

Vitamin D and Mental Illness

Abstract

We propose vitamin D plays a role in mental illness based on the following five reasons:

1. Epidemiological evidence shows an association between reduced sun exposure and mental illness.
2. Mental illness is associated with low 25-hydroxyvitamin D (25(OH)D) levels.
3. Mental illness shows a significant comorbidity with illnesses thought to be associated with vitamin D deficiency.
4. Theoretical models (*in vitro* or animal evidence) exist to explain how vitamin D deficiency may play a causative role in mental illness.
5. Studies indicate vitamin D improves mental illness.

First, we review recent evidence concerning the hitherto unexpectedly high human requirements for vitamin D. Then, we briefly review the physiology, toxicology, and evidence for widespread vitamin D deficiency.

After that we review epidemiological evidence that mental illness has increased as humans have migrated out of the sun followed by additional epidemiological evidence that associates vitamin D with mental illness. Studies associating season of birth with mental illness are briefly reviewed. Two small reports studied the association of low 25(OH)D levels with mental illness and both were positive.

[Depression](#) has significant co-morbidity with illnesses associated with hypovitaminosis D such as osteoporosis, diabetes, heart disease, hypertension, multiple sclerosis, and rheumatoid arthritis. Schizophrenia is associated with [cardiac disease](#), [diabetes](#) (before the introduction of the atypical antipsychotics), [osteoporosis](#) and [hypertension](#)—but not multiple sclerosis.

Vitamin D has a significant biochemistry in the brain. Nuclear receptors for vitamin D exist in the brain and vitamin D is involved in the biosynthesis of neurotrophic factors, synthesis of nitric oxide synthase, and increased glutathione levels—all suggesting an important role for vitamin D in brain function. Animal data indicates that tyrosine hydroxylase, the rate-limiting enzyme for all the brain's monoamines, is increased by vitamin D. Rats born to severely vitamin D deficient dams have profound brain abnormalities.

We found only three small studies in which vitamin D was given to improve mood, but two found a positive effect. The negative study used homeopathic doses (low doses) of vitamin D2 ergocalciferol.

Finally we briefly review toxicity and suggest treatment. Fear of [vitamin D toxicity](#) is unwarranted but rampant in the medical profession. Because vitamin D deficiencies are

so widespread in the western world, psychiatrists should suspect the deficiency—especially in [blacks](#), the aged, and those who avoid the sun. Serum 25(OH)D levels should be obtained when deficiency is suspected. Judicial exposure to sunlight, oral vitamin D, or both, aimed at restoring circulating levels of 25(OH)D between 35–55 ng/mL, is the treatment of choice for [vitamin D deficiency](#) in mentally ill patients. Cholecalciferol is the preferred oral preparation of vitamin D.

Human Requirements For Vitamin D

For otherwise healthy persons, the FNB reports adequate intake (AI) for vitamin D is 200, 400, or 600 IU a day, depending on your age. [Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride](#) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine Heaney, *et al*, writing in the American Journal of Clinical Nutrition in 2003 said: "The recommendations of the Food and Nutrition Board with respect to oral vitamin D input fall into a curious zone between irrelevance and inadequacy. For those persons with extensive solar exposure, the recommended inputs add little to their usual daily production, and for those with no exposure, the recommended doses are insufficient to ensure desired 25(OH)D concentration." [Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr. 2003;77:204–10](#)

It now appears that physiological human [requirements](#) for vitamin D (from all sources) are approximately ten times higher the current AI listed by the 1997 Food and Nutrition Board (FNB). [Vieth R Vitamin D supplementation, 25-hydroxyvitamin D concentration, and safety. Am J Clin Nutr. 1999;69:842–56](#) [Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr. 2003;77:204–10](#) [Zittermann A Vitamin D in preventive medicine: are we ignoring the evidence? Br J of Nutr. 2003;89:552–572](#) [Holick M Vitamin D: A millennium Perspective. J Cell Biochem. 2003;88:296–307 \(2003\)](#)

An AI is a crude estimate of the amount the FNB thought necessary to prevent vitamin D deficient diseases such as osteomalacia (softening of the bones) and rickets in 95% of the at-risk population. It is not a recommended intake. The FNB also reports that the upper limit (UL) of vitamin D is 2,000 IU/day. The FNB defines UL as, the highest daily level of chronic nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. [Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride](#). Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine Thus the definition of UL implies some risk to vulnerable members of the population who exceed the UL.

The problem with the FNB's recommendation is that most of us greatly exceed the UL of vitamin D by simply spending a few minutes outside in our bathing suits. [Holick MF Environmental factors that influence the cutaneous production of vitamin D. Am](#)

[J Clin Nutr. 1995 Mar; 61\(3 Suppl\):638S–645S](#) The authors could find nothing in the medical literature that contradicts Holick's 1995 demonstration that a brief dose of noontime summer sun is comparable to taking between 10,000–25,000 IU of vitamin D. Four earlier papers all found similar amounts of natural vitamin D production. Adam, *et al* found that up to 50,000 IU of vitamin D was released into the circulation of Caucasians after 30 minutes of noontime summer sun. [Adams JS, Clemens TL, Parrish JA, Holick MF Vitamin D synthesis and metabolism after ultraviolet irradiation of normal and vitamin D deficient subjects. N Engl J Med 1982, Mar 25;306\(12\):722–5](#) Three additional studies support the fact that at least 8,000–10,000 IU/day are routinely made in human skin following brief exposure to UVB. [Stamp TC Factors in human vitamin D nutrition and in the production and cure of classical rickets. Proc Nutr Soc 1975 Sep;34\(2\):119–30. Davie MW, Lawson DE, Emberson C, Barnes JL, Roberts GE, Barnes ND Vitamin D from skin: contribution to vitamin D status compared with oral vitamin D in normal and anticonvulsant-treated subjects. Clin Sci \(Lond\) 1982. Chel VG, Ooms ME, Popp-Snijders C, Pavel S, Schothorst AA, Meulemans CC, Lips P Ultraviolet irradiation corrects vitamin D deficiency and suppresses secondary hyperparathyroidism in the elderly. J Bone Miner Res 1998.](#)

Physiological Amounts

Holick now believes that a full body minimal erythema dose of summer sunlight at noontime produces 20,000 IU of vitamin D. [Holick M Personal communication. August, 2003.](#) The high amount of natural human production of vitamin D is the single most important fact every physician should know about vitamin D because it has such profound implications for the natural human condition. Furthermore, there has never been a reported case of vitamin D intoxication due to excessive sun-exposure such as lifeguards, sun-worshippers, etc. The reason is that once the skin makes enough vitamin D, the sun destroys the excess.

These amounts are, by definition, physiological. The skin makes them after relatively brief period in the sun, at least in Caucasians, in the summer, at temperate latitudes and as long as clothes, glass, or sunblock do not cover the skin. It is important to note that blacks need five to ten times longer in the sun than do whites to achieve similar vitamin D production.

Such seemingly high rate of vitamin D production leads us to, an overwhelming question . . . Why did nature do this? [T.S. Eliot The Love Song of J. Alfred Prufrock. Prufrock and Other Observations. London: The Egoist, Ltd, 1917.](#)

A Prehormone

Although vitamin D is technically a vitamin, according to Stedman's Medical Dictionary definition of the word, significant amounts of vitamin D are not found in the foods humans naturally consume. A hundred years ago, after we were steadily migrating out of the sun and into buildings, cars, and layers of sun block, Northern Europeans realized that adding a teaspoon of fish oil to infants' diets helped them thrive. How did we decide how

much to add? We guessed based on animal models of rickets. Correctly, it turned out, to prevent rickets in children, but since the same dose was applied to adults, the adult dose was off by a factor of ten. This mistake continues to this day. [Vieth RVitamin D supplementation, 25-hydroxyvitamin D concentration, and safety.Am J Clin Nutr. 1999;69:842–56.](#)

Cholecalciferol, the naturally occurring form of vitamin D, is a prohormone made in the skin by the action of sunlight on 7-dehydrocholesterol also known as provitamin D₃. As this is meant to be a clinical paper, we will not detail the physiology and biochemistry of vitamin D. For excellent clinical reviews that give more details of [vitamin D physiology](#), see Holick, [Holick MVitamin D: A millennium Perspective.J Cell Biochem. 2003;88:296–307 \(2003\).](#) Zittermann, [Zittermann AVitamin D in preventive medicine: are we ignoring the evidence?Br J of Nutr. 2003;89:552–572.](#) and Vieth. [Vieth RVitamin D supplementation, 25-hydroxyvitamin D concentration, and safety.Am J Clin Nutr. 1999;69:842–56.](#)

For our purposes, suffice it to say that nature designed a system in which humans go in the sun, make thousands of units of cholecalciferol which the liver then hydroxylates into 25-hydroxyvitamin D, or 25(OH)D. Our organs then make a steroid hormone, 1,25-hydroxyvitamin D, which has both endocrine and paracrine functions. Although the endocrine function of 1,25(OH)2D₃ made in the kidney is well known, the paracrine function is a relatively new discovery and appears to occur in every organ in the body. [Holick MVitamin D; A millennium Perspective.J Cell Biochem. 2003;88:296–307 \(2003\).](#)

1,25(OH)2D₃ helps regulate gene expression in more than thirty tissues and the list keeps growing. More succinctly, humans have a vitamin D system which makes thousands of units of the prohormone 25(OH)D within hours of sun exposure so various organs can then make the steroid hormone 1,25(OH)2D₃ to help regulate genes, apparently in every organ in the body. [Holick MVitamin D; A millennium Perspective.J Cell Biochem. 2003;88:296–307 \(2003\).](#) We assume nature created this system for a good reason.

3,000–5,000 IU Per Day

Support for the growing realization that humans need a minimum of 3,000 IU of vitamin D a day (from all sources, diet, sun and supplements) includes:

- Recent studies by Heaney, *et al* conclude healthy men utilize between 3,000–5,000 IU of cholecalciferol a day, mostly from stores made by the summer sun. [Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJHuman serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol.Am J Clin Nutr. 2003;77:204–10.](#)
- Humans living near the equator, where we evolved, have mean serum 25(OH)D levels of more than 40 ng/mL, levels requiring solar input of about 4,000 IU of vitamin D a day. [Linhares E, Jones D, Round J, Edwards RHEffect of nutrition on vitamin D status: studies on healthy and poorly nourished children.Am J](#)

- [Clin Nutr. 1984;39\(4\):625–630.](#) American lifeguards, working in swimsuits, have even higher 25(OH)D levels, at 64 ng/mL, in spite of temperate latitudes. [Holmes R, Kummerow F](#) **[The relationship of adequate and excessive intake of vitamin D to health and disease.](#)** [J Amer Coll Nutr. 1983;2:173–199.](#)
- In 2003, Gomez recently produced evidence that excessive secretion of the parathyroid gland, known as secondary hyperparathyroidism, is almost nonexistent when 25(OH)D levels exceed 30 ng/mL (requiring 3,000 IU/day). [Gomez Alonso C, Naves Diaz M, Rodriguez Garcia M, Fernandez Martin JL, Cannata Andia JB, Gomez A, et al.](#) **[Review of the Concept of sufficiency and insufficiency of Vitamin D.](#)** [Nefrologia. 2003;23 Suppl 2:73–7.](#) Vieth cited six studies that concluded, if the aim is to keep parathyroid hormone concentrations low, 25(OH)D levels should exceed 28 ng/mL (70 nmol/L). [Vieth R, Chan PC, MacFarlane G](#) **[Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level.](#)** [Am J Clin Nutr 2001 Feb;73\(2\):288–94.](#)
 - Heaney and his colleagues recently showed that calcium absorption increases as 25(OH)D blood levels increase. [Heaney RP, Dowell MS, Hale CA, Bendich A](#) **[Calcium Absorption Varies within the Reference Range for Serum 25-Hydroxyvitamin D.](#)** [J Am Coll Nutr. 2003 Apr;22\(2\):142–6.](#) With blood levels of 34 ng/mL (equivalent to about 3,000 IU/day total intake), calcium absorption was 65% higher than when levels are 20 ng/mL. This implies that part of the reason humans need to take so much extra calcium is because there is widespread deficiency of vitamin D. when speaking of 25(OH)D blood levels, the authors were blunt, "We conclude that the lower end of the current reference range is set too low."
 - Blood pressure is reduced significantly by ultraviolet radiation comparable to about oral intake of 3,000 IU of vitamin D a day [Krause R, Bohring M, Hopfenmüller W, Holick MF, Sharma AM](#) **[Ultraviolet B and blood pressure.](#)** [Lancet. 1998;352:709–710.](#) but blood pressure is not routinely reduced by small amounts of vitamin D. [Scragg R, Khaw KT, Murphy S](#) **[Effect of winter oral vitamin D3 supplementation on cardiovascular risk factors in elderly adults.](#)** [European Journal of Clinical Nutrition. 1995;49:640–646.](#)
 - Daily doses of 2,500 IU of vitamin D helped rheumatoid arthritis [Brohult J, Jonson B](#) **[Effects of large doses of calciferol on patients with rheumatoid arthritis.](#)** [Scandinavian Journal of Rheumatology. 1973;2:173–176.](#) but small amounts did not. [Zittermann A](#) **[Vitamin D in preventive medicine: are we ignoring the evidence?](#)** [Br J of Nutr. 2003;89:552–572.](#)
 - Infants receiving 2,000 IU a vitamin D a day were almost fully protected (relative risk 0.12) from developing type 1 diabetes 30 years later. [Hyponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM](#) **[Intake of vitamin D and risk of type 1 diabetes; a birth-cohort study.](#)** [Lancet. 2001;358:1500–1503.](#)
 - 5,000 IU of vitamin D a day, along with calcium and magnesium, decreased the relapse rate in multiple sclerosis patients. [Goldberg P, Fleming MC, Picard EH](#) **[Multiple Sclerosis decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D.](#)** [Medical Hypothesis. 1986;21:193–200.](#) Multiple sclerosis is rare around the equator.

[Zittermann A Vitamin D in preventive medicine: are we ignoring the evidence? Br J of Nutr. 2003;89:552–572.](#)

- To our knowledge, all studies of vitamin D and fractures demonstrate reduced fracture rates, as long as 25(OH)D levels increased to more than 40 ng/mL after treatment. [Dawson-Hughes B, Harris SS, Krall EA, Dallal GE Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997 Sep 4;337\(10\):670–6. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med. 1992 Dec 3;327\(23\):1637–42.](#)
- Breast milk (nature's perfect food) is deficient in vitamin D. Does this mean Paleolithic humans were supposed to expose their young to the sun (and thus to predators)? Hollis recently discovered that breast-feeding mothers need 4,000 units of vitamin D a day to sustain themselves and their infant. [Wagner CL, Howard CR, Lawrence RA, Fanning D, Hollis BW Maternal Vitamin D supplementation during lactation: A viable alternative to infant supplementation. Pediatr Res 2003; in press.](#) 2,000 units a day was not effective. It seems likely to the authors that the lack of vitamin D in human breast milk is due to widespread deficiency in mothers. [Wagner CL, Howard CR, Lawrence RA, Fanning D, Hollis BW Maternal Vitamin D supplementation during lactation: A viable alternative to infant supplementation. Pediatr Res 2003; in press.](#)
- Humans make thousands of units of vitamin D within minutes of whole body exposure to sunlight. From what we know of nature, it is unlikely such a system evolved by chance.

Deficiency Common In Older Adults

Vitamin D deficiency is common in older adults, even using conservative cutoff levels for 25(OH)D at <15 ng/mL, with a reported prevalence of 57% of medical inpatients. [Thomas M, Lloyd-Hones D, Thadhani R, Shaw A, Deraska D, Kitch B, Vamvakas E, Dick I, Prince R, Finkelstein J Hypovitaminosis D in medical inpatients. N Engl J Med 1998;338\(12\):777–83.](#) Thomas found that those patients with deficiencies were more likely to have nephrotic syndrome, hypertension and diabetes as well as higher parathyroid hormone concentrations.

Fourteen percent of 1569 otherwise healthy urban French adults had Vitamin D deficiency, with 25(OH)D levels lower than 12 ng/mL. [Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, Meunier PJ Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int. 1997;7\(5\):439–43.](#) 63% of 60 neonates had 25(OH)D levels less than 12 ng/mL and 14 of those 60 infants had serum PTH concentrations of more than 60 ng/mL. In Canada, more than 20% of healthy young women have low 25(OH)D levels at less than 16 ng/mL and the prevalence was higher among non-whites, as expected due to skin pigmentation. [Vieth R, Cole DE, Hawker GA, Trang HM, Rubin LA Wintertime vitamin D insufficiency is common in young Canadian women, and their vitamin D intake does not prevent it. Eur J Clin Nutr.](#)

[2001 Dec;55\(12\):1091–7.](#) Vieth clearly pointed out that vitamin D supplements (such as multivitamins or dairy products) did not prevent the deficiency, in fact the two were not even related. Fuller and Casparian, in 2001, reviewed the literature and concluded, "Previous studies that have found serum levels of vitamin D in their sun-protected subjects to be in the normal range may need to be reevaluated." [Fuller KE, Casparian JM Vitamin D: balancing cutaneous and systemic considerations. South Med J. 2001 Jan;94\(1\):58–64.](#) 42% of African American women had hypovitaminosis D (25(OH)D < 15 ng/mL) as compared to only 4.2% of whites. [Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, Allen C, Dougherty C, Gunter EW, Bowman BA Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr. 2002 Jul;76\(1\):187–92.](#) As early as 1992, other authors found a significant incidence of hypovitaminosis D. [McKenna M Differences in vitamin D status between countries in young adults and the elderly. Am J Med 1992;93:69–77.](#)

Reduced Sun Exposure

[Epidemiological evidence](#) suggests that mental illness has increased as humans have migrated out of the sun and into buildings, cars and sunblock. In a meticulously researched 2002 monograph, E. Fuller Torrey, systematically compiled statistics on the incidence of "insanity" from every conceivable source covering the last 250 years. [Torrey EF, Miller J The Invisible Plague: The Rise of mental illness from 1750 to the Present. 2002. Rutgers University Press.](#) His work indicated a dramatic increase in insanity (schizophrenia and severe bipolar disorder), that he labeled "The Invisible Plague." Although severe methodological limitations apply to any such endeavor, Torrey makes a convincing argument that the current incidence of insanity is not part of the human condition and has increased more than 20 fold in the last 250 years.

Torrey's work follows the classic 1989 paper by Klerman and Weissman which documented very significant temporal increases in the rates of major depression in cohorts born after World War II, including a decrease in the age of onset. [Klerman GL, Weissman M Increasing rates of depression. JAMA. 1989 Apr 21;261\(15\):2229–35.](#) The authors reviewed all available studies relevant to temporal trends in depression and concluded that dramatic increases were occurring in a relatively short time, much as Torrey would claim 12 years later. For example, Klerman and Weissman claimed that those born before 1915 had less than a ten percent lifetime risk of developing a diagnosable major affective disorder while their relative cohorts born after 1955 had a forty percent chance. Such dramatic increases in the rates of depression are known in psychiatry as the "Cohort Effect." The existence of such an effect has been heavily debated since Klerman and Weissman's original publication with other authors contending that recall bias or methods effects may explain these findings. [Patten SB Recall bias and major depression lifetime prevalence. Soc Psychiatry Psychiatr Epidemiol. 2003 Jun;38\(6\):290–6.](#) [Simon GE, VonKorff M, Ustun TB, Gater R, Gureje O, Sartorius N Is the lifetime risk of depression actually increasing? J Clin Epidemiol. 1995 Sep;48\(9\):1109–18.](#)

The implications for such an epidemic or cohort effect are staggering. A recent Consensus Development Conference on geriatric mental illness reported that the number of people older than 65 years with psychiatric disorders in the United States will increase from about 4 million in 1970 to 15 million in 2030, a 275% increase. [Jeste DV, Alexopoulos GS, Bartels SJ, Cummings JL, Gallo JJ, Gottlieb GL, Halpain MC, Palmer BW, Patterson TL, Reynolds CF 3rd, Lebowitz BD](#) **Consensus statement on the upcoming crisis in geriatric mental health: research agenda for the next 2 decades.** *Arch Gen Psychiatry.* 1999 Sep;56(9):848–53.

Although the cohort effect in depression shows dramatic increases, supporting Torrey's contention of a "Silent Epidemic," trends in schizophrenia over the last 50 years are less clear. [Harrison G, Mason P](#) **Schizophrenia—falling incidence and better outcome?** *Br J Psychiatry.* 1993 Oct;163:535–41. There is evidence that measures of long-term trends in perinatal sunshine duration are associated with epidemiological features of schizophrenia. [McGrath J, Selten JP, Chant D](#) **Long-term trends in sunshine duration and its association with schizophrenia birth rates and age at first registration—data from Australia and the Netherlands.** *Schizophr Res.* 2002 Apr 1;54(3):199–212. In 1997, Torrey, *et al*, reviewed more than 250 studies concluding they are "remarkably consistent in showing a 5–8% winter-spring excess of births for both schizophrenia and mania/bipolar disorder." [Torrey EF, Miller J, Rawlings R, Yolken RH](#) **Seasonality of births in schizophrenia and bipolar disorder: a review of the literature.** *Schizophr Res.* 1997 Nov 7;28(1):1–38. The same authors concluded a seasonal factor was also evident in schizoaffective disorder, major depression and autism.

Castrogiovanni, *et al*, also concluded a 10% birth excess during winter for schizophrenia with fewer studies supporting similar effects for bipolar disorder and major depressive disorder. [Castrogiovanni P, Iapichino S, Pacchierotti C, Pieraccini F](#) **Season of birth in psychiatry. A review.** *Neuropsychobiology.* 1998;37(4):175–81. Cassidy and Carroll reviewed the seasonal pattern of 304 psychiatric admissions for bipolar/mania and concluded manic hospitalizations peaked in early spring and reached a nadir in late fall. [Cassidy F, Carroll B](#) **Seasonal variation of mixed and pure episodes of bipolar disorder.** *J Affect Disord.* 2002 Feb;68(1):25–31. In Singapore, where UVB and vitamin D production remains constant year around, seasonal excess of schizophrenia birth rates was not evident in 9,655 patients, providing further evidence supporting a sunlight effect in schizophrenic births. [Parker G, Mahendran R, Koh ES, Machin D](#) **Season of birth in schizophrenia: no latitude at the equator.** *Br J Psychiatry.* 2000 Jan;176:68–71.

McGrath has long contended that widespread vitamin D deficiency leads to low prenatal vitamin D levels which, in turn, contribute to various adult disorders, including schizophrenia via "imprinting." [McGrath J](#) **Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia?** *Schizophr Res.* 1999 Dec 21;40(3):173–7. [McGrath J](#) **Does 'imprinting' with low prenatal vitamin D contribute to the risk of various adult disorders?** *Med Hypotheses.* 2001 Mar;56(3):367–71. He cites duration of sunshine, higher latitude, worse outcome at higher latitude, increased incidence in dark skinned migrants to northern latitudes, urban birth and season of birth as all being risk factors for schizophrenia and all consistent with a vitamin D effect. Kendell and Adams

were recently unable to support the hypothesis that vitamin D deficiency in pregnancy or early infancy may contribute to schizophrenia. [Kendell RE, Adams W Exposure to sunlight, vitamin D and schizophrenia. Schizophr Res. 2002 Apr 1;54\(3\):193–8.](#)

Low 25(OH)D levels

25(OH)D levels of 31 patients with schizophrenia and 25 with depression were compared to 30 alcoholics and 31 healthy controls. Mean 25(OH)D levels (in pg/mL) were lower in the depression (37.3) group and significantly lower in the schizophrenia (35.1) groups compared to normal controls (45.9). [Schneider B, Weber B, Frensch A, Stein J, Fritz J Vitamin D in schizophrenia, major depression and alcoholism. J Neural Transm. 2000;107\(7\):839–42.](#) More recently, sera from third trimester pregnant black women showed low maternal vitamin D might be a risk factor for schizophrenia among blacks, but the association didn't hold for white women. [McGrath J, Eyles D, Mowry B, Yolken R, Buka S Low maternal vitamin D as a risk factor for schizophrenia: a pilot study using banked sera. Schizophr Res. 2003 Sep 1;63\(1–2\):73–8.](#)

Vitamin D Deficiency Diseases

Mental illness is associated with most of the other illnesses that have been associated with vitamin D deficiency. [Zittermann A Vitamin D in preventive medicine: are we ignoring the evidence? Br J of Nutr. 2003;89:552–572.](#) [Holick M Vitamin D: A Millennium Perspective. J Cell Biochem. 2003;88:296–307.](#) For example, depression is associated with increased mortality, especially cardiac mortality. [Cuijpers P, Smit F Excess mortality in depression: a meta-analysis of community studies. J Affect Disord. 2002 Dec;72\(3\):227–36.](#) [Rugulies R Depression as a predictor for coronary heart disease. a review and meta-analysis. Am J Prev Med. 2002 Jul;23\(1\):51–61.](#) Recent studies have demonstrated that depression is a major risk for type 2 diabetes. [Musselman DL, Betan E, Larsen H, Phillips LS Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. Biol Psychiatry. 2003 Aug 1;54\(3\):317–29.](#) Type 1 diabetes appears to have similar associations. [Harris M Psychosocial aspects of diabetes with an emphasis on depression. Curr Diab Rep. 2003 Feb;3\(1\):49–55.](#) Poor quality of life was associated with high diastolic blood pressure among women. [Fletcher AE, Bulpitt CJ, Tuomilehto J, Browne J, Bossini A, Kawecka-Jaszcz K, Kivinen P, O'Brien E, Staessen J, Thijs L, Vanska O, Vanhanen H Quality of life of elderly patients with isolated systolic hypertension: baseline data from the Syst-Eur trial. Syst-Eur Trial Investigators. J Hypertens. 1998 Aug;16\(8\):1117–24.](#)

Michelson, *et al*, found past or current depression is associated with decreased bone mineral density in women. [Michelson D, Stratakis C, Hill L, Reynolds J, Galliven E, Chrousos G, Gold P Bone mineral density in women with depression. N Engl J Med. 1996 Oct 17;335\(16\):1176–81.](#) However, Amsterdam and Hooper observed no difference in mean BMD values between depressed patients and controls. [Amsterdam JD, Hooper M Bone density measurement in major depression. Prog Neuropsychopharmacol Biol](#)

[Psychiatry. 1998 Feb;22\(2\):267-77.](#) The Cardiovascular Health Study found significant associations between bone mineral density and depression after adjusting for osteoporosis risk factors. [Robbins J, Hirsch C, Whitmer R, Cauley J, Harris T](#)**The association of bone mineral density and depression in an older population.**[J Am Geriatr Soc. 2001 Jun;49\(6\):732-6.](#) The authors postulated, "there may be an unmeasured third factor, such as an endogenous steroid, that is responsible for both low BMD and depression," without mentioning that vitamin D is a steroid.

Patients with multiple sclerosis often have comorbid depressions. [Patti F, Cacopardo M, Palermo F, Ciancio MR, Lopes R, Restivo D, Reggio A](#)**Health-related quality of life and depression in an Italian sample of multiple sclerosis patients.**[J Neurol Sci. 2003 Jul 15;211\(1-2\):55-62.](#) [Buchanan RJ, Wang S, Tai-Seale M, Ju H](#)**Analyses of nursing home residents with multiple sclerosis and depression using the Minimum Data Set.**[Mult Scler. 2003 Mar;9\(2\):171-88.](#) Rheumatoid arthritis patients, especially urban residents, have more depression than osteoarthritis patients do, a difference not explained by disease severity or duration. [Abdel-Nasser AM, Abd El-Azim S, Taal E, El-Badawy SA, Rasker JJ, Valkenburg HA](#)**Depression and depressive symptoms in rheumatoid arthritis patients: an analysis of their occurrence and determinants.**[Br J Rheumatol. 1998 Apr;37\(4\):391-7.](#)

Schizophrenia has been reported to be comorbid with cardiac disease, diabetes and osteoporosis. [Green AI, Canuso CM, Brenner MJ, Wojcik J](#)**Detection and management of comorbidity in patients with schizophrenia.**[Psychiatr Clin North Am. 2003 Mar;26\(1\):115-39.](#) The increased rate of diabetes in schizophrenics was recognized before the atypical antipsychotics were introduced. [Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A, Lehman A](#)**Prevalence and correlates of diabetes in national schizophrenia samples.**[Schizophr Bull. 2000;26\(4\):903-12.](#) Schizophrenia also appears to be associated with hypertension. [Dixon L, Postrado L, Delahanty J, Fischer PJ, Lehman A](#)**The association of medical comorbidity in schizophrenia with poor physical and mental health.**[J Nerv Ment Dis. 1999 Aug;187\(8\):496-502.](#)

D's Function In The Brain

Garcion, *et al*, 2002, reviewed clues about vitamin D function in the brain. They concluded 1,25(OH)₂D₃ is involved in brain function with nuclear receptors for vitamin D localized in neurons and glial cells. Genes encoding the enzymes involved in the metabolism of this hormone are also expressed in brain cells. The reported biological effects of 1,25(OH)₂D₃ in the nervous system include the biosynthesis of neurotrophic factors and at least one enzyme involved in neurotransmitter synthesis. 1,25(OH)₂D₃ can also inhibit the synthesis of inducible nitric oxide synthase and increase glutathione levels, suggesting a role for the hormone in brain detoxification pathways.

Neuroprotective and immunomodulatory effects of this hormone have been described in several experimental models, indicating the potential value of pharmacological analogs in neurodegenerative and neuroimmune diseases. In addition, 1,25(OH)₂D₃ induces glioma cell death, making the hormone of potential interest in the management of brain tumors.

[Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D](#)**New clues about**

[vitamin D functions in the nervous system.Trends Endocrinol Metab. 2002 Apr;13\(3\):100–5.](#)

Tyrosine hydroxylase is the rate-limiting enzyme for production of the brain's monoamines. Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells of mice. [Puchacz E, Stumpf WE, Stachowiak EK, Stachowiak MK Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells.Brain Res Mol Brain Res. 1996 Feb;36\(1\):193–6.](#) Such a mechanism has been hypothesized to increase brain serotonin levels. [Partonen TVitamin D and serotonin in winter.Med Hypotheses. 1998 Sep;51\(3\):267–8.](#) Deficits of specific GABAergic neurons, defined by the presence of calcium-binding proteins parvalbumin, calbindin, and calretinin are present in schizophrenia. [Beasley CL, Zhang ZJ, Patten I, Reynolds GP Selective deficits in prefrontal cortical GABAergic neurons in schizophrenia defined by the presence of calcium-binding proteins.Biol Psychiatry. 2002 Oct 1;52\(7\):708–15.](#)

Eyles, *et al*, at The Queensland Centre for Schizophrenia Research Found that rat pups born to vitamin D deficient dams had profound alterations in the brain at birth. [Eyles D, Brown J, Mackay-Sim A, McGrath J, Feron F Vitamin D3 and brain development.Neuroscience. 2003;118\(3\):641–53.](#) Vitamin D is a potent inhibitor of mitosis and promoter of differentiation in numerous cells and specifically decreases the percentage of cultured hippocampal cells undergoing mitosis in conjunction with increases in both neurite outgrowth and nerve growth factor (NGF) in cultured brain cells. [Brown J, Bianco JJ, McGrath JJ, Eyles DW 1,25-dihydroxyvitamin D3 induces nerve growth factor, promotes neurite outgrowth and inhibits mitosis in embryonic rat hippocampal neurons.Neurosci Lett. 2003 Jun 5;343\(2\):139–43.](#)

Lambert, *et al*, drew arterial and venous blood samples from 101 healthy Australian men over a one-year period and found strong correlations between ambient sunlight and production of serotonin in the brain. [Lambert GW, Reid C, Kaye DM, Jennings GL, Esler M Effect of sunlight and season on serotonin turnover in the brain.Lancet. 2002 Dec 7;360\(9348\):1840–2.](#)

An alternate explanation, other than vitamin D production, explaining the feeling of well being after sun exposure, is related to the recent discovery of endorphin production by the skin after UV exposure. [Wintzen M, Yaar M, Burbach JP, Gilchrist BA Proopiomelanocortin gene product regulation in keratinocytes.J Invest Dermatol. 1996 Apr;106\(4\):673–8.](#) [Wintzen M, Zanello SB, Holick MF, Wiegant VM, Burbach JP, Vermeer BJ Condition-dependent presence of beta-lipotropin-like peptide in human keratinocytes.Peptides. 2000 May;21\(5\):691–7.](#) However, two recent studies have been unable to document any increase in circulating endorphins after UVA exposure. [Wintzen M, Ostijn DM, Polderman MC, le Cessie S, Burbach JP, Vermeer BJ Total body exposure to ultraviolet radiation does not influence plasma levels of immunoreactive beta-endorphin in man.Photodermatol Photoimmunol Photomed 2001 Dec;17\(6\):256–60.](#) [Gambichler T, Bader A, Vojvodic M, Avermaete A, Schenk M, Altmeyer P,](#)

[Hoffmann K Plasma levels of opioid peptides after sunbed exposures. Br J Dermatol. 2002 Dec;147\(6\):1207–11.](#)

Positive Effect

Vitamin D3 (400 and 800 IU) significantly enhanced positive affect when given to 44 healthy individuals. [Lansdowne AT, Provost SC Vitamin D3 enhances mood in healthy subjects during winter. Psychopharmacology \(Berl\). 1998 Feb;135\(4\):319–23.](#) 100,000 IU of ergocalciferol improved depression scales better than light therapy in a small group of patients with seasonal affective disorder. [Gloth FM III, Alam W, Hollis B Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. J Nutr Health Aging. 1999;3\(1\):5–7.](#) In the later study, improvement in 25(OH)D levels was significantly associated with improvement in depression scale scores.

400 IU of ergocalciferol did not effect mood scores in 125 Boston women compared to placebo. 25(OH)D levels were not drawn but we now know 400 IU of ergocalciferol is a homeopathic dose. [Harris S, Dawson-Hughes B Seasonal mood changes in 250 normal women. Psychiatry Res. 1993 Oct;49\(1\):77–87.](#)

The authors were unable to find any studies in the literature in which mentally ill patients were treated with physiological doses of vitamin D.

Toxicity

Vieth attempted to dispel unwarranted fears in medical community about physiological doses of vitamin D in 1999 with his exhaustive and well-written review. [Vieth R Vitamin D supplementation, 25-hydroxyvitamin D concentration, and safety. Am J Clin Nutr. 1999;69:842–56.](#) His conclusions: fear of vitamin D toxicity is unwarranted, and such unwarranted fear is rampant in the medical profession. [Vieth R, Chan PC, MacFarlane G Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. Am J Clin Nutr 2001 Feb;73\(2\):288–94.](#) Even Ian Monroe, the chair of the relevant IOM committee, wrote to the Journal to compliment Vieths work and to promise his findings will be considered at the time of a future Institute of Medicine review. [Munro I Derivation of tolerable upper intake levels of nutrients, Letter. Am J Clin Nutr 2001; 74:865.](#) That was more than two years ago.

Vieth indirectly asked the medical community to produce any evidence 10,000 units of vitamin D a day was toxic, saying, "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." He added, "If there is published evidence of toxicity in adults from an intake of 250 µg (10,000 IU) per day, and that is verified by the 25(OH)D concentration, I have yet to find it." [Vieth R Vitamin D supplementation, 25-hydroxyvitamin D concentration, and safety. Am J Clin Nutr. 1999;69:842–56.](#)

It is true that a few people may have problems with high calcium due to undiagnosed vitamin D hypersensitivity syndromes such as primary hyperparathyroidism, granulomatous disease (mainly sarcoidosis) or some cancers. This is not vitamin D toxicity and such syndromes often occur in patients with relative vitamin D deficiencies.

Cholecalciferol is certainly toxic in excess, and is used a rodent poison for this purpose. Animal data indicates signs of toxicity can occur with ingestion of 0.5 mg/kg (20,000 IU/kg), while the oral LD50 for cholecalciferol in dogs is about 88 mg/kg (3,520,000 IU/kg). [An Overview of Cholecalciferol Toxicosis](#) ABVT This would be equivalent to a 50 kg adult taking 176,000,000 IU or 440,000 standard 400 IU cholecalciferol capsules. Vieth reports human toxicity begins to occur after chronic consumption of approximately 40,000 IU a day. [Vieth R Vitamin D supplementation, 25-hydroxyvitamin D concentration, and safety.](#) Am J Clin Nutr. 1999;69:842–56.

One could compare vitamin D toxicity to water intoxication. For example, eight glasses of water a day is recommended consumption. However, regular consumption of 80 glasses a day (as seen in compulsive water intoxication) can be fatal. So you could say that water has a therapeutic index of ten (80/8).

Most vitamin D experts now say that humans should get about 4,000 units of vitamin D a day (from all sources) but 40,000 units a day will hurt them (over several years). [Vieth R Vitamin D supplementation, 25-hydroxyvitamin D concentration, and safety.](#) Am J Clin Nutr. 1999;69:842–56. Therefore, vitamin D has a therapeutic index of 10 (40,000/4,000), the same as water. Although we are not saying it is as safe as water, we are saying vitamin D is safe when used in the doses nature uses it.

The single most important fact anyone needs to know about vitamin D is how much nature supplies if we behave naturally, e.g., go into the sun. Whites make about 20,000 units of vitamin D within 30 minutes of full body exposure to the sun (minimal erythema dose). [Holick MF Environmental factors that influence the cutaneous production of vitamin D.](#) Am J Clin Nutr. 1995 Mar;61(3 Suppl):638S–645S. Vitamin D production in the skin occurs within minutes and is already maximized before your skin turns pink. Furthermore, if one stays in the sun long enough, the sun starts destroying excess vitamin D, a natural safeguard against toxicity.

Fear of the fatal form of skin cancer, malignant melanoma, keeps many people out of the sun. The problem with the theory is that the incidence of melanoma continues to increase dramatically although many people have been completely avoiding the sun for years. [Hemminki K, Zhang H, Czene K Incidence trends and familial risks in invasive and in situ cutaneous melanoma by sun-exposed body sites.](#) Int J Cancer. 2003 May 10;104(6):764–71. We are not saying sunburns are safe, they are not. We are saying that brief full body sun exposure (one-third minimal erythema doses) may slightly increase your risk of non-melanoma skin cancer but it is a much smarter thing to do than suffering from vitamin D deficiency.

Although there are documented cases of pharmacological overdoses from ergocalciferol, the only documented case of pharmacological, not industrial, toxicity from cholecalciferol we could find was intoxication from an over-the-counter supplement called Prolongevity. On closer inspection, however, it seemed more like an industrial accident but is interesting because it gives us some idea of the safety of cholecalciferol. The powder consumed contained up to 430 times the amount of cholecalciferol contained on the label (2,000 IU). The man had been taking between 156,000–2,604,000 IU of cholecalciferol (equivalent to between 390–6510 of the 400 IU capsules) a day for two years. He recovered uneventfully after treatment with glucocorticoids and sunscreen. [Koutkia P, Chen TC, Holick MF Vitamin D intoxication associated with an over-the-counter supplement. N Engl J Med. 2001 Jul 5;345\(1\):66–7.](#)

Treatment

It is too early to say that repletion of the vitamin D system will improve psychiatric symptoms, but there is limited evidence that it may. Once vitamin D deficiency is diagnosed in a psychiatric patient, or any patient, the physician needs to replete the vitamin D system with sunlight, an artificial source of UVB, oral vitamin D or a combination of the three alternatives. Regardless of the method used, the physician should be sure 25(OH)D levels are maintained between 35–55 ng/mL.

In Caucasian patients who want to avoid taking medication, judiciously exposure of as much skin as possible to direct midday sunlight for a few minutes (time needed depends on skin type) three times a week during those months when UVB occurs at their latitude (The Holick method) will maintain vitamin D levels. [Holick M Vitamin D; A millennium Perspective. J Cell Biochem. 2003;88:296–307 \(2003\).](#)

Black patients will need five to ten times longer in the sun. After several months of sun exposure, a 25(OH)D level should be obtained again to ensure levels between 35–55 ng/mL. Artificial light sources are available which emit UVB and which have been shown to increase serum 25(OH)D levels.

For those who want to avoid the sun or artificial light sources, cholecalciferol is the preferred form of vitamin D. It is the compound your skin makes naturally when exposed to UVB. It is more potent and is safer than the synthetic analog, ergocalciferol, in more common use. [Vieth R, Chan PC, MacFarlane GDEfficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. Am J Clin Nutr 2001 Feb;73\(2\):288–94.](#) Cholecalciferol is 1.7 times more efficient at raising 25(OH)D levels than is ergocalciferol. [Trang HM, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth REvidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. Am J Clin Nutr. 1998 Oct;68\(4\):854–8.](#) If oral cholecalciferol is the only source of vitamin D (complete lack of UVB exposure), between 3,000–5,000 IU per day will be needed to ensure serum 25(OH)D levels in the desirable range. [Vieth R, Chan PC, MacFarlane GDEfficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. Am J Clin Nutr 2001 Feb;73\(2\):288–94.](#)

Unfortunately, when doctors don't prescribe ergocalciferol, they sometimes prescribe newer vitamin D analogs, costing thousands of times more than cholecalciferol. Vitamin D analogs are contraindicated in vitamin D deficiency because they may cause hypercalcemia and fail to address the real problem: low stores of 25(OH)D. Cholecalciferol, or ergocalciferol, will replete the vitamin D system by filling up your gas tank with vitamin D. [Vieth R The pharmacology of vitamin D, including fortification strategies. In: Feldman D, Glorieux F, eds. Vitamin D, Chapter 61, in press, 2nd ed. Academic Press, San Diego.](#) Giving newer synthetic 1,25 vitamin D analogs for vitamin D deficiency is like shooting ether into your engine to keep your car running.

There is reason to hope that treating vitamin D deficiency will help improve the lives of psychiatric patients. It also seems clear that restoring physiological serum levels of 25(OH)D will hurt very few, if any, patients.