# Vitamin D and multiple sclerosis: epidemiology, immunology, and genetics

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## Abstract

**Purpose of review—**To provide a brief update of new research findings on the role of vitamin D in multiple sclerosis (MS).

**Recent Findings—**Evidence continues to accumulate supporting a protective role for vitamin D in MS etiology and progression. Notable recent findings are that high 25-hydroxyvitamin D (25(OH)D) at the time of a first demyelinating event predicts a lower MS risk , and a decreased risk of MS among offspring whose mothers had high predicted 25(OH)D levels. While a small vitamin D intervention study did not find an association between vitamin D and MS progression, this study had little statistical power, and larger trials will be needed to assess the therapeutic potential of vitamin D. Recent immunological studies also show modulation of the immune system by vitamin D that may be favorable for preventing or slowing the progression of MS. The demonstration that rare variants in *CYP27B1*, which encodes the enzyme that converts vitamin D to its active form, are strongly associated with MS risk supports a causal role of vitamin D deficiency as a risk factor for MS.

**Summary—**Research on the nature of the association between vitamin D and MS etiology and progression continues to progress, however, additional research on the timing and dose-response relationship will be crucial for designing future prevention and treatment trials.

### Keywords

multiple sclerosis; vitamin D; epidemiology

## Introduction

The possibility that vitamin D deficiency may be a risk factor for multiple sclerosis (MS) was proposed more than 30 years ago [1], primarily to explain the observation of a latitude gradient in MS prevalence. Latitude is strongly correlated with ultraviolet radiation (UV) duration and intensity and UVB is the main source of vitamin D in most populations. [2] Strong observational evidence and experimental work further support a potential causal

association [3]. Although the exact mechanism of action of vitamin D is not known, given the available data and the safety profile of vitamin D, there is strong interest in conducting vitamin D treatment and prevention trials of MS. The underlying biology may have important implications for timing an intervention; thus, continued epidemiologic, immunologic, and genetic studies are important to fully understand how vitamin D reduces MS risk and possibly slows disease progression. A comprehensive review on vitamin D and MS has been recently published [3] – here we provide an update based on selected contributions from 2011.

## Epidemiology

Epidemiologic investigations over the past year have focused on a variety of topics detailed below.

### UVB and 25(OH)D and MS risk

Epidemiologic evidence strongly supports a role for vitamin D insufficiency in the etiology of MS. [3] Findings from our study of U.S. military personnel showed that among non-Hispanic whites, low 25-hydroxy vitamin D (25(OH)D) levels in young adults predict a subsequent increased MS risk independent of latitude of residence at entry into the military. [4] Consistent with these findings, in a recent longitudinal Canadian study of 302 children with acute deymyelinating syndrome, low vitamin D levels were significantly associated with MS risk in the subsequent three years (HR for 10nmo/L decrease=1.11, 95% CI: 1.00-1.25). [5] However, these inverse associations could also be explained by a direct effect of UVB radiation, which has immunosuppressive effects independent from vitamin D. [6] An attempt to separate the effects of vitamin D from other effects of UVB radiation was made in the Ausimmune study. [7]* Both UVB (modeled as leisure time UV dose from age 6 onward, actinic skin damage, or UV dose prior to first episode) and 25(OH)D at time of first demyelinating event (FDE), when considered simultaneously in the same multivariate regression model, were independent predictors of FDE. The estimate of the relative risk was 0.95 (95% CI:0.88-1.02) for a 10nmol/L increase in 25(OH)D adjusted for UV dose. Similarly, the 25(OH)D adjusted relative risk of MS associated with a $10kJ/m^2$ increase in UV dose was 0.48 (95% CI:0.25-0.92). The authors concluded that 25(OH)D and UVB are independent risk factors suggesting the effects of UVB may act outside of the vitamin D pathway. However, these results are also consistent with the hypothesis that 25(OH)D alone may predict subsequent MS risk, as a lifetime UVR is likely to be a better measure of long-term 25(OH)D exposure than a single measure of 25(OH)D taken at the time of the FDE. [8]

### Early life vitamin D exposure and MS risk

A question central to a primary prevention trial or broad recommendations for vitamin D supplementation is the relevant age of exposure, which can range from from *in utero* to adolescence and adulthood. [9] Among participants in the prospective Nurses' Health Study II cohort, MS risk was lower among women whose mothers, while pregnant, had increased milk intake, increased vitamin D intake or higher predicted 25(OH)D. [10] Similarly, albeit not statistically significant, a reduced MS risk was reported among women reporting increased vitamin D intake from supplements in adolescence (RR =0.73, 95% CI: 0.50-1.07

comparing >=400IU/day to <400IU/day). [11] These results suggest that MS risk is related not only to recent vitamin D levels, as demonstrated previously, [4] but perhaps also on levels during childhood or even *in utero*.

## 25(OH)D and disease severity or progression

MS patients typically have lower serum 25(OH)D levels than healthy controls, [3] likely due to lifestyle changes associated with disease progression and, in fact, it has been shown that 25(OH)D levels tend to be stable before symptom onset but decline after. [4] However, with the widespread attention of the potential therapeutic effect of vitamin D, there is now evidence that use of vitamin D supplements by individuals with MS is increasing – in a recent survey, only 7% of MS patients reported taking vitamin D before their diagnosis compared to 66% after they were diagnosed, [12] thus potentially resulting in MS patients having higher 25(OH)D than those without MS.

African-Americans have, on average, lower circulating 25(OH)D levels than Caucasians [13], but the relation between 25(OH)D and MS risk among African-Americans is not clear. In a recent cross-sectional study of 339 African-American MS patients and 342 African-American controls, levels of vitamin D deficiency (71% in controls and 77% in patients) and insufficiency (93% in controls and 94% in patients) were high [14] and MS patients had lower 25(OH)D levels (30 vs. 37 nmol/L; p=0.0001) than controls, but this may reflect sun avoidance or decreased outdoor activity after MS onset rather than an effect of vitamin D deficiency on MS risk. In regards to disease severity, there was no observed correlation between 25(OH)D levels and Multiple Sclerosis Severity Score (MSSS) or Expanded Disability Severity Score (EDSS).

An negative correlation between 25(OH)D levels and disease severity was observed in a study of 193 MS patients (92% Caucasian) [15]. Higher 25(OH)D and 24,25(OH)D were significantly correlated with a decreased MSSS and marginally with decreased EDSS; but the cross-sectional design does not allow for inference regarding temporality. The strongest evidence of a possible inverse association between vitamin D levels and MS progression rests therefore on previous longitudinal studies. [16,17]

## Clinical trials of vitamin D supplementation

A small trial of supplementation with high dose vitamin D2 (13,000IU/day) versus low dose (I000IU/day) in 23 participants found no difference in number of new gadolinium enhancing (GE) lesions, difference in changes in total volume of T2 lesions, exit EDSS score or probability of relapse during a 6 month trial. [18] However, this study was based on an extremely small number of subjects in which randomization cannot be expected to achieve a balance of the relevant risk factors. In fact, the average age of those on the low-dose regime was ten years older than those on the high-dose regime. Similarly, the percent of females was 64% (7/11) in the high dose group and 75% (9/12) in the low dose group and there was an almost 2 year difference in average pretrial interferon or glatiramer acetate use (low dose=5.5 yrs vs. high dose=3.7 yrs). Albeit not statistically significant, these differences between the high and low dose groups could have a major impact on the reported results. Further, because of the small sample size, the power of this study was virtually zero to detect

a plausible effect of vitamin D supplementation on MS relapses or progression. Neither the results of this study, nor those of the previous small clinical trials of vitamin D3 that suggested a potential benefit on MS progression, however, provide credible evidence in favor or against a therapeutic effect of vitamin D. [19] Currently, a larger double blind, placebo controlled, randomized phase 3 trial of vitamin D3 in Europe is underway. The SOLAR (Supplementation of VigantOL(®) oil versus placebo as Add-on in patients with relapsing-remitting multiple sclerosis receiving Rebif(®) treatment) has a planned enrollment of 348 patients with 25(OH)D levels <150nmol/L. [20] Patients will receive 7000IU/day for 4 weeks and if well tolerated, will increase to 14,000IU/day through 96 weeks. This dose is expected to elevate 25(OH)D levels to over 250 nmol/L. Whether this high a level – which is rarely observed in physiologic conditions -- is necessary, or even desirable, is unclear, because current observational evidence suggests that achieving 100nmol/L could already have a substantial impact on disease burden. [3]

## Genetics

Several, small case-control studies of vitamin D related genes and MS risk have been conducted. They have been largely inconsistent with no associations firmly established. [3] Polmorphisms in the *vitamin D receptor (VDR)* gene have been of particular interest, including the functional *FokI* polymorphism [21] and the tightly linked *TaqI, ApaI* and *BsmI* variants. A recent meta-analysis, however, found no association between these polymorphisms and MS risk. [22] Although a recent large Australian study including 726 cases and 604 controls found weak evidence of the *TaqI* in relation to MS [23], this SNP has not been identified as a susceptibility allele in large GWA studies of MS [24] or in meta-analyses of genetic predictors of 25(OH)D. [25,26]

Investigations of other vitamin D metabolism related genes have become more comprehensive as genotyping methods have advanced and become less costly. Some have relied on a candidate gene approach and others leveraged the results of two recent GWAS for circulating 25(OH)D [25,26], which identified two vitamin D metabolism related genes, *CYP2R1 (*which encodes the enzyme responsible for the conversion of vitamin D to 25(OH)D) and *DBP/GC (*encoding the vitamin D binding protein) as significant predictors of 25(OH)D levels. Genotyping of 71 SNPs in four genes (*CYP24A1, VDR, DBP/GC* and *CYP27B1*) among 3037 individuals from 739 families enrolled in the ongoing Canadian Collaborative Project on the Genetic Susceptibility to MS (CCPGSMS), Orton and colleagues found no evidence of over-transmission after correction for multiple comparisons. [27] In a separate study, using a sub-set of participants in the International Multiple Sclerosis Genetics Consortium (IMSGC), there was a suggestion of a decreased MS risk associated with the 'A' allele of *CYP2R1,* which is associated with higher 25(OH)D levels. A decreased MS risk among carriers of the 'A' allele was observed primarily in *HLA-DR15* negative individuals, though the interaction was non-significant (p=0.06). [28] A recent Spanish investigation of 9 genes in 3637 MS cases and 3665 controls found no evidence of association with *CYP2R1.* (RR=1.03, 95% CI: 0.95, 1.11)[29] The authors did, however, find an increased risk of MS with the 'G' allele of *DHCR7*, rs12785878 (RR=1.10; 95% CI:1.02, 1.19; non-significant at genome wide level). Although the role of *DHCR7* in vitamin D metabolism is not known, it is of note that the reported variant is also a significant

predictor of decreased 25(OH)D in GWA studies [25,26] and recently associated with increased type 1 diabetes risk. [30]

The above studies have primarily relied on identified common variants and have not been particularly informative in providing further support for a causal relationship between vitamin D and MS. However, a more recent study provided interesting evidence by studying rare variants in *CYP27B1*, the gene that encodes the 1-α hydroxylase that converts 25(OH)D to calcitriol, the active hormonal form of vitamin D. [31]** In total, five rare mutations in *CYP27B1* (frequencies ranging from 0.05% to 0.67% in unrelated MS cases) were identified and showed significant evidence of transmission from heterozygous parents to MS offspring ($p=3\times10^{-9}$). Similarly, pooling the variants showed a significantly higher odds of MS comparing 3,564 unrelated MS cases to 1,873 controls (odds ratio = 4.7; 95% CI: 2.3 to 9.4). Because these mutations are associated with reduced activation of 25(OH)D to 1,25(OH)2D, the results of this study support a role of vitamin D deficiency as a risk factor for MS and a causal interpretation of the previous findings that individuals with high circulating 25(OH)D levels have a markedly reduced MS risk. [4] This striking convergence of genetic and epidemiological findings strengthens the rationale for designing supplementation trials of 25(OH)D based on the effective dose observed in epidemiologic studies.

## Interactions

The literature on statistical interactions between MS risk factors, including 25(OH)D, has increased several-fold in the last few years. In general, no compelling interactions with 25(OH)D have been reported to date. Three studies reported no evidence of a super-multiplicative interaction between 25(OH)D and anti-EBNA IgG Ab titers, [5,32,33], though one did find evidence of a statistical super-multiplicative interaction between 25(OH)D and BWRF-1 DNA load (a marker of EBV DNA load). [32] Considering modification by *HLA-DR15*, one study also found no evidence of a significant deviation from a multiplicative or additive association between the presence of *HLA-DR15* and serum 25(OH)D on MS risk. [5] However, the interpretation of statistically significant interactions (defined as a statistically significant deviation from an additive or multiplicative model) is challenging and does not necessarily provide information about underlying biological relationships.

## Animal models of MS

A possible role of vitamin D in MS is indirectly supported by numerous observations that administration of calcitriol (1,25(OH)2D) prevents and slows progression of experimental autoimmune encephalomyelitis (EAE). [3] Recent investigations suggest that this effect requires a functional VDR on T-lymphocytes , [34] as previously observed, [35] and involves modulation of Th17 cell differentiation and IL-17a expression. [36] STAT6 also appears necessary for amelioration of EAE following 1,25(OH)2D3 treatment in *ex vivo* studies. [37] Calcitriol, however, can cause hypercalcemia, and its effect may in part be mediated by increased calcium levels.

In one of the few studies using vitamin D3 (cholecalciferol) itself, at levels consistent with those observed in humans, a beneficial effect on EAE severity was only observed in female mice. [38] A recent study suggested that vitamin D deficiency could reduce EAE severity in

mice whose mothers were themselves vitamin D deficient, suggesting an epigenetic effect. [39] While the results of these studies are intriguing, their relationship to understanding multiple sclerosis in humans is uncertain.

## Immunological studies

The effects of vitamin D supplementation on immune responses in humans have not been extensively investigated. Using cells from 14 RRMS patients enrolled in a vitamin D supplementation trial of MS, no difference was seen between the number of circulating Treg cells or proportions of memory and naïve Treg before and after supplementation. However, there was a significant increase in IL-10+ CD4+ T cells (0.36% vs. 0.69%; p=0.02). Additionally, the Th1/Th2 (IFN-gamma+/IL-4+) balance decreased after supplementation (3.7 vs. 3.0; p=0.04). [40] Immune cell profiles have also been examined in cells from MS patients enrolled in a dose-escalation trial showing that MS-associated T-cell reactivities (particularly the neuronal antigen subset and total proliferation score subset) were suppressed *in vivo* in peripheral blood mononuclear cells (PBMCs) taken from patients supplemented with vitamin D3 over 1 year compared to those without such supplementation. [41]

A role for EBV in the etiology of MS is compelling [42] and some have suggested potential links between vitamin D and EBV particularly in relation to MS. [43,44] Two studies were undertaken to examine the sensitivity of EBV-specific T-cells to vitamin D metabolites. One found that *in vitro* addition of 1,25(OH)2D3 to CD8+ T-cells resulted in a more pro-inflammatory cytokine profile. [45] However, there were overall no differences in cytokine secretion between MS patients and healthy controls. Similarly, EBNA-1 reactive CD4+ T cell clones derived from the blood and CSF of 3 MS patients, showed modified proliferation and secretion of cytokines in response to 1,25(OH)2D3. [46] This effect, although previously reported in the blood [47,48], had not been shown in CSF. However, the same sensitivity was also shown for CMV-specific CD4+ T cells, suggesting a non-specific effect.

## Conclusion

The evidence for vitamin D sufficiency in reducing MS risk is compelling and the recent literature has provided additional evidence for a causal interpretation. Intervention with vitamin D supplementation could have a substantial impact on reducing disease burden; however, important questions remain about the timing of an intervention, the efficacy in slowing progression and the generalizability of findings to different ethnic groups. Most importantly, future investigations should be focused on refining the dose-response relation between vitamin D levels and MS risk or MS progression, which is critical to plan preventive or therapeutic interventions.

## Acknowledgements

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**Key Points**

1.  Growing evidence supports vitamin D deficiency as a risk factor for MS.

2.  The causality of this association is supported by increased MS risk among carriers of rare CYP27B1 variants.

3.  Further work is needed to determine the optimal vitamin D dose for MS prevention and treatment.