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VITAMIN D3 IN THE PATHOGENESIS AND CLINICAL COURSE OF MULTIPLE SCLEROSIS: A COMPREHENSIVE REVIEW OF CURRENT EVIDENCE (2015–2026)

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ABSTRACT

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system characterized by inflammatory activity, neuroaxonal degeneration, and progressive neurological disability. Over the past decade, converging epidemiological, genetic, and mechanistic evidence has positioned vitamin D3 as a biologically plausible environmental determinant influencing MS susceptibility and potentially modulating disease course. This comprehensive review synthesizes peer-reviewed literature published between 2015 and 2026, including Mendelian randomization analyses, large-scale genomic studies, randomized controlled trials, and contemporary meta-analyses. Independent Mendelian randomization studies consistently demonstrate that genetically determined lower circulating 25-hydroxyvitamin D concentrations increase the risk of MS, supporting a causal role in disease susceptibility. In contrast, randomized supplementation trials in established relapsing–remitting MS report heterogeneous and generally modest effects on relapse rates, MRI activity, and disability progression. Emerging data from early-stage disease, including clinically isolated syndrome, suggest a potential stage-dependent benefit. Collectively, current evidence indicates that vitamin D functions primarily as a susceptibility modifier and early immunological regulator rather than a definitive disease-modifying therapy in established MS. Future research should prioritize early-life exposure, genotype-informed stratification, and long-term clinical outcomes to clarify the translational potential of vitamin D optimization in multiple sclerosis.

KEYWORDS

Multiple Sclerosis, Vitamin D3, Mendelian Randomization, MRI Activity, Randomized Controlled Trials, Neuroimmunology

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) characterized by demyelination, axonal injury, gliosis, and progressive neurological dysfunction. It is one of the leading causes of non-traumatic neurological disability in young adults. Global epidemiological estimates indicate that approximately 2.8 million individuals are currently living with MS, with increasing prevalence observed in multiple geographic regions (Walton et al., 2020). The reasons for this rising prevalence are multifactorial and include improved diagnostic capabilities, increased survival, and possibly environmental changes.

The pathogenesis of MS is complex and involves an interplay between genetic predisposition and environmental exposures. Genome-wide association studies have identified over 200 susceptibility loci associated with MS risk, the majority of which localize to immune regulatory pathways (International Multiple Sclerosis Genetics Consortium [IMSGC], 2019). These loci implicate both adaptive and innate immune cells, particularly $CD4^+$ T lymphocytes and microglia, in disease initiation and propagation.

However, genetic predisposition alone does not fully explain the marked geographic variability in MS prevalence, including the well-documented latitude gradient. Individuals residing at higher latitudes exhibit increased MS prevalence compared with those closer to the equator. This geographic pattern has historically been attributed, at least in part, to differences in ultraviolet radiation exposure and consequently endogenous vitamin D synthesis.

Vitamin D3 (cholecalciferol) is synthesized in the skin upon ultraviolet B exposure and subsequently metabolized to 25-hydroxyvitamin D [25(OH)D], the principal circulating form used to assess vitamin D status. The active metabolite, 1,25-dihydroxyvitamin D, exerts genomic effects through binding to the vitamin D receptor (VDR), a nuclear transcription factor expressed in numerous immune cells. Given the central role of

immune dysregulation in MS pathophysiology, vitamin D has emerged as a biologically plausible environmental modifier.

Observational studies conducted prior to 2015 suggested associations between lower serum 25(OH)D concentrations and increased MS risk or greater disease activity. However, interpretation of these findings was limited by potential confounding and reverse causation. Reduced mobility and disability may lead to decreased sunlight exposure and consequently lower vitamin D levels, complicating causal inference.

Between 2015 and 2026, methodological advances have significantly strengthened the evidence base. Mendelian randomization studies have provided genetic support for a causal relationship between lower circulating vitamin D levels and increased MS susceptibility (Mokry et al., 2015; Rhead et al., 2016). In parallel, large-scale genomic mapping has demonstrated enrichment of MS-associated variants within immune regulatory regions that may be influenced by vitamin D signaling (IMSGC, 2019).

Despite strong etiological evidence, randomized controlled trials evaluating vitamin D supplementation in established MS have produced heterogeneous results. Major trials such as SOLAR (Hupperts et al., 2019), EVIDIMS (Dörr et al., 2020), and D-Lay MS (Thouvenot et al., 2025) provide critical insights but do not uniformly demonstrate robust clinical benefit.

The objective of this comprehensive review is to critically evaluate contemporary evidence (2015–2026) regarding the role of vitamin D3 in the pathogenesis and clinical course of MS. Specifically, this review aims to: (1) synthesize genetic and epidemiological evidence supporting causality; (2) examine mechanistic immunological pathways; (3) analyze randomized interventional trials; (4) integrate findings from meta-analyses; and (5) discuss clinical and translational implications.

Methodology

This comprehensive narrative review was conducted in accordance with contemporary methodological standards for evidence synthesis in biomedical research. The literature search was performed using PubMed as the primary database, covering publications from January 1, 2015, to March 2026. The time frame was selected to capture contemporary genetic, interventional, and meta-analytic evidence following the maturation of large-scale genome-wide association studies and the emergence of Mendelian randomization methodology.

Search terms included combinations of: “multiple sclerosis,” “vitamin D,” “vitamin D3,” “cholecalciferol,” “25-hydroxyvitamin D,” “Mendelian randomization,” “genome-wide association,” “randomized controlled trial,” “MRI activity,” “clinically isolated syndrome,” and “meta-analysis.”

Inclusion Criteria

Studies were included if they met the following criteria:

1. Peer-reviewed original research, systematic reviews, or meta-analyses.
2. Published between 2015 and 2026.
3. Human studies, large-scale genomic investigations, or interventional clinical trials.
4. Direct evaluation of vitamin D status, vitamin D supplementation, or genetically predicted vitamin D levels in relation to MS susceptibility or disease activity.

Exclusion Criteria

Studies were excluded if they:

- Were published prior to 2015.
- Focused exclusively on animal models without translational relevance.
- Addressed unrelated autoimmune diseases without specific MS data.
- Lacked methodological transparency or adequate statistical reporting.

Assessment of Methodological Quality

Randomized controlled trials were interpreted with reference to the revised Cochrane Risk of Bias tool (RoB 2), which evaluates domains including randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting (Sterne et al., 2019).

Systematic reviews and meta-analyses were considered within the framework of AMSTAR 2 to assess methodological rigor, risk of bias, and comprehensiveness of evidence synthesis (Shea et al., 2017).

Genetic causal inference studies were interpreted in accordance with the three core assumptions of Mendelian randomization:

1. Relevance – genetic variants must be robustly associated with circulating vitamin D levels.
2. Independence – variants must not be associated with confounders.
3. Exclusion restriction – variants influence MS risk exclusively through vitamin D levels.

Only studies meeting these methodological standards were incorporated into the integrative synthesis presented in this review.

Vitamin D Biology and Immune Regulation

Vitamin D3 (cholecalciferol) is synthesized in the skin following ultraviolet B radiation exposure. It undergoes hepatic hydroxylation to form 25-hydroxyvitamin D [25(OH)D], the major circulating metabolite used for clinical assessment of vitamin D status. Subsequent hydroxylation by 1α-hydroxylase generates the biologically active hormone 1,25-dihydroxyvitamin D.

While the kidney represents the primary site of endocrine activation, extra-renal synthesis occurs in immune cells, including macrophages and dendritic cells. This local production allows vitamin D to function as an autocrine and paracrine immunomodulator.

Vitamin D Receptor (VDR) Signaling

The active metabolite binds to the vitamin D receptor (VDR), a nuclear transcription factor expressed in T lymphocytes, B cells, antigen-presenting cells, and microglia. Upon ligand binding, VDR heterodimerizes with the retinoid X receptor and binds to vitamin D response elements within target gene promoters.

This interaction modulates transcription of genes involved in:

- Cytokine production
- T-cell differentiation
- Immune tolerance
- Oxidative stress regulation

The broad expression of VDR across immune subsets provides mechanistic plausibility for vitamin D as an immune-modulating factor in MS.

Adaptive Immune Modulation in MS

Multiple sclerosis is characterized by dysregulated adaptive immunity. $CD4^+$ T-helper subsets, particularly Th1 and Th17 cells, produce pro-inflammatory cytokines such as interferon-γ and interleukin-17, which contribute to blood–brain barrier disruption and demyelination.

Vitamin D signaling influences adaptive immunity by:

- Suppressing Th1 differentiation
- Inhibiting Th17 polarization
- Reducing IL-17 and IFN-γ production
- Promoting regulatory T-cell (Treg) differentiation

These effects are highly relevant in MS, where breakdown of peripheral tolerance precedes CNS inflammation. Olsson et al. (2017) emphasized that environmental exposures, including vitamin D deficiency, may interact with genetic susceptibility loci to shift immune balance toward autoimmunity.

Interaction with Genetic Architecture

The International Multiple Sclerosis Genetics Consortium (2019) identified over 200 MS susceptibility loci enriched within immune regulatory regions. Many of these loci overlap with transcription factor binding sites relevant to immune cell activation.

Vitamin D–responsive elements have been identified within regulatory regions of genes implicated in immune modulation. Although not all MS-associated variants are directly vitamin D–dependent, the convergence of immune regulatory networks supports a gene–environment interaction model.

Under this framework, genetically susceptible individuals exposed to chronic vitamin D deficiency may exhibit reduced immunoregulatory buffering capacity, increasing the likelihood of autoimmune activation.

Microglial and Innate Immune Effects

Beyond adaptive immunity, microglia contribute significantly to MS lesion evolution. Activated microglia produce pro-inflammatory mediators, reactive oxygen species, and nitric oxide, contributing to neuroaxonal damage.

Vitamin D signaling may attenuate pro-inflammatory microglial activation and modulate oxidative stress responses. While definitive translational confirmation in human MS remains limited, genomic enrichment of MS risk variants within microglial regulatory regions (IMSGC, 2019) supports further investigation of vitamin D–microglia interactions.

Mendelian Randomization and Causal Inference

Observational epidemiology has long suggested an association between lower serum 25-hydroxyvitamin D concentrations and increased risk of multiple sclerosis. However, observational designs are inherently vulnerable to confounding and reverse causation. Individuals with early neurological symptoms may reduce outdoor activity, leading to lower ultraviolet exposure and decreased endogenous vitamin D synthesis. Consequently, establishing causality requires methodologies that minimize such bias.

Mendelian randomization (MR) represents a powerful analytic approach that uses genetic variants as instrumental variables to infer causality between an exposure and an outcome. Because alleles are randomly allocated at conception, MR approximates the structure of a natural randomized trial.

Core Assumptions of Mendelian Randomization

Three assumptions are required:

1. Relevance – Genetic variants must be robustly associated with circulating 25(OH)D levels.
2. Independence – Variants must not be associated with confounders of the exposure–outcome relationship.
3. Exclusion Restriction – Variants must influence MS risk exclusively through vitamin D levels, not via alternative biological pathways.

Violations of these assumptions can introduce bias through horizontal pleiotropy.

Mokry et al. (2015): First Large-Scale Genetic Evidence

Mokry et al. (2015) performed a Mendelian randomization analysis using genome-wide association data to construct genetic instruments predicting circulating 25(OH)D concentrations. Single nucleotide polymorphisms (SNPs) located within genes involved in vitamin D synthesis and metabolism were used as instrumental variables.

The study integrated genetic data from large MS consortia and demonstrated that genetically predicted lower vitamin D levels were associated with increased MS risk. Importantly, sensitivity analyses suggested minimal pleiotropic bias.

The effect sizes were modest but statistically significant. These findings provided strong support for a causal role of vitamin D deficiency in MS susceptibility rather than merely a correlational association.

Rhead et al. (2016): Independent Replication

Rhead et al. (2016) conducted an independent MR analysis using alternative genetic instruments and datasets. This replication strengthened causal inference and reduced the likelihood that results were driven by dataset-specific artifacts.

Their findings were consistent with Mokry et al., demonstrating that genetically determined lower 25(OH)D concentrations increased MS risk.

Replication is critical in genetic epidemiology. Independent confirmation significantly enhances confidence in causal interpretation.

Interpretation of Genetic Causality

The MR evidence suggests that vitamin D deficiency is not simply a consequence of MS but contributes to disease susceptibility.

However, several nuances must be emphasized:

1. MR reflects lifelong exposure differences.
2. Effect sizes correspond to genetically determined differences in baseline vitamin D levels.
3. MR primarily addresses disease initiation, not progression.

This distinction is crucial. A factor that influences risk may not necessarily exert strong therapeutic effects once autoimmunity is established.

Susceptibility Versus Disease Modification

One of the most common misinterpretations in the literature is the assumption that causal risk factors automatically translate into effective therapeutic targets.

MS is a multifactorial disease influenced by:

- Genetic predisposition
- Viral exposures (e.g., EBV)
- Smoking
- Obesity
- Vitamin D status

Even if vitamin D deficiency contributes to susceptibility, supplementation initiated after immune dysregulation is entrenched may not fully reverse established autoreactive memory.

This conceptual distinction may explain the divergence between MR findings and randomized trial results.

Gene–Environment Interaction

Olsson et al. (2017) emphasized that MS emerges from interaction between genetic architecture and environmental exposures. Vitamin D represents a biologically plausible environmental modifier that may influence immune tolerance thresholds.

Genetically susceptible individuals exposed to chronic vitamin D deficiency may experience reduced regulatory buffering capacity, facilitating autoreactive T-cell expansion.

The IMSGC (2019) demonstrated that MS risk loci are enriched in immune regulatory regions. Some of these regulatory regions overlap with transcriptional networks influenced by nuclear receptors, including VDR-mediated pathways.

While direct functional mapping remains incomplete, the convergence of genomic and environmental evidence strengthens the plausibility of vitamin D–genome interaction.

Latitude Gradient Revisited

Although classical latitude gradient data predate the 2015–2026 window, contemporary analyses continue to acknowledge geographic variability in MS prevalence. Walton et al. (2020) reported increasing global prevalence but persistent regional heterogeneity.

Ultraviolet radiation exposure remains a compelling explanatory factor for these patterns. However, ultraviolet exposure may exert immunological effects independent of vitamin D synthesis. Thus, vitamin D may represent one component of a broader ultraviolet-mediated immunomodulatory axis.

Strengths and Limitations of Mendelian Randomization Evidence

Strengths:

- Reduction of confounding
- Protection against reverse causation
- Replication across independent cohorts
- Biological plausibility

Limitations

- Instrument strength may be modest
- Potential residual pleiotropy
- Population ancestry limitations

Inability to evaluate nonlinear exposure effects

Despite limitations, the MR evidence base between 2015 and 2016 remains one of the strongest causal arguments supporting vitamin D deficiency as a susceptibility factor in MS.

Integration with Epidemiological Evidence

Ascherio and Munger (2016) summarized epidemiological risk factors for MS, highlighting vitamin D deficiency as one of the most consistently observed environmental associations.

The convergence of:

- Epidemiology
- Genetic causal inference
- Biological plausibility
- creates a coherent etiological framework.

However, etiological relevance does not guarantee therapeutic efficacy. This tension becomes central when evaluating randomized controlled trials.

Clinical Evidence: Observational MRI Studies and Randomized Controlled Trials

Observational Correlates Between Vitamin D Status and Disease Activity

Before large randomized supplementation trials were completed, several prospective observational analyses suggested that higher circulating 25-hydroxyvitamin D concentrations were associated with reduced inflammatory activity in multiple sclerosis.

Fitzgerald et al. (2015) evaluated patients with relapsing-remitting MS receiving interferon beta-1b therapy. Serum 25(OH)D levels were longitudinally measured and correlated with relapse rate, MRI activity, and disability progression. The investigators reported that higher vitamin D concentrations were associated with reduced new T2 lesion formation and decreased gadolinium-enhancing lesion activity.

Importantly, the study attempted to control for seasonal variability and treatment status. Nevertheless, residual confounding could not be completely excluded. Patients with better overall health behaviors may exhibit both higher vitamin D levels and improved disease outcomes. Despite these limitations, the findings reinforced biological plausibility and provided impetus for interventional trials.

However, observational associations must be interpreted cautiously. Reverse causation remains possible: individuals with more aggressive disease may experience reduced outdoor activity, contributing to lower vitamin D status. Therefore, randomized trials became essential to clarify therapeutic relevance.

SOLAR Trial (Hupperts et al., 2019)

The SOLAR trial represents one of the largest and most rigorously designed randomized controlled trials evaluating vitamin D3 supplementation in relapsing-remitting MS.

Study Design

SOLAR was a multicenter, double-blind, placebo-controlled trial enrolling patients with relapsing-remitting MS receiving stable subcutaneous interferon beta-1a therapy. Participants were randomized to receive high-dose cholecalciferol or placebo in addition to standard disease-modifying therapy.

The primary endpoint was a composite measure incorporating relapse rate and MRI activity. Secondary endpoints included:

- Number of new T2 lesions
- Gadolinium-enhancing lesions
- Disability progression measured by EDSS

Results

The trial did not meet its predefined composite primary endpoint. However, certain MRI-based secondary outcomes demonstrated trends toward reduced inflammatory lesion activity in the high-dose vitamin D group.

No statistically significant effect on confirmed disability progression was observed over the study duration.

Interpretation

Several explanations may account for these findings:

1. Ceiling Effect of Background Therapy
2. Interferon beta-1a already reduces inflammatory activity. Additional benefit from vitamin D supplementation may therefore be modest.
3. Baseline Vitamin D Status
4. Not all participants were severely deficient at baseline. If therapeutic effects are limited to deficient individuals, inclusion of vitamin D–replete patients could dilute measurable impact.
5. Duration of Follow-Up
6. Disability progression in MS often requires longer follow-up to detect significant divergence.
7. Sample Size and Statistical Power
8. Although large for a vitamin D study, SOLAR may still have been underpowered to detect small additive effects.

Importantly, high-dose supplementation was generally well tolerated, with no major safety concerns.

EVIDIMS Trial (Dörr et al., 2020)

The EVIDIMS trial directly compared high-dose versus low-dose vitamin D supplementation in patients with MS.

Study Design

Participants were randomized to receive either high-dose or low-dose vitamin D3. Unlike SOLAR, both groups received supplementation, allowing evaluation of dose–response effects rather than placebo comparison.

Primary endpoints included MRI lesion activity. Secondary endpoints included relapse rate and EDSS progression.

No statistically significant superiority of high-dose supplementation was observed over low-dose supplementation in terms of MRI activity or clinical outcomes.

Interpretation

The absence of a placebo arm complicates interpretation. If even low-dose supplementation achieves sufficient immunological modulation, differences between dosing groups may be minimal.

Furthermore, relatively small sample size limits definitive conclusions. Nonetheless, EVIDIMS contributed important evidence suggesting that escalating vitamin D doses does not necessarily translate into proportionally greater clinical benefit.

D-Lay MS Trial (Thouvenot et al., 2025)

The D-Lay MS trial marks a critical evolution in the clinical investigation of vitamin D in MS.

Table 1. Randomized Controlled Trials Evaluating Vitamin D3 Supplementation in Multiple Sclerosis (2015–2026)

Study (Year)	Population	Intervention	Primary Outcomes	Main Findings
Hupperts et al. (2019) - SOLAR	RRMS patients receiving IFN β-1a	High-dose vitamin D3 (14,000 IU/day) vs placebo	MRI activity, relapse rate	No significant reduction in relapse rate; modest reduction in MRI activity; heterogeneous treatment response
Dörr et al. (2020) - EVIDIMS	RRMS patients	High-dose vs low-dose vitamin D3	MRI lesion load, relapse activity	No significant differences between groups; limited clinical effect
Thouvenot et al. (2025) – D-Lay MS	Patients with clinically isolated syndrome	High-dose vitamin D vs placebo	Time to conversion to clinically definite multiple sclerosis	Delayed conversion to clinically definite MS; strongest effect observed in early-stage disease

Note. RRMS = relapsing-remitting multiple sclerosis; IFN = interferon; MS = multiple sclerosis.

Study Population

Unlike SOLAR and EVIDIMS, which focused on established relapsing-remitting MS, D-Lay MS enrolled individuals with clinically isolated syndrome (CIS) suggestive of MS.

Rationale

If vitamin D exerts its primary influence during early immune dysregulation, intervention at the CIS stage may be more biologically effective than later supplementation.

Study Design

Participants were randomized to receive high-dose vitamin D supplementation or placebo. Primary endpoints included MRI inflammatory activity and conversion to clinically definite MS.

The trial demonstrated a reduction in inflammatory MRI activity in the high-dose group. While complete prevention of conversion to definite MS was not achieved, results suggested a delay or attenuation of inflammatory progression.

Clinical Significance

These findings align with Mendelian randomization evidence indicating that vitamin D plays a role in susceptibility and early disease stages.

D-Lay MS therefore supports a stage-dependent model:

- Stronger effect in preclinical or early inflammatory phase
- Limited effect in established chronic disease

Stage-Dependent Therapeutic Hypothesis

The divergence between SOLAR/EVIDIMS and D-Lay MS supports the hypothesis that vitamin D may be most effective before autoreactive immune memory becomes entrenched.

Once chronic CNS-compartmentalized inflammation develops, supplementation may be insufficient to reverse established immunopathology.

This model reconciles:

- Genetic evidence (susceptibility)
- Early-stage interventional benefit
- Modest late-stage therapeutic effects

Progressive Multiple Sclerosis

Progressive MS phenotypes are characterized by:

- Reduced overt inflammatory activity
- Chronic microglial activation
- Neuroaxonal degeneration
- Mitochondrial dysfunction

None of the major RCTs between 2015 and 2026 specifically targeted progressive MS as a primary population.

Given that vitamin D appears to exert primarily immunomodulatory rather than neuroregenerative effects, it is biologically plausible that therapeutic impact in progressive disease is limited.

Future studies focusing specifically on progressive phenotypes remain necessary.

Safety Considerations

Across SOLAR, EVIDIMS, and D-Lay MS, high-dose vitamin D supplementation was generally well tolerated.

Reported adverse events were infrequent and rarely clinically significant. Hypercalcemia and renal complications were uncommon when appropriate monitoring protocols were followed.

This favorable safety profile supports correction of deficiency in MS populations even in the absence of strong disease-modifying evidence.

Meta-Analyses and Quantitative Evidence Synthesis

Doosti-Irani et al. (2019): Disability Outcomes

Doosti-Irani et al. (2019) conducted a systematic review and meta-analysis evaluating the effects of vitamin D supplementation on disability progression in individuals with multiple sclerosis. The primary endpoint across included trials was change in the Expanded Disability Status Scale (EDSS).

The analysis incorporated randomized controlled trials with heterogeneous dosing regimens, treatment durations, and background disease-modifying therapies. Pooled estimates did not demonstrate a statistically significant reduction in EDSS progression among patients receiving vitamin D supplementation compared with controls.

Several methodological factors may have contributed to these findings:

1. Short follow-up duration – Disability progression in MS evolves over years rather than months. Many included trials were limited to 12–24 months.
2. Small sample sizes – Most vitamin D trials were underpowered to detect small changes in EDSS.
3. Heterogeneous baseline disease activity – Inclusion of both active and relatively stable patients may dilute detectable treatment effects.

4. Variability in achieved serum concentrations – Not all studies targeted uniform 25(OH)D levels.

Despite negative pooled findings, the meta-analysis did not exclude the possibility of modest effects in specific subgroups.

Mahler et al. (2024): Updated Meta-Analytic Integration

Mahler et al. (2024) provided an updated quantitative synthesis incorporating more recent randomized trials, including SOLAR and EVIDIMS. The analysis evaluated relapse rate, MRI lesion activity, and disability progression.

Consistent with earlier findings, pooled analyses did not demonstrate robust, clinically meaningful reductions in relapse rate or confirmed disability progression in established relapsing-remitting MS populations.

However, subgroup analyses suggested potential heterogeneity of effect depending on:

- Baseline vitamin D deficiency status
- Disease stage
- Background disease-modifying therapy

Importantly, the authors emphasized substantial inter-trial variability and methodological limitations.

Methodological Heterogeneity Across Trials

One of the central challenges in interpreting vitamin D supplementation studies lies in the heterogeneity of trial design.

Dose Variability

Supplementation regimens ranged from moderate replacement doses to pharmacological high-dose strategies. The relationship between serum 25(OH)D levels and immunological modulation may not be linear. A threshold effect may exist, beyond which additional supplementation yields diminishing returns.

Baseline Deficiency Stratification

Few trials stratified participants according to baseline vitamin D status. If supplementation primarily benefits individuals with severe deficiency, failure to preselect deficient populations could mask clinically relevant effects.

Duration of Intervention

MS disability progression is a slow, cumulative process. Trials with limited follow-up may underestimate long-term benefits or harms.

Outcome Measures

MRI inflammatory markers may be more sensitive to short-term immunological modulation than EDSS progression. Discrepancies between MRI endpoints and clinical disability endpoints may therefore arise.

Integrative Evidence Model

When synthesizing evidence across epidemiology, Mendelian randomization, randomized trials, and meta-analyses, a coherent pattern emerges.

1. Causal Role in Susceptibility
2. Genetic evidence strongly supports vitamin D deficiency as a causal risk factor for MS development (Mokry et al., 2015; Rhead et al., 2016).
3. Biological Plausibility
4. VDR-mediated immune modulation and gene–environment interactions provide mechanistic support (IMSGC, 2019; Olsson et al., 2017).
5. Modest Therapeutic Impact in Established Disease
6. Randomized trials demonstrate limited or modest additive benefit in patients receiving modern disease-modifying therapies (Hupperts et al., 2019; Dörr et al., 2020).
7. Potential Early-Stage Benefit
8. D-Lay MS (Thouvenot et al., 2025) suggests that early intervention may exert greater impact.

This pattern suggests that vitamin D functions primarily as a susceptibility modifier and early-stage immunological regulator rather than a potent disease-modifying therapy in chronic MS.

Expanded Limitations of the Current Evidence Base

A comprehensive appraisal requires acknowledgment of persistent gaps.

1. Population Ancestry Bias

Most MR and RCT data derive from European ancestry cohorts. Vitamin D metabolism, skin pigmentation, and genetic architecture differ across populations. Generalizability remains uncertain.

2. Nonlinear Exposure Effects

MR typically assumes linear exposure–outcome relationships. It remains unclear whether extreme deficiency confers disproportionately higher risk.

3. Interaction with Epstein–Barr Virus

Recent advances have implicated Epstein–Barr virus infection as a near-universal antecedent to MS. The interaction between EBV-related immune dysregulation and vitamin D status remains insufficiently explored within the 2015–2026 evidence window.

4. Progressive Disease Data Scarcity

Progressive MS remains underrepresented in supplementation trials. Neurodegeneration-dominant pathology may respond differently to immunomodulatory interventions.

5. Absence of Pediatric Longitudinal Trials

Given the susceptibility implications of vitamin D, early-life exposure studies are crucial. However, randomized pediatric prevention trials are lacking.

Precision Medicine and Stratified Approaches

Future investigations may benefit from:

- Stratification by baseline deficiency
- Integration of VDR polymorphism data
- Genotype-informed supplementation trials
- Early intervention cohorts (radiologically isolated syndrome, CIS)

Personalized medicine frameworks may reveal subsets of patients who derive measurable benefit.

Public Health and Clinical Practice Implications

Although high-dose pharmacological supplementation has not demonstrated strong disease-modifying effects, maintaining physiological vitamin D sufficiency is safe and inexpensive.

Routine monitoring of serum 25(OH)D concentrations in MS populations, particularly in high-latitude regions, appears justified.

Correction of deficiency aligns with general bone health and metabolic guidelines and poses minimal risk when appropriately supervised.

However, current evidence does not support replacing established disease-modifying therapies with vitamin D supplementation.

Discussion

The accumulated evidence published between 2015 and 2026 positions vitamin D3 as one of the most biologically plausible environmental modifiers implicated in multiple sclerosis susceptibility. However, a critical and nuanced interpretation is necessary to reconcile strong etiological evidence with modest therapeutic outcomes observed in interventional trials.

Reconciling Causality with Therapeutic Modesty

Mendelian randomization analyses by Mokry et al. (2015) and Rhead et al. (2016) provide compelling evidence that genetically determined lower circulating 25(OH)D levels increase the risk of developing MS. These findings are strengthened by the robustness of instrumental variable methodology and independent replication.

However, the causal inference derived from MR pertains to lifelong exposure. Genetic predisposition influences vitamin D levels from conception onward, potentially shaping immune system maturation, thymic selection processes, and regulatory T-cell development over decades.

By contrast, randomized controlled trials evaluate supplementation initiated after clinical disease onset, often years after subclinical immune dysregulation has occurred. At this stage, autoreactive T- and B-cell populations are already expanded, and chronic CNS-compartmentalized inflammation may be established. Consequently, supplementation may exert limited capacity to reverse entrenched immunopathology.

This distinction between susceptibility modulation and therapeutic reversal represents the central conceptual framework required to interpret the literature coherently.

Stage-Dependent Biological Model

The D-Lay MS trial (Thouvenot et al., 2025) provides important support for a stage-dependent model. Intervention at the clinically isolated syndrome stage demonstrated attenuation of inflammatory activity. This finding suggests that vitamin D may exert greater influence during early immune dysregulation, before irreversible neuroaxonal damage accumulates.

Under this model:

- Vitamin D deficiency contributes to lowering the threshold for autoimmune activation.
- Early supplementation may stabilize immune regulation.
- Late supplementation may have only marginal additive impact in the presence of established adaptive immune memory and neurodegeneration.

Such a framework aligns with both genetic evidence and clinical trial heterogeneity.

Interaction with Genetic Architecture

The International Multiple Sclerosis Genetics Consortium (2019) demonstrated enrichment of MS-associated loci within immune regulatory regions active in T cells and microglia. Although direct mechanistic mapping between VDR binding sites and specific MS risk variants remains incomplete, the overlap between immune regulatory pathways and vitamin D–responsive transcriptional networks supports a gene–environment interaction hypothesis.

In genetically susceptible individuals, chronic vitamin D deficiency may reduce immunoregulatory buffering capacity, facilitating expansion of autoreactive clones. This interaction may be subtle yet cumulative over time.

Future studies integrating vitamin D–related polymorphisms with MS susceptibility loci could clarify whether specific genetic backgrounds confer differential responsiveness to supplementation.

Heterogeneity of Clinical Outcomes

The variability observed across SOLAR (Hupperts et al., 2019), EVIDIMS (Dörr et al., 2020), and D-Lay MS (Thouvenot et al., 2025) underscores the complexity of translating immunological plausibility into clinical efficacy.

Several factors likely contribute:

1. Baseline vitamin D status variability
2. Differences in disease duration
3. Interaction with background disease-modifying therapies
4. Short follow-up relative to disability progression timelines
5. Modest magnitude of expected biological effect

It is unlikely that vitamin D functions as a high-potency disease-modifying therapy. Instead, it may exert incremental effects that are difficult to detect within conventional trial frameworks.

Implications for Progressive Multiple Sclerosis

Progressive MS phenotypes are characterized by chronic microglial activation and neurodegenerative mechanisms that may be less responsive to classical immunomodulation. If vitamin D primarily influences adaptive immune balance, its therapeutic relevance in progressive disease may be inherently limited.

The absence of large, progressive-specific RCTs between 2015 and 2026 represents a significant knowledge gap.

Safety and Clinical Pragmatism

Despite modest therapeutic efficacy signals, high-dose vitamin D supplementation across major trials demonstrated a favorable safety profile. Hypercalcemia and renal complications were rare with appropriate monitoring.

Given the low cost, general health benefits, and safety of physiological vitamin D replacement, maintaining sufficiency in MS populations remains a pragmatic and evidence-aligned strategy.

However, current data do not justify substituting established disease-modifying therapies with vitamin D supplementation.

Broader Environmental Context

MS is increasingly understood as a disease emerging from complex interactions among genetic predisposition, viral exposure (notably Epstein–Barr virus), smoking, obesity, and vitamin D status. Vitamin D likely represents one component of a multifactorial environmental network.

Understanding how vitamin D interacts with other environmental determinants may yield more comprehensive preventive strategies.

Future Research Directions

Several priorities emerge:

1. Early-life and pediatric longitudinal cohorts
2. CIS and radiologically isolated syndrome trials
3. Genotype-stratified supplementation studies
4. Long-term disability outcomes beyond MRI endpoints
5. Integration of immunophenotyping and transcriptomic profiling

Such approaches may clarify whether specific patient subsets derive meaningful benefit.

Extended Translational and Developmental Perspectives

Early-Life Exposure and Developmental Immunology

One of the most compelling implications of Mendelian randomization findings is the possibility that vitamin D influences immune system programming during early life. Because MR reflects genetically determined differences in circulating 25(OH)D levels from birth, the observed association with MS susceptibility suggests that vitamin D may shape immunological tolerance thresholds long before clinical onset.

The immune system undergoes critical developmental windows during childhood and adolescence. Thymic selection, regulatory T-cell expansion, and establishment of immune memory occur over extended periods. Chronic vitamin D deficiency during these windows may subtly alter immune calibration, increasing the probability of autoreactive lymphocyte survival.

Although randomized prevention trials in pediatric populations are lacking within the 2015–2026 window, observational epidemiology and genetic evidence converge on the hypothesis that maintaining adequate vitamin D status during early life could reduce long-term susceptibility.

This perspective aligns with the broader conceptualization of MS as a disease that begins years, if not decades, before clinical manifestation.

Radiologically Isolated Syndrome and Preventive Opportunities

Radiologically isolated syndrome (RIS) represents an asymptomatic stage characterized by incidental MRI findings suggestive of demyelination. Although not addressed directly in major vitamin D RCTs within the defined time window, RIS represents a potential target population for future intervention.

If vitamin D exerts maximal impact before irreversible neuroaxonal injury accumulates, supplementation during RIS or CIS may offer greater benefit than in established relapsing-remitting MS.

The D-Lay MS trial (Thouvenot et al., 2025) supports this preventive model by demonstrating attenuated inflammatory progression in early-stage disease.

Future research integrating radiologically isolated cohorts with vitamin D stratification could clarify preventive potential.

Vitamin D Receptor Polymorphisms and Interindividual Variability

While Mendelian randomization has focused primarily on variants influencing circulating vitamin D levels, polymorphisms within the vitamin D receptor (VDR) gene itself may contribute to interindividual variability in immune responsiveness.

Differences in VDR binding affinity, transcriptional activity, or cofactor recruitment could theoretically modify downstream immunomodulatory effects.

Although large-scale genotype-stratified supplementation trials are currently lacking within the verified 2015–2026 dataset, incorporation of VDR genotyping into future clinical trials could help identify subpopulations more likely to benefit.

Such precision approaches would align with contemporary trends in personalized medicine.

Health Economics and Risk–Benefit Considerations

From a public health perspective, vitamin D supplementation presents a uniquely favorable risk–benefit profile:

- Low cost
- Wide availability
- Established safety at physiological replacement doses
- Additional skeletal and metabolic benefits

Even modest reductions in inflammatory activity could translate into meaningful long-term societal impact when applied at population scale.

However, high-dose pharmacological supplementation without individualized monitoring may carry risks of hypercalcemia and renal complications. Therefore, targeted correction of deficiency rather than indiscriminate megadosing is supported by current evidence.

Integration with Epstein–Barr Virus and Multifactorial Risk Models

Recent advances outside the core vitamin D literature have strengthened the role of Epstein–Barr virus (EBV) as a near-universal antecedent to MS. Vitamin D may interact with viral immunity pathways, influencing antiviral responses and immune tolerance.

Although direct interventional data remain limited within the defined timeframe, integrating vitamin D status into broader multifactorial risk models—including EBV exposure, smoking, obesity, and genetic susceptibility—may enhance predictive accuracy.

MS likely arises from cumulative risk exposures rather than a single dominant factor. Vitamin D represents one modifiable component within this network.

Comprehensive Integrative Model

Synthesizing genetic, epidemiological, mechanistic, and interventional evidence allows formulation of a stage-specific integrative model:

1. Genetic susceptibility establishes immune vulnerability (IMSGC, 2019).
2. Chronic vitamin D deficiency lowers immunoregulatory buffering capacity (Mokry et al., 2015; Rhead et al., 2016).
3. Environmental triggers and viral exposures initiate autoreactive immune activation.
4. Early supplementation may attenuate inflammatory amplification (Thouvenot et al., 2025).
5. Established chronic disease demonstrates limited reversibility (Hupperts et al., 2019; Dörr et al., 2020).

This framework reconciles the apparent tension between strong etiological evidence and modest therapeutic outcomes.

Ethical and Clinical Implications

Given the available evidence, clinicians should:

- Monitor serum 25(OH)D levels in MS patients.
- Correct deficiency according to established endocrine guidelines.
- Avoid representing vitamin D as a substitute for disease-modifying therapy.
- Consider early-stage supplementation strategies where appropriate.

Ethically, transparency regarding the limits of current evidence is essential to prevent unrealistic expectations among patients.

Final Perspective

Vitamin D3 occupies a unique position in the MS research landscape. Few environmental exposures demonstrate such convergence of genetic causal inference, biological plausibility, and epidemiological consistency. Yet few also illustrate as clearly the distinction between risk modification and therapeutic reversal.

The evidence accumulated between 2015 and 2026 strongly supports vitamin D as a modifiable susceptibility determinant and early-stage immunological regulator. However, its role as a standalone disease-modifying therapy in established MS remains limited.

Future research should prioritize:

- Early-life and preventive cohorts
- Genotype-informed intervention
- Long-term disability endpoints
- Integration with broader environmental risk frameworks

Only through such targeted approaches can the full translational potential of vitamin D optimization in multiple sclerosis be clarified.

Advanced Molecular and Immunological Pathways

Beyond classical suppression of Th1 and Th17 responses, vitamin D signaling exerts multilayered regulatory effects across immune and neurobiological systems. Understanding these advanced molecular interactions is essential for interpreting the nuanced clinical impact observed in supplementation trials.

Cytokine Network Modulation

Vitamin D influences a broad cytokine network beyond interferon-γ and interleukin-17. VDR activation has been associated with:

- Reduced production of IL-2
- Downregulation of TNF-α
- Enhanced IL-10 expression
- Modulation of dendritic cell maturation

IL-10 is particularly relevant in MS, as it promotes regulatory immune balance and suppresses autoreactive lymphocyte activation. Even modest shifts in cytokine equilibrium may influence inflammatory lesion formation, particularly in early disease.

Epigenetic Regulation

Emerging evidence suggests that vitamin D may influence epigenetic mechanisms, including histone modification and DNA methylation patterns in immune cells. VDR binding to chromatin can alter transcriptional accessibility in regulatory regions.

Such epigenetic effects may partially explain why lifelong vitamin D exposure (as reflected in Mendelian randomization) has stronger associations with susceptibility than short-term supplementation after diagnosis.

Epigenetic modulation likely requires prolonged exposure, reinforcing the concept of early-life relevance.

Interaction with HLA-DRB1 Risk Alleles

The HLA-DRB1*15:01 allele represents the strongest genetic risk factor for MS. Experimental data suggest that vitamin D response elements may be present in regulatory regions near HLA genes.

Although definitive functional mapping remains incomplete, potential interaction between vitamin D signaling and HLA-mediated antigen presentation could represent a mechanistic bridge between environmental deficiency and genetic susceptibility.

This hypothesis further strengthens the gene–environment interaction model.

Oxidative Stress and Mitochondrial Function

Chronic inflammation in MS is associated with oxidative stress and mitochondrial dysfunction, particularly in progressive disease stages. Vitamin D has been implicated in modulation of antioxidant pathways and reduction of reactive oxygen species in immune cells.

While direct clinical confirmation in MS remains limited, these pathways may contribute to subtle neuroprotective effects not fully captured by conventional relapse or MRI endpoints.

Long-Term Clinical Trajectory and Real-World Implications

Randomized controlled trials often operate within limited time horizons. However, MS is a decades-long disease. Small immunomodulatory effects sustained over many years may cumulatively influence long-term disability trajectories.

Interaction with High-Efficacy Disease-Modifying Therapies

Modern MS treatment increasingly relies on high-efficacy monoclonal antibodies targeting B cells or immune trafficking pathways. In this therapeutic landscape, additive effects of vitamin D may be difficult to detect.

However, vitamin D optimization could theoretically:

- Reduce baseline inflammatory tone
- Support regulatory T-cell stability
- Enhance immunological resilience

These effects may not manifest as dramatic reductions in relapse rate but could contribute to overall immune homeostasis.

Risk Stratification Framework

Integrating vitamin D status into multifactorial risk models may enhance predictive accuracy for disease activation. A composite model incorporating:

- Genetic susceptibility
- EBV serostatus
- Smoking history
- Obesity
- Vitamin D levels

may better characterize individualized risk.

Such frameworks align with preventive neurology paradigms.

Consolidated Clinical Interpretation

Based on contemporary evidence (2015–2026), the most defensible clinical position is:

1. Vitamin D deficiency contributes causally to MS susceptibility.
2. Supplementation in early-stage disease may attenuate inflammatory progression.
3. Established chronic disease demonstrates limited but safe additive effects.
4. Correction of deficiency is advisable for general health and potentially modest neurological benefit.

This position avoids both therapeutic overstatement and undue dismissal of biologically meaningful evidence.

Conclusions

The cumulative evidence published between 2015 and 2026 supports a stage-dependent and biologically coherent interpretation of vitamin D3 in multiple sclerosis. Converging genetic, epidemiological, and mechanistic data provide strong support for a causal role of vitamin D deficiency in MS susceptibility. Mendelian randomization analyses, together with genomic mapping studies, reinforce the plausibility of gene–environment interactions underlying this association.

In contrast, randomized supplementation trials in established relapsing–remitting MS demonstrate modest and heterogeneous clinical effects, with limited evidence for meaningful long-term disability modification. These findings suggest that vitamin D functions primarily as a susceptibility determinant and early immunological regulator rather than as a high-efficacy disease-modifying therapy in chronic disease stages.

Accordingly, vitamin D optimization should be regarded as a rational and safe component of comprehensive MS management, aimed at correcting deficiency and supporting physiological immune regulation. Future investigations should prioritize early-stage intervention, genotype-informed stratification, and long-term disability outcomes to clarify the translational potential of vitamin D3 in multiple sclerosis.

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