MURAJ
Minnesota Undergraduate Research & Academic Journal

Volume 1 • Issue 1
z.umn.edu/MURAJ

Sunlight Exposure, Vitamin D Synthesis, and Multiple Sclerosis in the Northern and Southern Regions of the United States

Danielle Maeser and Nicole Maeser

Abstract:
A literature review was performed to understand the possible relationship between geographic latitude and MS prevalence in the United States. If higher latitudes are associated with higher prevalence than decreased sunlight exposure and subsequent hindered vitamin D synthesis may be as well. Based on the review, these relationships seem possible.

Multiple sclerosis (MS) is a neurological autoimmune disease that affects the brain and spinal cord. With MS, the immune system attacks the myelin sheath wrapped around nerve cell axons. Myelin protects nerve fibers and aids in propagating electrical impulses, allowing the brain to communicate with the rest of the body. If the myelin sheath degrades, communication between the brain and the body is disrupted. This is why individuals with MS often struggle with coordination, balance, and movement. Although the cause of MS is unknown, it has been hypothesized that genetic and environmental factors may influence its development. Individuals with the highest risk tend to be white and of Northern European ancestry; they also tend to live closer to the North Pole than to the Equator where the climate is temperate and sunrays hit at varying angles as opposed to from directly overhead e.g. Northern United States, Canada (9).

When exposed to sunlight, the skin produces a major source of vitamin D (10). Therefore, people with limited sun exposure produce small amounts of vitamin D and can be at risk for vitamin D deficiency. For instance, in Boston which has a high latitude of 42°N, the skin cannot make any vitamin D between the months of November and February (16). Considering the possible relationship between multiple sclerosis and regions of higher latitudes, perhaps sun exposure and vitamin D are linked to MS as well. The research question under consideration: How does the variable exposure to sunlight in the Northern and Southern regions of the United States relate to incidence of MS?

A literature review was performed to understand the possible relationship between geographic latitude and MS prevalence in the United States. If higher latitudes are associated with higher prevalence than decreased sunlight exposure and subsequent hindered vitamin D synthesis may be as well. Based on the review, these relationships seem possible.

A study was conducted with the goal of estimating the prevalence of MS in the United States. Four geographic regions were taken into consideration: Midwest, Northeast, South, and West. To determine each region's prevalence, researchers analyzed National Health Interview Surveys (NHIS) collected between 1989 and 1994. The NHIS is a cross-sectional survey administered annually by the U.S. Census Bureau. It's aimed at understanding the health status of individuals in the United States and involves personal household interviews on a variety of health related subjects like MS. Based on the years analyzed, the prevalence of MS in Southern men was 36:100,000, and the prevalence of MS in Southern women was 91:100,000. The Midwest, a region of higher latitude, had a prevalence of 54:100,000 in men and a prevalence of 138:100,000 in women. Therefore, the prevalence of multiple sclerosis in the South compared to that in the Midwest per 100,000 was 127:192. The latter was about 50% higher than the prevalence of MS in the South. Since the lowest prevalence of MS occurred in the South, the research supports the trend of individuals with highest risk of MS living far from the equator. The research also suggests that risk of MS declines in regions that receive direct sunlight and allow for unhindered vitamin D synthesis (11). In another study, a group of researchers divided the United States into four different regions with the goal of understanding the regional presence of MS. The four regions were the West,

South, Midwest, East (see fig. 1). Again, the Southern region was identified as having the lowest prevalence with 111.6 per 100,000 individuals relative to the Midwestern region (165.0 per 100,000) and the Eastern region (192.1 per 100,000): both geographic spaces of higher latitudes. The latter had the highest prevalence of all, with the Midwestern region second (5).

Since individuals who live far from the equator do not receive direct sunlight, their geographical location may challenge their body's ability to synthesize vitamin D and may contribute to MS onset. Upon absorbing ultraviolet light from the sun's rays, the skin converts it to vitamin D to be used by the body. When photons of ultraviolet light are absorbed by the molecule 7-dehydrocholesterol, which is located in the skin, a form of vitamin D called previtamin D3 is produced. Previtamin D is converted into vitamin D3, which metabolizes in the liver into 25-hydroxyvitamin D3. The kidney then metabolizes this fourth form into 1,25-dihydroxyvitamin D3, which is the body's active form of vitamin D; it is this form that the body uses in biological reactions (7). According to Harvard University, "10 to 15 minutes of sun on the arms and legs a few times a week can generate all the vitamin D we need. However, whether or not these periods of sunlight exposure can be obtained is subject to a variety of factors: season, time of day, where you live, cloud coverage, and pollution effect" (18). Unless individuals in the Northern region of the United States consume lots of fatty fish and vitamin fortified foods, the sunshine vitamin can be difficult if not impossible to synthesize. People living at latitudes above 37°N in the United States make little to no vitamin D during non-summer months and thus are at greater risk for vitamin D deficiency. The 37th parallel is indicated in fig. 2 (17).

Through analyzing the UV index, an understanding of sunlight exposure received by different regions in

Figure 2

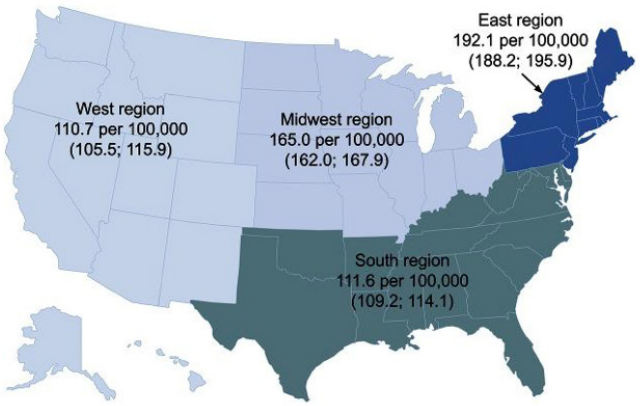

Figure 1

the United States can be attained. The UV index is a number used to represent the amount of skin-damaging UV radiation (radiation associated with overexposure) that reaches earth's surface at any point in time. A UV index of 1 is equivalent to 25 milliWatts per square meter (to give perspective, the FDA mandates the maximum radiation a microwave can emit is 5 milliWatts). Fortunately, the United States Environmental Protection Agency has mapped the average monthly UV index values for the United States in 2016. Each map reflects a similar trend: the Northern region of the United States tends to have the lowest UV index while the Southern region tends to have the highest (see fig. 3, 4 and 5 for maps of January, May, and September, respectively) (15). Since the Northern region receives the least direct sunlight, individuals who reside in there may produce less vitamin D and have higher risk of MS.

As the maps show, Boston, Massachusetts (42°N) is associated with lower UV index values; it receives less sun exposure compared to its southern counterparts. Therefore, vitamin D deficiency seems likely. In a study researchers determined the prevalence of vitamin D deficiency in 307 adolescents ages 11-18 living in Boston. The adolescents were studied from July 1, 2001 to June 30, 2003. Through conducting nutritional assessments, blood tests and questionnaires, researchers discovered that 24.1% of patients (74:307) were deficient in vitamin D. Individuals are defined as deficient if their serum 25-hydroxyvitamin D levels are 20 ng/mL. The participants' levels were 15 ng/mL (6). Serum 25-hydroxyvitamin D is a form of that is considered to be a reliable indicator of vitamin D status because its concentration determines the body's ability to synthesize 1 ,25-dihydroxyvitamin D (14). Among the 74 patients, 4.6% (14/74) were "severely" vitamin D deficient because their serum 25-hydroxyvitamin D levels were 8 ng/mL. Overall, the percentage of those with vitamin D

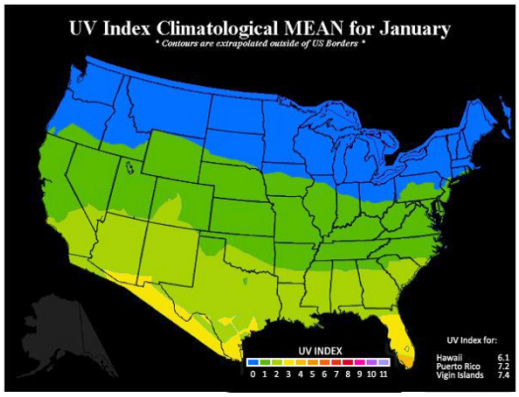

Figure 3

The Northern region of the United States is blue and dark green: colors that correspond to low UV index values of 0-1. The Southern region of the U.S. is primarily lime green and yellow: colors that correspond to higher UV index values of 2-3.

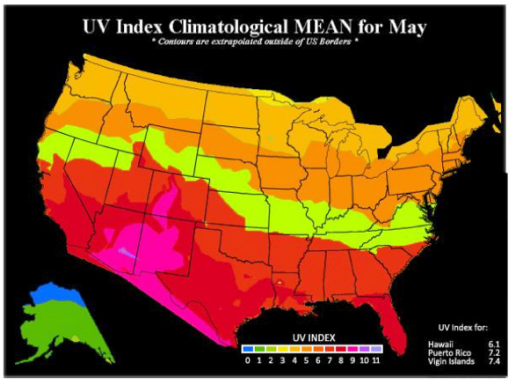

Figure 4

The Northern region of the United States is primarily light orange, dark orange, and bright green: colors that correspond to lower UV index numbers of about 2-5. The Southern region is primarily light red, dark red, and magenta: colors that correspond to high UV index values of 7-9.

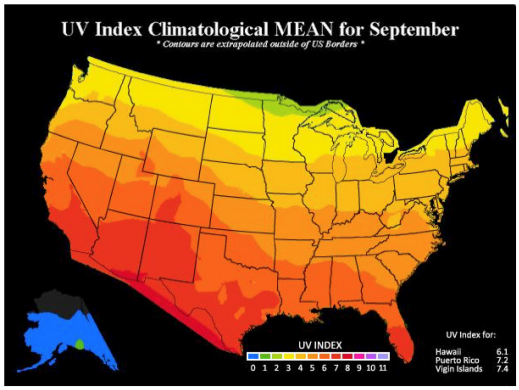

Figure 5

The Northern region of the United States is primarily yellow, light orange, and medium orange: colors that correspond to lower UV index numbers of 3-5. The Southern region is primarily medium orange, dark orange, and dark red: colors that correspond to high UV index numbers of 5-7.

deficiency was 42% (129:307). It was also concluded that the adolescents' serum 25-hydroxyvitamin D levels were lower during the winter season compared to the summer season. The percent of patients with deficiency during summer was 13%. Deficiency during fall was 15%, during winter 26%, and deficiency during spring was 20% (6).

Vitamin D influences immune cell regulation and differentiation (1). All immune cells have nuclear, ligand-dependent vitamin D receptors (3). The receptor's ligands include the vitamin D metabolite 1,25-dihydroxyvitamin D3. Once a vitamin D receptor binds to the metabolite, the receptor dimerizes with another receptor called retinoid X receptor (RXR). The dimer then translocates to the cell's nucleus and binds to DNA sequences called vitamin D response elements located in vitamin D-responsive genes. Vitamin D-responsive genes code proteins that are involved in a variety of biological responses such as the aforementioned processes of immune cell regulation and differentiation. The binding either turns the genes on or off, depending on the needs of the cell. The amount of metabolite available impacts the activity of the vitamin D receptor and influences immune cells (8). Without the vitamin D metabolite, the vitamin D receptor cannot be converted into a functionally active protein, and the cell loses an important mechanism for influencing immune cell regulation and differentiation. This loss of function can contribute to MS development.

Vitamin D affects all immune cells like T cells and B cells because all immune cells have vitamin D receptors. T cells help defend the body against foreign invaders like bacteria, viruses, and parasites. When vitamin D is absent, vitamin D receptors remain inactive and cannot be involved in immune cell regulation and differentiation. Specifically, when the receptor is inactive it cannot contribute to the development of T regulatory cells: cells which regulate the activity of T cells. When T cells are deregulated they can remain chronically active, leading to an overactive immune system and immune-mediated diseases such as MS (3).

In a study involving vitamin D and T cells, researchers concluded that the pathway triggered from the binding of vitamin D to the vitamin D receptor may prime T cells to fight infection. During the study, researchers introduced T cells to foreign molecules. They observed that T cells with the vitamin D receptor multiplied faster and produced more chemicals (e.g. phospholipase C-gamma 1) required for the immune response when compared to T cells that lacked the receptor (12). Since vitamin D influences the immune system and if deficient can lead to an overactive immune response, it may also induce the development of MS. In a study conducted on 132 Hispanic patients with

with MS, patients were separated into cohorts based on disease status. Their levels of the vitamin D metabolite 1,25-dihydroxyvitami were measured. Fifty-eight patients with a type of MS called relapsing-remitting MS (RRMS) were studied during remission, 34 patients with RRMS during relapse, and 40 patients with a type of MS called primary progressive MS (PPMS). A control group consisted of 60 healthy individuals. The control group and and the MS patients shared a similar place of residence, race/ethnicity, age, and gender, limiting the variables in the study. The RRMS patients had lower levels of the metabolite when compared to the control group. The relapse patients had the lowest levels of the metabolite of all. The PPMS patients and the control group, however, had similar levels. While the research study was not conducted in the U.S, the lower levels of the metabolite found in the first two groups of patients may support the possible relationship between vitamin D and MS and the idea that lower levels of vitamin D may contribute to MS development (4).

Dr. Ascherio of the Harvard School of Public Health and his team of researchers led a study with the goal of understanding how an individual's vitamin D status early in the disease process influences the long-term course of the disease. During the study, researchers measured levels of the vitamin D metabolite 1,25-dihydroxyvitami in the blood of 468 patients. Measurements were made at baseline, 6, 12, and 24 months. Additionally, physicians conducted standardized neurological evaluations on the patients to aid the researchers in understanding MS activity and progression. The evaluations provided insight into changes in brain volume and lesions—areas of myelin damage. It was observed that patients with higher levels of the vitamin D metabolite had few T2 lesions—seen as white spots on the brain when observed through magnetic resonance imaging (MRI) which serves as a diagnostic tool for MS. They also had higher brain volume which is promising considering that individuals with MS can experience a loss of brain volume due to tissue damage. The study also revealed that individuals who initially had higher levels of the vitamin D metabolite in their bloodstream during disease onset had more positive outcomes at their 5-year follow-up (2). This possible inverse relationship between blood concentrations of vitamin D metabolite and disease progression alludes to a connection between the disease and vitamin D.

Professors of neurology John W. Rose, Maria Houtchens, and Sharon G. Lynch mapped the higher incidence of the disease found at higher latitudes (see fig. 6). The dark red color on the map represents high risk for the disease. The color borders the 37th parallel of the United States and extends upward. According to figures 3-5,

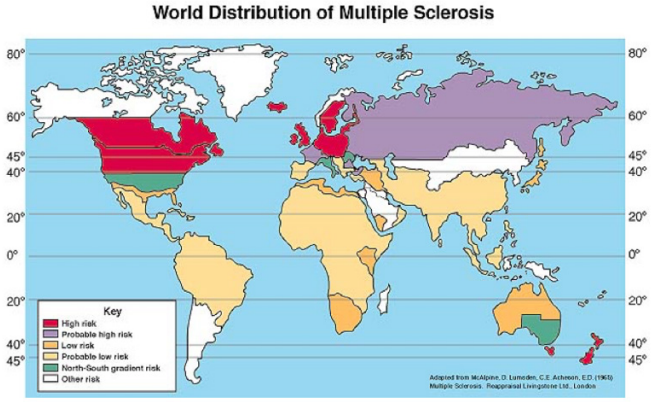

Figure 6

this area is associated with lower UV index values. Also, as discussed earlier, individuals in the United States who live above the 37th parallel (indicated in fig. 2) make little to no vitamin D during non-summer months. As a result, they are at a greater risk for vitamin D deficiency (13).

Using the information (reflected in fig. 1) on the prevalence of multiple sclerosis in the United States from 2008-2012 (5), the 2012 UV index values associated with major cities in the United States for the month of January (18) and a geographic information system, we generated the following map (fig. 7). The 37th parallel is also drawn on the map, marking the boundary between locations that enable individuals to synthesize vitamin D and those that impede its synthesis (17). Other than the fact that it is a winter month and is therefore associated with limited sunlight exposure, and may therefore reflect a more dramatic relationship between sunlight exposure, vitamin D deficiency, and MS prevalence, the month of January was arbitrarily chosen. The map shows that blue circles (representative of UV index values of 1) and black stars (representative of UV index values of 1.5) are concentrated in Northern United States and also above the 37th parallel. This region receives limited sunlight, making vitamin D difficult for the skin to synthesize. This region is also associated with darker pinks, marking a higher prevalence of MS. The map also shows that red circles (representative of UV index values that are >3) and black balloons (representative of UV index values of 3) are concentrated in Southern United States. They are also below the 37th parallel. This region receives more sunlight exposure than the Northern region, so vitamin D is easier for the skin to synthesize. This region is also associated with lighter pinks, marking a smaller prevalence of MS.

The focus of our research was on the relationship between sunlight exposure differentials of the United State's North and South and incidence of multiple sclerosis.

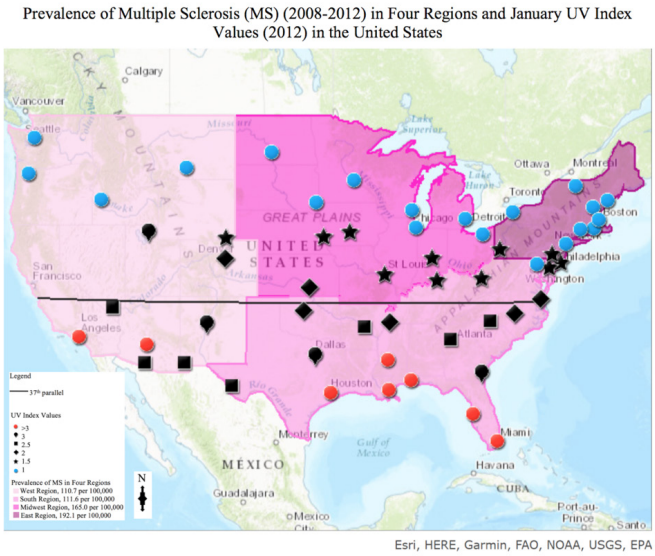

Figure 7

People located at high latitudes in the country generally have less sun exposure compared to individuals living in the South as evidenced by the lower UV index values associated with northern states and the higher UV index values of southern states. If individuals don't receive sufficient amounts of vitamin D through exposure to sunlight and fail to make up the deficiency through diet, they will be at risk for vitamin D deficiency. Vitamin D is instrumental in biological harmony as it plays a role in successful immune system function. Therefore, if vitamin D receptors that are located on immune system cells receive inadequate amounts of vitamin D or none at all, immune cell regulation and differentiation will suffer. This may lead to the overproduction of immune cells which may generate an autoimmune response—an immune system unhinged and driven to destroying the myelin sheath of nerve cells, thus leading to a disease of the central nervous system. Namely: multiple sclerosis.

References

1). Arnson, Yoav, Howard Amital, and Yehuda Shoenfeld. "Vitamin D and Autoimmunity: New Aetiological and Therapeutic Considerations." Annals of Rheumatic Diseases 66.9 (2007): 1137-142. BMJ Publishing Group Ltd & European League Against Rheumatism. Web. 29 Mar. 2017.

2). Ascherior, Alberto, Kassandra L. Munger, and Rick White. "Vitamin D as an Early Predictor of Multiple Sclerosis Activity and Progression." Jama Neurology 71.3 (2014): 306-14. Web. 13 Mar. 2017.

3). Cantorna, Margherita, Lindsay Snyder, Yang-Ding Lin, and Linlin Yang. "Vitamin D and 1,25(OH)2D Regulation of T Cells." Nutrients 7.4 (2015): 3011-021. MPDI. Web. 26 Apr. 2017

4). Correale, J., M. C. Ysrraelit, and M. I. Gaitan. "Immunomodulatory Effects of Vitamin D in Multiple Sclerosis." Brain 132.5 (2009): 1146-160. Oxford University Press. Web.

5). Dilokthornsakul, P., RJ Valuck, KV Nair, RR Allen, and JD Campbell. "Multiple Sclerosis Prevalence in the United States Commercially Insured Population." Neurology 86.11 (2016): 1014-021. American Academy of Neurology. Web. 29 Mar. 2017.

6).Gordon, Catherine M., Kerrin C. Depeter, Henry A. Feldman, Estherann Grace, and S. Jean Emans. "Prevalence of Vitamin D Deficiency Among Healthy Adolescents." Archives of Pediatrics & Adolescent Medicine 158.6 (2004): 531-37. American Medical Association. Web. 29 Mar. 2017.

7). Holick, MF. "Sunlight and Vitamin D for Bone Health and Prevention of Autoimmune Diseases, Cancers, and Cardiovascular Disease." The American Journal of Clinical Nutrition 80.6 (2004): n. pag. The American Society for Nutrition. Web. 28 Apr. 2017.

8). Kongsbak, Martin, Trine Levring, Carsten Geisler, and Marina Rode Von Essen. "The Vitamin D Receptor and T Cell Function." Frontiers in Immunology 4.148 (2013): n. pag. Frontiers Media. Web. 26 Apr. 2017

9). Mayo Clinic Staff Print. "Multiple Sclerosis." Mayo Clinic. Mayo Foundation for Medical Education and Research, 01 Oct. 2015. Web. 13 Mar. 2017.

10). Nair, Rathish, and Arun Maseeh. "Vitamin D: The 'sunshine' Vitamin." Journal of Pharmacology & Pharmacotherapeutics 3.2 (2012): 118–126. PMC. Web. 14 Mar. 2017.

11). Noonan, C. W., S. J. Kathman, and M. C. White. "Prevalence Estimates for MS in the United States and Evidence of an Increasing Trend for Women." Neurology 58.1 (2002): 136-38. American Academy of Neurology. Web. 16 Mar. 2017.

12). Rode Von Essen, Marina, Martin Kongsbak, Peter Schjerling, Klaus Olgaard, Niels Ødum, and Carsten Geisler. "Vitamin D Controls T Cell Antigen Receptor Signaling and Activation of Human T Cells." Nature Immunolo-

gy 11 (2010): 344-49. Macmillan Publishers Limited. Web. 29 Mar. 2017.

13). Rose, John W., Maria Houtchens, and Sharon G. Lynch. "Lectures: Epidemiology and Prevalence." Multiple Sclerosis: Epidemiology and Prevalence. University of Utah, n.d. Web. 28 Apr. 2017.

14). "Serum 25-hydroxyvitamin D Is a Reliable Indicator of Vitamin D Status." The American Journal of Clinical Nutrition 94.2 (2011): 619-20. The American Society for Nutrition. Web. 28 Apr. 2017.

15). "Sun Safety Monthly Average UV Index." EPA. Environmental Protection Agency, 14 Oct. 2016. Web. 28 Apr. 2017