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BD Beretich and TM Beretich

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Explaining multiple sclerosis prevalence by ultraviolet exposure: a geospatial analysis

BD Beretich¹ and TM Beretich²

Background Epidemiologic studies have shown a positive correlation of multiple sclerosis (MS) prevalence with latitude. However, there has not been a causal association found. Increased dietary intake and increased serum levels of vitamin D showed to be protective for the development of MS. Ultraviolet (UV) radiation plays an important role in vitamin D synthesis and could potentially explain both latitude differences in MS prevalence and the low levels of vitamin D in individuals with MS.

Objective To evaluate the relationship between UV radiation and MS prevalence using geospatial analysis.

Methods Geospatial analysis was performed on North American regions and separately for the continental United States. The correlation of UV radiation (measured as UV index [UVI]) versus MS prevalence and UV radiation versus case-control ratios was calculated. In addition, the relative risk (RR) of MS was determined for regions/states with low UV radiation exposure.

Results Case-control ratios by US state and MS prevalence by North American region showed a strong negative (inverse) correlation with UVI ($R = -0.72$ and -0.86 , respectively). The RR for the five highest risk states/lowest UVI versus the five lowest risk states/highest UVI was increased ($RR = 1.8$ – 5.4). The RR for MS, when comparing North American regions with lowest and highest UVI, was 3.78 and within US regions was 1.52.

Conclusion This analysis suggests a strong association between UV radiation and MS distribution, and an increase in risk for MS in those areas with a low UVI. *Multiple Sclerosis* 2009; 15: 891–898. <http://msj.sagepub.com>

Key words: epidemiology; geography; multiple sclerosis; prevalence; ultraviolet rays; sunlight; vitamin D

Introduction

Multiple sclerosis (MS) is an idiopathic inflammatory demyelinating disease of the central nervous system with incidence reaching a peak between the ages of 25 and 35 years. The etiology of MS is not definitely known, but it is thought that the cause could be infectious, environmental, or behavioral (lifestyle) factors in genetically susceptible persons [1–3].

In several studies, observations have been made that there is an increase in incidence and prevalence of MS with latitude, both north and south of the equator [4–6]. Although several theories on possible causes of this prevalence-latitude gradient have been published [3,7,8], this gradient is still unexplained.

Occupation and residence in high-sunlight areas have been found to be associated with a lower MS mortality [9] and higher sun exposure during early life has been associated with decreased risk of MS [10]. Recent studies have implicated low dietary vitamin D intake and low serum levels of 25(OH)D with increased risk of developing MS [11,12]. One possible explanation for this is an antiproliferative effect and downregulation of inflammatory markers by the vitamin D active metabolite, 1,25-dihydroxyvitamin D (1,25(OH)₂D) [13]. 1,25(OH)₂D is an inhibitor of maturation of dendritic cells, T-cell proliferation, and activation and recruitment of T-helper (Th)1 cells [14]. For most individuals, the majority of vitamin D is derived from casual exposure to sunlight [15]. It is estimated that approximately 90–95% of vitamin D3 requirement

¹Multiple Sclerosis Center, University of Massachusetts, Worcester, MA, USA

²B.I. Laboratories, Shrewsbury, MA, USA

Correspondence to: Biljana Beretich, Multiple Sclerosis Center, University of Massachusetts Memorial Campus, 119 Belmont Street, Worcester, MA 01605, USA. Email: Biljana.Beretich@umassmemorial.org

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comes from exposure to the sun. Ultraviolet (UV) radiation in the 290–330 nm portion of the solar spectrum photolyzes 7-dehydrocholesterol in the human skin to previtamin D₃, which is then converted to vitamin D₃ by a thermal process [16].

The UV radiation (especially UVB) by itself has an immunosuppressive effect. It alters the number of antigen-presenting cells in the skin (Langerhans cells), causes systemic suppression of cell-mediated immunity (through the release of immunosuppressive cytokines), and alters delayed-type hypersensitivity [17–19].

Latitude gradient is unlikely to be an independent risk factor for MS. This study uses geospatial analysis to evaluate whether the variation in MS prevalence can be explained by the UV radiation gradient. If UV radiation is shown to have an effect on MS prevalence, this could be one of the modifiable risk factors for MS and become important in the development of new therapies.

Methods

We used prevalence data from the previously published studies on MS prevalence and on case-control ratios in the United States and Canada to conduct our geospatial analysis [4,20,21]. The study by Beck, *et al.* evaluated regional prevalence of MS in Canada based on the data from the Canadian Community Health Survey (CCSH) conducted in years 2000 and 2001. Prevalence was calculated for five Canadian regions: Atlantic, Quebec, Ontario, Prairies, and British Columbia [20]. The study by Noonan, *et al.* estimated the MS prevalence for four US regions (West, Midwest, Northeast, and South), and it used the National Health Interview Survey (NHIS) data, including years 1989–1994 [21]. Finally, the case-control ratios for residence at entry on active duty for white male veterans at the level of continental United States were obtained from a study by Kurtzke, *et al.* This study evaluated MS risk in 5305 World War II and Korean Conflict veterans [22]. The methodology was previously described in the original studies in detail. In the study by Lauer, which evaluated sociogeographic variables using the data from Kurtzke, *et al.* study, it was shown that out of all variables studied, latitude proved to have the highest correlation to MS case-control ratio (+0.836 Spearman's coefficient) [23].

The data on UV radiation measured as UV Index (UVI) were obtained from the National Oceanic and Atmospheric Administration (NOAA) and National Weather Service, Camp Springs, Maryland, and from the Meteorological Service of Canada, Toronto, Ontario. UVI (WHO 1994, 1998) has become the internationally accepted standard for disseminating information on solar UV levels. UVI is the

amount of skin-damaging UV radiation expected to reach the earth's surface at the time when the sun is highest in the sky. The amount of UV radiation reaching the surface is primarily related to the elevation of the sun in the sky, the amount of ozone in the stratosphere, and the amount of clouds present. The UVI can range from 0 (when it is night time) to 15 or 16 (in the tropics at high elevations under clear skies). The UV radiation is greatest when the sun is highest in the sky and rapidly decreases as the sun approaches the horizon. The higher the UVI, the greater the dose rate of skin-damaging (and eye damaging) UV radiation [24]. The NOAA/EPA UVI is computed using forecasted ozone data, a radiative transfer model, forecasted cloud amounts, climatological aerosol loading, variable snow and constant bare earth albedo, and elevation. A radiative transfer model (TUV) is used to determine the UV irradiances from 290 to 400 nm (UVA 290–315 nm and UVB 315–400 nm) using the time of day, day of year, and latitude. TUV is then weighted by the McKinlay–Diffey erythema action spectrum to reflect the human skin response to each wavelength. These weighted irradiances result in an erythema dose rate. This erythema dose rate is then adjusted for other variables (elevation, surface albedo, and tropospheric aerosol loading) to calculate a “clear sky” UVI. The forecast due to the presence of clouds is given from the ratio of down-welling UV band radiation at the surface with clouds versus without clouds, which gives the cloud transmission in the UV. This transmission ratio is then applied to the clear-sky forecast to provide the “cloudy sky” UV dose rate [25]. Canadian UVI is calculated from Brewer spectral UV measurements collected at 12 monitoring sites across Canada (we used data from 10 of those sites) [26].

UVI includes both UVA and UVB, but only UVB is essential for vitamin D synthesis. However, it has been shown that there is a strong correlation between the measured UVB and erythemally weighted UV ($r = 0.948$) [27].

Mean 10-year UVI was calculated (from Brewer spectrophotometer data) for 10 Canadian sites and mean 9-year UVIs of cloudy sky and clear sky were calculated (from satellite-derived UV irradiance data) for 58 continental US monitoring sites (1994–2003). Spatial trends in MS prevalence and UV radiation were computed and analyzed by region for North America (using Brewer UVI for Canadian regions and UV cloudy-sky index for US regions) and by state for the United States (using UVIs of cloudy sky and clear sky). Latitude–longitude coordinates were assigned to all the UV monitoring sites and mapped using size-graduating point markers based on the UVI (bigger point size, higher UVI). Two kinds of maps were generated for geospatial analysis of data. In the first map that shows

geospatial distribution of MS and UVI by United States, besides point mapping the UVI, we mapped also the case-control ratios by state using color-coding (darker shade, higher case-control ratios). In the second map, North American regions were color-coded based on MS prevalence (darker shade, higher MS prevalence).

Pearson's correlations between the two geospatial variables (case-control ratios/MS prevalence and UVI clear/cloudy sky) were evaluated and linear and nonlinear analyses were conducted. In addition to a regression and correlation analysis, a relative risk (RR) matrix was built to compare the five highest risk states and regions (lowest UV exposure) with the five lowest risk states and regions (highest UV exposure).

Results

Figure 1 shows the geospatial distribution of MS case-control ratios (white male veterans) and UVI for cloudy sky by United States. UVI ranged from 2.72 (Washington) to 6.38 (Florida) and the case-control ratios ranged ($\times 100$) from 42 to 225. An increasing south-to-north gradient is seen for MS and a decreasing south-to-north gradient is seen for the UVI. When the case-control ratio data were compared against UVI, the correlation coefficient was -0.716 . After linear regression was applied to the data, the regression model was as follows: MS case-control ratio = $-34.114 \times \text{UVI} + 251.61$ (Figure 2). Coefficient of determination was

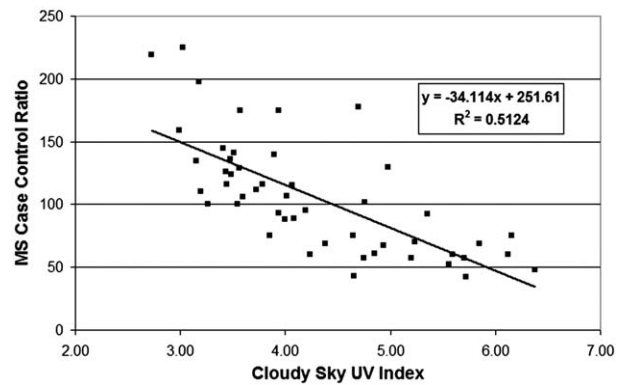


Figure 2 MS case-control ratio as a function of cloudy sky UVI (filled squares) fitted with linear regression line (continuous line). Continental US states.

$R^2 = 0.5124$. When the nonlinear (power type) model was applied to the same data, a stronger coefficient of determination ($R^2 = 0.6010$) was seen, as shown in Figure 3. Besides using cloudy-sky UVI, we evaluated the correlation between clear-sky UVI and case-control ratios. The clear-sky UVI yields a stronger correlation ($R = -0.78$, $R^2 = 0.61$) with MS distribution than that of the cloudy-sky UVI (Figure 4).

A matrix of the RR, shown in the Table 1, was built to compare each of the five highest risk states/lowest UVI (Washington, Oregon, Vermont, North Dakota, and Minnesota) with each of the five lowest risk states/highest UVI states (Florida, Arizona, New Mexico, Louisiana, and Alabama). All 25 possible combinations between the high- and

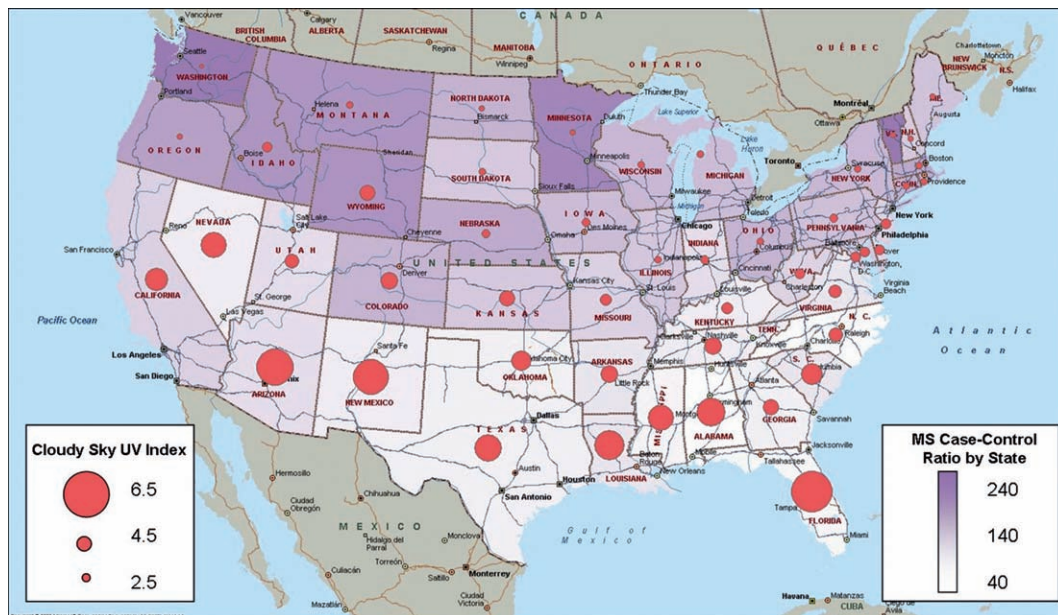


Figure 1 MS case-control ratio and UVI comparison map for continental US states.

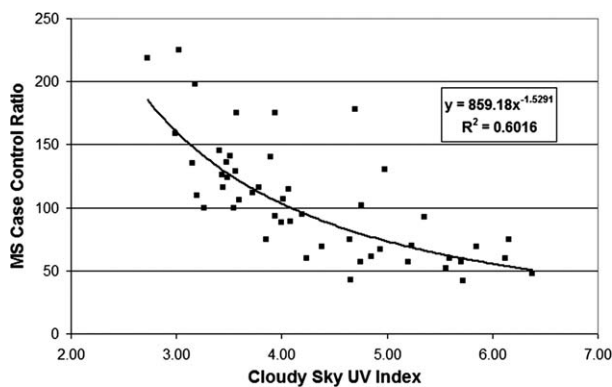


Figure 3 MS case-control ratio as a function of cloudy sky UVI (filled squares) fitted with non-linear regression line (continuous line). Continental US states.

low-risk states gave RR greater than 1, with the lowest being 1.8 (95% CI, 1.4–2.4) or an 80% increased risk for MS, and the highest being 5.4 (95% CI, 3.9–7.4) or a 440% increased risk for MS.

Figure 5 shows geospatial distribution of MS prevalence and cloudy-sky UVI by North American regions. The MS prevalence ranged from 63.5 in the South US region to 350 in the Atlantic region of Canada. Lowest yearly mean UVI was 1.45 in British Columbia and highest was 4.92 in the South US region. Similarly as in Figure 1, a north-to-south gradient can be visualized in Figure 5, with MS prevalence decreasing towards the south, and UVI decreasing towards the north. A strong inverse correlation between cloudy-sky UVI and MS prevalence, ($R = -0.86$, $R^2 = 0.72$) was found by linear regression (Figure 6). Nonlinear regression analysis of the cloudy-sky UVI data versus MS prevalence resulted in a coefficient of determination $R^2 = 0.89$ (Figure 7).

The RR of MS between the region with the lowest UVI/highest risk (British Columbia) and the region with the highest UVI/lowest risk (Southern United

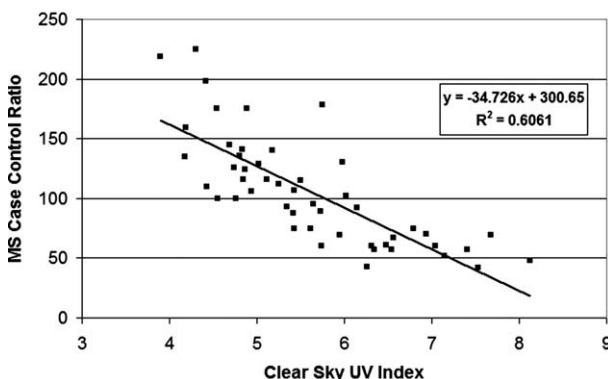


Figure 4 MS case-control ratio as a function of clear sky UVI (filled squares) fitted with linear regression line (continuous line). Continental US states.

States) was 3.78 (95% CI, 2.86–4.96). When analyzed only at the level of the US regions, RR of MS in the Northeast United States versus Southern United States was 1.52 (95% CI, 1.11–2.09).

Discussion

Both of our geospatial analyses, by United States and by North American region, have shown an inverse gradient and a strong inverse or negative correlation between MS distribution and UVI. This correlation was stronger for clear-sky UVI than for cloudy-sky UVI. Also, the correlation calculated using nonlinear regression was stronger than the one derived from linear regression. In this study, we showed that MS prevalence (as well as case-control ratios) at both the level of the North American regions and the level of United States follows a significant north-to-south trend, and that there is a strong inverse relationship to UV radiation measured as UVI.

Though there have been studies showing latitudinal increase of MS incidence and prevalence [4–6], only a limited number of studies tried to explain this phenomenon [28–30]. One study [29], evaluating the relationship of UV radiation and MS in Newfoundland and Labrador, Canada, found significant negative correlation of erythemal UVB and MS risk for place of residence at age one, less significant correlation for first 10 years of life, and no correlation for place of residence at age (31 years in average) when the first symptoms occurred. In another study, a strong negative correlation was found between MS prevalence and UV radiation in Australia [28]. Finally, Ebers in his review of environmental factors and MS [30], using the French farmers' prevalence study [31], shows the amount of winter sunlight visually paralleling MS prevalence. The incidence of MS seems to decrease in individuals migrating from a high-risk to a low-risk area, more so if migration occurs in childhood [32]. In our study, we used two types of MS distribution: case-control ratios from Kurtzke, *et al.* study and MS prevalence from Beck, *et al.* and Noonan, *et al.* studies. The case-control ratios by United States were mapped by residence at entry on active duty, which likely includes young people at the age of approximately 18 (data on the age of the case-control subjects were not provided in the original study). Kurtzke, *et al.* in their study [22] noted that the analysis by place of birth was virtually identical to that of residence at entry in active duty. This would mean that we found a significant negative correlation of case-control ratios and UV radiation up to the age of 18. Similarly, when we looked at the studies from the Canadian and US region prevalences, which were cross sectional, used surveys

Table 1 A matrix of the RR of MS in each of the lowest cloudy-sky UVI states calculated against each of the highest cloudy-sky UVI states

MS case-control ratio		Five states with highest cloudy-sky UVI				
		48 (Florida)	75 (Arizona)	60 (New Mexico)	69 (Louisiana)	42 (Alabama)
5 states with lowest cloudy-sky UVI	219 (Washington)	4.6	2.9	3.7	3.2	5.2
	159 (Oregon)	3.3	2.1	2.7	2.3	3.8
	225 (Vermont)	4.7	3.0	3.8	3.3	5.4
	135 (North Dakota)	2.8	1.8	2.3	2.0	3.2
	198 (Minnesota)	4.1	2.6	3.3	2.9	4.7

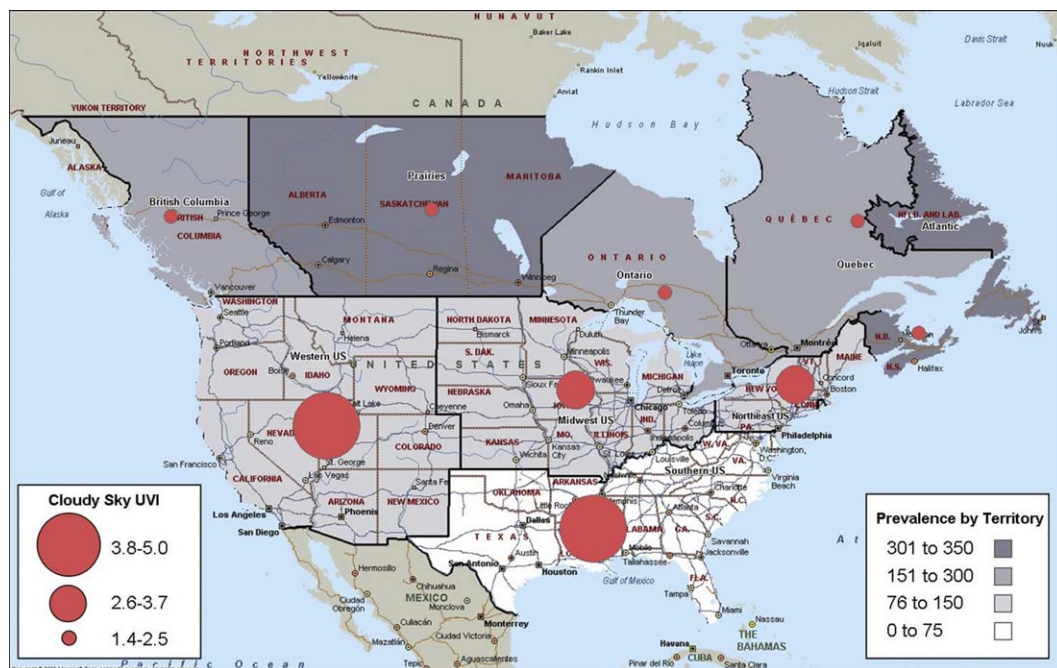
RR, relative risk; MS, multiple sclerosis; UVI, ultraviolet index.
RR values are italicized.

and included people diagnosed with MS of all ages (all subjects were age 18+ in the Canadian study, and 98% of all subjects in the United States by region study were age 30+), we also saw a strong negative correlation with UV radiation. Thus, our analysis shows that this strong correlation is not limited to the young of age, as was the case in the study by Sloka, *et al.* [29].

Our analysis of RR of those exposed to low UV radiation versus those exposed to high UV radiation in both models showed increased RR for development of MS, RR = 1.5–5.4. In the model using MS prevalence derived from two different studies and two likely different methodologies (Canadian and US regions), as a control, we calculated not only RRs between North American regions of lowest and highest UV exposure but also between US regions with the lowest and the highest UV expo-

sure. The RR was still above 1.0 (RR = 1.52 with 95% CI, 1.11–2.09).

These findings could have several possible explanations. The UV radiation has an immunosuppressive effect not only locally to the skin but also systemically. The epidermal Langerhans cells (antigen-presenting cells), within hours of UVB exposure, fail to stimulate Th1 cells but preferentially activate Th2 cells, resulting in increased generation of suppressor T cells [17,18]. However, prolonged exposure to UV radiation causes antigen-specific suppressor cell induction [19]. This form of immunosuppression involves soluble mediators such as interleukins IL-1 β , IL-10, IL-12, and tumor necrosis factor (TNF)- α , and it has systemic effects through suppression of Th1 cell function and preferential Th2 activation [17,19]. Another explanation of the role of UV radiation in the development of MS could be

**Figure 5** MS prevalence and UVI comparison map for North American regions.

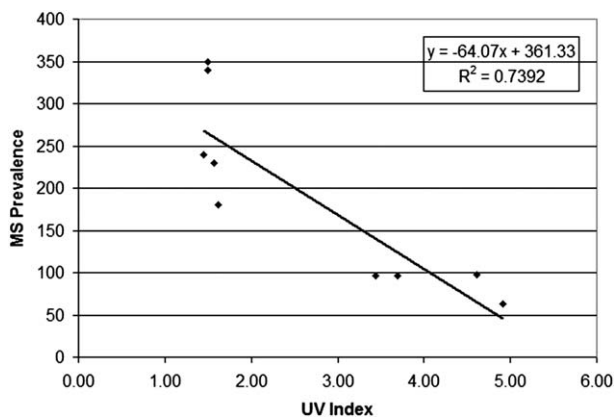


Figure 6 MS prevalence by region as a function of cloudy sky UVI (filled squares) fitted with linear regression line (continuous line).

through an indirect effect of UV radiation. The UV radiation is necessary for synthesis of vitamin D3 in the skin, and this synthesis covers more than 90% of requirements for vitamin D [5,16]. Active metabolite of vitamin D is 1,25(OH)2D, which, in addition to other functions, has a direct immunosuppressive effect on dendritic cells, reduces IL-12 production, IL-12-mediated Th1 response, and Th1-type cytokine production [interferon (IFN) γ and IL-2]. It also promotes Th2-type function and causes inhibition of pro-inflammatory cytokines such as IL-1 α , IL-1 β , and TNF- α [33].

Although we found a strong association between UV radiation, measured as UVI, and MS prevalence, a note should be made about some of the limitations of our study. One of these is the error rate traditionally found in UVI forecasting (10–15%) and the difference in UVI measurements between Canadian and US Meteorological services. There is a systematic difference between the satellite-derived UV

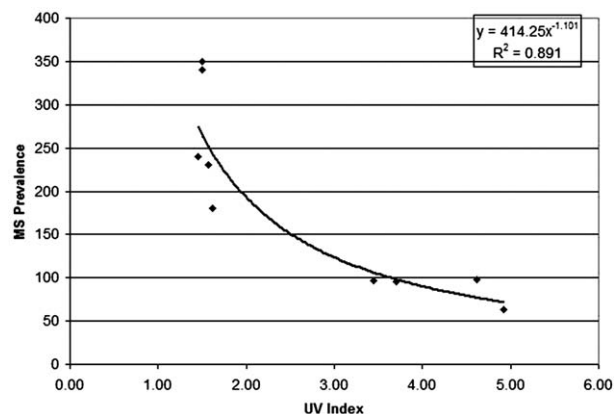


Figure 7 MS prevalence by region as a function of cloudy sky UVI (filled squares) fitted with nonlinear regression line (continuous line).

irradiance and Brewer measurements of approximately 10% (UVI estimates of United States are satellite based and Canadian are ground, Brewer spectrophotometer based). The difference is probably related to aerosol and pollution effects in the lower troposphere that are not currently detected from space [34]. These differences are likely lost when UVIs are averaged over a 9–10-year period, as we did in our study.

Another limitation is the reliability of MS prevalence data. These data were obtained from studies using cross-sectional surveys to calculate the prevalence. This methodology can introduce a sampling bias. Canadian regional prevalence data compared with the US regional data are much higher, and one possible explanation for this could be the different time period when these studies were conducted (2000/2001 vs 1989–1994). This could be possibly explained by the trend of increasing incidence and prevalence of MS observed over time [21,35–37]. These trends could be a function of many factors including changes in diagnostic criteria, improved access to health care, climate changes, changes in dietary habits, occupational shifts in the population, urbanization, and so on. There are other regional studies on MS prevalence that may be considered more preferable for inclusion in this analysis, such as several Canadian studies [35,38–41]; however, they all use different methodologies. Specifically, these studies ranged over a broad time period and prevalence figures were calculated in the earliest example (British Columbia) in 1982 [38] and in the latest study (Saskatchewan) in 2005 [41]. In addition, three of these studies included provincial data [35,38,40], whereas two were each limited to one urban area [39,41]. Among the five studies in question, different diagnostic criteria were used including Schumacher for earlier studies [38,39], Poser [40] or MacDonald [41] for later studies, or different combinations thereof [41]. Some studies included cases of definite and probable [38,39,41] or only definite MS [40], whereas another study relied on ICD 9 cm code 340 – a billing code taken from the Alberta Health Care Insurance Plan Billing records and not from physician records [35]. The authors think that these differences in methodology among the above-mentioned studies could introduce an unreasonable amount of bias in the current study.

One more unavoidable limitation is the paucity of data, which allows us to also differentiate prevalence rates between the sexes from a UV exposure standpoint. Two out of the three studies [20,22] that we used for prevalence data did not have prevalence available by gender, and one study – Kurtzke's [22] used case-control ratio by state for male gender only. However, Kurtzke did show in his study that there was an increasing case-control

ratio gradient over three geographic tiers (south, middle, north) for both males and females. Some studies have also shown that there is an increase in the female to male sex ratio over time [35–37]. Although, as we mentioned earlier, we cannot evaluate this increase based on our studies, changes in environmental and lifestyle factors as well as genetic and physiological factors could be the cause for this trend.

MS prevalence studies used in this study (North American analysis) involve large regions, some of these covering whole north to south territories of the United States (e.g., western region) or Canada (the case with all regions), which made our analysis more complicated and less likely to find a difference in the risk between low and high UV radiation. This was the main reason for use of both Canadian and US prevalence for analysis. Even so, the subanalysis within the Northeastern and Southern US regions showed a significant difference in the risk of developing MS in the region with a lower UV exposure.

Latitude has shown to be correlated with MS incidence and prevalence, but it is unlikely to be an independent factor in causality of MS. Latitude (and longitude) is a method of locating geographical positions on the earth and belongs to a category of so-called “grab bag” variables that is not able to explain the etiology of diseases [42]. Solar insolation (of which UV radiation is a component) is primarily a trigonometric function of the solar zenith angle (Solar Flux density $\times$ cosine (solar zenith angle)) [43]. The solar zenith angle is in turn a trigonometric function of time, date, and latitude [44]. There are other potential explanations for the MS/latitude correlation, such as genetics, infectious agents, and nutrition, though, again, it seems unlikely that any of these factors by itself influences latitude-associated risk of MS, especially when it has been shown that this risk changes with migrations [4,32,45]. The UV radiation exposure may play an important role in causality of latitude-dependent MS distribution, and as mentioned above, the two are related mathematically via the solar zenith angle. The UV radiation, as a crucial step in vitamin D synthesis, could be the link between low vitamin D levels and higher MS risk. We can see the possible link between vitamin D intake and MS risk in the Norway study of Kampman, *et al.* [10]. Although in their study increased prevalence was not found to be associated with latitude, it was found to be associated either with higher summertime outdoor activity (a possible cofounder with cumulative UV exposure which is a source of vitamin D) or with high intake of fish or high intake of cod liver oil supplements (also vitamin D sources).

New approaches in reporting and tracking of MS are necessary for epidemiological studies of this type, as survey-based studies and voluntary regis-

tries are often biased and unreliable. If this study is confirmed by further research, it could help better understand the etiology of MS and eventually lead towards the development of new treatments.

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