ORIGINAL ARTICLE

A Quantitative Analysis of Suspected Environmental Causes of MS

Scott Sloka, Claudia Silva, William Pryse-Phillips, Scott Patten, Luanne Metz, V. Wee Yong

ABSTRACT: ***Background:*** Multiple sclerosis (MS) is a disease with purported environmental causes. Consistent correlations have been found in various settings for latitude, smoking exposure, sunlight, and vitamin D deficiency. We analysed the contribution of various environmental factors to the risk of developing MS from a population perspective. ***Methods:*** We collated global data of MS prevalence from 54 studies over the previous ten years and calculated the degree of risk contributed by latitude, longitude, ultraviolet radiation (from NASA satellite data and formulae for available sunlight hours), population smoking rates (from WHO data), gender, study date, study demographics, and several socioeconomic factors. We report a very significant negative correlation between MS prevalence and available ultraviolet (UV) radiation. ***Results:*** The lack of available UV radiation outweighs other factors by at least 20 fold ($p<10^{-8}$) from single variate regression analysis. Multiple regression analysis revealed that latitude and longitude are also significant factors; smoking may also provide a very minimal role. The eight prevalence studies from Scandinavia produced prevalences that were lower than expected, given their global geospatial positioning. ***Conclusions:*** The available ultraviolet radiation is a significant environmental factor, moreso than all the other factors examined.

RÉSUMÉ: Analyse quantitative des causes environnementales soupçonnées de jouer un rôle dans la sclérose en plaques. ***Contexte :*** La sclérose en plaques (SP) est une maladie considérée comme ayant des causes environnementales. Des corrélations concordantes ont été établies dans différents contextes pour la latitude, l'exposition au tabagisme, la lumière du soleil et le déficit en vitamine D. Nous avons analysé la contribution de différents facteurs environnementaux au risque de développer la SP à partir d'une perspective populationnelle. ***Méthodes :*** Nous avons colligé les données globales de 54 études sur la prévalence de la SP au cours des 10 années antérieures et nous avons calculé le degré de risque attribuable à la latitude, la longitude, la radiation ultraviolette (UV) (données obtenues par satellite de la NASA et adaptées selon les heures d'ensoleillement) les taux de tabagisme des populations (données de l'OMS), le sexe, la date de l'étude, les données démographiques de l'étude ainsi que plusieurs facteurs socioéconomiques. Nous rapportons une corrélation négative très significative entre la prévalence de la SP et la radiation UV. ***Résultats :*** Le manque de radiation UV a plus d'influence que les autres facteurs dans une proportion d'au moins 20 fois ($p < 10^{-8}$) à l'analyse de régression univariée. L'analyse de régression multiple a montré que la latitude et la longitude sont également des facteurs significatifs et que le tabagisme peut jouer un rôle minime. Les huit études de prévalence scandinaves ont révélé des prévalences plus faibles que prévu étant donné la position géographique. ***Conclusions :*** La radiation UV disponible est un facteur environnemental significatif qui est plus important que tous les autres facteurs examinés.

Can. J. Neurol. Sci. 2011; 38: 98-105

Multiple sclerosis (MS) is an inflammatory disorder that causes demyelination and axonal injury within the central nervous system. The underlying etiology remains elusive but both environmental and genetic factors are believed to play a role[1,2] culminating in the over-activation of various immune subsets that accumulate in the central nervous system to produce injury. Familial inheritance, cigarette smoking, vitamin D deficiency, and ultraviolet (UV) light exposure may all contribute to the risk of MS[1,3]. While previous studies have attempted to quantify the risk of these factors, largely as a single entity and at a regional scale, no combined quantification has been made of these purported environmental effects in the context of each other, nor has the risk been investigated on a global scale.

In this study, we have collated prevalence data on MS from 54 published studies to obtain a global perspective, and we have captured geographic and demographic information, and population health indicators related to these locations. We then employed various mathematical analyses and numerical methods to examine the purported environmental effects and provide a relative weighting of their risk and relative

From the Hotchkiss Brain Institute (CS, SP, LM, VWY) and the Departments of Clinical Neurosciences, Community Health Sciences (SP), University of Calgary, Calgary, Alberta; Department of Neurology (WPP), Memorial University St John's, Newfoundland; Department of Neurology (SS), Grand River Hospital, Kitchener, Ontario, Canada.

Received April 19, 2010. Final Revisions Submitted June 29, 2010.

Correspondence to: Scott Sloka, Grand River Hospital, 835 King St W, Rm 554, 5th Floor Kaufman Bldg, Kitchener, Ontario, N2G 1G3, Canada. Email: p97jss@mun.ca.

contribution to MS in the context of each other, and on a worldwide scale.

We have found a very significant negative correlation between MS prevalence and available ultraviolet radiation, thereby providing quantification of the suspected inverse association of MS with sunlight. Importantly, the lack of available UV radiation outweighs other risk factors by at least 20 fold.

Methods and Materials

MS Study Ascertainment

A search was conducted of the MEDLINE, EMBASE and Cochrane databases for all articles published from November 1998 until October 2008 using PubMed, Google Scholar and the Cochrane website as search engines. No language restrictions were imposed. The following was used as a baseline search schema in PubMed: (multiple sclerosis or MS or optic neuritis) and (incidence or prevalence). Based on the title of the publication and its abstract, the full articles were either downloaded or requested from our medical library. To locate unpublished material and to decrease publication bias[4], references from original and review articles were manually searched. Some symposia proceedings from large neurology association meetings were also searched.

Inclusion Criteria

Abstracts and full articles were retrieved and screened for the following:

Established diagnosis of MS using the available clinical criteria of the time (eg Poser[5], McDonald[6]).
Statement of disease prevalence.

Reporting of the study population denominator, and sex ratio (or total male and female numbers).

Exclusion Criteria

Studies that did not state their method of case ascertainment were excluded.

Fifty-four MS prevalence studies met the above criteria. These are listed in the supplemental references.

Data Extraction

A standardized data collection form was used to increase uniformity and reduce bias in reporting. Extracted data included: first author, year of publication, journal, sex ratio (female (F), Male (M)), population size, an ordinal definition of the study area size (1-city, 2-region/county, 3-province, 4-country), and the population denominator for the study catchment area (Supplemental Table). The "Methods" designation in the

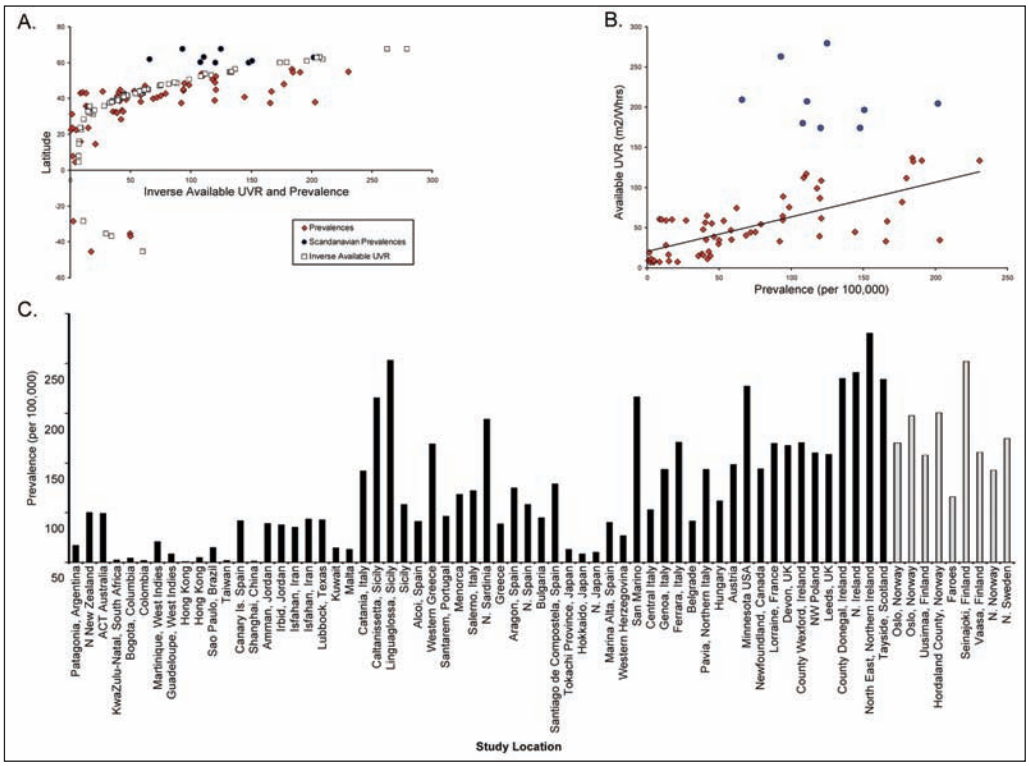

Figure 1: *MS prevalence correlates with available UV radiation in both hemispheres. a) MS prevalences (red diamond) are plotted vs. latitude for all of the 54 prevalence studies meeting our inclusion criteria (see Methods). The most northern studies (Scandinavian prevalences) are highlighted as blue circles. The available UV radiation (as calculated from NASA TOMS data) has been singly regressed (scaled and shifted) for all included studies, and its inverse (open squares) follows the same trend as the MS prevalence. b) The available UV radiation for each prevalence study is plotted vs. each study's prevalence; again, the blue circles represent the most northern (Scandinavian) studies, suggesting an outlier group. The regression line is plotted in black. c) The prevalences of all 54 studies are displayed and ordered by latitude, demonstrating that the outlier group has a physical relationship.*

https://doi.org/10.1017/S0317167100011124 Published online by Cambridge University Press

Supplemental Table denotes the extent of data sources used to derive the prevalence (1-multiple sources, 2-one source only, 3-questionnaire) and is meant to determine if potential underreporting of cases is related to the number of data sources employed.

The life expectancy of the country (from the World Health Organization (WHO) website – www.who.int) was included both because it may relate the incidence to the prevalence[7] and because socioeconomic factors may alter overall disease reporting. Gross domestic product (GDP) per capita (available from the WHO website) was also included in the analysis in order to account for socioeconomic factors.

For each study, population smoking statistics were abstracted from the World Health Organization website. If smoking statistics were not available from the WHO, a literature search using MEDLINE or EMBASE was used to identify missing population smoking rates.

Year of prevalence date was included in the regression analysis because an overall increase in prevalence has been observed over the last many decades[8]. The sex ratio was also included because an overall increase in female to male ratio has been observed over the past century[9,10].

The catchment population size of each study was included in the analysis to account for bias in the ascertainment of cases. We hypothesized that studies on smaller populations may be subject to counting errors and that studies done on larger populations could be subject to under-ascertainment from incomplete availability of records. This population size was included both as the denominator used for the prevalence and as an ordinal representing city, region/county, province, and country. The second representation was included in case institutional differences exist from institutional versus ministerial/governmental sources.

Latitude was included to compare to the significance of the available UV radiation. Longitude was included in the analysis because although a north-south gradient has been observed in many studies over the last several decades, previous analyses for an east-west gradient in MS prevalence are sparse and contradictory. The longitude was represented two ways: as a continuous gradient from east to west, and as a reflected gradient with the zero point set at ten degree increments with Greenwich as the reference point. This incremental system was analyzed to search for a similar gradient as observed with the apparent reflected north-south gradient observed at the equator. The latitude and longitude of the study population was derived from Google Earth site data. The approximate geometric mean of the study population (i.e. the location of most of the study population) was estimated to define the latitude and longitude of the study.

Determination of available UV radiation

Total Ozone Mapping Spectrometer (TOMS) is a satellite-mounted optical sensor used to measure the albedo (reflected power) of the earth's atmosphere at six narrow spectral bands, including several ultraviolet B (UVB) bands. Erythemal exposure represents the potential for biological damage due to solar UV radiation. Total Ozone Mapping Spectrometer erythemal exposure is calculated by NASA using UV irradiance

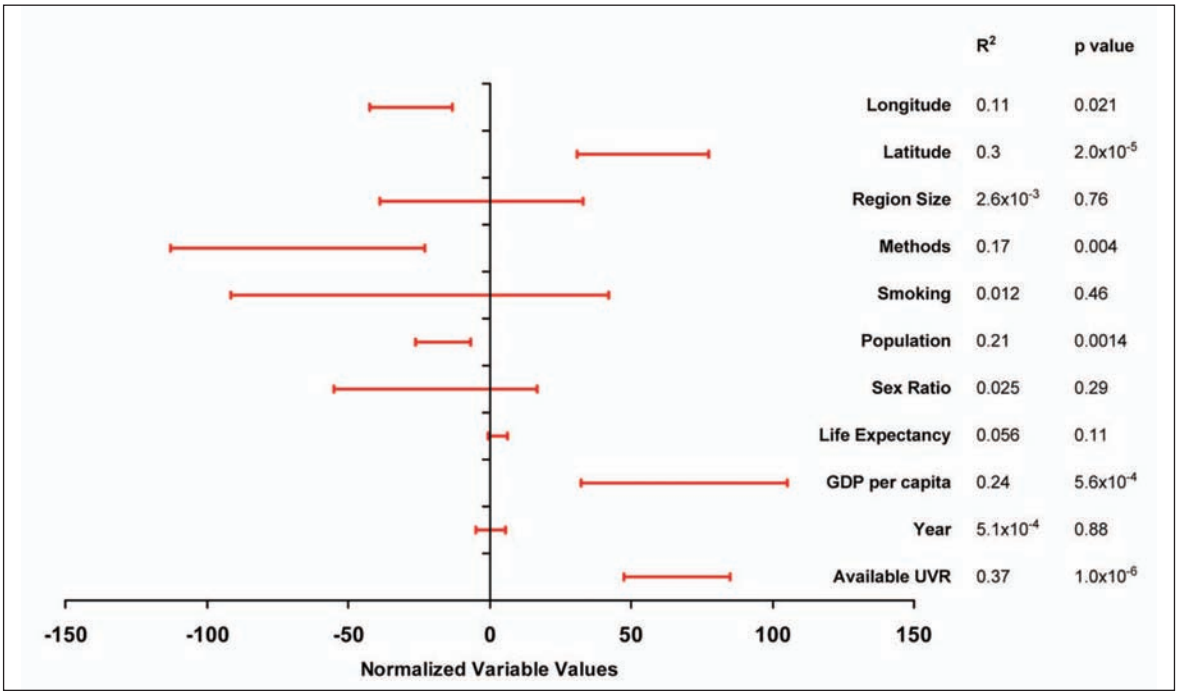

Figure 2: *Single regression analysis of environmental and potential confounding variables. Although some factors are statistically significant, the inverse of available ultra violet (UV radiation) is found to be the most statistically significant variable, outweighing the next significant factor, latitude, by a factor of 20.*

https://doi.org/10.1017/S0317167100011124 Published online by Cambridge University Press

Supplemental Table: Demographic and geographic information pertinent to the 54 studies used in the current investigation

Year	First Author	Prevalence	Location	Life Exp	GDP	Methods	Region Size	Population	Latitude	Longitude	Smoking	Sex Ratio	Available UVR
2000	Alshubaili[1]	14.77	Kuwait	77.53	55900	1	4	2700000	35.5	101.5	15.55	1.33	16.30
2003	Ares[2]	79	Santiago de Compostela, Spain	79.92	33600	1	1	90188	42.8	-8.5	33.65	1.43	54.32
2000	Bergamaschi[3]	94	Pavia, Northern Italy	80.07	30900	1	3	493753	45.2	9.2	24	1.72	64.25
2005	Bhigjee[4]	2.6	KwaZulu-Natal, South Africa	48.89	9700	1	3	9900000	-28.5	-30.8	27	2.80	10.99
2003	Cheng[5]	1.39	Shanghai, China	73.18	5400	2	1	8860000	31.2	121.5	35.5	1.80	19.07
1999	De Sa[6]	46.3	Santarem, Portugal	78.08	21800	1	2	62621	39.3	-8.7	21	2.90	38.89
2002	Debouverie[7]	120	Lorraine, France	80.87	32600	1	3	2310376	48.9	6.2	30	2.49	86.46
2005	El-Salem[8]	39	Amman, Jordan	78.71	4700	2	1	400000	31.9	35.9	29.5	2.80	15.87
2005	El-Salem[8]	38	Irbid, Jordan	78.71	4700	2	1	100000	32.5	35.9	29.5	2.80	17.58
2005	Etemadifar[9]	35.5	Isfahan, Iran	70.86	11700	1	3	3923295	32.7	51.7	12	3.66	14.89
2003	Granieri[10]	120.93	Ferrara, Italy	80.07	30900	1	3	347582	44.9	11.6	24	2.23	61.69
2005	Granieri[11]	166.7	San Marino	81.88	34100	1	4	29999	43.9	12.5	22.5	2.47	57.86
2004	Gray[12]	230.6	North East, Northern Ireland	78.07	46600	1	2	160446	54.9	-6.3	24	1.92	133.75
2006	Houzen[13]	13.1	Tokachi Province, Japan	82.07	33500	2	3	358439	42.9	143.1	29.3	1.84	59.03
2005	Iuliano[14]	72	Salerno, Italy	80.07	30900	2	2	259681	40.6	14.8	24	2.38	44.06
2003	Klupka-Saric[15]	27	Western Herzegovina	78.33	6100	2	3	310464	43.9	17.7	48	1.30	59.30
2006	Lau[16]	4.8	Hong Kong	81.77	42000	2	4	6990000	22.4	114.1	12.75	3.24	9.10
2003	McGuigan[17]	184.6	County Donegal, Ireland	78.07	46600	1	2	129994	54.6	-8.1	22.5	3.32	132.37
2003	McGuigan[17]	120.7	County Wexford, Ireland	78.07	46600	1	2	104372	52.3	-6.5	22.5	1.75	108.54
2002	Melcon[18]	17.2	Patagonia, Argentina	76.36	13100	1	1	417666	-45.5	-68.5	30	1.69	60.27
2001	Nicoletti[19]	203	Linguaglossa, Sicily	80.07	30900	1	1	5422	37.9	15.1	24	1.60	34.73
1999	Nicoletti[20]	92	Catania, Italy	80.07	30900	1	3	313110	37.5	15.1	24	1.27	33.03
2006	Saadatnia[21]	43.8	Isfahan, Iran	70.86	11700	1	3	3923255	32.7	51.7	12	3.63	14.89
1997	Solaro[22]	94	Genoa, Italy	80.07	30900	1	3	913218	44.4	8.9	24	1.76	59.62
2002	Toro[23]	4.41	Bogota, Columbia	72.54	7400	2	1	6574460	4.6	-74.1	19.05	2.21	6.93
2000	Williamson[24]	42.8	Lubbock, Texas	78.14	45800	1	2	424916	33.5	-101.9	19.3	4.13	20.04
1993	Tola[25]	58.3	N. Spain	79.92	33600	1	2	92632	41.8	-3.8	33.65	1.83	46.85
1990	Callegaro[26]	15	Sao Paulo, Brazil	71.71	9500	1	1	11380300	23.5	-46.6	31	2.36	8.54
1995	Chancellor[27]	50	N New Zealand	80.24	27200	1	2	171147	-36.8	174.7	28.6	4.11	34.47
1999	Dean[28]	13.2	Malta	79.3	23400	1	4	378500	35.9	14.4	28.65	1.36	28.34
1999	Forbes[29]	184	Tayside, Scotland	78.85	35000	1	2	395600	56.3	3.2	25.5	2.78	136.88
1999	Ford[30]	108.7	Leeds, UK	78.85	35000	1	2	728840	53.8	1.5	35.7	2.71	112.06
1999	Garcia-Gallego[31]	40.3	Marina Alta, Spain	79.92	33600	1	2	129426	43.4	-3.9	33.65	2.40	56.59
1999	Hernandez[32]	42	Canary Is. Spain	79.92	33600	1	2	81507	28.3	-16.6	33.65	2.73	11.40
1999	Houzen[13]	8.6	Hokkaido, Japan	82.07	33500	1	2	361726	43	142	29.3	2.67	60.57
1999	Itoh[33]	10.2	N. Japan	82.07	33500	1	1	363526	43.4	143	29.3	1.66	60.13
1998	Lau[34]	0.77	Hong Kong	81.77	42000	3	3	6800000	22.4	114.1	12.75	9.60	9.10
1998	Pugliatti[35]	144.4	N. Sardinia	79.92	33600	1	3	453628	40.8	9	24	2.49	44.74
2001	Fox[36]	118	Devon, UK	78.85	35000	1	2	341796	50.7	3.8	35.7	2.65	98.96
2000	Mayr[37]	177	Minnesota USA	78.14	45800	1	2	123386	48.1	-96.4	16.5	2.15	81.80
1996	Pekmezovic[38]	41.5	Belgrade	75.29	10400	2	1	1602226	45	20.3	41	1.92	64.71
1995	Nicoletti[39]	58.5	Sicily	80.07	30900	1	1	333075	38.2	13.8	27	1.13	35.31
1996	Totaro[40]	53	Central Italy	80.07	30900	1	8	297838	44.1	10	27	1.87	58.31
2002	Modrego[41]	75	Aragon, Spain	79.92	33600	1	2	58666	41.6	-1	33.65	1.99	44.75
1996	McDonnell[42]	190.7	N. Ireland	78.07	46600	1	2	151000	54.6	-6.8	24	2.13	133.29
2001	Sloka[43]	94.4	Newfoundland, Canada	81.16	38600	1	3	521986	48.4	54.7	22.7	2.68	88.68
2003	Grytten[44]	150.8	Hordaland County, Norway	79.81	53300	2	1	441660	60.9	6.3	26	1.74	196.06
2005	Smestad[45]	148	Oslo, Norway	79.81	53300	1	1	529846	59.9	10.7	26	2.22	174.00
1993	Gronlie[46]	93	N. Norway	79.81	53300	2	2	224794	67.5	14	26	1.53	262.87
1990	Sundstrom[47]	125	N. Sweden	80.74	37500	1	2	250134	67.5	18.4	22.05	1.90	279.27
1995	Celius[48]	120.4	Oslo, Norway	79.81	53300	1	1	483401	59.9	10.7	26	2.16	174.00
1998	Kurtzke[49]	66	Faroes	78.85	35000	1	3	44262	61.9	6.9		2.94	209.24
1993	Sumelahti[50]	111	Vaasa, Finland	78.82	36000	2	3	179079	63.1	21.6	28.1	1.90	206.81
1993	Sumelahti[50]	202	Seinajoki, Finland	78.82	36000	2	3	197042	62.8	22.9	28.1	1.90	204.30
1993	Sumelahti[50]	108	Uusimaa, Finland	78.82	36000	2	3	1277932	60.1	24.2	28.1	1.90	179.57

See text above under Data Extraction for an explanation of the following categories; Methods:1-multiple data sources, 2-single data source, 3-questionnaire; Region Size: 1-city, 2-region/county, 3-province, 4-country

reaching the surface of earth at noon weighted by the susceptibility of Caucasian skin to sunburn (erythema) and preferentially weights those frequencies that cause peripheral conversion of vitamin D in the skin[11]. The TOMS data is available through NASA from the years 1997 to 2002 with a resolution of approximately 85km x 100km.

A computer program (available on request) was developed from standard software provided by the TOMS project to use the daily data for calculating a linearly interpolated measurement of daily noontime erythemal UV for each study location based on latitude and longitude. The average daily UV data over the period from Jan 1, 1997 to Dec 31, 2002 was then calculated.

https://doi.org/10.1017/S0317167100011124 Published online by Cambridge University Press

Very little between-year variation of daily erythemal noontime UV measurements was noted.

Several equations are available to estimate the total sunlight hours for a given latitude and day; one was selected that permitted the specification of day, latitude, and the minimum angle of the sun with respect to the horizon[12]. Given that the amount of available ultraviolet radiation decreases sharply to much less than 10% of the amount available from directly overhead as the zenith angle of the sun increases beyond 60° (the angle to the horizon is less than 30°)[13], 30° was selected as a minimum angle to the horizon for these calculations.

The yearly[14] and daily[15] ultraviolet exposure generally follows a semi-circular or triangular distribution. Therefore, a relative estimate of the total UV availability can be made by multiplying the average daily maximum by the average available sunlight hours throughout the year. This total available UV radiation was calculated for each study location (latitude and longitude were determined using Google Earth). Lack of availability can be estimated by either the negative or the inverse of the available UV radiation.

The total sunlight hours for a horizon angle of greater than 30° was multiplied by the average daily erythemal noontime UV radiation to derive the henceforth named available UV radiation. For plotting the confidence intervals, the mean, minimum and maximum of the interval was normalized to the mean value of the variable of interest to permit comparison between variables of different scales.

To explore extra geographical factors under multiple regression analysis, a two dimensional model of distance to a source was developed. This model repeatedly selects a random latitude and longitude (run 50 times) and iteratively calculates the distance to the random location from each of the 54 study locations. This distance variable is added to the available UVR model to create a double regression model of available UVR and distance to the random location. The algorithm then iteratively minimizes the p value of the double regression model by selecting adjacent locations and comparing p values using a recalculated distance. This algorithm was designed to walk towards a globally minimal p value using an iteratively updated distance in the double regression model.

Results

Global MS Prevalence Trend

A total of 85 candidate studies were found for further examination using the search criteria above (see Methods). Fifty-four studies met our inclusion and exclusion criteria; only four studies were available from the southern hemisphere, reflecting the global geopolitical distribution. The distribution of MS prevalence vs. latitude for the 54 studies is shown in Figure 1A.

Quantification of Risk from Ultraviolet Radiation

Observation of the prevalence trend in Figure 1A is suggestive of an external, environmental contribution to disease prevalence given the mirrored reflection at the equator. Ultraviolet radiation, contained in sunlight, follows a very similar pattern and also demonstrates a change in trend at approximately 23° latitude (north and south). The available UV radiation is an environmental correlate that is a function of both the average maximum daily UV radiation and the number of daylight hours that sunlight is incident upon a location. Multiplication of both of these factors daily and then summing the daily values over the year, provides an estimate of the yearly available UV radiation for a given location.

For visualization, the available UV radiation was singly regressed (ultimately scaled, flipped and shifted) to the prevalence data and plotted with the results of the 54 MS prevalence studies above (Figure 1A). The correlation of MS prevalence to inverse available UV radiation provides a good fit (Figure 1A) and suggests that the latter factor is a dominant correlate of disease prevalence which outweighs the contribution of all other factors examined.

We next used single regression analysis on several environmental and (potentially) confounding factors to search for modulators of MS prevalence. We found that available UV radiation produced the most significant correlation with prevalence (Figure 2), and this outranks latitude by a factor of 20, both in terms of contribution to the fit of the model and statistical significance. All other factors are small contributors compared with the available UV radiation.

Plotting the available UV radiation against prevalence (Figure 1B), a separable group of studies is apparent from the rest of the trend (represented by the closed red circles). A standard, unbiased estimator of clusters, the k-means algorithm (Matlab), was used to confirm that this is a significantly separable group in the two dimensional space of available UV radiation vs. prevalence. This group of studies represents all of the Scandinavian studies and a study of the Faroe Islands (eight studies total) in the 54 studies used. They are also the most northern of all the prevalence studies, they are geographically proximate, and are therefore of interest. These studies were removed for a separate single regression analysis of available UV radiation and the correlation was increased to an R^2 of 0.54 (p value of 7.2×10^{-9}) for the remaining 46 studies. We plotted the prevalence of all studies ranked by latitude and the cluster of studies are the northernmost of all the studies (as expected).

For the single regression model of MS prevalence and available UV radiation, the final residuals with their confidence intervals were analyzed. Three of the 54 studies had confidence intervals outside of the expected range: Northern Ireland and Linguaglossa, Sicily had prevalences higher than expected and Belgrade had a prevalence lower than expected. Therefore, the prevalence for approximately 95% of the MS prevalence studies within the past ten years could be predicted reliably by this single regression model. Such a model that factors available UV radiation could be useful to health ministries both for estimating their MS patient population and for allocating appropriate resources for a given region.

Multiple Regression Analysis

To explore possible combined effects of the singly-regressed variables, multiple regression analysis was performed using the stepwise regression toolkit in Matlab. As expected, the most significant variable, available UV radiation, was included at a p value of 1.0×10^{-6}. The only other two variables added into the model were latitude and longitude (to a p value of 9.2×10^{-8}) – all other variables were non-significant after this initial three-variable model was developed. This suggested that further geographical correlation was inherent in the dataset and that it

https://doi.org/10.1017/S0317167100011124 Published online by Cambridge University Press

involved both latitude and longitude components. For 50 separate analyses, a negative correlation was found to minimize the p value (and maximize the R^2 value) of the double regression model (available UV radiation and the extra geographical factor) with the location 54.8°N, 8.1°E (a location centered over Northern Ireland, which is geographically reasonably close to the latitudes of the Faroe Islands and of Scandinavia). This extra geographical factor confirms again that the prevalence from the Scandinavian studies significantly influences any simple modeling of the available UV radiation to MS prevalence. This minimal p value ($2.0x10^{-8}$) in the double regression model (including both the available UV radiation and the extra geographical factor) is less than the model with available UV radiation, latitude and longitude ($9.2x10^{-8}$, as above).

Further regression analysis in addition to the available UV radiation and the distance to 54.8°N, 8.1°E included two marginally (negatively) significant variables: methodology and smoking. A p value of $5.4x10^{-9}$ (R^2=0.55) was achieved with the inclusion of all four of these variables – a very strong negative correlation was noted with the available UV radiation. Additional negative correlation was achieved with the distance from northern Europe, smoking, and the accuracy of the methods.

Discussion

It was observed many decades ago that MS prevalence follows a north-south, equitoriofugal (reflected at the equator) gradient, modeled using strictly latitude as the modifying environmental parameter. In order to characterize this distribution, 54 prevalence studies from the previous ten years were analyzed. This global approach permits quantification of the correlation between environmental factors, such as the available UV radiation, and worldwide MS prevalence trends, and yields a highly correlated result between these two factors. This relationship between available UV radiation and MS prevalence is more correlated than with latitude and MS prevalence given the shape of the curve – there is an abrupt change in the curve of both the MS prevalence and the regressed available UV radiation at approximately 23° latitude, coinciding with the Tropics of Cancer and Capricorn which are the most northern and southern extents respectively that the sun may appear directly overhead (zenith angle of zero) during a year. Therefore, this novel approach has added further evidence towards a link between MS prevalence and available UV radiation.

The inverse association of available UV radiation and MS prevalence implicates vitamin D, since ultraviolet B radiation (280 to 315 nm) converts 7-dehydroxycholesterol to vitamin D3 in the epidermal and dermal layers and is the primary source of vitamin D_3 in humans[16]. Vitamin D deficiency has previously[17] and recently been suggested as a potential contributing factor in the pathogenesis of MS[18-20]. Due to the changing angle of declination of the sun, vitamin D insufficiency is common in the winter months in latitudes north of 42°N latitude[21]. Therefore, vitamin D is of interest as the biological correlate of available UV radiation.

Several comments are appropriate regarding other observations made with the regression analysis. The clustering of Scandinavian studies that measured a lower prevalence than the available UV radiation may be from a plateau effect above the Arctic Circle. An alternative explanation could be that the model of available sunlight hours is less accurate above certain latitudes[22]. A third explanation may be genetic/environmental interaction[23,24]. It has been hypothesized that the distribution of MS is related to a genetic trait originating from the Scandinavian countries with a declining genetic influence[25]. This cluster could also reflect chance alone.

Several sources have observed an increase in MS prevalence over the past few decades including one of our own studies[7], but was non-significant in the current analysis (Figure 2). Possibly, MS prevalence has not increased significantly over the past decade given the generally increased availability of diagnostic tools and neurologists. The fact that our prevalence study noted a plateauing of incidence since the late 1990s may be relevant in this regard. The sex ratio is a non-significant contributor (shown to have increased over the past several decades in our and other studies) but this variation is likely too small to be significantly measurable over the single decade of this analysis.

In our single regression analyses, we found that population smoking rate is a minor contributor to risk (Figure 2). This supports the contention that while some meta-analyses of case control studies at the clinical level have implicated smoking[26], the combined increased risk is low (odds ratio of 1.25) compared to available UV radiation which accounts for a 20 fold increase of risk from the equatorial regions to 60°N latitude (Figure 1A). These meta-analysis data are from clinical studies. As far as we could find, no correlation with MS prevalence and smoking has been analyzed at the population level as we have done. We have shown that either there is no effect when other factors are accounted for, or if there is an effect it is small. This is in keeping with the meta-analysis of the clinical data that shows only a minor increased risk of 25% with the small number of available studies. This does not rule out the possibility that in some individuals, there may be a biological effect.

Others have studied correlations with multiple purported causative agents[23,27-30]. However, the available UV radiation appears to be by far the single most important correlate of MS prevalence globally, suggesting that this factor may be one of the most important etiologic determinants of MS. Nonetheless, although this model estimates a general population trend with reasonable accuracy, it does not explain why certain individuals are more susceptible than others. Other factors such as genetic susceptibility on a population level may play a role. Additionally, mitigating factors such as skin pigmentation and use of sunscreen may alter serum vitamin D levels, although population studies have shown that vitamin D levels are correlated to both latitude and season through peripheral conversion[21]. Cultural modulations of serum vitamin D are also possible; countries with significant fortification of food or with diets containing higher vitamin D content may also change average population-based serum vitamin D concentrations.

Conclusion

Quantitative analyses of global epidemiologic and prevalence data collated from 54 studies emphasize that lack of available ambient UV radiation is the most significant environmental factor affecting the prevalence of MS. A low level of incident UV radiation outweighs other suspected environmental factors

https://doi.org/10.1017/S0317167100011124 Published online by Cambridge University Press

by at least 20 fold as a contributor to MS risk. Available UV radiation is a likely proxy for endogenous vitamin D production.

These results strengthen the observation that adequate UV radiation and vitamin D as key determinants of reducing the risks of developing MS.

References

1. Ebers GC. Environmental factors and multiple sclerosis. Lancet Neurol. 2008; 7(3):268-77.
2. Ascherio A, Munger K. Epidemiology of multiple sclerosis: from risk factors to prevention. Semin Neurol. 2008; 28(1):17-28.
3. Marrie RA. Environmental risk factors in multiple sclerosis aetiology. Lancet Neurol. 2004; 3(12):709-18.
4. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ. 1994; 309(6964):1286-91.
5. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol. 1983; 13(3):227-31.
6. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001; 50(1):121-7.
7. Sloka JS, Pryse-Phillips WE, Stefanelli M. Incidence and prevalence of multiple sclerosis in Newfoundland and Labrador. Can J Neurol Sci. 2005; 32(1):37-42.
8. Alonso A, Hernan MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology. 2008; 71(2):129-35.
9. Orton SM, Herrera BM, Yee IM, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol. 2006; 5(11):932-6.
10. Sadovnick AD. The genetics and genetic epidemiology of multiple sclerosis: the "hard facts". Adv Neurol. 2006; 98:17-25.
11. McPeters R, Krueger A, Bhartia P, Herman J. Earth probe Total Ozone Mapping Spectrometer (TOMS) data products user's guide. NASA Reference Publication. 1998; 1998-206895.
12. Wier AH, Bragg PL, Porter JL, Ravner JH. A winter wheat crop simulation model without water or nutrient limitations. Agric Sci. 1984; 102:371-82.
13. Turnbull DJ, Parisi AV. Utilising share to optimize UV exposure for vitamin D. Atmos Chem Phys. 2008; 8:2841-6.
14. Kimlin MG, Schallhorn KA. Estimations of the human 'vitamin D' UV exposure in the USA. Photochem Photobiol Sci. 2004; 3(11-12):1067-70.
15. Grifoni D, Carreras G, Zipoli G, Sabatini F, Dalla MA, Orlandini S. Row orientation effect on UV-B, UV-A and PAR solar irradiation components in vineyards at Tuscany, Italy. Int J Biometeorol. 2008; 52(8):755-63.
16. Webb AR, Holick MF. The role of sunlight in the cutaneous production of vitamin D3. Annu Rev Nutr. 1988; 8:375-99.
17. Acheson ED, Bachrach CA, Wright FM. Some comments on the relationship of the distribution of multiple sclerosis to latitude, solar radiation, and other variables. Acta Psychiatr Scand. 1960; 35 Suppl 147:132-47.
18. Ponsonby AL, Lucas RM, van dM, I. UVR, vitamin D and three autoimmune diseases-multiple sclerosis, type 1 diabetes, rheumatoid arthritis. Photochem Photobiol. 2005; 81(6): 1267-75.
19. VanAmerongen BM, Dijkstra CD, Lips P, Polman CH. Multiple sclerosis and vitamin D: an update. Eur J Clin Nutr. 2004; 58(8): 1095-109.
20. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. Neurology. 2004; 62(1):60-5.
21. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab. 1988; 67(2): 373-8.
22. Forsythe WC, Rykiel EJ, Stahl RS, Wu H, Schoolfield RM. A model comparison for daylength as a function of latitude and day of year. Ecol Modelling. 1995; (80):87-95.
23. Sloka JS, Pryse-Phillips WE, Stefanelli M. Multiple sclerosis in Newfoundland and Labrador--a model for disease prevalence. Can J Neurol Sci. 2005; 32(1):43-9.
24. Ramagopalan SV, Maugeri NJ, Handunnetthi L, et al. Expression of the multiple sclerosis-associated MHC class II Allele HLA-DRB1*1501 is regulated by vitamin D. PLoS Genet. 2009; 5(2): e1000369.
25. Poser CM. Viking voyages: the origin of multiple sclerosis? An essay in medical history. Acta Neurol Scand Suppl. 1995; 161: 11-22.
26. Hawkes CH. Smoking is a risk factor for multiple sclerosis: a metanalysis. Mult Scler. 2007; 13(5):610-5.
27. De Jager PL, Simon KC, Munger KL, Rioux JD, Hafler DA, Ascherio A. Integrating risk factors: HLA-DRB1*1501 and Epstein-Barr virus in multiple sclerosis. Neurology. 2008; 70(13 Pt 2):1113-8.
28. Grant WB. Hypothesis--ultraviolet-B irradiance and vitamin D reduce the risk of viral infections and thus their sequelae, including autoimmune diseases and some cancers. Photochem Photobiol. 2008; 84(2):356-65.
29. Hayes CE, Donald AE. A unifying multiple sclerosis etiology linking virus infection, sunlight, and vitamin D, through viral interleukin-10. Med Hypotheses. 2008; 71(1):85-90.
30. Holmoy T. Vitamin D status modulates the immune response to Epstein Barr virus: synergistic effect of risk factors in multiple sclerosis. Med Hypotheses. 2008; 70(1):66-9.

Supplemental References

1. Alshubaili AF, Alramzy K, Ayyad YM, Gerish Y. Epidemiology of multiple sclerosis in Kuwait: new trends in incidence and prevalence. Eur Neurol. 2005; 53(3):125-31.
2. Ares B, Prieto JM, Lema M, Dapena D, Arias M, Noya M. Prevalence of multiple sclerosis in Santiago de Compostela (Galicia, Spain). Mult Scler. 2007; 13(2):262-4.
3. Bergamaschi R, Montomoli C, Candeloro E, et al. Bayesian mapping of multiple sclerosis prevalence in the province of Pavia, northern Italy. J Neurol Sci. 2006; 244(1-2):127-31.
4. Bhigjee AI, Moodley K, Ramkissoon K. Multiple sclerosis in KwaZulu Natal, South Africa: an epidemiological and clinical study. Mult Scler. 2007; 13(9):1095-9.
5. Cheng Q, Miao L, Zhang J, et al. A population-based survey of multiple sclerosis in Shanghai, China. Neurology. 2007; 68(18): 1495-500.
6. de Sa J, Paulos A, Mendes H, Becho J, Marques J, Roxo J. The prevalence of multiple sclerosis in the District of Santarem, Portugal. J Neurol. 2006; 253(7):914-18.
7. Debouverie M, Pittion-Vouyovitch S, Louis S, Roederer T, Guillemin F. Increasing incidence of multiple sclerosis among women in Lorraine, Eastern France. Mult Scler. 2007; 13(8): 962-7.
8. El Salem K, Al Shimmery E, Horany K, Al Refai A, Al Hayk K, Khader Y. Multiple sclerosis in Jordan: a clinical and epidemiological study. J Neurol. 2006; 253(9):1210-6.
9. Etemadifar M, Janghorbani M, Shaygannejad V, Ashtari F. Prevalence of multiple sclerosis in Isfahan, Iran. Neuroepidemiology. 2006; 27(1):39-44.
10. Granieri E, Economou NT, De Gennaro R, et al. Multiple sclerosis in the province of Ferrara: evidence for an increasing trend. J Neurol. 2007; 254(12):1642-8.
11. Granieri E, Monaldini C, De Gennaro R, et al. Multiple sclerosis in the Republic of San Marino: a prevalence and incidence study. Mult Scler. 2008; 14(3):325-9.
12. Gray OM, McDonnell GV, Hawkins SA. Factors in the rising prevalence of multiple sclerosis in the north-east of Ireland. Mult Scler. 2008; 14(7):880-6.
13. Houzen H, Niino M, Hata D, et al. Increasing prevalence and incidence of multiple sclerosis in northern Japan. Mult Scler. 2008; 14(7):887-92.
14. Iuliano G, Napoletano R. Prevalence and incidence of multiple sclerosis in Salerno (southern Italy) and its province. Eur J Neurol. 2008; 15(1):73-6.

15. Klupka-Saric I, Ristic S, Sepcic J, et al. Epidemiology of multiple sclerosis in western Herzegovina. Clin Neurol Neurosurg. 2007; 109(9):779-83.
16. Lau KK, Wong WW, Sheng B, et al. The clinical course of multiple sclerosis patients in Hong Kong. J Neurol Sci. 2008; 268(1-2): 78-82.
17. McGuigan C, McCarthy A, Quigley C, Bannan L, Hawkins SA, Hutchinson M. Latitudinal variation in the prevalence of multiple sclerosis in Ireland, an effect of genetic diversity. J Neurol Neurosurg Psychiatry. 2004; 75(4):572-6.
18. Melcon MO, Gold L, Carra A, et al. Argentine Patagonia: prevalence and clinical features of multiple sclerosis. Mult Scler. 2008; 14(5):656-62.
19. Nicoletti A, Lo FS, Reggio E, et al. A possible spatial and temporal cluster of multiple sclerosis in the town of Linguaglossa, Sicily. J Neurol. 2005; 252(8):921-5.
20. Nicoletti A, Lo Bartolo ML, Lo FS, et al. Prevalence and incidence of multiple sclerosis in Catania, Sicily. Neurology. 2001; 56(1): 62-6.
21. Saadatnia M, Etemadifar M, Maghzi AH. Multiple sclerosis in Isfahan, Iran. Int Rev Neurobiol. 2007; 79:357-75.
22. Solaro C, Allemani C, Messmer UM, et al. The prevalence of multiple sclerosis in the north-west Italian province of Genoa. J Neurol. 2005; 252(4):436-40.
23. Toro J, Sarmiento OL, Diaz dC, et al. Prevalence of multiple sclerosis in Bogota, Colombia. Neuroepidemiology. 2007; 28(1): 33-8.
24. Williamson DM, Henry JP, Schiffer R, Wagner L. Prevalence of multiple sclerosis in 19 Texas counties, 1998-2000. J Environ Health. 2007; 69(10):41-5.
25. Tola MA, Yugueros MI, Fernandez-Buey N, Fernandez-Herranz R. Prevalence of multiple sclerosis in Valladolid, northern Spain. J Neurol. 1999; 246(3):170-4.
26. Callegaro D, Goldbaum M, Morais L, et al. The prevalence of multiple sclerosis in the city of Sao Paulo, Brazil, 1997. Acta Neurol Scand. 2001; 104(4):208-13.
27. Chancellor AM, Addidle M, Dawson K. Multiple sclerosis is more prevalent in northern New Zealand than previously reported. Intern Med J. 2003; 33(3):79-83.
28. Dean G, Yeo TW, Goris A, et al. HLA-DRB1 and multiple sclerosis in Malta. Neurology. 2008; 70(2):101-5.
29. Forbes RB, Wilson SV, Swingler RJ. The prevalence of multiple sclerosis in Tayside, Scotland: do latitudinal gradients really exist? J Neurol. 1999; 246(11):1033-40.
30. Ford HL, Gerry E, Airey CM, Vail A, Johnson MH, Williams DR. The prevalence of multiple sclerosis in the Leeds Health Authority. J Neurol Neurosurg Psychiatry. 1998; 64(5):605-10.
31. Garcia-Gallego A, Morera-Guitart J. [Prevalence and characteristics of multiple sclerosis in the health district of the Marina Alta]. Rev Neurol. 2002; 34(8):732-7.
32. Hernandez MA. Epidemiology of multiple sclerosis in the Canary Islands (Spain): a study on the island of La Palma. J Neurol. 2002; 249(10):1378-81.
33. Itoh T, Aizawa H, Hashimoto K, et al. Prevalence of multiple sclerosis in Asahikawa, a city in northern Japan. J Neurol Sci. 2003; 214(1-2):7-9.
34. Lau KK, Wong LK, Li LS, Chan YW, Li HL, Wong V. Epidemiological study of multiple sclerosis in Hong Kong Chinese: questionnaire survey. Hong Kong Med J. 2002; 8(2): 77-80.
35. Pugliatti M, Sotgiu S, Solinas G, Castiglia P, Rosati G. Multiple sclerosis prevalence among Sardinians: further evidence against the latitude gradient theory. Neurol Sci. 2001; 22(2):163-5.
36. Fox CM, Bensa S, Bray I, Zajicek JP. The epidemiology of multiple sclerosis in Devon: a comparison of the new and old classification criteria. J Neurol Neurosurg Psychiatry. 2004; 75 (1):56-60.
37. Mayr WT, Pittock SJ, McClelland RL, Jorgensen NW, Noseworthy JH, Rodriguez M. Incidence and prevalence of multiple sclerosis in Olmsted County, Minnesota, 1985-2000. Neurology. 2003; 61 (10):1373-7.
38. Pekmezovic T, Jarebinski M, Drulovic J, Stojsavljevic N, Levic Z. Prevalence of multiple sclerosis in Belgrade, Yugoslavia. Acta Neurol Scand. 2001; 104(6):353-7.
39. Nicoletti A, Sofia V, Biondi R, et al. Epilepsy and multiple sclerosis in Sicily: a population-based study. Epilepsia. 2003; 44(11): 1445-8.
40. Totaro R, Marini C, Cialfi A, Giunta M, Carolei A. Prevalence of multiple sclerosis in the L'Aquila district, central Italy. J Neurol Neurosurg Psychiatry. 2000; 68(3):349-52.
41. Modrego PJ, Pina MA. Trends in prevalence and incidence of multiple sclerosis in Bajo Aragon, Spain. J Neurol Sci. 2003; 216(1):89-93.
42. McDonnell GV, Hawkins SA. An epidemiologic study of multiple sclerosis in Northern Ireland. Neurology. 1998; 50(2):423-8.
43. Sloka JS, Pryse-Phillips WE, Stefanelli M. Incidence and prevalence of multiple sclerosis in Newfoundland and Labrador. Can J Neurol Sci. 2005; 32(1):37-42.
44. Grytten N, Glad SB, Aarseth JH, Nyland H, Midgard R, Myhr KM. A 50-year follow-up of the incidence of multiple sclerosis in Hordaland County, Norway. Neurology. 2006; 66(2):182-6.
45. Smestad C, Sandvik L, Holmoy T, Harbo HF, Celius EG. Marked differences in prevalence of multiple sclerosis between ethnic groups in Oslo, Norway. J Neurol. 2008; 255(1):49-55.
46. Gronlie SA, Myrvoll E, Hansen G, Gronning M, Mellgren SI. Multiple sclerosis in North Norway, and first appearance in an indigenous population. J Neurol. 2000; 247(2):129-33.
47. Sundstrom P, Nystrom L, Forsgren L. Incidence (1988-97) and prevalence (1997) of multiple sclerosis in Vasterbotten County in northern Sweden. J Neurol Neurosurg Psychiatry. 2003; 74 (1):29-32.
48. Celius EG, Vandvik B. Multiple sclerosis in Oslo, Norway: prevalence on 1 January 1995 and incidence over a 25-year period. Eur J Neurol. 2001; 8(5):463-9.
49. Kurtzke JF, Heltberg A. Multiple sclerosis in the Faroe Islands: an epitome. J Clin Epidemiol. 2001; 54(1):1-22.
50. Sumelahti ML, Tienari PJ, Wikstrom J, Palo J, Hakama M. Increasing prevalence of multiple sclerosis in Finland. Acta Neurol Scand. 2001; 103(3):153-8.