# Vitamin D as a Neurosteroid Affecting the Developing and Adult Brain

Natalie J. Groves,[1] John J. McGrath,[1,2,3] and Thomas H.J. Burne[1,2,*]

[1]Queensland Brain Institute, The University of Queensland, St. Lucia, Queensland 4072, Australia; email: t.burne@uq.edu.au

[2]Queensland Center for Mental Health Research, The Park Center for Mental Health, Wacol, Queensland 4076, Australia

[3]Discipline of Psychiatry, The University of Queensland, St. Lucia, Queensland 4072, Australia

*Corresponding author

## Keywords

brain development, vitamin D, behavior, neurochemistry, animal models

## Abstract

Vitamin D deficiency is prevalent throughout the world, and growing evidence supports a requirement for optimal vitamin D levels for the healthy developing and adult brain. Vitamin D has important roles in proliferation and differentiation, calcium signaling within the brain, and neurotrophic and neuroprotective actions; it may also alter neurotransmission and synaptic plasticity. Recent experimental studies highlight the impact that vitamin D deficiency has on brain function in health and disease. In addition, results from recent animal studies suggest that vitamin D deficiency during adulthood may exacerbate underlying brain disorders and/or worsen recovery from brain stressors. An increasing number of epidemiological studies indicate that vitamin D deficiency is associated with a wide range of neuropsychiatric disorders and neurodegenerative diseases. Vitamin D supplementation is readily available and affordable, and this review highlights the need for further research.

## Contents

# INTRODUCTION

Vitamin D deficiency is prevalent throughout the world, particularly in high-risk groups including pregnant woman, infants, dark-skinned migrants, and the elderly (115). In Australia, a recent study showed that 31% of the population has vitamin D deficiency, which is defined as a serum concentration of 25-dihydroxyvitamin D [25(OH)D] below 50 nmol/L (44). Although vitamin D is essential for calcium homeostasis and bone metabolism, it also has a role in other physiological functions, such as an immune modulator (9) and in cell proliferation and differentiation (16). Research over the past 15 years has revealed many functions of vitamin D in brain development and adult brain function. More recently, evidence has accumulated that suggests low vitamin D levels during adulthood may also be associated with adverse brain-related outcomes. A growing body of evidence from epidemiology and neuroscience links vitamin D deficiency with a range of neuropsychiatric disorders and neurodegenerative diseases (53). If low vitamin D is associated with adverse brain outcomes, this could have important public health implications because the treatment of vitamin D insufficiency (i.e., supplementation) is safe, cheap, and publicly acceptable.

This review has three broad aims: (*a*) to summarize the role vitamin D plays within the healthy developing and adult brain, (*b*) to highlight the impact that vitamin D deficiency has on brain function in health and disease, and (*c*) to provide up-to-date evidence supporting the links between vitamin D deficiency and neuropsychiatric disorders and neurodegenerative diseases.

## Vitamin D Synthesis

Vitamin D is synthesized from 7-dehydrocholesterol within the skin via UVB radiation. The amount of synthesis is dependent on a wide range of factors including latitude, season, atmospheric conditions, skin pigmentation, and age as well as personal habits including type of attire worn during exposure to sunlight (84a), sunscreen use, and time spent outdoors (36). Importantly, at high latitudes during winter and spring months, it is not possible to synthesize sufficient vitamin D from sunlight, and therefore dietary intake and supplementation are vital to maintain adequate levels of vitamin D (49).

The conversion of 7-dehydrocholesterol in the skin of humans and animals forms vitamin $D_3$, whereas the conversion of ergosterol in plants, yeast, and fungi forms vitamin $D_2$ (112). Both forms can be converted to the biologically active vitamin, but they may not have equal nutritional value in people (81), although this is likely to vary in different species, such as rodents (84, 88). Vitamin $D_3$ is reported to be 87% more potent in raising and maintaining serum 25(OH)D levels compared to vitamin $D_2$ in people, and it provides two- to threefold greater storage capacity of vitamin D in adipose tissue (81). Additionally, vitamin $D_2$ supplementation may even suppress endogenously formed vitamin $D_3$ (176).

Vitamin D is converted to its biologically active form via two enzymatic steps, the first of which occurs in the liver. Vitamin D is hydroxylated to 25(OH)D via either the microsomal (CYP2R1) or the mitochondrial (CYP27A1) P450 25-hydroxylase enzymes (171). 25(OH)D is then converted to the biologically active 1,25 dihydroxyvitamin D (vitamin D) in the kidney via 1α-hydroxylase (CYP27B1). This enzyme is tightly controlled via feedback mechanisms from parathyroid hormone, calcium, phosphate, calcitonin, fibroblast growth factor 23, and vitamin D itself (112).

Although the main expression of 1α-hydroxylase is within the kidney, a variety of other tissues also express this enzyme, including the skin, immune cells, placental tissue, and pancreas (54, 203). The presence of extrarenal 1α-hydroxylase suggests that an autocrine/paracrine mechanism plays a role in localized effects of vitamin D (82).

## Genomic Versus Nongenomic Pathways of Action

Vitamin D exerts its effects via both genomic and nongenomic pathways (18). The genomic pathway begins with vitamin D binding to the vitamin D receptor (VDR), which is a member of the steroid/thyroid superfamily of nuclear transcription factors (184). VDR is present throughout the body in almost all tissue types (13, 54, 72, 195).

Once vitamin D is bound to the receptor, VDR is phosphorylated to induce a change in conformation to release corepressors and allow VDR to heterodimerize with the retinoid X receptor (18). This heterodimer then recruits coregulatory protein complexes and binds one of many vitamin D response elements within the genome to influence gene transcription. The vitamin D response element is composed of two hexameric binding sites on DNA, arranged as either direct repeats interspaced with a small but varying number of nucleotides or as inverted palindromes interspaced by nine nucleotides (80, 170).

The ability of this heterodimer to influence gene transcription is dependent upon the range of coregulatory protein complexes, such as steroid receptor coactivators and VDR-interacting

protein, which determines whether repression or activation occurs (57). The recently established genome-wide map of VDR binding identified over 2,700 genomic positions occupied by the VDR, showing the pleiotropic nature of vitamin D (163).

Like other neurosteroid hormones, vitamin D initiates nongenomic rapid responses via either a membrane-bound VDR (130) or a protein-disulfide isomerase-associated 3 (PDIA3) protein (35). The variety of signal transduction systems that are rapidly activated by vitamin D include influx of $Ca^{2+}$; intracellular release of $Ca^{2+}$ stores; modulation of adenylate cyclase, phospholipase C, and protein kinases; and alteration of the phosphorylation states of cellular proteins (35, 55).

Rapid nongenomic effects of vitamin D may therefore play a role in a variety of cellular processes, with evidence supporting the role of vitamin D in proliferation and immune function (102). Importantly, both the VDR and PDIA3 receptors are present in the adult brain (51, 150).

## Vitamin D Metabolism in the Brain

The activating enzyme of vitamin D, 1α-hydroxylase, is found in a wide variety of tissues throughout the body, including the brain (54, 203), along with 25-hydroxylase (68) and the enzyme required for the degradation of the biologically active form of vitamin D, 24-hydroxylase (CYP24A1) (11). Animal studies have shown that the VDR is also found within specific brain regions, including the hippocampus, amygdala, hypothalamus, thalamus, cortex, and cerebellum (159, 191).

The distribution of the VDR and 1α-hydroxylase has also been elucidated in the adult human brain and is similar to that found in the rat (54). The VDR and the 1α-hydroxylase enzyme are colocalized and are found in both neurons and glial cells. The VDR seems to be exclusively nuclear in mature neurons, whereas 1α-hydroxylase is located within the cytosol (54). One recent study showed some immunohistochemical staining of VDR in the soma of mature dopaminergic cells; however, western blots confirmed that the VDR was restricted to the nucleus of both the developing and mature midbrain (43). In contrast, previous studies have shown that unliganded VDR constantly shuttles between nucleus and the cytoplasm (158).

The VDR is present early in the development of the rat, between embryonic day (E)12 and E15, with levels of VDR increasing until weaning (postnatal day 21) and still present in the adult brain (25, 43, 190). The time-dependent expression of VDR in the brain during fetal development supports a role for vitamin D in brain development. The initial VDR expression in brain corresponds within the appearance of dopaminergic neurons within the mesencephalon. Additionally, VDR is present within dopaminergic neurons in the adult substantia nigra (43).

## THE ACTIONS OF VITAMIN D WITHIN THE BRAIN

Growing evidence shows that vitamin D has many functions in both the developing and adult brain, including maintaining calcium balance and signaling, regulating neurotrophic factors, providing neuroprotection, modulating neurotransmission, and contributing to synaptic plasticity.

## Vitamin D and Calcium Signaling Within the Brain

A high level of calcium in the brain leads to neurotoxicity, and one action of vitamin D within the brain is associated with a reduction in calcium levels. Vitamin D has been shown to downregulate or modulate L-type voltage-gated calcium channels (L-VGCCs) (202, 205). This occurs through downregulation of L-type voltage-sensitive calcium channel (L-VSCC)-A1C subunit mRNA and protein, mediated by VDR mechanisms (71). Vitamin D treatment has also been shown to downregulate L-VSCC-A1D subunit mRNA, but this does not occur via VDR (71). In mice

lacking vitamin D, L-VGCCs are shown to be upregulated, leading to increased $Ca^{2+}$ influx (205). Evidence suggests that vitamin D can directly provide neuroprotection against excitotoxic insults in vitro by its downregulation of L-VGCCs (19).

Vitamin D also regulates the gene expression of a number of calcium-binding proteins, including parvalbumin and calbindin D28k (46, 187), and proteins associated with $Ca^{2+}$ homeostasis (51). The evidence suggests that the effects of vitamin D on $Ca^{2+}$ occur via both genomic and nongenomic actions (51, 144, 202).

## Neurotrophic Properties

The first evidence to support the role of vitamin D in neuronal differentiation, maturation, and growth came from in vitro studies showing that treatment with vitamin D led to changes in several neurotrophic factors, with increased synthesis of nerve growth factor (NGF) (146, 198), glial cell line–derived neurotrophic factor (GDNF) (143), and neurotrophin 3 (NT-3), and with decreased synthesis of NT-4 (145). Vitamin D treatment was also shown to increase levels of the low-affinity neurotrophin receptor (p75$^{NTR}$) in vitro (142). Depletion of vitamin D during rat fetal development leads to a reduction in NGF, GDNF, and p75$^{NTR}$ in newborn pups (52).

NGF is essential for the survival and differentiation of sensory and sympathetic neurons as well as the cholinergic basal forebrain neurons (108), and GDNF is integral to the development of dopaminergic (183) and noradrenergic systems (161). Although NT-3 stimulates the production of neurons and has widespread effects on their function and survival (120), the p75$^{NTR}$, along with NGF, is essential for necessary programmed cell death in the brain (34).

Initial in vitro work in several cancer cell lines, including mouse myeloid leukemia cells and melanoma cells, showed that the addition of vitamin D inhibited cell growth, led to a reduction in proliferation, and increased differentiation (153). Vitamin D's ability to induce differentiation was shown to be extended to normal bone marrow progenitor cells in vitro (133), and its antiproliferative effects were confirmed in vivo against malignant cancers (48). Furthermore, the addition of vitamin D to cultured embryonic hippocampal cells was shown not only to increase NGF but also to increase neurite outgrowth and decrease mitosis (22).

## Neuroprotection

Evidence indicates that vitamin D provides neuroprotection by regulating NGF and GDNF. In vitro studies have shown that NGF protects against glutamate toxicity and $Ca^{2+}$ ionophore and nitric oxide (NO) donor toxicity (109). Animal studies have shown that NGF is able to protect against excitotoxic injury (63), and in an animal model of Parkinson's disease, GDNF is neuroprotective against ischemia (194), 6-hydroxydopamine (6-OHDA) toxicity (96), and injury (69).

Vitamin D itself has also been shown to provide neuroprotection against excitotoxic injury from 6-OHDA, both in vitro and in vivo (192), which may occur by its downregulation of L-VGCCs (19). Pretreatment with vitamin D ameliorated the locomotor deficits seen with 6-OHDA lesions into the medial forebrain bundle. In addition, pretreatment protected against 6-OHDA-mediated depletion of dopamine and metabolites within the substantia nigra (192). Injection of vitamin D into adult rats leads to an increase in GDNF mRNA and protein expression within the striatum (165), and pretreatment with vitamin D has also been shown to significantly increase GDNF protein expression and TH immunoreactivity in the substantia nigra after 6-OHDA lesioning (166).

It is well known that vitamin D has an effect on the immune system and directly affects immune cells (134). Within the CNS, vitamin D exerts immunomodulatory effects directly on infiltrating

macrophages and parenchymal microglia (141). Treatment of microglia in vitro with vitamin D inhibits the production of tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), and NO by activated microglia, which suggests an anti-inflammatory role for vitamin D within the brain (111). Vitamin D has been shown to downregulate the expression of inducible nitric oxide synthesis (iNOS) (66) and to regulate the expression of gamma glutamyl transpeptidase (65), an enzyme important in the glutathione pathway; these findings suggest that vitamin D has an important role in antioxidant metabolism. Vitamin D–deficient animals have elevated inflammatory proteins in the brain, including TNFα and IL-6, indicating that baseline brain inflammation may be increased even without injury (11, 33).

A recent animal study showed elevated levels of vitamin D metabolism enzymes, VDR, and 25(OH)D in the hippocampus following a chronic unpredictable mild stress paradigm in rats when compared to controls (90). Vitamin D is known to be neuroprotective, and therefore it may be that upregulation of vitamin D can protect against the damaging effects of stress within otherwise-healthy subjects.

## Neurotransmission

Vitamin D has been shown to regulate a number of neurotransmitter systems. For example, vitamin D treatment leads to increased choline acetyltransferase activity in specific brain regions, which may impact on cholinergic neurotransmission (175). In rats, vitamin D has been shown to protect against methamphetamine-induced reductions in dopamine and serotonin in both the striatum and accumbens (32). Vitamin D treatment has also been shown to increase both potassium- and amphetamine-evoked overflow of striatal dopamine as well as increase substantia nigra tissue levels of dopamine and its main metabolites (31).

Not only can vitamin D act to transiently alter neurotransmitters upon exposure, but there is also evidence to suggest that hormonal imprinting that occurs during the neonatal period permanently alters biogenic amine levels in adulthood. For example, male rats treated with vitamin D at birth showed altered brain stem dopamine and striatal and hypothalamus homovanillic acid (HVA) levels three months later (179). In addition, hormonal imprinting with vitamin D that occurred during the neonatal period in female rats was shown to alter biogenic amine levels in two-month-old offspring. Alterations included increased norepinephrine, dopamine, and serotonin levels in the brainstem; decreased serotonin levels in the hippocampus; and decreased serotonin and HVA levels in the frontal cortex. These changes most likely occurred as a result of epigenetic mechanisms (180).

## Synaptic Plasticity

Long-term potentiation (LTP) is a long-lasting enhancement of signal transmission between neurons. LTP is one of the mechanisms underlying synaptic plasticity and is important in learning and memory. Prenatal vitamin D deficiency has been shown to alter many genes involved in synaptic plasticity (51), and evidence suggests that prenatal vitamin D deficiency induces an enhanced LTP in adult rats. Treatment with haloperidol, a high-affinity dopamine $D_2$ receptor antagonist, reverses the enhanced LTP (74).

Optimal levels of vitamin D were shown to be required for the induction of LTP within the adult rat brain (164). Vitamin D–deficient adult rats showed a reduction in serum calcium, which may have led to the impaired LTP (164), as increased postsynaptic intracellular calcium is necessary for the induction of LTP (23).

## RODENT MODELS OF VITAMIN D DEFICIENCY

In rodents, vitamin D deficiency from weaning, during adulthood, or throughout life has produced a range of significant impairments, including reduced body weight, musculoskeletal deficits, impaired prepulse inhibition of the acoustic startle response, and spatial learning deficits (3, 27, 178). Neurochemical changes have also been noted, with significant increases in NE, dopamine, dihydroxyphenylacetic acid (a breakdown product of dopamine), and γ-aminobutyric acid (GABA) (10, 181). However, all of these studies (3, 10, 27, 178, 181) found a reduction in serum calcium levels with vitamin D deficiency, which suggests that the impairments may have been due to altered calcium metabolism. This demonstrates the importance of maintaining normal serum calcium levels and appropriate musculoskeletal function.

### Developmental Vitamin D Deficiency

A developmental vitamin D (DVD)-deficient model was first created in Sprague-Dawley rats, in which vitamin D is removed from the diet for six weeks prior to and throughout conception. Under these conditions, dams have a serum concentration of 25(OH)D at the lower limit of detection (<5 nmol/L), which represents a frank vitamin D deficiency seen in less than 4% of the Australian population (44). However, dams are placed back on normal rat chow at the birth of the pups, and 25(OH)D concentrations return to control levels within two weeks (53). Use of this model of transient prenatal vitamin D deficiency in rodents has provided compelling proof-of-principle evidence for the association between DVD deficiency and a wide range of alterations in neuroanatomical, neurochemical, and behavioral measures while normal serum calcium levels are maintained. The DVD-deficient rodent model is reviewed in detail elsewhere (77, 99).

**Neurogenesis.** Vitamin D deficiency has been shown to alter the gene expression of many cell cycle genes and apoptotic genes during fetal development, leading to changes in cell proliferation and apoptosis (107). Cells dissociated from neonatal rat subventricular zone following vitamin D deficiency during gestation showed increased neurosphere production, which suggests that the absence of vitamin D leads to greater proliferation of neuroprogenitor cells (41). One study looked at the effects of maternal vitamin D deficiency on adult hippocampal neurogenesis and found that the prenatal vitamin D deficiency resulted in decreased neurogenesis in adult rats and that the decrease in neurogenesis could be reversed by treatment with haloperidol, a dopamine inverse agonist (97).

The 1α-hydroxylase knockout mouse lacks the ability to make $1,25(OH)_2D$, and this is associated with increased cell proliferation in the hippocampal dentate gyrus and a reduction in the survival of newborn neurons at 8 weeks of age (205). The $1,25(OH)_2D$ deficiency also significantly increased apoptosis in the hippocampal dentate gyrus, which suggests that this deficiency may be responsible for the loss of the newborn neurons. These results were independent of extracellular calcium (205).

**Proliferation, differentiation, and apoptosis.** In the rat model of DVD deficiency, the vitamin D–depleted pups had brains that were larger and longer, with larger ventricular volume and a thinner neocortex, than brains from control pups. It was shown that the changes in brain morphology were at least in part due to an increase in cell proliferation (52). Moreover, analysis of genes involved in the regulation of apoptosis found that the DVD-deficient pups had a significant reduction in apoptosis during gestation compared with control pups (107). Lack of vitamin D during development also led to a multitude of changes in gene expression of proapoptotic and cell

cycle genes, which corresponded to observed changes in apoptosis and increased cell proliferation (107). These studies confirmed that loss of vitamin D leads to alterations in cell proliferation, differentiation, and apoptosis during critical periods of brain development.

**Vitamin D and dopaminergic pathways.** A consistent finding from the DVD-deficient rat model is altered dopamine signaling. In neonatal rats, DVD deficiency decreases dopaminergic turnover by a reduction in the expression of catechol-O-methyl transferase enzyme, which is responsible for the breakdown of a dopamine metabolite (100). DVD deficiency has also been shown to significantly reduce factors crucial for specifying dopaminergic phenotype, such as Nurr1 and p57Kip2, during fetal development (42). Nurr1 knockout animals have complete agenesis of dopamine neurons (204), and p57Kip2 knockouts have no tyrosine hydroxylase (TH)-positive mesencephalic cells at E18.5 (93).

Adult female DVD-deficient rats have a significantly increased dopamine transporter density in the caudate putamen and binding affinity in the nucleus accumbens compared with controls and are more sensitive to amphetamine, a dopamine-releasing agent (101). It was recently confirmed that the VDR is present in the nucleus of TH-positive neurons in both human and rat substantia nigra (43).

**DVD-deficient model and schizophrenia.** A wide range of epidemiological findings have pointed to developmental vitamin D deficiency as a risk factor for the development of schizophrenia (126); these findings are discussed in more detail below (see Schizophrenia section). In this section we discuss findings in the DVD-deficient animal model that are relevant to schizophrenia.

The enlarged lateral ventricles and reduced cortical thickness seen in the DVD-deficient pups are frequently reported in schizophrenia patients (79). Adult DVD-deficient C57BL/6 and 129svJ mice (78) and adult DVD-deficient rats had greater spontaneous hyperlocomotion (26) compared with control rats. DVD-deficient rats also show increased locomotion in response to MK-801, a noncompetitive *N*-methyl-D-aspartate receptor antagonist, and a reduction in both MK-801-induced and spontaneous hyperlocomotion with haloperidol, a dopamine receptor antagonist, which was selective for DVD-deficient rats (98). DVD-deficient adult rats also show impaired latent inhibition (14), another feature of schizophrenia (197).

DVD deficiency also led to cognitive impairments in mice (60) and impaired response inhibition in the rodent version of the continuous performance task in rats (186), a key feature of the cognitive deficits seen with schizophrenia. These impairments were reversed by acute treatment with clozapine, an atypical antipsychotic (186). Although the DVD-deficient model does not replicate all of the features of schizophrenia [sensorimotor gating is normal (98)], it is a plausible model that can be used to explore the neurobiological mechanisms in schizophrenia.

## Adult Vitamin D Deficiency in Rodents

Vitamin D deficiency has recently been investigated in adult Sprague-Dawley rats to determine whether similar disruptions occur in both the developing and adult brain. In the adult vitamin D (AVD)-deficient model, rats were placed on a vitamin D–deficient diet at 10 weeks of age and at 16 weeks began behavioral testing. They were tested on a wide range of behavioral domains, and overall, AVD deficiency was not associated with an altered phenotype. In a cognitive test of attention and vigilance, the AVD-deficient rats had no learning or attentional deficits but showed a mildly impulsive phenotype. The AVD-deficient rats had increased levels of GABA and an increased dihydroxyphenylacetic acid:HVA ratio in the striatum. The AVD-deficient rats were

shown to be vitamin D deficient and, importantly, had normal calcium levels after eight to ten weeks on the diet (28).

The impact of AVD deficiency on brain function and behavior was also investigated in two strains of inbred mice, C57BL/6J and BALB/c. The mice were placed on a vitamin D–deficient diet at 10 weeks of age for a period of 10 weeks prior to behavioral testing. This procedure resulted in serum calcium levels and body weight in AVD-deficient mice that were not different from those of controls. AVD deficiency was found to result in spontaneous hyperlocomotion in both strains (76). The C57BL/6J strain showed no other behavioral effects of AVD deficiency. However, the BALB/c AVD-deficient mice showed altered behavior on the elevated plus maze, a test used to measure anxiety levels, as well as altered responses to heat, shock, and sound (76).

Brain neurochemistry was also analyzed, and the effects of AVD deficiency in the two strains differed markedly. In the C57BL/6J strain, dopamine and 5-hydroxytryptamine turnover was increased by AVD deficiency, whereas the BALB/c strain showed decreases in levels of glutamate and glutamine and increased levels of GABA and glycine. Of particular interest, both strains showed a small but significant decrease in the level of an enzyme involved in GABA synthesis, glutamate decarboxylase (GAD65/67) (76).

These studies show the importance of background strain, with BALB/c mice more susceptible to AVD deficiency than C57BL/6J mice or Sprague-Dawley rats. These general bodies of research also indicate that the timing of exposure to low vitamin D has different impacts on brain outcomes. The absence of vitamin D during development alters the orderly cascade of brain development, which results in a range of neurobiological outcomes as discussed above and reviewed by Kesby and colleagues (99). In contrast, low vitamin D during adulthood is associated with only subtle changes in some behavior and selective changes in neurochemistry that may be related to excitatory/inhibitory systems.

## Two-Hit Animal Models

### Vitamin D and experimental autoimmune encephalomyelitis: An animal model of multiple sclerosis.

The experimental autoimmune encephalomyelitis (EAE) animal model is a model of multiple sclerosis (MS). A range of studies have used this model to look at the effects of both vitamin D treatment and a vitamin D–deficient diet on EAE outcomes (29, 114, 141).

Treatment with vitamin D before or during the induction of EAE is effective in preventing EAE, and treatment with vitamin D after the induction of EAE is effective in decreasing the clinical signs of EAE (29, 114, 141). In addition, vitamin D deficiency increases the susceptibility to EAE and increases the clinical signs of EAE (29, 67). Recently, an animal model of MS pretreated with high-dose vitamin D was shown to have a reduction in demyelination and attenuated microglia activation and macrophage infiltration (196).

Vitamin D is known to be an immune modulator with immunosuppressant activity. Its actions in the EAE animal model and in human MS are most likely to involve, in part, the regulation of inflammatory cytokines. For example, vitamin D decreases the production of proinflammatory cytokines and increases the production of anti-inflammatory cytokines (30, 121). One study showed that vitamin D treatment for MS patients significantly increased serum levels of transforming growth factor-$\beta$1, which is an anti-inflammatory cytokine (119). Vitamin D also directly affects cellular immunity. It has been shown to inhibit Th1 cell development in EAE as well as dendritic cell maturation to suppress inflammatory activity (75, 113) and regulate the actions of other T cells (123).

Recently, studies have shown that vitamin D inhibits T-cell proliferation, inhibits the development of IL-6- and IL-17-producing cells, and enhances IL-10 production and the number of regulatory T cells, all mechanisms to promote anti-inflammatory actions (39). It seems clear that

vitamin D can alter the immune response, which is vitally important in autoimmune disorders such as MS.

Unexpectedly, adult offspring of a DVD mouse model showed milder and delayed EAE when compared with control offspring (58). One hypothesis proposed was that mice deprived of vitamin D in utero and subsequently placed on a vitamin D diet from birth actually grew up in an enriched-like environment (58). This hypothesis is supported by epidemiological data showing that a reduced risk of MS is associated with higher sun exposure in children (95, 188). In mice it was shown that offspring born to either a DVD-deficient mother or father displayed early and more severe EAE when compared with control mice (59). More studies are required to examine the molecular basis for the discordant effects between first and second generations.

**Vitamin D deficiency and stroke.** Studies with animal models of ischemic stroke have also looked at the effects of vitamin D on stroke severity and prognosis (11, 201). For example, a study examined the impact of vitamin D deficiency on stroke severity in the adult rat and found that vitamin D–deficient animals had greater infarct volumes compared with controls, and this corresponded with greater impairments, post stroke, in sensorimotor behavioral testing. Investigations into the mechanism showed that vitamin D–deficient animals had significantly lower plasma, brain, and liver levels of insulin-like growth factor 1 (IGF-1) compared to controls. IGF-1, a neuroprotectant that is usually elevated after injury to protect the tissue, has been attenuated with vitamin D deficiency, which indicates that lower IGF-1 levels may contribute to the greater infarct volume seen with vitamin D deficiency (11).

The inflammatory response was also altered in the vitamin D–deficient rats compared with controls with a reduction in the levels of a variety of cytokines/chemokines including IL-1$\beta$, IL-10, and IFN-$\gamma$ and with an increase in IL-6. These changes could also contribute to the greater infarct volume seen. The same study (11) also looked at the effects of an acute treatment with vitamin D immediately following stroke injury and found no effects on infarct volume or functional capabilities.

**Vitamin D deficiency and traumatic brain injury.** Vitamin D–deficient rats with traumatic brain injury show increased inflammation and greater open field test behavioral deficits in comparison with controls (33). Although progesterone, a neurosteroid that has been beneficial as a treatment in traumatic brain injury in recent clinical trials (199, 200), was beneficial in injured control animals, there was no improvement with treatment in vitamin D–deficient animals. This suggests that vitamin D deficiency exacerbates traumatic brain injury and diminishes the benefits of progesterone treatment (33).

A combination treatment of progesterone and low-dose vitamin D after brain injury in vitamin D–sufficient animals was found to preserve spatial and reference memory in comparison with controls, and the combination treatment was more effective than progesterone treatment alone (89). The combination treatment also stimulated astrocytic activity around the injury site, which suggests that the neuroprotective effects are mediated through activated astrocytes (89).

**Vitamin D deficiency, aging, and cognition.** Aged rats (20 months old) were analyzed for the effects of vitamin D treatment on a spatial memory task and on a spontaneous object recognition task, inflammatory state, and amyloid-$\beta$ (A$\beta$) load and clearance. Aged controls demonstrated significant learning and memory impairment compared to young control animals. However, vitamin D treatment significantly improved this age-related decline (20). Age-related changes in inflammatory state were also mitigated by vitamin D treatment, with increased expression of the anti-inflammatory IL-10 and decreased expression of the inflammatory mediator IL-1$\beta$

after treatment with vitamin D. The aged control animals showed an increase in amyloid burden compared to young controls. However, this was reduced by vitamin D treatment (20).

**Vitamin D deficiency and amyloid-β toxicity.** The introduction of Aβ into cortical neuron culture leads to neurodegeneration via upregulation of L-VGCCs and suppression of VDR, whereas additional treatment of vitamin D protected the neurons from cytotoxicity by downregulating L-VGCCs and upregulating VDR (46). Alzheimer's disease (AD) is believed to progress in part from inflammatory processes, including oxidative damage and elevated levels of NO, that occur via iNOS induction. In vitro studies using cortical neurons show that iNOS is elevated following Aβ treatment, whereas vitamin D treatment prevents Aβ-induced cytotoxicity and iNOS upregulation via VDR (47). Previous studies have shown that vitamin D regulates the expression of iNOS (66). Therefore, vitamin D supplementation could lead to a reduction in NO-mediated inflammation in AD, a possibility that should be further investigated.

Furthermore, treatment with a PDIA3 receptor agonist has been shown to significantly improve performance of object recognition memory, reduce amyloid plaques and neurofibrillary tangles, and reduce degenerated axons and presynaptic terminals in a mouse model of AD (182). Vitamin D, a known endogenous agonist of PDIA3, may therefore be important for anti-AD therapy (182).

Polymorphisms in the VDR gene have been shown to be associated with the risk of AD (15, 70). A recent genetic and functional study found that an AD risk allele was associated with lower VDR promoter activity and that overexpression of VDR or vitamin D treatment suppressed amyloid precursor protein transcription in vitro (193). An analysis of mRNA expression following vitamin D treatment of mixed neuron-glia cell culture showed upregulation of genes related to neurodegenerative disorders, including 10 genes that encode proteins that could possibly limit AD development (147). Growing evidence supports a protective role of vitamin D against the progression of AD, which is highly relevant owing to endemic vitamin D deficiency, particularly in the elderly. Randomized controlled trials that examine the benefits of vitamin D supplements in AD subjects are needed.

## LINKS WITH NEUROPSYCHIATRIC AND NEURODEGENERATIVE DISORDERS

Recent convergent evidence indicates that vitamin D deficiency has an impact during brain development and on the adult brain, and that it is biologically plausible that vitamin D deficiency would affect human health in terms of neuropsychiatric and neurodegenerative disorders. These disorders tend to have a complex etiology, with both gene and environmental influences. However, vitamin D deficiency seems to be a common risk factor. In this section, we provide the evidence from epidemiology, prospective studies, and clinical trials that links vitamin D to a range of disorders involving the central nervous system. A brief summary of various vitamin D–related pathologies and the strength of evidence that connects vitamin D to a range of disorders is shown in **Figure 1**.

### Cognitive Impairment

Many epidemiological studies have found an association between serum 25(OH)D and cognitive function, including memory and orientation (117) and executive function (24, 110). In older adults living independently, low serum 25(OH)D concentrations were significantly associated with cognitive impairment (151). In a recently published systematic review and meta-analysis, lower vitamin D concentrations were significantly associated with poorer cognitive function (12).
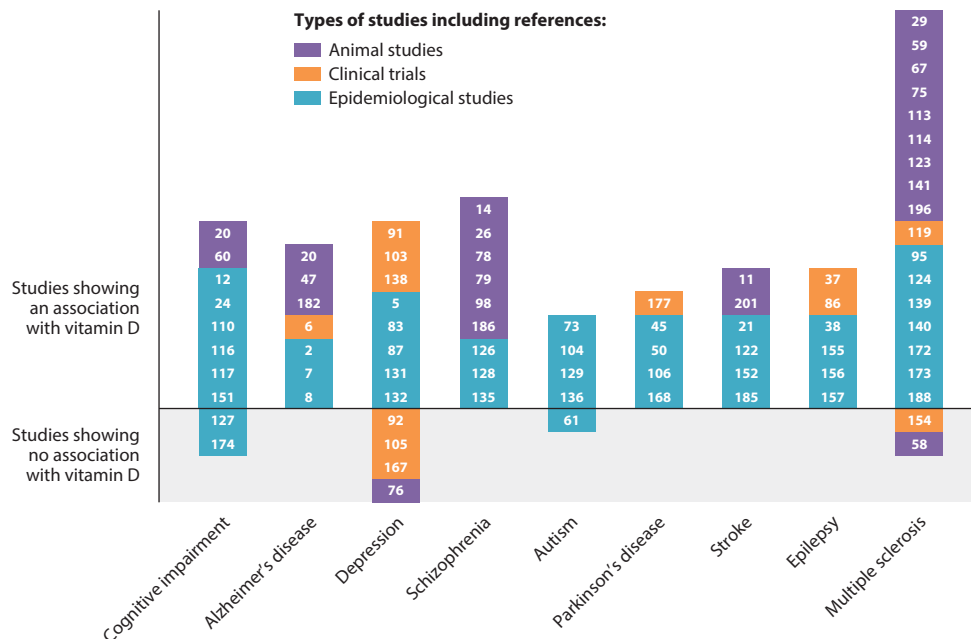
**Types of studies including references:**
- Animal studies
- Clinical trials
- Epidemiological studies

**Studies showing an association with vitamin D**

| Cognitive impairment | Alzheimer's disease | Depression | Schizophrenia | Autism | Parkinson's disease | Stroke | Epilepsy | Multiple sclerosis |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 29 |
| | | | | | | | | 59 |
| | | | | | | | | 67 |
| | | | | | | | | 75 |
| | | | | | | | | 113 |
| | | | | | | | | 114 |
| | | | | | | | | 123 |
| | | | | | | | | 141 |
| | | | 14 | | | | | 196 |
| 20 | | 91 | 26 | | | | | 119 |
| 60 | 20 | 103 | 78 | | | 11 | 37 | 95 |
| 12 | 47 | 138 | 79 | | 177 | 201 | 86 | 124 |
| 24 | 182 | 5 | 98 | 73 | 45 | 21 | 38 | 139 |
| 110 | 6 | 83 | 186 | 104 | 50 | 122 | 155 | 140 |
| 116 | 2 | 87 | 126 | 129 | 106 | 152 | 156 | 172 |
| 117 | 7 | 131 | 128 | 136 | 168 | 185 | 157 | 173 |
| 151 | 8 | 132 | 135 | | | | | 188 |

**Studies showing no association with vitamin D**

| Cognitive impairment | Alzheimer's disease | Depression | Schizophrenia | Autism | Parkinson's disease | Stroke | Epilepsy | Multiple sclerosis |
|---|---|---|---|---|---|---|---|---|
| 127 | | 92 | | 61 | | | | 154 |
| 174 | | 105 | | | | | | 58 |
| | | 167 | | | | | | |
| | | 76 | | | | | | |

**Figure 1**

Strength of evidence based on animal studies, clinical trials, and epidemiological studies that show evidence of an association between vitamin D and various disorders. Numbers in boxes correspond to reference numbers.

However, an association is not always found (127, 174), and moreover, from epidemiological studies it is not clear if low vitamin D levels precede the development of cognitive impairments or are a result of poor diet and disability.

A prospective study found that patients identified as vitamin D deficient at initial assessment had greater impairment of cognitive function at baseline and during follow-up three and six years later (116). Cognition was measured using the Mini-Mental State Examination (MMSE), a widely used neuropsychological test of cognitive function, and Trail-Making Tests A and B. At initial assessment, scores on all three tests were significantly worse in subjects who were vitamin D deficient or severely deficient compared to those who were vitamin D sufficient. At the six-year follow-up, subjects who were severely 25(OH)D deficient at baseline were more likely to experience substantial later cognitive decline as assessed by the MMSE and the Trail B, which measures executive functioning, but not on the Trail A, which measures attention (116).

## Alzheimer's Disease

AD is a neurodegenerative disorder characterized by progressive and irreversible cognitive deficits and behavioral alterations. The most common symptom is that of memory impairment and loss of spatial memory. A recent meta-analysis (7) looked at the association between low serum 25(OH)D and AD and found that serum 25(OH)D concentrations were overall significantly lower in AD cases than in controls. The meta-analysis revealed a large association of low 25(OH)D concentration with AD. A recent prospective study on the risk of AD in the general population showed an increasing risk of AD with decreasing levels of vitamin D (2).

One study showed an association between higher dietary vitamin D intake and a lower risk of developing AD among older women (8). A small pilot study found that patients who took memantine, an *N*-methyl-D-aspartate receptor antagonist, plus vitamin D for six months had a statistically and clinically relevant gain in cognition, whereas those who took memantine or vitamin D alone showed no effect. This suggests that there may be a synergistic effect in combining the treatments (6).

## Depression

Clinical depression is characterized by an all-encompassing low mood and loss of interest in normally enjoyable activities (118). It is generally associated with significant disability, due to an inability to function normally, and with a decreased health status (137). Epidemiological studies have shown a number of risk factors for depression, including gender (higher incidence in females), prior depression, low socioeconomic status, psychiatric comorbidity, medical illness, major adverse life events (94), and, more recently, low vitamin D levels (5).

Many observational and prospective studies suggest an association between low vitamin D levels and depression, particularly in the elderly (83, 87, 131, 132). A recent large systematic review and meta-analysis found that low vitamin D was significantly associated with an increased risk of depression (5); however, from these types of studies, it is not clear whether low vitamin D levels precede depressive symptoms or are a result of having depression.

A randomized, double-blind trial examined the effects of vitamin D supplementation on depressive symptoms in overweight and obese subjects. At the start of the trial there was an association between low serum 25(OH)D and symptoms of depression. Treatment with 20,000 or 40,000 IU vitamin D per week for one year, but not placebo, resulted in significant improvement in depressive symptoms. This study suggests a possible causal link between low vitamin D and depression, at least in the overweight and obese (91).

Treatment with fluoxetine, a serotonin selective reuptake inhibitor, is known to improve depressive symptoms; however, a recent study showed that combining vitamin D treatment with fluoxetine improved depressive symptoms significantly more than fluoxetine alone did (103). Another recent clinical trial (138) was undertaken in adults who were vitamin D deficient and suffering from depression. Participants were given either a single dose of 150,000 IU or 300,000 IU vitamin D or no treatment and were tested again for depression three months later. The single dose of 300,000 IU vitamin D not only proved safe but also was effective at significantly improving depression. This study shows that correcting vitamin D deficiency can improve the depression state (138).

However, in subjects who were not vitamin D deficient, high-dose vitamin D treatment did not have the same benefits (92), nor did all studies find improvement of depression with vitamin D treatment (105). Randomized controlled studies based on general population samples also have not found an association between vitamin D supplementation and scores on measures of depression (167).

## Schizophrenia

Schizophrenia is a group of disorders with symptoms including hallucinations, delusions, thought disorder, blunted affect, social withdrawal, and cognitive impairments (64, 149). It is most likely a neurodevelopmental disorder and is characterized by alterations in brain morphology and abnormal laminar organization as well as altered expression of proteins related to the early migration of neurons and glia, cell proliferation, formation of neural circuitry, and apoptosis (56). Risk factors for the development of schizophrenia include both genetic factors and environmental influences.

Some environmental risk factors include pregnancy and birth complications, maternal infection, immigration, adverse life events, and substance abuse (125).

Developmental vitamin D deficiency was first suggested as a risk factor for schizophrenia in 1978 because people with schizophrenia tend to be born in winter (135). Additional epidemiological findings, including increased schizophrenia in dark-skinned migrants to cold climates and in the urban versus rural setting and an increased risk of schizophrenia with prenatal famine, led McGrath (126) to propose that vitamin D deficiency during development could adversely affect the developing brain and lead to an increased risk of adult-onset schizophrenia (126).

Recently, a case-controlled study analyzed neonatal vitamin D status and risk of schizophrenia. It was found that low neonatal vitamin D is significantly associated with an increased risk of schizophrenia (128). A recent genome-wide analysis comparing genes involved in schizophrenia and genes related to vitamin D found a significant overlap of 70 genes (4).

## Autism

Autism is a neurodevelopmental disorder characterized by impaired social interaction, communication, and stereotypical behavior. Although it is well known that autism has a strong genetic component, research has also shown that environmental factors are likely to contribute to the development of autism (1). Epidemiological data have shown a number of factors that are associated with autism, including prenatal exposure to mutagens and advanced paternal age. A number of the other exposures can be linked to vitamin D deficiency. These include regions at higher latitudes (especially for dark-skinned individuals), urban residence, and regions with high precipitation rates (104).

Studies have shown that autistic children have lower serum 25(OH)D levels compared to healthy controls (129, 136). For example, a cross-sectional study in Egypt showed that children with autism have significantly lower serum 25(OH)D, 1,25(OH)$_2$D, and calcium levels compared to controls (129). Other studies have found no significant association between serum 25(OH)D and autism (61). Recently, autism prevalence was shown to be inversely correlated with solar UVB doses in an ecological study, which suggests that vitamin D deficiency during fetal brain development or early life could be relevant to the development of autism (73).

## Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disease. It is characterized by slow, selective dopaminergic neuronal loss. Symptoms include dyskinesia, rigidity, and tremor as well as postural instability and gait disorders (17).

Epidemiological evidence from cross-sectional studies provides some support for a link between vitamin D deficiency and PD incidence (50, 168). Furthermore, the first longitudinal study investigating the association between vitamin D status and subsequent occurrence of PD showed that low serum vitamin D levels predicted an elevated risk of PD (106). Subsequent studies have shown that vitamin D deficiency is also associated with more advanced severity of disease (45).

A recently published study related to PD has lent support for the neuroprotective properties of vitamin D. Using a placebo-controlled, randomized trial, Suzuki and colleagues (177) examined the impact of vitamin D supplementation (1,200 IU per day, for one year) on various PD-related outcomes. Those on placebo had a steady worsening of PD outcomes. In contrast, those on vitamin D supplements had no change in PD outcomes over the year. The results strongly suggest that low vitamin D status exacerbates progression of PD (40).

## Stroke

Studies in humans have revealed that low levels of serum vitamin D are independently predictive for the occurrence of strokes (122, 152), and a large population-based prospective study showed stepwise increases in the risk of ischemic stroke with decreasing serum 25(OH)D (21). A further study in China not only showed that patients with acute ischemic stroke had significantly lower vitamin D levels compared to controls, but also that vitamin D levels were a prognostic marker of short-term functional outcome and death in stroke patients (185).

## Epilepsy

Epilepsy is a brain disorder characterized by recurrent and unpredictable interruptions in normal brain function (epileptic seizures) (62). Epidemiological studies indicate that epilepsy is another brain disorder that shows seasonal variation of birth, with an excess of those with epilepsy born in winter compared to summer (155–157). Additionally, epileptic seizures themselves show seasonal variation, with a reduction in seizures during summer (38). A very early small controlled pilot study showed a reduction in the number of seizures following treatment with vitamin D compared to placebo (37). Nearly 40 years later this study was followed up with another pilot study showing a median reduction in seizures of 40% following vitamin D supplementation (86).

## Multiple Sclerosis

Multiple sclerosis (MS) is a slow progressive disorder of the central nervous system that is characterized by demyelination of the brain and spinal cord. Although its etiology is unclear, it seems to be multidimensional, with environmental factors, genetic factors, and dysregulation of the immune response all playing a part (189). Environmental risk factors include infection, cigarette smoking, and low vitamin D (148, 160). A significant positive association exists between MS prevalence and latitude globally, which supports the role of UV radiation and vitamin D in its development (173). Additionally, studies show that vitamin D intake is inversely associated with the risk of MS (139, 140), and serum 25(OH)D levels are significantly lower in patients with MS compared to healthy subjects (124). Furthermore, vitamin D concentrations correlate with the severity of MS (172). Genetic studies have shown links between MS susceptibility and both CYP27B1 and CYP24A1, vitamin D metabolism enzymes (162, 169). However, not all studies show a significant effect of vitamin D on MS, and more work is required (154).

## FUTURE DIRECTIONS

Accumulating evidence supports the need for optimal vitamin D levels both during development and throughout adulthood for proper brain function. However, it is still unknown what the optimal vitamin D level is for the brain or how the timing or length of vitamin D deficiency can alter the risk of disease. Recommendations for optimal vitamin D concentrations are usually based on bone outcomes (e.g., parathyroid concentrations) (85). More research is required to determine if vitamin D treatment of brain diseases is an effective tool or if prevention of vitamin D deficiency is the only method to lower risk.

The results from recent animal and human studies suggest that vitamin D deficiency during adulthood may exacerbate underlying brain disorders and/or worsen recovery from brain stressors. Therefore, research is required to determine the molecular mechanism behind this possible vulnerability. For example, the direct regulation of calcium by vitamin D within the brain

may be a key molecular mechanism to protect against the neurotoxicity that can occur in disease and aging, or it may be vitamin D's immunomodulatory and neurotrophic effects providing neuroprotection to maintain a healthy brain. Therefore, both animal experiments and in vitro research are required to explicate these mechanisms within the brain, such as electrophysiology of calcium transport. Research in animals that combines vitamin D deficiency with relevant animal models of neuropsychiatric and neurodegenerative disorders is also required.

Additionally, with the extensive links between vitamin D deficiency and a wide range of neuropsychiatric, neurodegenerative, and other brain disorders now evident, there is a need for large, well-controlled clinical trials.

## CONCLUSION

This review has shown that vitamin D is a neurosteroid that exerts a multitude of effects that are important in both the correct development of the brain and the proper functioning of the adult brain. In addition, mounting evidence suggests that maintaining optimal vitamin D levels may lower the risk of developing a wide range of brain disorders. With vitamin D deficiency widespread throughout the world, it is no wonder that research is focusing on elucidating the mechanisms of vitamin D's actions within the brain. In light of the advantage that vitamin D supplementation is readily available and affordable, this review highlights the need for further research.

## DISCLOSURE STATEMENT

## ACKNOWLEDGMENTS

## LITERATURE CITED

1. Abrahams BS, Geschwind DH. 2008. Advances in autism genetics: on the threshold of a new neurobiology. *Nat. Rev. Genet.* 9:341–55
2. Afzal S, Bojesen SE, Nordestgaard BG. 2014. Reduced 25-hydroxyvitamin D and risk of Alzheimer's disease and vascular dementia. *Alzheimer's Dement.* 10:296–302
3. Altemus KL, Finger S, Wolf C, Birge SJ. 1987. Behavioral correlates of vitamin D deficiency. *Physiol. Behav.* 39:435–40
4. Amato R, Pinelli M, Monticelli A, Miele G, Cocozza S. 2010. Schizophrenia and vitamin D related genes could have been subject to latitude-driven adaptation. *BMC Evol. Biol.* 10:351
5. Anglin RE, Samaan Z, Walter SD, McDonald SD. 2013. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. *Br. J. Psychiatry* 202:100–7
6. Annweiler C, Herrmann FR, Fantino B, Brugg B, Beauchet O. 2012. Effectiveness of the combination of memantine plus vitamin D on cognition in patients with Alzheimer disease: a pre-post pilot study. *Cogn. Behav. Neurol.* 25:121–27
7. Annweiler C, Llewellyn DJ, Beauchet O. 2013. Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis. *J. Alzheimer's Dis.* 33:659–74

8. Annweiler C, Rolland Y, Schott AM, Blain H, Vellas B, et al. 2012. 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.* 67:1205–11

9. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. 2010. Vitamin D: modulator of the immune system. *Curr. Opin. Pharmacol.* 10:482–96

10. Baksi SN, Hughes MJ. 1982. Chronic vitamin D deficiency in the weanling rat alters catecholamine metabolism in the cortex. *Brain Res.* 242:387–90

11. Balden R, Selvamani A, Sohrabji F. 2012. Vitamin D deficiency exacerbates experimental stroke injury and dysregulates ischemia-induced inflammation in adult rats. *Endocrinology* 153:2420–35

12. Balion C, Griffith LE, Strifler L, Henderson M, Patterson C, et al. 2012. Vitamin D, cognition, and dementia: a systematic review and meta-analysis. *Neurology* 79:1397–405

13. Barchetta I, Carotti S, Labbadia G, Gentilucci UV, Muda AO, et al. 2012. Liver vitamin D receptor, CYP2R1, and CYP27A1 expression: relationship with liver histology and vitamin D3 levels in patients with nonalcoholic steatohepatitis or hepatitis C virus. *Hepatology* 56:2180–87

14. Becker A, Eyles DW, McGrath JJ, Grecksch G. 2005. Transient prenatal vitamin D deficiency is associated with subtle alterations in learning and memory functions in adult rats. *Behav. Brain Res.* 161:306–12

15. Beecham GW, Martin ER, Li YJ, Slifer MA, Gilbert JR, et al. 2009. Genome-wide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. *Am. J. Hum. Genet.* 84:35–43

16. Bikle D. 2009. Nonclassic actions of vitamin D. *J. Clin. Endocrinol. Metab.* 94:26–34

17. Bonnet AM, Houeto JL. 1999. Pathophysiology of Parkinson's disease. *Biomed. Pharmacother.* 53:117–21

18. Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, et al. 2008. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr. Rev.* 29:726–76

19. Brewer LD, Thibault V, Chen KC, Langub MC, Landfield PW, Porter NM. 2001. Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons. *J. Neurosci.* 21:98–108

20. Briones TL, Darwish H. 2012. Vitamin D mitigates age-related cognitive decline through the modulation of pro-inflammatory state and decrease in amyloid burden. *J. Neuroinflamm.* 9:244

21. Brondum-Jacobsen P, Nordestgaard BG, Schnohr P, Benn M. 2013. 25-Hydroxyvitamin D and symptomatic ischemic stroke: an original study and meta-analysis. *Ann. Neurol.* 73:38–47

22. Brown J, Bianco JI, McGrath JJ, Eyles DW. 2003. 1,25-Dihydroxyvitamin D3 induces nerve growth factor, promotes neurite outgrowth and inhibits mitosis in embryonic rat hippocampal neurons. *Neurosci. Lett.* 343:139–43

23. Brown TH, Chapman PF, Kairiss EW, Keenan CL. 1988. Long-term synaptic potentiation. *Science* 242:724–28

24. Buell JS, Scott TM, Dawson-Hughes B, Dallal GE, Rosenberg IH, et al. 2009. Vitamin D is associated with cognitive function in elders receiving home health services. *J. Gerontol. A Biol. Sci. Med. Sci.* 64:888–95

25. Burket R, McGrath J, Eyles D. 2003. Vitamin D receptor expression in the embryonic rat brain. *Neurosci. Res. Commun.* 33:63–71

26. Burne TH, Becker A, Brown J, Eyles DW, Mackay-Sim A, McGrath JJ. 2004. Transient prenatal vitamin D deficiency is associated with hyperlocomotion in adult rats. *Behav. Brain Res.* 154:549–55

27. Burne TH, Feron F, Brown J, Eyles DW, McGrath JJ, Mackay-Sim A. 2004. Combined prenatal and chronic postnatal vitamin D deficiency in rats impairs prepulse inhibition of acoustic startle. *Physiol. Behav.* 81:651–55

28. Byrne JH, Voogt M, Turner KM, Eyles DW, McGrath JJ, Burne TH. 2013. The impact of adult vitamin D deficiency on behaviour and brain function in male Sprague-Dawley rats. *PLoS ONE* 8:e71593

29. Cantorna MT, Hayes CE, DeLuca HF. 1996. 1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. *Proc. Natl. Acad. Sci. USA* 93:7861–64

30. Cantorna MT, Woodward WD, Hayes CE, DeLuca HF. 1998. 1,25-Dihydroxyvitamin D3 is a positive regulator for the two anti-encephalitogenic cytokines TGF-beta 1 and IL-4. *J. Immunol.* 160:5314–19

31. Cass WA, Peters LE, Fletcher AM, Yurek DM. 2012. Evoked dopamine overflow is augmented in the striatum of calcitriol treated rats. *Neurochem. Int.* 60:186–91

32. Cass WA, Smith MP, Peters LE. 2006. Calcitriol protects against the dopamine- and serotonin-depleting effects of neurotoxic doses of methamphetamine. *Ann. N. Y. Acad. Sci.* 1074:261–71

33. Cekic M, Cutler SM, VanLandingham JW, Stein DG. 2011. Vitamin D deficiency reduces the benefits of progesterone treatment after brain injury in aged rats. *Neurobiol. Aging* 32:864–74

34. Chao MV. 1994. The p75 neurotrophin receptor. *J. Neurobiol.* 25:1373–85

35. Chen J, Olivares-Navarrete R, Wang Y, Herman TR, Boyan BD, Schwartz Z. 2010. Protein-disulfide isomerase-associated 3 (PDIA3) mediates the membrane response to 1,25-dihydroxyvitamin D3 in osteoblasts. *J. Biol. Chem.* 285:37041–50

36. Chen TC, Chimeh F, Lu Z, Mathieu J, Person KS, et al. 2007. Factors that influence the cutaneous synthesis and dietary sources of vitamin D. *Arch. Biochem. Biophys.* 460:213–17

37. Christiansen C, Rodbro P, Sjo O. 1974. "Anticonvulsant action" of vitamin D in epileptic patients? A controlled pilot study. *Br. Med. J.* 2:258–59

38. Clemens Z, Hollo A, Kelemen A, Rasonyi G, Fabo D, et al. 2013. Seasonality in epileptic seizures. *J. Neurol. Transl. Neurosci.* 1:1016

39. Correale J, Ysrraelit MC, Gaitan MI. 2009. Immunomodulatory effects of vitamin D in multiple sclerosis. *Brain* 132:1146–60

40. Cui X, Groves NJ, Burne TH, Eyles DW, McGrath JJ. 2013. Low vitamin D concentration exacerbates adult brain dysfunction. *Am. J. Clin. Nutr.* 5:907–8

41. Cui X, McGrath JJ, Burne TH, Mackay-Sim A, Eyles DW. 2007. Maternal vitamin D depletion alters neurogenesis in the developing rat brain. *Int. J. Dev. Neurosci.* 25:227–32

42. Cui X, Pelekanos M, Burne TH, McGrath JJ, Eyles DW. 2010. Maternal vitamin D deficiency alters the expression of genes involved in dopamine specification in the developing rat mesencephalon. *Neurosci. Lett.* 486:220–23

43. Cui X, Pelekanos M, Liu PY, Burne TH, McGrath JJ, Eyles DW. 2013. The vitamin D receptor in dopamine neurons; its presence in human substantia nigra and its ontogenesis in rat midbrain. *Neuroscience* 236:77–87

44. Daly RM, Gagnon C, Lu ZX, Magliano DJ, Dunstan DW, et al. 2012. Prevalence of vitamin D deficiency and its determinants in Australian adults aged 25 years and older: a national, population-based study. *Clin. Endocrinol.* (*Oxf.*) 77:26–35

45. Ding H, Dhima K, Lockhart KC, Locascio JJ, Hoesing AN, et al. 2013. Unrecognized vitamin D3 deficiency is common in Parkinson disease: Harvard Biomarker Study. *Neurology* 81:1531–37

46. Dursun E, Gezen-Ak D, Yilmazer S. 2011. A novel perspective for Alzheimer's disease: vitamin D receptor suppression by amyloid-beta and preventing the amyloid-beta induced alterations by vitamin D in cortical neurons. *J. Alzheimer's Dis.* 23:207–19

47. Dursun E, Gezen-Ak D, Yilmazer S. 2013. A new mechanism for amyloid-β induction of iNOS: vitamin D-VDR pathway disruption. *J. Alzheimer's Dis.* 36:459–74

48. Eisman JA, Barkla DH, Tutton PJ. 1987. Suppression of in vivo growth of human cancer solid tumor xenografts by 1,25-dihydroxyvitamin D3. *Cancer Res.* 47:21–25

49. Engelsen O, Brustad M, Aksnes L, Lund E. 2005. Daily duration of vitamin D synthesis in human skin with relation to latitude, total ozone, altitude, ground cover, aerosols and cloud thickness. *Photochem. Photobiol.* 81:1287–90

50. Evatt ML, Delong MR, Khazai N, Rosen A, Triche S, Tangpricha V. 2008. Prevalence of vitamin D insufficiency in patients with Parkinson disease and Alzheimer disease. *Arch. Neurol.* 65:1348–52

51. Eyles D, Almeras L, Benech P, Patatian A, Mackay-Sim A, et al. 2007. Developmental vitamin D deficiency alters the expression of genes encoding mitochondrial, cytoskeletal and synaptic proteins in the adult rat brain. *J. Steroid Biochem. Mol. Biol.* 103:538–45

52. Eyles D, Brown J, Mackay-Sim A, McGrath J, Feron F. 2003. Vitamin D3 and brain development. *Neuroscience* 118:641–53

53. Eyles DW, Burne TH, McGrath JJ. 2013. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Front. Neuroendocrinol.* 34:47–64

54. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. 2005. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *J. Chem. Neuroanat.* 29:21–30

55. Falkenstein E, Tillmann HC, Christ M, Feuring M, Wehling M. 2000. Multiple actions of steroid hormones—a focus on rapid, nongenomic effects. *Pharmacol. Rev.* 52:513–56

56. Fatemi SH, Folsom TD. 2009. The neurodevelopmental hypothesis of schizophrenia, revisited. *Schizophr. Bull.* 35:528–48

57. Fernandes de Abreu DA, Eyles D, Feron F. 2009. Vitamin D, a neuro-immunomodulator: implications for neurodegenerative and autoimmune diseases. *Psychoneuroendocrinology* 34(Suppl. 1):S265–77

58. Fernandes de Abreu DA, Ibrahim EC, Boucraut J, Khrestchatisky M, Feron F. 2010. Severity of experimental autoimmune encephalomyelitis is unexpectedly reduced in mice born to vitamin D-deficient mothers. *J. Steroid Biochem. Mol. Biol.* 121:250–53

59. Fernandes de Abreu DA, Landel V, Barnett AG, McGrath J, Eyles D, Feron F. 2012. Prenatal vitamin D deficiency induces an early and more severe experimental autoimmune encephalomyelitis in the second generation. *Int. J. Mol. Sci.* 13:10911–19

60. Fernandes de Abreu DA, Nivet E, Baril N, Khrestchatisky M, Roman F, Feron F. 2010. Developmental vitamin D deficiency alters learning in C57Bl/6J mice. *Behav. Brain Res.* 208:603–8

61. Fernell E, Barnevik-Olsson M, Bagenholm G, Gillberg C, Gustafsson S, Saaf M. 2010. Serum levels of 25-hydroxyvitamin D in mothers of Swedish and of Somali origin who have children with and without autism. *Acta Paediatr.* 99:743–47

62. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, et al. 2005. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 46:470–72

63. Frim DM, Yee WM, Isacson O. 1993. NGF reduces striatal excitotoxic neuronal loss without affecting concurrent neuronal stress. *Neuroreport* 4:655–58

64. Frith C. 1996. Neuropsychology of schizophrenia. What are the implications of intellectual and experiential abnormalities for the neurobiology of schizophrenia? *Br. Med. Bull.* 52:618–26

65. Garcion E, Sindji L, Leblondel G, Brachet P, Darcy F. 1999. 1,25-Dihydroxyvitamin D3 regulates the synthesis of gamma-glutamyl transpeptidase and glutathione levels in rat primary astrocytes. *J. Neurochem.* 73:859–66

66. Garcion E, Sindji L, Montero-Menei C, Andre C, Brachet P, Darcy F. 1998. Expression of inducible nitric oxide synthase during rat brain inflammation: regulation by 1,25-dihydroxyvitamin D3. *Glia* 22:282–94

67. Garcion E, Sindji L, Nataf S, Brachet P, Darcy F, Montero-Menei CN. 2003. Treatment of experimental autoimmune encephalomyelitis in rat by 1,25-dihydroxyvitamin D3 leads to early effects within the central nervous system. *Acta Neuropathol.* 105:438–48

68. Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. 2002. New clues about vitamin D functions in the nervous system. *Trends Endocrinol. Metab.* 13:100–5

69. Gash DM, Zhang Z, Gerhardt G. 1998. Neuroprotective and neurorestorative properties of GDNF. *Ann. Neurol.* 44:S121–25

70. Gezen-Ak D, Dursun E, Bilgic B, Hanagasi H, Ertan T, et al. 2012. Vitamin D receptor gene haplotype is associated with late-onset Alzheimer's disease. *Tohoku J. Exp. Med.* 228:189–96

71. Gezen-Ak D, Dursun E, Yilmazer S. 2011. The effects of vitamin D receptor silencing on the expression of LVSCC-A1C and LVSCC-A1D and the release of NGF in cortical neurons. *PLoS ONE* 6:e17553

72. Girgis CM, Clifton-Bligh RJ, Mokbel N, Cheng K, Gunton JE. 2013. Vitamin D signaling regulates proliferation, differentiation and myotube size in C2C12 skeletal muscle cells. *Endocrinology* 155:347–57

73. Grant WB, Cannell JJ. 2013. Autism prevalence in the United States with respect to solar UV-B doses: an ecological study. *Dermatoendocrinology* 5:159–64

74. Grecksch G, Ruthrich H, Hollt V, Becker A. 2009. Transient prenatal vitamin D deficiency is associated with changes of synaptic plasticity in the dentate gyrus in adult rats. *Psychoneuroendocrinology* 34(Suppl. 1):S258–64

75. Griffin MD, Lutz W, Phan VA, Bachman LA, McKean DJ, Kumar R. 2001. Dendritic cell modulation by 1α,25 dihydroxyvitamin D3 and its analogs: a vitamin D receptor-dependent pathway that promotes a persistent state of immaturity in vitro and in vivo. *Proc. Natl. Acad. Sci. USA* 98:6800–5

76. Groves NJ, Kesby JP, Eyles DW, McGrath JJ, Mackay-Sim A, Burne TH. 2013. Adult vitamin D deficiency leads to behavioural and brain neurochemical alterations in C57BL/6J and BALB/c mice. *Behav. Brain Res.* 241:120–31

77. Harms LR, Burne TH, Eyles DW, McGrath JJ. 2011. Vitamin D and the brain. *Best Pract. Res. Clin. Endocrinol. Metab.* 25:657–69

78. Harms LR, Eyles DW, McGrath JJ, Mackay-Sim A, Burne TH. 2008. Developmental vitamin D deficiency alters adult behaviour in 129/SvJ and C57BL/6J mice. *Behav. Brain Res.* 187:343–50

79. Harrison PJ. 1999. The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain* 122(Part 4):593–624

80. Haussler MR, Whitfield GK, Haussler CA, Hsieh JC, Thompson PD, et al. 1998. The nuclear vitamin D receptor: biological and molecular regulatory properties revealed. *J. Bone Miner. Res.* 13:325–49

81. Heaney RP, Recker RR, Grote J, Horst RL, Armas LA. 2011. Vitamin $D_3$ is more potent than vitamin $D_2$ in humans. *J. Clin. Endocrinol. Metab.* 96:E447–52

82. Hewison M, Burke F, Evans KN, Lammas DA, Sansom DM, et al. 2007. Extra-renal 25-hydroxyvitamin $D_3$-1α-hydroxylase in human health and disease. *J. Steroid Biochem. Mol. Biol.* 103:316–21

83. Hoang MT, Defina LF, Willis BL, Leonard DS, Weiner MF, Brown ES. 2011. Association between low serum 25-hydroxyvitamin D and depression in a large sample of healthy adults: the Cooper Center Longitudinal Study. *Mayo Clin. Proc.* 86:1050–55

84. Hohman EE, Martin BR, Lachcik PJ, Gordon DT, Fleet JC, Weaver CM. 2011. Bioavailability and efficacy of vitamin $D_2$ from UV-irradiated yeast in growing, vitamin D-deficient rats. *J. Agric. Food Chem.* 59:2341–46

84a. Holick MF. 1995. Environmental factors that influence the cutaneous production of vitamin D. *Am. J. Clin. Nutr.* 61(3 Suppl.):638–45S

85. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, et al. 2012. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. *J. Clin. Endocrinol. Metab.* 97:1153–58

86. Hollo A, Clemens Z, Kamondi A, Lakatos P, Szucs A. 2012. Correction of vitamin D deficiency improves seizure control in epilepsy: a pilot study. *Epilepsy Behav.* 24:131–33

87. Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. 2008. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. *Arch. Gen. Psychiatry* 65:508–12

88. Horst RL, Napoli JL, Littledike ET. 1982. Discrimination in the metabolism of orally dosed ergocalciferol and cholecalciferol by the pig, rat and chick. *Biochem. J.* 204:185–89

89. Hua F, Reiss JI, Tang H, Wang J, Fowler X, et al. 2012. Progesterone and low-dose vitamin D hormone treatment enhances sparing of memory following traumatic brain injury. *Horm. Behav.* 61:642–51

90. Jiang P, Zhang WY, Li HD, Cai HL, Liu YP, Chen LY. 2013. Stress and vitamin D: altered vitamin D metabolism in both the hippocampus and myocardium of chronic unpredictable mild stress exposed rats. *Psychoneuroendocrinology* 38:2091–98

91. Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. 2008. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *J. Intern. Med.* 264:599–609

92. Jorde R, Strand Hutchinson M, Kjaergaard M, Sneve M, Grimnes G. 2013. Supplementation with high doses of vitamin D to subjects without vitamin D deficiency may have negative effects: pooled data from four intervention trials in Tromsø. *ISRN Endocrinol.* 2013:348705

93. Joseph B, Wallen-Mackenzie A, Benoit G, Murata T, Joodmardi E, et al. 2003. p57[Kip2] cooperates with Nurr1 in developing dopamine cells. *Proc. Natl. Acad. Sci. USA* 100:15619–24

94. Kaelber CT, Moul DE, Farmer ME. 1995. Epidemiology of depression. In *Handbook of Depression*, ed. EE Beckham, WR Leber, pp. 3–35. New York: Guilford

95. Kampman MT, Wilsgaard T, Mellgren SI. 2007. Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. *J. Neurol.* 254:471–77

96. Kearns CM, Cass WA, Smoot K, Kryscio R, Gash DM. 1997. GDNF protection against 6-OHDA: time dependence and requirement for protein synthesis. *J. Neurosci.* 17:7111–18

97. Keilhoff G, Grecksch G, Becker A. 2010. Haloperidol normalized prenatal vitamin D depletion-induced reduction of hippocampal cell proliferation in adult rats. *Neurosci. Lett.* 476:94–98

98. Kesby JP, Burne TH, McGrath JJ, Eyles DW. 2006. Developmental vitamin D deficiency alters MK 801-induced hyperlocomotion in the adult rat: an animal model of schizophrenia. *Biol. Psychiatry* 60:591–96

99. Kesby JP, Cui X, Burne TH, Eyles DW. 2013. Altered dopamine ontogeny in the developmentally vitamin D deficient rat and its relevance to schizophrenia. *Front. Cell Neurosci.* 7:111

100. Kesby JP, Cui X, Ko P, McGrath JJ, Burne TH, Eyles DW. 2009. Developmental vitamin D deficiency alters dopamine turnover in neonatal rat forebrain. *Neurosci. Lett.* 461:155–58

101. Kesby JP, Cui X, O'Loan J, McGrath JJ, Burne TH, Eyles DW. 2010. Developmental vitamin D deficiency alters dopamine-mediated behaviors and dopamine transporter function in adult female rats. *Psychopharmacology (Berl.)* 208:159–68

102. Khanal RC, Nemere I. 2007. The ERp57/GRp58/1,25D3-MARRS receptor: multiple functional roles in diverse cell systems. *Curr. Med. Chem.* 14:1087–93

103. Khoraminya N, Tehrani-Doost M, Jazayeri S, Hosseini A, Djazayery A. 2013. Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. *Aust. N. Z. J. Psychiatry* 47:271–75

104. Kinney DK, Barch DH, Chayka B, Napoleon S, Munir KM. 2010. Environmental risk factors for autism: Do they help cause de novo genetic mutations that contribute to the disorder? *Med. Hypotheses* 74:102–6

105. Kjaergaard M, Waterloo K, Wang CE, Almas B, Figenschau Y, et al. 2012. Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomised clinical trial. *Br. J. Psychiatry* 201:360–68

106. Knekt P, Kilkkinen A, Rissanen H, Marniemi J, Saaksjarvi K, Heliovaara M. 2010. Serum vitamin D and the risk of Parkinson disease. *Arch. Neurol.* 67:808–11

107. Ko P, Burkert R, McGrath J, Eyles D. 2004. Maternal vitamin $D_3$ deprivation and the regulation of apoptosis and cell cycle during rat brain development. *Brain Res. Dev. Brain Res.* 153:61–68

108. Korsching S, Auburger G, Heumann R, Scott J, Thoenen H. 1985. Levels of nerve growth factor and its mRNA in the central nervous system of the rat correlate with cholinergic innervation. *EMBO J.* 4:1389–93

109. Kume T, Nishikawa H, Tomioka H, Katsuki H, Akaike A, et al. 2000. p75-mediated neuroprotection by NGF against glutamate cytotoxicity in cortical cultures. *Brain Res.* 852:279–89

110. Lee SJ, Lee HK, Kweon YS, Lee CT, Lee KU. 2009. The impact of executive function on emotion recognition and emotion experience in patients with schizophrenia. *Psychiatry Investig.* 6:156–62

111. Lefebvre d'Hellencourt C, Montero-Menei CN, Bernard R, Couez D. 2003. Vitamin $D_3$ inhibits proin-flammatory cytokines and nitric oxide production by the EOC13 microglial cell line. *J. Neurosci. Res.* 71:575–82

112. Lehmann B, Meurer M. 2010. Vitamin D metabolism. *Dermatol. Ther.* 23:2–12

113. Lemire JM, Adams JS. 1992. 1,25-Dihydroxyvitamin $D_3$ inhibits the passive transfer of cellular immunity by a myelin basic protein-specific T cell clone. *J. Bone Miner. Res.* 7:171–77

114. Lemire JM, Archer DC. 1991. 1,25-Dihydroxyvitamin $D_3$ prevents the in vivo induction of murine experimental autoimmune encephalomyelitis. *J. Clin. Invest.* 87:1103–7

115. Lips P. 2010. Worldwide status of vitamin D nutrition. *J. Steroid Biochem. Mol. Biol.* 121:297–300

116. Llewellyn DJ, Lang IA, Langa KM, Muniz-Terrera G, Phillips CL, et al. 2010. Vitamin D and risk of cognitive decline in elderly persons. *Arch. Intern. Med.* 170:1135–41

117. Llewellyn DJ, Langa KM, Lang IA. 2009. Serum 25-hydroxyvitamin D concentration and cognitive impairment. *J. Geriatr. Psychiatry Neurol.* 22:188–95

118. Lorr M, Sonn TM, Katz MM. 1967. Toward a definition of depression. *Arch. Gen. Psychiatry* 17:183–86

119. Mahon BD, Gordon SA, Cruz J, Cosman F, Cantorna MT. 2003. Cytokine profile in patients with multiple sclerosis following vitamin D supplementation. *J. Neuroimmunol.* 134:128–32

120. Maisonpierre PC, Belluscio L, Squinto S, Ip NY, Furth ME, et al. 1990. Neurotrophin-3: a neurotrophic factor related to NGF and BDNF. *Science* 247:1446–51

121. Manolagas SC, Provvedini DM, Tsoukas CD. 1985. Interactions of 1,25-dihydroxyvitamin $D_3$ and the immune system. *Mol. Cell Endocrinol.* 43:113–22

122. Marniemi J, Alanen E, Impivaara O, Seppanen R, Hakala P, et al. 2005. Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects. *Nutr. Metab. Cardiovasc. Dis.* 15:188–97

123. Mayne CG, Spanier JA, Relland LM, Williams CB, Hayes CE. 2011. 1,25-Dihydroxyvitamin $D_3$ acts directly on the T lymphocyte vitamin D receptor to inhibit experimental autoimmune encephalomyelitis. *Eur. J. Immunol.* 41:822–32

124. Mazdeh M, Seifirad S, Kazemi N, Seifrabie MA, Dehghan A, Abbasi H. 2013. Comparison of vitamin D3 serum levels in new diagnosed patients with multiple sclerosis versus their healthy relatives. *Acta Med. Iran.* 51:289–92

125. McDonald C, Murray RM. 2000. Early and late environmental risk factors for schizophrenia. *Brain Res. Brain Res. Rev.* 31:130–37

126. McGrath J. 1999. Hypothesis: Is low prenatal vitamin D a risk-modifying factor for schizophrenia? *Schizophr. Res.* 40:173–77

127. McGrath J, Scragg R, Chant D, Eyles D, Burne T, Obradovic D. 2007. No association between serum 25-hydroxyvitamin $D_3$ level and performance on psychometric tests in NHANES III. *Neuroepidemiology* 29:49–54

128. McGrath JJ, Eyles DW, Pedersen CB, Anderson C, Ko P, et al. 2010. Neonatal vitamin D status and risk of schizophrenia: a population-based case-control study. *Arch. Gen. Psychiatry* 67:889–94

129. Meguid NA, Hashish AF, Anwar M, Sidhom G. 2010. Reduced serum levels of 25-hydroxy and 1,25-dihydroxy vitamin D in Egyptian children with autism. *J. Altern. Complement. Med.* 16:641–45

130. Menegaz D, Mizwicki MT, Barrientos-Duran A, Chen N, Henry HL, Norman AW. 2011. Vitamin D receptor (VDR) regulation of voltage-gated chloride channels by ligands preferring a VDR-alternative pocket (VDR-AP). *Mol. Endocrinol.* 25:1289–300

131. Milaneschi Y, Bandinelli S, Penninx BW, Vogelzangs N, Corsi AM, et al. 2011. Depressive symptoms and inflammation increase in a prospective study of older adults: a protective effect of a healthy (Mediterranean-style) diet. *Mol. Psychiatry* 16:589–90

132. Milaneschi Y, Shardell M, Corsi AM, Vazzana R, Bandinelli S, et al. 2010. Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. *J. Clin. Endocrinol. Metab.* 95:3225–33

133. Miyaura C, Abe E, Nomura H, Nishii Y, Suda T. 1982. 1α,25-Dihydroxyvitamin $D_3$ suppresses proliferation of murine granulocyte-macrophage progenitor cells (CFU-C). *Biochem. Biophys. Res. Commun.* 108:1728–33

134. Mora JR, Iwata M, von Andrian UH. 2008. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat. Rev. Immunol.* 8:685–98

135. Moskovitz RA. 1978. Seasonality in schizophrenia. *Lancet* 1:664

136. Mostafa GA, Al-Ayadhi LY. 2012. Reduced serum concentrations of 25-hydroxy vitamin D in children with autism: relation to autoimmunity. *J. Neuroinflammation* 9:201

137. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. 2007. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet* 370:851–58

138. Mozaffari-Khosravi H, Nabizade L, Yassini-Ardakani SM, Hadinedoushan H, Barzegar K. 2013. The effect of 2 different single injections of high dose of vitamin D on improving the depression in depressed patients with vitamin D deficiency: a randomized clinical trial. *J. Clin. Psychopharmacol.* 33:378–85

139. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. 2006. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 296:2832–38

140. Munger KL, Zhang SM, O'Reilly E, Hernan MA, Olek MJ, et al. 2004. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 62:60–65

141. Nataf S, Garcion E, Darcy F, Chabannes D, Muller JY, Brachet P. 1996. 1,25 Dihydroxyvitamin $D_3$ exerts regional effects in the central nervous system during experimental allergic encephalomyelitis. *J. Neuropathol. Exp. Neurol.* 55:904–14

142. Naveilhan P, Neveu I, Baudet C, Funakoshi H, Wion D, et al. 1996. 1,25-Dihydroxyvitamin $D_3$ regulates the expression of the low-affinity neurotrophin receptor. *Brain Res. Mol. Brain Res.* 41:259–68

143. Naveilhan P, Neveu I, Wion D, Brachet P. 1996. 1,25-Dihydroxyvitamin $D_3$, an inducer of glial cell line-derived neurotrophic factor. *Neuroreport* 7:2171–75

144. Nemere I, Garbi N, Hammerling G, Hintze KJ. 2012. Role of the $1,25D_3$-MARRS receptor in the $1,25(OH)_2D_3$-stimulated uptake of calcium and phosphate in intestinal cells. *Steroids* 77:897–902

145. Neveu I, Naveilhan P, Baudet C, Brachet P, Metsis M. 1994. 1,25-Dihydroxyvitamin $D_3$ regulates NT-3, NT-4 but not BDNF mRNA in astrocytes. *Neuroreport* 6:124–26

146. Neveu I, Naveilhan P, Jehan F, Baudet C, Wion D, et al. 1994. 1,25-Dihydroxyvitamin $D_3$ regulates the synthesis of nerve growth factor in primary cultures of glial cells. *Brain Res. Mol. Brain Res.* 24:70–76

147. Nissou MF, Brocard J, El Atifi M, Guttin A, Andrieux A, et al. 2013. The transcriptomic response of mixed neuron-glial cell cultures to 1,25-dihydroxyvitamin $D_3$ includes genes limiting the progression of neurodegenerative diseases. *J. Alzheimer's Dis.* 35:553–64

148. O'Gorman C, Lucas R, Taylor B. 2012. Environmental risk factors for multiple sclerosis: a review with a focus on molecular mechanisms. *Int. J. Mol. Sci.* 13:11718–52

149. Pearlson GD. 2000. Neurobiology of schizophrenia. *Ann. Neurol.* 48:556–66

150. Pendyala G, Ninemire C, Fox HS. 2012. Protective role for the disulfide isomerase PDIA3 in methamphetamine neurotoxicity. *PLoS ONE* 7:e38909

151. Peterson A, Mattek N, Clemons A, Bowman GL, Buracchio T, et al. 2012. Serum vitamin D concentrations are associated with falling and cognitive function in older adults. *J. Nutr. Health Aging* 16:898–901

152. Pilz S, Dobnig H, Fischer JE, Wellnitz B, Seelhorst U, et al. 2008. Low vitamin D levels predict stroke in patients referred to coronary angiography. *Stroke* 39:2611–13

153. Pols HA, Birkenhager JC, Foekens JA, van Leeuwen JP. 1990. Vitamin D: a modulator of cell proliferation and differentiation. *J. Steroid Biochem. Mol. Biol.* 37:873–76

154. Pozuelo-Moyano B, Benito-Leon J, Mitchell AJ, Hernandez-Gallego J. 2013. A systematic review of randomized, double-blind, placebo-controlled trials examining the clinical efficacy of vitamin D in multiple sclerosis. *Neuroepidemiology* 40:147–53

155. Procopio M, Marriott PK. 1998. Seasonality of birth in epilepsy: a Danish study. *Acta Neurol. Scand.* 98:297–301

156. Procopio M, Marriott PK, Davies RJ. 2006. Seasonality of birth in epilepsy: a Southern Hemisphere study. *Seizure* 15:17–21

157. Procopio M, Marriott PK, Williams P. 1997. Season of birth: aetiological implications for epilepsy. *Seizure* 6:99–105

158. Prufer K, Barsony J. 2002. Retinoid X receptor dominates the nuclear import and export of the unliganded vitamin D receptor. *Mol. Endocrinol.* 16:1738–51

159. Prufer K, Veenstra TD, Jirikowski GF, Kumar R. 1999. Distribution of 1,25-dihydroxyvitamin D3 receptor immunoreactivity in the rat brain and spinal cord. *J. Chem. Neuroanat.* 16:135–45

160. Pugliatti M, Harbo HF, Holmoy T, Kampman MT, Myhr KM, et al. 2008. Environmental risk factors in multiple sclerosis. *Acta Neurol. Scand. Suppl.* 188:34–40

161. Quintero EM, Willis LM, Zaman V, Lee J, Boger HA, et al. 2004. Glial cell line-derived neurotrophic factor is essential for neuronal survival in the locus coeruleus-hippocampal noradrenergic pathway. *Neuroscience* 124:137–46

162. Ramagopalan SV, Dyment DA, Cader MZ, Morrison KM, Disanto G, et al. 2011. Rare variants in the CYP27B1 gene are associated with multiple sclerosis. *Ann. Neurol.* 70:881–86

163. Ramagopalan SV, Heger A, Berlanga AJ, Maugeri NJ, Lincoln MR, et al. 2010. A ChIP-seq defined genome-wide map of vitamin D receptor binding: associations with disease and evolution. *Genome Res.* 20:1352–60

164. Salami M, Talaei SA, Davari S, Taghizadeh M. 2012. Hippocampal long term potentiation in rats under different regimens of vitamin D: an in vivo study. *Neurosci. Lett.* 509:56–59

165. Sanchez B, Lopez-Martin E, Segura C, Labandeira-Garcia JL, Perez-Fernandez R. 2002. 1,25-Dihydroxyvitamin $D_3$ increases striatal GDNF mRNA and protein expression in adult rats. *Brain Res. Mol. Brain Res.* 108:143–46

166. Sanchez B, Relova JL, Gallego R, Ben-Batalla I, Perez-Fernandez R. 2009. 1,25-Dihydroxyvitamin $D_3$ administration to 6-hydroxydopamine-lesioned rats increases glial cell line-derived neurotrophic factor and partially restores tyrosine hydroxylase expression in substantia nigra and striatum. *J. Neurosci. Res.* 87:723–32

167. Sanders KM, Stuart AL, Williamson EJ, Jacka FN, Dodd S, et al. 2011. Annual high-dose vitamin $D_3$ and mental well-being: randomised controlled trial. *Br. J. Psychiatry* 198:357–64

168. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. 2005. Abnormal bone and calcium metabolism in immobilized Parkinson's disease patients. *Mov. Disord.* 20:1598–603

169. Sawcer S, Hellenthal G, Pirinen M, Spencer CC, Patsopoulos NA, et al. 2011. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature* 476:214–19

170. Schrader M, Kahlen JP, Carlberg C. 1997. Functional characterization of a novel type of $1\alpha,25$-dihydroxyvitamin $D_3$ response element identified in the mouse c-*fos* promoter. *Biochem. Biophys. Res. Commun.* 230:646–51

171. Schuster I. 2011. Cytochromes P450 are essential players in the vitamin D signaling system. *Biochim. Biophys. Acta* 1814:186–99

172. Shahbeigi S, Pakdaman H, Fereshtehnejad SM, Nikravesh E, Mirabi N, Jalilzadeh G. 2013. Vitamin $D_3$ concentration correlates with the severity of multiple sclerosis. *Int. J. Prev. Med.* 4:585–91

173. Simpson S Jr, Blizzard L, Otahal P, Van der Mei I, Taylor B. 2011. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. *J. Neurol. Neurosurg. Psychiatry* 82:1132–41

174. Slinin Y, Paudel ML, Taylor BC, Fink HA, Ishani A, et al. 2010. 25-Hydroxyvitamin D levels and cognitive performance and decline in elderly men. *Neurology* 74:33–41

175. Sonnenberg J, Luine VN, Krey LC, Christakos S. 1986. 1,25-Dihydroxyvitamin $D_3$ treatment results in increased choline acetyltransferase activity in specific brain nuclei. *Endocrinology* 118:1433–39

176. Stephensen CB, Zerofsky M, Burnett DJ, Lin YP, Hammock BD, et al. 2012. Ergocalciferol from mushrooms or supplements consumed with a standard meal increases 25-hydroxyergocalciferol but decreases 25-hydroxycholecalciferol in the serum of healthy adults. *J. Nutr.* 142:1246–52

177. Suzuki M, Yoshioka M, Hashimoto M, Murakami M, Noya M, et al. 2013. Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson disease. *Am. J. Clin. Nutr.* 97:1004–13

178. Taghizadeh M, Talaei SA, Salami M. 2013. Vitamin D deficiency impairs spatial learning in adult rats. *Iran. Biomed. J.* 17:42–48

179. Tekes K, Gyenge M, Folyovich A, Csaba G. 2009. Influence of neonatal vitamin A or vitamin D treatment on the concentration of biogenic amines and their metabolites in the adult rat brain. *Horm. Metab. Res.* 41:277–80

180. Tekes K, Gyenge M, Hantos M, Csaba G. 2009. Transgenerational hormonal imprinting caused by vitamin A and vitamin D treatment of newborn rats. Alterations in the biogenic amine contents of the adult brain. *Brain Dev.* 31:666–70

181. Tenenhouse A, Warner M, Commissiong JW. 1991. Neurotransmitters in the CNS of the vitamin D deficient, hypocalcemic rat. *Neurochem. Int.* 18:249–55

182. Tohda C, Urano T, Umezaki M, Nemere I, Kuboyama T. 2012. Diosgenin is an exogenous activator of $1,25D_3$-MARRS/Pdia3/ERp57 and improves Alzheimer's disease pathologies in 5XFAD mice. *Sci. Rep.* 2:535

183. Tomac A, Widenfalk J, Lin LF, Kohno T, Ebendal T, et al. 1995. Retrograde axonal transport of glial cell line-derived neurotrophic factor in the adult nigrostriatal system suggests a trophic role in the adult. *Proc. Natl. Acad. Sci. USA* 92:8274–78

184. Tsai MJ, O'Malley BW. 1994. Molecular mechanisms of action of steroid/thyroid receptor superfamily members. *Annu. Rev. Biochem.* 63:451–86

185. Tu WJ, Zhao SJ, Xu DJ, Chen H. 2014. Serum 25-hydroxyvitamin D predicts the short-term outcomes of Chinese patients with acute ischaemic stroke. *Clin. Sci. (Lond.)* 126:339–46

186. Turner KM, Young JW, McGrath JJ, Eyles DW, Burne TH. 2013. Cognitive performance and response inhibition in developmentally vitamin D (DVD)-deficient rats. *Behav. Brain Res.* 242:47–53

187. Van Cromphaut SJ, Dewerchin M, Hoenderop JG, Stockmans I, Van Herck E, et al. 2001. Duodenal calcium absorption in vitamin D receptor-knockout mice: functional and molecular aspects. *Proc. Natl. Acad. Sci. USA* 98:13324–29

188. van der Mei IA, Ponsonby AL, Dwyer T, Blizzard L, Simmons R, et al. 2003. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. *BMJ* 327:316

189. VanAmerongen BM, Dijkstra CD, Lips P, Polman CH. 2004. Multiple sclerosis and vitamin D: an update. *Eur. J. Clin. Nutr.* 58:1095–109

190. Veenstra TD, Prufer K, Koenigsberger C, Brimijoin SW, Grande JP, Kumar R. 1998. 1,25-Dihydroxyvitamin D$_3$ receptors in the central nervous system of the rat embryo. *Brain Res.* 804:193–205

191. Walbert T, Jirikowski GF, Prufer K. 2001. Distribution of 1,25-dihydroxyvitamin D$_3$ receptor immunoreactivity in the limbic system of the rat. *Horm. Metab. Res.* 33:525–31

192. Wang JY, Wu JN, Cherng TL, Hoffer BJ, Chen HH, et al. 2001. Vitamin D$_3$ attenuates 6-hydroxydopamine-induced neurotoxicity in rats. *Brain Res.* 904:67–75

193. Wang L, Hara K, Van Baaren JM, Price JC, Beecham GW, et al. 2012. Vitamin D receptor and Alzheimer's disease: a genetic and functional study. *Neurobiol. Aging* 33:1844e1–9

194. Wang Y, Chang CF, Morales M, Chiang YH, Hoffer J. 2002. Protective effects of glial cell line-derived neurotrophic factor in ischemic brain injury. *Ann. N. Y. Acad. Sci.* 962:423–37

195. Wang Y, Zhu J, DeLuca HF. 2012. Where is the vitamin D receptor? *Arch. Biochem. Biophys.* 523:123–33

196. Wergeland S, Torkildsen O, Myhr KM, Aksnes L, Mork SJ, Bo L. 2011. Dietary vitamin D3 supplements reduce demyelination in the cuprizone model. *PLoS ONE* 6:e26262

197. Williams JH, Wellman NA, Geaney DP, Cowen PJ, Feldon J, Rawlins JN. 1998. Reduced latent inhibition in people with schizophrenia: an effect of psychosis or of its treatment. *Br. J. Psychiatry* 172:243–49

198. Wion D, MacGrogan D, Neveu I, Jehan F, Houlgatte R, Brachet P. 1991. 1,25-Dihydroxyvitamin D3 is a potent inducer of nerve growth factor synthesis. *J. Neurosci. Res.* 28:110–14

199. Wright DW, Kellermann AL, Hertzberg VS, Clark PL, Frankel M, et al. 2007. ProTECT: a randomized clinical trial of progesterone for acute traumatic brain injury. *Ann. Emerg. Med.* 49:391–402.e2

200. Xiao G, Wei J, Yan W, Wang W, Lu Z. 2008. Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial. *Crit. Care* 12:R61

201. Yasuhara T, Hara K, Maki M, Masuda T, Sanberg CD, et al. 2008. Dietary supplementation exerts neuroprotective effects in ischemic stroke model. *Rejuvenation Res.* 11:201–14

202. Zanatta L, Goulart PB, Goncalves R, Pierozan P, Winkelmann-Duarte EC, et al. 2012. 1α,25-dihydroxyvitamin D$_3$ mechanism of action: modulation of L-type calcium channels leading to calcium uptake and intermediate filament phosphorylation in cerebral cortex of young rats. *Biochim. Biophys. Acta* 1823:1708–19

203. Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, et al. 2001. Extrarenal expression of 25-hydroxyvitamin D$_3$-1α-hydroxylase. *J. Clin. Endocrinol. Metab.* 86:888–94

204. Zetterström RH, Solomin L, Jansson L, Hoffer BJ, Olson L, Perlmann T. 1997. Dopamine neuron agenesis in Nurr1-deficient mice. *Science* 276:248–50

205. Zhu Y, Zhou R, Yang R, Zhang Z, Bai Y, et al. 2012. Abnormal neurogenesis in the dentate gyrus of adult mice lacking 1,25-dihydroxy vitamin D$_3$ (1,25-(OH)$_2$D$_3$). *Hippocampus* 22:421–33