

Does Vitamin D Supplementation, Reduce The Risk of Multiple Sclerosis, Compared to Usual Preventive Measures, In Young Adults Living In High Latitudes Who Have Experienced The First Episode of Neurological Dysfunction Highly Suggestive of Multiple Sclerosis?

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Summary

Objective:

To determine the likelihood of developing multiple sclerosis due to vitamin D supplementation is the primary objective of this study. This study also investigates what kind of relationship exists between vitamin D exposure and likelihood of multiple sclerosis.

Methodology:

The electronic database PubMed was searched to extract relevant and suitable studies. These studies were selected after applying proper exclusion and inclusion criteria. The included studies were then critically reviewed and analyzed to derive the most relevant and useful information to generate desired outcomes.

Results:

The findings were based on the data obtained by the studies included. Majority of the available literature has shown that exposure or Vitamin D supplementation significantly lowers the likelihood of developing autoimmune disorders like MS. Very minimal data was found contrary to this statement.

Conclusion:

Considering the data extracted from our reviewed literature and studies, it can be concluded that there is a strong inverse correlation between vitamin D and MS likelihood. So, it is strongly suggested that the more exposure or supplementation of vitamin D, the less will be the chances of developing multiple sclerosis and other autoimmune disorders.

Keywords: Multiple Sclerosis, M.S., Vitamin D, Neurodegenerative diseases, M.S. and Vitamin D.

Abbreviations: (M.S.) Multiple Sclerosis, (TGF beta 1) Transforming growth factor beta, (RTC) Randomized controlled trial, (MSSS) Multiple Sclerosis Severity Score.

Background: Multiple Sclerosis is a condition widely documented as a core contributor to neurological dysfunction in young adults (Ascherio et al., 2014). For patients who develop MS, bouts of inflammatory demyelination, which is the relapsing of MS, brain atrophy, and treatment-resistance disease progression, are among the imminent occurrences (Ascherio et al., 2014). However, it is reported that most young adults who have undergone the first episode of strongly suggestive MS neurological disorder also have a poor intake of vitamin D (Sintzel et al., 2018). Nevertheless, there is a general lack of RCT exploring the Vitamin D effectiveness in reducing the MS risk among young adults living in high latitudes. More significantly, the existing body of research on vitamin D and MS seems to concentrate more on the impact of serum levels of vitamin D in the progression of MS instead of its part in reducing the risk of MS for young adults in high latitudes. (Deluca & Cantorna, 2001). As for the existing meta-analytical and systematic reviews of RCTs on the topic, the findings have been inconclusive and concentrate primarily on the role of vitamin D in MS progression. In light of the general lack of evidence and inclusive findings on the topic within the existing body of research, this study seeks to determine the efficacy of vitamin D supplementation in reducing risk of MS among young adults who have witnessed the first episode of strongly suggestive MS neurological dysfunction. (Smolders et al., 2020).

Methods: The required data and studies included in this research paper were searched and extracted using an electronic database. The search engine PubMed was used to obtain beneficial and suitable research studies. When we initiated our data search, we needed to choose appropriate mesh terms or keywords, which could help us find the most suitable and relevant articles. The keywords we used here were Vitamin D, Multiple sclerosis, young adults, neurological dysfunction. These keywords yielded many relevant studies; only the mesh terms “multiple sclerosis and Vitamin D” provided us around 1431 results on PubMed. However, as we had to focus on most germane articles that can meet our research criteria, so ini-

tially, after removing the duplicates, many studies that did not meet inclusion criteria were excluded. Once the duplicates were removed, and irrelevant studies were roughly eliminated, an appropriate inclusion and exclusion criterion was designed and implemented to shrink our data findings.

The inclusion criteria included:

1. English language articles;
2. Full-text articles;
3. Articles that included the case definition of multiple sclerosis or autoimmune disorders;
4. Articles including at least two keywords.

Any article not meeting the inclusion criteria or written and published in non-English language was excluded. After going through this process of identifying, exclusion, and selecting relevant articles, seven articles were finally included in this research paper. One systematic review was included in these seven articles, and the rest of the six articles consisted of three descriptive studies, one RCT, one comparative study, and one cohort study. These studies were thoroughly checked and reviewed, their findings were critically appraised, and their results were systematically analyzed.

Once these studies were critically reviewed and verified, their relevant information was taken out and used in our research paper. These studies have provided us with profound knowledge and pertinent data, which was essential to produce a specific outcome regarding our review topic.

Results: These research studies we have discussed so far have demonstrated that the available literature and evidence-based studies done so far clearly supports the fact that there is a clear association between sensitivity to vitamin D and multiple sclerosis. A significant finding extracted from these studies is that an inverse relationship has been confirmed between vitamin D exposure and the likelihood of developing MS. It means that if a person/ subject is exposed to via sunlight or supplements to vitamin D, especially in early years of age, then the chances of developing multiple sclerosis are significantly minimized.

Frequent exposure to vitamin D has also been shown to improve overall immunity-related functions, e.g., accelerating B cells' production and proliferation, building strong immunity against autoimmune disorders like multiple sclerosis. Since vitamin D plays an essential role in protecting the body from autoimmune disorders such as MS, many beneficial prevention strategies can be planned and introduced in the future.

Discussion: If we talk about the available research work related to our topic, we can say that a remarkable amount of data can be found regarding vitamin D exposure with the development of autoimmune disorders like multiple sclerosis. Though very few studies suggest that no such association exists, most research work favors this association based on evidence-based practice. We discuss a few of the studies that provided the most relevant and suitable evidence-based data in favor of our research topic.

A systematic review conducted by Duan et al. determined the relation between vitamin D status and risk of multiple sclerosis. Electronic databases including PubMed, EMBASE, and Cochrane library were searched to extract the relevant studies. Finally, 11 studies were included which met the inclusion criteria. The meta-analysis of results have indicated that MS patients were having lower mean levels of 25-hydroxyvitamin D, which strongly suggests that low vitamin D levels enhance the risk of developing multiple sclerosis. (Duan et al., 2014).

In 2018, Helen Tremlett conducted a study that focuses on the association between sun exposure and the development of MS over the course of 10 years. The age range for the survey was 5-15 years and 16-20 years. Case and Test groups completed season, winter, and lifetime sun exposure questionnaires. Seasonal sun exposure was classified as hours of low and high exposure. It was observed during the trial that people with high hours of exposure to the sun displayed a better risk of MS (45% less risk of MS) than those with low hours of exposure. This observation shows that exposure to the sun (vitamin D exposure) visibly decreases the likelihood of MS growth. While this research yielded consistent conclusions and high validity, because there was a small sample size, these findings should not be applied to larger population groups. (Tremlett, Zhu, Ascherio, & Munger, 2018).

Mandia et al. performed a study focusing on the impact of exposure to sunlight on MS, it was observed that patients who indicated daily exposure to sunlight (vitamin D) had lower scores on MSSS. (2.6 ± 2.4 h vs. 4.6 ± 2.6 h, $p < 0.001$). Those who had more frequent exposure to sunlight showed mild symptoms of MS and lower MSSS scores. The study further found that less risk of developing severe MS was associated with increased levels of serum vitamin D. It can also be inferred that there is a clear inverse association between repeated exposure to sunlight (vit D) and the risk of severe MS. The analysis provided valuable and important

knowledge about our research subject, but due to the less sample size, the generalizability of the findings is doubtful. (Mandia et al., 2014).

A study conducted by Islam et al. determined the effect of childhood sun exposure on the likelihood of having multiple sclerosis. This study included 79 pairs of twins, sought by the yearly newspaper throughout North America. The MS diagnosis was medically verified, and a sun exposure index SI was used to determine the extent of sun exposure. The study continued from 1980 to 1992 with nine sun exposure activities. Later on, when the results were analyzed, it was found that each of these nine-sun exposure behaviours offered major protection within the twin pair against MS. The probability of developing MS was considerably smaller for the twin who spent more time exposed to the sun (OR 0.40, 95% CI 0.19 to 0.83), as compared to the other twin.

In light of these conclusions, it was assumed that early sun exposure could result in markable protection against MS. We can say that this study has provided us with beneficial findings regarding the sun exposure effect on MS, but it also has few limitations. One of them is that the study only included the twin pairs, so the results cannot be applied to other population groups with different ages and altered genetic background. Moreover, the region in which the study was carried out was North America, so again the generalizability of the results on other areas' subjects is questionable. (Islam, Gauderman, Cozen, & Mack, 2007).

A study conducted by Deluca and Cantorna focuses on the non-calcemic effect of vitamin D on immune cells, particularly on T cells. The laboratory results revealed that 1,25-dihydroxyvitamin D3 could either fully prevent or inhibit different autoimmune disorders, including MS. The mechanism by which vitamin D3 suppresses autoimmune disorders are based on the fact that the hormone vitamin D stimulates the development of TGFbeta-1 and interleukin 4 transforming growth factor, which can sequentially suppress the activity of inflammatory T cells. This study demonstrates the crucial function of vitamin D in the prevention of autoimmune diseases, thereby offering a research field that is productive and thought-provoking and can create valuable information in the future. (Deluca & Cantorna, 2001).

Chen et al. performed one more study in which they sought to figure out the impact of vitamin D3 on the differentiation of human B cells. It was noticed that in people with an elevated level of the disorder there were very low plasma levels of vitamin D, strongly indicating the part of vitamin

D in controlling autoantibodies. 1,25(OH)(2)D(3) (vitamin D3) up-regulates the expression of p27, which is very important for differentiation and proliferation of activated B cells, which further accelerates the immunity. This research thus concludes that the reversal of vitamin D deficiency is effective for the treatment of autoimmune diseases mediated by B cells. In this analysis, the link between vitamin D and autoimmune disorders is very apparent, providing us with important and appropriate knowledge about our research subject. (Chen et al., 2007).

Considering the findings of the studies listed above, it is apparent that a substantial association exists between vitamin D and the growth of MS. While these studies have provided us with fruitful evidence-based information, when we see that most of the studies are descriptive, one can easily doubt the verification of their outcomes. This is because descriptive experiments do not statistically test or validate the study issue, and the risks of bias are therefore strong. Because of these difficulties, the findings of descriptive experiments will not be applied to other persons or subjects, rendering the outcomes dubious. Hence, future research should focus on maximum cross-sectional studies to confirm the association of vitamin D with MS so that their results are more reliable and can be generalized without any doubt. Much research is required in this field, so it is highly recommended for future researchers to use cross-sectional approaches in their upcoming research to produce verified results, which can be further generalized over large population groups. Another limitation that was obvious in these studies was the small or limited sample size. This again causes hindrance in the generalizability of the results over many people. That is why prospective research experiments are encouraged to deliver profound and implementable findings using broad sample sizes.

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				Study Design		Variables		
	Author (all names), Title, Journal	Year	Study Purpose	Type	Random assignment &/or selection	Dependent	Independent	Primary Predictor Variable
1	Sheng Chen, Gary P. Sims, Xiao Xiang Chen, Yue Ying Gu, Shunle Chen and Peter E. Lipsky. Modulatory effects of 1, 25-dihydroxyvitamin D3 on human B cell differentiation. <i>The Journal of Immunology</i> .	2007	To examine the effect of vitamin D (Dihydroxy vitamin D(3) (1,25(OH)(2) D(3))) on B cell (immune cell) responses.	Descriptive study	N/A	B cell	Vitamin D	DihydroxyvitaminD(3)
2	Hector F. Deluca, Margherita T. Cantorna. Vitamin D: its role and uses in immunology. <i>The FASEB journal</i> .	2001	To understand possible non-calceemic roles of vitamin D, including its role in the immune system and, in particular, on T cell-mediated immunity	Descriptive study	Yes	immunology	Vitamin D	Vitamin D
3	Shurong duan, Zheng Lv, Xiaoxue Fan, le wang, feihan, hongwong, sheng bi. Vitamin D status and risk of multiple sclerosis. <i>Neurosciences letters</i> , volume 570.	2014	To estimate the associations between vitamin D status and multiple sclerosis (MS)	Systematic review	N/A	Multiple Sclerosis	Vitamin D	Vitamin D

4	Talat Islam, W James Gauderman, Wendy Cozen, Thomas M Mack. Childhood sun exposure influences risk of multiple sclerosis in monozygotic twins. Neurology.	2007	To address the role of childhood sun exposure on the risk of multiple sclerosis (MS) after controlling for genetic susceptibility, we investigated the association between sun exposure and MS comparing disease-discordant	Comparative Study	No	Multiple Sclerosis	Childhood sun exposure	Childhood sun exposure
5	Daniele Mandia, Ottavia E Ferraro, Guido Nasari, Cristina Montomoli, Elisabetta Zardini. Environmental factors and multiple sclerosis severity: a descriptive study. International journal of environmental research and public health	2014	To examine whether environmental factors (like sunlight) may also be associated with the evolution of the disease (multiple sclerosis)	Descriptive Study	Yes	Development of disease	Environmental Factors	Environmental Factors (sunlight)
6	Joost Smolders, Max Mimpfen, Johanna Oechtering, Jan Damoiseaux, Jody van den Ouweland, Raymond Hupperts, Jens Kuhle. Vitamin D3 supplementation and neurofilament light chain in multiple sclerosis. Acta Neurologica Scandinavica.	2020	Low circulating vitamin D levels are associated with an increased risk of active MRI lesions and relapses in several cohorts with relapsing remitting multiple sclerosis (RRMS) We explored whether 48-week high-dose vitamin D3 supplements were associated with lower circulating NFL levels.	RCT	Yes	Neurofilament light chain in multiple sclerosis	Vitamin D3 supplementation	Vitamin D3 supplementation
7	Helen Tremlett, Feng Zhu, Alberto Ascherio, Kassandra I, Munger Sun exposure over the life course and associations with multiple sclerosis. Neurology.	2018	To examine sun exposure and multiple sclerosis (MS) over the life course (ages 5–15 and 16–20 years, every 10 years thereafter).	Cohort study	yes	Multiple sclerosis	Sun exposure	Sun exposure

Subjects		Data						
# Subjects	Subject Characteristics	Source or Instrument	Year data collected	Results	Results	conclusions	My additional notes/areas for further research	
1	N/A	N/A	Tests	2007	Patients with systemic lupus erythematosus, especially those with antinuclear Abs and increased disease activity, had decreased 1,25 (OH)(2) D(3) levels, suggesting that vitamin D might play a role in regulating autoantibody production. These results indicate that 1,25(OH)(2)D(3) may play an important role in the maintenance of B cell homeostasis	Nil	The correction of vitamin D deficiency may be useful in the treatment of B cell-mediated autoimmune disorders.	Nil
2	N/A	N/A	Tests	2001	Results show that 1,25-dihydroxyvitamin D3 can either prevent or markedly suppress experimental autoimmune encephalomyelitis, rheumatoid arthritis, systemic lupus erythematosus, type I diabetes, and inflammatory bowel disease.	Nil	Possible mechanisms of suppression of these autoimmune disorders by the vitamin D hormone have been presented. The vitamin D hormone stimulates transforming growth factor TGFbeta-1 and interleukin 4 (IL-4) production, which in turn may suppress inflammatory T cell activity.	Nil
3	N/A	N/A	Review of articles	2014	Results of our meta-analysis show that MS patients had lower mean levels of 25-hydroxyvitamin D [25(OH)D] than healthy controls (weighted mean difference[MD], -14.52, 95% confidence interval [CI], -23.83 to -5.22).	There were statistically significant heterogeneity The significant heterogeneity may be due to the differences in ethnicity, country, season of blood sampling and age of the participants studied	Low vitamin D levels are associated with an increased risk of MS	More interventional studies should be encouraged in future.

4	2	Twins with early sun exposure	Sought by yearly newspaper	2007	Each of the nine sun exposure-related activities during childhood seemed to convey a strong protection against MS within MZ twin pairs. Depending on the activity, the odds ratio (OR) ranged from 0.25 to 0.57. For example, the risk of subsequent MS was substantially lower (OR 0.40, 95% CI 0.19 to 0.83) for the twin who spent more time suntanning in comparison with the co-twin. For each unit increase in SI, the relative risk of MS decreased by 25%	As the sample size is very small (only 2), so results cannot be generalized over large population.	Early sun avoidance seems to precede the diagnosis of multiple sclerosis (MS). This protective effect is independent of genetic susceptibility to MS.	nil
5	131	MS	interviews	2014	The results showed a strong association between serum vitamin D concentration and both sunlight exposure. Patients reporting frequent sunlight exposure had a lower MSSS. The mild MS patients reported much more frequent sunlight exposure. A higher serum vitamin D concentration determined a lower risk of developing severe MS, adjusted for sunlight exposure (OR = 0.92 for one unit increase in vitamin D, 95% CI: 0.86–0.97, p = 0.005). A stronger inverse association emerged between frequent sunlight exposure and the risk of severe MS (OR = 0.26, 95% CI: 0.09–0.71, p = 0.009).	The study focused on other factors like smoking and diet, so results cannot be completely associated with sun exposure only.	data show that an appropriate diet and adequate exposure to sunlight are associated with less aggressive MS	nil
6	40	Dutch interferon beta-treated participants with RRMS of the SOLAR trial	Clinical trial	2020	Serum 25(OH)D3 levels at 48 weeks were increased in the vitamin D3 when compared to placebo group (median level 281 [IQR 205–330] vs 72 [39–88] nmol/L; P < .01).	nil	Supplementation of high-dose vitamin D3 for 48 weeks was not associated with lower NFL levels. This study does not support an effect of vitamin D3 on this biomarker of neuro-axonal injury.	nil

7	386	(Ages 5–15 and 16–20 years, every 10 years thereafter).	Questionnaires	2018	<p>Most participants were white (98%); the mean age at MS onset was 39.5 years. Living in high (vs low) UV-B areas before MS onset was associated with a 45% lower MS risk (adjusted RR 0.55, 95% CI 0.42–0.73). Similar reduced risks (51%–52%) for medium or high exposure were observed at ages 5 to 15 years and at 5 to 15 years before MS onset (adjusted $p < 0.05$). At age 5 to 15 years, living in a high (vs low) UV-B area and having high (vs low) summer sun exposure were associated with a lower MS risk (RR 0.45, 95% CI 0.21–0.96).</p>	nil	<p>Living in high ambient UV-B areas during childhood and the years leading up to MS onset was associated with a lower MS risk. High summer sun exposure in high ambient UV-B areas was also associated with a reduced risk.</p>	nil
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