MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Temperature dependence of multiple sclerosis mortality rates in the United States

Multiple Sclerosis Journal

1–8

DOI: 10.1177/1352458516688954

Hongbing Sun

Correspondence to:
H Sun
Center for Healthcare Studies, GEMS Department, Rider University, 2083 Lawrenceville Road, Lawrenceville, NJ 08648, USA.
hsun@rider.edu

Hongbing Sun
Center for Healthcare Studies, GEMS Department, Rider University, Lawrenceville, NJ, USA

Abstract

Background: It is well known that multiple sclerosis (MS) patients are very sensitive to heat events. However, how MS patients respond to the significant temperature difference between the high- and low-latitude regions is not understood.

Objective: The goal is to identify the primary factor responsible for the fact that MS mortality rates of the United States is more than three times higher in the northern states than in the southern states.

Methods: Correlation coefficients between the age-adjusted mortality rate of MS as the underlying cause of death and the state average temperature, altitude, latitude, duration of sunshine hours, and solar radiation in the 48 contiguous states were compared.

Results: MS mortality rates correlate significantly and inversely with temperatures in the 48 states (correlation coefficient $r = -0.812$ and significance $p = 0.00$). Durations of sunshine hours and solar radiation do not correlate significantly with MS mortality rates ($r = -0.245$, -0.14, and $p = 0.101$, 0.342, respectively).

Conclusion: High environmental temperature is the primary reason for the low MS mortality rates and likely the low MS prevalence in low-latitude regions. Implication of the study result is that benefits of long-term heat acclimation through gradual and prolonged exposure to environmental heat for MS patients may be greatly underappreciated.

Keywords: Multiple sclerosis, temperature dependence, solar radiation, vitamin D, heat acclimation

Date received: 13 July 2016; revised: 15 December 2016; accepted: 20 December 2016

Introduction

One of the famous early observations regarding the geographical distribution of multiple sclerosis (MS) is the significant inverse (negative) correlation between the MS incidence rates and average annual hours of sunshine and average solar radiation in December at birthplaces among the US veterans.[1] Since then, inverse correlation between MS incidence–prevalence rates and latitudes was reported in many places, including the United States, Australia, and European countries.[2–7] Studies of population migration also indicate that individuals moving from areas of low risk to areas of high risk, particularly before the age of 15 years, can have similar incidence frequency as those populations of adopted countries.[8] This relation is the so-called latitudinal gradient of MS incidence and prevalence.[9,10] The popular explanation is that low MS prevalence rates in lower latitude regions may be related to the longer duration of sunshine and the associated high vitamin D production in people of these regions.[1,9,11] There is ample evidence supporting the beneficial effect of vitamin D for MS patients.[12–15] However, two recent review articles disputed the significance of the association between vitamin D deficiency and MS prevalence because the evidence for vitamin D had large heterogeneities.[9,16] MS is a serious disease with an average annual deaths of 3642 (MS as the underlying cause of death) between 1999 and 2014 in the Unites States alone according to the database of Centers for Disease Control and Prevention (CDC). If the latitudinal gradient of MS prevalence cannot be satisfactorily explained by the association with vitamin D levels, then what can explain it?

Ever since Uhthoff's[17] phenomenon was reported and a hot bath test was used as a mean of diagnosing MS,[18] the heat reaction by people with MS has been fascinating to the MS community.[19] Although Uhthoff's test was discontinued after 1983 by more accurate diagnostic methods, significant data on the heat reaction of MS patients have been accumulated.[20]

It has been reported that short-term exposure to elevated environmental heat could result in visual impairment, fatigue, motor disability, and deterioration of certain neural conditions in MS patients, although most of these negative effects have been reported to be transitory.[19–22] Recently, studies also reported that MS patients tend to have higher body temperatures than those of healthy people, that is, heat reaction in MS patients can be endogeneous.[23,24] It is apparent that most MS patients have a strong reaction to changes in the environmental temperatures.[19,20,25,26] Then, how do MS patients respond to the significant temperature differences between the high- and low-latitude regions?

Hence, the aim of this study is to examine whether temperature is the main underlying factor responsible for the fact that MS mortality rates in the northern states of the United States is more than three times higher than that in the southern states and the likely fact that MS prevalence is higher in the northern states than in the southern states. Because MS prevalence/incidence rates are only available for subpopulation groups in the United States, age-adjusted rates of the 55,129 mortalities with MS as the underlying cause of death between 1999 and 2014 in the 48 states will be main MS data set used in this study.

Data

Age-adjusted mortality rates for MS (AAMR-MS) as the underlying cause of death between 1999 and 2014 for the lower 48 states of United States were obtained from the CDC WONDER database (http://wonder.cdc.gov) where MS has the code G35 following the 10th Revision of the International Classification of Diseases. Mortality rates in the CDC database were from the death certificates of US residents, and each death certificate identifies a single underlying cause of death and demographic data. The underlying cause of death in the CDC database is defined as "the disease or injury which initiated the train of events leading directly to death." Age-adjusted rates in the CDC database were calculated by applying the age-specific rates of various populations to a single standard population.[27] Populations of 2007 (or a specific year) for the general population and corresponding genders (if male or female, age-adjusted mortality rates is desired) were selected as their corresponding standard populations to calculate their respective annual AAMR-MS between 1999 and 2014.

The annual average maximum and minimum air temperatures from 1219 stations between 1999 and 2014 were obtained directly from the United States Historical Climatology Network (http://cdiac.ornl.gov/epubs/ndp/ushcn/ushcn.html). The state annual average of maximum and minimum temperature was calculated utilizing the data from all stations that geographically fall in a state and will be referred to as the state average annual temperature or average temperature hereafter. The corroborating state average temperature data were also obtained from https://www.currentresults.com/Weather/US/average-annual-state-temperatures.php. The average altitudes of the 48 states were obtained from https://simple.wikipedia.org/wiki/List_of_U.S._states_by_elevation. The corroborating state average altitudes were calculated from the arithmetic mean of the altitudes of 1219 stations that fall in each state. Inclusion of the altitude data is because the altitude is a significant controlling factor for the sunlight hour, temperature, and solar radiation in a region. Given the same latitude, regions of high altitude tend to have lower temperature, more sunshine hours, and higher solar radiation. The average latitudes of the 48 states were obtained from the averaged latitudes of the 1219 temperature stations that fall in each state. The state average duration of the sunshine hours was obtained from https://www.currentresults.com/Weather/US/average-annual-state-sunshine.php. The corroborating maximum daylight hours in comparable latitudes were obtained from a United Nation's report.[28] Annual state average solar radiation between 1998 and 2010 was obtained from the national renewable energy website which was generated using the State University of New York/Albany satellite radiation model (http://www.nrel.gov/gis/data_solar.html).

Methods

Isopleth maps

An isopleth map of the AAMR-MS of the 48 contiguous states was plotted using the inverse distance weighted (IDW) interpolation method to reduce the effect of a sharp state boundary for spatial analysis in ArcGIS (ESRI software). An isopleth map of state average annual temperature for the 48 states was also plotted using the same method.

Slopes of the regression lines of the AAMR-MS of the 48 states versus years were calculated between 1999 and 2014. These slopes represent the growth or reduction rates of AAMR-MS of a state between 1999 and 2014. Slopes of the regression lines of annual average temperatures between 1999 and 2014 were calculated for each of the 48 states as well. They represent the temperature rise or decline of a state between 1999 and 2014. Isopleth maps of the two regression slopes

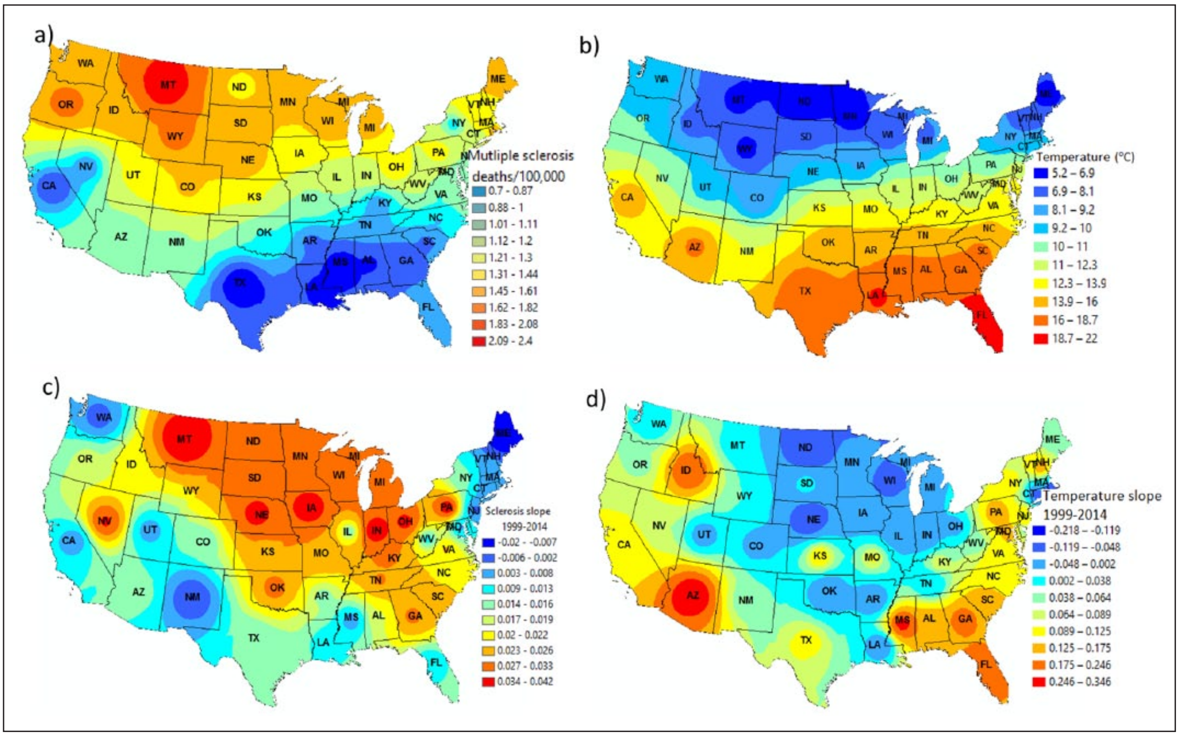

Figure 1. Isopleth maps of (a) state average annual age-adjusted MS mortality rates of all races and genders and (b) state average annual maximum and minimum temperatures and (c) the regression slopes of state average annual age-adjusted MS mortality rates and (d) the regression slopes of state average annual maximum and minimum temperatures between 1999 and 2014. The correlations between isopleth maps of (a) and (b) and (c) and (d) are $r = -0.899$, -0.403, respectively. For (c) and (d), high slopes reflect the high growth rates of MS mortality and fast rises of temperature, respectively.

were plotted. Pearson's correlation coefficients were calculated between the two pairs of isopleth maps using the Band Collection Statistics tool in ArcGIS.

Statistical correlations and regression models

Pearson's correlation coefficients and their significance levels were calculated between the MS mortality rates (represented by AAMR-MS) and state annual average temperatures, sunshine hours, latitudes, and altitudes. The correlation was also calculated between the regression slopes of MS mortality rates and temperatures between 1999 and 2014. Because the skewnesses of data for all parameters except for the state annual average sunshine hours are smaller than the two standard errors of their corresponding skewness, non-parametric Kendall's tau-*b* tests were only shown for correlations related to the sunshine hours to corroborate results from Pearson's correlation. Stepwise multivariate linear regression models were analyzed using the age-adjusted MS mortality rates as the dependent variable and the average state temperature, solar radiation, sunlight hour (potential proxy for vitamin D level), and altitudes as predictors. Latitude was not considered as a predictor in the model because it is likely to be a proxy for the physical factor temperature (correlation between temperature and latitude is −0.94 with a significance level of 0.00). Both the correlation coefficients and model parameters were calculated using the SPSS software.

Results

Similarity between isopleth maps

Regions of high MS mortality rates in the northern United States apparently correlate to regions of low temperatures, and regions of low MS mortality rates in southern United States correlate to regions of high temperatures (Figure 1(a) and (b)) with Pearson's correlation coefficient $r = -0.899$ and significance level $p = 0.00$. Notice the match between isopleth lines of MS mortality rates and temperatures for the states of Montana (MT), Wyoming (WY), and Colorado (CO). Isopleth lines of the MS mortality rates follow the temperature lines instead of the latitude lines in these states.

In addition, the faster average temperature rises shown in the isopleth map (Figure 1(d)) are along the coastal states between 1999 and 2014. These states are also the states with slower increase in MS mortality rates during this period. Pearson's correlation coefficient between isopleth maps of the AAMR-MS slopes and temperature slopes is −0.403 with a $p=0.00$.

Statistics, correlations, and model results

A total of 55,129 deaths were attributed to MS as the underlying cause of death in the 48 contiguous states in the CDC database between 1999 and 2014. Of the 55,129 deaths, 48,860 are Whites, 36,342 are female, and 18,787 are male. District of Columbia (DC) was excluded from the statistics of the 48 states because DC's data were suppressed in multiple years in the CDC database. White constitutes 88.6% of the total mortalities in the 48 states. The age-adjusted MS mortality rate of female is 1.93 times that of male during this period. The increase in the age-adjusted MS mortality rates (Figure 2) between 1999 and 2014 is likely the combination result of multiple factors. These factors include the increased survival rates for comorbid diseases[29,30] (such as heart disease and breast cancers etc.), the significant advancement in MS diagnoses,[31] as well as the net change of mortality rates resulted from the reduced temperature variations (as a result of temperature control) in the living environment in the 48 states.

Correlation between the data of state average MS mortality rates and the state average latitudes and correlation between the MS mortality rates and temperatures are significantly negative for all races ($r=-0.815$, -0.812, $p=0.0$, 0.0, respectively, Table 1). The significant inverse (or negative) correlations also exist between age-adjusted female and male mortality rates and temperature. The coefficient is considered statistically significant in this study only when the significance level (p) is <0.05. On the contrary, the MS mortality rates and the average annual sunshine hours have an inverse, but statistically insignificant correlation ($r=-0.245$, $p=0.101$). The correlation between MS mortality rates and solar radiations is also statistically insignificant ($r=-0.14$, $p=0.342$). The MS mortality rates are significantly positively correlated with the altitudes of the 48 states ($r=0.297$, $p=0.04$). Also, notice the significant positive correlations between the altitudes and sunshine hours ($r=0.647$, $p=0.00$) and the significant inverse (negative) correlation between the temperatures and the latitudes ($r=-0.94$, $p=0.00$) and between the temperatures and the altitudes ($r=-0.291$, $p=0.045$). Gender differences are not significant in correlations of MS mortality rates with other parameters except for the altitudes. The differences in the correlation coefficients were only in the second or third digits when a corroborating data set (mentioned in the "Data" section) was used and they are not statistically significant.

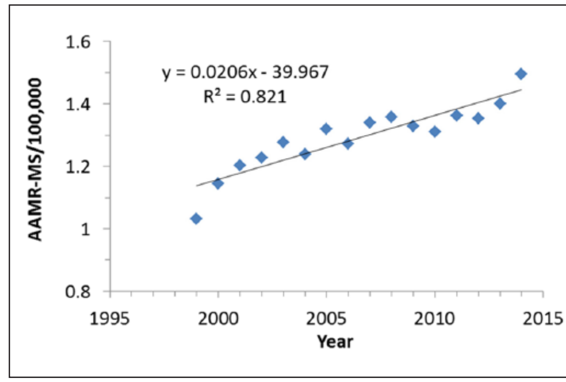

Figure 2. Regression plot of average age-adjusted MS mortality rates (AAMR-MS) of 48 contiguous states between 1999 and 2014. The regression slope (0.0206) can be obtained from the plot.

In the stepwise multivariate linear regression model, among the predictors (temperature, solar radiation, sunlight hours, and altitude) examined, only temperature was identified as the main predictor for the age-adjusted MS mortality rates. R^2 value of 0.658 in the model (F test value is 84.8, and model significance level p is 0.00) indicates that temperature variations can explain 65.8% of the spatial variations of MS mortality rates in the 48 contiguous states. Removal of MS mortality rates of the outlier states can improve the R^2 of the regression model (Figure 3). However, when both temperature and latitude were added in as predictors, temperature dropped out of the stepwise multivariate regression model for the MS-all-gender mortality rate (as dependent variable). Temperature remained and latitude dropped out of the model when either MS mortality rate of the male population or the female population was used as dependent variable.

Discussion

There are three distinct observations in this study (Table 1). The first observation is the strong correlation between the MS mortality rates and the temperatures. Even though the MS mortality rates are correlated with the latitudes at about the same correlation level, it is clear that the isopleth lines of MS mortality rates (Figure 1(a) and (b)) follow more closely with the isopleth lines of temperatures than with the latitude lines. The three low-temperature and high-altitude states MT, WY, and CO, constitute the north–south low-temperature high-altitude alley in the

Table 1. Correlation coefficients between the state average MS mortality rates, temperatures, daily sunshine hours, latitudes, and altitudes of the 48 contiguous US states.

	Temperature	Latitude	Sun hours	Solar radiation	Altitude (48)
MS_all	**−0.812**	**0.815**	**−0.245, −0.181**	**−0.14**	**0.293**
sig. (48)	*0*	*0*	*0.10, 0.084*	*0.342*	*0.043*
MS_female	**−0.786**	**0.772**	**−0.1, −0.084**	**0.055**	**0.49**
sig. (48)	*0*	*0*	*0.507, 0.425*	*0.709*	*0*
MS_male	**−0.798**	**0.773**	**−0.177, −0.127**	**−0.036**	**0.389**
sig. (48)	0	0	0.238, 0.232	0.809	0.006
temperature	**1**	**−0.94**	**0.267, 0.168**	**0.206**	**−0.294**
sig. (48)		*0*	*0.073, 0.099*	*0.16*	*0.043*
Latitude		**1**	**−0.388, −0.281**	**−0.289**	**0.151**
sig. (48)			*0.008, 0.006*	*0.046*	*0.305*
sun hours			**1**	**0.866, 0.675**	**0.635, 0.298**
sig. (46)				*0, 0*	*0, 0.004*
solar radiation				**1**	**0.798**
sig. (48)					*0*

MS_all: age-adjusted state average mortality rate for all genders between 1999 and 2014; **MS_female, male**: age-adjusted state average mortality rates for female and male between 1999 and 2014, respectively; **temperature**: state average temperature; **latitude**: state average latitudes; altitude: state average altitude; **sun hours**: state average annual sunshine hours; **solar radiation**: state average solar radiation; ***sig***.: two-tailed significance level of the correlation coefficients. Bold numbers are the correlation coefficients and italic numbers are significance levels of the correlation coefficients.
For two numbers in one cell separated by a comma, the first number is Pearson's coefficient and the second number is Kendall's tau-*b* coefficient. Numbers in the parentheses are the numbers of states used in calculation. A coefficient is considered statistically significant only when significant level (p) is <0.05.

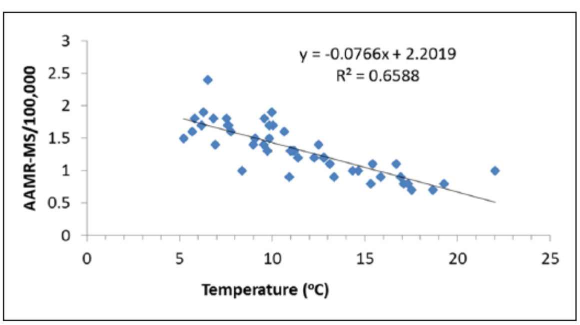

Figure 3. State average age-adjusted MS mortality rates (AAMR-MS)/100,000 people versus state average maximum and minimum temperature (°C) between 1999 and 2014.

Unites States (Figure 1(b)). These three states also constitute the north–south high MS mortality rate alley in the United States (Figure 1(a)). The second observation is that MS mortality rates have no significant correlation (Table 1) with the duration of the sunshine hours and radiations. The lack of significant correlation between MS mortality rates and radiation excludes the ultraviolet radiation as a primary cause[32] of association between the MS mortality rates and the latitude (Table 1). It is evident that both the sunshine hours and solar radiation levels correlate more significantly with the altitudes of the 48 states than with the geographical latitudes. High-altitude states are the states with average low temperatures and high MS mortality rates (Figure 1). The third observation is the significant correlation between isopleth maps of growth rates of MS mortality (shown by the high slope values in Figure 1(c)) and isopleth maps of temperature rises (Figure 1(d)). The faster rise of average temperature along the coastal states is mainly due to the fact that temperature rises faster in the ocean than in the inland states of the United States.

These three observations point to a fact it is the temperature that MS mortality rates are primarily responding to, not duration of sunshine, the solar radiation, or latitudes.

There is no nationwide database for MS incidence and prevalence rates in the United States.[30] However, previous studies of subpopulation groups and review articles have reported that there is a high MS prevalence in the low-temperature region and the north–south gradient of MS prevalence seems to have been attenuating in the United States.[10,11,31,33] It is commonly believed that the north–south temperature gradients in the living environment are weakening because of the increasing utilization of heating and air conditioning equipment for temperature control. The "northerners" are getting warmer in the winter and "southerners" are getting cooler in the summer. Could the weakened north–south temperature gradient in the living environment and the possible benefits of long-term heat acclimation be responsible, at least partially, for this recent attenuation of north–south gradient of MS prevalence among the 48 states?

It is well known that MS patients are very sensitive to heat events, including hot water bath, high outdoor temperatures, and exercises-induced hyperthermia.[19,20,25,26,34] However, most of the heat-related detrimental effects for MS patients are from short-term exposures.[34] Improvement of heat tolerance for people living in the temperate regions after short-term heat acclimation is through the increase in sweat output, while improvement of heat tolerance after long-term heat acclimation for people living in the tropic regions is mainly through minimizing the loss of body fluid.[35] The long-term heat acclimation blunts the sensitivity to the acetylcholine which is the primary neurotransmitter that induces sweating in response to nerve stimulation. Sweat suppression through heat acclimation for people living in high-temperature region improves the preservation of their body fluid and osmoregulation. The improved thermoregulation through increased heat storage and decreased blood flow to the skin results in a more sustainable heat loss with relative easiness in a heat event, although the exact mechanism is still not clear.[35]

Given the similarities between spatial distributions of MS prevalence rates implicated from the US veterans' data[33] and that of MS mortality rates in the 48 states, the main underlying cause of spatial variations of MS prevalence and mortality rates is likely to be similar as well. Hence, the author's explanation is that long-term heat acclimation through gradual, repeated, and prolonged exposure to high environmental temperature might be the primary reason for the low MS mortality and prevalence rates in the low-latitude regions, instead of duration of sunshine hours, radiation, and associated vitamin D level. MS mortality rates are more than three times higher in the low-temperature regions than in the high-temperature regions of the 48 contiguous states. The author speculates that long-term and short-term heat acclimations contribute differently to the MS mortality and prevalence rates. While short-term heat exposure may be a stressful and detrimental event for MS patients, the long-term heat acclimation (or adaption) improves the thermoregulations of MS patients in the high-temperature region[35] and helps reduce the stress of central nervous system during heat events. This implies that the benefit of long-term heat adaption by MS patients to the high environmental temperature in the low-latitude regions may be greatly underappreciated.

The weakness of this study is that only the effect of the physical environmental factors on the mortality rates was examined, and the mechanism of long-term heat acclimation still needs to be studied. Other confounding factors such as smoking, obesity, and comorbidities[11,29,30] can also contribute to the spatial variations of MS mortality rates. One also needs to be cautious that current results are obtained from statistics of large data sets, and responses of an individual MS patient or a small group of MS patients to the long-term heat acclimation can deviate significantly and erroneously from the average responses of a large group. Given the significant implications of this study, researches using more sophisticated designs are needed to further substantiate the current results.

Conclusion

MS mortality rates are more than three times higher in the low-temperature states than in the high-temperature states of the United States. There is an apparent strong and inverse correlation ($r = -0.81$) between the state average MS mortality rates and state average temperatures in the 48 contiguous states between 1999 and 2014. Temperature variations can explain 65.1% of the spatial variations of the age-adjusted mortality rates in the 48 states between 1999 and 2014. The correlations between the state average MS mortality rates and duration of sunshine hours and solar radiations between 1999 and 2014 are statistically insignificant. The author believes that long-term heat acclimation to high environmental temperatures at the low-latitude regions helps improve the body's thermoregulation and is associated with the low MS mortality rate and likely the low MS prevalence rate as well. Given the implication of this result for the MS community, studies using more sophisticated designs are needed to further clarify the role of long-term heat acclimation to high environmental temperature in the low-latitude regions.

Acknowledgements

The author wishes to thank two anonymous reviewers for their constructive comments which helped improve this manuscript significantly. The author also thanks the editorial guidance of Dr Jack Antel. Editorial assistance of Michael Sun from Johns Hopkins University is appreciated as well.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

References

1. Acheson ED, Bachrach CA and Wright FM. Some comments on the relationship of the distribution of multiple sclerosis to latitude, solar radiation, and other variables. *Acta Psychiatr Scand Suppl* 1960; 35: 132–147.
2. Hammond SR, McLeod JG, Millingen KS, et al. The epidemiology of multiple sclerosis in three Australian cities: Perth, Newcastle and Hobart. *Brain* 1988; 111: 1–25.
3. Kurtzke JF, Beebe GW and Norman JE Jr. Epidemiology of multiple sclerosis in US veterans: 1. Race, sex, and geographic distribution. *Neurology* 1979; 29: 1228–1235.
4. Sutherland JM, Tyrer JH and Eadie MJ. The prevalence of multiple sclerosis in Australia. *Brain* 1962; 85: 146–164.
5. Van der Mei IAF, Ponsonby A-L, Blizzard L, et al. Regional variation in multiple sclerosis prevalence in Australia and its association with ambient ultraviolet radiation. *Neuroepidemiology* 2001; 20: 168–174.
6. Taylor BV, Pearson JF, Clarke G, et al. MS prevalence in New Zealand, an ethnically and latitudinally diverse country. *Mult Scler* 2010; 16: 1422–1431.
7. Marrie RA. Environmental risk factors in multiple sclerosis aetiology. *Lancet Neurol* 2004; 3: 709–718.
8. Gale CR and Martyn CN. Migrant studies in multiple sclerosis. *Prog Neurobiol* 1995; 47: 425–448.
9. O'Gorman G, Lucas R and Taylor B. Environmental risk factors for multiple sclerosis: A review with a focus on molecular mechanisms. *Int J Mol Sci* 2012; 13: 11718–11752.
10. Norman JE Jr, Kurtzke JF and Beebe GW. Epidemiology of multiple sclerosis in US veterans: 2. Latitude, climate and the risk of multiple sclerosis. *J Chronic Dis* 1983; 36: 551–559.
11. Ascherio A and Munger KL. Epidemiology of multiple sclerosis: From risk factors to prevention—An update. *Semin Neurol* 2016; 36: 103–114.
12. Faguy K. Multiple sclerosis: An update. *Radiol Technol* 2016; 87: 529–553.
13. Lucas RM, Ponsonby AL, Dear K, et al. Sun exposure and vitamin D are independent risk factors for CNS demyelination. *Neurology* 2011; 76: 540–548.
14. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004; 62: 60–65.
15. Correale J and Gaitán MI. Multiple sclerosis and environmental factors: The role of vitamin D, parasites, and Epstein–Barr virus infection. *Acta Neurol Scand* 2015; 132(Suppl. 199): 46–55.
16. Belbasis L, Vanesa B and Evangelos E. Environmental risk factors and multiple sclerosis: An umbrella review of systematic reviews and meta-analyses. *Lancet Neurol* 2015; 14: 263–273.
17. Uhthoff W. Untersuchungen fiber die bei der multiplen Herdsklerose vorkommenden Augenstörungen. Arch 11. *Psychiatr Nervenkrankh* 1890; 21: 305–410.
18. Davis FA. The hot bath test in the diagnosis of multiple sclerosis. *J Mt Sinai Hosp* 1966; 33: 280–282.
19. Guthrie TC and Nelson DA. Influence of temperature changes on multiple sclerosis: Critical review of mechanisms and research potential. *J Neurol Sci* 1995; 129: 1–8.
20. Opara JA, Brola W, Wylegata AA, et al. Uhthoff's phenomenon 125 years later—What do we know today? *J Med Life* 2016; 9: 101–105.
21. Bol Y, Smolders J, Duits A, et al. Fatigue and heat sensitivity in patients with multiple sclerosis. *Acta Neurol Scand* 2012; 126: 384–389.
22. Watad A, Azrielant S, Soriano A, et al. Association between seasonal factors and multiple sclerosis. *Eur J Epidemiol*. Epub ahead of print 25 May 2016. DOI: 10.1007/s10654-016-0165-3.
23. Leavitt VM, De Meo E, Riccitelli G, et al. Elevated body temperature is linked to fatigue in an Italian sample of relapsing-remitting multiple sclerosis patients. *J Neurol* 2015; 262: 2440–2442.
24. Sumowski JF and Leavitt VM. Body temperature is elevated and linked to fatigue in relapsing-remitting multiple sclerosis, even without heat exposure. *Arch Phys Med Rehabil* 2014; 95: 1298–1302.
25. Watson CW. Effect of lowering of body temperature on the symptoms and signs of multiple sclerosis. *N Engl J Med* 1959; 261: 1253–1259.
26. Flensner G, Ek EC, Söderhamn O, et al. Sensitivity to heat in MS patients: A factor strongly influencing symptomology—An explorative survey. *BMC Neurol* 2011; 11: 27.
27. Anderson RN and Rosenberg HM. Age standardization of death rates: Implementation of the year 2000 standard. *Natl Vital Stat Rep* 1998; 47: 1–17.
28. United Nations (FAO). *Crop water requirement*. Food and agricultural organization, irrigation and

drainage paper. 24 (data on p. 13), 1977, http://www.fao.org/3/a-f2430e.pdf

29. Marrie RA, Cohen J, Stuve O, et al. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: Overview. *Mult Scler* 2015; 21: 263–281.
30. Redelings MD, McCoy L and Sorvillo F. Multiple sclerosis mortality and patterns of comorbidity in the United States from 1990 to 2001. *Neuroepidemiology* 2006; 26: 02–107.
31. Koch-Henriksen N and Sorensen PS. Why does the north–south gradient of incidence of multiple sclerosis seem to have disappeared on the Northern hemisphere? *J Neurol Sci* 2011; 311: 58–63.
32. Beretich B and Beretich TMD. Explaining multiple sclerosis prevalence by ultraviolet exposure: A geospatial analysis. *Mult Scler* 2009; 15: 891–898.
33. Wallin MT, Page WF and Kurtzke JF. Multiple sclerosis in US veterans of the Vietnam era and later military service: Race, sex, and geography. *Ann Neurol* 2004; 55: 65–71.
34. Davis SL, Wilson TE, White AT, et al. Thermoregulation in multiple sclerosis. *J Appl Physiol* 2010; 109: 1531–1537.
35. Lee JB. Heat acclimatization in hot summer for ten weeks suppress the sensitivity of sweating in response to iontophoretically-administered acetylcholine. *Korean J Physiol Pharmacol* 2008; 12: 349–355.