

Confounded by the sun: multiple sclerosis and vitamin D

Eschle Daniel

Kantonsspital Uri, Altdorf, Switzerland

Summary

BACKGROUND: Low serum levels of vitamin D have been implicated as a risk factor for developing multiple sclerosis (MS), and increased disease activity. MS treatment – to avert relapses and long-term disability – is expensive. This is where vitamin D supplementation might fill the gap as an affordable and safe alternative.

METHODS: PubMed was searched with the terms “multiple sclerosis” AND “vitamin D” AND “randomized controlled trial”. Additionally, reviews and meta-analyses were checked for further references. Studies using vitamin D supplementation were relevant if they looked at certain clinical, laboratory and/or brain magnetic resonance imaging parameters of disease activity during a follow-up of at least a year and included a control group.

RESULTS: The final yield was nine relevant trials. Six of these demonstrated outright negative results concerning possible benefits of vitamin D supplementation regarding relapse rate, disability status, changes in brain lesion load and/or serum concentrations of neurofilament light chain. The remaining three studies, although reporting “positive” outcomes, actually did not find any statistically robust improvements when scrutinised more closely because results were skewed by numerous dropouts or other confounders.

CONCLUSIONS: Randomised controlled trials have not been able to provide an evidence base for vitamin D as a disease-modifying treatment in people with MS. This statement comes with the caveat that practically all study patients were already taking established disease-modifying drugs, which could have “diluted” any possible vitamin D effects. But the role of vitamin D in MS could well be just a case of correlation and not causality: Epidemiological studies suggest that sunlight exposure, although correlating with vitamin D levels, is a more decisive factor than vitamin D when it comes to modulating MS risk, in particular in non-white populations.

Keywords: annualised relapse rate, disease modifying drugs, Extended Disability Status Scale, magnetic resonance imaging, sunlight exposure

Introduction and aim

Multiple sclerosis (MS) is the most common inflammatory disease of the central nervous system affecting young adults [1]. Mortality (years of lives lost) is only a minor issue according to epidemiological data, more important are the potential years lived with disability if left untreated [2]. Disease-modifying drugs (DMDs) – to avert relapses and long-term disability – are expensive. This is where vitamin D supplementation might fill the gap as an affordable and save alternative because “numerous observational studies have suggested that there is a correlation between the level of serum vitamin D and MS risk and disease activity” [3] or, for example, “among patients with MS treated with interferon beta-1b, higher (vitamin D) levels were associated with lower rates of MS activity observed on (magnetic resonance imaging)” [4].

This review looked at randomised controlled trials (RCTs) that might provide an evidence base for using vitamin D as a DMD in people with MS, and how to implement these findings in clinical practice, because inappropriate prescribing or self-medication can sometimes make vitamin D supplementation downright dangerous [5]. So far, vitamin D supplementation trials for health outcomes other than MS have been disappointing; for example, there were no benefits in treating diabetic neuropathy, and preventing cancer, cardiovascular events or Parkinson’s disease [6–8]. Is the situation any different regarding MS?

Some vitamin D facts

When skin is exposed to sunlight this leads to the endogenous production of biologically inert vitamin D₃ (cholecalciferol). Hydroxylation in the liver converts vitamin D₃ to 25-hydroxyvitamin D₃ (25-OH-D₃ or calcidiol), which undergoes a further transformation to the active compound

ABBREVIATIONS

DMD	disease-modifying drug
EDSS	Extended Disability Status Scale
MRI	magnetic resonance imaging
MS	multiple sclerosis
NfL	neurofilament light chain
RCT	randomised controlled trial
T2	part of an MRI protocol

Correspondence:
Daniel Eschle, MD, MSc,
Consultant Neurologist,
Kantonsspital Uri,
CH-6460 Altdorf, daniel.es-
chle[at]ksuri.ch

called 1,25-dihydroxyvitamin D₃ (calcitriol) [3]. The generic term “vitamin D” is used in several ways. In the context of food and in particular supplements, “vitamin D” refers to vitamin D₃ (cholecalciferol). Additionally, certain foods can also contain vitamin D₂ (which behaves in an equivalent manner to vitamin D₃). Serum concentrations of “vitamin D” on the other hand refer to 25-hydroxyvitamin D₃ and D₂. Because of its much longer half-life, the 25-hydroxy form is the preferred measure to reflect the body’s vitamin D stores. Vitamin D serum concentrations are expressed in ng/ml or nmol/l: 1 ng/ml is equal to 2.5 nmol/l. Typically, the following cut-offs are in use: vitamin D concentrations above 30 ng/ml (75 nmol/l) are sufficient, levels between 20 and 30 ng/ml (50–75 nmol/l) are insufficient and less than 20 ng/ml (50 nmol/l) is called deficient. But reference values and terminology vary according to different professional bodies [9]. The German Nutrition Society determined that a daily vitamin D supply of 800 units is adequate for children and adults. Dietary intake will usually not suffice to meet this need. In the absence of relevant exposure to sunlight, a vitamin D supplement is needed [10]. The tolerable upper intake level for adults is considered to be 4000 units/day, and serum levels above 125–150 nmol/l should be avoided to prevent hypercalcaemia. At the other end of the spectrum, concentrations below 12 ng/ml (30 nmol/l) are particularly worrisome because of the association with rickets in children, and osteomalacia in adults [11]. The scientific literature is rife with statements that supplementing vitamin D will have a beneficial effect on a whole variety of other health issues, but subsequently this did not stand up to scrutiny in large RCTs [7].

Search strategy and results

PubMed was searched with the terms “multiple sclerosis” AND “vitamin D” AND “randomized controlled trial” on 04 August 2020 (with a total of 41 hits). Additionally, reviews and meta-analyses were checked for further references [12–14].

Studies using vitamin D supplementation were relevant if they looked at certain clinical, laboratory and/or brain

magnetic resonance imaging (MRI) parameters of disease activity during a follow-up of at least a year and included a control group. Results were grouped into the following themes. (1) Analysis of the effect of vitamin D supplementation on the serum levels of neurofilament light chain (NfL), which is considered a promising in-vitro parameter with regards to disease activity and therapeutic efficiency [15]. Papers examining other biochemical parameters were excluded. (2) Studies looking at vitamin D supplementation and clinical or MRI indicators of disease activity. Criteria in clinical trials of new DMDs typically include the following: annualised relapse rate, Expanded Disability Status Scale (EDSS) [16] and/or lesion load seen in MRI (new T2 and enhancing plaques in a follow-up MRI of the brain). Patient-reported outcome measures were not included. Because indicators of disease activity such as the annualised relapse rate are meaningful only after a longer period of observation, studies with a follow-up of significantly less than a year were excluded (the shortest follow-up was 48 weeks).

The final yield was nine publications pertinent to the aim of this review [17–25]. Additionally, Holmøy [26] reported the serum NfL results of the patients already presented by Kampman a few years earlier [18]. These two publications were counted as one and evaluated together as a single trial.

Results were deemed significant at a level of chance <5%, and wherever possible they refer to the intention-to-treat population. Drop-out rates of ≥20% were considered as problematic for robust conclusions. Pooling individual trial data and meta-analysis did not seem pragmatic owing to the heterogeneity of study designs.

All results are summarised in table 1.

As practically every study used a different vitamin D supplementation regimen, all doses were converted to units/day in table 1. Range of vitamin D doses was from 2860 to 14000 units/day. One treatment group received “active” vitamin D instead, namely, 0.5 µg/day calcitriol [19]. In two studies, the control group was not a placebo arm as such,

Table 1: Results of the randomised controlled trials of vitamin D supplementation in multiple sclerosis.

First author and year	Vitamin D (n)	Control (n)	DMD (%)	Units/day	Duration in weeks	ARR	EDSS	MRI	NfL
Burton, 2010 [17]	24	23	56/58	14000	52	Ø	Ø	–	–
Kampman, 2012 [18]	35	33	49/52	2860	96	Ø	Ø	–	Ø
Shaygannejad, 2012 [19]	25	25	92/88	a	52	Ø	Ø	–	---
Soilu-Hänninen, 2012 [20]	32	30	100/100	2860	52	Ø	Ø	(+)	–
Golan, 2013 [21]	15	15	100/100	4370/800	52	Ø	Ø	–	–
Camu, 2019 [22]	45	45	100/100	7140	96	(+)	(+)	Ø	–
Hupperts, 2019 [23]	113	116	100/100	13400	48	Ø	Ø	(+)	–
Dörr, 2020 [24]	28	25	100/100	10200/200	78	Ø	Ø	Ø	–
Smolders, 2020 [25]	24	16	100/100	13415	48	–	–	–	Ø

a = the treatment group received “active” vitamin D, i.e., 0.5 µg/day calcitriol; ARR = annualised relapse rate; DMD = disease modifying drugs (used in % of intervention/control group); EDSS = Expanded Disability Status Scale; MRI = brain magnetic resonance imaging (new enhancing and new T2 lesions); n = number of patients in the intervention (vitamin D supplementation) and control group evaluated (mostly intention-to-treat population); NfL = neurofilament light chain (serum concentration) + statistically significant improvement in the vitamin D in comparison to the control group at end of follow-up with significance level set at <5%; (+) result is not robust, e.g. far too many dropouts or other confounders (see main text for details); Ø no statistically significant improvement between vitamin D and control group at end of follow-up Kampman [18]: Additional vitamin D supplements taken by some patients (also in control group)! Patients without disease modifying drugs (about 50%) not evaluated separately except for NfL. The serum NfL results are also included here, although they were reported in a separate paper [26]: Holmøy et al. *Acta Neurol Scand.* 2019;139(2):172–76. Soilu-Hänninen [20]: A subgroup analysis found similarly low levels of NfL in both groups, see Hänninen et al. *Brain Behav.* 2020;e01772. Golan [21]: intervention group 4370 units vitamin D per day and 800 units/day for controls with per-protocol analysis of only 15/21 in intervention and 15/24 in control group Camu [22]: per-protocol analysis Dörr [24]: 20,400 units vitamin D every other day in the treatment group and 400 units every other day for controls

but also received a form of low dose vitamin D supplementation.

Some studies also prescribed calcium supplements for all participants. Sunlight exposure was not assessed in any of the RCTs (see “Discussion” for relevance).

In only two out of the nine studies a relevant number of participants did *not* use DMDs: in the study by Burton [17] a little over 40% did not use DMD and in the Kampman trial around 50% were DMD naïve [18]. Both reported outcome data irrespective of DMD use for annualised relapse rate and EDSS. NfL data for the patients studied by Kampman were published separately at a later date [26], and no differences between those with and without DMDs were found.

Six of the nine trials demonstrated outright negative results concerning possible benefits of vitamin D supplementation regarding relapse rate, EDSS, changes in brain MRI lesion load and/or serum concentrations of NfL [17–19, 21, 24, 25]. The remaining three studies, although reporting “positive” outcomes, actually did not find any statistically robust improvements when scrutinised more closely, for the following reasons:

- Soilu-Hänninen et al. [20]: number of enhancing lesions were significantly lower in vitamin D group, but not the number of new/enlarging T2 lesions, thus, there was no strict indication that there was less disease progression in the vitamin D group.
- Camu et al. [22]: over 28% dropouts from original cohort in the vitamin D group and nearly 32% in the placebo group.
- Hupperts et al. [23]: Only 98/115 (85%) in the vitamin D and 88/117 (75%) in the placebo group finished the study, but data were not shown separately for these, so data are for all patients, i.e., intention-to-treat population.

Adverse events were mostly mild and similar to the perceived side effects reported by the control/placebo groups. Both Camu [22] and Hupperts [23] reported all serious health issues during the study period as adverse events, including a case of appendicitis in the vitamin D group and a malignant lung neoplasm in the placebo group (which does not truly reflect possible vitamin D side effects). One trial made no mention of possible adverse events [25].

Discussion

Because food is only a minor source of vitamin D, humans need exposure to sunlight, which in the end determines vitamin D synthesis. A lack of sunlight and (by consequence) vitamin D have been implicated as risk factors for developing MS and increased disease activity. Disease modifying treatment – to avert relapses and long-term disability – is expensive. This is where vitamin D supplementation might fill the gap as an affordable and safe alternative. Previous meta-analyses and reviews of this topic found no or at best unclear benefits for vitamin D supplementation in MS. For instance, the 2018 Cochrane Review categorically states: “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” [12].

This update looked once again at the RCTs that examined the effect of vitamin D supplementation on relapse rate, EDSS, changes in brain MRI lesion load and/or serum concentrations of NfL, and provided an adequate follow-up of at least a year. There were nine RCTs in patients with MS, all with a follow-up of ≥ 48 weeks [17–26]. Six out of nine studies were outright negative; that is, supplementing vitamin D did not improve any of the various outcome measures in MS. In the remaining three studies, one or more positive outcomes were attributed to vitamin D supplementation by the authors (see table 1). But these positive results have to be viewed critically. None of them is robust, because either the results were skewed by numerous dropouts or other confounders.

Apart from these methodological considerations, it should be kept in mind that practically all study patients already used established DMDs, which could have “diluted” any possible vitamin D effects. Strictly speaking, the lack of convincing evidence that vitamin D supplementation acts as a DMD in MS only applies when vitamin D is used as an “add-on” measure. Unfortunately, no RCT has actually studied vitamin D supplementation as a stand-alone alternative for other DMDs (despite the numerous speculations on this topic).

Furthermore, if there were any benefit from vitamin D, we cannot automatically assume that “more is better”. In two (negative) trials the controls also received vitamin D supplements (at a much lower dose), which theoretically still might have been effective [21, 24]. In the Kampman study, just over a quarter of the placebo group made continued use of previous vitamin D supplements (not seen as a protocol violation), which might have had a confounding effect [18]. Although “a protective effect of vitamin D intake on risk of developing MS” has been shown in large cohort studies [27], this association does not automatically imply that supplementation at a later date will reverse or attenuate the underlying pathophysiology in established disease.

Hedström et al. studied the hypothesis that vitamin D, although dependent on sunlight, might actually be just an innocent bystander. They calculated that the influence of vitamin D deficiency (on developing MS) is only 30%; i.e., there are effects mediated by sunlight but independent from vitamin D [28].

A similar conclusion has previously been published by an Australian group (again in predominantly white participants): “Sun exposure and vitamin D status may have independent roles in the risk of (central nervous system) demyelination. Both will need to be evaluated in clinical trials for multiple sclerosis prevention” [29].

In a multi-ethnic case/control study, Langer-Gould found evidence of an association between higher 25-hydroxyvitamin D levels and reduced MS risk among whites, “but no evidence of any protective effect in Hispanics and blacks” and they concluded that “the protective association of sun exposure is not explained by current serum (25-hydroxyvitamin D) levels in blacks, Hispanics or even fully in whites. This indicates that the protective effect of sun exposure is most likely mediated through immunomodulatory mechanisms independent of vitamin D” [30].

Previous studies have also indicated that vitamin D deficiency is not relevant for MS risk in blacks or Hispanics

(only in whites) [31]. It seems that a person's genetic make-up (which differs by race/ethnicity) is more relevant to individual MS risk than the actual vitamin D status.

The available evidence presently gives sunlight a bigger role than vitamin D – at least when it comes to the development of MS. Sunlight is a confounding factor in this scenario because it influences vitamin D levels and also the risk of developing MS, or potentially modifies the course of MS in persons with a certain genetic make-up (the association of low vitamin D levels and MS risk would be erroneously construed as causality).

How sunlight can be harnessed is unclear: On the one hand, because the crucial period regarding protective effects of sunlight exposure seems to be during childhood and early adolescence, before MS becomes symptomatic in the majority of cases [32]. And on the other hand, excessive sunlight exposure is generally discouraged by health authorities because of the risk of inducing skin cancer [33]. Clinical applications are still in their infancy (one underpowered RCT without a statistically significant effect regarding phototherapy) [34].

Apart from MS, vitamin D supplementation trials for other health outcomes have also been disappointing [35]. And inappropriate prescribing or self-medication can sometimes make vitamin D supplementation downright dangerous [5]. Does this mean that we can forget about vitamin D in MS entirely? To prove that vitamin D might be an alternative DMD we would have to conduct studies in a very large number of DMD-naïve patients for at least a year or more to reliably assess relapse rate, disability, brain MRI lesion load and/or NfL over time, and also assess sunlight exposure as a possible confounder. Given the enthusiastic publicity “vitamin D and MS” have generated so far, it might be hard (and some may consider it downright unethical) to recruit patients, because nobody wants to run the risk of being randomised into the placebo arm (or the results could be “contaminated” by participants using additional over-the-counter vitamin D supplements). The effort and expense for such a trial could be used to give all MS patients a vitamin D supplement at a reasonable and safe dose from the start, see “some vitamin D facts”. Even if we postulate that vitamin D is neutral with regards to MS, it is still a vital substance for the prevention of osteomalacia [11]. This would benefit in particular those MS patients with mobility issues who spend less time outdoors (in the sun), and those that do not tolerate heat/sun very well. Furthermore, when discussing affordable treatment options, bear in mind that giving up smoking is always worthwhile for people with MS [36, 37].

The appeal of vitamin D as a potential DMD in MS is its low cost. But presently we lack the evidence to recommend it for this purpose. The challenge now is to either conduct an appropriate trial or find other affordable DMDs for MS patients worldwide, for example by “resurrecting” a generic compound that has some data to back it up [38]. One might add that the World Health Organization list of essential medicines does not mention any DMD for MS (with the possible exception of rituximab) [39]. This is an area where further research and resources are needed in the future.

Disclosure statement

The author declares that there are no conflicts of interest, in particular none with a manufacturer of pharmaceutical products or nutritional supplements. This manuscript is not under review by another journal. This paper is based on previously published work, so no new studies in humans or animals were necessary.

References

- 1 Dobson R, Giovannoni G. Multiple sclerosis - a review. *Eur J Neurol*. 2019;26(1):27–40. doi: <http://dx.doi.org/10.1111/ene.13819>. PubMed.
- 2 Wallin MT, Culpepper WJ, Nichols E, Bhutta ZA, Gebrehiwot TT, Hay SI, et al.; GBD 2016 Multiple Sclerosis Collaborators. Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(3):269–85. doi: [http://dx.doi.org/10.1016/S1474-4422\(18\)30443-5](http://dx.doi.org/10.1016/S1474-4422(18)30443-5). PubMed.
- 3 Sintzel MB, Rametta M, Reder AT. Vitamin D and multiple sclerosis: a comprehensive review. *Neurol Ther*. 2018;7(1):59–85. doi: <http://dx.doi.org/10.1007/s40120-017-0086-4>. PubMed.
- 4 Fitzgerald KC, Munger KL, Köchert K, Amason BG, Comi G, Cook S, et al. Association of vitamin D levels with multiple sclerosis activity and progression in patients receiving interferon beta-1b. *JAMA Neurol*. 2015;72(12):1458–65. doi: <http://dx.doi.org/10.1001/jamaneurol.2015.2742>. PubMed.
- 5 Taylor PN, Davies JS. A review of the growing risk of vitamin D toxicity from inappropriate practice. *Br J Clin Pharmacol*. 2018;84(6):1121–7. doi: <http://dx.doi.org/10.1111/bcp.13573>. PubMed.
- 6 Eschle D. Vitamin D und die diabetische Neuropathie: (k)ein Alleskönner? [Vitamin D and diabetic neuropathy: no all-rounder?] *psychopraxis-neuropraxis*. 2018;21(5):218–22. doi: <http://dx.doi.org/10.1007/s00739-018-0482-2>.
- 7 Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al.; VITAL Research Group. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med*. 2019;380(1):33–44. doi: <http://dx.doi.org/10.1056/NEJMoa1809944>. PubMed.
- 8 Eschle D. Vitamin D und Parkinson – Assoziationen und Nutzen [Vitamin D and Parkinson – guilt by association?]. *J Neurol Neurochir Psychiatr*. 2019;20(4):129–33.
- 9 Lips P, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermayer-Pietsch B, Bianchi ML, et al. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. *Eur J Endocrinol*. 2019;180(4):P23–54. doi: <http://dx.doi.org/10.1530/EJE-18-0736>. PubMed.
- 10 German Nutrition Society. New reference values for vitamin D. *Ann Nutr Metab*. 2012;60(4):241–6. doi: <http://dx.doi.org/10.1159/000337547>. PubMed.
- 11 Office of Dietary Supplements (National Institutes of Health). Vitamin D. Fact Sheet for Health Professionals. Link: <https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/> (last accessed 22.04.2020)
- 12 Jagannath VA, Filippini G, Di Pietrantonj C, Asokan GV, Robak EW, Whamond L, et al. Vitamin D for the management of multiple sclerosis. *Cochrane Database Syst Rev*. 2018;9:. doi: <http://dx.doi.org/10.1002/14651858.CD008422.pub3>. PubMed.
- 13 Smolders J, Torkildsen Ø, Camu W, Holmøy T. An update on vitamin D and disease activity in multiple sclerosis. *CNS Drugs*. 2019;33(12):1187–99. doi: <http://dx.doi.org/10.1007/s40263-019-00674-8>. PubMed.
- 14 Feige J, Moser T, Bieler L, Schwenker K, Hauer L, Sellner J. Vitamin D supplementation in multiple sclerosis: a critical analysis of potentials and threats. *Nutrients*. 2020;12(3):783. doi: <http://dx.doi.org/10.3390/nu12030783>. PubMed.
- 15 Varhaug KN, Torkildsen Ø, Myhr KM, Vedeler CA. Neurofilament light chain as a biomarker in multiple sclerosis. *Front Neurol*. 2019;10:338. doi: <http://dx.doi.org/10.3389/fneur.2019.00338>. PubMed.
- 16 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444–52. doi: <http://dx.doi.org/10.1212/WNL.33.11.1444>. PubMed.
- 17 Burton JM, Kimball S, Vieth R, Bar-Or A, Dosch HM, Cheung R, et al. A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis. *Neurology*. 2010;74(23):1852–9. doi: <http://dx.doi.org/10.1212/WNL.0b013e3181e1cec2>. PubMed.
- 18 Kampman MT, Steffensen LH, Mellgren SI, Jørgensen L. Effect of vitamin D3 supplementation on relapses, disease progression, and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomised controlled trial. *Mult Scler*.

- 2012;18(8):1144–51. doi: <http://dx.doi.org/10.1177/1352458511434607>. PubMed.
- 19 Shaygannejad V, Janghorbani M, Ashtari F, Dehghan H. Effects of adjunct low-dose vitamin D on relapsing-remitting multiple sclerosis progression: preliminary findings of a randomized placebo-controlled trial. *Mult Scler Int*. 2012;2012:. doi: <http://dx.doi.org/10.1155/2012/452541>. PubMed.
 - 20 Soilu-Hänninen M, Aivo J, Lindström BM, Elovaara I, Sumelahti ML, Färkkilä M, et al. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon β -1b in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2012;83(5):565–71. doi: <http://dx.doi.org/10.1136/jnnp-2011-301876>. PubMed.
 - 21 Golan D, Halhal B, Glass-Marmor L, Staun-Ram E, Rozenberg O, Lavi I, et al. Vitamin D supplementation for patients with multiple sclerosis treated with interferon-beta: a randomized controlled trial assessing the effect on flu-like symptoms and immunomodulatory properties. *BMC Neurol*. 2013;13:60. doi: <http://dx.doi.org/10.1186/1471-2377-13-60>. PubMed.
 - 22 Camu W, Lebert P, Pierrot-Deseilligny C, Hauteceur P, Besserve A, Jean Deleglise AS, et al. Cholecalciferol in relapsing-remitting MS: A randomized clinical trial (CHOLINE). *Neurol Neuroimmunol Neuroinflamm*. 2019;6(5):. doi: <http://dx.doi.org/10.1212/NXI.0000000000000597>. PubMed.
 - 23 Hupperts R, Smolders J, Vieth R, Holmøy T, Marhardt K, Schlupe M, et al.; SOLAR Study Group. Randomized trial of daily high-dose vitamin D₃ in patients with RRMS receiving subcutaneous interferon β -1a. *Neurology*. 2019;93(20):e1906–16. doi: <http://dx.doi.org/10.1212/WNL.0000000000008445>. PubMed.
 - 24 Dörr J, Bäcker-Koduah P, Wernecke KD, Becker E, Hoffmann F, Faiss J, et al. High-dose vitamin D supplementation in multiple sclerosis - results from the randomized EVIDIMS (efficacy of vitamin D supplementation in multiple sclerosis) trial. *Mult Scler J Exp Transl Clin*. 2020;6(1):. doi: <http://dx.doi.org/10.1177/2055217320903474>. PubMed.
 - 25 Smolders J, Mimpfen M, Oechtering J, Damoiseaux J, van den Ouweland J, Hupperts R, et al. Vitamin D₃ supplementation and neurofilament light chain in multiple sclerosis. *Acta Neurol Scand*. 2020;141(1):77–80. doi: <http://dx.doi.org/10.1111/ane.13185>. PubMed.
 - 26 Holmøy T, Røsjo E, Zetterberg H, Blennow K, Lindström JC, Steffensen LH, et al. Vitamin D supplementation and neurofilament light chain in multiple sclerosis. *Acta Neurol Scand*. 2019;139(2):172–6. doi: <http://dx.doi.org/10.1111/ane.13037>. PubMed.
 - 27 Munger KL, Zhang SM, O'Reilly E, Hernán MA, Olek MJ, Willett WC, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology*. 2004;62(1):60–5. doi: <http://dx.doi.org/10.1212/01.WNL.0000101723.79681.38>. PubMed.
 - 28 Hedström AK, Olsson T, Kockum I, Hillert J, Alfredsson L. Low sun exposure increases multiple sclerosis risk both directly and indirectly. *J Neurol*. 2020;267(4):1045–52. doi: <http://dx.doi.org/10.1007/s00415-019-09677-3>. PubMed.
 - 29 Lucas RM, Ponsonby AL, Dear K, Valery PC, Pender MP, Taylor BV, et al. Sun exposure and vitamin D are independent risk factors for CNS demyelination. *Neurology*. 2011;76(6):540–8. doi: <http://dx.doi.org/10.1212/WNL.0b013e31820a9f3d>. PubMed.
 - 30 Langer-Gould A, Lucas R, Xiang AH, Chen LH, Wu J, Gonzalez E, et al. MS Sunshine Study: Sun exposure but not vitamin D is associated with multiple sclerosis risk in blacks and Hispanics. *Nutrients*. 2018;10(3):268. doi: <http://dx.doi.org/10.3390/nu10030268>. PubMed.
 - 31 Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA*. 2006;296(23):2832–8. doi: <http://dx.doi.org/10.1001/jama.296.23.2832>. PubMed.
 - 32 Magalhaes S, Pugliatti M, Riise T, Myhr KM, Ciampi A, Bjornevik K, et al. Shedding light on the link between early life sun exposure and risk of multiple sclerosis: results from the EnvIMS Study. *Int J Epidemiol*. 2019;48(4):1073–82. doi: <http://dx.doi.org/10.1093/ije/dyy269>. PubMed.
 - 33 Fartasch M, Diepgen TL, Schmitt J, Drexler H. The relationship between occupational sun exposure and non-melanoma skin cancer: clinical basics, epidemiology, occupational disease evaluation, and prevention. *Dtsch Arztebl Int*. 2012;109(43):715–20. PubMed.
 - 34 Hart PH, Jones AP, Trend S, Cha L, Fabis-Pedrin MJ, Cooper MN, et al. A randomised, controlled clinical trial of narrowband UVB phototherapy for clinically isolated syndrome: The PhoCIS study. *Mult Scler J Exp Transl Clin*. 2018;4(2):. doi: <http://dx.doi.org/10.1177/2055217318773112>. PubMed.
 - 35 Okereke OI, Reynolds CF, 3rd, Mischoulon D, Chang G, Vyas CM, Cook NR, et al. Effect of long-term vitamin D₃ supplementation vs placebo on risk of depression or clinically relevant depressive symptoms and on change in mood scores. A randomized clinical trial. *JAMA*. 2020;324(5):471–80. doi: <http://dx.doi.org/10.1001/jama.2020.10224>. PubMed.
 - 36 Rosso M, Chitnis T. Association between cigarette smoking and multiple sclerosis. *JAMA Neurol*. 2020;77(2):245–53. doi: <http://dx.doi.org/10.1001/jamaneurol.2019.4271>. PubMed.
 - 37 Ramanujam R, Hedström AK, Manouchehrinia A, Alfredsson L, Olsson T, Bottai M, et al. Effect of smoking cessation on multiple sclerosis prognosis. *JAMA Neurol*. 2015;72(10):1117–23. doi: <http://dx.doi.org/10.1001/jamaneurol.2015.1788>. PubMed.
 - 38 Mao Z, Álvarez-González C, De Trane S, Yildiz O, Albor C, Doctor G, et al. Cladribine: Off-label disease modification for people with multiple sclerosis in resource-poor settings? *Mult Scler J Exp Transl Clin*. 2018;4(2):. doi: <http://dx.doi.org/10.1177/2055217318783767>. PubMed.
 - 39 World Health Organization Model List of Essential Medicines. 21st List (2019) [cited 2020 April 22]. Available from: <https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1>

Appendix 1

Related and ongoing studies

The following three trials are under way or have already tried to look at vitamin D supplementation as a *stand-alone* DMD. But they differ from the studies reported in this manuscript, because the participants started vitamin D supplementation (or placebo) *before* they had developed definite MS. The rationale still remains the same in all cases: Does vitamin D attenuate disease activity or progression?

1. A RCT in DMD-naïve patients at risk of developing MS is currently ongoing in Australia and New Zealand [ACTRN12612001160820]: “Preventing the risk of multiple sclerosis using vitamin D in patients with a first demyelinating event in Australia and New Zealand (PrevANZ).” Participants will be randomised to receive placebo or vitamin D supplementation (ranging from 1000 to 10,000 units/day) for 48 weeks. The primary outcome is the efficacy of vitamin D in reducing the risk of recurrent disease (clinical relapse or MRI disease activity). Patients should refrain from DMDs, additional vitamin D supplements and sunbeds. No mention is made of estimating potential sunlight exposure according to latitude. Data collection is expected to continue until the end of 2020. So, results will be available at the beginning of 2021 at the earliest. Link (accessed 14 August 2020): <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12612001160820>
2. A French study is looking at the “Efficacy of cholecalciferol (vitamin D3) for delaying the diagnosis of MS after a clinically isolated syndrome (D-Lay-MS)” [NCT01817166]. Patients will receive 100,000 units of vitamin D or a placebo every two weeks for up to 24 months or until a conversion to full MS has occurred. “The main objective of this study is to evaluate the efficacy and tolerance of 2 years of treatment with cholecalciferol (vitamin D3) in patients with a clinically isolated syndrome at high risk for MS.” The inclusion and exclusion criteria make no mention of whether additional vitamin D supplements or the use of sunbeds are allowed or not. No mention is made of estimating potential sunlight exposure according to latitude. The study description gives the impression that after a clinically isolated syndrome, French patients are not eligible for DMDs (in Switzerland this would be possible). The estimated primary completion date is January

2023. Link (accessed 14 August 2020): <https://clinicaltrials.gov/ct2/show/NCT01817166>

3. Derakhshandi evaluated the potential effects of vitamin D administration (versus placebo) on the conversion to MS (primary outcome) and on brain MRI lesions (secondary outcome) in patients with previous optic neuritis and low vitamin D levels. The intervention consisted of 50,000 units of vitamin D per week, i.e., around 7100 units/day. Exclusion criteria were the use of DMDs and vitamin D supplements of more than 400 units/day before the onset of optic neuritis. Presumably, skin exposure to sunlight was limited for cultural reasons, but the use of sunbeds is not mentioned. The two groups were followed-up for 12 months from their inclusion time point. Analysis was possible for 13 patients in the vitamin D and 11 in the placebo group. None in the vitamin D group and five in the placebo group experienced a second demyelinating attack (highly significant difference). The vitamin D group also demonstrated significantly fewer new enhancing and T2 brain MRI plaques after 1 year. These results have to be viewed in the light of the fact that the trial only analysed a very small number of participants and that the outcome might also have been skewed by uneven baseline characteristics. The number of enhancing MRI lesions was higher in the placebo group at baseline, so these patients might have driven the increased disease activity, thus decreased disease activity was not due to the intervention (vitamin D) per se. See: Derakhshandi H, Etemadifar M, Feizi A, et al. Preventive effect of vitamin D3 supplementation on conversion of optic neuritis to clinically definite multiple sclerosis: a double blind, randomized, placebo-controlled pilot clinical trial. *Acta Neurol Belg.* 2013;113(3):257–63.

How can potential sunlight exposure be estimated? This is possible in several ways, such as by looking at a person's occupation (indoors versus outdoors) or by collating meteorological data with regards to the place of residence. This was done in studies looking at sunlight exposure and the risk of Parkinson's disease. See: (1) Kenborg L, Lassen CF, Ritz B, et al. Outdoor work and risk for Parkinson's disease: a population-based case-control study. *Occup Environ Med.* 2011;68(4):273–8. (2) Kravietz A, Kab S, Wald L, et al. Association of UV radiation with Parkinson disease incidence: a nationwide French ecological study. *Environ Res.* 2017;154:50–6.