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Vitamin D for the management of multiple sclerosis

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ABSTRACT

Background

This review is an update of a previously published review, “Vitamin D for the management of multiple sclerosis” (published in the Cochrane Library; 2010, Issue 12). Multiple sclerosis (MS) is characterised by inflammation, demyelination, axonal or neuronal loss, and astrocytic gliosis in the central nervous system (CNS), which can result in varying levels of disability. Some studies have provided evidence showing an association of MS with low levels of vitamin D and benefit derived from its supplementation.

Objectives

To evaluate the benefit and safety of vitamin D supplementation for reducing disease activity in people with MS.

Search methods

We searched the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Specialized Register up to 2 October 2017 through contact with the Information Specialist with search terms relevant to this review. We included references identified from comprehensive electronic database searches and from handsearches of relevant journals and abstract books from conferences.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs that compared vitamin D versus placebo, routine care, or low doses of vitamin D in patients with MS. Vitamin D was administered as monotherapy or in combination with calcium. Concomitant interventions were allowed if they were used equally in all trial intervention groups.

Data collection and analysis

Two review authors independently extracted data and assessed the methodological quality of studies, while another review author sorted any disagreements. We expressed treatment effects as mean differences (MDs) for continuous outcomes (Expanded Disability Status Scale and number of magnetic resonance imaging (MRI) gadolinium-enhancing T1 lesions), as standardised MDs for health-related quality of life, as rate differences for annualised relapse rates, and as risk differences (RDs) for serious adverse events and minor adverse events, together with 95% confidence intervals (CIs).

Main results

We identified 12 RCTs enrolling 933 participants with MS; 464 were randomised to the vitamin D group, and 469 to the comparator group. Eleven trials tested vitamin D₃, and one trial tested vitamin D₂. Vitamin D₃ had no effect on the annualised relapse rate at 52 weeks' follow-up (rate difference -0.05, 95% CI -0.17 to 0.07; I² = 38%; five trials; 417 participants; very low-quality evidence according to the GRADE instrument); on the Expanded Disability Status Scale at 52 weeks' follow-up (MD -0.25, 95% CI -0.61 to 0.10; I² = 35%; five trials; 221 participants; very low-quality evidence according to GRADE); and on MRI gadolinium-enhancing T1 lesions at 52 weeks' follow-up (MD 0.02, 95% CI -0.45 to 0.48; I² = 12%; two trials; 256 participants; very low-quality evidence according to GRADE). Vitamin D₃ did not increase the risk of serious adverse effects within a range of 26 to 52 weeks' follow-up (RD 0.01, 95% CI -0.03 to 0.04; I² = 35%; eight trials; 621 participants; low-quality evidence according to GRADE) or minor adverse effects within a range of 26 to 96 weeks' follow-up (RD 0.02, 95% CI -0.02 to 0.06; I² = 20%; eight trials; 701 participants; low-quality evidence according to GRADE). Three studies reported health-related quality of life (HRQOL) using different HRQOL scales. One study reported that vitamin D improved ratings on the psychological and social components of the HRQOL scale but had no effects on the physical components. The other two studies found no effect of vitamin D on HRQOL. Two studies reported fatigue using different scales. One study (158 participants) reported that vitamin D₃ reduced fatigue compared with placebo at 26 weeks' follow-up. The other study (71 participants) found no effect on fatigue at 96 weeks' follow-up. Seven studies reported on cytokine levels, four on T-lymphocyte proliferation, and one on matrix metalloproteinase levels, with no consistent pattern of change in these immunological outcomes. The randomised trials included in this review provided no data on time to first treated relapse, number of participants requiring hospitalisation owing to progression of the disease, proportion of participants who remained relapse-free, cognitive function, or psychological symptoms.

Authors' conclusions

To date, very low-quality evidence suggests no benefit of vitamin D for patient-important outcomes among people with MS. Vitamin D appears to have no effect on recurrence of relapse, worsening of disability measured by the Expanded Disability Status Scale (EDSS), and MRI lesions. Effects on health-related quality of life and fatigue are unclear. Vitamin D₃ at the doses and treatment durations used in the included trials appears to be safe, although available data are limited. Seven ongoing studies will likely provide further evidence that can be included in a future update of this review.

PLAIN LANGUAGE SUMMARY

Vitamin D for the management of multiple sclerosis

Review question

Does vitamin D supplementation reduce disease activity in people with multiple sclerosis (MS)?

What is the issue?

Several epidemiological, immunological, and genetic studies have reported an association between low vitamin D, measured as low blood 25-hydroxyvitamin D levels, and MS before and after the disease is triggered. Hence people with MS are screened for vitamin D deficiency, and vitamin D preparations are given along with immunomodulatory therapy. Whether vitamin D supplementation improves relevant clinical outcomes (recurrence of relapse, worsening of disability) or decreases the number of lesions observed by magnetic resonance imaging (MRI) is not clear.

What did we do?

We evaluated the benefits and harms of vitamin D in people with MS. We included randomised controlled trials (RCTs) and quasi-RCTs that compared the effects of vitamin D supplementation versus placebo, routine care, or low doses of vitamin D.

What did we find?

Our systematic search identified 12 studies enrolling 933 people with MS. Research shows that vitamin D has no effect on recurrence of relapse, worsening of disability measured by the Expanded Disability Status Scale (EDSS), or new MRI gadolinium-enhancing T1 lesions. Its effects on health-related quality of life and fatigue are unclear. Our confidence in these results is very low because vitamin

D has been evaluated in only a few small trials that we judged as having high risk of bias. Vitamin D supplementation appears to be safe for people with MS included in our review, but available data are limited.

Conclusions

For people with MS, vitamin D supplementation appears to have no effect on relevant clinical outcomes or new MRI lesions. Vitamin D supplementation at the doses and treatment durations used in the included trials appears to be safe, although available data are limited. Seven trials are ongoing; they will likely provide further evidence for a future update of this review.

Currentness of evidence

This evidence is up-to-date as of October 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

[Vitamin D] compared with [Placebo] for [Multiple Sclerosis]					
Patient or population: [People] with [Multiple Sclerosis] Settings: [Centers providing care for PwMS] Intervention: [Vitamin D] Comparison: [Placebo]					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (no. of studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Vitamin D			
Annualised relapse rate (ARR) (number of relapses per patient per year) Follow-up: 52 weeks	Mean ARR in the control group ranged from 0.28 to 0.45. ^a	Mean ARR in the intervention group was 0.05 lower (0.17 lower to 0.07 higher)	-	417 (5)	⊕○○○ ^{b,c} very low
Expanded Disability Status Scale (EDSS) score Follow-up: 52 weeks	Mean EDSS score in the control group ranged from 1.6 to 3.6 on a 0 to 10-point scale (best to worst). ¹	Mean EDSS score in the intervention group was 0.25 lower (0.61 lower to 0.10 higher)	-	221 (5)	⊕○○○ ^{b,d} very low
MRI gadolinium-enhancing T1 lesions Follow-up: 52 weeks	Mean number of MRI lesions in the control group ranged from 0.1 to 0.36. ¹	Mean number of MRI lesions in the intervention group was 0.02 higher (0.45 lower to 0.48 higher)	-	256 (2)	⊕○○○ ^{b,e} very low
Serious adverse events Follow-up: range 26 to 52 weeks	3 per 100 (10 events)	6 per 100 (19 events)	Risk difference 0.01 (-0.03 to 0.04)	621 (8)	⊕⊕○○ ^{f,g} low

Minor adverse events Follow-up: range 26 to 96 weeks	37 per 100 (130 events)	40 per 100 (143 events)	Risk difference 0.02 (- 701 0.02 to 0.06) (8)	⊕⊕○○ ^{g,h} low
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
 ARR: annualised relapse rate; CI: confidence interval; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; PwMS: person with multiple sclerosis; SAE: serious adverse event

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: we are very uncertain about the estimate

^aSource of assumed baseline risk was the range of outcomes in control groups of the trials included in the meta-analysis

^bDowngraded by two levels because studies considered at serious or unclear risk of selection bias, performance and detection bias, and attrition bias

^cDowngraded by one level for imprecision: studied in only 5/12 studies not reaching the optimal information size

^dDowngraded by one level for imprecision: studied in only five small studies; the 95% CI of the pooled estimate includes both reduction and increase in disability score with vitamin D

^eDowngraded by one level for imprecision: studied in only 2 studies; the 95% CI of the pooled estimate includes both reduction and increase in MRI lesions with vitamin D

^fDowngraded by one level for serious risk of selective reporting: 4/12 studies did not report SAEs

^gDowngraded by one level for imprecision

^hDowngraded by one level for serious risk of selective reporting: minor adverse events were not collected through a systematic assessment

BACKGROUND

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS). Epidemiological studies have shown a characteristic geographical distribution of MS, with prevalence of the disease minimal at the Equator and increasing with North or South latitude (Simpson 2011). This distribution would appear to be supported by circumstantial evidence implicating environmental factors of inadequate sunlight exposure and lack of vitamin D as predisposing factors for MS (Freedman 2000; Ponsonby 2005). A large volume of epidemiological and genetic studies have reported an association between low serum 25-hydroxyvitamin D (25OHD) concentration and MS before and after the disease is triggered (Pierrot-Deseilligny 2017). Low serum 25OHD levels (around 50 nmol/L) have been associated with an increased incidence of MS (Embry 2000; Munger 2006). Nielsen 2017 recently reported increased MS risk in newborns 15 to 30 years later, but a previous study provided no evidence of an association between neonatal vitamin D levels and disease risk (Ueda 2014). Mowry 2010 and Soilu-Hanninen 2005 reported a positive association between low 25OHD serum levels and early MS or clinically isolated syndrome (CIS). Observational studies on vitamin D supplementation in people with MS have shown that relapse rate was significantly reduced after supplementation was provided (Pierrot-Deseilligny 2017).

Many factors, such as season, ageing, latitude, adiposity, physical activity, smoking, and diet, can affect the association between 25OHD and health outcomes, but because of the large number of factors and inaccuracies in their measurement, observational studies might not be able to control fully for their confounding effects. Furthermore, the list of disorders associated with low 25OHD has continually increased. These issues have raised the question of whether low 25OHD might be the result, rather than the cause, of physiological disturbances involved in MS (Autier 2014). In the report on Dietary Reference Intakes for Calcium and Vitamin D issued by the Institute of Medicine (IOM) in 2011, the nature of the association between vitamin D levels and MS is judged as unclear and their relationship is considered associative rather than causative, that is, causation has not been proved (IOM 2011).

Description of the condition

Multiple sclerosis is characterised by inflammation, demyelination, axonal or neuronal loss, and astrocytic gliosis in the CNS. The disease manifests in a wide range of clinical presentations and with a variable clinical course. Typical clinical features include visual loss, double vision, motor weakness, spasticity, ataxia, tremor, sensory loss or impairment, sphincter dysfunction, and cognitive impairment. The course of the disease is so variable that some people become significantly disabled in a very short time, but others can live their entire lives with minimal or no disability. Complex

interactions between genetic susceptibility, environmental risk factors, such as viral infections, and protective factors could occur at different times and could lead to development of MS. Vitamin D may serve as one of several protective factors.

Researchers have reported many dysimmune processes involving T and B lymphocytes and several cytokines in MS (Thompson 2018). Cytokines are small proteins important for cell signalling that have crucial functions in the development, differentiation, and regulation of immune cells. A vast majority of cytokines are produced by T-helper (Th) cells. Interleukin (IL)-1, tumour necrosis factor (TNF), gamma-interferon (IFN- γ), IL-12, IL-17, IL-18, and granulocyte-macrophage colony stimulating factor are pro-inflammatory cytokines. IL-4, IL-10, IL-13, IFN- α , and transforming growth factor (TGF)- β are anti-inflammatory cytokines. Cytokines can also be classified by immunological response; type 1 cytokines (e.g. TNF- α , IFN- γ) enhance cellular immune responses, and type 2 cytokines (e.g. TGF- β , IL-4, IL-10, IL-13) favour antibody responses. Dysregulation of cytokine function causing an imbalance between pro-inflammatory and immunosuppressive functions is postulated to have a central role in the development of autoimmune disease. Some cytokines, such as IL-2, TNF, and interferons, are well known to promote immune and inflammatory responses, but they also serve crucial immunosuppressive functions (O'Shea 2002). The matrix metalloproteinase-9 (MMP9) protein has been found to be associated with numerous pathological processes and has been demonstrated to play an important role in the immunopathogenesis of MS (Mirshafiey 2014).

Description of the intervention

Vitamin D is a steroid hormone with pleiotropic and tissue-specific effects due to wide expression of the nuclear vitamin D receptor in many different tissues and the many genes that are targeted by its actions. Vitamin D is a fat-soluble vitamin that is naturally present in very few foods (e.g. fatty fish, fish liver oils), is added to others (e.g. milk), and is available as a dietary supplement. It is also produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis. Vitamin D obtained through sun exposure, food, and supplements is biologically inert and must undergo two hydroxylations within the body for activation. The first occurs in the liver and converts vitamin D to 25OHD, also known as calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D, also known as calcitriol (IOM 2010). Serum concentration of 25OHD is the best indicator of vitamin D status. It has a fairly long circulating half-life of 15 days; it reflects vitamin D produced cutaneously and that obtained from food and supplements. 25OHD functions as a biomarker of exposure, but it is not clear to what extent 25OHD levels also serve as a biomarker of effect (i.e. relation to health status or outcomes). Serum 25OHD

levels do not indicate the amount of vitamin D stored in body tissues (IOM 2010).

Considerable discussion surrounds the serum concentrations of 25OHD associated with deficiency (e.g. rickets), adequacy for bone health, and other diseases including autoimmune disorders (Holick 2011; IOM 2011; Rosen 2012). The committee of the Institute of Medicine concluded that persons are at risk of vitamin D deficiency at serum 25OHD concentrations < 30 nmol/L (< 12

ng/mL) (IOM 2011). Some are potentially at risk for inadequacy at levels ranging from 30 to 50 nmol/L (12 to 20 ng/mL). Levels $\geq$ 50 nmol/L ($\geq$ 20 ng/mL) are sufficient for practically all people. The committee stated that 50 nmol/L is the serum 25OHD level that covers the needs of 97.5% of the population. Serum concentrations > 125 nmol/L (> 50 ng/mL) are associated with potential adverse effects such as hypercalcaemia, nephrolithiasis, and vascular calcifications (IOM 2011).

Serum 25-hydroxyvitamin D (25OHD) concentrations and health ^a	Serum concentrations of 25OHD	
	nmol/L ^b	ng/mL
Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults	< 30	< 12
Generally considered inadequate for bone and overall health in healthy individuals	30 to 50	12 to 20
Generally considered adequate for bone and overall health in healthy individuals	$\geq$ 50	$\geq$ 20
Emerging evidence links potential adverse effects to such high levels, particularly > 150 nmol/L (> 60 ng/mL)	> 125	> 50

^aSerum concentrations of 25OHD are reported in both nanomoles per litre (nmol/L) and nanograms per millilitre (ng/mL). ^b1 nmol/L = 0.4 ng/mL.

How the intervention might work

Vitamin D is important for normal growth and development of bone mediated through absorption of calcium from food and its ultimate deposition in bone. Apart from its involvement in bone metabolism, some reports suggest that vitamin D has other biologic mechanisms, including the action of limiting autoimmunity by suppressing inappropriate immune responses; regulating T-helper cells, B lymphocytes, and dendritic cells (Danner 2016; Niino 2008); and reducing levels of inflammatory cytokines through control of gene expression (Danner 2016; Hupperts 2016). It has been reported that vitamin D is involved in immunomodulatory protective effects on the brain (Shirazi 2015), and that suboptimal levels of vitamin D may contribute to axonal inflammation and degeneration in patients with MS (Sandberg 2016). Other trial authors have reported that vitamin D has a direct immunomodulatory effect on T cells of patients with early MS and is associated with improved regulatory T-cell suppressive

function (Bartosik-Psujek 2010; Lysandropoulos 2011; Mahon 2003). The doses required to exert an immunoregulatory effect have been observed to be much higher than the recommended daily intake dose.

Why it is important to do this review

It has been proposed that vitamin D supplementation at moderate oral doses can already be undertaken in all types of people with MS, including pregnant women (Wagner 2017), and it is recommended that in temperate countries, supplementation should never be stopped because there is no durable storage of this vitamin within the organism (Pierrot-Deseilligny 2017). However, no consensus has been reached on the possible benefit of vitamin D for patients with MS. The IOM Committee concluded that evidence suggesting that vitamin D reduces risk of non-skeletal chronic disease outcomes is inconsistent and inconclusive and does not meet the criteria for establishing cause-and-effect relationships (IOM 2011). This uncertainty regarding effects of vitamin D in MS is due to the limited number of randomised trials providing

the most rigorous and valid research evidence on the relative benefit and safety of treatment. A summary of review results may help to clarify the stated uncertainty.

OBJECTIVES

To evaluate the benefit and safety of vitamin D supplementation for reducing disease activity in people with MS.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for randomised controlled trials (RCTs) looking at treatment for MS. We excluded cross-over studies because the effects if any of vitamin D are more likely to develop over a longer time, and therefore an appropriate washout period cannot be clearly defined.

Types of participants

We sought participants 18 years of age or older with a diagnosis of MS according to the diagnostic criteria of Schumacker (Schumacker 1965), Poser (Poser 1983), or McDonald (McDonald 2001; Polman 2005; Polman 2011). We included all subgroups of MS (relapsing-remitting (RRMS), secondary-progressive, primary-progressive, and progressive-relapsing), regardless of sex of the individual, degree of disability, and disease duration.

Types of interventions

We included all preparations of vitamin D at any dose, frequency, duration, or administration route. Vitamin D can be compared with placebo, routine care, or low dose of vitamin D. Vitamin D was administered as monotherapy or in combination with calcium. Concomitant interventions were allowed if they were used equally in all intervention groups in the trial.

Types of outcome measures

Primary outcomes

- Mean number of relapses per patient per year or annualised relapse rate (ARR)
- Change in Expanded Disability Status Scale (EDSS) score (Kurtzke 1983)

- Number of participants experiencing change in EDSS score (i.e. at least one point for EDSS < 6.0 or 0.5 point for EDSS > 5.5 over a period of six months)
- Mean change in magnetic resonance imaging (MRI) parameters of disease activity, including new lesions on T2-weighted images, preexisting lesions enlarged on T2-weighted images, or gadolinium-enhancing lesions in T1-weighted images
- Time to the first treated relapse
- Quality of life measured by validated generic or MS-specific scales (e.g. MS Quality of Life (MSQOL-54) (Vickrey 1995); Functional Assessment of MS (FAMS) (Cella 1996); RAYS Scale (Rotstein 2000))
- Adverse events (AEs) as defined by study authors in the following groups:
 - Proportion of participants with at least one serious adverse event (SAE)
 - Proportion of participants with minor AEs (or rate of AEs, i.e. number of AEs per person-years)

Secondary outcomes

- Number of participants requiring hospitalisation owing to progression of the disease
- Proportion of participants who remained relapse-free
- Cognitive functions: memory, concentration measured by validated and disease-specific scales (e.g. Brief Repeatable Battery of Neuropsychological Tests (BRBNT)) (Rao 1991)
- Physical symptoms:
 - Fatigue measured by validated scales (e.g. Fatigue Severity Scale (FSS) (Krupp 1989); MS-specific FSS (MFSS) (Schwartz 1993); Modified Fatigue Impact Scale (MFIS); visual analogue scale (VAS) (Krupp 1995))
 - Spasticity or spasms measured by the Ashworth Scale (Bohannon 1987)
 - Bladder function, bowel symptoms, self-reported symptom count, or change in symptoms assessed by validated questionnaires
- Psychological symptoms: profile of mood states (McNair 1981); self-efficacy (Johnston 1995); self-esteem (Rosenberg 1965); change in psychological symptoms assessed by validated questionnaires (Johnston 1995)
- Serum levels of 25-hydroxyvitamin D (25OHD) and calcium
- Bone mineral density (BMD) changes during the study period
- Immunological outcomes:
 - Mean change in cytokine profile
 - Mean change in T-lymphocyte proliferation response
 - Mean change in plasma metalloprotease-9 activity

All outcomes were evaluated at six months (24/26 weeks), at 12 months (48/52 weeks), and annually thereafter. Other timing of outcome measurements was considered and evaluated separately.

A glossary is available ([Table 1](#)).

Search methods for identification of studies

This review is an update of a previously published review ([Jagannath 2010](#)). We conducted a systematic search with no restrictions to identify all relevant published and unpublished RCTs. We included trials published in any language.

Electronic searches

The Information Specialist searched the Trials Register of the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group (2 October 2017), which, among other sources, contains the following.

- Cochrane Central Register of Controlled Trials (CENTRAL; October 2017 to most recent issue).
- MEDLINE (PubMed) (1966 to 2 October 2017).
- Embase (Embase.com) (1974 to 2 October 2017).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO host) (1981 to 2 October 2017).
- Latin American and Caribbean Health Science Information Database (LILACS) (Bireme) (1982 to 2 October 2017).
- ClinicalTrial.gov (www.clinicaltrials.gov).
- World Health Organization (WHO) International Clinical Trials Registry Portal (apps.who.int/trialsearch).

Information on the Trial Register of the Review Group and details of search strategies used to identify trials can be found in the “Specialised Register” section within the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group [module](#). We have listed in [Appendix 1](#) the keywords used to search for studies for inclusion in this review.

Searching other resources

In addition, we used the following methods.

- We screened the bibliographic references of identified studies or review articles to identify additional studies.
- We screened abstract books of the main MS meetings (European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), European Federation of Neurological Societies (EFNS), European Neurological Society (ENS), American Academy of Neurology (AAN), American Neurological Association (ANA)) from 1990 to 2017.
- We contacted authors of relevant trials or reviews and other MS consumer societies and experts.

Data collection and analysis

Selection of studies

We used the search strategy described above to identify titles and abstracts of studies that might be relevant to the review. Two review authors (VJ and ZF) independently screened the titles and abstracts and discarded studies that were not applicable. We obtained full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, and those for which data in the title and abstract were insufficient to allow a decision. The two review authors then independently assessed the full-text papers and resolved disagreements on the eligibility of included studies through discussion and consensus, or through consultation with a third review author party (GVA). Review authors excluded all irrelevant records and noted details of studies and reasons for their exclusion in the [Characteristics of excluded studies](#) table.

Data extraction and management

Two review authors (VJ and CDP) independently obtained and extracted data using a predetermined form designed for this purpose. If disagreement arose between the two review authors, we met to achieve consensus. If studies were reported in multiple publications, we extracted data from different publications and then combined them onto a single data extraction form, so no data were omitted.

We recorded on the data extraction form the following characteristics of included studies.

- Methods.
- Participants.
- Interventions.
- Outcomes, including adverse events.
- Funding source for studies.

Assessment of risk of bias in included studies

Two review authors (VJ and ZF) independently assessed the risk of bias of included studies using Cochrane criteria ([Deeks 2011](#)). We assessed the following items: adequacy of sequence generation and allocation concealment; adequacy of blinding of participants, personnel, and outcome assessors; completeness of outcome data; and no selective outcome reporting. Another potential risk of bias that we considered was follow-up at six months or sooner because these trials measured outcomes that were too short-term to be clinically relevant for patients with MS. We planned to resolve discrepancies in judgement through discussion with a third review author (GVA); however this proved unnecessary. We judged the overall risk of bias of each included study according to the following criteria.

- Low risk of bias (plausible bias unlikely to seriously alter the results) if all of the above criteria were met.
- Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more items were assessed as unclear.

- High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more items did not meet the above criteria.

Measures of treatment effect

For each pairwise comparison and each outcome at each time point, we expressed individual study results as rate difference for the ARR; mean difference (MD) for continuous outcomes (i.e. changes in EDSS score and number of MRI gadolinium-enhancing T1 lesions); standardised MD (SMD) for HRQOL because included studies measured this outcome on different scales; and risk difference (RD) for serious adverse events and minor adverse events because some included studies reported no events in either group. We reported all measures together with their 95% confidence intervals (CIs). If we could not enter available data for analysis owing to missing values, we reported data in appropriate sections of the review and in the Additional tables.

Unit of analysis issues

We included only studies using a parallel-group design, so participants were randomised to intervention or control with subsequent analysis performed at the individual allocation level. We excluded cross-over studies. Cluster and multi-arm trials have not been carried out to evaluate vitamin D in MS.

Dealing with missing data

We contacted the principal investigator for [Burton 2010](#) and were able to obtain missing data and to clarify some inconsistencies in the published article. Communication with the principal investigator of [Lakatos 2000](#) revealed that only two participants with MS were included in the study, and separate data for them were unavailable. [Achiron 2015](#) did not provide data on baseline HRQOL score, and email communication did not help in obtaining those data. Imputation was used to address missing data for standard deviations when possible, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Revman calculator](#)).

Assessment of heterogeneity

Potential sources of heterogeneity included different participant baseline clinical characteristics, different vitamin D formulations, different doses, and different treatment durations. We examined the distribution of these characteristics in the included studies. We assessed for statistical heterogeneity by visually inspecting forest plots and by performing the Chi² test using an alpha of 0.05 for statistical significance, along with the I² statistic. I² values of 0% to 40% might not be important; 30% to 60% may indicate moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may show considerable heterogeneity ([Deeks 2011](#)).

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we conducted a comprehensive search for eligible studies and remained alert to duplication of data. We assessed within-study reporting bias and judged a study to be at low risk if all of the study's prespecified primary outcomes were reported as outlined in the study protocol. We were not able to assess the possibility of reporting bias using a funnel plot, as we included fewer than 10 studies in all analyses.

Data synthesis

Pairwise meta-analysis was feasible only for some outcome measures in the small number of included studies. We pooled data using a random-effects model. We expressed dichotomous outcome results as RDs, continuous outcome results as MDs and SMDs, and count data as rate differences, together with 95% confidence intervals. We conducted pairwise meta-analyses using RevMan 5 software ([RevMan 2017](#)).

Subgroup analysis and investigation of heterogeneity

We planned to carry out subgroup analyses based on age, gender, type of MS, country of residence (based on sunlight exposure), co-intervention with disease-modifying drugs, and serum 25OHD levels. We aimed to take any statistical heterogeneity into account when interpreting the results, especially if we noted any variation in the direction of effect.

Sensitivity analysis

We considered risk of bias of included studies when interpreting evidence using the GRADE approach.

'Summary of findings' table

We present the main results of this review in a 'Summary of findings' (SoF) table, as recommended by Cochrane. The SoF table provides an overall grading of the quality of evidence related to each outcome based on GRADEpro GDT ([www.grade-pro.org; GRADEproGDT 2015](#)). We graded the quality of evidence as high, moderate, low, or very low upon considering within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias. Assumed baseline risks used in calculating absolute risks were based on the range of outcomes measured in comparison groups in the included studies. We present the following outcomes in the SoF.

- ARR.
- Change in EDSS score.
- New MRI gadolinium-enhancing T1 lesions.
- Serious adverse events.
- Minor adverse events.

RESULTS

Description of studies

Results of the search

See [Figure 1](#).

Figure 1. Study flow diagram.

We identified 386 citations through electronic searches conducted on 2 October 2017. We reviewed in detail 26 full-text articles, which led to the inclusion of 20 articles of 11 unique studies. We found seven additional ongoing reports through searching [clinicaltrials.gov](#) (see [Characteristics of ongoing studies](#)).

Included studies

See [Characteristics of included studies](#).

In this update we included 11 new studies (Achiron 2015; Ashtari 2016; Etemadir 2015; Golan 2013; Hupperts 2016; Kampman 2012; Mosayebi 2011; Shaygannejad 2012; Soilu-Hanninen 2012; Sotirchos 2016; Stein 2011); these were not included in the previous published version of the review (Jagannath 2010). This update includes a total of 12 RCTs evaluating vitamin D in participants with MS.

Trial characteristics

All included trials used a parallel-group design. Trials were conducted between 2006 and 2015. The earliest trial was published in 2010, and the most recent in 2016. Seven trials were not funded by industry. Trials were conducted in Iran (n = 4) (Ashtari 2016; Etemadir 2015; Mosayebi 2011; Shaygannejad 2012), Europe (n = 3) (Hupperts 2016; Kampman 2012; Soilu-Hanninen 2012), North America (n = 2) (Burton 2010; Sotirchos 2016), Israel (n = 2) (Achiron 2015; Golan 2013), and Australia (n = 1) (Stein 2011).

Participants

Overall studies included 933 participants; 464 were randomised to the vitamin D group and 469 to the comparator group. The number of participants in each trial ranged from 23 in Stein 2011 to 232 in Hupperts 2016 (median 56). All studies, except Etemadir 2015, which evaluated pregnant women with RRMS, included participants of both genders with a relapsing-remitting MS course, with age range between 18 and 60 years, most of whom were receiving ongoing immunomodulatory therapy. Of the 12 included trials, nine (75%) reported the baseline vitamin D status of participants based on serum 25-hydroxyvitamin D levels. Participants in six trials had baseline 25-hydroxyvitamin D levels at or above vitamin D adequacy (20 ng/mL) (Burton 2010; Hupperts 2016; Kampman 2012; Soilu-Hanninen 2012; Sotirchos 2016; Stein 2011). Participants in the other three trials had baseline 25-hydroxyvitamin D levels considered vitamin D insufficient (< 20 ng/mL) (Etemadir 2015; Golan 2013; Mosayebi 2011). Two trials reported baseline vitamin D status of participants as inclusion criteria only: Ashtari 2016 and Shaygannejad 2012

included participants with 25-hydroxyvitamin D₃ serum levels < 85 ng/mL and > 40 ng/mL, respectively. Achiron 2015 did not report any data on the vitamin D status of participants. The main outcomes in these trials were relapse rate, disability worsening as measured by the EDSS, MRI lesions, quality of life, and adverse events.

Experimental interventions

Vitamin D

3

Five trials (with 93 participants) administered vitamin D as vitamin D₃. Four trials tested vitamin D₃ singly (Ashtari 2016; Etemadir 2015; Golan 2013; Mosayebi 2011), and one trial tested vitamin D₃ combined with calcium (Burton 2010). Four trials administered vitamin D₃ orally, and one trial administered it as an intramuscular injection (Mosayebi 2011). Two trials gave vitamin D₃ daily (Burton 2010; Golan 2013); the dose was 40,000 IU over 28 weeks, followed by 10,000 IU for 12 weeks, and further down-titrated to 0 IU for 12 weeks in Burton 2010; and 4370 IU plus 800 IU over 52 weeks in Golan 2013. Ashtari 2016 treated participants with 50,000 IU of vitamin D₃ every five days for three months. Etemadir 2015 treated pregnant women with 50,000 IU of vitamin D₃ once a week from 12 to 16 weeks' gestation until delivery. Mosayebi 2011 gave 300,000 IU of vitamin D₃ by intramuscular injection once monthly for six months.

Vitamin D

3 - cholecalciferol

Four trials (with 409 participants) administered vitamin D as vitamin D₃ (cholecalciferol). Two trials tested vitamin D₃ singly (Soilu-Hanninen 2012; Sotirchos 2016); one trial tested vitamin D₃ combined with interferon beta-1a (Rebif) (Hupperts 2016); and one trial tested vitamin D₃ combined with calcium (Kampman 2012). All trials administered vitamin D₃ orally. Two trials gave vitamin D₃ daily (Hupperts 2016; Sotirchos 2016); the dose was 6670 IU for four weeks followed by 14,007 IU for 44 weeks plus interferon beta-1a (Rebif) 44 mcg three times a week in Hupperts 2016, and 10,000 IU for six months in Sotirchos 2016. Two trials administered vitamin D₃ at intervals. Kampman 2012 treated participants with 20,000 IU of vitamin D₃ per week for 96 weeks, and Soilu-Hanninen 2012 gave vitamin D₃ supplementation of 20,000 IU once a week for one year.

Vitamin D

3 - alfalcidol (1 α -hydroxyvitamin D₃)

One trial (with 158 participants) administered vitamin D orally as alfalcidol at a dose of 1 μ g daily for six months (Achiron 2015).

Vitamin D

2

One trial (with 23 participants) administered vitamin D₂ orally at a test dose of 6000 IU + 1000 IU daily for a one-year period (Stein 2011).

Calcitriol - 1,25-dihydroxyvitamin D

One trial (with 50 participants) administered vitamin D orally as calcitriol at a test dose of 0.25 µg daily, increased to 0.5 µg (20 IU) after two weeks for one year (Shaygannejad 2012).

Comparator interventions

Six trials used placebo (Ashtari 2016; Hupperts 2016; Kampman 2012; Mosayebi 2011; Shaygannejad 2012; Soilu-Hanninen 2012); one trial used arachis oil (Achiron 2015); and one provided routine care (Etemadir 2015). Four trials compared high versus low doses of vitamin D (Burton 2010; Golan 2013; Sotirchos 2016; Stein 2011).

Follow-up

Length of follow-up was three months in Ashtari 2016; six months in Mosayebi 2011, Sotirchos 2016, and Stein 2011; eight months in Achiron 2015; 11 months in Hupperts 2016; 12 months in Burton 2010, Golan 2013, Shaygannejad 2012, and Soilu-Hanninen 2012; and 22 months in Kampman 2012. Etemadir 2015 included pregnant women from 12 to 16 weeks' gestation until delivery and six months after delivery.

Ongoing studies

We identified seven ongoing RCTs (NCT01198132; NCT01440062; NCT01490502; NCT01753375; NCT01768039; NCT01817166; O'Connell 2013). We will include these studies in a future update of this review. The [Characteristics of ongoing studies](#) table provides details on the characteristics of these seven studies.

Excluded studies

See [Characteristics of excluded studies](#).

We excluded six studies. Four were not randomised studies (Najafipour 2015; Pierrot-Deseilligny 2012; Shirvani-Farsani 2015; Wingerchuk 2005). One study did not include the appropriate population; participants had received a diagnosis of systemic lupus erythematosus, MS, rheumatoid arthritis, or asthma bronchiale; and communication with the study author by email revealed that only two participants in the study had MS, and separate data for these participants were not available (Lakatos 2000). Røsjø 2017, which reported on an included trial (Kampman 2012), provided only data on antibodies against Epstein-Barr virus, which are outcome measures not included in the review.

Risk of bias in included studies

We have summarised risk of bias in [Figure 2](#) and [Figure 3](#). In the light of our predefined criteria ([Assessment of risk of bias in included studies](#)), we judged that five out of 12 (42%) trials were at unclear risk of bias (Achiron 2015; Hupperts 2016; Kampman 2012; Shaygannejad 2012; Soilu-Hanninen 2012), and the remaining seven (58%) trials had high risk of bias for one or more of the components assessed.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Achiron 2015	?	+	+	+	?	+
Ashtari 2016	?	?	?	+	+	-
Burton 2010	-	-	-	-	+	+
Etemadir 2015	-	-	-	-	+	+
Golan 2013	?	-	?	-	?	+
Hupperts 2016	?	+	?	?	?	?
Kampman 2012	+	?	+	+	?	+
Mosayebi 2011	?	-	+	?	?	-
Shaygannejad 2012	?	?	+	+	?	+
Soilu-Hanninen 2012	+	?	+	+	?	+
Sotirchos 2016	+	?	+	-	+	-
Stein 2011	+	?	+	-	?	-

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

Generation of the allocation sequence was adequate in four trials ([Kampman 2012](#); [Soilu-Hanninen 2012](#); [Sotirchos 2016](#); [Stein 2011](#)), but it was inadequate in two trials ([Burton 2010](#); [Etemadir 2015](#)). The remaining six trials were described as randomised, but study authors did not describe the method used for sequence generation. We judged the method used for allocation concealment to be adequate in two trials ([Achiron 2015](#); [Hupperts 2016](#)), inadequate in four trials ([Burton 2010](#); [Etemadir 2015](#); [Golan 2013](#); [Mosayebi 2011](#)), and unclear in six trials ([Ashtari 2016](#); [Kampman 2012](#); [Shaygannejad 2012](#); [Soilu-Hanninen 2012](#); [Sotirchos 2016](#); [Stein 2011](#)).

Blinding

Seven trials adequately described the method of blinding. In three trials the method of blinding was unclear ([Ashtari 2016](#); [Golan 2013](#); [Hupperts 2016](#)), and two trials were not blinded ([Burton 2010](#); [Etemadir 2015](#)).

Incomplete outcome data

Five trials did not adequately address incomplete data ([Burton 2010](#); [Etemadir 2015](#); [Golan 2013](#); [Sotirchos 2016](#); [Stein 2011](#)). For two trials ([Hupperts 2016](#); [Mosayebi 2011](#)), information was insufficient to allow assessment of attrition bias. The remaining five trials adequately addressed incomplete outcome data.

Selective reporting

We judged eight trials to be at unclear risk of reporting bias because study authors made no mention of an a priori protocol or clinical trial registration information. We judged the remaining four trials to be at low risk of bias for this domain ([Ashtari 2016](#); [Burton 2010](#); [Etemadir 2015](#); [Sotirchos 2016](#)).

Other potential sources of bias

Seven included trials appear to be free of other components that could put them at risk of bias. Four trials reported follow-up of six months or less and we considered them to be at high risk of bias ([Ashtari 2016](#); [Mosayebi 2011](#); [Sotirchos 2016](#); [Stein 2011](#)). One trial provided insufficient information to allow assessment of other potential sources of bias ([Hupperts 2016](#)).

Effects of interventions

See: [Summary of findings for the main comparison](#)

[Summary of findings for the main comparison](#) provides overall estimates of effects of vitamin D compared with placebo, along with quality of available evidence for benefit outcomes (annualised relapse rate and EDSS scores over 52 weeks, the number of MRI gadolinium-enhancing T1 lesions over 26 weeks), obtained through pairwise meta-analyses.

Primary outcomes

Mean number of relapses per patient per year or annualised relapse rate (ARR)

See [Summary of findings for the main comparison](#), [Analysis 1.1](#), and [Table 2](#).

Five studies involving 417 participants (45% of those included in this review) reported the annualised relapse rate (ARR) at 52 weeks ([Burton 2010](#); [Golan 2013](#); [Hupperts 2016](#); [Shayannejad 2012](#); [Soilu-Hanninen 2012](#)). Researchers found that vitamin D did not reduce the number of relapses (rate difference -0.05, 95% confidence interval (CI) -0.17 to 0.07). The heterogeneity I^2 for this meta-analysis was 38%, which we considered low. Using GRADE criteria, we considered the evidence to be of very low certainty, downgrading by two levels because we judged the evidence to be at serious risk of suffering from selection bias, performance bias, and attrition bias. We downgraded certainty an additional level for imprecision. A sixth study involving 68 participants (7% of those included in this review) measured ARR at 96 weeks and found no differences between groups (rate difference 0.06, 95% CI -0.08 to 0.20) ([Kampman 2012](#)). Two studies reported ARR, but the data were unsuitable for data extraction. [Etemadir 2015](#) reported the mean number of relapses in pregnant women as 0.0 (standard deviation (SD) 0) (with six participants) in the intervention group and 0.4 (SD 0.5) (with nine participants) in the comparison group after six months of delivery. [Achiron 2015](#) reported that the proportion of participants free of relapse was significantly higher in the alfacalcidol treatment arm than in the comparison arm (89.5% vs 67.1%, respectively; $P = 0.007$). Reduction in relapses with alfacalcidol became significant at four months of treatment and was sustained at six months (end of study). This beneficial effect was diminished at the follow-up visit two months after alfacalcidol discontinuation.

Change in the Expanded Disability Status Scale (EDSS) score

See [Summary of findings for the main comparison](#) and [Analysis 1.2](#).

Five studies involving 221 participants (24% of those included in this review) reported the EDSS score change at 52 weeks ([Burton 2010](#); [Etemadir 2015](#); [Golan 2013](#); [Shayannejad 2012](#); [Soilu-Hanninen 2012](#)). These studies found no differences in EDSS change between groups (mean difference (MD) -0.25, 95% CI -0.61 to 0.10). The heterogeneity I^2 for this meta-analysis was 35%, which we considered low. We downgraded the certainty of the evidence by two levels because we judged the evidence to be at serious risk of suffering from selection bias, performance bias, and attrition bias. We downgraded certainty an additional level for imprecision, as the confidence interval of the pooled effect included both reduction and increase in disability score with vitamin

D. [Achiron 2015](#) and [Mosayebi 2011](#) (217 participants) reported EDSS score at 26 weeks and found no differences between groups (MD -0.10, 95% CI -0.37 to 0.17). [Kampman 2012](#) (68 participants) reported EDSS score at 96 weeks and found no differences between comparison groups (MD 0.35, 95% CI -0.21 to 0.91). Data from [Stein 2011](#) (20 participants) were unsuitable for data extraction because the article reported median (interquartile ratio (IQR)) EDSS scores at six months. This study found that treatment with high-dose vitamin D₂ was marginally associated with higher EDSS scores at the end of the study ($P = 0.051$).

Number of participants experiencing a change/reduction in the Expanded Disability Status Scale (EDSS) score

No trials reported this outcome.

Number of MRI gadolinium-enhancing T1 lesions

See [Summary of findings for the main comparison](#) and [Analysis 1.3](#).

Two studies involving 82 participants with multiple sclerosis (9% of the participants in this review) reported the number of MRI gadolinium-enhancing T1 lesions over 26 weeks ([Mosayebi 2011](#); [Stein 2011](#)), and two studies with 256 participants (27% of those included in this review) reported this number over 52 weeks ([Hupperts 2016](#); [Soilu-Hanninen 2012](#)). Mean differences were -0.09 (95% CI -0.52 to 0.34) and 0.02 (95% CI -0.45 to 0.48), respectively, at 26 and 52 weeks. Values for heterogeneity (I^2) for timing of each outcome seem to show no evidence of heterogeneity.

Time to the first treated relapse

None of the included studies reported this outcome.

Quality of life (QOL) (validated and specific scales, i.e. MSQOL-54, RAYS, FAMS)

See [Analysis 1.4](#).

Three studies reported QOL outcomes using three different validated scales ([Achiron 2015](#); [Ashtari 2016](#); [Golan 2013](#)). [Achiron 2015](#) (158 participants; 17% of those included in this review) used the RAYS Scale and reported that vitamin D led to improvement in the psychological and social components of RAYS but had no effects on the physical components. [Ashtari 2016](#) (94 participants; 10% of those included in this review) measured physical, mental, and sexual satisfaction and health change components of the MSQOL and found no difference in any component between comparison groups. [Golan 2013](#) (45 participants; 5%) used the FAMS questionnaire, a functional assessment of MS, and found no differences between groups.

Serious adverse events (SAEs)

See [Summary of findings for the main comparison](#), [Analysis 1.5](#), and [Table 3](#).

Eight studies involving 621 participants (67% of those included in this review) reported SAEs ([Achiron 2015](#); [Burton 2010](#); [Etemadir 2015](#); [Golan 2013](#); [Hupperts 2016](#); [Shaygannejad 2012](#); [Soilu-Hanninen 2012](#); [Sotirchos 2016](#)). Combined analysis of the results of these eight trials yielded a combined risk difference of 0.01 (95% CI -0.03 to 0.04). The heterogeneity I^2 for this meta-analysis was 35%, which we considered low. Using GRADE criteria, we downgraded the certainty of the evidence by two levels from high to low, in part because of imprecision, in part because of risk of selective reporting. Four of 12 studies did not report SAEs, and the absence of a protocol did not allow us to assess whether measurement of SAEs may have been planned but not reported. None of the participants in six trials experienced SAEs ([Achiron 2015](#); [Burton 2010](#); [Etemadir 2015](#); [Golan 2013](#); [Shaygannejad 2012](#); [Sotirchos 2016](#)). In the [Hupperts 2016](#) trial, 18 (16%) of the 113 participants in the intervention group and eight (7%) of the 116 participants in the placebo group experienced SAEs, and the risk difference in this trial was 0.09 (95% CI 0.01 to 0.17), sug-

gesting that high-dose vitamin D³ supplementation is associated with significant serious adverse events ([Table 3](#)). [Soilu-Hanninen 2012](#) reported that one participant with erysipelas in the vitamin D group required intravenous antibiotics, as did two participants with elective hip surgery and elbow fracture in the placebo group. None of the eight studies that reported SAEs observed nephrolithiasis.

Minor adverse events

See [Summary of findings for the main comparison](#) and [Analysis 1.6](#).

Eight studies involving 701 participants (75% of those included in this review) reported minor adverse events ([Achiron 2015](#); [Burton 2010](#); [Golan 2013](#); [Hupperts 2016](#); [Kampman 2012](#); [Shaygannejad 2012](#); [Soilu-Hanninen 2012](#); [Sotirchos 2016](#)). Combined analysis of the results of these eight trials yielded a combined risk difference of 0.02 (95% CI -0.02 to 0.06). The heterogeneity I^2 for this meta-analysis was 20%, which we considered low. Using GRADE criteria, we judged the certainty of the evidence as low. We downgraded by one level for risk of selective reporting because minor adverse events were not collected via a systematic assessment. We downgraded an additional level for imprecision. [Burton 2010](#), [Golan 2013](#), and [Kampman 2012](#) reported no adverse events with vitamin D and no withdrawals due to adverse events, suggesting that the intervention was tolerated well and resulted in no clinical or biochemical adverse effects in either intervention group. [Shaygannejad 2012](#) reported adverse events in both groups that included diarrhoea, constipation, fever, fatigue, headache, and dyspepsia (12/25 in the placebo group vs 18/25 in the vitamin D group). [Soilu-Hanninen 2012](#)

reported adverse events with no significant differences between groups. Study authors reported no hypercalcaemia or other biochemical abnormalities in the vitamin D group and reported minor adverse events such as lack of induction of the myxovirus resistance protein A, fever, and diarrhoea in 10/30 in the placebo group versus 10/32 in the vitamin D group. [Sotirchos 2016](#) reported nausea in three participants (1/21 in the low-vitamin D group vs 2/19 in the high-vitamin D group) who withdrew from the study, and elevated serum calcium levels above the safe level of 10 mg/dL in one patient in the high-vitamin D group who had to discontinue treatment, and in one patient with hypercalciuria in each group, all of whom were shifted to an alternate-day treatment regimen. [Ashtari 2016](#), [Etemadir 2015](#), and [Stein 2011](#) reported no adverse events.

Secondary outcomes

Number of participants requiring hospitalisation owing to disease progression

No trials reported on this outcome.

Proportion of relapse-free participants

[Achiron 2015](#) found that alfacalcidol increased the proportion of relapse-free participants compared with placebo (89% vs 67%, respectively; $P = 0.007$) at six months. [Stein 2011](#) reported four relapses with high-dose vitamin D² and none with low-dose vitamin D² ($P = 0.04$).

Cognitive functions (memory, concentration)

No trials reported these outcomes.

Physical symptoms

Two studies reported fatigue using two different validated scales ([Achiron 2015](#); [Kampman 2012](#)). [Achiron 2015](#) used the Fatigue Impact Scale (FIS), and [Kampman 2012](#) used the Fatigue Severity Scale (FSS). Results were different between the two studies. In [Achiron 2015](#), the standardised mean difference (SMD) was -0.62 (95% CI -0.94 to -0.30), suggesting that alfacalcidol reduced fatigue compared with placebo at 26 weeks. [Kampman 2012](#) found that cholecalciferol did not reduce fatigue at 96 weeks (SMD 0.13, 95% CI -0.34 to 0.61).

Psychological symptoms

No trials reported this outcome.

Serum levels of 25-hydroxyvitamin D (25OHD)

In Table 4, we report 25OHD levels at baseline and during the intervention along with the range of vitamin D dose supplementation provided in the included trials. Three of the 12 included trials evaluated patients with mean 25OHD concentration less than 50 nmol/L at baseline and provided supplementation of 50 µg or more per day (Etemadir 2015; Golan 2013; Mosayebi 2011). The other trials reported mean 25OHD concentrations above 50 nmol/L at baseline among included participants.

Bone mineral density (BMD) changes during the study period

Steffensen 2011 (sub-reference under Kampman 2012) reported on BMD changes at the hip, spine, and radius between baseline and end of study. At the hip, BMD decreased by 1.4% in the placebo group (95% CI -2.3 to -0.4; $P = 0.006$) and by 0.7% in the treatment group (95% CI -1.6 to 0.2; $P = 0.118$). Both groups showed bone loss in weight-bearing bones among people with MS. At the spine, BMD decreased by 0.1% (95% CI -1.3 to 1.2) and by 0.3% (95% CI -1.2 to 0.7), and at the radius, data show an increase of 1.3% (95% CI -0.7 to 3.3) and 2.3% (95% CI 0.3 to 4.2) after 96 weeks, indicating no change in bone loss due to the intervention.

Cytokine profile, T-lymphocyte proliferation response, and plasma metalloprotease-9 activity

Ashtari 2015 and Toghianifar 2015 (sub-references under Ashtari 2016) found no differences in anti-inflammatory IL-10 levels

nor in pro-inflammatory IL-17 levels between vitamin D₃ and placebo groups. Burton 2010 compared T-cell proliferative responses at first and final visits, 52 weeks apart, for all participants. The number of positive proliferative responses to antigenic stimulation decreased significantly in the treatment group during the trial (sign test; $P = 0.002$), with no change reported among controls. Data show no consistent patterns of change in cytokine levels between comparison groups. Golan 2013 reported that IL-17 levels were significantly increased in the low-dose group, while participants receiving high-dose vitamin D had a heterogeneous IL-17 response (Table 5). Mosayebi 2011 found that after six months, levels of peripheral blood mononuclear cell proliferation in the vitamin D treatment group were significantly lower than in the control group, and that levels of transforming growth factor-beta and of anti-inflammatory IL-10 in the vitamin D treatment group were significantly higher than in the control group (Table 6). Røsjø 2015 (sub-reference under Kampman 2012) reported no significant differences between vitamin D and placebo groups for any of the inflammation markers, including plasma metalloprotease-9 activity (Table 7). Muris 2016 (sub-reference under Hupperts 2016) measured levels of various cytokines to assess functional effects of

vitamin D₃ on the T-helper cell compartment. T cells within peripheral blood mononuclear cells were activated in vitro, and anti-CD3 and cytokine levels were measured. Proportions of T-helper

subsets were not affected by vitamin D₃, except the proportion of IL-4 T-helper cells, which was decreased in the placebo group but

not in the vitamin D₃ group. T-cell cytokine secretion increased most notably for IL-5 in the placebo group but not in the vitamin

D₃ group. This study found that vitamin D₃ supplementation prevented an imbalance in cytokine production upon T-cell activation (Table 8). Sotirchos 2016 found that high-dose cholecalciferol supplementation exhibited in vivo immunomodulatory effects, which included reduced production of IL-17 by CD41 T cells and decreased proportions of effector memory CD41 T cells, with a concomitant increase in central memory CD41 T cells and naive CD41 T cells (Table 9).

Subgroup and sensitivity analyses

We did not perform any predefined subgroup analyses (i.e. age, gender, type of MS, country of residence, disease-modifying drug or immunomodulatory co-therapy, serum 25(OH) vitamin D levels) nor sensitivity analyses, as we included an insufficient number of studies in this review.

DISCUSSION

Summary of main results

This updated review included 12 randomised controlled trials (RCTs) (with 933 participants) comparing the effects of different

doses of vitamin D supplements in the form of vitamin D₃ or

vitamin D₂ versus placebo in people with multiple sclerosis (MS) at a median of 52 weeks' follow-up.

Data on annualised relapse rate (ARR) over the 52 weeks from randomisation were available from five RCTs and 417 participants. We found that vitamin D supplements had no clear effect on reduction of ARR in participants with MS who were receiving disease-modifying drugs. Based on the GRADE approach, we assessed our confidence in the evidence for this result as very low owing to substantial risks of bias and imprecision. Assessment of disability progression was based on serial in-trial changes in the Expanded Disability Status Scale (EDSS). Data on this primary outcome over 52 weeks from randomisation available from five RCTs and 221 participants show that vitamin D supplements were not effective in preventing worsening of disability. However, this finding should be interpreted with caution because we graded our

confidence in the result as 'very low' according to the GRADE approach. Information on effects of vitamin D on magnetic resonance imaging (MRI) lesions was available only for the number of MRI gadolinium-enhancing T1 lesions that were reported over 26 weeks in two studies (82 participants) and over 52 weeks in two other studies (256 participants). Vitamin D supplements had no effect on reduction of MRI gadolinium-enhancing lesions compared with placebo at both times. Vitamin D had very uncertain effects on health-related quality of life; evidence for this outcome was limited. We found low-certainty evidence showing the absence of serious adverse events (SAEs) reported in eight studies with 621 participants. Vitamin D alone or combined with calcium supplements did not increase nephrolithiasis and had no clear effects on SAEs nor on other minor adverse events, as reported in the studies included in this review. However, information on adverse events was scanty and was poorly reported. None of the included studies reported numbers of participants experiencing changes in EDSS score and time to first treated relapse.

In terms of secondary outcomes, vitamin D had no effect on bone mineral density changes and very uncertain effects on fatigue. High-dosage regimens of vitamin D seem more effective in achieving serum 25-hydroxyvitamin D levels at or above vitamin D adequacy (20 ng/mL). Seven included studies focused on cytokine levels, inflammatory marker levels, or T-lymphocyte proliferation with no consistent pattern of change in these immunological outcomes after vitamin D supplementation. None of the included studies reported numbers of participants requiring hospitalisation, cognitive function, or psychological symptoms.

Overall completeness and applicability of evidence

In this updated review, we included all eligible randomised trials up to October 2017. Four trials were conducted in Iran (upper middle income), and the other eight in high-income countries (Australia, Canada, Europe, Israel, and USA). Trials included participants of both genders. Most participants had relapsing-remitting MS, so our confidence in concluding anything about patients with progressive MS is limited. The included trials examined vitamin D-deficient participants and those who had adequate vitamin D levels at entry; we noted no substantial differences regarding this baseline condition in terms of effects of vitamin D on the outcomes assessed in this review. Eleven of the 12 included trials assessed vitamin D₃, so our major conclusions pertain to this intervention.

Quality of the evidence

Most of the included studies had major weaknesses. The most common flaws were inadequate or unclear method of allocation concealment, high dropout rates after randomisation, and imprecision. Using GRADE criteria, we considered the evidence to be

of very low certainty for relapse rate, worsening of disability, and MRI gadolinium-enhancing T1 lesions measured at 52 weeks' follow-up, and of low certainty for serious and minor adverse events. Our review did not find evidence of benefit of vitamin D for patients with MS, but conservative interpretation of the results is warranted because they were reported by a few small trials that we considered to be at high risk of bias.

Potential biases in the review process

We attempted to limit bias in the review process by ensuring a comprehensive search for potentially eligible studies, which included searching major databases and clinical trial registries, which nevertheless resulted in the retrieval of few studies. The two review authors' independent assessments of study eligibility for inclusion in this review and recording of extracted data minimised the potential for additional biases beyond those detailed in the risk of bias tables. We found no strong evidence of heterogeneity in any of the primary outcome analyses, which may emphasise the consistency of our findings but might also raise concerns, given that treatment schemes and comparison groups were different among the included studies. The included studies used different forms, doses, and durations of vitamin D supplementation. Most used

vitamin D₃, one trial tested vitamin D₂, and in three trials, participants in the comparator group were allowed to take low doses of vitamin D. Finally, the possible presence of reporting bias could not be totally excluded.

Agreements and disagreements with other studies or reviews

We found that vitamin D had no effect on MS clinical or MRI activity, although in view of the very low certainty of the evidence, these results should be interpreted with caution. Our findings are consistent with the conclusions of other published reviews (Autier 2014; CADTH 2016; Ganesh 2013; Hempel 2017; James 2013; Khosravi-Largani 2018; Pozuelo-Moyano 2013; Zheng 2018). CADTH 2016 included four systematic reviews, eight RCTs, and three non-randomised studies on the clinical effectiveness of vitamin D supplementation for prevention or treatment of MS. Evidence for most clinical outcomes was judged as limited and often conflicting owing to substantial heterogeneity between studies. Review authors concluded that results of treatment of MS with vitamin D were inconsistent, with most evidence suggesting no effect on disability scores or relapse rates. Researchers reported both positive and negative results for immunological factors, imaging studies, and functional outcomes. Safety data suggest that high-dose vitamin D was well tolerated and was associated with minimal risk. Zheng 2018 published a systematic review that included six RCTs (all of them included in our review) published up to October 2017 (with 337 participants) reporting that vitamin D as add-on

treatment had no significant therapeutic effect on MS according to EDSS score (six RCTs; 318 participants; mean difference (MD) -0.01, 95% CI -0.34 to 0.33), but it increased the annualised relapse rate compared with placebo (five RCTs; 259 participants; MD 0.05, 95% CI 0.01 to 0.1). Review authors concluded that vitamin D appeared to have no therapeutic effect on EDSS score or relapse rate in patients with MS. [Hempel 2017](#) conducted a systematic review including five RCTs (all of them included in our review) published up to March 2015 (with 295 participants). Review authors found that vitamin D as add-on treatment had no significant effect on EDSS score (standardised mean difference -0.15, 95% CI -0.33 to 0.02). [James 2013](#) published a systematic review including five RCTs (all of them included in our review) published up to 28 September 2012 (with 254 participants). Review authors reported an overall odds ratio for recurrence of relapse of 0.98 (95% CI 0.44 to 2.17) and concluded that there was no significant association between treatment with high-dose vitamin D and relative risk of relapse in MS. [Autier 2014](#) conducted an updated systematic review and meta-analyses of vitamin D supplementation for non-skeletal conditions published between 1 January 2013, and 31 May 2017, and searched for trials published at any time up to 21 May 2017, that were not included in the meta-analyses they selected. This review included the meta-analyses published by [James 2013](#) and [Hempel 2017](#) and concluded that vitamin D supplementation had no effects on relapse rates nor on changes in EDSS score over the trial duration. [Khosravi-Largani 2018](#) published a narrative review and cited a previous review to conclude that available trials were not able to clearly support the hypothesis that vitamin D consumption can control MS outcomes ([Dörr 2013](#)). [Ganesh 2013](#) and [Pozuelo-Moyano 2013](#) reported narratively that some individual trials in patients with unspecified MS phenotypes or with relapsing-remitting MS reported no differences in relapse rates following high-dose vitamin D treatment, and these review authors concluded that the evidence for vitamin D as a treatment for MS was inconclusive.

Despite the growing body of evidence indicating that vitamin D is unlikely to be efficacious for people with MS, some study authors strongly support its use in MS ([Pierrot-Deseilligny 2017](#); [Wagner 2017](#)), emphasising benefit reported by observational studies and its relatively low toxicity. For these researchers, the lack of benefit noted in most trials should be attributed to participants not sufficiently deficient in vitamin D at baseline or to inadequate supplementation or a too short treatment period, as well as to the low quality of studies.

The discrepancy between epidemiological studies, which reported an association between low serum 25OHD concentration and MS,

and randomised interventional trials, which did not find benefit of vitamin D supplementation for people with MS, can be explained by the assumption that low vitamin D is not a cause but a consequence of ill health. Inflammatory processes involved in disease occurrence and clinical course would reduce 25-hydroxyvitamin D (25OHD), which would explain why low vitamin D status is reported in a wide range of disorders ([Autier 2014](#)).

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review show that vitamin D supplementation, irrespective of the form and dose used, provides no apparent benefit for people with MS. Moreover, short-term trials have provided scanty and poorly reported safety data and have not provided evidence that can be used to determine a reliable risk profile for vitamin supplementation. Conservative interpretation of these results is warranted because vitamin D has been evaluated in a few small trials providing low- to very low-quality evidence. We used a comprehensive, transparent, and pragmatic system for rating the quality of the evidence (i.e. the GRADE approach); according to this approach, any estimate of effect based on low- to very low-quality evidence is very uncertain, and further research is likely to change the estimate.

Implications for research

Seven new trials are currently ongoing, and we are hopeful that their findings will contribute better evidence towards informing practice. Also, given the limited available evidence for patient-important outcomes, such as disability and health-related quality of life, and for the risk profile of vitamin D in patients with MS, new studies should include these outcomes in a standardised way. Additionally, these trials need to report high-quality data on the benefit of vitamin D for patients with MS who are vitamin D deficient.

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Wagner 2017

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Zheng 2018

Zheng C, He L, Liu L, Zhu J, Jin T. The efficacy of vitamin D in multiple sclerosis: a meta-analysis. *Multiple Sclerosis and Related Disorders* 2018;**23**:56–61. [PUBMED: 29778041]

References to other published versions of this review**Jagannath 2010**

Jagannath VA, Fedorowicz Z, Asokan GV, Robak EW, Whamond L. Vitamin D for the management of multiple sclerosis. *Cochrane Database of Systematic Reviews* 2010, Issue 12. DOI: 10.1002/14651858.CD008422

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Achiron 2015

Methods	Randomised, placebo-controlled, parallel-group, double-blind, single-site trial Country: Israel Study years: not reported
Participants	Randomised: n = 158 Stage 1: fatigue recognition: patients assessed for eligibility (n = 600). In patients with clinically definitive MS according to McDonald criteria, randomly selected from Sheba Medical Center MS database, fatigue was assessed by the self-reported Fatigue Severity Scale (FSS). Respondents to item 9 of the FSS - "Fatigue interferes with my work, family, or social life" - with a score ≥ 3 on a 1 to 7 rating were selected Stage 2: severe fatigue: patients assessed for eligibility (n = 259) Inclusion criteria: Fatigue Impact Scale (FIS) score ≥ 40 points; age 18 to 55 years; Expanded Disability Status Scale (EDSS) score at screening up to 5.5 Exclusion criteria: relapse within 30 days before the study; serum calcium level > 10.5 mg/dL; history of hypersensitivity or intolerance to alfacalcidol or related substances; a life-threatening and/or unstable clinical condition and/or alcohol or drug abuse
Interventions	Intervention group: vitamin D ₃ alfacalcidol (1-alpha-hydroxycholecalciferol) (1 μ g or 40 IU) daily (n = 80) Comparator group: matched capsules of arachis oil (n = 78) for a 6-month period; participants were followed for a 2-month period Co-intervention: 66% of participants in the alfacalcidol group and 69% in the placebo group received treatment with interferon-beta or glatiramer acetate
Outcomes	Primary outcome: change in FIS score (the cutoff point for improvement was defined as a 30% FIS score decrease) Secondary outcomes: <ul style="list-style-type: none"> Quality of life measured by the RAYS questionnaire - an MS-specific instrument consisting of 3 dimensions: physical, psychological, and social-familial, each containing 15 self-reported items scored from 1 (best) to 4 (worse), and focusing on the preceding week. RAYS scores range between 45 and 180; the questionnaire was validated in MS patients and demonstrated high internal validity with the quality of life measure - SF-36 Neurological disability measured by the EDSS score Number of acute relapses during the study and proportion of participants who were relapse-free
Notes	First RCT evaluating effect of vitamin D on fatigue Study was supported by an unrestricted research grant from Teva Pharmaceuticals Ltd., Israel. The sponsor had no role in study design, data collection, data analysis, interpretation, writing of the manuscript, or the decision to submit the manuscript for publication Trial was not registered, as alfacalcidol is considered a natural supplement - not a drug - in Israel
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	<p>"Randomization included a clear allocation concealment process performed on balanced blocks of four patients each and was conducted independently of the trial team delivering the medications and recruiting the patients"</p> <p>"The various placebo and treatment blocks were issued with a medication number and assigned to consecutive patients in a sequential order"</p>
<p>Blinding (performance bias and detection bias)</p> <p>All outcomes</p>	Low risk	<p>"All study personnel, patients, and sponsor personnel involved in the conduct of the study were unaware of treatment assignments throughout the study"</p> <p>"The placebo soft gelatin capsules were filled with arachis oil and were identical in appearance to Alfacalcidol capsules"</p>
<p>Incomplete outcome data (attrition bias)</p> <p>All outcomes</p>	Low risk	<p>Intervention group: completed follow-up: 72 (90%). Eight participants discontinued treatment (3 had adverse events; 3 requested withdrawal; 2 were non-compliant)</p> <p>Placebo group: completed follow-up: 71 (91%). Seven participants discontinued placebo (3 had adverse events; 3 requested withdrawal; 1 was non-compliant)</p>
Selective reporting (reporting bias)	Unclear risk	<p>Study protocol not available and trial not registered</p> <p>"The trial was not registered as Alfacalcidol is considered a natural supplement and not a drug in Israel. Ethical and standard operating procedures were kept to ensure patients safety along the study period and during follow-up"</p>
Other bias	Low risk	Comment: trial appears to be free of other components that could put it at risk of bias

Ashtari 2016

Methods	Randomised, placebo-controlled, parallel-group, double-blind clinical trial Study started on 22 December 2013, and was approved by the Ethical Committee of the Isfahan University of Medical Sciences Country: Iran Study years: December 2013 to March 2014
Participants	Randomised: N = 94 Inclusion criteria: RRMS according to McDonald criteria, age 18 to 55 years, EDSS score < 4, no relapse 30 days before inclusion, negative human chorionic gonadotropin (β -hCG) test for women of child-bearing age Exclusion criteria: pregnancy, lactation, any disease other than MS, vitamin D ₃ serum level > 85 ng/mL, past history of renal or hepatic disease, received corticosteroids in the previous 30 days, calcium > 11 mg/dL, aspartate transaminase or alanine transaminase > 3 times normal values, alkaline phosphatase > 2.5 times normal values
Interventions	Intervention group: vitamin D ₃ (50,000 IU) every 5 days (n = 47) Comparator group: matched placebo tablets (n = 47) for a 3-month period; participants were followed for the 3-month period of treatment Co-intervention: all participants received treatment with interferon beta
Outcomes	Primary outcome: quality of life measured by the MSQOL-54 (Persian version) - mental and physical health composites reported at 3 months' follow-up Vitamin D ₃ levels also recorded
Notes	Hypothesis of the study was that high-dose vitamin D intake improves quality of life in MS patients Same participants as in Ashtari 2015 who reported serum levels of interleukin-10 outcomes after 3 months, and in Toghianiifar 2015 who reported serum levels of interleukin-17 outcomes after 3 months. Both articles are sub-references under Ashtari 2016 . This work was supported by the Deputy of Research, Isfahan University of Medical Sciences. Registry No. 192165

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"After giving informed consent, eligible patients were randomised to one of two groups"
Allocation concealment (selection bias)	Unclear risk	"The patients were visited by the neurologist, who gave medication or placebo to the patient according to randomization and allocation"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study was reported as a "double blind randomised study".

Ashtari 2016 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	“After 12 weeks, all subjects completed the study”.
Selective reporting (reporting bias)	Low risk	Study reported and published the outcome it set out to investigate. The protocol is mentioned in the Iranian Registry of Clinical Trials: IRCT2015010910891N2
Other bias	High risk	Short follow-up period

Burton 2010

Methods	Phase I/II randomised, controlled, parallel-group, open-label trial Country: Canada Study years: June 2006 to March 2008
Participants	Randomised: N = 49 (40 females, 9 males), mean age 40.5 years (range 21 to 54) Inclusion criteria: age 18 to 55 years, clinically definitive MS according to diagnostic criteria of McDonald 2001 , Polman 2005 , Poser 1983 , and Schumacker 1965 . EDSS score of 0 to 6.5 Exclusion criteria: relapse within 60 days before randomisation, steroid use within 30 days, chemotherapy within 12 months, pregnancy or inadequate contraception, vitamin D intake > 4000 IU daily, serum 25OHD level > 50 nmol/L, lymphoma, granulomatous disease, cardiac arrhythmia, kidney dysfunction, disordered calcium metabolism
Interventions	Intervention group: escalating vitamin D ₃ doses up to 40,000 IU daily over 28 weeks, followed by 10,000 IU daily for 12 weeks, and further down-titrated to 0 IU daily. Calcium 1200 mg daily was given throughout the trial (n = 25) Comparator group: permitted to take 4000 IU daily of vitamin D ₃ and supplemental calcium (n = 24) for a 52-week period Co-intervention: interferon beta in 56% and 58% of participants in the intervention and comparator groups; glatiramer acetate in 8% of participants in the intervention and comparator groups; no disease-modifying drugs in 44% and 42% of participants in the intervention and comparator groups
Outcomes	Primary outcome: mean change in serum calcium at each vitamin D dose, comparison of serum calcium between groups Secondary outcomes: 25OHD and other biochemical measures, immunological biomarkers, relapse events, EDSS score Safety: adverse events; ultrasound monitoring for renal calculi done at baseline, at mid-trial, and at end of trial; EKG for cardiac rhythm at baseline and at end of trial
Notes	Trial focused on vitamin D safety. Trial used the escalating dose titration schedule, which minimised the risk of toxicity at higher doses, as doses were stepped up only if the previous dose was confirmed safe Supported by peer-reviewed grants from Direct-MS Charity and from the MS Society of Canada Registered with ClinicalTrials.gov: ID NCT00644904

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Patients were matched for age, disease duration, EDSS, and disease-modifying drug (interferon, glatiramer acetate, none). Members of pairs were randomised to treatment or control groups based on blinded drawing from a hat"
Allocation concealment (selection bias)	High risk	Not reported; probably no concealed allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	"Two patients in each group withdrew during the trial, none related to adverse events. More frequent monitoring of the intervention group could have been a factor in the disclosure of relapses and may have missed possible events or use of undisclosed agents in the less frequently assessed comparator group"
Selective reporting (reporting bias)	Low risk	All outcomes indicated in the protocol were reported.
Other bias	Low risk	Comment: trial appears to be free of other components that could put it at risk of bias

Etemadir 2015

Methods	Phase I/II randomised, controlled, parallel-group, open-label, single-centre trial Country: Iran Study years: July 2011 to December 2012
Participants	Randomised: N = 43 Pregnant women with MS and low serum 25-hydroxyvitamin D (25OHD) Inclusion criteria: stable neurological findings for 1 month before randomisation, EDSS ≤ 6, serum vitamin D levels < 20 ng/mL
Interventions	Intervention group: vitamin D ₃ (50,000 IU/week) (n = 21) Comparator group: routine care (n = 22) Co-intervention: not reported Period: from 12 to 16 weeks' gestation until delivery; participants were followed for a 6-

Etemadir 2015 (Continued)

	month period after delivery
Outcomes	Primary outcome: mean change in serum 25OHD levels from baseline to 6 months after delivery Secondary outcomes: mean changes in EDSS and number of relapses Safety and tolerability were assessed by vital signs, safety lab, EKG, and adverse event reporting
Notes	First RCT of vitamin D ₃ in pregnant women with MS Trial not registered Study grant not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No random sequence generation
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Both participants and investigators were aware of the treatment received
Incomplete outcome data (attrition bias) All outcomes	High risk	15 (71%) of 21 from the intervention group and 13 (59%) of 22 from the control group were lost to follow-up and did not receive the allocated intervention
Selective reporting (reporting bias)	Low risk	All outcomes specified in the protocol were reported.
Other bias	Low risk	Comment: trial appears to be free of other components that could put it at risk of bias

Golan 2013

Methods	Randomised, placebo-controlled, parallel-group, double-blind, single-centre study Country: Israel Study years: October 2010 to April 2012
Participants	Randomised: N = 45 Clinical and laboratory definitive relapsing-remitting MS according to revised McDonald's criteria Inclusion criteria: age $\geq$ 18 years, assigned to initiate IFN β treatment or continued to suffer from flu-like symptoms beyond 4 months of treatment with IFN β , 25OHD blood levels < 75 nmol/L, EDSS score < 7

	Exclusion criteria: abnormalities in vitamin D-related hormonal system other than low dietary intake or decreased sun exposure (e.g. intestinal malabsorption, cirrhosis, nephrotic syndrome, hyperthyroidism, creatinine clearance < 40 mL/min, rickets, hypoparathyroidism, hypercalcaemia at baseline, known malignancy, granulomatous disorders, lymphomas); medications that influence vitamin D metabolism, namely, orlistat, anticonvulsants, rifampin, isoniazid, ketoconazole, 5-FU, and leucovorin; conditions of increased susceptibility to hypercalcaemia (known arrhythmia, heart disease, nephrolithiasis, and treatment with digitalis or hydrochlorothiazide); pregnancy	
Interventions	Intervention group: vitamin D ₃ (800 IU) daily by tablets plus a bottle of vitamin D ₃ (75,000 IU) solution every 3 weeks (total vitamin D ₃ : 4370 IU daily) (n = 24) Active comparator: vitamin D ₃ (800 IU) daily by tablets plus a placebo solution every 3 weeks (total vitamin D ₃ : 800 IU daily) (n = 21) for a 1-year period Co-intervention: all participants received treatment with interferon beta	
Outcomes	Primary outcome: change in flu-like symptoms (FLS) score from time of enrolment to vitamin D supplementation - FLS assessed by monthly phone interviews; patients rated the extent of FLS on a Likert scale (total FLS score ranging from 0 to 35) Secondary outcomes: <ul style="list-style-type: none">• EDSS• Relapses• Quality of life measured by the Functional Assessment of Multiple Sclerosis (FAMS) - a self-reported health-related quality of life instrument for people with MS. It consists of 44 scored items in 6 quality of life domains: mobility (7 items), symptoms (7 items), emotional well-being (7 items), general contentment (7 items), thinking/fatigue (9 items), and family/social well-being (7 items). An additional concerns subscale consists of 15 other items that fall outside of the 6 domains. The total FAMS score is calculated by summing all subscale scores, ranging from 0 to 232. High score denotes decreased QOL• Serum levels of 25-hydroxyD (25OHD), calcium, PTH, IL17, IL10, and IFNγ measured periodically at 3 months, 6 months, and 1 year	
Notes	Primary objective of the study was to test whether vitamin D supplementation may ameliorate IFN- β -induced flu-like syndrome Study was supported by Merck Serono-Israel and Bayer Schering-Israel. Vitamin D supplements and placebos were donated by CTS - Israel and Altman - Israel Registered with ClinicalTrials.gov: NCT01005095	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	High risk	“The assignment to groups was randomly set in advance, according to recruitment order”

Golan 2013 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	“Vitamin D supplementation was double-blind in this study - both participants, treating physician and investigators were unaware of the ingredients of the solution bottles” No information on blinding of the vitamin D ₃ dose
Incomplete outcome data (attrition bias) All outcomes	High risk	15 (62.5%) participants out of 24 in the intervention group and 15 (71%) participants out of 21 in the comparator group completed 12 months’ follow-up Numbers and reasons for dropout and withdrawal were different in the 2 groups, e.g. 4 (17%) and 2 (9.5%) participants in the intervention group and in the comparator group, respectively, withdrew consent
Selective reporting (reporting bias)	Unclear risk	Primary outcome designed by the study was to assess flu-like symptoms of IFN therapy; not designed to evaluate clinical and radiological outcomes that were reported only when participants presented with symptoms
Other bias	Low risk	Comment: trial appears to be free of other components that could put it at risk of bias

Hupperts 2016

Methods	Randomised, 3-arm, placebo-controlled, parallel-group, double-blind, multi-centre phase II study (SOLAR) Country: Europe: 53 sites across Belgium, Denmark, Estonia, Finland, Germany, Hungary, Latvia, Lithuania, Norway, Switzerland, The Netherlands, and Italy Study years: February 2011 to May 2015. Last update posted in trials.gov: 28 November 2016 Receiving treatment with 44 mg tiw of Rebif®: SOLAR study
Participants	Randomised: N = 232 (original estimate N = 348) Inclusion criteria: 25-hydroxy-vitamin D plasma levels < 150 nmol/L; mean age 33.9 (SD 8.8); diagnosis of relapsing-remitting MS; brain and/or spinal MRI with findings typical of MS; first clinical event before screening; EDSS score ≤ 4.0; currently treated with interferon-beta-1a 44 mg Exclusion criteria: pregnancy or lactation; any disease other than MS that could better explain signs and symptoms; complete transverse myelitis or bilateral optic neuritis; relapse within 30 days before enrolment; use of corticosteroids or adrenocorticotrophic hormone within 30 days before enrolment; abnormalities of vitamin D-related hormonal system other than those due to low dietary intake or decreased sun exposure;

	urine calcium/creatinine (mmol/mmol) ratio > 1.0 or hypercalcaemia (11 mg/100 cc (5.5 mEq/L)); inadequate liver function (alanine aminotransferase > 3 times upper limit of normal (ULN); aspartate aminotransferase > 3 times ULN; alkaline phosphatase > 2.5 times ULN; or bilirubin > 1.5 times ULN, if associated with any elevation of alanine aminotransferase or alkaline phosphatase); concomitant medications that influence vitamin D metabolism other than corticosteroids; currently taking > 400 IU (> 10 µg) of vitamin D supplement daily; conditions with increased susceptibility to hypercalcaemia (e.g. known arrhythmia or heart disease, treatment with digitalis or hydrochlorothiazide, nephrolithiasis)
Interventions	Intervention group: vitamin D ₃ (cholecalciferol, vigantol oil) (6670 IU) daily administered orally for 4 weeks, followed by 14,007 IU daily administered orally for 44 weeks (n = 115) Comparator group: matching placebo daily, orally administered for 48 weeks (n = 117) Co-intervention: interferon beta-1a (Rebif) 44 mcg 3 times per week administered subcutaneously for a 48-week period
Outcomes	Primary outcome: percentage of participants with disease activity-free status up to week 48, defined as no relapses, no EDSS progression, and no new gadolinium (Gd)-enhancing or T2 magnetic resonance imaging lesions Secondary outcomes: <ul style="list-style-type: none"> • Annualized relapse rate at week 48 • Percentage of relapse-free participants at week 48 • Percentage of participants free from any EDSS progression at week 48 • Number of participants with confirmed EDSS progression, defined as an increase in EDSS score $\geq$ 1.0 point compared to baseline for participants with baseline EDSS $\leq$ 4.0. For participants with EDSS score of 0 at baseline, EDSS progression was defined as an increase of $\geq$ 1.5 points. Confirmed EDSS progression was defined as EDSS progression confirmed after 24 weeks • Cumulative number of T1 gadolinium-enhancing lesions at week 48
Notes	Study was moved from ongoing studies in the previous version of the review to included studies, as results were available in ClinicalTrials.gov: NCT01285401. Results of this study are not yet published at the time of preparation of this updated review Study was supported by Merck KGaA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Allocation by means of an interactive voice-response system as reported in the protocol (reference for the study protocol is provided as a sub-reference under Hupperts 2016)

Hupperts 2016 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind is reported. No other information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomised: N = 232 (original estimate N = 348, as reported in the study protocol, provided as a sub-reference under Hupperts 2016) Participants analysed: 113 (98%) of 115 participants in group 1, 116 (99%) of 117 in group 2 (Hupperts 2016). Prematurely withdrawn from the study: 17 (15%) of 115 participants in group 1, 29 (25%) of 117 in group 2. Reasons for withdrawals not reported
Selective reporting (reporting bias)	Unclear risk	Several amendments of outcomes described in the original protocol (sub-reference under Hupperts 2016)
Other bias	Unclear risk	We deemed this study to have unclear risk of within-study bias. Data included in this review were obtained from information provided by the sponsor (Merck KGaA) to ClinicalTrials.gov: NCT01285401; however these data were not published

Kampman 2012

Methods	Randomised, double-blind, placebo-controlled, parallel-group, single-centre, 96-week study Country: Norway Study years: 5 November 2008 to 5 September 2011
Participants	Randomised: N = 71 Inclusion criteria: 18 to 50 years of age; clinically definitive multiple sclerosis according to the McDonald criteria; EDSS score ≤ 4.5 Exclusion criteria: inability to walk 500 metres or more; history of conditions or diseases affecting bone; pregnancy or lactation during the past 6 months; use of bone-active medications other than intravenous methylprednisolone for treatment of relapse; history of nephrolithiasis during the previous 5 years; menopause defined by not having regular menstruation; unwillingness to use appropriate contraception
Interventions	Intervention group: vitamin D ₃ (cholecalciferol) (20,000 IU) once a week (n = 35) Comparator group: identical placebo capsules (n = 36) for a 96-week period Participants were allowed to continue vitamin D supplements they had used at baseline Co-intervention: interferon beta in 46% of participants in intervention and comparator groups; glatiramer acetate in 3% of participants in intervention and comparator groups;

Kampman 2012 (Continued)

	natalizumab in 1 participant in the comparator groups; no disease-modifying drugs in 47% and 48% of participants in intervention and comparator groups Elemental calcium 500 mg daily
Outcomes	Serum 25OHD levels, ARR, EDSS, MSFC components, grip strength, FSS (FSS scale 1 to 7: no fatigue to worse)
Notes	Study was reported in 3 other publications (sub-references under Kampman 2012). Study received financial support from the University of Tromsø, the Research Council of Norway, and Odd Fellows. Research Foundation for Multiple Sclerosis Registered at ClinicalTrials.gov: NCT00785473

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A statistician at the Clinical Research Centre, who was not otherwise involved in the study, performed the randomisation by blocks of six, stratified by sex, with a concealed, computer-generated randomisation procedure"
Allocation concealment (selection bias)	Unclear risk	"An identification number and a randomisation number were created for each participant"
Blinding (performance bias and detection bias) All outcomes	Low risk	"All study personnel and participants were blinded to treatment assignment for the duration of the study" "Identical placebo capsules were provided by the manufacturer of Dekristol™ (SWISS CAPS AG, Kirchberg, Switzerland)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intervention group: none lost to follow-up. Comparator group: 4 (11%) of 36 participants lost to follow-up (3 discontinued study medication before week 48 for personal reasons; 1 discontinued study medication at week 60 owing to pregnancy)
Selective reporting (reporting bias)	Unclear risk	No access to the protocol; we could not contact study authors to ask if they published all outcomes that they set out to assess. Annualised relapse rate reported only for IV methylprednisolone-treated relapses

Kampman 2012 (Continued)

Other bias	Low risk	Comment: trial appears to be free of other components that could put it at risk of bias
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Mosayebi 2011

Methods	Randomised, placebo-controlled, parallel-group, double-blind, single-centre study Country of study: Iran Study years: October 2009 to April 2010
Participants	Randomised: N = 62 Participants from hospitals of the Medical University of Arak were recruited from October 2009 to April 2010 Inclusion criteria: relapsing-remitting MS; age 18 to 60 years; ≥ 1 relapse in the previous 12 months; more than 3 lesions on spinal or brain MRI or both; baseline EDSS from 0 to 3.5 Exclusion criteria: clinically isolated syndrome; progressive MS; MS patients with clinical relapse occurring during the study; drug abuse; use of digitalis or vitamin D supplementation; any condition predisposing to hypercalcaemia; nephrolithiasis or renal insufficiency; pregnancy or unwillingness to use contraception; unwillingness to restrict dietary calcium
Interventions	Intervention group: vitamin D ₃ (300,000 IU) every month as intramuscular injection (n = 28) Comparator group: placebo as intramuscular injection (n = 34) for a 6-month period Co-intervention: all participants received interferon beta 1a
Outcomes	Primary outcome was not defined. Outcomes measured at baseline and at 1 month after last vitamin D injection: <ul style="list-style-type: none"> • EDSS score • MRI: number of gadolinium-enhancing lesions • Level of 25OHD • Levels of cell proliferation; levels of transforming growth factor-beta and interleukin-10
Notes	Study hypothesis was to determine the potential of vitamin D as an immune modulator in MS Trial not registered Study received financial support from the Arak University of Medical Sciences, in Iran

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	High risk	Allocation concealment probably not done

Mosayebi 2011 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	“Throughout the study, the neurologist, physician and the radiologist were unaware of the treatment assigned to each patient”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two (7%) of 28 participants in the intervention group and 1 (3%) of 34 in the comparator group discontinued participation, and no data from these participants were included in the analysis. Reasons for treatment discontinuation not described
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge selective reporting
Other bias	High risk	Follow-up period was short.

Shaygannejad 2012

Methods	Randomised, placebo-controlled, parallel-group, double-blind study Country: Iran Study period: October 2007 to March 2009
Participants	Randomised: N = 50 with normal 25(OH)D levels Inclusion criteria: either sex; age between 15 and 60 years; MRI, clinical, or laboratory-supported diagnosis of relapsing-remitting MS; mean disease duration 4.3 (SD 2.2) years; stable neurological functioning for at least 1 month before study entry; EDSS score ≤ 6 ; serum 25-hydroxyvitamin D level > 40 ng/mL; willingness to continue current medications for the duration of the study
Interventions	Intervention group: vitamin D ₃ (calcitriol; 1,25-dehydroxyvitamin D ₃) (0.25 μ g) daily, increased to 0.5 μ g daily (20 IU) after 2 weeks (n = 25) Comparator group: placebo (n = 25) for a 12-month period Both interventions were administered as capsules twice a day orally before meals Co-intervention: interferon beta in 88% and 84% of participants in intervention and comparator groups; immunosuppressive drugs in 4% of participants in intervention and comparator groups; statin in 8% and 12% of participants in intervention and comparator groups
Outcomes	Primary outcome: EDSS change from baseline to 12 months Secondary outcome: change in relapse rate from baseline to 12 months
Notes	Study aimed to evaluate effects of low-dose oral vitamin D in combination with current disease-modifying therapy for prevention of progression of relapsing-remitting MS Study was partially supported by grants from the Isfahan University of Medical Sciences, in Iran. No pharmaceutical company supported the study financially Registered with Iranian Registry of Clinical Trials (ID IRCT201104166202N1)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised according to a preexisting list produced by a computer program"
Allocation concealment (selection bias)	Unclear risk	"The hospital pharmacist was informed of all randomization assignments and was responsible for labelling the study drug and maintaining a master list linking participants and their treatment assignments"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Both patient and physician who assessed the outcome were unaware of the type of treatment each patient received. Masking of the active and placebo treatment was preserved by creating treatments that looked identical"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts in either group
Selective reporting (reporting bias)	Unclear risk	No access to protocol
Other bias	Low risk	Comment: trial appears to be free of other components that could put it at risk of bias

Soilu-Hanninen 2012

Methods	Randomised, placebo-controlled, parallel-group, double-blind, multi-centre study Country: Finland Study period: not reported
Participants	Randomised: N = 66 Inclusion criteria: age 18 to 55 years; relapsing-remitting MS according to the McDonald criteria, with IFNB-1b used for at least 1 month; no neutralising antibodies to IFNB, as measured by the indirect myxovirus A test; EDSS score < 5.0 Exclusion criteria: serum calcium > 2.6 mmol/L; serum 25OHD > 85 nmol/L; primary hyperparathyroidism; pregnancy or unwillingness to use contraception; alcohol or drug abuse; use of immunomodulatory therapy other than IFNB-1b; known allergy to cholecalciferol or peanuts; therapy with digitalis, calcitonin, vitamin D ₃ analogues or vitamin D; any condition predisposing to hypercalcaemia (such as any type of cancer), sarcoidosis, nephrolithiasis, or renal insufficiency; significant hypertension; hyperthyroidism, or hypothyroidism in the year before the study began; history of kidney stones in the previous 5 years; cardiac insufficiency or significant cardiac dysrhythmia; unstable ischaemic heart disease; depression; inability to perform serial MRI scans

Interventions	Intervention group: vitamin D ₃ (cholecalciferol) (20,000 IU) in arachis oil inside a refined gelatin capsule given once weekly plus interferon beta-1b (Betaseron) (n = 34) Comparator group: matching placebo capsules once weekly plus Betaseron (n = 32) for a 12-month period Co-intervention: all participants received treatment with interferon beta
Outcomes	Primary outcomes: <ul style="list-style-type: none"> • MRI T2 burden of disease • Proportion of participants with serum levels of 25OHD > 85 nmol/L or parathormone < 20 ng/L at 6 and 12 months • Safety and tolerability (number of adverse events) Secondary outcomes: <ul style="list-style-type: none"> • Numbers of MRI-enhancing T1 lesions and new T2 lesions • Annual relapse rate • Changes in EDSS score • Timed 25-foot walk test and timed 10-foot tandem walk tests
Notes	Study aimed to evaluate the safety and efficacy of vitamin D ₃ as an add-on therapy to interferon b-1b in patients with MS Bayer provided an unrestricted grant. Sponsor did not have any role in the design of the study, data collection, statistical analysis, or interpretation of data Registered with ClinicalTrials.gov: NCT01339676

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Separate randomisation was done for each centre using randomly permuted blocks. Randomisation was performed at 4Pharma Ltd using SAS for Windows software, V.8.2"
Allocation concealment (selection bias)	Unclear risk	"Eligible patients were randomised 1:1 to treatment with either vitamin D ₃ or identically appearing matching placebo capsules"
Blinding (performance bias and detection bias) All outcomes	Low risk	"The investigator, patients, study nurses, radiologists and other persons directly involved in the conduct of the study were blinded to the treatment code, which was not opened until the database was locked. .. Laboratory values that could have revealed treatment allocation to the investigators were sent directly to the data manager at 4Pharma Ltd"

Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants dropped out at different intervals in each group
Selective reporting (reporting bias)	Unclear risk	Data were insufficient to judge selective reporting.
Other bias	Low risk	Comment: trial appears to be free of other components that could put it at risk of bias

Sotirchos 2016

Methods	Randomised (comparing high- vs low-dose cholecalciferol), parallel-group, double-blind, single-centre pilot study Country: USA Study period: April 2010 to January 2013
Participants	Randomised: N = 40 Inclusion criteria: diagnosis of relapsing-remitting MS; age 18 to 55 years; screening (within 1 month of baseline) for serum 25OHD level of 20 to 50 ng/mL Exclusion criteria: high-dose vitamin D supplementation (daily intake > 1000 IU) or change in immunomodulatory therapy within the past 3 months; systemic glucocorticoid therapy or relapse within 30 days; pregnancy; serum creatinine > 1.5 mg/dL; hypersensitivity to vitamin D preparations; history of hyperparathyroidism, tuberculosis, sarcoidosis, or nephrolithiasis
Interventions	Intervention group: vitamin D ₃ (cholecalciferol) (10,000 IU) daily (n = 19) Active comparator group: vitamin D ₃ (cholecalciferol) (400 IU) daily (n = 21) for a 6-month period All participants received a daily multi-vitamin including cholecalciferol (400 IU) and calcium 1000 mg Co-intervention: interferon beta in 32% and 29% of participants in intervention and comparator groups; glatiramer acetate in 16% and 33% of participants in intervention and comparator groups; natalizumab in 32% and 24% of participants in intervention and comparator groups; fingolimod in 11% and 10% of participants in intervention and comparator groups; abatacept in 1 participant in the comparator group; no disease-modifying drugs in 2 participants in the intervention group
Outcomes	Primary outcomes: <ul style="list-style-type: none"> • Change in proportions of IFN-gamma and interleukin-17 • CD4+ T cells • Adverse events Secondary outcome: changes in other immune cell subtypes
Notes	Study aimed to evaluate the immunological effects of high-dose compared to low-dose vitamin D in patients with MS Study was supported by funding from the Kenneth and Claudia Silverman Family Foundation and the Montel Williams Foundation (P.A.C.); and by the National Multiple Sclerosis Society Sylvia Lawry Physician Fellowship (FP-1787-A-1) (P.B.)

Registered with ClinicalTrials.gov: NCT01024777		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed by the Johns Hopkins Investigational Drug Pharmacy using a validated, automated system.. . Participants were stratified by sex and randomised by blocks of 4, to ensure a similar sex ratio in the 2 intervention groups, since the immunologic effects of cholecalciferol may differ by sex"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Study personnel and participants were blinded to the study intervention dose
Incomplete outcome data (attrition bias) All outcomes	High risk	Amongst the 40 randomised participants, only 35 completed all study visits, 2 completed baseline and mid-study visits, and 3 completed only baseline visits eventually after withdrawal due to side effects or otherwise Only 18 and 17 in vitamin D and placebo groups, respectively, were analysed
Selective reporting (reporting bias)	Low risk	No reporting bias
Other bias	High risk	Follow-up period was short.

Stein 2011

Methods	Randomised, placebo-controlled, parallel-group, double-blind study Country: Australia Study period: December 2006 to May 2009
Participants	23 participants were randomised. Inclusion criteria: relapsing-remitting MS according to the McDonald criteria, age 18 years, relapse within preceding 24 months despite immunomodulatory therapy, declined or could not tolerate such therapy Exclusion criteria: primary or secondary progressive MS, pregnancy, clinical relapse or systemic glucocorticoid therapy within the prior 30 days, EDSS score > 5, current MS treatment other than glatiramer acetate or interferon, hypercalcaemia, renal dysfunction 11 were allocated and received intervention and 12 were allocated to placebo group; 1

	participant in the intervention group discontinued treatment, as did 2 in the placebo group
Interventions	Intervention group: vitamin D ₂ (6000 IU) daily in a vegetable capsule (n = 11) Comparator group: placebo matching capsules without vitamin D ₂ (n = 12) for a 6-month period All participants received 1000 IU vitamin D ₂ daily. Co-intervention: interferon beta in 54% and 67% of participants in intervention and comparator groups; glatiramer acetate in 27% and 17% of participants in intervention and comparator groups; no disease-modifying drugs in 2 participants in intervention and comparator groups
Outcomes	Primary outcomes: cumulative number of new gadolinium-enhancing lesions, change in total volume of T2 lesions Secondary outcomes: changes in EDSS score and in number of clinical relapses
Notes	“The study aimed to examine whether adding high-dose oral vitamin D ₂ reduced MRI indices of disease activity in comparison with ongoing low-dose supplementation and to provide effect size estimates for larger definitive RCTs” Study was supported by grants from the Myer Foundation. Registered with the Australian Clinical Trials Registry: ACTRN12606000359538

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Participants were recruited in 5 groups. Each group was subject to computer randomization by an off-site statistician blocking on specific MS therapy (glatiramer acetate, interferon, no specific therapy), except for the first 2 participants who were computer randomised by the unblinded investigator as the statistician was unavailable” “In a separate random allocation, each participant on high dose vitamin D ₂ was paired with a “buddy” on placebo. With every change in high-dose D ₂ capsule dose, the buddy was contacted by a study nurse to make the same capsule dose change”
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	“Neurologists were blinded to treatment allocation”. “Two blinded neuroradiologists evaluated scans”. “Nurses remained blinded”.

Incomplete outcome data (attrition bias) All outcomes	High risk	3 withdrawals: 2 (17%) in the comparator group (1 at 2 weeks with nausea and 1 after 4 months to electively enter a different MS trial), and 1 (9%) in the intervention group after relapse at 3 months to receive natalizumab
Selective reporting (reporting bias)	Unclear risk	Insufficient data about selective reporting
Other bias	High risk	Follow-up period was short.

25OHD: 25-hydroxyvitamin D

5-FU: 5-fluorouracil

ARR: annualised relapse rate

EDSS: Expanded Disability Status Scale

EKG: electrocardiogram

FAMS: Functional Assessment of Multiple Sclerosis.

FIS: Fatigue Impact Scale

FLS: flu-like symptoms

FSS: Fatigue Severity Scale

Gd: gadolinium

hCG: human chorionic gonadotropin

IFN: interferon

IFNB: interferon beta

IL: interleukin

MRI: magnetic resonance imaging

MS: multiple sclerosis

MSFC: Multiple Sclerosis Functional Composite

MSQOL-54: Multiple Sclerosis Quality of Life-54

PTH: parathyroid hormone

QOL: quality of life

RCT: randomised controlled trial

RRMS: relapsing-remitting multiple sclerosis

SD: standard deviation

SF-36: Short Form-36

ULN: upper limit of normal

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Lakatos 2000	Wrong population: RCT evaluating the effect of vitamin D ₃ (alfacalcidol) compared with placebo on bone metabolism in participants with systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, or asthma bronchiale who were placed on glucocorticoid therapy. Communication with the study author by email revealed that only 2 participants in the study had multiple sclerosis, and separate data for these participants were unavailable
Najafipour 2015	Not a randomised study
Pierrot-Deseilligny 2012	Not a randomised study
Røsjo 2017	RCT included in the review (Kampman 2012). This article reports only data on antibodies against Epstein-Barr virus, which are outcome measures not included in the review
Shirvani-Farsani 2015	Not a randomised study
Wingerchuk 2005	Not a randomised study

RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

[NCT01198132](#)

Trial name or title	A Multicentre Study of the Efficacy and Safety of Supplementary Treatment With Cholecalciferol in Patients With Relapsing Multiple Sclerosis Treated With Subcutaneous Interferon Beta-1a 44 µg 3 Times Weekly (CHOLINE)
Methods	Multi-centre, randomised, double-blind, placebo-controlled study
Participants	RRMS according to Poser criteria (clinically definitive multiple sclerosis (CDMS) or laboratory-supported definitive multiple sclerosis (LSDMS)) or according to McDonald criteria (2005). 18 to 65 years of age
Interventions	Intervention: 100,000 IU twice monthly, i.e. 1 dose fortnightly (equivalent to a daily dose of approximately 7142 IU) during the 96-week treatment period along with subcutaneous. Rebif 3 times weekly Control :placebo with subcutaneous. Rebif 3 times weekly
Outcomes	Primary outcome measure: <ul style="list-style-type: none"> Reduction in rate of relapse [Time Frame: after 2 years of treatment, relapse rate is expressed as percentage difference between the 2 groups] Secondary outcome measures: <ul style="list-style-type: none"> Time to first documented relapse [Time Frame: after 2 years of treatment] Mean number of relapses per participant per year [Time Frame: after 2 years of treatment] Number of relapse-free (documented) participants [Time Frame: after 2 years of treatment] Cumulative probability of progression of disability (Kaplan-Meier curves) [Time Frame: after 2 years]

NCT01198132 (Continued)

	<p>of treatment]</p> <ul style="list-style-type: none"> • Number of new or extended lesions by T1- and T2-weighted MRI [Time Frame: after 2 years of treatment] • Changes in measured lesion load (T2) [Time Frame: after 2 years of treatment] • Measurement and evaluation of cognitive ability by Paced Auditory Serial Addition Task (PASAT) [Time Frame: after 2 years of treatment] • Change in quality of life (QOL) using EQ-5D (EuroQoL-5 dimension questionnaire) [Time Frame: after 2 years of treatment] • Safety of treatment assessed by recording of adverse events, clinical laboratory evaluations (blood biochemistry and urinalysis) and vital signs [Time Frame: after 2 years of treatment]
Starting date	8 September 2010
Contact information	Medical responsible
Notes	NCT01198132: multi-centre study from France

NCT01440062

Trial name or title	Efficacy of Vitamin D Supplementation in Multiple Sclerosis (EVIDIMS Trial)
Methods	Double-blind RCT, high- vs low-dose study
Participants	<ul style="list-style-type: none"> • Age between 18 and 65 at randomisation • Relapsing-remitting MS according to revised McDonald criteria (2005) • EDSS $\leq$ 6.0
Interventions	Vitamin D oil 20000 IU/g and 400 IU/g every second day vs neutral oil and 400 IU/g of vitamin D every second day
Outcomes	<p>Primary outcome measure:</p> <ul style="list-style-type: none"> • Number of new lesions detected on T2-weighted cranial MRI at 3 tesla <p>Secondary endpoints:</p> <ul style="list-style-type: none"> • Additional MRI and optical coherence tomography parameters for neuro-inflammation and degeneration • Clinical parameters for disease activity, cognition, fatigue, depression, and quality of life • Safety and tolerability of high-dose vitamin D supplementation
Starting date	
Contact information	.
Notes	NCT01440062: multi-centre study from Germany

NCT01490502

Trial name or title	The Vitamin D to Ameliorate Multiple Sclerosis (VIDAMS) Trial: Study Design for a Multicenter, Randomised, Double-Blind, Controlled Trial of Vitamin D in Multiple Sclerosis
Methods	After completing a 1-month run-in of glatiramer acetate, 172 patients will be randomised 1:1 to oral vitamin D 5000 IU vs 600 IU daily
Participants	RRMS, age 18 to 50 years, Expanded Disability Status Scale score ≤ 4.0
Interventions	Oral vitamin D 5000 IU vs 600 IU daily
Outcomes	<p>Primary outcome measure:</p> <ul style="list-style-type: none"> Proportion of participants who experience a relapse [Time Frame: 2 years] <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> Annualised relapse rate [Time Frame: 2 years] Number of relapses requiring treatment [Time Frame: 2 years] Number of new T2 lesions [Time Frame: in the 2-year study, compared to baseline] Occurrence of sustained disability progression [Time Frame: at years 1 and 2, compared to baseline]. <p>Participant will be considered to have had sustained progression of disability if an increase of at least 1.0 point is seen in the Expanded Disability Status Scale score at month 12 and is confirmed on the final examination 1 year later.</p> <ul style="list-style-type: none"> Change in MS Functional Composite Score [Time Frame: over the 2-year study compared to baseline] Change in low-contrast acuity [Time Frame: over the 2-year study compared to baseline] Change in health-related quality of life [Time Frame: over the 2-year study compared to baseline] Change in brain parenchymal volume [Time Frame: over the 2-year study compared to baseline] Change in normalised grey matter volume [Time Frame: over the 2-year study compared to baseline] Change in cortical thickness [Time Frame: over the 2-year study compared to baseline] Development of hypercalcaemia/related adverse effects [Time Frame: 2 years]
Starting date	6 December 2011
Contact information	Ellen M Mowry, MD, MCR; Sandra D Cassard, ScD
Notes	NCT01490502: multi-centre study from USA

NCT01753375

Trial name or title	Role of Vitamin D in Reducing the Relapse Rate in Patients With Multiple Sclerosis
Methods	Double-blind, randomised, controlled trial
Participants	Patients with multiple sclerosis
Interventions	Vitamin D vs placebo
Outcomes	<ul style="list-style-type: none"> Relapse rate in patients with multiple sclerosis [Time Frame: 12 months] Improvement in Expanded Disability Status Scale scores after vitamin D is received [Time Frame: 12 months]

NCT01753375 (Continued)

Starting date	January 2013
Contact information	Prof. Abdulkader Daif, MD
Notes	Single institute: King Khalid Hospital

NCT01768039

Trial name or title	Vitamine D in Multiple Sclerosis (MSVit)
Methods	Randomised, double-blind, placebo-controlled trial
Participants	Patients with multiple sclerosis; 18 to 65 years of age
Interventions	Vitamin D group will be treated with 50,000 International Units weekly and placebo
Outcomes	<p>Primary outcome measure:</p> <ul style="list-style-type: none"> Expanded Disability Status Scale (EDSS) score [Time Frame: changes in EDSS from baseline to 6 months] <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> Annual relapse rate (ARR) [Time Frame: changes in ARR from baseline to 12 months]
Starting date	11 January 2013
Contact information	Mahmoud Abedini, MD
Notes	NCT01768039: Mazandaran University of Medical Sciences, in Iran

NCT01817166

Trial name or title	Efficacy of Cholecalciferol (Vitamin D3) for Delaying the Diagnosis of MS After a Clinically Isolated Syndrome (D-Lay-MS)
Methods	Multi-centre, randomised, double-blind vs placebo
Participants	<ul style="list-style-type: none"> Age 18 to 65 years Clinically isolated symptoms Classic CIS in past 90 days Reference cerebromedullary MRI scheduled within 90 days after beginning of symptoms MRI (cerebro ± medullary) showing demyelination according to spatial spread criteria by Swanton (2006) <ul style="list-style-type: none"> At least 1 lesion in at least 2 of the following 4 territories: (1) periventricular; (2) juxtacortical; (3) subtentorial; (4) medullary
Interventions	100,000 IU cholecalciferol every 14 days for maximum of 24 months or until conversion to full multiple sclerosis

Outcomes	<ul style="list-style-type: none"> • Delay to conversion; number of relapses/episodes per year • Evaluating efficacy in terms of resonance imaging parameters (cerebral/spinal MRI) • Evaluating efficacy in terms of slowing the progression of disability as measured by EDSS score and subscores • Measuring and assessing cognitive abilities (PASAT) • Evaluating changes in quality of life (EQ-5D questionnaires, SF-36, and TLS-QoL10), fatigue questionnaire (FSMC), and anxiety/depression questionnaire (HADS) • Evaluating treatment tolerance • Correlating changes in clinical and imaging parameters with the evolution of serum levels of 25OHD2 and 25OHD3 • Establishing a bio bank of DNA and RNA from all patients in the study and conducting analyses of gene polymorphisms involved in the metabolism of vitamin D and the HLA system based on increased levels of vitamin D after supplementation • Establishing a bio bank of CSF, plasma, blood cells, serum, and RNA samples for patients at selected centres for research on prognostic biomarkers of conversion • Establishing a bio bank consisting of plasma tubes collected for determination of 25-hydroxy-vitamin D • Estimating the rate of discordance between the conversion decision made by the study neurologist and the result of the MRI re-interpretation performed at the end of the study, as well as the proportion of patients identified a posteriori as erroneously included according to the centralised reading
Starting date	20 March 2013
Contact information	Eric Thouvenot, MD, PhD
Notes	NCT01817166

O'Connell 2013

Trial name or title	Dose-Related Effects of Vitamin D3 on Immune Responses in Patients With Clinically Isolated Syndrome (CISAVID)
Methods	Exploratory, double-blind, placebo-controlled, randomised study
Participants	<ul style="list-style-type: none"> • CIS: patients with a clinically isolated syndrome with onset relapse within the previous 3 months and ≥ 2 asymptomatic T2 lesions on MRI brain scan • Age 18 to 55 years
Interventions	Vitamin D supplementation at 2 doses (5000 IU and 10,000 IU daily)
Outcomes	<p>Primary outcome measures:</p> <ul style="list-style-type: none"> • Effects of 2 doses of vitamin D and placebo therapy on the change in frequency of CD4 T-cell subsets and cytokine responses of peripheral blood mononuclear cells over 24 weeks of therapy from baseline [Time Frame: this outcome measure will be assessed at baseline and at 24 weeks]. Several measures will be examined, in particular IL-10 production and frequency of Th17 cells. <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> • Numbers of new T2 and gadolinium-enhancing lesions compared to baseline amongst the study group [Time Frame: baseline and 24 weeks] • MRI outcome measure will assess (1) number of gadolinium-enhancing lesions; (2) numbers of new and enlarging T2 lesions; (3) combined unique lesion count (new and enlarging T2 lesions plus

	<p>gadolinium-enhancing lesions) after 24 weeks of therapy in the 3 arms: 5000 IU, 10,000 IU vitamin D and placebo. Mean and median new T2 and gadolinium-enhancing lesions at 24 weeks (end of trial) will be compared for each treatment allocation group. In addition mean and median numbers of new T2 lesions plus gadolinium-enhancing lesions in all CIS patients on vitamin D will be compared to mean and median values in the placebo group.</p> <ul style="list-style-type: none"> • Relapse occurrence in CIS patients during 24 weeks of the trial [Time Frame: at each clinic visit or as the need arises] • Relapse occurrence in CIS patients during 24 weeks of the trial: (1) annualised relapse rate (ARR), (2) percentage of patients free from relapses, and (3) time to first relapse will be compared for each treatment allocation group. In addition, the same relapse measures will be applied to both vitamin D-treated groups combined and will be compared to those in the placebo group. • Percentage of CIS patients in each treatment arm free from any evidence of disease activity (no relapses, no new T2 lesions, no gadolinium-enhancing lesions) [Time Frame: at 24 weeks] <p>Other outcome measures:</p> <ul style="list-style-type: none"> • Serum calcium [Time Frame: every 4 weeks for 24 weeks] - a measure of calcium homeostasis • Number of participants with adverse events as a measure of safety and tolerability of vitamin D at doses of 5000 IU and 10,000 IU daily [Time Frame: 4 weekly assessments over 24 weeks] • Serum urea [Time Frame: 4-weekly over 24 weeks] - a measure of renal function • Serum creatinine [Time Frame: 4-weekly over 24 weeks] - a measure of renal function • Serum 25OHD levels [Time Frame: 4-weekly over 24 weeks] - a measure of response to oral dosing and adherence to therapy • Serum parathormone (PTH) [Time Frame: 4-weekly over 24 weeks] - a measure of parathyroid function
Starting date	November 2012
Contact information	Michael Hutchinson, MB, FRCP, St Vincent's University Hospital, Ireland
Notes	NCT01728922

25OHD: 25-hydroxyvitamin D

ARR: annualised relapse rate

CDMS: clinically definitive multiple sclerosis

CIS: clinically isolated syndrome

CSF: cerebrospinal fluid

EDSS: Expanded Disability Status Scale

EQ-5D: EuroQoL-5 dimension questionnaire

FSMC: Fatigue Scale for Motor and Cognitive Functions

HADS: Hospital Anxiety and Depression Scale

HLA: human leucocyte antigen

LSDMS: laboratory-supported definitive multiple sclerosis

MRI: magnetic resonance imaging

PASAT: Paced Auditory Serial Addition Task

QOL: quality of life

RCT: randomised controlled trial

RRMS: relapsing-remitting multiple sclerosis

SF-36: Short Form-36

TLS-QoL10: Two-Life Scale quality of life 10

DATA AND ANALYSES

Comparison 1. Vitamin D vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Annualised relapse rate	6	485	Rate Difference (Random, 95% CI)	-0.02 [-0.13, 0.09]
1.1 Follow-up at 52 weeks	5	417	Rate Difference (Random, 95% CI)	-0.05 [-0.17, 0.07]
1.2 Follow-up at 96 weeks	1	68	Rate Difference (Random, 95% CI)	0.06 [-0.08, 0.20]
2 EDSS	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Follow-up at 26 weeks	2	217	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.37, 0.17]
2.2 Follow-up at 52 weeks	5	221	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.61, 0.10]
2.3 Follow-up at 96 weeks	1	68	Mean Difference (IV, Random, 95% CI)	0.35 [-0.21, 0.91]
3 Number of MRI gadolinium-enhancing T1 lesions	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Follow-up at 26 weeks	2	82	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.52, 0.34]
3.2 Follow-up at 52 weeks	2	256	Mean Difference (IV, Random, 95% CI)	0.02 [-0.45, 0.48]
4 QOL	3		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 QOL (Physical)	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 MSQOL (Mental)	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 MSQOL (Sexual satisfaction)	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 MSQOL (Health change)	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.5 FAMS QOL	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.6 RAYS Physical	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.7 RAYS Psychological	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.8 RAYS Social	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Serious adverse events	8	621	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.03, 0.04]
6 Minor adverse events	8	701	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.02, 0.06]

Analysis 1.1. Comparison 1 Vitamin D vs placebo, Outcome 1 Annualised relapse rate.

Review: Vitamin D for the management of multiple sclerosis

Comparison: 1 Vitamin D vs placebo

Outcome: 1 Annualised relapse rate

Analysis 1.2. Comparison 1 Vitamin D vs placebo, Outcome 2 EDSS.

Review: Vitamin D for the management of multiple sclerosis

Comparison: 1 Vitamin D vs placebo

Outcome: 2 EDSS

Analysis 1.3. Comparison 1 Vitamin D vs placebo, Outcome 3 Number of MRI gadolinium-enhancing T1 lesions.

Review: Vitamin D for the management of multiple sclerosis

Comparison: 1 Vitamin D vs placebo

Outcome: 3 Number of MRI gadolinium-enhancing T1 lesions

Analysis 1.4. Comparison 1 Vitamin D vs placebo, Outcome 4 QOL.

Review: Vitamin D for the management of multiple sclerosis

Comparison: 1 Vitamin D vs placebo

Outcome: 4 QOL

Analysis 1.5. Comparison 1 Vitamin D vs placebo, Outcome 5 Serious adverse events.

Review: Vitamin D for the management of multiple sclerosis

Comparison: 1 Vitamin D vs placebo

Outcome: 5 Serious adverse events

Analysis 1.6. Comparison 1 Vitamin D vs placebo, Outcome 6 Minor adverse events.

Review: Vitamin D for the management of multiple sclerosis

Comparison: 1 Vitamin D vs placebo

Outcome: 6 Minor adverse events

ADDITIONAL TABLES

Table 1. Glossary

Arrhythmia	Any disturbance of the normal rhythmic beating of the heart
Cytokine	A small protein released by cells that has a specific effect on interactions or communications between cells, or on the behaviour of cells. Cytokines include interleukins, lymphokines, and cell signal molecules, such as tumour necrosis factor, and the interferons, which trigger inflammation and respond to infection
Demyelination	Damage to the myelin sheath of neurons
Metalloproteases	Proteolytic enzymes whose catalytic mechanism involves a metal, important in many aspects of biology, ranging from cell proliferation, differentiation, and remodelling of the extracellular matrix (ECM) to vascularisation and cell migration

Table 1. Glossary (Continued)

Nephrolithiasis	The process of forming stones in the kidney, or lower down in the urinary tract
Osteoporosis	Thinning of the bones with reduction in bone mass due to depletion of calcium and bone proteins
Phytohaemagglutinin	Proteins isolated from the bean. They are used mainly in the study of immune mechanisms and in cell culture

Table 2. Annualised relapse rate (ARR)

ARR	Vitamin D			Control group		
	ARR	SD	n	ARR	SD	n
Burton 2010	0.26	0.62	25	0.45	0.59	21
Golan 2013	0.51	0.34	15	0.34	0.27	15
Kampman 2012	0.14	0.04 to 0.24 ^a	35	0.08	-0.02 to 0.18*	33
Shaygannejad 2012	0.32	0.48	25	0.40	0.58	25
Hupperts 2016	0.28	0.59	113	0.39	0.83	116
Soilu-Hanninen 2012	0.26	0.48	32	0.28	0.58	30

^a95% confidence interval**Table 3. Serious adverse events (SAEs)**

Hupperts 2016	VigantOL oil plus interferon beta-1a (Rebif) Number of participants with at least 1 SAE out of 113 participants	Placebo plus interferon beta-1a (Rebif) Number of participants with at least 1 SAE out of 116 participants
Number of participants with at least one SAE	18/113 (15.9%)	8/116 (6.9%)
Cardiac disorders/failure	1/113 (0.9%)	0/116
Gastrointestinal disorders	3/113 (2.6%)	1/116 (0.9%)
Cellulitis	1/113 (0.9%)	0/116
Eye infection	0/113	1/116 (0.9%)

Table 3. Serious adverse events (SAEs) (Continued)

Pneumonia	1/113 (0.9%)	0/116
Pyelonephritis	1/113 (0.9%)	0/116
Overdose	8/113 (7.1%)	6/116 (5.2%)
Breast cancer	1/113 (0.9%)	0/116
Ovarian cancer	1/113 (0.9%)	0/116
Headache	0/113	1/116 (0.9%)
Syncope	1/113 (0.9%)	0/116
Depression	1/113 (0.9%)	0/116
Menorrhagia	1/113 (0.9%)	0/116
Uterine polyp	1/113 (0.9%)	0/116
Hypertension	1/113 (0.9%)	0/116

Events were not collected via systematic assessment.

Table 4. 25OHD levels at baseline and during the intervention with the range of vitamin D dose supplementation in the included trials

Study and country	Duration (months)	Participants included in trials (n)	Range of vitamin D dose (µg)	Baseline 25OHD in intervention groups (nmol/L)	25OHD during the intervention (nmol/L)	Number of clinical benefit outcomes assessed by trials (n)	Number of clinical benefit outcomes with significant improvement (n)
Achiron 2015 Israel	8	158	1 per day	NR	NR	4	3
Ashtari 2016	3	94	1250 every 5 days	Median (IQR) 70.56 ± 72.45	Median (IQR) 211.33 ± 107.00	1	0
Burton 2010	12	49	1000 per day over 6 months followed by 250 per day for 3	Mean (range) 73 (38 to 146)	Mean 413	2	0

Table 4. 25OHD levels at baseline and during the intervention with the range of vitamin D dose supplementation in the included trials (Continued)

			months, then down-titrated to 0 for the last 3 months				
Etemadir 2015	12	43	1250 once a week	Mean (SD) 38.25 ± 7.25	Mean (SD) 84.25 ± 38	2	2
Golan 2013	12	45	109.25 per day	Mean (SD) 48.2 ± 13.9	Mean (SD) 122.6 ± 32	3	0
Hupperts 2016 (Muris 2016)	11	232	167 per day for 4 weeks increased to 350 per day for 44 weeks	Median (IQR) 60 (38 to 85)	Median (IQR) 231 (162 to 250)	5	1
Kampman 2012	22	71	500 once a week	Mean (95% CI) 55.56 (46.87 to 64.26)	Mean (95% CI) 123.17 (112.99 to 133.36)	5	0
Mosayebi 2011	6	62	7500 every month as intramuscular injection	Mean 25	Mean 140	1	0
Shaygannejad 2012	12	50	Calcitriol 0.25 per day increased to 0.5 per day	NR	NR	2	0
Soilu-Hanninen 2012	12	66	500 once a week	Mean (range) 54 (19 to 82)	Mean (range) 110 (67 to 163)	3	0
Sotirchos 2016	6	40	250 per day	Mean (SD) 67 (22)	Mean (SD) 166 (46)	0	-
Stein 2011	6	23	Vitamin D ₂ 150 per day	Median (IQR) 59 (47 to 61)	Median (IQR) 120 (89 to 170)	2	0

25OHD: 25-hydroxyvitamin D

CI: confidence interval

IQR: interquartile ratio

NR: not reported

SD: standard deviation

Table 5. Serum inflammatory markers levels

Golan 2013	Vitamin D ₃ - low dose (21 participants)		Vitamin D ₃ - high dose (24 participants)	
	Baseline	After 3 months of treatment	Baseline	After 3 months of treatment
IFN- γ (ρ g/mL)	0.20 (0.22)	0.14 (0.2)	0.51 (1.1)	0.58 (1.3)
IL-10 (ρ g/mL)	Undetected	Undetected	Undetected	Undetected
IL-7 (ρ g/mL)	4.01 (3.99)	9.14 (9.9)	5.8 (6.1)	6.4 (6.7)

Cytokine levels are given as means (SD).

IFN- γ : interferon gamma

IL-7: interleukin-7

IL-10: interleukin-10

pg/mL: picogram/millilitre

Table 6. Serum inflammatory markers levels

Mosayebi 2011	Vitamin D ₃ (26 participants)		Placebo (33 participants)	
	Baseline	After 6 months	Baseline	After 6 months
IFN- γ (ρ g/mL)	2530 (230)	2250 (143)	2100 (98)	1980 (120)
IL-10 (ρ g/mL)	3600 (430)	4950 (530) ^a	3430 (312)	3750 (325)
TGF- β (ρ g/mL)	2.9 (1.68)	5.2 (2.4) ^a	3.1 (1.8)	3.3 (2)

Cytokine levels are given as means (SD).

^aP value = 0.0001.

IFN- γ : interferon gamma

IL-10: interleukin-10

pg/mL: picogram/millilitre

TGF- β : tumour growth factor beta

Table 7. Serum inflammatory marker levels

Mean change in inflammation markers from baseline to end of study in the vitamin D group and the placebo group			
Røsjø 2015 (sub-reference under Kampman 2012)	Vitamin D ₃ (36 participants)	Placebo (32 participants)	Group difference crude change (P value)
ALCAM (ng/mL)	4 (31)	9 (22)	-5 (0.130)

Table 7. Serum inflammatory marker levels (Continued)

CCL21 (pg/mL)	66 (129)	30 (115)	36 (0.284)
CXCL16 (pg/mL)	42 (224)	47 (242)	-5 (0.763)
IL-1Ra (pg/mL)	98 (478)	-10 (115)	108 (0.175)
MMP-9 (ng/mL)	170 (464)	84 (529)	86 (0.719)
OPG (pg/mL)	43 (307)	-33 (228)	76 (0.390)
OPN (ng/mL)	-1.4 (3.1)	-2.0 (2.5)	0.5 (0.252)
PTX3 (pg/mL)	-39 (566)	-95 (458)	56 (0.638)
sFRP3 (pg/mL)	13 (3775)	129 (736)	-115 (0.995)
sTND-r1 (pg/mL)	107 (164)	83 (139)	24 (0.589)
TGF- β 1 (ng/mL)	0.0 (2.9)	0.1 (2.2)	-0.1 (0.717)

Levels of markers are given as mean change (SD); P value calculated by the Mann-Whitney test.

ALCAM: activated leucocyte cell adhesion molecule

CCL21: chemokine (C-C motif) ligand 21

CXCL16: chemokine (C-X-C motif) ligand 16

IL-1Ra: interleukin-1 receptor antagonist

MMP-9: matrix metalloproteinase-9

ng/mL: nanogram/millilitre

OPG: osteoprotegerin

OPN: osteopontin

pg/mL: picogram/millilitre

PTX3: pentraxin 3

sFRP3: secreted frizzled-related protein 3

sTND-r1: soluble tumour necrosis factor receptor 1

TGF- β 1: transforming growth factor beta 1

Table 8. Serum inflammatory markers levels

Muris 2016 (sub-reference under Hupperts 2016)	Effect of vitamin D ₃ supplementation on cytokine production		
Marker	Placebo plus IFN beta (Rebif) (23 participants)	Vitamin D ₃ plus IFN-beta (Rebif) (30 participants)	Log ratio

Table 8. Serum inflammatory markers levels (Continued)

	Week 0	Week 48	P value	Week 0	Week 48	P value	P value
IL-10 (pg/mL)	713.9 (397.5 to 1319.9)	806.1 (391.7 to 1618.8)	0.07	913.8 (646.3 to 1431.0)	934.3 (548.1 to 1388.7)	0.35	0.12
IL-4 (pg/mL)	1.6 (0.6 to 3.0)	1.8 (0.7 to 2.7)	0.69	1.2 (0.8 to 4.0)	1.6 (0.8 to 2.2)	0.53	0.87
IL-5 (pg/mL)	54.4 (22.5 to 171.9)	105.5 (52.5 to 335.1)	0.02	71.9 (45.4 to 134.7)	75.6 (45.8 to 145.1)	0.47	0.06
IFN- γ (pg/mL)	1451.4 (898.1)	1365.4 (877.7)	0.61	1673.1 (846.7)	1562.4 (798.4)	0.51	0.55
IL-17 (pg/mL)	1112.2 (540.6 to 1713.7)	1181.0 (683.4 to 2408.2)	0.06	825.0 (456.4 to 2311.9)	1233.1 (582.5 to 2504.3)	0.76	0.72
IL-22 (pg/mL)	261.3 (128.6 to 302.7)	132.1 (58.0 to 434.2)	0.49	181.8 (123.3 to 502.6)	234.3 (116.7 to 390.0)	0.81	0.09
GM-CSF (pg/mL)	674.5 (391.3 to 903.1)	843.9 (406.3 to 1456.0)	0.06	737.4 (474.6 to 1054.1)	765.7 (495.7 to 1038.4)	0.98	0.68
TNF- α (pg/mL)	499.3 (196.1 to 800.5)	765.6 (479.7 to 1080.4)	0.02	676.1 (434.7 to 1022.4)	897.2 (428.2 to 1394.9)	0.04	0.13
LAP (pg/mL)	543.1 (410.2 to 674.0)	894.6 (689.1 to 1097.7)	0.001	762.0 (527.0 to 907.3)	753.9 (549.8 to 942.2)	0.98	0.01
IFN- γ /IL-5	29.8 (3.6 to 50.0)	17.7 (11.9 to 35.3)	0.01	10.9 (2.4 to 28.6)	15.1 (5.7 to 34.3)	0.56	0.43

Cytokine production in supernatant of anti-CD3 stimulated peripheral blood mononuclear cells in participants included in this review.

Mean and standard deviation (paired t test) or median and range (Wilcoxon Rank test) and P value of $^{10}\log$ ratio week 48/week 0 (t test or Mann Whitney U test).

GM-CSF: granulocyte-macrophage colony-stimulating factor

IFN- γ : interferon-gamma

IL: interleukin

LAP: latency-associated peptide

pg/mL: picogram/millilitre

TNF- α : tumour necrosis factor- α

Table 9. Immune cell subtype changes

Immune cell subtype changes during the study, mean difference, % (95% CI)		
Sotirchos 2016	Comparison of change during study between groups, mean difference, % (95% CI)	P value
IL-17 ⁺ CD4 ⁺ T cells ^a	2.68 (0.13 to 5.23)	0.039
IFN- γ ⁺ CD4 ⁺ T cells ^a	5.32 (-2.89 to 13.53)	0.20
IFN- γ ⁺ IL-17 ⁺ CD4 ⁺ T cells ^a	1.21 (-0.66 to 3.07)	0.20
Effector memory CD4 ⁺ T cells ^a	8.24 (-2.19 to 18.67)	0.12
Central memory CD4 ⁺ T cells ^a	-8.08 (-19.23 to 3.07)	0.16
Naive CD4 ⁺ T cells ^b	-1.99 (-6.0 to 2.02)	0.33
CD161 ⁺ CD4 ⁺ T cells ^b	0.48 (-0.57 to 1.52)	0.37
CD85j ⁺ CD8 ⁺ T cells ^b	2.64 (-0.18 to 5.46)	0.066

^aAfter stimulation with anti-CD3/CD28 for 5 days followed by stimulation for 4 hours with phorbol myristate acetate and ionomycin

^bAbsence of immune stimulation

CD: mature T-helper cells express the surface protein CD4 and are referred to as CD4 T cells

IFN- γ : interferon-gamma

IL: interleukin

T cells: T-helper cells

APPENDICES

Appendix I. Keywords

{vitamin D2} OR {vitamin D3} OR {1-alpha hydroxyvitamin D3} OR {1-alpha-hydroxy-vitamin D3}} OR {1-alpha hydroxy calciferol} OR {1-alpha-hydroxy-calciferol} OR {1,25 dihydroxyvitamin D3} OR {1,25-dihydroxy-vitamin D3} OR {1,25 dihydroxycholecalciferol} OR {1,25-dihydroxycholecalciferol} OR {25-hydroxy-vitamin D} OR {25 hydroxy vitamin D} OR {alfacalcidol} OR {calcidiol} OR {calcitriol} OR {calciferol} OR {ergocalciferol} OR {cholecalciferol} OR {"ultra violet rays"} OR {UV rays} OR {sunlight} OR {ergocalciferols} OR {vitamin D} OR {ergocalciferols}

FEEDBACK

Amanda Burls, 3 January 2013

Summary

Comment: The table 1 link in the section:

Types of outcome measures

Primary outcomes

The mean number of relapses per patient per year or annualised relapse rate (ARR) and proportion of patients who remain relapse free (Table 1)

Does not go to the results but to a glossary. Where can I find the numerical results of the included study within your systematic review?

Reply

The numerical values are included in the update as analysis and results ([Analysis 1.1](#))

Contributors

Vanitha Jagannath

WHAT'S NEW

Date	Event	Description
20 July 2018	New citation required and conclusions have changed	We added 11 new studies and 884 new participants. The review now includes 12 studies and 933 participants. To this version of the review, we added new analyses and discussion. We assessed the quality of evidence from the included studies using the GRADE approach, and we added a 'Summary of findings' table
9 April 2018	New search has been performed	Background. We added new insights into mechanisms of action of vitamin D, as well as new results from epidemiological and immunological studies in relation to biological mechanisms of vitamin D. We supplied up-to-date references to support this information
2 October 2017	New search has been performed	We updated the search to 2 October 2017.
8 September 2016	Feedback has been incorporated	Feedback 1

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
Drafting the protocol	VJ/AG/ZF/TR/LW
Developing the search strategy and running the search	MS Group in collaboration with review authors
Obtaining copies of studies	AG/ZF
Selecting which studies to include	VJ/AG/ZF
Extracting data from studies	VJ/AG/ZF
Entering data into RevMan	VJ/CDP
Carrying out the analysis	CDP/VJ
Interpreting the analysis	CDP/AG/ZF/VJ
Drafting the final review	VJ/AG/ZF/TR/LW/CDP/SR
Updating the review	VJ/AG/ZF/TR/LW/CDP/SR

DECLARATIONS OF INTEREST

Vanitha A Jagannath: none.

Graziella Filippini: none.

Zbys Fedorowicz: none.

GV Asokan: none.

Edward W Robak: none.

Liz Whamond: none.

Carlo Di Pietrantonj: none.

Sarah Robinson: none.

SOURCES OF SUPPORT

Internal sources

- No source of support, Other.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We included only RCTs, unlike the protocol and the previous version, which included quasi-RCTs as well, in view of increased risk of bias.
- The outcome annualised relapse rate (ARR) and the proportion of relapse-free participants were grouped together in the previous version but were removed in this later version and are listed under secondary outcomes.
- The outcome change in EDSS score was added because that is more universally recorded during MS follow-up.
- The outcome mean change in MRI parameters of disease activity (number and/or volume of gadolinium-enhancing T1 lesions and new T2 lesions), although a non-clinical outcome, is significant in reflecting disease activity; hence we shifted this to a primary outcome.

INDEX TERMS

Medical Subject Headings (MeSH)

Cholecalciferol [*therapeutic use]; Ergocalciferols [*therapeutic use]; Fatigue [drug therapy]; Multiple Sclerosis [*drug therapy]; Quality of Life; Randomized Controlled Trials as Topic; Vitamins [*therapeutic use]

MeSH check words

Humans