

## Regional Variation in Multiple Sclerosis Prevalence in Australia and Its Association with Ambient Ultraviolet Radiation

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### Key Words

Multiple sclerosis · Prevalence · Photoimmunology · Ultraviolet radiation · Vitamin D<sub>3</sub>

### Abstract

The aim of this study was to conduct an ecological analysis of the extent to which ultraviolet radiation (UVR) levels might explain the regional variation of multiple sclerosis (MS) in Australia. MS prevalence data for six Australian regions were compared with UVR levels of the largest city in each region, with some other climatic variables and with the melanoma incidence in the same regions. A close association was found between the theoretical MS prevalence predicted from UVR levels and the actual prevalence. Furthermore, the negative correlation between UVR and MS prevalence ( $r = -0.91$ ,  $p = 0.01$ ) was higher than the positive correlation observed for UVR and malignant melanoma incidence ( $r = 0.75$ ,  $p = 0.15$  for males and  $r = 0.80$ ,  $p = 0.10$  for females). This study demonstrated that the regional variation in MS prevalence in the continent of Australia could be closely predicted by regional UVR levels. It is consistent with the hypothesis that UVR exposure may reduce the risk of MS

possibly via T-lymphocyte-mediated immunosuppression. Analytical epidemiology studies are required to investigate this specific hypothesis.

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Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS). It is the most common neurological condition occurring during young adulthood and, despite extensive research, the aetiology of this serious disease remains unclear. To date, the key pathology of MS appears to involve a defect in immunological self-tolerance, possibly in conjunction with an infectious agent, resulting in a subsequent attack on myelin proteins mediated by T helper cells [1]. It is thought that type 1 T helper cells (Th1) mediate this attack and that experimental allergic encephalomyelitis (EAE), the animal model of MS, is initiated by Th1 cells [2]. There is accumulating evidence that one or more infectious agents trigger the disease in a genetically susceptible host, but the diverse nature of viral peptides that are capable of stimulating myelin basic protein-specific T cells indicate that a number of common pathogens may initiate the disease [1]. If one or more infectious agents trigger the disease, the

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status of the Th1 cell activity at the time of infection or during the period of host response could be of critical importance.

One of the most striking epidemiological features of MS is a gradient of increasing prevalence with increasing latitude [3]. In Australia, a more than sixfold increase in age-standardized MS prevalence has been demonstrated from tropical Queensland to Tasmania [4–7]. Within Europe and the United States, there is also an at least two- to threefold gradient of increasing MS prevalence with increasing latitude [3]. These geographical differences were initially interpreted to represent environmental influences which varied by latitude, such as climatic factors [8–12], dietary characteristics [13] and infectious agents [14]. More recent analyses indicate that geographical MS variation, at least in North America, may result from a complex interplay of genes and environment [15]. The marked Australian latitudinal gradient found in the national prevalence survey of 1981 [4–7] is unlikely to be explained by genetic factors only, because the gradient is evident even among UK and Irish immigrants to Australia, a population subgroup that is predominantly Caucasian [16]. These findings together with the large latitudinal spread across the continent, stretching from 10° to 44° South in latitude, and a uniform health care system provide a good opportunity to examine the relationship between latitude-related factors and MS.

Several early studies reported MS prevalence to be inversely associated with levels of solar radiation [8–10], especially winter solar radiation [8], but others did not [11, 12]. In the study by Acheson et al. [8], the inverse association between solar radiation and MS prevalence persisted after adjustment for latitude. The possible protective effect of solar radiation on MS was not intensively investigated, partly because research evidence to support UVR-mediated changes in immune function was not then available. However, new insights into photoimmunology have provided support for the possibility that solar radiation exposure may have a beneficial effect on the autoimmune processes that underlie MS via an immunosuppressive effect on Th1 cell activity [17–20]. Thus, recent immunological evidence indicates that a re-examination of the relationship between UVR, latitude and MS is required [17].

The aim of this study was to conduct an ecological analysis of the extent to which UVR levels might explain the regional variation of MS in Australia. We contrasted the relationship between UVR and MS prevalence with that of UVR and melanoma incidence, because the latter association has previously been demonstrated to be causal [21].

## Methods

### *Sources of Data*

Australian MS data (crude prevalence, age-standardized prevalence, number of MS patients, total populations) for tropical Queensland, subtropical Queensland, Western Australia, New South Wales, South Australia and Hobart (Tasmania) were obtained from MS prevalence surveys carried out in 1981 [4–7]. The state of Queensland is divided by the Tropic of Capricorn (at ca. 23.5° S latitude) into a tropical and a subtropical zone. The crude prevalence was defined as the ratio of persons with an acceptable diagnosis of MS living in the defined area on June 30th, 1981 (National Census Day) to the total population of the same area on the same day, and was expressed per 100,000 of population [4–7]. Age-standardized prevalences were calculated using the Australian population on June 30th, 1981 as the reference population [4–7]. Cases were ascertained from hospital records, treating doctors, MS Societies, Department of Veteran Affairs records and the Australian Bureau of Statistics [4]. The State Chronic Care Hospital Register and Commonwealth Department of Health notifications were also used in the Hobart region [6]. All patients were interviewed and examined, in regions other than New South Wales, where only 57% of the patients were interviewed and examined due to the large number of patients notified [4]. However, almost all of the remaining 43% of patients in New South Wales had been examined previously by a neurologist [4]. All patients in whom the diagnosis of MS was considered to be correct were classified, according to the diagnostic criteria of Rose et al. [22], into clinically Definite, Probable or Possible groups. A 10% sample of examined MS patients were also reviewed by an independent assessor to assess the correctness of the diagnosis and of the diagnostic classification of each patient [4–7]. The veracity of the basic diagnosis was not disputed in any case in Queensland, Western Australia and Hobart, but the category of subtype disease was reclassified in 17, 30 and 20% of cases, respectively [5–7]. This information was not provided for New South Wales and South Australia [4].

Monthly climate data – bright sunshine hours per day, maximum temperature (°C), minimum temperature (°C) and rainfall (mm) – were obtained from the Bureau of Meteorology of the Commonwealth of Australia for the largest city in each region (Townsville, Brisbane, Perth, Sydney, Adelaide and Hobart) for the 10-year period 1971–1980. Erythema (skin-reddening) estimates for the nearest latitude and longitude to those cities were taken from data published on the website of the National Center for Atmospheric Research (Germany). Those measurements were derived from satellite-based observations of atmospheric ozone and cloud reflectivity over the period 1979–1992. Spectral irradiance was calculated every 30 min at 1-mm steps from 280 to 400 nm (covering the UVA and UVB spectrum) using a geographical resolution of 1.25° longitude by 1.00° latitude.

Because UVR is an environmental causal factor for cutaneous malignant melanoma [21], melanoma incidence data were compared with MS prevalence data. Melanoma incidence data were used for the regions Western Australia, New South Wales, South Australia and Tasmania for the period 1978–1982 [23]. For Queensland, data for the entire state in 1982 were used. Separate data for tropical and subtropical Queensland and for the other years were not available. The incidence densities were the average annual world age-standardized rates per 100,000 population by sex and were provided by the State Cancer Registries.

**Table 1.** Observed MS prevalence in Australia and theoretical UVR-predicted MS prevalence with prevalence ratios (PR) relative to Tasmania and 95% confidence intervals (CI)

Region	Crude observed			Predicted from UVR levels		
	prev.	PR	95% CI	prev.	PR	95% CI
Hobart (Tasmania)	74.2	1.00		71.7	1.00	
New South Wales	37.2	0.50	0.42–0.60	36.7	0.51	0.49–0.53
South Australia	29.4	0.40	0.32–0.49	32.7	0.46	0.44–0.47
Western Australia	25.0	0.34	0.27–0.41	23.0	0.32	0.30–0.34
Subtropical Queensland	20.9	0.28	0.23–0.35	22.0	0.31	0.29–0.32
Tropical Queensland	11.1	0.15	0.11–0.21	10.1	0.14	0.12–0.16

**Table 2.** Pearson correlations between climatic variables and age-standardized MS prevalence in Australia

	Correlation	p value
Mean annual maximum temperature, °C	-0.93	0.01
Mean annual UVR level, kJ/m <sup>2</sup> /day	-0.91	0.01
Latitude	0.89	0.02
Mean annual bright sunshine, h	-0.87	0.03
Mean annual minimum temperature, °C	-0.84	0.04
Mean annual rainfall, mm	-0.54	0.26

#### Statistical Analysis

Average annual means of climatic variables were calculated for the largest city of each region. The latitudes used for each region were the latitudes of those cities. Poisson regression under standard assumptions (log-linear relationship, Poisson errors, logarithm of population as an offset, maximum likelihood fitting) was used to calculate the crude prevalence for each region relative to Tasmania using binary (0, 1) terms for regions other than Tasmania. The 95% confidence intervals were calculated from the standard errors. To estimate the prevalence in each region that was predicted by its climate, a linear predictor taking the values for each city of one of the climate variables was used in the Poisson regression model in place of binary (0, 1) predictors. In a separate regression for each region the predictor variable was centered to have the zero value for that region. The predicted prevalence of that region was then calculated by exponentiating the model intercept. To estimate the prevalence of a region relative to the predicted value for Tasmania, the logarithm of the predicted value for Tasmania was subtracted from the offset term. The prevalence ratio was then obtained by exponentiating the intercept. The 95% confidence intervals were calculated from the standard error of the intercept. Pearson correlation coefficients were calculated for associations of climatic variables and latitude with age-standardized MS prevalence. For the correlations with the melanoma incidence the age-standardized MS prevalence in total Queensland was used (18.3 per 100,000), but data for Brisbane (its capital city) were used for the climatic variables. Correlation coefficients of climatic variables with MS prevalence and melanoma incidence were compared using Fisher's transform. The relationships between UVR, sunshine, latitude, melanoma incidence and age-standardized MS prevalence were fitted with polynomial curves which included the

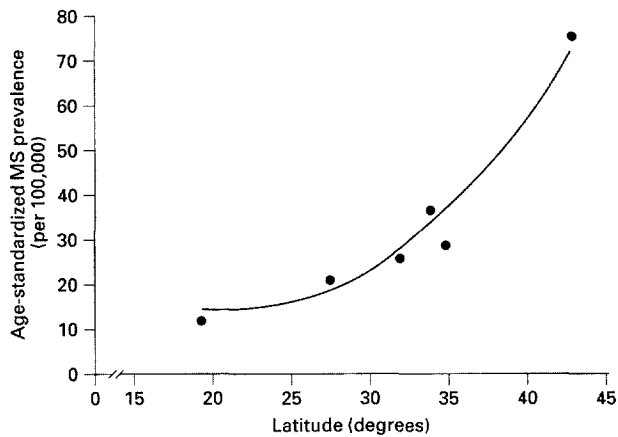
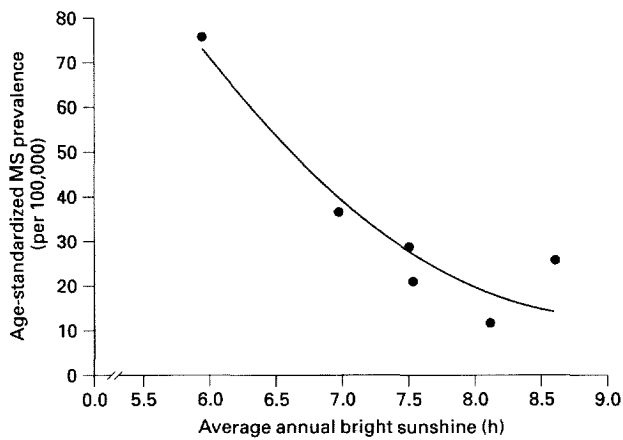
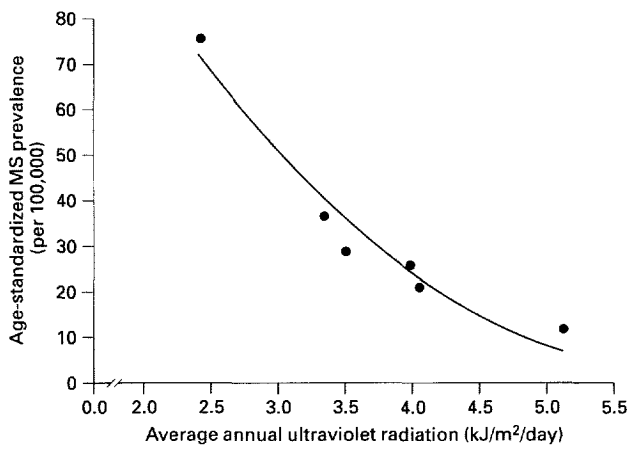
predictor and its square. Comparing state-wide prevalence data with climate or latitude of the largest city in the region would be subject to error if the climate or latitude of the city was not representative of the entire region. However, the representative latitudes, temperatures or rainfalls calculated for the populations of the six largest cities of South Australia, New South Wales and Western Australia in every case differed by less than 3% from the value of that variable for the capital city. For Hobart, the MS prevalence and climate data were obtained from the same area. To check whether or not the annual UVR levels changed substantially from 1979 to 1992 the linear association between annual UVR levels and year was estimated in a linear regression model that allowed the intercept but not the slope to differ between states (there was no evidence that the slope differed between cities). The annual increase in UVR levels was small ( $\beta = 0.003$ ,  $p = 0.41$ ).

## Results

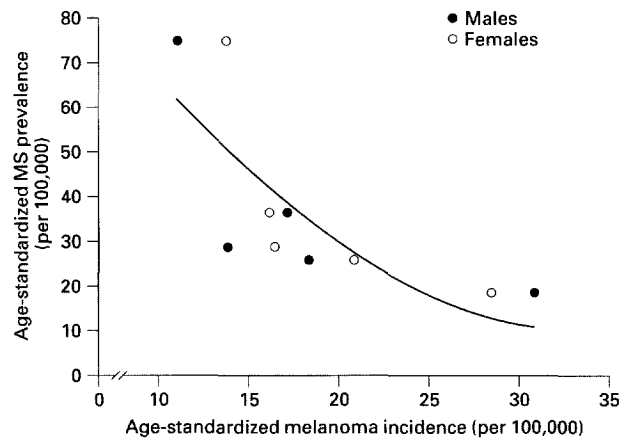
### Relationship between Climatic Variables and MS Prevalence

In Australia, average annual UVR levels increased by a factor of 2.1 from 2.4 kJ/m<sup>2</sup>/day in Tasmania to 5.1 kJ/m<sup>2</sup>/day in tropical Queensland. Table 1 shows that the UVR-predicted MS prevalences closely matched the actual crude MS prevalences observed in each region. Similarly, the UVR-predicted prevalence ratios for each of the five regions compared to Tasmania were very close to the actual prevalence ratios, with the UVR-predicted prevalence ratios within the 95% confidence interval of the observed prevalence ratios for each region. Prevalence ratios estimated from mean annual maximum temperature were also close to those actually observed, but prevalence ratios estimated from annual minimum temperature were not (data not shown).

The age-standardized MS prevalences were 75.6, 36.6, 28.8, 25.9, 21.0 and 11.8 for Hobart, New South Wales, South Australia, Western Australia, subtropical Queensland and tropical Queensland, respectively and they only differed slightly from the crude values. Correlation coeffi-



**Fig. 1.** The relationships of UVR, bright sunshine and latitude to Australian age-standardized MS prevalence with fitted polynomial curves.



**Fig. 2.** The relationship of melanoma incidence to Australian age-standardized MS prevalence with a fitted polynomial curve.

coefficients for the association of the different climatic variables with the age-standardized MS prevalences are shown in table 2. Again, UVR levels and maximum temperature were most strongly correlated with observed MS prevalence, providing correlations of  $-0.91$  ( $p = 0.01$ ) and  $-0.93$  ( $p = 0.01$ ), respectively. Figure 1 shows scatter diagrams with polynomial curves fitted to show the relationships between UVR, hours of bright sunshine and latitude and age-standardized MS prevalence. The UVR level was highly correlated with maximum temperature ( $r = 0.94$ ,  $p = 0.05$ ) and bright sunshine hours ( $r = 0.82$ ,  $p = 0.05$ ).

#### *Comparison of Melanoma and MS Prevalence with Regard to UV Radiation*

The correlation of melanoma incidence with latitude ( $r = -0.88$ ,  $p = 0.05$  for both, males and females) was of similar magnitude but in opposite direction to the correlation of MS prevalence with latitude, while the correlations with UVR ( $r = 0.75$ ,  $p = 0.15$  for males and  $r = 0.80$ ,  $p = 0.10$  for females) and bright sunshine ( $r = 0.42$ ,  $p = 0.49$  for males and  $r = 0.54$ ,  $p = 0.35$  for females) were both non-significantly lower than for MS. The correlations between melanoma incidence and MS prevalence were  $-0.69$  ( $p = 0.19$ ) for males and  $-0.72$  ( $p = 0.17$ ) for females. The scatter diagram with fitted polynomial curves shows the inverse relationship between melanoma incidence and age-standardized MS prevalence (fig. 2).

## Discussion

We examined associations of regional MS prevalence within Australia and UVR levels experienced by a significant proportion of the population in several regions. We found a close association between theoretical prevalence predicted from the UVR levels and the actual MS prevalence by region.

The development of MS appears to involve a complex interaction between genetic and environmental factors [15]. This study was conducted on a relatively homogeneous population, which has advantages when examining environmental exposures as conducted in this study. Furthermore, the population covers a large geographic area with marked climatic variation, and the data of the prevalence studies used had been obtained by a nearly identical method of estimating prevalence in the different regions which makes the occurrence of selection bias unlikely.

These ecological data support the previously proposed inverse relationship between UVR and MS, but they need to be interpreted with caution because of possible ecological biases. Exposure misclassification may have occurred as UVR doses have not been measured at an individual level. For most individuals, personal UVR exposure varies between 5 and 15% of daily total ambient UVR [24]. The dose an individual receives will depend on ambient UVR, the time spent outside and the amount of clothing/sunscreen worn. We were unable to take those behavioral factors into account, although it seems likely that if we could control for them, the observed inverse pattern between UVR and MS would be strengthened. In a colder climate, behavioral changes (less outdoor activity and more outdoor clothing) will further decrease personal UV exposure. Here, the finding that maximum, but not minimum, temperature correlated highly with the age-standardized MS prevalence is consistent with maximum temperature increasing individual sun exposure behavior as well as with the correlation between UVR and maximum temperature. We cannot exclude the contribution of selective migration after onset of MS as we examined disease prevalence, not incidence. We were unable to control for latitude when examining the relationship between UVR and MS due to collinearity and the low number of data points. In addition, other potential ecological confounders or effect modifiers, such as gender, age or skin type, were also unable to be assessed in this ecological analysis. In particular, the transmission of infectious disease is influenced by climate, and infectious agents have been implicated in the pathogenesis of MS [14]. The observation that MS is generally more common in fe-

males [25] is consistent with our findings, as it has been previously reported that females generally have a lower UVR exposure than males [24]. It will be important to examine whether control for personal UVR exposure reduces the previously established [25] positive association between female gender and MS prevalence.

New insights into photoimmunology have provided support for the possibility that UVR could attenuate the autoimmune process that underlies MS [17]. Recent reviews indicate that UVR is able to influence the local and systemic immune response to viral or other infections [26, 27]. The mechanisms by which UVR might suppress the cellular immune response are diverse. UVR has demonstrated effects on Langerhans cells, natural killer cell activity and cytokine profile which all influence antigen presentation and suppress Th1-cell-mediated immune responses [26, 27]. These intracellular and intercellular signalling alterations may explain why UVR exposure has been found to prevent or delay the clinical symptoms of EAE in mice [28].

UVR could also act via alterations in vitamin D<sub>3</sub> [18] or melatonin [19, 20]. The active form of vitamin D<sub>3</sub>, 1,25-(OH)<sub>2</sub> D<sub>3</sub>, displays immunomodulatory properties in vivo as well as in vitro [29–32]. Research on EAE has shown that administration of 1,25-(OH)<sub>2</sub> D<sub>3</sub> at the time of immunization has protective effects, such as delayed onset, decreased severity of symptoms and prolonged survival [33], while vitamin D deficiency accelerates EAE onset [34]. Vitamin D-supplemented MS patients experienced, after a period of 1–2 years, less than half the number of exacerbations expected on the basis of their case histories [35]. In a Japanese MS case-control study, an excessive representation of the b allele for the vitamin D receptor gene (OR 2.45; 95% CI 1.20–5.00) was found among MS patients compared to controls [36], but no evidence for linkage or association of vitamin D receptor gene or other candidate genes for MS was found in a Canadian population [37].

The high correlation between UVR and bright sunshine hours in our study indicates that light itself could also be an important environmental factor. An increased amount of light would decrease melatonin production by the pineal gland [38] and this decrease has been hypothesized to attenuate the autoimmune process underlying MS [19, 20]. Melatonin or constant darkness have been shown to enhance Th1 cell-mediated autoimmunity [39–41], while pinealectomy or continuous light exposure have been demonstrated to have an inhibitory effect on autoimmunity in animal models [39]. Blocking the interaction between melatonin and its receptor by luzindole

prevented the development of EAE in 22 of 23 mice [39]. In conclusion, it seems that sun exposure can exert an effect via different mechanisms which all suppress the Th1 cell activity and is thought to play a central role in the autoimmune process of MS.

These ecological data are unable to provide information on timing of sun exposure. UVR could play a critical role in the acquisition, clinical manifestation and progression of the disease. Animal models have demonstrated that UVR, vitamin D injections, continuous light exposure or melatonin blocking could prevent autoimmunity, delay the onset of EAE, decrease the severity of symptoms and/or prolong survival, and that the timing of treatment influences the results [28, 33, 34, 39]. So it seems that the immunological status may be altered by UVR or vitamin D<sub>3</sub> and that this status at the time of immunization is important in order to prevent the clinical signs of EAE. It is known that in humans UVR can suppress Th1 cell activity for several weeks [27]. The status of the Th1 cell activity, influenced by the amount of sunlight, could potentially play a critical role in the pathogenesis of MS, either at the time of initial infection or during the period of host response to that infection. A viral candidate for infection could be the Epstein-Barr virus (EBV). A recent meta-analysis reviewing case-control studies that assess the relationship between anti-EBV seropositivity and MS, estimated a summary odds ratio of 13.5 (95% confidence interval 6.4–31.4) [42].

The inverse associations between MS prevalence and melanoma incidence in this analysis were also consistent with a postulated protective effect of UVR on MS. UVR is a well-established environmental causal factor for melanoma, although the associations are complex in regard to timing, sun exposure intensity and duration and skin type

[43, 44]. The association of latitude with melanoma incidence was of a magnitude similar to that with MS prevalence, but the correlation between UVR and malignant melanoma was weaker than that between UVR and MS prevalence. Freedman et al. [45] contrasted the relative strength of associations between solar radiation and both MS and nonmelanoma skin cancer. Using a case-control approach, the negative association between the combined effect of the highest level of residential and occupational exposure to sunlight and MS mortality was high (OR = 0.24, 95% confidence interval 0.15–0.38) compared with the positive association for nonmelanoma skin cancer (OR = 1.38, 95% confidence interval 1.12–1.69). Both comparative analyses indicate that further assessment of UVR as a causal protective factor in the aetiology of MS is warranted.

In conclusion, this ecological analysis demonstrates that the regional variation of MS prevalence on the continent of Australia can be closely predicted by regional ambient UVR levels. This is consistent with recent immunological evidence suggesting that personal exposure to ultraviolet radiation may reduce the risk of acquiring MS due to UVR-induced immunosuppression. Analytical epidemiology studies investigating this specific hypothesis are now required.

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