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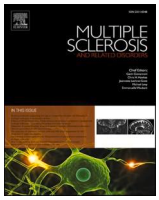

Review article

Effects of high-dose vitamin D supplementation in patients with multiple sclerosis: A systematic review of efficacy and safety

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ABSTRACT

Background: Multiple sclerosis (MS), a chronic autoimmune disease, is the leading cause of non-traumatic neurological disability in young adults. Vitamin D plays a vital immunomodulatory role, and deficiency has been linked to increased MS risk and activity. High-dose vitamin D supplementation has been proposed as a therapeutic approach. However, safety concerns and inconsistent evidence on efficacy highlights the need for systematic evaluation.

Objectives: To evaluate the efficacy and safety of high-dose vitamin D supplementation in patients with MS, with emphasis on immune markers, disability progression, magnetic resonance imaging (MRI) findings, and reported adverse-events.

Methods: This systematic review follows the PRISMA 2020 guidelines. The protocol was registered on PROSPERO (CRD420251128444). Relevant studies were systematically retrieved and searched in public databases. Randomized controlled trials were included that evaluates high-dose vitamin D supplementation (≥10,000 IU/day) in adults with multiple sclerosis, reporting efficacy and/or safety. Data extraction was performed independently by two reviewers. Risk of bias was assessed using RoB-2 for randomized trials. Outcomes of interest are safety, MRI findings, clinical measures, and immunological biomarkers.

Results: Eleven randomized controlled trials were included. High-dose vitamin D increased serum 25-hydroxy vitamin D levels and was surprisingly safe, with rare and transient disturbances in calcium serum levels. MRI and clinical outcomes showed variable effects. Several trials demonstrated immunomodulatory effects, particularly reductions in interleukin-17-related pro-inflammatory activity.

Conclusion: High-dose vitamin D is safe under appropriate monitoring. While clinical and radiological benefits remain inconsistent, evidence of immune modulation suggests a promising adjunctive role requiring further investigation in larger, long-term trials.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disorder characterized by immune-mediated damage to the myelin sheath within the central nervous system (CNS) (Tafti et al., 2026). It affects >2.8 million individuals worldwide and remains the leading cause of non-traumatic neurological disability among young adults (Lugaresi et al., 2024). Current management relies on immunosuppressive disease-modifying therapies to reduce relapses and inflammatory activity, with supportive physical rehabilitation. However, many patients continue to experience relapses, progressive disability, and adverse effects with long-term immunosuppressive treatment (Harrison et al., 2022). Latest MS management prioritizes early initiation of high-efficacy disease-modifying therapies (DMTs) to achieve complete suppression of disease activity, alongside a growing focus on addressing "smoldering" progression. Smoldering progression refers to slow, chronic, low-grade damage that continues in the brain and spinal cord in MS, even when there are no obvious relapses or new lesions visible on standard

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magnetic resonance imaging (MRI) scans (Tur and Rocca, 2024). Emerging trends in MS treatment include promising bruton tyrosine kinase (BTK; a protein essential for B-cell growth, survival, and signalling) inhibitors for progressive MS, precision medicine guided by biomarkers such as neurofilament light chain (NfL) to detect subclinical activity, and monoclonal antibodies offering powerful reduction in relapses (Arredondo-Robles et al., 2025).

Vitamin D is a secosteroid hormone; a type of steroid with a "broken/cut" ring retaining a similar structure to conventional steroids with different conformational shapes while preserving the endocrine activity (Norman, 2008). Its active form, 1α,25-dihydroxycholecalciferol, exerts key immunomodulatory effects by influencing both innate and adaptive immune responses. In particular, vitamin D modulates T-cell activity, suppresses pro-inflammatory cytokines, and enhances regulatory T-cell development, all of which are mechanisms relevant to MS pathophysiology (Aranow, 2011; Galoppin et al., 2022). These properties have led to growing interest in vitamin D as an adjunctive therapy for MS (Sintzel et al., 2017). Epidemiological evidence further supports this notion, with studies demonstrating higher MS prevalence in regions with limited sunlight exposure and consequently reduced endogenous vitamin D synthesis (Gandhi et al., 2021).

Regarding safety, excessive vitamin D intake can lead to persistent hypercalcemia and hypercalciuria, as elevated vitamin D levels increase intestinal calcium absorption, subsequently raising serum calcium concentrations and suppressing parathyroid hormone (PTH) secretion as a response. The resulting persistent hypercalcemia and hypercalciuria rises the risk of complications such as nephrocalcinosis, kidney stones, and impaired renal function (Goltzman et al., 2018). These risks emphasize the need for careful monitoring of serum calcium, PTH, renal function, and urinary calcium, alongside dietary calcium restriction and increased fluid intake (Asif and Farooq, 2026; Marcinowska-Suchowierska et al., 2018).

Despite these precautions, the long-term safety and therapeutic efficacy of high-dose vitamin D in MS remain uncertain. Most existing systematic reviews have not differentiated between standard-dose and high-dose regimens, limiting the assessment of potential dose-dependent benefits and harms. This highlights the need for a focused systematic review to evaluate whether high-dose vitamin D supplementation provides clinically meaningful benefit in MS management while maintaining an acceptable safety profile.

This systematic review aimed to evaluate the efficacy and safety of high-dose vitamin D supplementation in patients with MS, with emphasis on immune markers, disability progression, MRI findings, and reported adverse-events.

2. Methods

2.1. Protocol and registration

This systematic review was conducted following the PRISMA 2020 guidelines (Page et al., 2021). The protocol was registered in PROSPERO (registration number: CRD420251128444).

2.2. Eligibility criteria

Eligible articles include randomized controlled trials from peer-reviewed that are available as full-text. Case reports, prospective and retrospective cohort studies, narrative reviews, editorials, conference abstracts, and non–peer-reviewed sources were excluded. The study population was restricted to adults (≥18 years) with a confirmed diagnosis of MS of any subtype (relapsing-remitting, secondary progressive, or primary progressive). Pediatric populations, animal studies, and in vitro experiments were excluded. The intervention of interest was high-dose vitamin D supplementation (≥10,000 IU/day). No specific comparator was required for inclusion; eligible studies could include placebo or standard-dose vitamin D as controls. Studies were included if they reported at least one of the following outcomes: immune markers, relapse rate, disability progression (measured by Expanded Disability Status Scale, EDSS) (Kurtzke, 1983), MRI activity, serum vitamin D or calcium levels, parathyroid hormone levels, adverse events such as hypercalcemia or kidney complications, or quality of life (QOL) measures.

2.3. Information sources and search strategy

Two reviewers independently conducted systematic searches of PubMed, Scopus, Web of Science, and EBSCOhost (including CINAHL). No restrictions were applied based on publication year or country of origin. Only studies published in English were included. A combination of Medical Subject Headings (MeSH) and free-text keywords was used in the search strategy.

The PubMed search string used was: ("Multiple Sclerosis"[MeSH Terms] OR "Multiple Sclerosis"[Title/Abstract] OR "MS"[Title/Abstract]) AND ("Vitamin D"[MeSH Terms] OR "Cholecalciferol"[MeSH Terms] OR "Vitamin D"[Title/Abstract] OR "Cholecalciferol"[Title/Abstract]) AND ("High-Dose Therapy"[MeSH Terms] OR "High dose"[Title/Abstract] OR "High-dose vitamin D"[Title/Abstract] OR "Mega dose"[Title/Abstract] OR "Pharmacologic dose"[Title/Abstract]) AND ("Treatment Outcome"[MeSH Terms] OR "Disease Progression"[MeSH Terms] OR "Relapse"[Title/Abstract] OR "MRI lesions"[Title/Abstract] OR "Disability"[Title/Abstract]).

Equivalent search terms were adapted for use in Scopus, Web of Science, and EBSCO. Additionally, the reviewers manually screened the reference lists of included articles to identify further eligible studies.

2.4. Study selection

All search results from PubMed, Scopus, Web of Science, and EBSCO were imported into Rayyan AI for study management. Two independent reviewers screened the titles and abstracts of all retrieved records to assess eligibility based on predefined inclusion and exclusion criteria. Disagreements between the reviewers were resolved through discussion, and when consensus could not be reached, a third reviewer acted as an arbitrator. Full-text articles were obtained for studies deemed potentially eligible, and the same two reviewers independently assessed the full texts for final inclusion. The study selection process is demonstrated using a PRISMA 2020 flow diagram (Fig. 1).

2.5. Data extraction

Two reviewers independently extracted data using a standardized extraction form developed by the review team. Extracted variables included study ID, study design, country, population characteristics, intervention details, comparator, duration of follow-up, and reported outcomes.

2.6. Risk of bias assessment

Two reviewers independently assessed the risk of bias for all included studies. Any discrepancies were resolved through discussion, with involvement of a third reviewer when necessary to reach consensus. As all included studies were randomized controlled trials (n = 11), the Cochrane Risk of Bias 2 (RoB-2) tool was uniformly applied to evaluate methodological quality across all studies. A summary graph of the risk of bias assessment is presented in (Fig. 2).

2.7. Data synthesis

A narrative synthesis was conducted due to heterogeneity in study designs, interventions, and reported outcomes. Studies were grouped according to their primary outcome of interest: Safety, MRI outcomes, clinical outcomes including relapse rate, EDSS, No Evidence of Disease Activity (NEDA-3), and biomarkers, including interleukin (IL)-10, IL-17,

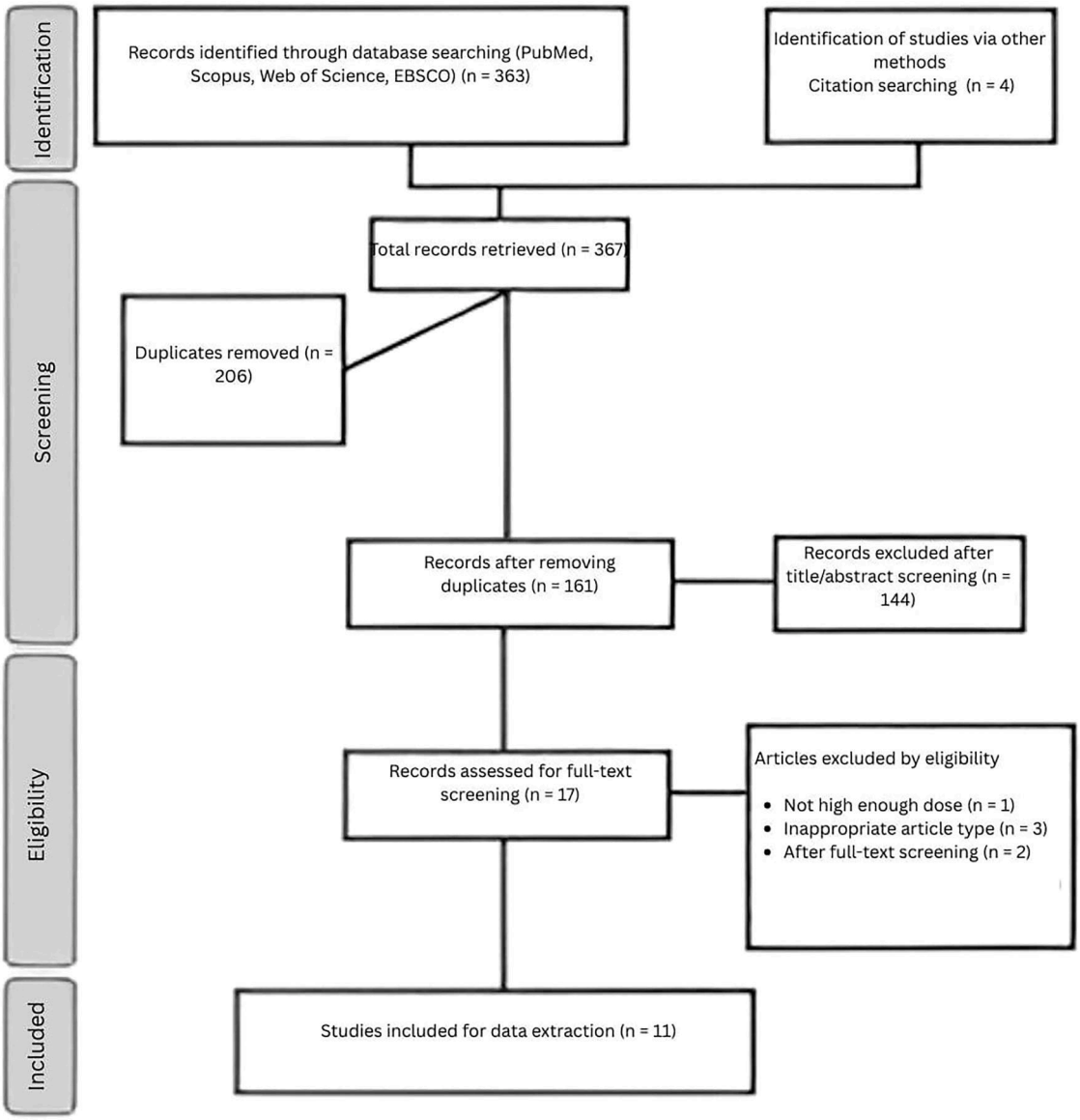

Fig. 1. PRISMA 2020 Flowchart.

neurofilament light chain (NfL), and others. Results were summarized descriptively within each outcome category to highlight patterns, consistencies, and differences across studies.

3. Results

3.1. Search results

The systematic literature search identified a total of 363 records through electronic database search, including PubMed, Scopus, Web of Science, and EBSCO. In addition, four further records were identified through snowballing, resulting in a total of 367 records retrieved. After removal of duplicates (n = 206), 161 records remained and were screened based on titles/abstracts. Out of these, one hundred forty-four records were excluded for not meeting the inclusion criteria. Articles were subsequently assessed for full-text availability where 17 were excluded. Following full-text screening, six studies were excluded due to the following: Insufficient vitamin D dosage (n = 1), excluded study design or article type (n = 3), or failure to meet eligibility criteria after detailed assessment (n = 2). Ultimately, eleven studies met all predefined inclusion criteria and were included in the final qualitative synthesis and data extraction. Study selection process is summarized and documented using a PRISMA 2020 flow diagram (Fig. 1).

3.2. Study characteristics

Following study selection, a total of 11 randomized controlled trials were included in the final analysis. General characteristics of the included studies were extracted and summarized. Extracted data included study identification (author and year), country of conduct, sample size, vitamin D dosage and duration of supplementation, comparator or control group, follow-up duration, and the main outcomes reported. These characteristics provide an overview of the study designs, interventions, and outcome measures across the included trials and are presented in (Table 1).

3.3. Risk of bias assessment

The risk of bias assessment for the 11 included randomized controlled trials is summarized in the traffic-light plot and overall risk-of-bias graph (Fig. 2). Overall, the majority of studies were judged to be at low risk of bias across most of the domains. Bias arising from the

Fig. 2. Risk-of-Bias Graph: Traffic-light plot and overall risk-of-bias graph.

randomization process (D1), bias in measurement of outcomes (D4), and bias in selection of the reported results (D5) were predominantly rated as low risk in nearly all included trials. Some concerns were identified primarily in the domains of bias due to deviations from intended interventions (D2) and bias due to missing outcome data (D3), affecting a minority of studies. One study was judged to be at high risk of bias overall, mainly driven by concerns related to the randomization process.

3.4. Outcomes

3.4.1. Safety outcomes

High-dose vitamin D supplementation carries a theoretical risk of hypercalcemia and related disturbances in calcium metabolism. However, across the included randomized controlled trials, high-dose regimens were generally safe and well tolerated when administered under laboratory monitoring. Most studies reported no clinically meaningful abnormalities in serum calcium, renal, or hepatic parameters, with only rare and transient cases of asymptomatic hypercalcemia or hypercalciuria reported (Sotirchos et al., 2015). Overall, safety findings were consistent and among the most robust outcomes in this review, supporting the clinical feasibility of high-dose vitamin D under appropriate monitoring. Table 2 further details the safety outcomes of vitamin D supplementations.

3.4.2. Radiological outcomes

T2-weighted lesion burden and combined unique active (CUA) lesions are key MRI markers of inflammatory activity in MS. Across the included studies, high-dose vitamin D showed inconsistent and generally modest effects on MRI outcomes, with one study reporting significant reductions observed in CUA lesions or T2 lesion progression

Table 1
Summary of characteristics of included trials.
QOL, quality of life; NEDA-3, no evidence of disease activity-3, EDSS, Expanded Disability Status Scale; IL-17, interleukin-17; IL-10, interleukin-10; Anti-EBV, antibodies against Epstein–Barr virus, NfL, neurofilament light chain; IL-17 CD4 T cells (Th17 cells), IL-17–producing CD4⁺ T lymphocytes; memory T cells, antigen-experienced T lymphocytes, T2-weighted lesion count, number of hyperintense lesions on T2-weighted MRI; IFN-β, interferon beta; IU, international unit, NA: Not applicable.

Study ID	Country	Sample Size	Vitamin D Dose and Duration	Comparator Group	Follow-Up Duration	Main Outcomes
Ashtari et al. (2016)	Iran	94	10,000 IU/day for 3 months	IFN-β−1a only	13 weeks	Quality of life
Hupperts et al. (2019)	Multiple countries	232	6670 IU/day for 4 weeks, then 14,007 IU/day for 44 weeks.	IFN-β−1a only	48 weeks	NEDA-3 and EDSS
Bhargava et al. (2015)	United States	32	10,400 IU/day vs 800 IU/day for 6 months	800 IU/day	26 weeks	IL-17 and memory T cells
Toghianifar et al. (2015)	Iran	94	10,000 IU/day for 12 weeks	IFN-β−1a only	12 weeks	IL-17 and EDSS
Rolf et al. (2017)	Netherlands	53	7000 IU/day for 4 weeks then 14,000 IU/day until week 48.	IFN-β−1a only	48 weeks	Anti-EBV
Ashtari et al. (2015)	Iran	94	≈10,000 IU/day for 3 months	IFN-β−1a only	13 weeks	EDSS and IL-10
Muri et al. (2016)	Netherlands	53	14,000 IU/day for 48 weeks	IFN-β−1a only	48 weeks	Immunomodulation
Burton et al. (2010)	Canada	49	≈14,000 IU/day for 52 weeks	NA	52 weeks	Safety
Dörr et al. (2020)	Germany	53	20,400 IU every other day for 18 months vs. 400 IU every other day	low-dose vitamin D group	78 weeks	difference in T2-weighted lesion count
Smolders et al. (2019)	Netherlands	40	7000 IU/day for 4 weeks, then 14,000 IU/day for 44 weeks	placebo	48 weeks	NFL
Sotirchos et al. (2015)	United States	40	10,400 IU/day vs 800 IU/day for 6 months	800 IU/day	26 weeks	Interleukin-17 CD4Tcells

Table 2
Safety outcomes of vitamin D supplementation.
PTH = parathyroid hormone; IU = international units; D_3 = vitamin D_3 (cholecalciferol); Ca = calcium; AE = adverse event; CI = confidence interval; SOLAR trial = Supplementation of Vigorous Vitamin D in Relapsing-Remitting Multiple Sclerosis; mg/dL = milligrams per deciliter; μmol/L = micromoles per liter.

Study ID	Safety
Ashtari et al. (2016)	Well-tolerated, no safety concerns.
Hupperts et al. (2019)	Well-tolerated with no safety concerns. Adverse events were mostly mild–moderate. Serious adverse events slightly higher. Nevertheless, they were not causally linked.
Toghianifar et al. (2015)	Well-tolerated, no safety concerns.
Rolf et al. (2017)	Safety was measured in Hupperts et al. (2019).
Ashtari et al. (2015)	Well-tolerated with no safety concerns. Serum calcium remained within the normal range in both groups.
Burton et al. (2010)	Well-tolerated with no safety concerns. No significant changes in serum calcium. PTH stayed within normal range.
Dörr et al. (2020)	No change in mild adverse events. no renal dysfunction or change in calcium levels. no reported adverse events.
Smolders et al. (2019)	This sub study followed the parent SOLAR trial protocol, in which high-dose vitamin D_3 (up to 14,000 IU/day) was previously shown to be safe and well tolerated with no new safety concerns identified. Nausea in three patients resolved after dose discontinuation. Two low-dose patients withdrew due to adverse events unrelated to vitamin D.
Sotirchos et al. (2015)	One case of mild asymptomatic hypercalcemia in the high-dose group that resolved after discontinuation. Urinary calcium elevations occurred in both groups, with no significant differences between them. End-study urine calcium:creatinine ratio was higher in the high-dose group, while serum calcium and renal markers remained stable.

Table 3
MRI outcomes of vitamin D supplementation.
MRI = magnetic resonance imaging; D_3 = vitamin D_3 (cholecalciferol); CUA = combined unique active lesions; T1 = T1-weighted lesions; T2 = T2-weighted lesions; Gd+ = gadolinium-enhancing lesions; EBNA-1 = Epstein–Barr nuclear antigen-1; SOLAR trial = Supplementation of Vigorous Vitamin D in Relapsing-Remitting Multiple Sclerosis.

Study ID	MRI
Hupperts et al. (2019)	High-dose vitamin D_3 reduced MRI-defined inflammation, lowering CUA lesions by 32% and slowing T2 lesion accumulation but showed no effect on T1-hypointense lesions or clinical outcomes.
Rolf et al. (2017)	This study linked reduced anti-EBNA-1 antibody levels from high-dose vitamin D_3 to the parent SOLAR trial's MRI findings, suggesting vitamin D_3 may lower brain lesion activity through immunological effects.
Dörr et al. (2020)	No significant differences were seen in T2 lesions, brain atrophy, or Gd+ lesions, leaving the study underpowered to show radiological benefit.
Smolders et al. (2019)	At 48 weeks, MRI activity was minimal with no significant difference between vitamin D_3 and placebo, showing only a small, clinically irrelevant radiological effect.

(Hupperts et al., 2019). Overall, radiological findings suggest limited and context-dependent benefits. Table 3 further details the radiological outcomes of vitamin D supplementations.

3.4.3. Biomarkers outcomes

Biomarkers were measured to confirm vitamin D exposure and explore potential immunomodulatory effects relevant to MS. Across all studies, serum 25(OH)D levels increased significantly with high-dose supplementation, while immune marker responses were variable, with some evidence of reduced pro-inflammatory activity (e.g. Il-17, anti-EBNA-1 IgG) (Bhargava et al., 2015; Sotirchos et al., 2015; Toghianifar et al., 2015; Rolf et al., 2017). Overall, biomarker findings support biological plausibility but show inconsistent downstream clinical or radiological impact. Table 4 further details the biomarkers outcomes of vitamin D supplementations.

3.4.4. Clinical efficacy outcomes

Clinical efficacy was evaluated using relapse rate, EDSS progression, and patient-reported quality-of-life outcomes. The results indicated no statistically significant differences between intervention and control groups in relapses or disability progression, despite improvement in mental quality-of-life that was observed in the study by Ashtari and their colleagues (2016). Several trials showed non-significant trends toward fewer relapses and slight EDSS improvement (Burton et al., 2010; Toghianifar et al., 2015). Immunological studies demonstrated possible positive effects on stabilizing pro-inflammatory and anti-inflammatory activity (e.g. IL-17, IL-10) without clear translation into clinical

Table 4
Biomarker outcomes of vitamin D supplementation.
25(OH)D = 25-hydroxyvitamin D; D_3 = vitamin D_3 (cholecalciferol); IL = interleukin; IgG = immunoglobulin G; EBNA-1 = Epstein–Barr nuclear antigen-1; VCA = viral capsid antigen; CMV = cytomegalovirus; NfL = neurofilament light chain; MS = multiple sclerosis; nmol/L = nanomoles per liter; ng/mL = nanograms per milliliter.

Study ID	Biomarkers (Inflammatory markers and Serum 25(OH)D
Ashtari et al. (2016)	High-dose vitamin D_3 supplementation significantly increased serum 25(OH)D_3 levels over 3 months compared with placebo ($p < 0.001$), confirming effective treatment exposure and adherence.
Hupperts et al. (2019)	fourfold increase in serum 25-hydroxyvitamin D [25(OH)D] concentrations from baseline in treatment group.
Bhargava et al. (2015)	High-dose vitamin D significantly increased serum 25(OH)D and reduced pro-inflammatory immune markers, indicating a clear treatment effect.
Toghianifar et al. (2015)	High-dose vitamin D effectively raised serum 25(OH)D_3 levels but did not reduce IL-17, with regression suggesting vitamin D intake may be associated with increased pro-inflammatory activity.
Rolf et al. (2017)	High-dose vitamin D_3 markedly increased serum 25(OH)D over 48 weeks and specifically reduced anti-EBNA-1 IgG levels, without affecting VCA or CMV antibodies, indicating selective modulation of humoral immunity.
Ashtari et al. (2015)	High-dose vitamin D significantly raised serum 25(OH)D but only modestly increased IL-10, with regression suggesting a potential supportive yet indirect anti-inflammatory effect in MS.
Muri et al. (2016)	High-dose vitamin D_3 raised serum 25(OH)D without changing immune cell numbers but stabilized cytokine activity, preserving anti-inflammatory responses and preventing immune dysregulation seen in the placebo group.
Burton et al. (2010)	High-dose vitamin D safely raised serum 25(OH)D above 250 nmol/L for over 18 weeks, with variable immune effects suggesting modest modulation but no consistent pro- or anti-inflammatory cytokine changes.
Dörr et al. (2020)	Serum 25(OH)D rose markedly in the high-dose arm (≈19→62 ng/mL) versus a small rise in the low-dose arm (≈17→23 ng/mL), confirming biological separation of dosing.
Smolders et al. (2019)	High-dose vitamin D_3 markedly raised serum 25(OH)D_3 but had no effect on plasma NfL, indicating no detectable impact on neuroaxonal injury over 48 weeks.
Sotirchos et al. (2015)	High-dose vitamin D substantially raised serum 25(OH)D and shifted immune cell phenotypes toward a less inflammatory profile, reducing pro-inflammatory T cells and promoting anti-inflammatory subsets, without changing circulating cytokine levels.

benefit (Sotirchos et al., 2015; Toghianifar et al., 2015). Together, these findings suggest that high-dose vitamin D may provide modest supportive effects, particularly in subjective or immunological outcomes, while showing variable impact on major clinical endpoints. Table 5 further details the clinical efficacy outcomes of vitamin D supplementations.

4. Discussion

This review highlights the safety and efficacy of high dose vitamin D supplementation in MS patients. It reports that high-dose vitamin D is found to be safe under appropriate monitoring. While clinical and radiological benefits remain inconsistent, evidence of immune modulation suggests a promising adjunctive role requiring further investigation in larger, long-term trials.

Despite advances in immunomodulatory therapy, MS continues to be associated with persistent inflammatory activity and progressive neurological disability in a substantial proportion of patients. Vitamin D has gained attention as a potential adjunctive intervention because of its immunoregulatory properties and observational associations with disease activity.

While previous trials evaluating moderate vitamin D doses (> 5000 IU/day) reported favourable safety profiles without clear effects on relapse rates (Kampman et al., 2012). The present review specifically focuses on randomized controlled trials using substantially higher dosing regimens, typically exceeding 10,000 IU/day. Vitamin D toxicity has been reported in the broader clinical literature including cases of hypercalcemia and renal complications across varying supplementation doses (Ross et al., 2011). However, the randomized controlled trials included in this review demonstrated that episodes of toxicity were uncommon and generally mild or reversible, with no clinically significant safety concerns reported (Ashtari et al., 2016; Burton et al., 2010; Hupperts et al., 2019; Toghianifar et al., 2015). Consequently, high-dose vitamin D regimens appear largely safe when administered under controlled clinical conditions.

Table 5
Clinical efficacy outcomes of vitamin D supplementation.
MSQOL-54 = Multiple Sclerosis Quality of Life–54 questionnaire; EDSS = Expanded Disability Status Scale; ARR = annualized relapse rate; MSFC = Multiple Sclerosis Functional Composite; MS = multiple sclerosis; NEDA-3 = no evidence of disease activity (no relapses, no disability progression, and no MRI activity); EBNA-1 = Epstein–Barr nuclear antigen-1; SOLAR trial = Supplementation of Vigorous Vitamin D in Relapsing-Remitting Multiple Sclerosis.

Study ID	Clinical Efficacy
Ashtari et al. (2016)	Vitamin D supplementation significantly improved mental quality-of-life outcomes, with higher MSQOL-54 mental health scores and better self-reported health status compared with placebo. Treatment was well tolerated with good compliance.
Hupperts et al. (2019	No significant differences were observed in relapse outcomes, EDSS progression, or time to first relapse over 48 weeks. ARR was lower with vitamin D_3, though not statistically significant. No measurable clinical benefit over 48 weeks.
Toghianifar et al. (2015)	Mean EDSS was significantly lower in the vitamin D group compared with placebo, while disease duration and prior relapse rates were similar between groups.
Rolf et al. (2017)	As an immunological sub study of the SOLAR trial, this study did not assess clinical efficacy. The parent trial showed no benefit on relapses or disability, despite significant reductions in anti-EBNA-1 IgG levels.
Ashtari et al. (2015	Baseline EDSS differed between groups, with lower disability in the vitamin D group, whereas relapse rates and disease duration were comparable.
Burton et al. (2010)	The study showed non-significant trends toward fewer relapses and slight EDSS improvement with treatment, suggesting a possible but unproven clinical benefit.
Dörr et al. (2020)	After 18 months, relapses, EDSS, and MSFC scores showed only minor, non-significant differences, leaving EVIDIMS inconclusive on vitamin D's clinical benefit in MS.
Smolders et al. (2019)	This sub study did not assess clinical outcomes, and the parent SOLAR trial showed no effect of high-dose vitamin D_3 on NEDA-3, relapses, or other clinical measures.
Sotirchos et al. (2015)	Over 6 months, relapses and EDSS were similar between high- and low-dose vitamin D, showing no detectable clinical benefit of high-dose supplementation.

Vitamin D levels were the most consistent and robust outcome across all studies, with nearly universal, statistically significant increases in serum 25(OH)D concentrations in high-dose arms compared with baseline and placebo or low-dose comparators, often reaching several-fold elevations (Ashtari et al., 2016; Hupperts et al., 2019; Toghianifar et al., 2015). This finding confirms pharmacological efficacy and adherence and represents the most uniform effect observed.

Clinical outcomes, however, were considerably more heterogeneous and generally modest, with the majority of trials failing to demonstrate statistically significant between-group differences in relapse rates, time to first relapse, or confirmed EDSS progression over the study periods (Burton et al., 2010; Toghianifar et al., 2015). These findings are consistent with previous randomized trials evaluating moderate-dose vitamin D supplementation, which similarly reported limited effects on relapse activity and disability progression (Cassard et al., 2023). Occasional non-statistically significant trends favouring vitamin D

effects were observed where clinical benefits were noted. Nevertheless, they tended to be domain-specific (e.g., mental health–related quality of life measures).

Magnetic Resonance Imaging (MRI) outcomes were variable and context-dependent across the included randomized trials. While some studies particularly those achieving higher serum 25(OH)D levels or enrolling patients with active inflammatory disease reported reductions in combined unique active lesions or smaller increases in total T2 lesion volume (Hupperts et al., 2019), others did not demonstrate consistent effects on new lesion formation, overall lesion burden, or brain atrophy measures (Dörr et al., 2020; Smolders et al., 2019). Observational studies have reported inverse associations between serum vitamin D levels and inflammatory MRI activity in multiple sclerosis (Galus et al., 2022); however, the randomized trials included in this review yielded mixed radiological results, with observed benefits largely confined to selected inflammatory endpoints rather than consistent structural or atrophy-related improvements. Importantly, most participants were receiving interferon-β therapy, which may have reduced baseline inflammatory activity and limited the ability to detect an independent or additive radiological effect of high-dose vitamin D.

Immune marker findings supported biologically plausible immunomodulatory effects which lacked uniformity, with several studies reporting reductions in IL-17–producing $CD4^+$ T cells and effector-memory T-cell subsets consistent with attenuation of Th17-related inflammatory pathways, while circulating cytokine levels such as IL-17 or IL-10 showed mixed or inconsistent changes across trials (Ashtari et al., 2015; Bhargava et al., 2015; Burton et al., 2010; Muri et al., 2016; Sotirchos et al., 2015; Toghianifar et al., 2015). In some cases, unexpected associations were found that did not parallel clinical outcomes. Finally, other biomarkers were infrequently assessed and study-specific, with isolated findings such as reductions in Epstein-Barr Nuclear Antigen 1 (anti-EBNA-1) IgG levels suggesting potential interactions with Epstein–Barr virus–related immune pathways (Rolf et al., 2017), whereas neurodegeneration-associated markers like neurofilament light chain (NfL) generally did not demonstrate measurable change despite substantial increases in serum vitamin D (Smolders et al., 2019).

Most included trials were limited by short follow-up durations, often ranging from 12 weeks to 48 weeks, which is insufficient to assess long-term clinical or immunological effects in multiple sclerosis. Many studies had small sample sizes, reducing statistical power and limiting the ability to detect meaningful differences in multiple clinical outcomes such as relapse rate, disability progression, or MRI activity. Several trials focused primarily on immunological or laboratory markers without consistent correlation to clinical endpoints. In addition, most participants were receiving interferon-β therapy, which may have confounded results and masked the independent effects of high-dose vitamin D supplementation. Methodological issues, including open-label designs, early termination, and baseline imbalances, further limit interpretability. Some studies also excluded patients with severe vitamin D deficiency or included populations with low disease activity, potentially underestimating treatment effects.

5. Conclusion

Collectively, these findings indicate that while high-dose vitamin D reliably increases vitamin D status and is generally safe under monitoring, its effects on clinical, radiological, and immunological outcomes are variable, modest in magnitude, and likely contingent on achieved vitamin D levels, baseline inflammatory activity, treatment duration, and concomitant immunomodulatory therapy. Taken together, the generally favourable safety profile and biologically plausible immunomodulatory effects observed across studies support the need for larger, adequately powered trials with longer follow-up and sustained higher achieved 25(OH)D levels to determine whether these immune changes can translate into consistent radiological and clinical benefit. Larger trials with longer follow-up and sustained higher achieved vitamin D levels are needed to confirm the clinical impact of high-dose vitamin D supplementation.

During the preparation of this work the authors used QuillBot to improve the wording and readability of the manuscript without altering the scientific content or conclusions. After using this service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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CRediT authorship contribution statement

Kholoud Al Ghamdi: Writing – review & editing, Supervision, Conceptualization. **Mohammed Alqarni:** Writing – original draft, Methodology, Formal analysis, Data curation. **Ziyad Alamri:** Writing – original draft, Methodology, Investigation, Formal analysis. **Mohand AL Wahhas:** Methodology, Investigation, Data curation. **Muhammad Alkhaldi:** Writing – original draft, Investigation, Formal analysis, Conceptualization. **Abdulrahman Alsanni:** Methodology, Investigation, Conceptualization. **Ali Fouad Alhawaj:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

All authors have nothing to declare.

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