ABSTRACT

Objective: To assess the potential relationship of ultraviolet B radiation (UVB) and Epstein-Barr virus (EBV) exposure in explaining the period prevalence of multiple sclerosis (MS) in England.

Methods: English national Hospital Episode Statistics covering all admissions to National Health Service hospitals in England in the 7 years from 1998 to 2005 were used to obtain the period prevalences of MS and infectious mononucleosis (IM) in England. The United States National Aeronautics and Space Administration’s data on UVB intensity for England from the Nimbus 7 satellite was collected. The relationships among the 3 variables (MS prevalence, IM prevalence, and UVB intensity) were investigated.

Results: The regression of MS against UVB intensity for all seasons had an $r^2$ of 0.61; when including the interaction of IM with seasonal UVB, the $r^2$ rose to 0.72.

Conclusions: UVB exposure and IM together can explain a substantial proportion of the variance of MS. The effect of UVB on generating vitamin D seems the most likely candidate for explaining its relationship with MS. There is a pressing need to investigate the role of vitamin D and EBV and how they might interact to influence MS risk to identify potential prevention strategies.

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GLOSSARY
EBV = Epstein-Barr virus; HES = Hospital Episode Statistics; ICD = International Classification of Diseases; IM = infectious mononucleosis; MS = multiple sclerosis; NHS = National Health Service; NASA = National Aeronautics and Space Administration; SHA = English Strategic Health Authorities; UVB = ultraviolet B radiation.

Multiple sclerosis (MS) is the most common disease of the CNS in young adults of Northern European descent.1 MS seems unlikely to result from a single causative event; instead, the disease seems to develop in genetically susceptible populations as a result of environmental exposures.2

The most striking illustration of the importance of the environment in MS is its geographical distribution.3 Within regions of temperate climate, MS incidence and prevalence are thought to increase with latitude.3,4 The latitudinal trend starts around 42 degrees of latitude North.5 A cutoff at this latitude implicates solar wavelengths in the shorter UV range (ultraviolet B [UVB]) as UVB is strongly affected by the solar zenith angle.6 There is also a month of birth effect for MS,7 which is also indicative of solar-correlated processes, and this effect is itself strongly latitude-dependent.

We have recently reported period prevalence values for MS across England.8 Epstein-Barr virus (EBV) is a B-lymphotropic human DNA herpesvirus that infects most individuals asymptomatically but in some people causes infectious mononucleosis (IM) upon infection.9 Because the risk of MS is increased in individuals with a clinical history of IM,10-12 we also compared the geography of MS with the distribution of IM, and observed a strong correlation, but this was
not enough to fully account for the variance of MS. Recent studies have documented the inverse relationship between MS prevalence and UV exposure. In the present study, we assess how the prevalence of MS and IM relates to UVB exposure.

**METHODS** Standard protocol approvals, registrations, and patient consents. The English NHS Central Office for Research Ethics approved this study.

**MS and IM prevalence data.** As published, we analyzed data on hospital admissions for MS from linked hospital admission statistics, assembled from the English national Hospital Episode Statistics (HES) system. This covered all admissions to National Health Service (NHS) hospitals in England in the 7 years from April 1, 1998, to March 31, 2005 (population: 51 million). We identified cases of MS as code G35 in the 10th revision of the International Classification of Diseases (ICD). The English national linked HES database includes information about all people who are admitted to hospital (including day care as well as overnight stays). Using data linkage, we identified each person only once for MS, regardless of how many admissions each person had, and recorded their residence out of 28 English Strategic Health Authorities (SHAs) at first known admission for MS. Admission rates were calculated using numbers of admissions for residents of each area as the numerators and the total resident populations of the area as the denominators. To adjust for differences in the age structure of different areas, age standardization was undertaken using the indirect method and the age-specific rates in 5-year age groups in the English population as the standard. We undertook the same calculations for hospital admissions for people with IM, varicella, infection, and cytomegalovirus infections using the ICD codes B27, B01, and B25 to identify them.

**UV.** We used the US National Aeronautics and Space Administration’s (NASA’s) data for the single wavelength of 305 nm at noon (J.R. Herman, 2003, NASA Goddard Centre, Greenbelt, MD). This single wavelength data slightly overestimates the amount of UVB at its prime physiologically active wavelengths which are 290–295 nm. The data also tend to overestimate ground availability of UVB by approximately 15% in areas where there is dense optical pollution from particulates and aerosols formed from oxides of sulfur and nitrogen. The data model has allowances for natural clouds but the sensor will read the reflection from the top of polluted cloud formations, thereby overestimating ground values. The magnitude of this error is not expected to be large for the United Kingdom because it is on the oceanic side of the prevailing wind and so does not carry much pollution. The error will be greater in urban areas. The NASA data for the single wavelength of 305 nm at noon collected on the Nimbus 7 satellite from 1978–1992 was sampled for 5 days centered on the 22nd of each month and averaged over the whole period. This data reduction was necessary due to the enormous size of the dataset comprising more than 60,000 readings a day for 14 years. This solar month sampling also has the advantage of catching the full range of the annual variation because it captures the solstices and overcomes the problem of differing numbers of days per calendar month. The data were further averaged into seasons and integrated for the area of each of the 28 SHAs using ArcGIS (ESRI, 2009, Redlands, CA, 9.3.1 ArcInfo). See figure 1 for a map of spring season UVB 305 nm for the SHAs of England.

**Analysis.** The data were subjected to exploratory data analysis, consisting of inspecting the correlation matrix and evaluation using principal component analysis. The final analysis was a least-squares regression analysis. To test for geographic dependencies the data were tested by looking at quantile–quantile plots of the residuals, and performing geographically weighted regression. The data were considered suitable for ordinary least squares regression, ArcGIS, and Geospatial Analyst (ESRI 2009) and S-Plus (Insightful Corp., S-PLUS 6.2 [2003], Insightful Corp., Seattle, WA).

**RESULTS** Correlations between seasonal UVB and MS and IM. The correlations between seasonal UVB intensity with latitude and both MS and IM prevalence are shown in table 1. As shown previously, MS was highly correlated with IM (0.69). As a control, we also examined the correlations of MS with cytomegalovirus prevalence (0.05), and MS with varicella prevalence (0.21), which were both nonsignificant. Annual average UVB was not correlated with IM (0.02) nor with cytomegalovirus (0.19), and was only moderately correlated with varicella (−0.41), whereas the annual average UVB is more weakly correlated with MS (−0.29). The correlation between MS and latitude was stronger than the correlation between IM and latitude (0.46 and 0.16, respec-
Principal components analysis. The first 2 components in the principal components analysis together accounted for 99.7% of the variance for MS (table 2). The interaction term for MS and IM together with spring UVB were the most important factors in determining MS variance. Next were the interaction terms for MS and IM together with summer and autumn UVB. Of more minor importance were the interaction terms for MS on its own with spring, summer, or autumn UVB as well as IM with spring UVB. The way MS and IM interact with UVB is more important to MS prevalence than just MS and UVB independently.

Multivariate regression. The regression of MS against a single season UVB had $r^2$ values ranging between 0.03 (summer, $p = 0.38$) and 0.23 (spring, $p = 0.009$) (table 3). The regression of MS against UVB for all seasons had an $r^2$ of 0.61 ($p = 0.0001$). When including the interaction of IM with seasonal UVB the $r^2$ rose to 0.72 ($p = 0.001$). The regression line for the relationship of UVB to MS for all seasons is a very good fit to the data (figure 2A) and the residuals show little nonrandom structure (figure 2B). Most of the variance has therefore been explained by this model.

**DISCUSSION** We show that the distribution of MS across England is explained both by UVB exposure and the prevalence of IM. In England, there is a definite latitudinal cline in MS occurrence but a weaker cline in IM, and as expected, IM prevalence could not entirely explain the variance of MS. Incorporating a linear model for MS with an interaction term for IM and UVB could explain 72% of the variance of MS prevalence across England. Interestingly, it is spring UVB that is most strongly associated. Lower levels of UVB in the spring season would coincide with late gestation for offspring born in late spring/early summer. This corresponds with the time for peak risk of MS by month of birth.7

There are several possible mechanisms through which UVB radiation could be mediating the effect

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**Table 1** Correlations between seasonal UVB with latitude, MS, and IM prevalence

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>IM</th>
<th>UVB summer</th>
<th>UVB autumn</th>
<th>UVB winter</th>
<th>UVB spring</th>
<th>Latitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>1.00</td>
<td>0.69</td>
<td>−0.17</td>
<td>−0.47</td>
<td>−0.39</td>
<td>−0.48</td>
<td>0.46</td>
</tr>
<tr>
<td>IM</td>
<td>0.69</td>
<td>1.00</td>
<td>0.10</td>
<td>−0.13</td>
<td>−0.07</td>
<td>−0.21</td>
<td>0.16</td>
</tr>
<tr>
<td>UVB summer</td>
<td>−0.17</td>
<td>0.10</td>
<td>1.00</td>
<td>0.88</td>
<td>0.95</td>
<td>0.90</td>
<td>−0.91</td>
</tr>
<tr>
<td>UVB autumn</td>
<td>−0.47</td>
<td>−0.13</td>
<td>0.88</td>
<td>1.00</td>
<td>0.95</td>
<td>0.96</td>
<td>−0.98</td>
</tr>
<tr>
<td>UVB winter</td>
<td>−0.39</td>
<td>−0.07</td>
<td>0.95</td>
<td>0.95</td>
<td>1.000</td>
<td>0.97</td>
<td>−0.99</td>
</tr>
<tr>
<td>UVB spring</td>
<td>−0.48</td>
<td>−0.21</td>
<td>0.90</td>
<td>0.96</td>
<td>0.97</td>
<td>1.000</td>
<td>−0.99</td>
</tr>
<tr>
<td>Latitude</td>
<td>0.46</td>
<td>0.16</td>
<td>−0.91</td>
<td>−0.98</td>
<td>−0.99</td>
<td>−0.99</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Table 2** Principal component analysis for MS

<table>
<thead>
<tr>
<th>Component 1 loadings</th>
<th>Component 2 loadings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS: IM</td>
<td></td>
</tr>
<tr>
<td>MS: spring</td>
<td>−0.450</td>
</tr>
<tr>
<td>MS: summer</td>
<td>−0.51</td>
</tr>
<tr>
<td>MS: autumn</td>
<td>−0.16</td>
</tr>
<tr>
<td>IM: winter</td>
<td></td>
</tr>
<tr>
<td>IM: spring</td>
<td>0.11</td>
</tr>
<tr>
<td>IM: summer</td>
<td></td>
</tr>
<tr>
<td>IM: autumn</td>
<td></td>
</tr>
<tr>
<td>MS: IM: winter</td>
<td></td>
</tr>
<tr>
<td>MS: IM: spring</td>
<td>0.72</td>
</tr>
<tr>
<td>MS: IM: summer</td>
<td>0.60</td>
</tr>
<tr>
<td>MS: IM: autumn</td>
<td>0.35</td>
</tr>
<tr>
<td>Cumulative variance</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Abbreviations: IM = infectious mononucleosis; MS = multiple sclerosis; UVB = ultraviolet B radiation.
on MS risk. The most attractive explanation is UVB-induced synthesis of cutaneous vitamin D, which is the principal source of this important sterol hormone.\textsuperscript{15,16} It has been suggested that low vitamin D levels may lead to an increase in EBV infection. The pleiotropic roles of vitamin D on the immune system\textsuperscript{17} may lead to an abnormal or variant response to EBV infection as manifested by IM when an individual is vitamin D deficient.\textsuperscript{18}

There are limitations to our study. Limitations of record linkage studies using routinely collected administrative data are well-known, and include the facts that the data are limited to hospitalized patients and that information about some variables of potential interest, such as social circumstances and ethnic-
search support from Bayer Schering Pharma, the Multiple Sclerosis Society of the United Kingdom, and the Multiple Sclerosis Society of Canada Scientific Research Foundation. G. Chaplin reports no disclosures.

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REFERENCES


Historical Abstract: April 1, 1985

NEURONAL ANTINUCLEAR ANTIBODY IN SENSORY NEURONOPATHY FROM LUNG CANCER
Francesc Graus, Carlos Cordon-Cardo, and Jerome B. Posner
Neurology 1985;35:538–543

We found an antinuclear antibody highly restricted to nuclei of neurons in two patients with subacute sensory neuropathy complicating oat cell carcinoma of the lung. Serum was tested by indirect immunofluorescence and immunoperoxidase staining. At low concentrations of antibody, only the nuclei of the neurons were stained. At high concentrations, there was also staining of the nuclei of glial cells and fetal nonneural tissues. The cytoplasm of most neurons was stained with the immunoperoxidase method.

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Comment from Richard M. Ransohoff, MD, Associate Editor: A groundbreaking demonstration that paraneoplastic syndromes were associated with antibodies to neuronal components.