Original Paper

Neuro-epidemiology

Neuroepidemiology 2008;31:271–279
DOI: 10.1159/000166602

Received: July 14, 2008
Accepted: August 10, 2008
Published online: October 30, 2008

Monthly Ambient Sunlight, Infections and Relapse Rates in Multiple Sclerosis

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Key Words

Multiple sclerosis, relapsing-remitting · Relapse rate · Remission rate · Meteorological factors · Ambient environmental factors · Sunlight · Erythemal ultraviolet radiation · Vitamin D · Upper respiratory tract infections

Abstract

Background: Monthly variation in multiple sclerosis (MS) relapses has been found. The relationship between seasonal environmental factors, infections, serum vitamin D [25(OH)D] and MS relapses is undetermined. ***Methods:*** We prospectively followed a population-based cohort of relapsing-remitting (RR) MS patients in Southern Tasmania for a mean 2.3 years (January 2002–April 2005). Associations between monthly ambient environmental factors, estimated serum 25(OH)D, upper respiratory tract (URT) infections and relapse rates were examined using weighted Pearson's correlation and linear regression. ***Results:*** Of 199 definite MS patients, 142 had RRMS. The lowest relapse rate of 0.5 per 1,000 days (95% CI: 0.2–1.3) occurred in February (mid-late summer) versus the March–January RR of 1.1 per 1,000 days (95% CI: 0.9–1.3; p = 0.018, weighted regression). Monthly relapse rates correlated with: (1) prior erythemal ultraviolet radiation (EUV): lagged 1.5 months, r = −0.32, p = 0.046; (2) URT infection rate: no lag, r = 0.39, p = 0.014; (3) 25(OH)D: no lag, r = −0.31, p = 0.057. The association between URT infections and relapses was reduced after adjustment for monthly EUV. ***Conclusions:*** Relapse rates were inversely associated with EUV and serum 25(OH)D levels and positively associated with URT infections. The demonstrated lag between EUV but not 25(OH)D and relapse rates is consistent with a role for EUV-generated 25(OH)D in the alteration of relapse rates. Future work on the association between URT infections and relapses should be considered in the context of ultraviolet radiation and vitamin D.

Introduction

Multiple sclerosis (MS) is a chronic neurological disease, and the most common cause of non-trauma-related disability in young adults [1]. The majority of patients (80–90%) present with a relapsing-remitting (RR) disease course. MS relapses are presently unpredictable and unpreventable, although their occurrence can be reduced by immunomodulatory drug treatment and is reduced dur-

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ing pregnancy [2]. Relapses have been shown to vary by season in some [3–12], but not all [13–17], studies. Several factors vary according to the season, any of which might provide putative mechanism(s) for the preferential triggering of relapses at specific times of the year. Factors could include: ambient environmental factors (such as sunlight, rainfall, ozone or particulate matter [18]); a cyclic fluctuation in the incidence of infections [6] and related physiological changes (including epidermal vitamin D synthesis, release of melatonin and interferon-γ production [19]). MS relapses have been linked with an array of infectious micro-organisms, including viral, bacterial and parasitic [6, 10, 11, 20–27]. However, it is possible that infections are also influenced by monthly vitamin D, as higher levels boost innate immunity [28]. Biomarkers of MS disease activity, such as magnetic resonance imaging (MRI) and immunological aspects, also display seasonal changes [16, 19, 29–31], with monthly MRI lesions being related inversely to monthly serum 25-hydroxyvitamin D [25(OH)D] levels, when lagged 2 months [31].

The majority of 25(OH)D is produced endogenously through exposure of bare skin to ultraviolet radiation (particularly UVB) which results in the conversion of 7-dehydrocholesterol to vitamin D_3 (via pre-vitamin D_3). Subsequent hydroxylation in the liver produces 25(OH)D, the preferred marker of vitamin D status [32]. In Tasmania, the lag time between the maximum ambient ultraviolet radiation and the maximum serum 25(OH)D levels in a healthy adult population is 1.5 months [33, 34].

The seasonal relationships between MS relapses, infection, ambient environmental factors and serum vitamin D from MS patients have yet to be determined. We set out to examine these ecological links in a Southern Hemisphere (Tasmania) population-based longitudinal study.

Methods

Patients

A prospective, longitudinal study design was used to follow a cohort of patients from residents of Southern Tasmania (telephone code 62, source population = 226,559 on 30 June 2000) contacted via multiple resources such as medical records, MS clinics, the Tasmanian MS Society and the media. Definite RRMS patients (fulfilling both Poser [35], and McDonald criteria [36]) were included.

Procedures

Questionnaires covering basic demographics, relapse and infection data were administered at baseline and every 6 months for up to 3 years (January 2002–April 2005) by trained individuals, independent of the patients' medical care. In addition, weekly diary and telephone reporting of relapses (to the study physician) and infections (to the study nurse) were encouraged.

Relapses were verified by the same study doctor and were defined as the acute or subacute appearance or reappearance of a neurological abnormality (lasting at least 24 h), immediately preceded by a stable, improving or slowly progressive neurological state for 30 days, in the absence of fever, known infection or concurrent steroid withdrawal.

Ambient Environmental Measurements. These were collected from Hobart, Tasmania, and included: (1) erythemal ultraviolet radiation (EUV, milliwatts/square meters, sum of the surface UV irradiance modulated by human skin); (2) ambient temperature (°C): (i) 24-hour daily minimum (before 9 a.m.), (ii) 24-hour daily maximum (after 9 a.m.) and (iii) average (mean of minimum and maximum); (3) relative humidity (percentage average at 9 a.m. and 3 p.m.); (4) ozone (Dobson units), obtained from the Earth Probe spacecraft of NASA; (5) sea level pressure (hPa, mean of 3-hourly measurements between 12:00 a.m. and 9:00 p.m.); (6) rainfall (millimetres, monthly mean and monthly total); (7) particulate matter PM10 (air particles with an aerodynamic diameter $\leq 10\ \mu g/m^3$).

Calendar monthly means were calculated from the daily information. Serum vitamin D 25(OH)D levels (nmol/l) were taken from a previous case-control study of Tasmanian MS patients [34].

Blinding and Patient/Examiner Awareness. Relapse/infection information was embedded alongside other questions, masking the specific hypothesis being addressed; relapses and infections were verified by independent examiners, each being blinded to the other factor being collected.

Statistical Analyses

For each calendar month, a relapse rate per 1,000 days of follow-up was calculated as:

$$\frac{\text{number of relapses that month}}{\text{days of follow-up that month}} \times 1{,}000.$$

Relapse rates were also grouped by season: spring (September to November), summer (December to February), autumn (March to May) and winter (June to August). The monthly infection rate was similarly expressed. Correlations between the monthly relapse rates, monthly infection rates (all infections and only upper respiratory tract [URT] infections [3, 6, 10, 11, 15, 20–22]) were calculated using weighted Pearson's correlation coefficients (p values were derived from F test results) and weighted linear regression analysis (weighted least-squares model) to account for the differing number of patients contributing to the study over time. Data was lagged in half-month increments, up to 2 months prior. To account for the declining infection reporting rates over time, we replaced each monthly infection rate by the overall infection rate mean plus the regression residual. EUV, serum 25(OH)D, infections and relapses were examined using weighted linear regression (as described earlier), with results expressed as the regression coefficient (β), 95% confidence intervals and R^2 (the coefficient of determination) to indicate variation accounted for by the model.

Consideration was given to other factors that could cause relapse rates to alter during the study.

The above analyses were repeated, excluding each patient's data from: pregnancy through to 6 months post-partum and also initiation of a new immunomodulatory drug (IMD) through to the study end. Patients taking an IMD for at least 1 month prior to the study start were deemed to be stabilized on that drug, and their data was not excluded. Ethical approval was obtained from the ethics committee of the Royal Hobart Hospital, and written consent was obtained from each patient.

Results

Patient Characteristics

Two-hundred and three patients participated in the longitudinal study, 199 of whom fulfilled criteria for definite MS. An estimated 78% of the eligible MS population participated (prevalence of definite MS in Southern Tasmania was 256 in August 2001, unpublished data).

Of the 199 with definite MS, 149 (74.9%) had RRMS, of which 7 were excluded for completing baseline assessments only. Patient characteristics of the RR cohort (n = 142) are shown in table 1. The mean follow-up time was 2.3 years (SD = 0.55; range: 6 months to 3 years) and 17/142 (12.0%) developed a secondary progressive MS course. At study start, 111/142 (78.2%) were taking an IMD, an additional 6 patients started on IMD during the study. Ten women became pregnant. Seven patients left the study early (no patient died): 2 for unspecified reasons and 5 moved away after 6–30 months of follow-up.

Relapses

One hundred and thirty relapses were experienced by 72/142 (50.7%) of patients; 41 experienced 1 relapse only and 31 experienced 2 or more, averaging 0.92 relapses per patient over the whole study (range 0–5), equivalent to an annualized relapse rate of 0.40. Telephone-reported relapses totalled 73 of all recorded relapses, the remainder being captured by the study physician at the 6-monthly reviews. Half of all relapses (65/130) were mono-symptomatic, the remainder poly-symptomatic. Sensory symptoms were found in 46.1% (60/130) of relapses, motor symptoms in 35.4% (46), brainstem or cerebellar symptoms in 30.8% (40), fatigue in 28.5% (37), optic neuropathy in 13.8% (18) and 'other' symptoms in 15.4% (20).

The relapse rate exhibited modest seasonal variation, with a peak in winter [relapse rate = 1.3 (95% CI: 1.0–1.8) per 1,000 days of follow-up] and a nadir in summer [relapse rate = 0.9 (95% CI: 0.7–1.4)]. Figure 1 shows that there were fluctuations in the monthly relapse rate. Overall, the lowest relapse rate occurred in the summer month of February. This month had a lower relapse rate compared to March–January inclusive (p = 0.018).

Table 1. Baseline characteristics of the RRMS patients in southern Tasmania

Total, n	142
Women, n	106 (74.6)
Age, years	45.8 ± 10.31 (21–76)
Disease duration, years	11.4 ± 9.23 (0.1–57.6)
EDSS score (median)	2.5 (0–8.5)
IMD at baseline, n	111 (78.2)
Time on IMD drug at baseline, months (n = 111)	25.5 ± 19.10 (0–84)
IMD type at baseline: glatiramer acetate (s.c., 20 mg daily)	14
IFNB-1b (s.c., 250 μg, alternate days)	73
IFNB-1a (s.c., 44 μg, thrice weekly)	20
IFNB-1a (i.m., 30 μg, weekly)	3
Mitoxantrone (i.v., variable dose) [1]	5

Figures in parentheses are percentages or ranges. Where indicated, values are means ± SD.

IFNB = β-interferon; EDSS = Expanded Disability Status Scale.

[1] Also taking IFNB (n = 5).

Infections

In total, 647 infections were recorded, averaging 4.6 infections per person over the study (SD = 4.75, range 0–32) or 1.9 infections per patient per year. Overall, 21/142 (14.8%) of patients did not report any infections. Telephone-reported infections comprised 122 of all infections, the remainder being captured by the diaries. Infections exhibited a similar seasonal pattern as relapses, with a peak in winter (2.5; 95% CI: 2.2–2.9) and nadir in summer (1.5; 95% CI: 1.2–1.7). The majority of infections involved the respiratory tract, with 453 (70.1%) affecting the URT and 68 (10.5%) the lower respiratory tract.

Ambient Environmental Data and Relapses

Of all the ambient environmental variables, EUV was the only one to exhibit a significant (inverse) correlation with the monthly relapse rate (table 2), peaking when EUV was lagged 1.5 months prior to the relapse rate (r = –0.32, p = 0.046; table 2). Henceforth, we will restrict attention to this climatic variable only, and have termed it prior monthly EUV. Monthly EUV and relapse rates exhibited a strikingly similar, but inverse, seasonal pattern (see fig. 2a).

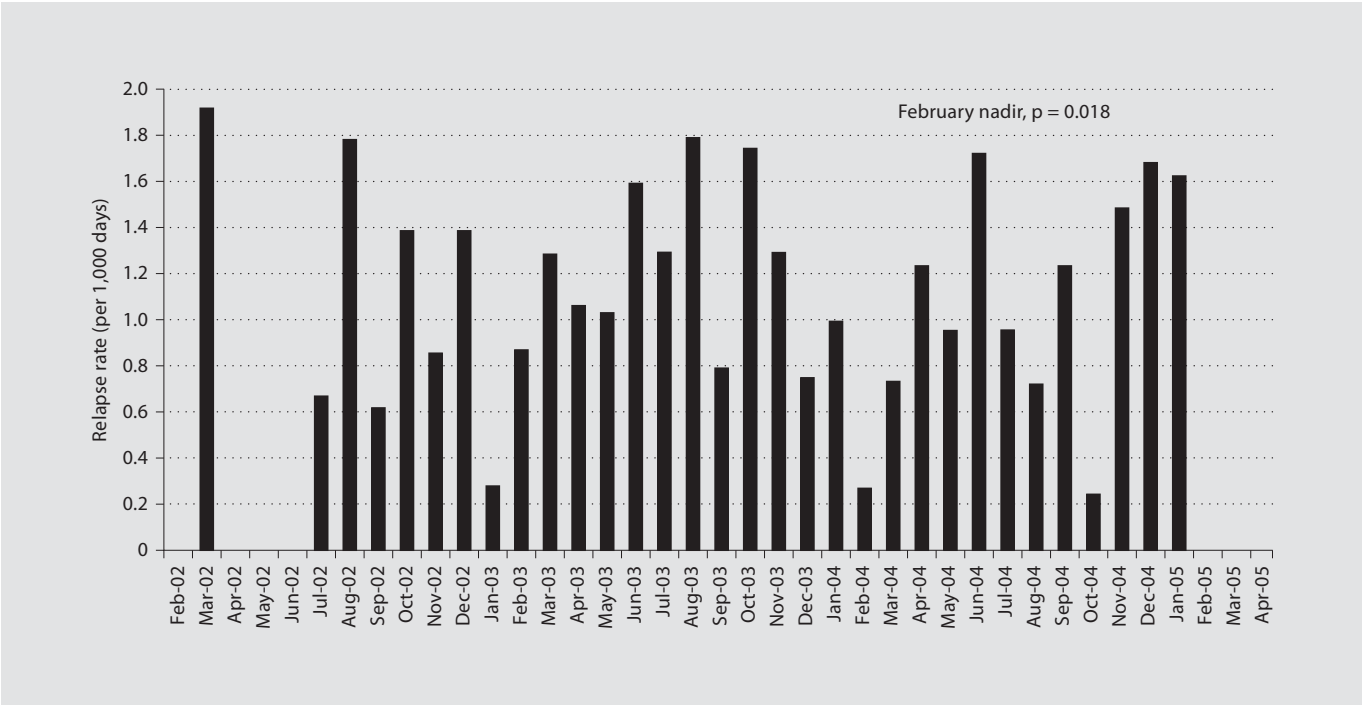

Fig. 1. Monthly variation in the crude relapse rates (per 1,000 days of follow-up). A nadir was observed in February, being lower than all other months combined (p = 0.018, weighted regression analysis).

Table 2. Time-lagged associations between ambient environmental factors and serum 25(OH)D and the on-study monthly relapse rate

	No lag r	0.5-month lag, r	1-month lag, r	1.5-month lag, r	2-month lag, r
Monthly ambient environmental factor					
EUV (mW/m^2)	–0.05	–0.13	–0.23	–0.32	–0.31
Temperature (°C)					
Average (°C)	–0.24	–0.26	–0.25	–0.24	–0.16
Minimum (°C)	–0.20	–0.25	–0.24	–0.22	–0.13
Maximum (°C)	–0.27	–0.27	–0.25	–0.25	–0.18
Sea pressure (hPa)	0.02	–0.02	–0.04	0.20	0.19
Relative humidity (%)	0.23	0.19	0.15	0.25	0.23
Particulate matter (PM 10 μg/m^3)	–0.05	0.10	0.10	0.22	0.06
Ozone (Dobson units)	0.07	–0.03	0.14	0.16	–0.01
Mean rainfall (mm)	0.09	n.a.	0.09	n.a.	0.22
Total rainfall (mm)	0.09	n.a.	0.09	n.a.	0.21
Estimated mean serum 25(OH)D	–0.31	–0.28	–0.16	–0.17	0.11

Application of a lag indicates that the environmental factor of interest [or 25(OH)D] was lagged 0.5, 1, 1.5 or 2 months prior to the relapse rate. r = Weighted Pearson's correlation coefficient; correlations larger than 0.31 in absolute size are statistically significant ($p < 0.05$) in this sample size. n.a. = mid-monthly levels not available.

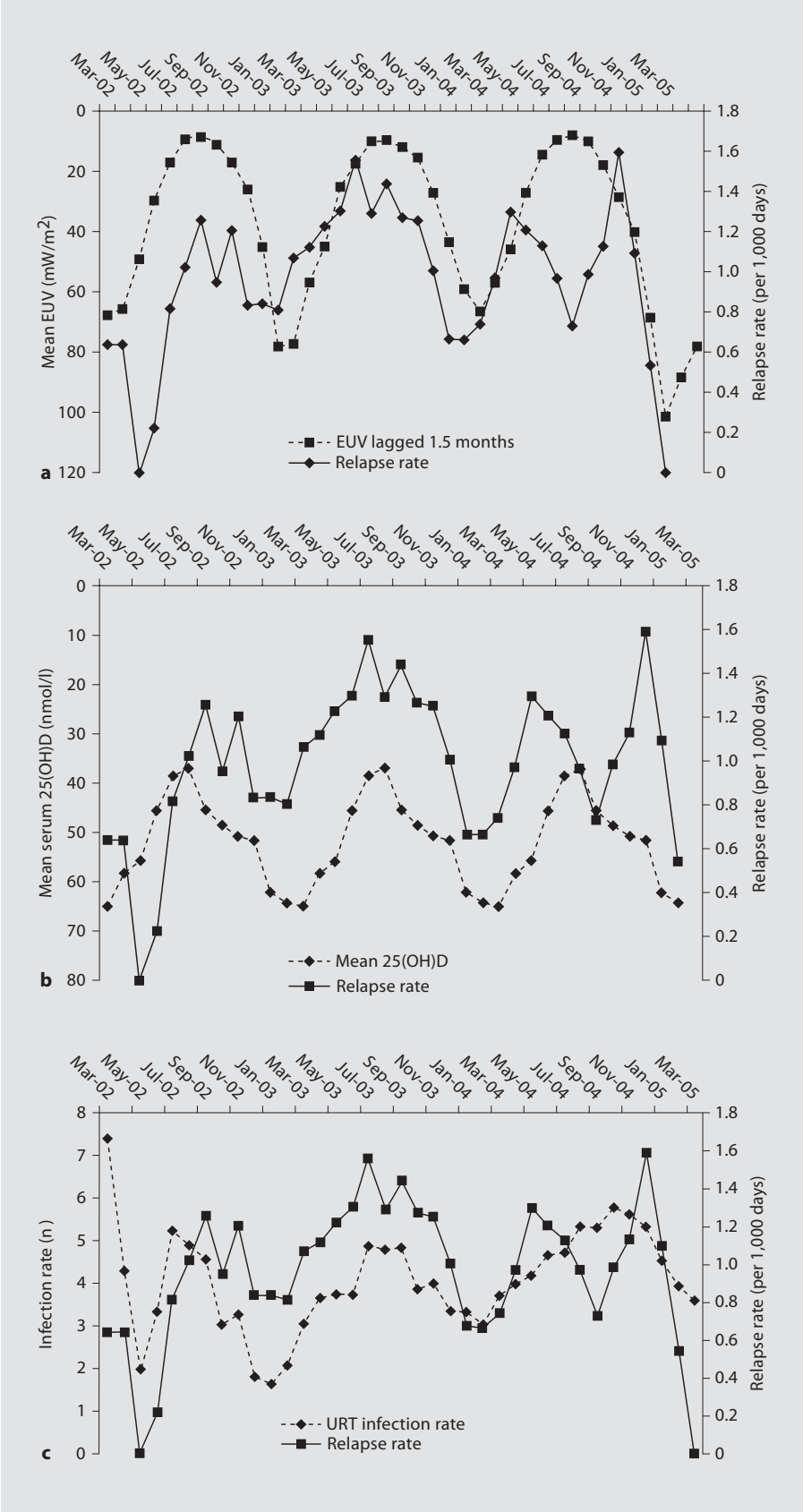

Fig. 2. a Monthly EUV and relapse rates. **b** Monthly serum 25(OH)D and relapse rates. **c** Monthly URT infections and relapse rates. Smoothed relapse rates, infections (per 1,000 days of follow-up) and estimated serum 25(OH)D are shown (using a centred 3-month average). EUV was lagged 1.5 months prior to the relapse rate and data was inverted. Serum 25(OH)D was inverted but not lagged, and were obtained from a previous study of MS patients in southern Tasmania [34]. URT infection rates were de-trended and not lagged.

Serum 25(OH)D and Relapses

A negative association was found between relapses and estimated serum 25(OH)D, being strongest when no lag was applied ($r = -0.31$, $p = 0.057$, see table 2 and fig. 2b).

Infections and Relapses

The infection and relapse rates exhibited some positive correlation ($r = 0.23$, $p = 0.163$, weighted). Lagging the infection rates up to 2 months prior to the relapse rates did not strengthen this correlation. A similar relationship was found when only respiratory infections were considered (upper and lower, $r = 0.23$, $p = 0.166$, weighted), this strengthened further when URT infections alone were considered ($r = 0.39$, $p = 0.014$). Henceforth, we restrict attention to URT infections. Both relapses and URT infection rates exhibited a similar seasonal variation (see fig. 2c).

Associations between EUV, Serum 25(OH)D and URT Infection

Prior monthly EUV was positively related to the estimated mean monthly serum 25(OH)D, peaking when EUV was lagged 1.5 months before serum 25(OH)D level measurements ($r = 0.79$, $p < 0.0005$). Prior monthly EUV was negatively associated with URT infection rate, with a 1.5-month ($r = -0.44$, $p = 0.002$) lag. An inverse association between monthly estimated serum 25(OH)D and URT infection rate was evident ($r = -0.40$, $p = 0.006$, no lag).

Linear Regression: EUV, Serum 25(OH)D, URT Infections and Relapses

Prior EUV (lagged 1.5 months prior to the relapse rate) and the estimated serum 25(OH)D (no lag applied) exhibited a similar effect on the relapse rate; either prior EUV [$\beta = -6.6$ (95% CI: –13.1 to –0.13) $\times 10^{-3}$, $p = 0.046$] or serum 25(OH)D [$\beta = -12.6$ (95% CI: –25.7 to 0.4) $\times 10^{-3}$, $p = 0.057$] individually accounted for around one tenth of the variation in relapses [$R^2 = 10.3\%$ for EUV and 9.5% for 25(OH)D].

URT infections also exhibited a strong association with relapses [$\beta = 124.3$ (95% CI: 27.2–221.3) $\times 10^{-3}$, $p = 0.014$], accounting for 15.4% of the variation in relapses. However, the association between URT infection and relapses and between prior EUV (lagged 1.5 months) and relapses were reduced after further adjustment for each other, suggesting that the URT infection-relapse association was not independent of prior EUV. The model containing both prior EUV and URT explained 18.1% of the relapse rate ($p = 0.028$), results being as follows: for URT, $\beta = 98.4$ (95% CI: –9.8 to 206.6) $\times 10^{-3}$, $p = 0.073$; EUV, $\beta = -3.8$ (95% CI: –10.8 to 3.3) $\times 10^{-3}$, $p = 0.28$.

Similarly, the associations between URT infection and relapses and between estimated 25(OH)D and relapses were reduced after adjustment for each other (URT, $\beta = 101.5$ [95% CI: –4.2 to 207.2] $\times 10^{-3}$, $p = 0.059$; 25(OH)D, $\beta = -7.4$ [95% CI: –21.2 to 6.3] $\times 10^{-3}$, $p = 0.28$). The model containing both estimated serum 25(OH)D and URT explained 18.1% of the relapse rate ($p = 0.027$). This data might suggest that URT infections and EUV (1.5-month lag) or 25(OH)D (no lag) might be partly on the same pathway.

The magnitude of findings did not substantially change when data collected during new IMD use or pregnancy were excluded. The proportion of cohort members on IMD did not differ by month of survey.

Discussion

Monthly relapse rates were inversely associated with ambient ultraviolet radiation and estimated vitamin D levels, and positively associated with upper respiratory tract infections.

We observed a modest seasonal variation in relapse rates with a peak in winter and a nadir in summer – the lowest relapse rate being observed in February (mid-late summer) in our southern hemisphere MS cohort. This variation echoes findings from MS cohorts residing in the northern hemisphere, although subtle differences can be seen in the timing of the relapse peaks and troughs across different studies [3–12]. The interesting monthly relapse pattern, with a reduction particularly in February, suggests that thresholds for EUV exposure may be involved, and this should be considered in further work.

Methodological Issues

To capture the seasonal patterns of ambient measures and vitamin D levels, we used ambient data from Hobart, the largest city in southern Tasmania, and monthly mean vitamin D levels from MS patients from a previous Tasmanian study [34]. One might assume that the high use of IMD could mask associations or variations in the relapse rates. However, despite the high use of IMD, we were still able to observe a seasonal trend and monthly effect and our relapse rate was similar to other studies [37–39]. Further, IMD use did not vary by month. In addition, others have shown that the use of IMD does not alter the relationship between relapses and infection [11].

One third of infections are likely subclinical [40], in the absence of serological testing, we were neither able to detect subclinical infections, nor confirm the presence/source of infection. Neither did we attempt to measure the duration or severity of infections; both are highly subjective outcomes difficult to quantify meaningfully. However, by capturing clinically apparent infections, we may have considered more severe infections.

Relapses, UV and Vitamin D

We found that the variation in monthly relapse rates was inversely related to the variation of monthly ambient erythemal ultraviolet radiation, with low EUV levels associated with a subsequent higher risk of relapses some one and a half months later. This lag time is compatible with a role for UV-generated vitamin D. Firstly, EUV was most strongly associated with monthly vitamin D if the estimated vitamin D was lagged by 1.5 months – this same lag has been previously found in a healthy Tasmanian adult population [33]. Secondly, relapse rates were most strongly associated with estimated monthly 25(OH)D levels when no lag was applied. Sun exposure is the main source of 25(OH)D for humans [32]; this is also true in Tasmania, where we have confirmed that the contribution of dietary vitamin D to serum 25(OH)D is small [34]. Vitamin D has a biologically plausible role in MS as an immunomomodulatory agent capable of down regulating T lymphocytes (which express vitamin D receptors) [41]. This modulation of the immune system could conceivably have a direct impact on relapses. UV radiation could also produce similar immunomodulatory effects via mechanisms not involving vitamin D, including direct suppression of Th1 cytokines or suppression of melatonin [41].

Relapses, Infections, UV and Vitamin D

We also found that relapses were positively associated with infections, with upper respiratory tract infections showing the strongest associations. Others examining different infection types in relation to MS relapses also found the strongest association with upper respiratory tract infections [10, 11]. Interestingly, we found both prior EUV levels (1.5 month lag) and estimated serum vitamin D levels (no lag) to be inversely associated with upper respiratory tract infection rates. Further, the associations between upper respiratory tract infection and relapses and between 25(OH)D (or prior EUV, lagged 1.5 months) were both substantially reduced after adjustment for each other, suggesting they might be acting partly on the same pathway. While this study is unable to prove causality, recent evidence shows that vitamin D affects the innate immune system [28, 42], and could therefore influence infection rates. It appears biologically plausible that vitamin D could modify the infection rate in people with MS, which in turn influences the relapse rate. The interplay between UV exposure, vitamin D, upper respiratory tract infections and relapse rate would best be explored in a prospective individual-level analysis, with repeated measures of vitamin D and infection, on MS individuals.

None of the other ambient environmental factors examined were significantly associated with relapses. An association between environmental pollutants such as particulate matter (PM10) and relapses was found in a Finnish study [18]. We found no association in Tasmania; neither did we find an association with another pollutant, ozone.

Contextualizing Findings

Greater sunlight exposure, higher vitamin D supplement intake and/or higher serum 25(OH)D levels appear protective against the development of MS or autoimmune encephalomyelitis [43]. Our study indicates that low ambient sunlight and low serum 25(OH)D are also associated with clinical disease activity (relapses) in MS. Given that low sunlight exposure and serum 25(OH)D deficiency occurs in a high proportion of MS and healthy populations in Tasmania [34] and worldwide [32], our findings point to putative modifiable factors in the quest to modify MS relapses.

Even in this predominantly IMD-treated MS population, a further reduction in relapses might be possible. If the cross-sectional effect is causal, raising the UV from the yearly average (Jan 2003–Dec 2004) of 34 mW/m^2 to the summer average of 67.4 mW/m^2 could translate into a decline in the relapse rate by 0.08, which in this population with an annual relapse rate of 0.4 could mean a 20% reduction in relapse rates (based on β estimates derived from the weighted linear regression). Equally, raising the serum 25(OH)D from the yearly average of 51.9 nmol/l to the maximum levels reached (74.8 nmol/l in February) could translate into a decline in the relapse rate by 0.05, which in this population with an annual relapse rate of 0.4 could mean a 14% reduction in relapse rates. These estimates are based on a possible causal interpretation of higher EUV and lower subsequent relapse rates. The causality of the observed associations and the complex interrelationship between UV, vitamin D, infections and relapse rates requires further investigation.

Acknowledgements

The current analysis was made possible through a Multiple Sclerosis International Federation (MSIF) Du Pré Grant (MSIF, http://www.msif.org). The Longitudinal Study of Multiple Sclerosis in Southern Tasmania was funded by the Australian National Health and Medical Research Council and the MS Trish Foundation. H.T. is a Michael Smith Foundation for Health Research Scholar, holds a 'Don Paty Career Development Award' from the MS Society of Canada and is funded by the Christopher Foundation.

We thank the MS patients who participated in this study.

References

1 Compston A, Coles AJ: Multiple Sclerosis. Lancet 2002;359:1221–1231.
2 Compston A, Confavreux C, Lassmann H, McDonald I, Miller D, Noseworthy J, Smith K, Wekerle H: McAlpine's Multiple Sclerosis, ed 4. London, Churchill Livingstone Elsevier, 2006.
3 Sibley WA, Foley JM: Infection and immunization in multiple sclerosis. Ann NY Acad Sci 1965;122:457–466.
4 Wuthrich R, Rieder HP: The seasonal incidence of multiple sclerosis in Switzerland. Eur Neurol 1970;3:257–264.
5 Bamford CR, Sibley WA, Thies C: Seasonal variation of multiple sclerosis exacerbations in Arizona. Neurology 1983;33:697–701.
6 Gay D, Dick G, Upton G: Multiple sclerosis associated with sinusitis: a case-controlled study in general practice. Lancet 1986;I:815–819.
7 Goodkin DE, Hertsgaard D, Rudick RA: Exacerbation rates and adherence to disease type in a prospectively followed-up population with multiple sclerosis: implications for clinical trials. Arch Neurol 1989;46:1107–1112.
8 O'Reilly MA, O'Reilly PM: Temporal influences on relapses of multiple sclerosis. Eur Neurol 1991;31:391–395.
9 Sandyk R, Awerbuch GI: Multiple sclerosis: relationship between seasonal variations of relapse and age of onset. Int J Neurosci 1993; 71:147–157.
10 Andersen O, Lygner PE, Bergstrom T, Andersson M, Vahlne A: Viral infections trigger multiple sclerosis relapses: a prospective seroepidemiological study. J Neurol 1993; 240:417–422.
11 Buljevac D, Flach HZ, Hop WC, Hijdra D, Laman JD, Savelkoul HF, van Der Meche FG, van Doorn PA, Hintzen RQ: Prospective study on the relationship between infections and multiple sclerosis exacerbations. Brain 2002;125:952–960.
12 Ogawa G, Mochizuki H, Kanzaki M, Kaida K, Motoyoshi K, Kamakura K: Seasonal variation of multiple sclerosis exacerbations in Japan. Neurol Sci 2004;24:417–419.
13 Hopkins CE, Swank RL: Multiple sclerosis and the local weather; a four-year study of correlation between multiple sclerosis exacerbation and local weather factors in Montreal. AMA Arch Neurol Psychiatry 1955;74: 203–207.
14 Schapira K: The seasonal incidence of onset and exacerbations in multiple sclerosis. J Neurol Neurosurg Psychiatry 1959;22:285–286.
15 Panitch HS: Influence of infection on exacerbations of multiple sclerosis. Ann Neurol 1994;36(suppl):S25–S28.
16 Koziol JA, Feng AC: Seasonal variations in exacerbations and MRI parameters in relapsing-remitting multiple sclerosis. Neuroepidemiology 2004;23:217–223.
17 Tataru N, Vidal C, Decavel P, Berger E, Rumbach L: Limited impact of the summer heat wave in France (2003) on hospital admissions and relapses for multiple sclerosis. Neuroepidemiology 2006;27:28–32.
18 Oikonen M, Laaksonen M, Laippala P, Oksaranta O, Lilius EM, Lindgren S, Rantio-Lehtimaki A, Anttinen A, Koski K, Eralinna JP: Ambient air quality and occurrence of multiple sclerosis relapse. Neuroepidemiology 2003;22:95–99.
19 Balashov KE, Olek MJ, Smith DR, Khoury SJ, Weiner HL: Seasonal variation of interferon gamma production in progressive multiple sclerosis. Ann Neurol 1998;44:824–827.
20 Edwards S, Zvartau M, Clarke H, Irving W, Blumhardt LD: Clinical relapses and disease activity on magnetic resonance imaging associated with viral upper respiratory tract infections in multiple sclerosis. J Neurol Neurosurg Psychiatry 1998;64:736–741.
21 Sibley WA, Bamford CR, Clark K: Clinical viral infections and multiple sclerosis. Lancet 1985;1:1313–1315.
22 De Keyser J, Zwanikken C, Boon M: Effects of influenza vaccination and influenza illness on exacerbations in multiple sclerosis. J Neurol Sci 1998;159:51–53.
23 Correale J, Farez M: Association between parasite infection and immune responses in multiple sclerosis. Ann Neurol 2007;61:97–108.
24 Buljevac D, van Doornum GJJ, Flach HZ, Groen J, Osterhaus ADME, Hop W, van Doorn PA, van der Meche FGA, Hintzen RQ: Epstein-Barr virus and disease activity in multiple sclerosis. J Neurol Neurosurg Psychiatry 2005;76:1377–1381.
25 Ordonez G, Pineda B, Garcia-Navarrete R, Sotelo J: Brief presence of varicella-zoster vral DNA in mononuclear cells during relapses of multiple sclerosis. Arch Neurol 2004;61:529–532.
26 Sotelo J, Ordonez G, Pineda B: Varicella-zoster virus at relapses of multiple sclerosis. J Neurol 2007;254:493–500.
27 Alvarez-Lafuente R, De Las Heras V, Bartolome M, Garcia-Montojo M, Arroyo R: Human herpesvirus 6 and multiple sclerosis: a one-year follow-up study. Brain Pathol 2006; 16:20–27.
28 Zasloff M: Fighting infections with vitamin D. Nat Med 2006;12:388–390.
29 Stewart N, Taylor B, Ponsonby AL, Pittas F, van der Mei I, Woods G, Walters H: The effect of season on cytokine expression in multiple sclerosis and healthy subjects. J Neuroimmunol 2007;188:181–186.
30 Auer D, Schumann E, Kumpfel T, Gossel C, Trenkwalder C: Seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis (letter). Ann Neurol 2000;47:276–277.
31 Embry AF, Snowdon LR, Vieth R: Vitamin D and seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis (letter). Ann Neurol 2000;48:271–272.
32 Holick MF: Vitamin D deficiency. N Engl J Med 2007;357:266–281.
33 van der Mei IA, Ponsonby AL, Engelsen O, Pasco JA, McGrath JJ, Eyles DW, Blizzard L, Dwyer T, Lucas R, Jones G: The high prevalence of vitamin D insufficiency across Australian populations is only partly explained by season and latitude. Environ Health Perspect 2007;115:1132–1139.
34 van der Mei IA, Ponsonby AL, Dwyer T, Blizzard L, Taylor BV, Kilpatrick T, Butzkueven H, McMichael AJ: Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. J Neurol 2007; 254:581–590.

35 Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW: New Diagnostic criteria for multiple sclerosis: guidelines for research proposals. Ann Neurol 1983;13:227–231.
36 McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinsky JS: Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol 2001;50:121–127.
37 Tremlett H, Zhao Y, Joseph J, Devonshire V: Relapses in multiple sclerosis are age and time-dependent. J Neurol, Neurosurg Psychiatry 2008, E-pub ahead of print.
38 Milanese C, La Mantia L, Palumbo R, Martinelli V, Murialdo A, Zaffaroni M, Caputo D, Capra R, Bergamaschi R: A post-marketing study on interferon beta 1b and 1a treatment in relapsing-remitting multiple sclerosis: different response in drop-outs and treated patients. J Neurol Neurosurg Psychiatry 2003;74:1689–1692.
39 Khan OA, Tselis AC, Kamholz JA, Garbern JY, Lewis RA, Lisak RP: A prospective, open-label treatment trial to compare the effect of IFNbeta-1a (Avonex), IFNbeta-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis: results after 18 months of therapy. Mult Scler 2001;7:349–353.
40 Hsu SB, Hsieh YH: On the Role of asymptomatic infection in transmission dynamics of infectious diseases. Bull Math Biol 2008; 70:134–155.
41 Ponsonby AL, McMichael A, van der Mei I: Ultraviolet radiation and autoimmune disease: insights from epidemiological research. Toxicology 2002;181–182, 71–78.
42 Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, Tavera-Mendoza L, Lin R, Hanrahan JW, Mader S, White JH: Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol 2004;173:2909–2912.
43 Ascherio A, Munger KL: Environmental risk factors for multiple sclerosis. II. Noninfectious factors. Ann Neurol 2007;61:504–513.