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Multiple sclerosis prevalence in Italy associated with temperature variation towards 8.60°C

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ABSTRACT

Introduction: Italy is an exception to the association of increasing Latitudinal prevalence of multiple sclerosis (MS) with temperature. This is noteworthy because even though northern Italy's average yearly temperature is significantly colder than southern Italy's MS rates are lower instead of higher. If the reason for this inverse epidemiology of MS were determined it would give important insight as to the causes of MS.

Aim: This study was done to determine if variation towards a particular temperature was responsible for MS prevalence rates in Italy.

Material and methods: Multivariate analysis was used to determine average yearly temperatures that had the highest effect on MS prevalence rates and variation towards which MS rates would be the most affected. Multivariate analysis was used to determine the significance of a correlation between average yearly temperature and MS prevalence. When this was determined the same method was repeated with variation towards a particular temperature.

Results and discussion: The results showed the average yearly temperature at which MS prevalence rates peaked was 10.11°C and the temperature towards which temperature variation would have the most significant impact on prevalence rates was 8.60°C.

Conclusions: The temperature that both the average yearly temperature and variation towards a particular temperature has the most impact on MS prevalence rates corresponds to the point at which the TRPM8 thermoreceptor peaks in activity and below which it ceases to be reactive, respectively. That receptor has been shown to be a mediator of immune system function. It's dysfunction could explain the development of MS.

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1. INTRODUCTION

Multiple sclerosis (MS) is a condition that has been associated repeatedly with latitudinal prevalence: the further north a prevalence rate is tested for the higher the rates of MS are typically reported. Italy does not follow this trend: Sicily, which is located to the south of the mainland, has higher prevalence rates[1–5] than the mainland.[6–9] Northern Italy, however, has lower rates on the average[10–13] than either Sicily or southern Italy. Most of this variation has been attempted to be explained as due to genetic pool differences within Italy.[14,15] There is some truth to this: Sardinia has some of the highest rates of MS in the world at between 144–152 cases per 100 000 population[16,17] and it's residents are genetically different than mainland Italy. Malta also has an ethnically unique population and has much lower rates (4 cases per 100 000 population)[18] than the rest of Italy. In northern Italy there is one population of ethnically distinct people in Valle d'Aosta which are reported to have higher rates of MS than the rest of Italy (90 / 100000)[19] although another study has questioned this with a rate of 39 / 100000.[10]

One factor that has not been explored is whether average yearly temperature is a factor that explains this reversed latitudinal MS prevalence rates in Italy. The Alps in Northern Italy provide extremely cold temperatures in some locations while more southerly locations like Sicily provide comparative warm ones. This makes the apparent reversed latitudinal trends even more intriguing because the temperature gradient appears to be consistent with what would be expected of a northerly direction – and that gradient is exaggerated further because of the Alps. If there is a specific temperature range in which MS prevalence rates would be expected to increase then it is possible that by comparing average yearly temperature with MS prevalence rates in Italy a peak temperature for association with MS development could be determined. It's also possible to analyze yearly temperature variation in order to determine if there is a particular temperature at which variation above or below that temperature would be expected to affect MS prevalence rates.

2. AIM

The purpose of this study is to examine whether a correlation exists between MS prevalence rates, average yearly temperature, and monthly variation throughout the year in Italy that explains the difference between Italy's MS prevalence rates and the general worldwide trend of increased latitudinal incidence for MS.

3. MATERIAL AND METHODS

Numerous studies done at later dates appear to be showing drastic increases in MS prevalence[20,21] – particularly in Sicily.[22–24] The reasons for this increase in prevalence has not been explained and could well be due to methodological study method changes or diagnostic criterion changes that have taken place since 2000. Studies consulted ($n = 16$) were done prior to 2000[1–15,25] and were examined for prevalence rate. Their locations were then matched for average temperature and temperature variations based on data from the Norwegian Meteorological Institute.[26] Average yearly temperature was defined as data collected from 1961–1990. In order to determine an average yearly temperature with the highest MS prevalence rate the average yearly temperatures was subtracted from temperatures between 1°C–14°C and the absolute value of the result was calculated in data analysis of Excel 2013 (Table 1) as multivariate analysis with MS prevalence rate and average temperature variation set as independent variables and the absolute difference calculated as the dependent variable. Variation was determined in this test by determining standard deviation of temperature throughout the year. The way a temperature with the highest significance was determined was to use the intercept of the absolute value of all locations to determine the point at which the significance level was the highest. The result in this test was determined to be significant if $P < 0.05$.

The way variation was calculated was that the variation from that temperature in a given month was subtracted from the temperature of highest MS prevalence that was determined first and an absolute value was taken for that difference. Each of these values was collected monthly and then added together from the entire year. Multivariate analysis was then conducted with the added difference as the dependent variable and the set difference from the determined temperature of high significance for each location and MS

Table 1. MS Prevalence Rate, location of tested area, Average Yearly temperature of that area, and the difference from 10.11°C of that area.

MS prevalence rate per 100 000	Location	Average yearly temperature	Average difference from 10.11°C
58	Vallagarina-Rovereto	2.23	7.89
45	Biella	11.27	1.16
90	Valle D'Aosta	–5.63	15.74
38	Macerata	12.70	2.59
43	Ascoli Piceno	14.45	4.34
53	L'Aquila Province	4.98	5.12
35	Salerno	9.20	0.91
62	Terni Province	13.23	3.12
56	Valdarno-Firenze	2.45	7.65
69	Ferrara province	13.02	2.91
52	San Marino	13.04	2.93
61	Monreale Province	16.79	6.68
45	Bagheria	17.99	7.88
51	Caltanissetta	17.55	7.44
53	Enna	13.67	3.56
58	Catania	17.66	7.55

prevalence rates as independent variables. This was done under regression in 'data analysis' of Excel 2013. Significance was determined if $P < 0.01$. The highest confidence interval is necessary because since the highest probability of temperature has already been selected then it would require a higher confidence interval to determine whether the results of the second test are truly valid. Additionally, because of the potential confounds that could be presented by genetically distinct populations Sardinia and Malta are not included in the analysis. Due to its later date of study the Valle D'Aosta prevalence rate of 90 / 100 000 was used. The locations tested are shown in Table 1. Before conducting these tests multivariate analysis was used to determine if the association between these factors was significant.

4. RESULTS

The results for multivariate analysis of average temperature and temperature variation were highly significant ($P < 0.0003$) meaning that an association was present. Average temperature was then plotted between 1°C and 14°C (Figure 1). The results showed that the highest point of significance was 10.11°C ($P < 0.0016$) with a range of significance between 13.25°C ($P < 0.05$) and 7.70°C ($P < 0.05$). This marks 10.11°C as the temperature that amount of variation from a given temperature will be tested. Variation from 10.11°C showed the highest point of significance for variation from that temperature was 8.60°C ($P < 0.005$) with a range of significance by 1% confidence interval of 7.5°C and 9.3°C (Figure 2).

5. DISCUSSION

One of the limitations on this study was the fact that there were almost no prevalence rates reported for an area with an average temperature between 11.26°C and 4.98°C. Salerno, alone, was a sole representative with an average temperature of 9.20°C and a prevalence rate of 35 / 100 000.[10] This leaves a small degree of uncertainty about how accurate the peak variation result is, since it cannot be compared to any MS prevalences in the study itself. However, study of the highest incidences of MS in the world – The Orkney Islands and the Shetland Islands – reveal that the average yearly temperature of those islands is very close to this predicted average. The Orkneys have an average temperature of 7.83°C and a prevalence rate of 193 / 100 000.[27] The Shetlands have an average temperature of 7.12°C and a prevalence rate of 152 / 100 000.[28] Additionally, their variations in temperature are very narrow, at 2.95°C and 2.84°C[26] respectively, which means that these locations are never very far away from the average temperature.

A temperature sensor in the body named the TRPM8 receptor has an active range between 8°C–28°C.[29] It's activity has been shown to peak between 8°C and 10°C.[29–31] Immune functions have been associated with this sensor and some of these have been linked to the central nervous system.[32,33] It is possible that this temperature sensor in the body, if dysfunctional, is associated with the incidence of MS reported in the world and may explain temperature dependent incidences and prevalences of multiple sclerosis. The reason why variation towards a particular temperature would affect the results is presumably because this is roughly the point at which the

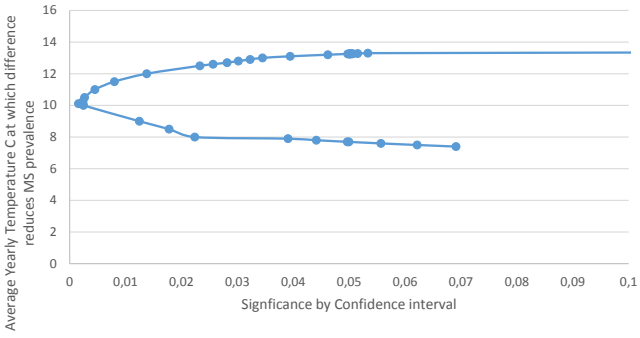

Figure 1. Average yearly temperature at which a difference from that temperature is associated with a reduction in MS prevalence rates. Peak MS prevalence is associated with the average difference from 10.11°C. This temperature is with variation considered a factor, not without.

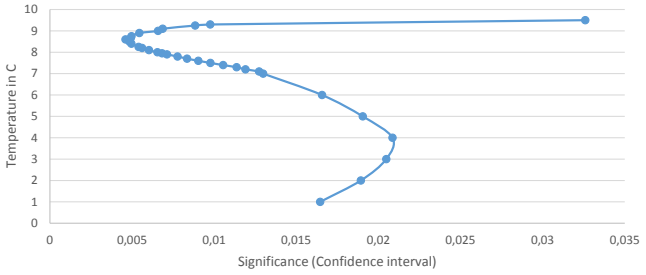

Figure 2. Variation from 10.11°C as a function of MS prevalence. The results show that 8.60°C is the peak temperature around which variation towards would be predicted to have the greatest effect of changing MS prevalence.

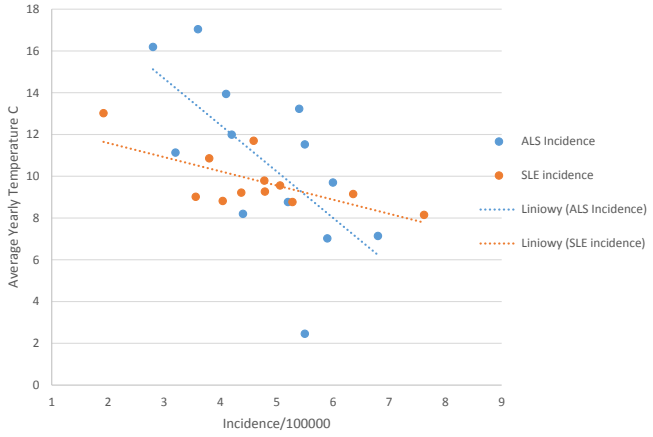

Figure 3. Incidence rates of ALS ($n = 13, P < 0.01$) and SLE ($n = 12, P < 0.02$) vs. the average yearly temperature of the location tested.

TRPM8 receptor would cease to be reactive and crossing this point would cause prevalence rates to rise or fall. Northern Italy's average temperatures were also below the reactive range of this receptor, which could explain why that regions' MS prevalence rates were lower than the rest of Italy.

Systemic lupus erythematosus (SLE) is a similar disease to MS[34] that has been speculated to be autoimmune. Its development occurs roughly 10 years later than the average onset of MS. Like MS it is significantly more common in women than men, although that development is even more lopsided with a 9 : 1 ratio of female to male patients. Far fewer epidemiology studies on SLE prevalence or incidence have been done than MS, but those that do have shown a similar correlation between SLE incidence in the United Kingdom[35] – where the highest rates of MS in the world exist – and those of Ferrara province in Italy: UK rates ranged between 3.56 / 100 000 and 7.62 / 100 000, whereas the incidence rates in Ferrara were an average of 1.92 / 100 000 from 2000–2002.[34] The association between the average yearly temperature of these locations and SLE incidence was significant ($n = 12$, $P < 0.02$) (Figure 3) which strongly suggests that the factors that affect MS development also regulate the development of SLE development. Prevalence rates for Ferrara were calculated at 57 / 100 000,[34] which would suggest that SLE is similar in geographic distribution and prevalence rates to MS if the correlation between incidence rates was directly associated with prevalence rates. The reduction between MS prevalence and SLE prevalence could be entirely accounted for by the more advanced age of SLE development.

Amyotrophic lateral sclerosis (ALS) is another autoimmune condition with a very late age of onset (after 53 at the earliest, in general after 65)[36] and a much lower life expectancy than either MS or SLE. It is also a much rarer disease owing to the shorter life expectancy at higher ages and as a result prevalence rates are not well studied. Incidence rates for ALS do show a significant association between average yearly temperature and location[37–48] ($n = 13$, $P < 0.01$) (Figure 3) suggesting that development of ALS may be governed by the same factors that affect MS development. It is worth noting that one location from Northern Italy[47] (Figure 3) has a drop in ALS incidence consistent with the cutoff point of the TRPM8 receptor.

6. CONCLUSIONS

The fact that multivariate analysis was significant is remarkable because neither temperature variation ($P < 0.40$) nor average temperature ($P < 0.10$) were significant by themselves. Only by combining the two variables was a significant correlation established between average yearly temperature and MS prevalence. This is largely due to the fact that no average yearly temperatures were reported between 9.20°C and 4.98°C – which made this multivariate analysis necessary. The results demonstrate that the most common average temperature when variation was included to expect MS prevalence to increase is 10.11°C and the temperature towards which variation could cause a change in prevalence was 8.60°C. This roughly reflects the cutoff point for activity of the TRPM8 receptor.[29]

Conflict of interest

Author declare to have no conflict of interest.

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Conflict of interest

No conflict of interest exists in this relationship.

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