Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: January 31, 2022

Citation: Plum LA and DeLuca HF, 2022. Suppression of Multiple Sclerosis by Ultraviolet Light, Medical Research Archives, [online] 1(1). https://doi.org/10.18103/mra.v11i1.3458

DOI
https://doi.org/10.18103/mra.v11i1.3458

ISSN: 2375-1924'

RESEARCH ARTICLE

Suppression of Multiple Sclerosis by Ultraviolet Light

LA Plum[1] and HF DeLuca*[1]

[1] Department of Biochemistry, University of WI-Madison, Madison, WI 53706

*deluca@biochem.wisc.edu

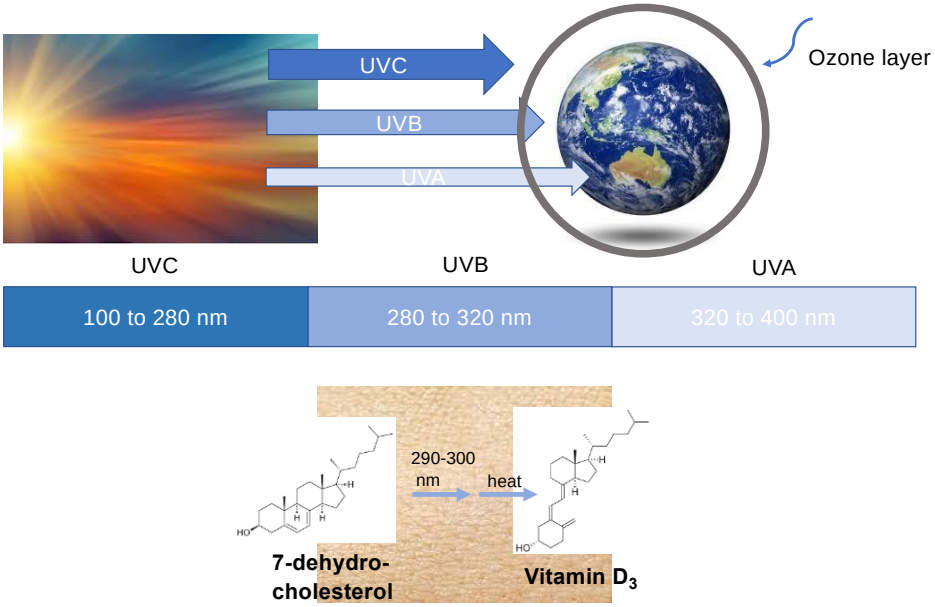
ABSTRACT

The inverse relationship of multiple sclerosis to sunlight exposure was proposed at least 50 years ago but conclusive evidence is unavailable. Since the proposal was made, many researchers have jumped to the conclusion vitamin D mediates this effect. Vitamin D is a pro-hormone produced in the skin by ultraviolet irradiation and/or sun exposure. In addition, an inverse relationship between plasma levels of the vitamin D metabolite, 25(OH)D_3, and a reduced incidence of multiple sclerosis has been noted. As a result of the relationship clinical trials have been carried out to determine if vitamin D supplementation can suppress the disease. The results have not supported this idea. In an animal model of multiple sclerosis (experimental autoimmune encephalomyelitis) the vitamin D hypothesis was refuted. Ultraviolet irradiation, on the other hand, consistently reduces the incidence and severity of experimental autoimmune encephalomyelitis. Because experimental autoimmune encephalomyelitis is a widely accepted model of human multiple sclerosis, clinical trials testing the efficacy of the narrow band ultraviolet light in suppression of multiple sclerosis appear warranted. If in fact this narrow band light does suppress human multiple sclerosis, isolation and identification of the compound produced by this light should be initiated.

Introduction:

Multiple sclerosis (MS) is one of a number of diseases classified as an autoimmune disease. The initiator(s) of MS is not known, but multiple risk factors have been identified including reduced sun light exposure [1]. Sunlight is comprised of predominantly (99%) ultraviolet light which can be further subdivided into UVA, UVB and UVC (**Figure 1**) [2]. UVC is largely absorbed by the ozone layer and has the highest energy. UVA has the lowest energy but, nearly all of it reaches the earth and is not removed by glass or clouds. UVB lies in the middle with higher energy but is readily filtered by regular glass and clouds. It is UVB that has the most pronounced effect on changing the course of multiple sclerosis, at least in a mouse model of MS [3]. A brief summary of current and emerging therapies for multiple sclerosis will be presented. This review will also discuss the possible role of segments of UV light in the suppression of MS. The original observation of sun exposure as a risk factor for MS will be covered as well in this review. A literature review was completed using the following search terms: "uv light" AND "multiple sclerosis", "uv" AND "multiple sclerosis", "uv light" AND "EAE", "uv" AND "EAE", "sunlight" AND "multiple sclerosis" and "sunlight" AND "EAE" within PubMed. Additional relevant work was also considered from citations within the manuscripts identified using the described search terms.

Figure 1. Sunlight produces primarily UV radiation. When UVB is not filtered out, it will produce vitamin D in skin. Using a lamp that predominantly produces energy at 311 nm provides protection against EAE without changing circulating levels of 25(OH)D.



Types of multiple sclerosis:

Multiple sclerosis is a chronic debilitating autoimmune disease that attacks the myelin sheath protecting the brain, spinal cord and optic nerves. The body can repair the damage, but not without causing scarring or sclerosis. There are two types of multiple sclerosis: 1. relapsing remitting and 2. primary progressive [4]. The majority (85%) of individuals suffer from relapsing remitting MS. Individuals with this disease type have periods of time when the symptoms disappear or dissipate (remission). Those suffering from the primary progressive form of the disease do not go into remission but can have periods of low or inactive

disease. Eventually, patients with relapsing remitting disease will enter a progressive phase similar to those diagnosed with primary progressive disease, and are then classified as having secondary progressive MS. Most (80%) MS patients first experience neurological inflammation or demyelination resulting in vision problems or tingling in extremities, lasting at least 24 hours before full diagnosis of multiple sclerosis occurs [5]. This is called clinically isolated syndrome (CIS). The recognition of this early risk factor by regulatory authorities opens the door for testing disease-modifying agents very early in the development of the disease.

Demographics of MS

Worldwide estimates of people living with this disease is 2.8 million [6]. Over 700,000 adults are living with multiple sclerosis in the US. There are nearly 3 times as many women than men suffering this disease. The incidence is much higher in the northern half of the US [7]. Most individuals are diagnosed between the ages of 20 and 40 and live on average 6-7 years less than people without MS [8-9]. Those diagnosed later in life typically have primary progressive disease, whereas children and younger adults suffer relapsing remitting disease [10]. On average individuals with MS live for ~30 to 40 years at an estimated cost of treatment of $90,000/year [11].

Multiple sclerosis therapies

Despite recognition of multiple sclerosis as a disease since the middle of the 19th century, it was only about 30 years ago that the first drug, interferon beta-1b, was approved by the FDA for treatment [12]. There are now nearly 20 drugs approved for MS [13]. These therapies reduce relapse rates and slow progression, but do not reverse or prevent completely disease progression. Some therapies have very undesirable side effects. Emerging therapies include B cell depletion such as Rituximab. It is an anti-CD20 monoclonal antibody originally approved for the treatment of B cell lymphoma but shows some promise in the treatment of MS [14]. Inhibitors of a tyrosine kinase known as Bruton's tyrosine kinase (BTK) also show promise. Inhibiting BTK leads to modulation of B cell activities without depletion of the cell population and thus, mitigating some obvious off-target effects [15]. Therapies targeting later stage disease include simvastatin, a statin and ibudilast, an inhibitor of cyclic nucleotide phosphodiesterases. Phase 2 trials testing both these drugs in MS patients with secondary progressive disease demonstrated reduced brain atrophy [16-17].

Vitamin D and MS

Vitamin D is another compound that has been extensively studied as a possible therapy for MS. Investigation of vitamin D for MS treatment was prompted by the finding that individuals living further from the equator have a higher risk of getting MS. This observation was first noticed in the 1960's in Europe [18], but this latitudinal relationship has since been shown throughout most of the world and extended to include not only incidence but also severity of disease [1,19]. UV radiation is much higher at the equator and since UV also produces vitamin D, vitamin D was proposed as the mediator of the protective effect [20]. In support of this idea, MS patients have lower circulating levels of $25(OH)D_3$, the major metabolite of vitamin D [21-24]. Whether the depressed $25(OH)D_3$ levels are a cause, or a consequence of the disease is not known, however. Several clinical trials have been completed to determine if vitamin D can suppress MS, but to-date the results have been inconclusive at best and most meta-analyses do not support the idea of using vitamin D as a therapy for MS patients [25-31]. One larger clinical trial initiated nearly 10 years ago is still on-going (NCT01817166). The study is designed to test vitamin D in preventing progression from CIS to MS and is placebo-controlled. Data obtained with animal models of MS (discussed below) do not support the idea that vitamin D therapy can have any impact on the disease without associated hypercalcemia. To avoid hypercalcemia, vitamin D itself as opposed to the active hormone, i.e. 1 alpha, 25-dihydroxy vitamin D have been tested in MS patients. However high dose vitamin D without associated hypercalcemia have led to some cases of worsening disease [32]. Two studies, one unreported and one still in progress, are attempting to address this concern (NCT01490502 and NCT03610139). It appears unlikely that vitamin D or its active form 1,25-dihydroxy vitamin D can be used to suppress MS.

Interestingly, a large (n = 25,871 subjects) randomized, placebo-controlled study (VITAL trial) recently completed in the vitamin D field to assess the effect of vitamin D supplementation in the prevention of cancer and cardiovascular disease showed a reduced incidence in autoimmune disorders. These patients were provided with a daily vitamin D supplement of 2000 IU for 5 years [33]. This finding is very surprising for several reasons: the population was not deficient in vitamin D, the average age of the subjects was 67 years, and there were equal number of men and women in the study population. Most autoimmune disorders begin before 50 years of age, and more women than men typically get autoimmune diseases [34-35]. Furthermore, the data generated to-date would

strongly suggest only those individuals deficient in vitamin D are likely to benefit in any way from supplementation [36]. It should also be noted that only a single case of multiple sclerosis was reported in this study population. Since most clinical trials do not support the idea of a beneficial effect of vitamin D supplementation in MS patients coupled with the possibility of worsening conditions, the VITAL trial results should not be used to encourage additional trials. The resources should be directed towards the idea that UV light independent of vitamin D may suppress MS.

A commonly used preclinical animal model of multiple sclerosis is the experimental autoimmune encephalitis (EAE). In this model mice or rats are injected with a myelin basic protein peptide together with Complete Freund's adjuvant, inactivated mycobacteria and pertussis toxin [37]. This model has been successfully utilized to identify therapies currently prescribed for MS patients. One of the first preclinical studies testing vitamin D in EAE showed a strong protective effect [38] (**Figure 2**). However, in this study, hypercalcemia was evident in the mice receiving $1,25(OH)_2D_3$, the hormonal form of vitamin D, and subsequent studies showed elevated calcium is the protective effector of this action of vitamin D, at least in females [39]. More recent studies conducted in EAE show that UV, specifically a very narrow band of UVB radiation, can suppress the onset and disease severity in wild-type C57BL6/J mice as well as those that lack the receptor necessary for vitamin D action [3,40]. Furthermore, mice that lack the ability to produce vitamin D in the skin when exposed to UV light still experience delayed onset and reduced disease severity when subjected to narrow band UVB [40]. These results are consistent with the lack of clinical evidence that vitamin D supplementation can prevent or suppress MS and should direct researchers to focus on other possible mediators of UV in suppression of MS.

Figure 2. Summary of in vivo evidence indicating UV's action in multiple sclerosis is separate from the vitamin D pathway.

Agent Administered	EAE Mouse Model	Beneficial?	Citation
Vitamin D hormone or $1,25(OH)_2D_3$		Yes, but increases blood calcium	Lemire JM, Archer DC. 1,25-dihydroxyvitamin D3 prevents the in vivo induction of murine experimental autoimmune encephalomyelitis. *Journal of Clinical Investigation*. 1991;87(3):1103-1107.
Various levels of dietary calcium +/$1,25(OH)_2D_3$		Best response observed with increases in blood calcium and low calcium diet +$1,25(OH)_2D_3$ eliminates most of the beneficial effect	Cantorna MT, Humpal-Winter J, DeLuca HF. Dietary calcium is a major factor in 1,25-dihydroxycholecalciferol suppression of experimental autoimmune encephalomyelitis in mice. *Journal of Nutrition*.1999;129(11):1966-1971.
Infuse PTH to cause rise in blood calcium without using vitamin D hormone		Yes, hypercalcemia protects against disease	Meehan TF, Vanhooke J, Prahl J, DeLuca HF. Hypercalcemia produced by parathyroid hormone suppresses experimental autoimmune encephalomyelitis in female but not male mice. *Archives of Biochemistry and Biophysics*. 2005;442(2):214-221.
Narrow Band UVB		Yes, no need for the vitamin D pathway	Irving AA, Marling SJ, Seeman J, Plum LA, DeLuca HF. UV light suppression of EAE (a mouse model of multiple sclerosis) is independent of vitamin D and its receptor. *Proceedings of the National Academy of Sciences*. 2019;116(45):22552-22555.
Narrow Band UVB		Yes, no need to produce vitamin D in the skin **NOTE:** LATHOSTEROL requires Sc5d to produce 7-DEHYDROCHOLESTEROL, the substrate necessary for making VITAMIN D in the skin.	Irving AA, Marling SJ, Seeman J, Plum LA, DeLuca HF. UV light suppression of EAE (a mouse model of multiple sclerosis) is independent of vitamin D and its receptor. *Proceedings of the National Academy of Sciences*. 2019;116(45):22552-22555.

Targets of UV action

Molecular mechanisms underlying the benefit of UV light on EAE remain undefined, although several proposed mechanisms exist. Wang et al. found a general decrease in cytokines in the spinal cord following UV treatment and the reverse in the skin and spleen [41]. A chemokine known as CCL5/RANTES was also found to be decreased in the spinal cords of UV-treated animals. This chemokine has been shown to be important in leukocyte infiltration and is present in the active lesions of MS patients. The depression of this chemokine by UVB in the spinal cord is consistent with a decrease in the lesions of psoriatic patients treated with UVB [42]. Another group has provided some evidence that an antimicrobial peptide, β-defensin-14, may have a role [43]. Mice injected with this UV-inducible peptide prevented development of the disease and also reduced disease severity in mice that were given the peptide after clear clinical scores were evident. More recently, the sphingosine pathway has been implicated in playing a role in UV-mediated protection [44]. Sphingosine-1-phosphate (S1P) is increased by UV irradiation (~92% UVA and ~8% UVB) in the lymph nodes. SIP acts as a chemoattractant causing T-lymphocytes to move from the blood to skin-draining lymph nodes. These results in mice are corroborated with findings in CIS patients where increases in circulating T-cells were observed after exposure to narrow band UVB [45]. Several drugs based on this pathway are currently marketed for MS treatment [13]. Another potential target for explaining the UV suppression of multiple sclerosis is the folic acid pathway. Folates are found in the skin and upon UV irradiation form various pertin derivatives [46]. Interestingly, the degradation of folic acid is most effective with UVB as opposed to UVA. UVA is much less effective at reducing EAE incidence or severity [3]. It has been noted that macrophages express folate receptors upon activation. One synthetic folate-aminopterin derivative has been tested in animal models of both relapsing-remitting as well as progressive forms of EAE and found to be effective [47-48]. Another candidate molecule proposed to play a role in UV mediated protection of MS is urocanic acid [49]. Trans-urocanic acid found in the skin absorbs UV to form cis-urocanic acid. Cis-urocanic has been shown to have several immunomodulatory roles and is reduced in the blood of MS patients [50]. However, it was tested for activity in the EAE mouse and shows no protection against the disease [51]. Whether none, one or several of these potential UV targets is responsible for the UVB mediated protection observed in animal models of EAE remains to be determined, but this area should continue to be intensively explored. The need for new therapies with less detrimental side effects is high and understanding the mechanism of UV action should provide more opportunities for designing precise therapies.

Clinical trials using UV in MS patients

To-date, only two very small clinical trials have been completed to assess the effectiveness of UVB light in suppressing MS. The first trial was completed in 9 patients suffering from relapsing-remitting disease for an average of 13 years. They were administered narrow band UV light 5 days/week for six weeks [52]. Eighteen to twenty-four weeks after the UV exposure stopped, MRI's and neurological examinations were completed neither of which showed any changes from baseline. A more recent study was conducted in patients with clinically isolated syndrome [53]. Again, the number of patients was very small and the treatment for only 8 weeks, and at a frequency of 3 times per week. Interestingly, 3 out of 10 patients receiving phototherapy did not convert to multiple sclerosis while all 9 of the patients in the non-treatment arm did. Unfortunately, the results are preliminary and did not confront the gender effect in the disease. These results and the evidence generated in the EAE model strongly support the initiation of a larger study to test the effectiveness of narrow band UV light provided daily to prevent the development of MS.

Conflicts of Interest Statement: LAP has no conflicts of interest to report. HFD serves as a consultant for Cytokind.

Acknowledgements: The authors wish to thank Deb Noltner for her administrative assistance with this manuscript.

References:

1. Simpson S, Wang W, Otahal P, Blizzard L, van der Mei IA, Taylor BV. Latitude continues to be significantly associated with the prevalence of multiple sclerosis: An updated meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry*. 2019;90(11):1193-1200. doi:10.1136/jnnp-2018-320189
2. Skotarczak K, Osmola-Mańkowska A, Lodyga M, Polańska A, Mazur M, Adamski Z. Photoprotection: facts and controversies. *European Review for Medical and Pharmacological Sciences*. January 2015:98-112.
3. Wang Y, Marling SJ, McKnight SM, Danielson AL, Severson KS, Deluca HF. Suppression of experimental autoimmune encephalomyelitis by 300–315 nm ultraviolet light. *Archives of Biochemistry and Biophysics*. 2013;536(1):81-86. doi:10.1016/j.abb.2013.05.010
4. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology*. 2014;83(3):278-286. doi:10.1212/wnl.0000000000000560
5. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. *Clinical Medicine*. 2017;17(6):530-536. doi:10.7861/clinmedicine.17-6-530
6. Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the atlas of MS, Third edition. *Multiple Sclerosis Journal*. 2020;26(14):1816-1821. doi:10.1177/1352458520970841
7. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States. *Neurology*. 2019;92(10). doi:10.1212/wnl.0000000000007035
8. Kaufman DW, Reshef S, Golub HL, et al. Survival in commercially insured multiple sclerosis patients and comparator subjects in the U.S. *Multiple Sclerosis and Related Disorders*. 2014;3(3):364-371. doi:10.1016/j.msard.2013.12.003
9. Marrie RA, Elliott L, Marriott J, et al. Effect of comorbidity on mortality in multiple sclerosis. *Neurology*. 2015;85(3):240-247. doi:10.1212/wnl.0000000000001718
10. Graves JS, Krysko KM, Hua LH, Absinta M, Franklin RJ, Segal BM. Ageing and multiple sclerosis. *The Lancet Neurology*. 2022. doi:10.1016/s1474-4422(22)00184-3
11. Bebo B, Cintina I, LaRocca N, et al. The economic burden of multiple sclerosis in the United States. *Neurology*. 2022;98(18). doi:10.1212/wnl.0000000000200150
12. Lublin F. History of modern multiple sclerosis therapy. *Journal of Neurology*. 2005;252(S3):iii3-iii9. doi:10.1007/s00415-005-2010-6
13. Freeman L, Longbrake EE, Coyle PK, Hendin B, Vollmer T. High-efficacy therapies for treatment-naïve individuals with relapsing–remitting multiple sclerosis. *CNS Drugs*. 2022. doi:10.1007/s40263-022-00965-7
14. Liyanage G, Brilot F. Targeting B cell dysregulation with emerging therapies in autoimmune demyelinating disorders. *Current Opinion in Neurobiology*. 2022;77:102643. doi:10.1016/j.conb.2022.102643
15. Carnero Contentti E, Correale J. Current perspectives: Evidence to date on BTK inhibitors in the management of multiple sclerosis. *Drug Design, Development and Therapy*. 2022;Volume 16:3473-3490. doi:10.2147/dddt.s348129
16. Chataway J, Schuerer N, Alsanousi A, et al. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-stat): A randomised, placebo-controlled, phase 2 trial. *The Lancet*. 2014;383(9936):2213-2221. doi:10.1016/s0140-6736(13)62242-4
17. Fox RJ, Coffey CS, Conwit R, et al. Phase 2 trial of ibudilast in progressive multiple sclerosis. *New England Journal of Medicine*. 2018;379(9):846-855. doi:10.1056/nejmoa1803583
18. Kurtzke JF. THE DISTRIBUTION OF MULTIPLE SCLEROSIS AND OTHER DISEASES. *Acta Neurologica Scandinavica*. 2009;42(2):221-243. doi:10.1111/j.1600-0404.1966.tb01178.x
19. Vitkova M, Diouf I, Malpas C, et al. Association of latitude and exposure to ultraviolet B radiation with severity of multiple sclerosis. *Neurology*. 2022;98(24). doi:10.1212/wnl.0000000000200545
20. Goldberg P. Multiple sclerosis: Vitamin D and calcium as environmental determinants of prevalence. *International Journal of Environmental Studies*. 1974;6(1):19-27. doi:10.1080/00207237408709630
21. 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. doi:10.1001/jama.296.23.2832

22. Munger KL, Hongell K, Åivo J, Soilu-Hänninen M, Surcel H-M, Ascherio A. 25-hydroxyvitamin D deficiency and risk of MS among women in the Finnish maternity cohort. *Neurology*. 2017;89(15):1578-1583. doi:10.1212/wnl.0000000000004489
23. Salzer J, Hallmans G, Nystrom M, Stenlund H, Wadell G, Sundstrom P. Vitamin D as a protective factor in multiple sclerosis. *Neurology*. 2012;79(21):2140-2145. doi:10.1212/wnl.0b013e3182752ea8
24. Duan S, Lv Z, Fan X, et al. Vitamin D status and the risk of multiple sclerosis: A systematic review and meta-analysis. *Neuroscience Letters*. 2014;570:108-113. doi:10.1016/j.neulet.2014.04.021
25. 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. doi:10.1016/j.msard.2018.05.008
26. Doosti-Irani A, Tamtaji OR, Mansournia MA, et al. The effects of vitamin D supplementation on Expanded Disability Status Scale in people with multiple sclerosis: A critical, systematic review and metaanalysis of randomized controlled trials. *Clinical Neurology and Neurosurgery*. 2019;187:105564. doi:10.1016/j.clineuro.2019.105564
27. Martínez-Lapiscina EH, Mahatanan R, Lee C-H, Charoenpong P, Hong J-P. Associations of serum 25(OH) vitamin D levels with clinical and radiological outcomes in multiple sclerosis, a systematic review and meta-analysis. *Journal of the Neurological Sciences*. 2020;411:116668. doi:10.1016/j.jns.2020.116668
28. McLaughlin L, Clarke L, Khalilidehkordi E, Butzkueven H, Taylor B, Broadley SA. Vitamin D for the treatment of multiple sclerosis: A meta-analysis. *Journal of Neurology*. 2018;265(12):2893-2905. doi:10.1007/s00415-018-9074-6
29. Jagannath VA, Fedorowicz Z, Asokan GV, Robak EW, Whamond L. Vitamin D for the management of multiple sclerosis. *Cochrane Database of Systematic Reviews*. 2010. doi:10.1002/14651858.cd008422
30. Yuan X, Guo L, Jiang C, Yang X, Huang J. The effect of different administration time and dosage of vitamin D supplementation in patients with multiple sclerosis: A meta-analysis of randomized controlled trials. *Neuroimmunomodulation*. 2021;28(3):118-128. doi:10.1159/000515131
31. Ghajarzadeh M, Hanaei S, Sahraian MA, Mohammadifar M, Ramagopalan SV. Effect of vitamin D supplements on relapse rate and expanded Disability Status Scale (EDSS) in multiple sclerosis (MS): A systematic review and meta-analysis. *International Journal of Preventive Medicine*. 2021;12(1):42. doi:10.4103/ijpvm.ijpvm_208_20
32. Stein MS, Liu Y, Gray OM, et al. A randomized trial of high-dose vitamin D2 in relapsing-remitting multiple sclerosis. *Neurology*. 2011;77(17):1611-1618. doi:10.1212/wnl.0b013e3182343274
33. Hahn J, Cook NR, Alexander EK, et al. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: Vital randomized controlled trial. *BMJ*. 2022. doi:10.1136/bmj-2021-066452
34. Amador-Patarroyo MJ, Rodriguez-Rodriguez A, Montoya-Ortiz G. How does age at onset influence the outcome of autoimmune diseases? *Autoimmune Diseases*. 2012;2012:1-7. doi:10.1155/2012/251730
35. Kronzer VL, Bridges SL, Davis JM. Why women have more autoimmune diseases than men: An evolutionary perspective. *Evolutionary Applications*. 2020;14(3):629-633. doi:10.1111/eva.13167
36. Lips P, Bilezikian JP, Bouillon R. Vitamin D: Giveth to those who needeth. *JBMR Plus*. 2019;4(1). doi:10.1002/jbm4.10232
37. Smith P. Animal models of multiple sclerosis. *Current Protocols*. 2021;1(6). doi:10.1002/cpz1.185
38. Lemire JM, Archer DC. 1,25-dihydroxyvitamin D3 prevents the in vivo induction of murine experimental autoimmune encephalomyelitis. *Journal of Clinical Investigation*. 1991;87(3):1103-1107. doi:10.1172/jci115072
39. Meehan TF, Vanhooke J, Prahl J, DeLuca HF. Hypercalcemia produced by parathyroid hormone suppresses experimental autoimmune encephalomyelitis in female but not male mice. *Archives of Biochemistry and Biophysics*. 2005;442(2):214-221. doi:10.1016/j.abb.2005.08.011
40. Irving AA, Marling SJ, Seeman J, Plum LA, DeLuca HF. UV light suppression of EAE (a mouse model of multiple sclerosis) is independent of vitamin D and its receptor.

Proceedings of the National Academy of Sciences. 2019;116(45):22552-22555. doi:10.1073/pnas.1913294116

41. Wang Y, Marling SJ, Beaver EF, Severson KS, Deluca HF. UV light selectively inhibits spinal cord inflammation and demyelination in experimental autoimmune encephalomyelitis. *Archives of Biochemistry and Biophysics*. 2015;567:75-82. doi:10.1016/j.abb.2014.12.017
42. Rateb AA, Fawzi MMT, Abdel Hay RM, Mohammed FN, Amr KS. Reduction of RANTES expression in lesional psoriatic skin after narrow band ultraviolet therapy: A possible marker of therapeutic efficacy. *European Journal of Dermatology*. 2012;22(4):481-487. doi:10.1684/ejd.2012.1730
43. Bruhs A, Schwarz T, Schwarz A. Prevention and mitigation of experimental autoimmune encephalomyelitis by murine β-defensins via induction of regulatory T cells. *Journal of Investigative Dermatology*. 2016;136(1):173-181. doi:10.1038/jid.2015.405
44. Tse BC, Ireland RA, Lee JY, et al. Exposure to systemic immunosuppressive ultraviolet radiation alters T cell recirculation through sphingosine-1-phosphate. *The Journal of Immunology*. 2021;207(9):2278-2287. doi:10.4049/jimmunol.2001261
45. Trend S, Jones AP, Cha L, et al. Short-term changes in frequencies of circulating leukocytes associated with narrowband UVB phototherapy in people with clinically isolated syndrome. *Scientific Reports*. 2019;9(1). doi:10.1038/s41598-019-44488-6
46. Goossens J-F, Thuru X, Bailly C. Properties and reactivity of the folic acid and folate photoproduct 6-formylpterin. *Free Radical Biology and Medicine*. 2021;171:1-10. doi:10.1016/j.freeradbiomed.2021.05.002
47. Elo P, Li X-G, Liljenbäck H, et al. Efficacy and tolerability of folate-aminopterin therapy in a rat focal model of multiple sclerosis. *Journal of Neuroinflammation*. 2021;18(1). doi:10.1186/s12974-021-02073-7
48. Lu Y, Wollak KN, Cross VA, et al. Folate receptor-targeted aminopterin therapy is highly effective and specific in experimental models of autoimmune uveitis and autoimmune encephalomyelitis. *Clinical Immunology*. 2014;150(1):64-77. doi:10.1016/j.clim.2013.10.010
49. Hart PH, Norval M. The multiple roles of urocanic acid in health and disease. *Journal of Investigative Dermatology*. 2021;141(3):496-502. doi:10.1016/j.jid.2020.07.017
50. Correale J, Farez MF. Modulation of multiple sclerosis by Sunlight Exposure: Role of cis-Urocanic Acid. *Journal of Neuroimmunology*. 2013;261(1-2):134-140. doi:10.1016/j.jneuroim.2013.05.014
51. Irving AA, Marling SJ, Plum LA, DeLuca HF. Suppression of experimental autoimmune encephalomyelitis by ultraviolet light is not mediated by isomerization of Urocanic Acid. *BMC Neuroscience*. 2017;18(1). doi:10.1186/s12868-016-0323-2
52. Breuer J, Schwab N, Schneider-Hohendorf T, et al. Ultraviolet B light attenuates the systemic immune response in central nervous system autoimmunity. *Annals of Neurology*. 2014;75(5):739-758. doi:10.1002/ana.24165
53. Hart PH, Jones AP, Trend S, et al. A randomised, controlled clinical trial of narrowband UVB phototherapy for clinically isolated syndrome: The Phocis Study. *Multiple Sclerosis Journal - Experimental, Translational and Clinical*. 2018;4(2):205521731877311. doi:10.1177/2055217318773112