Temperature dependence of multiple sclerosis mortality rates in the United States

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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 US 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). Duration 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).

Conclusions

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.
1. Introduction

One of the famous early observations regarding the geographical distribution of MS is the significant inverse (negative) correlations between the MS incidence rates and average annual hours of sunshine and average solar radiation in December at birthplaces among the US veterans\textsuperscript{1}. Since then, inverse correlation between MS incidence-prevalence rates and latitudes were reported in many places, including the US, Australia, and European countries \textsuperscript{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, can have similar incidence frequency as those populations of adopted countries\textsuperscript{8}. This relation is the so called latitudinal gradient of MS incidence and prevalence\textsuperscript{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\textsuperscript{1,9,11}. There is ample evidence supporting the beneficial effect of vitamin D for MS patients\textsuperscript{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\textsuperscript{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 US alone according to the database of Centers for Disease Control and Prevention (CDC). If the latitudinal gradient of MS prevalence can’t be satisfactorily explained by the association with vitamin D levels, then what can explain it?

Ever since Uhthoff’s Phenomenon\textsuperscript{17} was reported and a hot bath test was used as a mean of diagnosing multiple sclerosis\textsuperscript{18}, the heat reaction by people with multiple sclerosis has been fascinating to the MS community\textsuperscript{19}. Though Uhthoff’s test was discontinued after 1983 by more accurate diagnostic methods, significant data on the heat reaction of MS patients have been accumulated\textsuperscript{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, though most of these negative effects have been reported to be transitory\textsuperscript{19-22}. Recently, studies also reported that MS patients tend to have higher body temperatures than those of healthy people, i.e., heat reaction in MS patients can be endogeneous\textsuperscript{23,24}. It is apparent that most MS patients have a strong reaction to changes in the environmental temperatures\textsuperscript{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 US 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 US, 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 dataset used in this study.

2. Data

Age-adjusted mortality rates for MS as the underlying cause of death (AAMR-MS) between 1999 and 2014 for the lower 48 states of US were obtained from the CDC WONDER database (http://wonder.cdc.gov) where MS has the code G35 following the Tenth 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\textsuperscript{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 was 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 were 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. Annual state average solar radiation between 1998 and 2010 were 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).

3. Methods
3.1. 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 vs. 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 were plotted. Pearson correlation coefficients were calculated between the two pairs of isopleth maps using the Band Collection Statistics tool in ArcGIS.

3.2. Statistical correlations and regression models

Pearson 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 the 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.

4. Results

4.1. Similarity between isopleth maps

Regions of high MS mortality rates in the northern US apparently correlates to regions of low temperatures, and regions of low MS mortality rates in southern US correlates to regions of high temperatures (Figure 1a,b) with a Pearson 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 1d) are along the coastal states between 1999 and 2014. These states are also the states with slower increases of MS mortality rates during this period. The Pearson correlation coefficient between isopleth maps of the AAMR-MS slopes and temperature slopes is -0.403 with a \( p = 0.00 \).

4.2. Statistics, correlations, and model results

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 are likely the combination result of multiple factors. These factors include the increased survival rates for comorbid diseases\textsuperscript{29,30} (such as heart disease and breast cancers etc.), the significant advancement in MS diagnoses\textsuperscript{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 dataset (mentioned in the Data section) was used and they are not statistically significant.

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. 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.

5. Discussion

There are three distinct observations in the current 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 1a-b) follows 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 US (Figure 1b). These three states also constitute the north-south high MS mortality rate alley in the US (Figure 1a). 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 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 1c) and isopleth maps of temperature rises (Figure 1d).
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 US.

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 US\(^3\). 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 US\(^10,11,31,33\). 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, though the exact mechanism is still not clear\textsuperscript{35}.

Given the similarities between spatial distributions of MS prevalence rates implicated from the US veteran’s data\textsuperscript{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\textsuperscript{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 the current 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\textsuperscript{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 datasets 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.

6. Conclusions

MS mortality rates are more than 3 times higher in the low temperature states than in the high temperature states of the US. 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 correlation 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.

References


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

<table>
<thead>
<tr>
<th></th>
<th>temperature</th>
<th>latitude</th>
<th>sun hours</th>
<th>solar radiation</th>
<th>altitude (48)</th>
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<tbody>
<tr>
<td>MS_all</td>
<td>-0.812</td>
<td>0.815</td>
<td>-0.245, -0.181</td>
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<tr>
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<td>Sig. (48)</td>
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For two numbers in one cell separated by a comma, the 1st number is the Pearson coefficient and the 2nd number is the Kandell Tau-b coefficient. Numbers in the parentheses are the numbers of states used in calculation. Abbreviation notes: 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. A coefficient is considered statistically significant only when Sig. level (p) is <0.05.
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 the regression slopes of c), state average annual age-adjusted MS mortality rates and d), state average annual maximum and minimum temperatures between 1999 and 2014. The correlation 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.
Figure 2. Regression plot of average age-adjusted MS mortality rates (AAMR-MS) of 48 contiguous states between 1999 and 2014. Notice the regression slope (0.0206) can be obtained from the plot.

\[ y = 0.0206x - 39.967 \]

\[ R^2 = 0.821 \]
Figure 3. State average age-adjusted MS mortality rates (AAMR-MS)/100,000 people vs. state average maximum and minimum temperature (°C) between 1999 and 2014.

\[ y = -0.0766x + 2.2019 \]

\[ R^2 = 0.6588 \]