, it is estimated that 1500 and 3600 International Units (IU) of vitamin D₃ are required daily for a 50% reduction in risk of colorectal and breast cancer, respectively (Garland et al, 2007). A recent randomized, double-blind, placebo-controlled clinical trial that studied postmenopausal women in Nebraska found a 77% reduction in all-cancer incidence between the ends of the first and fourth years (Lappe et al. 2007) adding strong support to the observational studies.

Autoimmune Disease

Several studies have shown that vitamin D affects the growth and differentiation of immune modulator cells such as macrophages, dendritic cells, T cells, and B cells (Holick, 2004; Adorni & Penna, 2008; Szodoray, 2008). This immune-modulatory effect has implications for a variety of autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, type I DM, inflammatory bowel disease, and MS (Adorni & Penna, 2008).

Vitamin D3 receptors have strong immune-modulating effects. There is now biologic evidence to back up the belief that vitamin D may protect against autoimmune diseases.

Vitamin D receptor binding has been demonstrated to gene regions previously identified with different diseases, they found evidence of increased binding for multiple sclerosis, Crohn's disease, lupus, rheumatoid arthritis, colorectal cancer, and chronic lymphocytic leukemia (CLL). The conclusion: Genes involved in autoimmune disease and cancer were regulated by vitamin D,

Heart Disease

Several studies are providing evidence that the protective effect of vitamin D on the heart could be mediated by the renin-angiotensin hormone system, through the suppression of inflammation, or directly on the cells of the heart and blood-vessel walls. In the Framingham Heart Study, patients with low vitamin D concentrations (<15 ng/mL) had a 60% higher risk of heart disease than those with higher concentrations. The Health Professional Follow Up Study (HPFS) found that subjects with low vitamin D concentrations (<15 ng/mL) were two times more likely to have a heart attack than those with high concentrations (>30 ng/mL). In another study, which followed men and women for 4 years, patients with low vitamin D concentrations (<15 ng/mL) were three times more likely to be diagnosed with hypertension than those with high concentrations (>30 ng/mL).

Observational studies have shown a relationship between low vitamin D levels and blood pressure, coronary artery calcification, and existing cardiovascular disease (Wang et al, 2008).

Multiple Sclerosis (MS)

MS is an autoimmune disease, where the body's immune system attacks and destroys its own cells. With multiple sclerosis, T cells in the adaptive immune system, Th1 cells (CD4 T helper type 1 cells), attack the myelin sheath (insulation) of the nerve fibers. Vitamin D regulates and tones down the potentially self-destructive actions of Th1 cells. These cells make their own 1,25-dihydroxyvitamin D if there is a sufficient amount of vitamin D (25-hydroxyvitamin D) circulating in the blood. Researchers have shown that the risk of MS decreases as the level of vitamin D in the blood increases (*JAMA* 2006;296:2832–2838).

The development of MS correlates most strongly with rising latitude in both the northern and southern hemispheres (Ebers, 2008). Migration studies show that risk can be modified at an early age from both low to high and high to low prevalence rates.²⁸ Exposure to sun in early childhood is associated with reduced risk of developing MS (Kampman et al, 2007)

Low serum vitamin D at the time of a first demyelinating event increases the risk of subsequent MS in children.. By placing deficiency so close to onset, strengthens the argument that vitamin deficiency plays a causal role in MS. The study was presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting. There was also a dose response. Those in the highest quartile, above 81 nmol/L, had one quarter of the risk of subsequent MS outcome, The study calculated that an increase of 10 nmol/L, for instance, would amount to a 20% risk reduction (Ponsonby et al, 2011).

Several other studies have supported the finding that lower levels of vitamin D in MS patients are associated with more severe disability (van der Mei et al, 2007). Lower levels during relapses have also been reported in patients with relapse-remitting MS (Soilu-Hänninen et al, 2005; Smolders et al 2008; Brown, 2006)

One small safety study of 12 patients taking 1000 micrograms (1 milligram) per day (40,000 IU) of vitamin D for 28 weeks showed a decline in the number of gadolinium-enhancing lesions on magnetic resonance imaging per patient; this led to a 25(OH)D serum concentration of 386 nmol/L (158 ng/mL) without causing hypercalcemia, hypercalciuria, or other complication (Kimball et al, 2007).

A study published by Joshi & Christakos, and colleagues at UMDNJ-New Jersey Medical School and Stanford in the journal *Molecular and Cellular Biology* appears to have uncovered the mechanism by which vitamin D helps MS; by directly terminating the production of a disease-causing protein.

Parkinsons Disease & Alzheimers

Having low vitamin D levels may increase a person's risk of developing Parkinson's disease later in life, say Finnish researchers. Their study of 3,000 people, published in *Archives of Neurology*, found people with the lowest levels of vitamin D had a three-fold higher risk.

Low levels of Vitamin D are associated with Alzheimers disease and compromised mental function (Buell & Dawson-Hughes, 2008; Oudshoorn et al, 2008)

Fractures and Falls and Osteoporosis

Vitamin D is known to help the body absorb calcium, and it plays a role in bone health. A low vitamin D level is an established risk factor for osteoporosis. Inadequate serum vitamin D levels will decrease the active transcellular absorption of calcium.

It seems that the concurrent intake of Vitamin D with calcium may be necessary for bone remineralisation ((Kulie et al, 2009).

A combined analysis of 12 fracture-prevention trials found that supplementation with about 800 IU of vitamin D per day reduced hip and non-spinal fractures by about 20%, whereas supplementation with about 400 IU per day showed no benefit. Researchers have examined the best trials of vitamin D versus placebo for falls with a conclusion that "fall risk reduction begins at 700 IU and increases progressively with higher doses." Overall, the evidence is strong in support of supplementing with vitamin D to prevent fractures and falls.

Also, vitamin D receptors are located on the fast-twitch muscle fibres, which are the first to respond in a fall. It is theorized that vitamin D may increase muscle strength, thereby preventing falls.

Muscle injury in sportsmen

In a study of 80 American football players (mean age 25) 80% were found to be Vit D deficient. Those who had muscle injuries tended to have lower levels of Vit D. Black players tended to have lower Vit D levels than white players (Shindle & Lattermann, 2011).

Recent studies have even suggested that higher levels of D can benefit athletes – improving fasttwitch muscle strength and power, reducing inflammation and the chance of stress fractures, and boosting the body's ability to fight off colds and the flue during training.

Improved Lung Function

A Belgian study showed that high doses of vitamin D supplementation on top of a standard rehabilitation program improved the outcome in terms of exercise capacity and respiratory muscle strength. Patients in the vitamin D group were given 100,000 IUs (international units) of vitamin D as their monthly dose.

Infection

Oregon State University scientists found vitamin D induces cathelicidin, an anti-microbial peptide gene that helps serve as the first line of defense in the immune response against minor wounds, cuts, and both bacterial and viral infections. this mechanism is partly responsible for vitamin D's capacity to function as one's primary immune response (Gombart, 2009). Vitamin D-expressed genes instruct macrophages, the front-line defenders in the innate immune system, to make antimicrobial peptides, which are like antibiotics (*Science* 2006;311:1770–1773).

In a Japanese randomized, controlled trial, children given a daily vitamin D supplement of 1,200 IU had a 40% lower rate of Influenza Type A compared with those given placebo; there was no significant difference in rates of influenza type B.

A six-fold lowered risk of respiratory syncytial virus (RSV) in infants al (Belderbos et al, 2011)

Depression

A Norwegian trial of overweight subjects showed that those receiving a high dose of vitamin D (20,000 or 40,000 IU weekly) had a significant improvement in depressive symptom scale scores after 1 year versus those receiving placebo (*J Intern Med.* 2008 Dec;264(6):599-609. Epub 2008 Sep 10).

In another study published in the Archives of General Psychiatry in 2008, researchers in the Netherlands studied over 1200 patients age 65 and above. In this study they found that vitamin D levels were 14% lower in the 169 patients with minor depression and 14% lower in the 26 patients with major depression, compared with over 1000 control patients. These findings held up after many other factors including body mass index, smoking status, chronic disease status, age, level of physical activity etc, were controlled for.

The authors of this study came to the conclusion that "the results of this large population-based study show an association of depression status and severity with decreased serum vitamin D levels... in older individuals." (Witte et al, 2008)

A study conducted by researchers at the University of Bristol, analyzed vitamin D levels in more than 2,700 children who were age nine, and followed them up at age 13. Researchers found that children who had the lowest vitamin D levels were more likely to experience symptoms of depression. The children with higher levels of vitamin D were 10 percent less likely to have depression. These children also showed a decrease in symptoms of depression as they became teenagers Tolppanen et al, 2012).

Infant Health

In addition to rickets and the risk of developing type I diabetes, other paediatric and adult health conditions may be impacted by insufficient vitamin D levels in infants and their mothers. This is discussed more fully and referenced elsewhere (Paediatr Child Health 2007).

Anti-Inflammatory

In patients not on dialysis, low vitamin D levels are associated with increased levels of inflammation and oxidative load. It is known to regulate inflammatory cytokines.

Diabetes

An association between low vitamin D and Type 1 and 2 diabetes is well recognised (Kulie et al, 2009).

Allergies

Allergies are more likely to affect children with low vitamin D levels. (Sharief et al, 2011)

All-cause mortality

A recent meta-analysis demonstrated that intake of a vitamin D supplement at normal doses also was associated with decreased all-cause mortality rates.(Autier & Gandini, 2007)

Blood Levels and Supplement Dosage

Experts say that adequate levels of vitamin D would be achieved by 15 minutes of unfiltered sun two to three times weekly, depending on your skin type and the time of day. Arms and legs should be exposed, whilst still protecting the face.

The Endocrine Society and the International Osteoporosis Foundation, note that 30 ng/ml is necessary for optimal bone health.

Current recommended daily vitamin D intake of 200 IU (international units) for those up to age 50; 400 IU for people 51 to 70; and 600 IU for those over 70 are now deemed by most experts to be too low. Many experts say 2,000 IU of the vitamin may be optimal for preventing disease. Anthony W.

Norman, a professor of biochemistry and biomedical sciences at the University of California, Riverside, who has been studying vitamin D for five decades. He recommends 2,000 to 4,000 IUs per day and says doctors are behind the times on research.

The two forms of vitamin D used in supplements are D2 (ergocalciferol) and D3 (cholecalciferol). D3 is the preferred form, as it is chemically similar to the form of vitamin D produced by the body and is more effective than D2 at raising the blood concentration of vitamin D (D3 (cholecalciferol), the kind our skin makes, and vitamin D2 (ergocalciferol), a synthetic variant made by irradiating plants. Vitamin D2 is only 10–30% as effective in raising 25-hydroxyvitamin D blood levels compared to vitamin D3).

Without sun exposure, to reach a level of 50 ng/ml requires a 5,000 IU/day vitamin D supplement. Vitamin D3 should be the choice for oral supplementation of Vitamin D.

Some feel that Vitamin D intoxication can occur when serum levels are greater than 150 ng/mL. Symptoms of hypervitaminosis D include fatigue, nausea, vomiting, and weakness probably caused by the resultant hypocalcaemia.

It is good practice if regular supplements are being taken on a longterm basis to consider keeping a check on blood levels. Fortunately, there is now a simple way of doing this using a home-kit based blood test (see below).

Vitamin D Testing Made Simple

If electing to test vitamin D status, serum 25-hydroxyvitamin D is the accepted biomarker. Although 1,25-OH-D is the active circulating form of vitamin D, measuring this level is not helpful because it is quickly and tightly regulated by the kidney. Actual values of 25-OH-D that determine vitamin D insufficiency in children have not been defined. The 20 ng/mL of 25-OH-D that determines a sufficient vitamin D level for adults has been used for children (Wagner et al, 2008).

Please contact The Natural Doctor to access your home kit for Vitamin D3 testing.

Both D₂ and D₃ can now be tested in dried blood spots. A few drops of blood from a quick and nearly painless nick of the finger are placed on a filter paper to dry. This can be performed easily either at a health practitioner's office or the convenience of home.

D-FICIENCY SCALE:

0-20 –deficient

20-30 – low

30-100 sufficient

40-60 – optimal

*Supplementing with 1,200 IU of Vitamin D daily. It takes about 1.000 IU to raise blood levels by 10 units.

Conclusion

Research suggesting a protective role for vitamin D against non-bone-related disease “compelling” even if it is not conclusive. Leading vitamin D experts have stated. "We won't know the true burden of chronic disease until we eradicate vitamin D deficiency."

As the number of positive effects of vitamin D on the body, as highlighted above, continue to be uncovered, the weight of circumstantial evidence would certainly support checking one's own levels particularly if sun exposure is not an option because of where you live.

It is possible that there have not been more clinical trials of vitamin D supplementation clinical trials since there is little income in selling vitamin D3 (a year's supply of 1500 IU/day is inexpensive), and such trials are expensive.

The guidelines between for intakes of Vitamin D in the range 400-800IU are directed towards maintaining bone health and are sufficient to prevent rickets and osteomalacia – but not cancer, cardiovascular disease, multiple sclerosis, or influenza. Without evidence to support it, the US Food and Nutrition Board arbitrarily set the safe upper limit for vitamin D consumption at 2,000 IU/day. 10,000 IU vitamin D supplement every day, month after month safely, with no evidence of adverse effect. (*Am J Clin Nutr* 1999;69:842–856). Vitamin D in dose (5,000 IU/day) prevents the build up of calcium in blood vessels. (*Circulation* 1997;96:1755–1760).

The cost of taking a 5,000 IU supplement of vitamin D every day for a year is cheap. Not taking it may turn out to be far more expensive!

For more information or to book an appointment, please don't hesitate to contact us:

THE NATURAL DOCTOR

69 Harley Street

London W1G 8QW

0207 2244 622

www.thenaturaldoctor.org

info@thenaturaldoctor.org

References

- Adorini L, Penna G. Control of autoimmune diseases by the vitamin D endocrine system. *Nat Clin Pract Rheumatol* 2008;4:404–12.
- Autier P, Gandini S. Vitamin D supplementation and total mortality. *Arch Intern Med* 2007;167:1730–7.
- Belderbos, et al. Cord Blood Vitamin D Deficiency is Associated With Respiratory Syncytial Virus Bronchiolitis. *Pediatrics* Vol. 127 No. 6 June 1, 2011 pp.1513 -1520
- Bertone-Johnson ER. Vitamin D and Breast Cancer *Annals of Epidemiology* Volume 19, Issue 7 , Pages 462-467, July 2009
- Brannon PM, Yetley EA, Bailey RL, Picciano MF. Overview of the conference “Vitamin D and Health in the 21st Century: an Update”. *Am J Clin Nutr* 2008;88(Suppl):483S–90S.
- Brown SJ. The role of vitamin D in multiple sclerosis. *Ann Pharmacother* 2006;40:1158–61.
- Buell JS, Dawson-Hughes B. Vitamin D and neurocognitive dysfunction: preventing “D”ecline? *Mol Aspects Med* 2008;29:415–22.
- Ebers GC. Environmental factors and multiple sclerosis. *Lancet Neurol* 2008;7:268 –77.
- Foss YJ. *Med Hypotheses*. 2009 Mar;72(3):314-21. Epub 2008 Dec 2. Vitamin D deficiency is the cause of common obesity.
- Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention. *Am J Public Health* 2006;96:252– 61.
- Garland, F, Gorham ED, . Mohr Sharif B, Garland FC. Vitamin D for Cancer Prevention: Global Perspective. *Annals of Epidemiology* Volume 19, Issue 7 , Pages 468-483, July 2009
- Garland CF, Grant WB, Mohr SB, Gorham ED, Garland FC. 2007. What is the dose-response relationship between vitamin D and cancer risk? *Nutr Rev*. 65(8 Pt 2):S91-5.
- Gombart AF. “The vitamin D–antimicrobial peptide pathway and its role in protection against infection.” *Future Microbiology*, November 2009, Vol. 4, No. 9, Pages 1151-1165.
- Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* 2004;80(6Suppl):1678S– 88S.
- Kampman MT, Wilsgaard T, Mellgren SI. Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. *J Neurol* 2007;254:471–7.
- Kimball SM, Ursell MR, O’Connor P, Vieth R. Safety of vitamin D3 in adults with multiple sclerosis. *Am J Clin Nutr* 2007;86:645–51.
- Kulie T, , Amy Groff, DO, Jackie Redmer, MD, MPH, Jennie Hounshell, MD, and Sarina Schragar, MD, MS. Vitamin D: An Evidence-Based Review. *J Am Board Fam Med* 2009;22:698–706
- Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007;85:1586 –91.
- Mohr SB. A Brief History of Vitamin D and Cancer Prevention *Annals of Epidemiology* Volume 19, Issue 2 , Pages 79-83, February 2009

Osborne JE, Hutchinson PE. Vitamin D and systemic cancer: is this relevant to malignant melanoma? *Br J Dermatol* 2002;147:197–213.

Oudshoorn C, Mattace-Raso FU, van der Velde N, Colin EM, van der Cammen TJ. Higher serum vitamin D3 levels are associated with better cognitive test performance in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord* 2008;25:539–43.

Peppone LJ, Huston AJ, Reid ME, Rosier RN, Zakharia Y, Trump DL, Mustian KM, Janelsins MC, Purnell JQ, Morrow GR. The effect of various vitamin D supplementation regimens in breast cancer patients. *Breast Cancer Res Treat*. 2011 May;127(1):171-7. Epub 2011 Mar 8.

Ponsonby AL, Ann Maree Hughes¹ & Robyn Marjorie Lucas: The 'hygiene hypothesis' and the development of multiple sclerosis *Neurodegenerative Disease Management*. August 2011, Vol. 1, No. 4, Pages 285-294

Sharief S et al. 2011. Vitamin D levels and food and environmental allergies in the United States: Results from the National Health and Nutrition Examination Survey 2005-2006. *Journal of Allergy and Clinical Immunology*, 2011; DOI: 10.1016/j.jaci.2011.01.017

Shindle & Lattermann. *American Orthopaedic Society for Sports Medicine (AOSSM) 2011 Annual Meeting: Abstract 46. Presented July 10, 2011.*

Soilu-Haˆnninen M, Airas L, Mononen I, Heikkilˆ A, Viljanen M, Haˆnninen A. 25-Hydroxyvitamin D levels in serum at the onset of multiple sclerosis. *Mult Scler* 2005;11:266 –71.

Smolders J, Menheere P, Kessels A, Damoiseaux J, Hupperts R. Association of vitamin D metabolite levels with relapse rate and disability in multiple sclerosis. *Mult Scler* 2008;14:1220–4.

Szodoray P, Nakken B, Gaal J, et al. The complex role of vitamin D in autoimmune diseases. *Scand J Immunol* 2008;68:261–9.

Tolppanen AM, Adrian Sayers, William D. Fraser, Glyn Lewis, Stanley Zammit and Debbie A. Lawlor, *The association of serum 25-hydroxyvitamin D3 and D2 with depressive symptoms in childhood – a prospective cohort study* has just been published online in the *Journal of Child Psychology and Psychiatry*, Volume 53, Issue 1, January 2012. DOI : 10.1111/j.14697610.2011.02518.x.

van der Mei IAF, Ponsonby A, Dwyer T, et al. Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. *J Neurol* 2007;254:581–90.

Vieth R. Vitamin D and Cancer Mini-Symposium: The Risk of Additional Vitamin D. *Annals of Epidemiology* Volume 19, Issue 7 , Pages 441-445, July 2009

Vitamin D supplementation: recommendations for Canadian mothers and infants. *Paediatr Child Health* 2007;12:583–9.

Wagner CL, Greer FR, American Academy of Pediatrics Section on Breastfeeding, American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 2008;122:1142–52.

Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008;117:503–11.

Witte J. G. Hoogendijk, MD, PhD; Paul Lips, MD, PhD; Miranda G. Dik, PhD; Dorly J. H. Deeg, PhD; Aartjan T. F. Beekman, MD, PhD; Brenda W. J. H. Penninx, PhD. Depression Is Associated With Decreased 25-Hydroxyvitamin D and Increased Parathyroid Hormone Levels in Older Adults. *Arch Gen Psychiatry*. 2008;65(5):508-512.

Wortsman J, Matsuoka LY, Chen TC, Lu Z, and Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000;72:690–3.