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VITAMIN D STATUS AND ITS IMPACT ON DISEASE ACTIVITY IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS: A COMPREHENSIVE NARRATIVE REVIEW

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ABSTRACT

Pediatric-onset multiple sclerosis (POMS), defined as the onset of multiple sclerosis (MS) before the age of 18 years, accounts for approximately 3–5% of all MS cases and is characterized by a markedly inflammatory disease course with high relapse rates and earlier accrual of cognitive and physical disability than adult-onset disease [22–25]. Among the modifiable environmental risk factors implicated in MS susceptibility and activity, vitamin D has attracted sustained scientific attention [3,4,48]. This narrative review synthesizes current evidence on the role of vitamin D in POMS, integrating epidemiological, immunological, genetic (Mendelian randomization), observational and interventional data. Mendelian randomization analyses provide robust evidence for a causal relationship between genetically lowered 25-hydroxyvitamin D [25(OH)D] concentrations and increased POMS susceptibility (OR 0.72, 95% CI 0.55–0.94, p = 0.02 for higher genetically predicted vitamin D) [1].

Observational studies consistently report that each 10 ng/mL (25 nmol/L) increase in serum 25(OH)D is associated with an approximately 34% reduction in subsequent relapse rate in POMS [2], and with comparable reductions in new T2 and gadolinium-enhancing magnetic resonance imaging (MRI) lesions in mixed adult-pediatric cohorts [17,19]. Despite biologically plausible immunomodulatory and remyelinating effects demonstrated in experimental models [36–39], randomized controlled trials of vitamin D supplementation have predominantly failed to meet primary clinical endpoints, with positive signals largely confined to secondary MRI outcomes [5,6,41–43]. Pediatric-specific randomized data remain scarce. Current expert consensus supports avoidance of insufficiency (25(OH)D < 20 ng/mL) and targeting serum levels of 30–50 ng/mL (75–125 nmol/L) using daily doses up to 2000–4000 IU of cholecalciferol, with biochemical monitoring [3,27,28,50]. Future research priorities include adequately powered pediatric trials, harmonized dosing protocols, and long-term safety surveillance.

KEYWORDS

Pediatric-Onset Multiple Sclerosis; Vitamin D; 25-Hydroxyvitamin D; Cholecalciferol; Relapse Rate; Magnetic Resonance Imaging; Immunomodulation; Mendelian Randomization

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1. Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating and neurodegenerative disease of the central nervous system (CNS) that typically manifests between the ages of 20 and 40 years [26]. However, in approximately 3–5% of all cases, the first clinical event occurs before the age of 18 years, defining pediatric-onset multiple sclerosis (POMS) [22,23]. The International Pediatric Multiple Sclerosis Study Group revised diagnostic criteria in 2013 to harmonize POMS diagnosis with the McDonald criteria while preserving developmental and pathophysiological specificity, particularly with respect to the differential diagnosis of acute disseminated encephalomyelitis (ADEM) and other acquired demyelinating syndromes [22].

POMS is overwhelmingly relapsing-remitting at onset (>97% of cases) and is characterized by a higher relapse frequency, more pronounced inflammatory MRI burden and slower long-term progression to fixed disability than adult-onset MS, although ultimate disability milestones are reached at a younger chronological age [22–25]. The cognitive and psychosocial sequelae of MS during a critical neurodevelopmental window — affecting school performance, vocational trajectory and quality of life — render the identification and modification of risk factors for disease activity in POMS a priority for both clinicians and public health [23,24].

Among environmental risk factors, the role of vitamin D has been investigated extensively for more than four decades [4,48]. Historically, the latitudinal gradient in MS prevalence and the inverse association between ultraviolet B (UVB) exposure and MS incidence first suggested a protective role for vitamin D [14,30]. Subsequent serological, genome-wide association, Mendelian randomization, and prospective cohort studies

have refined this hypothesis and provided convergent evidence for a causal contribution of low 25-hydroxyvitamin D [25(OH)D] to MS susceptibility [1,12,13,14]. However, the translation of these mechanistic and epidemiological findings into clinically effective supplementation strategies remains a matter of unresolved debate, with recent randomized controlled trials in adults — most notably the SOLAR and CHOLINE studies and the Vitamin D to Ameliorate MS (VIDAMS) trial — providing largely negative results on primary clinical endpoints [5,6,40,41].

The pediatric population is of particular biological relevance for two reasons. First, both vitamin D status and body mass index (BMI) during childhood and adolescence appear to exert independent and causal effects on subsequent MS susceptibility, as demonstrated by Mendelian randomization analyses incorporating genetic instrumental variables for 25(OH)D and BMI [1]. Second, vitamin D plays a recognized role in skeletal mineralization, neuronal maturation, and immune programming during this developmental window, raising the possibility that early correction of insufficiency may have larger effects in POMS than in established adult disease [28,30,31].

The aim of this narrative review is to synthesize and critically appraise the current evidence on (i) the epidemiology and burden of vitamin D deficiency in POMS, (ii) the biological plausibility of vitamin D-mediated immunomodulation and neuroprotection, (iii) the observational, genetic, and interventional evidence linking vitamin D status to POMS susceptibility and disease activity, and (iv) the practical and safety implications of vitamin D supplementation in pediatric clinical practice.

2. Methods

This work is a narrative review and does not constitute a systematic review or meta-analysis. The methodology was nonetheless designed to maximize transparency and to minimize selection bias, with explicit description of the formal analytical framework and investigation strategy used to identify, appraise and synthesize the evidence.

2.1.Formal analysis

The formal analytical strategy followed a structured, narrative-synthesis approach informed by the principles of the Scale for the Assessment of Narrative Review Articles (SANRA).

Studies were qualitatively appraised across five analytical dimensions: (a) study design and risk-of-bias profile; (b) operational definition and assay methodology of vitamin D status; (c) population characteristics, with particular attention to age at MS onset; (d) outcome ascertainment, including clinical (relapse rate, Expanded Disability Status Scale [EDSS]) and radiological (new or enlarging T2-weighted lesions, gadolinium-enhancing T1 lesions, total T2 lesion volume, brain volume change) endpoints; and (e) effect-size reporting (incidence rate ratio [IRR], odds ratio [OR], hazard ratio [HR], and corresponding 95% confidence intervals).

For comparability across studies that reported associations using heterogeneous units (ng/mL versus nmol/L) and effect-size scales, reported risk metrics were linearly recalculated where appropriate to a uniform 25 nmol/L (≈10 ng/mL) increment of 25(OH)D, using the published continuous models. The conversion factor of 1 ng/mL = 2.5 nmol/L was applied throughout. When studies presented categorical comparisons (quartiles or tertiles), point estimates were retained without re-scaling, and this limitation is explicitly acknowledged in the synthesis.

Causal inference was distinguished from associational inference using the analytical framework of Hill's criteria — strength, consistency, biological gradient, plausibility, coherence and experimental evidence — applied separately to (i) susceptibility outcomes (POMS onset) and (ii) disease-activity outcomes (relapses, MRI). Mendelian randomization studies were treated as the highest-tier evidence for causal inference on susceptibility, on account of their resistance to confounding by reverse causation and unmeasured environmental variables; randomized controlled trials (RCTs) were treated as the highest-tier evidence for the disease-activity question. The discrepancy between observational signals and RCT findings was systematically interpreted in terms of three competing explanations: (1) reverse causality, by which subclinical inflammation lowers circulating 25(OH)D; (2) residual confounding, particularly by ultraviolet B (UVB) exposure, BMI, physical activity, and disease-modifying therapy use; and (3) inadequate statistical power or duration of intervention in pediatric-relevant trials.

Effect-size estimates from observational pediatric studies were placed into context against trial-derived effect estimates by computing the implied minimum detectable effect for representative trial designs. For example, an observed 34% reduction in relapse rate per 10 ng/mL increase in 25(OH)D would translate, under the assumption of full additivity, to an approximate 60% relapse reduction for the 18 ng/mL average between-

group difference reported in supplementation trials — a magnitude that has not been reproduced in RCTs and which therefore raises substantial concerns regarding non-causal contributions to the observational association. This analytical step served to calibrate the strength of evidence and to inform the practical recommendations advanced in the discussion.

Heterogeneity across studies was not quantitatively pooled (no I^2 statistic was computed) given the deliberately narrative scope of this review. Instead, sources of heterogeneity were qualitatively mapped, including: (i) the assay used to measure 25(OH)D (radioimmunoassay, chemiluminescent immunoassay, liquid chromatography-tandem mass spectrometry [LC–MS/MS]); (ii) seasonal variation in sample timing; (iii) ethnic and geographical population characteristics; (iv) the threshold used to define insufficiency (<20 ng/mL versus <30 ng/ mL); and (v) co-administered disease-modifying therapy. Each of these was tracked qualitatively in the evidence synthesis and flagged in the discussion.

All quantitative statements regarding effect sizes, confidence intervals, and p-values reproduced in this review are direct citations of the original publications. No new primary statistical analyses were performed, and no individual patient-level data were extracted or reanalyzed.

2.2.Investigation

The investigation phase was conducted between January and April 2026. A multi-database literature search strategy was implemented across PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials. The search was supplemented by hand-searching of references from key identified articles and by consulting specialty registries (ClinicalTrials.gov, EU Clinical Trials Register) for ongoing or completed interventional studies relevant to vitamin D in MS.

The core search syntax combined Medical Subject Headings (MeSH) and free-text terms across two thematic axes: the disease term and the exposure term. The disease term used Boolean combinations of ("multiple sclerosis" OR "clinically isolated syndrome" OR "acquired demyelinating syndrome") with pediatric specifiers including ("pediatric" OR "paediatric" OR "childhood-onset" OR "adolescent" OR "juvenile" OR "early-onset"). The exposure term combined ("vitamin D" OR "25-hydroxyvitamin D" OR "25(OH)D" OR "cholecalciferol" OR "ergocalciferol" OR "calcitriol" OR "calcidiol" OR "alfacalcidol") with mechanistic and outcome qualifiers ("relapse" OR "disease activity" OR "MRI" OR "disability" OR "EDSS" OR "immunomodulation" OR "supplementation").

Studies were eligible for inclusion if they (i) reported original empirical data, systematic reviews, meta-analyses, narrative reviews, expert consensus statements, or clinical practice guidelines; (ii) addressed vitamin D status, supplementation, or pathophysiology in MS, with priority for pediatric populations; (iii) were published in English-language peer-reviewed journals; and (iv) reported clinically interpretable outcomes (susceptibility, relapse, MRI activity, disability, biomarker change, or safety). Polish-language sources were retained where they offered region-specific data on vitamin D status or supplementation guidance directly applicable to the central European context. Conference abstracts were excluded unless they provided unique data not later published in full. No formal date restriction was imposed, but priority was given to publications from 2010 onward, after the seminal Mowry et al. paper on vitamin D and pediatric-onset MS relapse rate.

Records identified through the database search were screened first by title and abstract, with full-text retrieval for those that potentially met inclusion criteria. Reference lists of included articles, along with related-citations and 'cited by' linkages within PubMed, were used to identify additional relevant work. The final corpus of evidence for this review comprised: one Mendelian randomization study specifically addressing pediatric-onset MS (Gianfrancesco et al., Neurology 2017); the foundational pediatric vitamin D–relapse cohort study (Mowry et al., Annals of Neurology 2010); pediatric and mixed-age observational cohorts examining 25(OH)D in relation to MRI outcomes; the principal adult-MS randomized controlled trials (SOLAR, CHOLINE, VIDAMS, Soilu-Hänninen, Kampman, Stein, Sotirchos, Hupperts, Camu, Burton); contemporary systematic reviews and meta-analyses; and consensus practice guidelines from neurological and endocrine societies. Mechanistic and immunological evidence was extracted from peer-reviewed in vitro and animal-model studies, particularly experimental autoimmune encephalomyelitis (EAE) and toxic demyelination (cuprizone, ethidium bromide) paradigms.

Data extraction was performed using a structured template capturing: study design, country and setting, sample size, age range and mean age at MS onset, MS subtype, definition and method of measurement of vitamin D status, exposure or intervention details (dose, frequency, duration), comparator, outcome measures, follow-up duration, principal effect estimates with confidence intervals and p-values, adjustment for confounders, and adverse events. For interventional studies, particular attention was paid to: baseline

25(OH)D, achieved 25(OH)D in the intervention arm, primary endpoint specification, the use of intention-to-treat versus per-protocol analyses, and concurrent disease-modifying therapy.

Risk of bias in interventional studies was qualitatively assessed using the Cochrane Risk of Bias 2 (RoB 2) framework, considering randomization, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Risk of bias in observational studies was appraised using the Newcastle–Ottawa Scale conceptual framework. The narrative synthesis was structured by exposure pathway (susceptibility versus disease activity) and within each section, by level of evidence (Mendelian randomization > randomized trial > prospective cohort > retrospective cohort > cross-sectional > mechanistic).

An a priori list of pediatric-specific knowledge gaps was generated during the protocol-development phase to focus the narrative synthesis: (a) absence of adequately powered pediatric RCTs of vitamin D supplementation; (b) interaction between BMI, vitamin D, and MS susceptibility in childhood; (c) the optimal pediatric target serum 25(OH)D concentration; (d) safety of supraphysiological dosing in skeletally immature patients; and (e) effects of vitamin D on cognitive trajectory in POMS. These knowledge gaps were carried forward to the discussion and conclusions.

3. Vitamin D: Sources, Metabolism and Mechanism of Action

The term "vitamin D" comprises a family of fat-soluble secosteroid molecules of which the two principal forms are ergocalciferol (vitamin D2), of plant and fungal origin, and cholecalciferol (vitamin D3), the predominant endogenous form synthesized in human skin upon exposure to ultraviolet B radiation (wavelength 290–315 nm) acting on 7-dehydrocholesterol [30,31]. Ergocalciferol contributes only modestly to total vitamin D status in most populations, whereas cholecalciferol — derived both from cutaneous synthesis and from a limited range of dietary sources (oily fish, egg yolks, fortified dairy products) — is the major source [30,31]. In central European latitudes, including Poland, cutaneous synthesis is effectively confined to the period from late April to early September, with sunscreen use (sun protection factor ≥15) reducing dermal production by 90–95% [27,28,30].

Cholecalciferol is transported via vitamin D-binding protein (DBP) to the liver, where the cytochrome P450 enzyme CYP2R1 (and to a lesser extent CYP27A1) catalyzes 25-hydroxylation to yield 25-hydroxyvitamin D [25(OH)D, calcidiol], the principal circulating storage form and the standard biomarker of vitamin D status [30,31]. A second hydroxylation by CYP27B1 (1α-hydroxylase) — predominantly renal but also expressed in immune cells, neurons, glia and other tissues — generates the biologically active hormone 1,25-dihydroxyvitamin D [1,25(OH)2D, calcitriol] [31,32]. Catabolism is mediated by CYP24A1 (24-hydroxylase), with rare loss-of-function mutations in this enzyme producing idiopathic infantile hypercalcemia and conferring susceptibility to vitamin D toxicity at otherwise routine doses [31].

Calcitriol exerts its biological effects by binding to the nuclear vitamin D receptor (VDR), a member of the steroid hormone receptor superfamily, which heterodimerizes with the retinoid X receptor (RXR) and binds vitamin D response elements (VDREs) in the regulatory regions of more than 2,000 genes [31]. VDR is expressed in nearly all immune cell subsets — including CD4+ and CD8+ T lymphocytes, B lymphocytes, monocytes, macrophages, dendritic cells, microglia, astrocytes — and in neurons, with the highest density observed in the hypothalamus and substantia nigra [31,32,34]. The local conversion of 25(OH)D to 1,25(OH)2D within immune and CNS cells implies an autocrine/paracrine signaling axis that can operate independently of circulating calcitriol concentrations [31,32]. Of direct relevance to MS pathobiology, both VDR and CYP27B1 are upregulated within active MS plaques, and 25(OH)D is detectable in cerebrospinal fluid of MS patients [33].

The most widely accepted thresholds for vitamin D status are: severe deficiency, 25(OH)D<10 ng/mL (<25 nmol/L); deficiency, 10–20 ng/mL (25–50 nmol/L); suboptimal, 20–30 ng/mL (50–75 nmol/L); optimal, 30–50 ng/mL (75–125 nmol/L); high, 50–100 ng/mL (125–250nmol/L); and toxic, >100 ng/mL (>250 nmol/L) [27,28,30]. Hypovitaminosis D is highly prevalent in European populations: in a Polish cohort of 5,775 adults, 89.9% had 25(OH)D below 30 ng/mL [3,29].

3.1.Immunomodulatory effects relevant to MS

Calcitriol exerts pleiotropic effects on the innate and adaptive immune system [34,35]. In the innate compartment, it promotes monocyte differentiation and enhances macrophage chemotaxis, phagocytosis, and antimicrobial peptide production [34]. In the adaptive compartment, calcitriol inhibits the maturation and antigen-presenting capacity of dendritic cells, induces a tolerogenic phenotype, and shifts the T-helper balance away from Th1 and Th17 (proinflammatory) toward Th2 and regulatory T-cell (Treg) phenotypes [34,35].

Concretely, vitamin D suppresses the production of interferon-γ, interleukin (IL)-17 and IL-6, promotes IL-10-producing regulatory cells, and increases the activity of indoleamine 2,3-dioxygenase, which expands CD4+CD25+ Treg populations [35].

B-cell biology is similarly modulated: calcitriol inhibits B-cell proliferation, promotes B-cell apoptosis, and suppresses immunoglobulin production by plasma cells [34,35]. Given the now well-established pathogenic role of B cells in MS — underscored by the dramatic efficacy of CD20-depleting monoclonal antibodies — these effects offer an additional mechanistic bridge between vitamin D status and disease activity [4,35]. In RRMS patients, supplementation studies have reported reductions in IL-17+ CD4+ T cells, effector memory CD4+ T cells, and CD161+ CD4+ T cells, although the clinical correlates of these immunological shifts remain to be definitively established [10].

3.2.Neuroprotection and remyelination

Beyond classical immunomodulation, mounting experimental evidence implicates vitamin D in oligodendrocyte biology and remyelination [36,37]. In vitro, calcitriol promotes neural stem cell proliferation and their differentiation into oligodendrocytes [36]. In experimental autoimmune encephalomyelitis (EAE) and in toxic demyelination models — cuprizone-induced and ethidium bromide–induced — administration of vitamin D enhances remyelination, increases oligodendrocyte numbers, and protects against axonal damage as quantified by neurofilament-positive axon counts [37–39]. Mechanistically, the VDR–RXRγ heterodimer has been shown to act as a positive regulator of oligodendrocyte progenitor cell (OPC) differentiation, providing a molecular pathway by which vitamin D may influence not only inflammatory disease activity but also tissue repair and long-term outcomes [36].

4. Epidemiology of Vitamin D Deficiency in Pediatric-Onset MS

POMS represents 3–5% of all MS cases [22,23]. Within this population, the burden of vitamin D insufficiency is substantial. Across reported pediatric MS cohorts, mean serum 25(OH)D concentrations cluster in the range of 18–28 ng/mL (45–70 nmol/L), with the proportion of patients meeting criteria for deficiency or insufficiency commonly exceeding 60% [2,29]. These figures consistently exceed the prevalence reported in age- and geography-matched non-MS controls, although the magnitude of the differential varies between studies and depends on adjustment for season, latitude, ethnicity and BMI [2,3,29].

Several factors contribute to elevated rates of insufficiency in POMS. First, the disease typically manifests in adolescence, a developmental period associated with reduced outdoor activity, increased indoor screen time, and more variable dietary intake [3,29]. Second, MS-related fatigue, mobility limitation, and ultraviolet light avoidance behaviour (sometimes promoted by photosensitizing concomitant medications) reduce solar exposure [4,48]. Third, MS patients have been shown to mount a diminished serological response to a given vitamin D supplementation dose compared to healthy controls, suggesting altered vitamin D pharmacokinetics in MS itself, possibly mediated by adipose-tissue sequestration in patients with elevated BMI [4,11].

The independent effect of obesity is particularly relevant to POMS. Pediatric obesity has emerged as an independent risk factor for the disease, with a higher childhood and adolescent BMI conferring a roughly 2-fold increased risk of MS development [1]. The Mendelian randomization analysis by Gianfrancesco and colleagues demonstrated that the BMI–MS association is not fully mediated by reduced 25(OH)D in obese individuals: BMI and vitamin D each exerted independent causal contributions, with no significant attenuation of either when modeled jointly [1].

5. Genetic and Causal Evidence: Mendelian Randomization in Pediatric-Onset MS

The most rigorous causal evidence linking vitamin D to POMS susceptibility is provided by Mendelian randomization (MR) analyses [1,12,13]. MR uses germline genetic variants — assigned at random at conception and unaffected by reverse causation or environmental confounding — as instrumental variables for a modifiable exposure [12,13]. Single nucleotide polymorphisms (SNPs) at three loci (CYP2R1 [rs2060793, rs10741657], DHCR7/ NADSYN1 [rs3829251], and GC [rs2282679]) influence the conversion or transport of vitamin D and have been validated as instruments for circulating 25(OH)D in genome-wide association studies [1,12,13].

Gianfrancesco and colleagues (Neurology 2017) reported the first MR analysis specifically addressing POMS [1]. The investigators constructed a vitamin D genetic risk score (vitD GRS) from three 25(OH)D-associated SNPs and a BMI GRS from 97 BMI-associated variants, and applied them to a meta-analyzed dataset of 569 POMS cases and 16,251 non-Hispanic white controls drawn from US Network of Pediatric MS Centers sites and from the Swedish EIMS and GEMS studies [1]. After adjustment for sex, genetic ancestry, HLA-DRB1*15:01, and a weighted GRS comprising more than 100 non-HLA MS risk variants, a higher genetically predicted 25(OH)D was associated with a significantly reduced odds of POMS (OR 0.72, 95% CI 0.55–0.94, p = 0.02) [1]. The BMI GRS was independently

associated with increased POMS risk (OR 1.17, 95% CI 1.05–1.30, p = 0.01) [1]. When modeled jointly in a multivariable analysis, both genetic risk scores retained independent significance, supporting independent and additive causal contributions [1].

Notably, the magnitude of the causal effect of vitamin D was larger in pediatric-onset disease than in adult-onset disease (the latter estimated at OR ≈0.85 in comparable adult MR analyses), suggesting either a developmental sensitivity window or differences in the population structure of unmeasured residual confounders [1,12,13]. The childhood BMI GRS — using 28 variants specifically associated with pediatric BMI — was not significantly associated with POMS, whereas a significant gene–environment interaction was detected between the adult-derived BMI GRS and HLA-DRB1*15:01 carriership in the US dataset (p-interaction = 0.04), albeit not replicated in the Swedish dataset, possibly reflecting limited statistical power [1].

These findings, together with two additional MR analyses in adult-onset MS (Mokry et al. 2015; Rhead et al. 2016), establish low circulating 25(OH)D as a causal risk factor for MS susceptibility [1,12,13]. They do not, however, address the question of whether modifying vitamin D status after disease onset influences disease activity, which requires interventional rather than genetic evidence [4,42,43].

6. Observational Evidence: Vitamin D and Disease Activity in POMS

6.1.Vitamin D and relapse rate

The seminal study linking vitamin D status to disease activity specifically in POMS is the retrospective cohort study by Mowry and colleagues (Annals of Neurology 2010) [2]. The investigators studied 110 patients with pediatric-onset MS or clinically isolated syndrome (CIS) consecutively enrolled at the University of California San Francisco and the State University of New York at Stony Brook pediatric MS centers, with a mean follow-up of 1.7 years [2]. After adjustment for age, sex, race, ethnicity, disease-modifying therapy use, season of blood draw, and disease duration, every 10 ng/mL (25 nmol/L) increase in serum 25(OH)D was associated with a 34% reduction in subsequent relapse rate (incidence rate ratio for relapse 0.66, p = 0.024) [2]. Recalculated linearly to permit cross-study comparison, this effect size is among the largest reported in any MS subpopulation [2,20,21].

A practical implication, articulated by the original investigators, is that an increase of approximately 15 ng/mL in 25(OH)D — achievable with daily supplementation of approximately 2,000 IU of cholecalciferol in most pediatric patients — could theoretically halve the relapse rate [2,28]. This estimate provides the principal scientific rationale for randomized controlled trials of vitamin D supplementation in POMS, several of which are now in progress [2,40].

Subsequent analyses of overlapping pediatric cohorts have refined this signal [2]. Graves and colleagues, examining genetic predictors of relapse rate in pediatric MS, demonstrated that polymorphisms within vitamin D-related genes (notably CYP27B1 and CYP24A1) modify the relapse-rate phenotype, providing an additional layer of biological plausibility [4,48].

6.2.Vitamin D and conversion from CIS to definite MS

Children presenting with a first demyelinating event constitute a high-risk group for subsequent MS diagnosis [22]. Evidence from mixed pediatric/adolescent cohorts indicates that for each 10 nmol/L decrease in baseline 25(OH)D, the risk of conversion from CIS to clinically definite MS is significantly elevated [17,18]. In the BENEFIT cohort, comprising adolescents and adults with CIS treated with interferon β-1b, baseline and serial 25(OH)D measurements predicted long-term disease activity: a 50 nmol/L (≈20 ng/mL) increment in 25(OH)D within the first 12 months was associated with a 57% reduction in new gadolinium-enhancing MRI lesions, a 57% reduction in new clinical relapses, a 25% reduction in T2 lesion volume accumulation, and a 0.41% reduction in 5-year brain volume loss [17,18].

6.3.Vitamin D and MRI markers of disease activity

Across cohort studies in CIS and relapsing-remitting MS — including pediatric and mixed-age populations — each 25 nmol/L (≈10 ng/mL) increment in serum 25(OH)D is associated with an approximately 15–50% reduction in the risk of new T2 lesions and an analogous reduction in gadolinium-enhancing T1 lesions [17–19]. Pediatric-specific MRI data, while less abundant than adult data, are concordant [2,19]. In the EPIC cohort, every increase in 25(OH)D was associated with a 15% reduction in risk of new T2 lesions and a 32% reduction in gadolinium-enhancing lesions, with effect sizes preserved across the relapsing-remitting subgroup [19].

It should be emphasized that the observational MRI signal appears more robust and reproducible than the clinical relapse signal, possibly because MRI captures subclinical inflammatory activity at a higher temporal resolution than the discrete and often retrospectively reconstructed event of a clinical relapse [4,19].

6.4.Vitamin D and disability accrual

Evidence linking 25(OH)D to fixed disability accrual in POMS is more limited and less consistent [44,45]. In adult MS cohorts, meta-analytic data (Moosazadeh et al. 2020) demonstrate a significant negative correlation between 25(OH)D and Expanded Disability Status Scale (EDSS) score, but pediatric-specific data are sparse [44]. The short median follow-up of most pediatric cohorts and the typically low EDSS scores at the time of measurement limit the statistical power to detect disability-related effects [2,22].

In one relevant Saudi cross-sectional study of 39 patients with MS using automated CANTAB-based cognitive testing (Alhussain et al. 2021), low vitamin D levels were associated with worse executive function on the Spatial Working Memory test (between-search errors correlated with 25(OH)D, $r = 0.335$, $p < 0.05$), independent of physical disability and depressive symptoms [46]. While not exclusively pediatric, this finding raises the possibility that vitamin D status influences cognitive trajectory in MS — a domain of particular relevance to POMS, in which cognitive impairment occurs at neurodevelopmentally critical ages [23,46].

7. Interventional Evidence: Randomized Controlled Trials

Despite the strength of the observational and Mendelian randomization signals, the translation of these findings into evidence-based supplementation strategies has been less successful [4,42,43]. The major randomized controlled trials of vitamin D supplementation in MS have been performed predominantly in adult populations; pediatric-specific RCTs are largely absent from the published literature [5,6,40,41].

7.1.Adult RCTs with relevance to POMS

The SOLAR trial (Hupperts et al., Neurology 2019) randomized 232 patients with relapsing-remitting MS receiving subcutaneous interferon β-1a to either cholecalciferol 14,000 IU/day (after a 4-week run-in at 6,670 IU/day) or placebo for 48 weeks [5]. Median 25(OH)D rose from 53 to 215 nmol/L in the active arm versus a small decline in placebo [5]. The primary endpoint of NEDA-3 (no evidence of disease activity) was not met (36.3% vs 35.3%, $p = 0.80$) [5]. However, vitamin D was associated with a 32% reduction in combined unique MRI lesion activity ($p = 0.0045$) and a smaller increase in T2 lesion volume (3.57% vs 6.07%, $p = 0.035$) [5]. A non-significant 30% reduction in annualized relapse rate was also observed [5].

The CHOLINE trial (Camu et al., Neurology Neuroimmunology & Neuroinflammation 2019) randomized 129 RRMS patients on interferon β-1a to cholecalciferol 100,000 IU every two weeks or placebo for 96 weeks [6]. The primary endpoint of annualized relapse rate reduction was not met in the intention-to-treat analysis (rate ratio 0.799, 95% CI 0.481–1.32, $p = 0.379$), but per-protocol completers ($n = 90$) showed a 60% reduction in annualized relapse rate (rate ratio 0.403, $p = 0.012$), a reduction in new T1 lesions, lower hypointense T1 lesion volume, and reduced EDSS progression [6].

The Vitamin D to Ameliorate MS (VIDAMS) trial (NCT01490502) randomized RRMS adults on glatiramer acetate to high-dose (5,000 IU/day) versus low-dose (600 IU/day) cholecalciferol for two years [40,41]. The primary endpoint — proportion of participants with a clinical relapse — was not met, providing further evidence that high-dose vitamin D supplementation as add-on to first-line disease-modifying therapy does not reduce clinical relapse risk in adult RRMS [41].

Smaller earlier RCTs (Soilu-Hänninen 2012, Kampman 2012, Stein 2011, Sotirchos 2016, Burton 2010, Golan 2013, Achiron 2015) provided heterogeneous and largely negative results on primary clinical endpoints, with occasional positive signals in MRI secondary endpoints (e.g., reduction in gadolinium-enhancing lesions in the Soilu-Hänninen trial, $p = 0.004$) and immunological surrogate markers (reduction in IL-17+ CD4+ T cells in Sotirchos) [7–11,42,43].

7.2.Pediatric-specific interventional evidence

To date, no adequately powered randomized controlled trial of vitamin D supplementation has been completed in a strictly pediatric MS population with relapse rate or MRI activity as a primary endpoint [4,42,43]. Pediatric trials are challenging for several reasons: the relative rarity of POMS, parental and clinician reluctance to randomize children to placebo when supplementation is widely viewed as harmless, regulatory complexity, and ethical considerations regarding long-term safety surveillance in skeletally immature patients [22–24]. Several pediatric-focused observational supplementation studies and dose-finding pilots are nonetheless under way, and the existence of large pediatric MS registries (US Network of Pediatric MS Centers, Pediatric MS-International Study Group, Italian and Swedish pediatric MS networks) creates an infrastructure within which definitive trials could be conducted [22,23].

7.3.Interpretation of the observational–interventional discordance

The persistent discrepancy between robust observational signals and largely null RCT primary endpoints requires interpretation [4,42,43,47]. Three explanations dominate. First, observational associations are at least partly confounded by reverse causality: subclinical inflammatory activity itself reduces circulating 25(OH)D, generating a non-causal correlation between low vitamin D and high disease activity [4,47,48]. Second, residual confounding by UVB exposure — itself biologically active independently of vitamin D synthesis — and by BMI, physical activity, smoking and adherence to disease-modifying therapy may exaggerate the observational effect estimate [1,4,47]. Third, RCTs may be underpowered to detect modest effects, particularly when (i) baseline 25(OH)D is not severely deficient, (ii) follow-up duration is shorter than the 5-year prediction window of the BENEFIT cohort, and (iii) co-administered first-line disease-modifying therapy already substantially suppresses inflammatory activity, narrowing the margin in which vitamin D might exert detectable effects [4,17,18,42].

The signals of MRI benefit in secondary endpoints across SOLAR, CHOLINE, and Soilu-Hänninen, and the per-protocol clinical benefit in CHOLINE, suggest that a true biological effect may exist but is smaller than observational data predict [5,6,7]. This calibration is critical when designing future pediatric trials and when counselling families [4,50].

8. Safety of Vitamin D Supplementation in Pediatric Patients

Doses up to 4,000 IU/day of cholecalciferol — the upper level of intake established by the European Food Safety Authority and the United States National Institutes of Health for adults

— are well tolerated in pediatric MS cohorts and adolescents [27,28]. Across published RCTs in adult MS using doses up to approximately 14,000–20,000 IU/day, treatment-emergent hypercalcemia, hypercalciuria, nephrolithiasis or nephrocalcinosis have not been reported at higher rates than placebo [5,6,10,11]. Importantly, concomitant calcium supplementation should generally be avoided unless dietary calcium intake is documented to be inadequate, given the case-report-level evidence of hypercalcemia when very high vitamin D doses are combined with calcium loading [11,28,50].

Reports of clinically significant toxicity are concentrated in cases of supraphysiological dosing (e.g., ≥50,000 IU/day for prolonged periods, including the so-called Coimbra protocol), in patients with idiopathic infantile hypercalcemia (CYP24A1 mutations), or following abrupt withdrawal of disease-modifying therapy in favour of vitamin D monotherapy [3,30,50]. The Brazilian case series of 19 MS patients (Fragoso et al. 2014) in whom DMT was discontinued and replaced with mean cholecalciferol doses of 87,000 IU/day documented EDSS deterioration and new MRI activity, illustrating the dangers of misappropriated megadose strategies [3,4,50]. Individual case reports of life-threatening toxicity (calcium >3.2 mmol/L, acute kidney

injury, 25(OH)D >160 ng/mL) reinforce the principle that vitamin D supplementation should be biochemically monitored [27,28,30].

In skeletally immature patients, additional considerations apply. Avoidance of vitamin D deficiency is essential for skeletal mineralization during the pubertal growth spurt [27,28,30]. MS patients have an increased risk of bone loss and fractures, even at the time of diagnosis, in part due to physical inactivity and intermittent corticosteroid exposure [4,49]. While high-dose supplementation has not been shown to improve bone mineral density beyond the correction of deficiency, ensuring adequate vitamin D status across childhood and adolescence is supported on bone-health grounds alone [27,28].

9. Current Recommendations and Practical Implications

International recommendations for vitamin D in healthy populations vary modestly [27–30]. The European Food Safety Authority (EFSA) recommends 600–4,000 IU/day for healthy adults; the United States National Institutes of Health recommends 600 IU/day with a tolerable upper limit of 4,000 IU/day for those aged 19–70 years; and the United Kingdom Scientific Advisory Committee on Nutrition recommends 400 IU/day for individuals over 4 years of age [29,30]. Polish national recommendations advise 800–2,000 IU/day in healthy adults from October to April, with year-round supplementation when sun exposure is inadequate, and explicitly identify autoimmune diseases — including MS — as indications for measurement of 25(OH)D and supplementation under biochemical monitoring [3,27,28].

For patients with MS, including POMS, contemporary expert opinion converges on the following principles: (i) measure baseline 25(OH)D in all patients at the time of diagnosis;

(ii) avoid insufficiency (<20 ng/mL) and aim for an optimal serum 25(OH)D of 30–50 ng/mL (75–125 nmol/L); (iii) use cholecalciferol as the preparation of choice, given its superior raise in 25(OH)D compared to ergocalciferol; (iv) typical daily doses of 1,000–4,000 IU achieve target levels in the majority of patients without need for calcium co-supplementation; (v) monitor 25(OH)D every 3–6 months until target is reached, then annually; (vi) do not exceed 4,000 IU/day empirically without serial biochemical monitoring [3,4,27,28,48,50]. There is no convincing evidence of additional benefit, and a measurable safety signal, when targeting supraphysiological 25(OH)D >150 nmol/L [4,50].

Adherence and lifestyle measures should be addressed in parallel: appropriate but not excessive sun exposure, weight management given the independent causal effect of BMI on POMS susceptibility and progression, smoking cessation, and a balanced diet [1,3,30].

10. Discussion

This narrative review consolidates a coherent body of evidence on the role of vitamin D in pediatric-onset multiple sclerosis [3,4,48]. The Mendelian randomization data (Gianfrancesco et al. 2017) provide compelling support for a causal contribution of low 25(OH)D to POMS susceptibility, with an effect size larger than that observed in adult-onset disease [1,12,13].

The observational pediatric data — anchored by the Mowry et al. 2010 cohort — demonstrate a strong, dose-dependent inverse association between 25(OH)D and subsequent relapse rate [2]. The mechanistic literature, drawn from in vitro studies, EAE and toxic demyelination models, supports plausible immunological and oligodendroglial effects [34–39].

Against this backdrop, the failure of major adult RCTs (SOLAR, CHOLINE, VIDAMS) to meet primary clinical endpoints requires a measured interpretation [5,6,41]. Rather than refuting the role of vitamin D, the trial data calibrate it: the magnitude of effect is smaller than observational analyses predicted, likely reflecting reverse causality and residual confounding in the latter [4,47,48]. Secondary MRI endpoints and per-protocol analyses nonetheless suggest a true, modest biological effect, particularly in patients with low baseline 25(OH)D, early disease, and on first-line therapy [5,6,7,17,18].

For POMS specifically, several considerations strengthen the case for active management of vitamin D status notwithstanding the imperfect interventional evidence: (i) the larger MR-derived causal effect estimate in pediatric than in adult disease [1]; (ii) the developmental window argument, by which early correction may exert more durable effects [15,16]; (iii) the demonstrated importance of vitamin D for skeletal health during the pubertal growth spurt, particularly relevant in chronically corticosteroid-exposed children [27,28]; (iv) the favourable safety profile of moderate doses [3,28,50]; and (v) the very low cost of cholecalciferol relative to disease-modifying therapy [3,50].

Critical gaps remain. There is no adequately powered pediatric RCT of cholecalciferol with relapse rate or MRI activity as a primary endpoint [4,42,43]. The optimal target 25(OH)D for POMS is not empirically established and is currently extrapolated from adult and cohort data

[3,4,50]. The interaction between vitamin D and modern high-efficacy disease-modifying therapies (B-cell-depleting antibodies, sphingosine-1-phosphate receptor modulators, fumarates) — which now constitute first-line treatment in many pediatric settings — has not been characterized [23,24]. The contribution of vitamin D to cognitive trajectory, a critical outcome in POMS given the developmental window of disease onset, requires dedicated longitudinal study [23,46].

11.Conclusions

Vitamin D status is a robust biomarker of, and a probable causal contributor to, pediatric-onset multiple sclerosis susceptibility [1,2]. Observational data consistently indicate that lower 25(OH)D is associated with higher subsequent relapse rate and more pronounced MRI disease activity, with each 10 ng/mL increase in 25(OH)D corresponding to an approximately 34% reduction in relapse rate in the seminal pediatric cohort [2,17–19]. Mendelian randomization analyses provide rigorous causal evidence for the susceptibility relationship [1,12,13]. Despite mechanistic plausibility and observational signal, randomized controlled trials in adult MS — and the absence of pediatric-specific definitive trials — preclude unequivocal conclusions on the disease-modifying efficacy of supplementation [4,5,6,41–43].

Pending such evidence, current best practice in POMS supports the routine measurement of serum 25(OH)D at diagnosis, the avoidance of deficiency and insufficiency, and the targeting of optimal serum 25(OH)D concentrations of 30–50 ng/mL (75–125 nmol/L) using cholecalciferol at daily doses up to 2,000–4,000 IU under biochemical monitoring [3,4,27,28,48,50]. This strategy is supported by skeletal-health, safety, cost-effectiveness, and biological-plausibility considerations [27,28,50]. Future research priorities include adequately powered pediatric RCTs, harmonized dosing protocols, integration with high-efficacy disease-modifying therapy regimens, and dedicated assessment of cognitive outcomes [4,46].

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