Association of UV radiation with multiple sclerosis prevalence and sex ratio in France

S.-M. Orton, PhD
L. Wald, PhD
C. Confavreux, MD
S. Vukusic, PhD
J.P. Krohn, MSc
S.V. Ramagopalan, PhD
B.M. Herrera, PhD
A.D. Sadovnick, PhD
G.C. Ebers, MD, FMedSci

Address correspondence and reprint requests to Professor George C. Ebers, University Department of Clinical Neurology, West Wing, John Radcliffe Hospital, Oxford OX3 9DU, UK
george.ebers@clneuro.ox.ac.uk

ABSTRACT

Background: French farmers and their families constitute an informative population to study multiple sclerosis (MS) prevalence and related epidemiology. We carried out an ecological study to evaluate the association of MS prevalence and ultraviolet (UV) radiation, a candidate climatologic risk factor.

Methods: Mean annual and winter (December–March) UVB irradiation values were systematically compared to MS prevalence rates in corresponding regions of France. UVB data were obtained from the solar radiation database (SoDa) service and prevalence rates from previously published data on 2,667 MS cases registered with the national farmer health insurance system, Mutualité Sociale Agricole (MSA). Pearson correlation was used to examine the relationship of annual and winter UVB values with MS prevalence. Male and female prevalence were also analyzed separately. Linear regression was used to test for interaction of annual and winter UVB with sex in predicting MS prevalence.

Results: There was a strong association between MS prevalence and annual mean UVB irradiation ($r = -0.80$, $p < 0.001$) and average winter UVB ($r = -0.87$, $p < 0.001$). Both female ($r = -0.76$, $p < 0.001$) and male ($r = -0.46$, $p = 0.032$) prevalence rates were correlated with annual UVB. Regression modeling showed that the effect of UVB on prevalence rates differed by sex; the interaction effect was significant for both annual UVB ($p = 0.003$) and winter UVB ($p = 0.002$).

Conclusions: The findings suggest that regional UVB radiation is predictive of corresponding MS prevalence rates and supports the hypothesis that sunlight exposure influences MS risk. The evidence also supports a potential role for gender-specific effects of UVB exposure. *Neurology*® 2011;76:425–431

GLOSSARY

MS = multiple sclerosis; **MSA** = Mutualité Sociale Agricole; **SoDa** = solar radiation database; **UV** = ultraviolet.

One of the most striking features of multiple sclerosis (MS) epidemiology has long been its remarkable geographic distribution of prevalence. The frequency of MS follows a general north–south gradient in the northern hemisphere, reversing in the southern hemisphere, such that MS is uncommon near the equator.[1,2] Ultraviolet (UV) radiation, which is highly correlated with latitude, has been the most favored explanation for this nonrandom geographic distribution.

Another hallmark of MS is the higher frequency in women, with a sex ratio usually above 2:1, but which is also variable worldwide.[2] Recent data suggest that MS incidence is increasing.[3-7] In regions where incidence is on the rise, including France,[8] the increased frequency appears to result from excess females.[9-11] The escalation in MS rates has occurred relatively rapidly over the past century, implicating environmental or genetic–environmental factors. Coherent with possible explanations for the geographic prevalence pattern, one

From the Wellcome Trust Centre for Human Genetics and Department of Clinical Neurology (S.-M.O., J.P.K., S.V.R., B.M.H., G.C.E.), University of Oxford, Oxford, UK; Centre Energétique et Procédés (L.W.), MINES ParisTech, Sophia Antipolis cedex; Service de Neurologie A and EDMUS Coordinating Center (C.C., S.V.), Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Bron, France; INSERM U842 (C.C., S.V.), Lyon, France; Université Lyon 1 (C.C., S.V.), Lyon, France; and Department of Medical Genetics and Faculty of Medicine (A.D.S.), Division of Neurology, University of British Columbia, Vancouver, Canada.

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hypothesis for the increasing MS sex ratio has been changes to sunlight exposure of vitamin D synthesizing skin.

France is considered a region of medium to high MS prevalence.[8,12-14] The estimated rate in individuals under Mutualité Sociale Agricole (MSA) care is 65.0 per 100,000 (62.5 to 67.5).[15] The MS rates in France appear to follow a south–north increasing gradient, although a SW–NE gradient appears to also be operative.[15,16]

Here we examine UVB radiation in relation to male and female MS prevalence in the French farming population, who are cared for under the Agricole health care system, MSA. This is an ideal population because the MSA has exclusive coverage of farmers, their families, and farm workers, as well as being ethnically homogeneous, having low migration rates, and having a relatively even population distribution throughout France. We focused specifically on the biologically active part of the UV spectrum, UVB, which contains the light wavelengths required for cutaneous photoproduction of vitamin D.[17]

METHODS In this cross-sectional ecological study, we used UV satellite data estimates and reported prevalence figures for France to examine whether the MS prevalence gradient was correlated with annual or seasonal UVB measures. We similarly examined sex differences with respect to UVB levels across regions.

Study group and prevalence data. The regional prevalence figures were obtained from a previously published study[15] (prevalence day of January 1, 2003), in which the rates were calculated from the computerized database of the MSA, and standardized for age to the general French population.[15] Rates are expressed per 100,000 individuals.

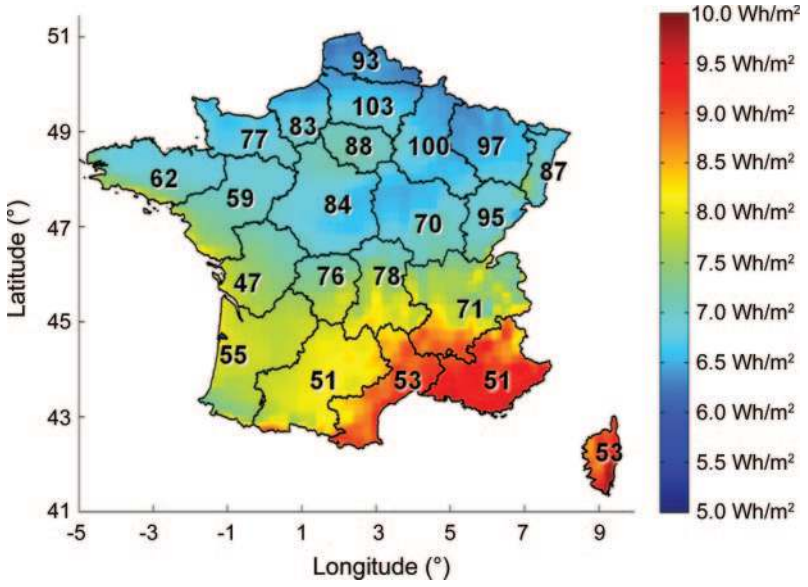
There are 22 regions of the MSA, which provides health insurance to farmers in France. It is a branch of the social security system under social protection in France. The MSA manages the social risk of rural workers, comprising farmers, salaried workers, and their families.[15] The MSA population has complete and exclusive coverage of this farmer group,

Table 1 Epidemiologic characteristics of each Mutualité Sociale Agricole region in France and corresponding mean of daily UVB irradiation

Administrative region of France	Latitude, degrees north	Standardized prevalence of MS per 100,000 (95% confidence interval)[a]	F:M sex ratio	Annual mean UVB,[b] Wh/m^2	Winter mean UVB,[b] Wh/m^2
Picardie	49.9	103.2 (86.6-119.8)	2.29	5.7	1.6
Champagne	49.0	99.6 (83.4-115.8)	2.97	5.8	1.7
Lorraine	49.1	97.4 (78.0-116.8)	1.53	5.5	1.6
Franche-Comte	47.2	95.4 (73.5-117.3)	3.84	6.1	1.8
Nord	50.6	92.8 (77.2-108.4)	1.87	5.2	1.5
Ile de France	48.9	88.2 (73.0-103.4)	2.49	5.9	1.7
Alsace	48.6	87.3 (64.5-110.1)	3.12	5.6	1.8
Centre	47.9	84.2 (72.2-96.2)	1.93	6.1	1.8
Haute-Normandie	49.2	82.5 (64.0-101.0)	1.82	6.0	1.7
Auvergne	45.8	78.4 (64.5-92.3)	3.20	6.8	2.3
Basse-Normandie	49.2	77.0 (63.9-90.1)	2.41	6.0	1.8
Limousin	45.8	76.1 (58.7-93.5)	2.88	6.8	2.3
Rhone Alpes	45.8	70.5 (61.2-79.8)	2.95	6.8	2.6
Bourgogne	47.3	70.1 (56.9-83.3)	2.37	6.1	1.9
Bretagne	48.1	61.5 (53.4-69.6)	2.82	6.1	2.3
Pays de la Loire	47.1	59.3 (51.5-67.1)	3.88	6.6	2.3
Aquitaine	44.8	55.4 (47.5-63.3)	2.94	7.1	2.5
Languedoc-Roussillon	43.6	53.2 (44.0-62.4)	2.20	8.3	3.1
Corse	41.9	53.0 (21.6-84.4)	0.94	8.8	3.3
Midi-Pyrenees	43.6	51.0 (42.9-59.1)	1.97	7.9	2.7
Provence Cote D'Azur	43.3	50.9 (41.5-60.3)	1.98	8.7	3.2
Poitou-Charentes	46.6	46.8 (37.8-55.8)	1.72	6.8	2.5

Abbreviations: MS = multiple sclerosis; UVB = ultraviolet B.
[a] Per 100,000 Mutualité Sociale Agricole affiliates: prevalence figures obtained with permission from previously published data.[15]
[b] Based on typical values determined for global UVB all sky, derived from Meteostat, Switzerland, accessed from www.soda-is.com/eng/services. Winter: December to March average.

Figure 1 Annual mean ultraviolet B (Wh/m^2) radiation in France



Multiple sclerosis prevalence rates (per 100,000) for each Mutualité Sociale Agricole region are shown.

hence limiting ascertainment bias. Treatment costs for chronic diseases such as MS are fully reimbursed and most cases are captured soon after diagnosis.[15]

Solar radiation values. For this study, we focused specifically on UVB, which includes wavelengths of 280 to 320 nm. UVB data for each MSA region in France were compiled for monthly means and annual mean of daily UVB irradiation. The annual mean is an average of monthly values over a 12-month period. Mean monthly values from December to March were used to calculate the winter mean UVB.

UV data were collected from the Internet-based Solar Radiation Database (SoDa) service, a Web site of the MINES ParisTech (www.soda-is.com[18]). This Web site provides a range of databases, algorithms, and time series services for collecting information on solar radiation and associated climate features.[19] These databases are produced by the processing of satellite images, largely from the Meteosat series of satellites.[20,21] UVB is measured by a biometer for solar light which assesses global irradiance (290–320 nm) with a measurement error of less than 5%.[20]

The services we employed for the current study are accessed through the SoDa Web site, under the "climate normals typical values" heading. The data used are standard monthly means of daily sums for UVB radiation. Model input criteria selected for latitude and longitude were based on prefecture cities of the 22 MSA regions in France. Default model input variables provided by the service were used for ozone levels, altitude, and inclination. The "all sky" UVB model was selected over "clear sky" as the latter provides the maximum value, whereas the former provides an average value. Output data for global irradiation were used for analysis as they comprise both diffuse and direct radiation. Verification of the models used and a review of the services have been previously published.[20,22]

A map of France illustrating the variation in intensity of total irradiation was produced from data available through SoDa services.[18] The quantities illustrated are the annual irradiation (kWh/m^2) calculated from 2004. The irradiation data are computed from satellite observations which calculate quantity of energy that reaches the ground in Europe (DLR, University of Oldenburg, MINES ParisTech, 2005).

Data analyses. Pearson correlation was used to examine the relationship of overall prevalence rates and annual UVB per MSA region. This was also completed for average winter UVB. Both annual and winter UVB values were then analyzed separately in males and females. We employed Pearson correlation to assess the association of latitude with MS prevalence, and with mean UVB.

Sex ratio was calculated by dividing the number of female patients with MS per 100,000 MSA affiliates by the number of male cases per 100,000 MSA affiliates for each region. Given that ratios have infinite variance and are problematic variables to model, they were not used in regression analysis. A linear model with prevalence rate predicted by UVB, sex, and UVB-sex interaction was employed to examine gender differences in MS prevalence.

Data were analyzed and graphs produced in SPSS 16.0 (Chicago[23]) and regression modeling was done using *R* statistical package (Vienna[24]).

Table 2 Association of regional age-standardized MS prevalence rates with annual and winter means of daily UVB irradiation

	UVB annual mean		UVB winter[b] mean	
MS prevalence	Correlation coefficient	*p* Value[a]	Correlation coefficient	*p* Value[a]
Total	−0.80	<0.001	−0.87	<0.001
Female	−0.76	<0.001	−0.80	<0.001
Male	−0.46	0.032	−0.56	0.006

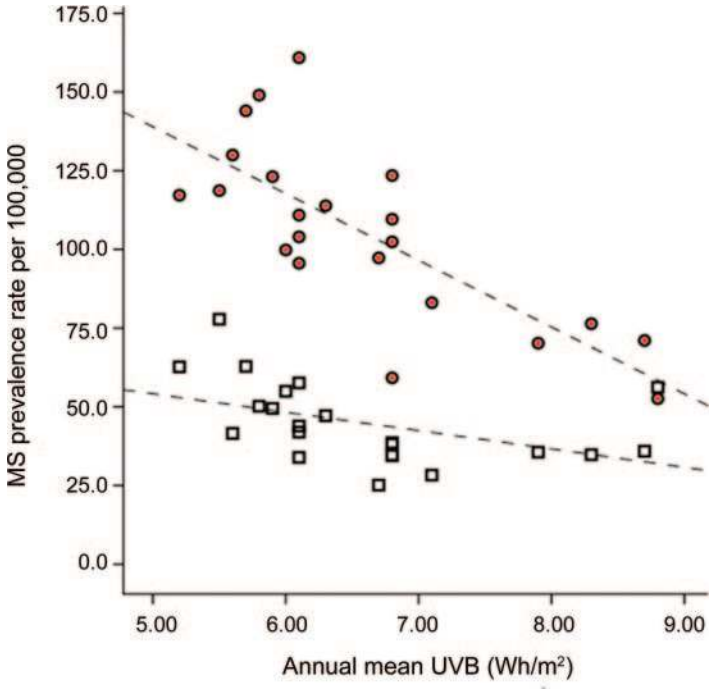
Abbreviations: MS = multiple sclerosis; UVB = ultraviolet B.
[a] Threshold for significance was set at $p < 0.05$.
[b] Winter: December to March average.

RESULTS

Characteristics of dataset. The population size, prevalence rates, sex ratio, and latitude for each of the 22 MSA regions in France are given in table 1. For each region, typical values of solar UVB are shown for annual mean (monthly values averaged over a 12-month period) and winter mean (average of December to March monthly values, table 1). MS prevalence rates increased with increasing latitude and decreasing UVB values. Latitude was strongly correlated with prevalence rates ($r = 0.78$, $p < 0.001$) and with annual global UVB ($r = -0.96$, $p < 0.001$) in the 22 regions of France we studied. The correlation of MS prevalence with longitude was not significant (data not shown).

Prevalence, gender, and UVB. Descriptively, it can be seen that overall prevalence rates for MS are related to the intensity of solar UV radiation in the corresponding regional districts of France (figure 1). MS prevalence was strongly associated with annual global UVB ($r = -0.80$, $p < 10^{-5}$) and winter mean ($r = -0.87$, $p < 10^{-6}$; table 2).

Figure 2 Association of annual mean of daily ultraviolet B (UVB) irradiation and multiple sclerosis (MS) prevalence in females (circles: $r = -0.76$) and males (squares: $r = -0.46$) in the 22 regions of France



The regression fit line for males and females is shown.

There was a notable difference between the strength of the correlation of MS prevalence with UVB between men and women (table 2). Female MS prevalence was correlated with average annual UVB ($r = -0.76$, $p < 10^{-4}$), as well as winter UVB average ($r = -0.80$, $p < 10^{-5}$; table 2). Similarly, male MS prevalence was correlated with annual ($r = -0.46$, $p = 0.032$) and winter UVB ($r = -0.56$, $p = 0.016$; table 2). The association of male and female prevalence rates with annual UVB irradiation is illustrated (figure 2). As annual UVB decreases, the rate at which female prevalence increases is higher than the rate at which male prevalence increases (figure 2 and table 3).

Table 3 Effects of UVB, sex, and UVB-by-sex interaction on MS prevalence rates

	Estimate (SE)	*t* Statistic	*p* Value[a]
Annual	−21.2 (3.4)	−6.23	<0.0001
UVB			
Sex	−162.0 (32.0)	−5.06	<0.0001
UVB × sex interaction	15.4 (4.8)	3.21	0.0026
Winter[b]	−41.0 (5.8)	−7.05	<0.0001
UVB			
Sex	−120.6 (18.4)	−6.55	<0.0001
UVB × sex interaction	27.7 (8.2)	3.37	0.0017

Abbreviations: MS = multiple sclerosis; UVB = ultraviolet B.
[a] Threshold for significance was set at $p < 0.05$.
[b] Winter: December to March average.

These sex differences were examined using linear regression and a significant interaction between sex and UVB was observed. For mean annual UVB, an interaction with gender was observed ($\beta = 15.4$, $t[40] = 3.2$, $p = 0.003$) and the predictor variables explained a significant proportion of the variance in prevalence ($R^2 = 0.82$, $F_{3,40} = 66.9$, $p < 10^{-14}$; table 3). Similarly, for mean winter UVB, there was an interaction with gender ($\beta = 27.7$, $t[40] = 3.4$, $p = 0.002$; table 3). Again, the predictors explained a significant proportion of the variance ($R^2 = 0.85$, $F_{3,40} = 79.8$, $p = 10^{-14}$; table 3).

DISCUSSION The correlation of increasing latitude and increasing MS prevalence has been well-established. However, latitude itself is unlikely to be an independent MS risk factor, and presumably it is the correlates of latitude which explain these observations. Although sunshine exposure is a primary candidate, there are surprisingly few studies that have directly examined the UVR–MS relationship.[25] Here we examined measurements of UVB radiation data from France and how they varied in different zones of MS frequency.

Higher levels of UVB irradiation were strongly associated with lower MS prevalence rates in the French population using the MSA health system. Given their relatively homogenous genetic background, this implicates UV exposure as an environmental or genetic–environmental factor in MS susceptibility. Similar findings in Newfoundland and Labrador, Canada, showed a correlation of increasing MS incidence with decreasing erythemal UVR[25] and in Australia between prevalence and UVR.[26] The latter study examined 6 regions in Australia, finding similar correlation values to the current findings ($r = -0.91$, $p = 0.01$[26]), albeit slightly higher. We also observed a trend for increasing prevalence in a west–east direction, although this cline seems to be restricted to regions above 45°N. This has been previously reported[15] and reasons may be a result of proximity to coastal regions. Indeed, looking at inland regions such as Limousin, Centre, Ile de France, and Picardie, they all have higher prevalence rates than neighboring coastal MSA regions at similar latitude (see figure 1). This could occur as a direct result of higher UV intensity around the ocean/sea border or result from other lifestyle factors related to living in coastal areas.

It has been proposed that the higher preponderance of MS in females results from ubiquitous population-based environmental factors, one of which is sunlight exposure.[11,27] We found that MS

prevalence in females was more highly correlated with UVB exposure than it was in males. Regression modeling showed that the effect of UVB on prevalence rates differed by gender. In other words, the rate at which MS prevalence increased with decreasing UVB was higher in females than in males. These data are cautiously interpreted given that ecological data are limited in their ability to postulate conclusions. Gender-specific prevalence data and corresponding UV data from other geographic locations will be informative in determining if this relationship is replicable and significant in other populations.

It is unclear whether these results can extend to other countries, but it is tempting to propose that they would at least be applicable to regions with MS epidemiology similar to France. Although it is probable that this is a general trend consistent in other populations, it is not always amenable to study as we have done here. Homogenous patient groups (genetically and culturally) are needed as ethnically diverse groups within a small geographic location can have significantly different prevalence rates.[28] Relatively low frequencies of migration and consistent ascertainment methods across latitudes are also important in limiting bias. Some countries are intrinsically less discriminating, simply due to lack of latitudinal variation and UV variability throughout the country. These qualities give the data from the France MSA a unique advantage.[15]

UVB data were only available at a population level, which limits the ability to account for individual variance in exposure. Lack of outdoor activity, use of sunscreen, and UV-restrictive clothing are examples of lifestyle factors which that could impact the assessment of UVB exposure with MS risk. However, it is possible that accounting for such behaviors would actually serve to strengthen the observed association. Exposure data on individual patients may be most useful in populations or locations that are exceptions to the UV gradient hypothesis. These include the reverse latitude gradient observed in Norway,[29] prevalence variability among different ethnic groups in the same region,[6,28,30] resistance to MS in indigenous populations,[29,31,32] and the high prevalence of MS in Sardinia,[33] among others. Such exceptions may result from putative protective environmental factors including fish-rich diets,[29,34] protective/predisposing genetic factors, cultural practices, or other as yet unidentified reasons.

Other correlates of latitude may include factors such as genetic risk profile, distribution and timing of exposure to viral infections, cultural practices, socioeconomic factors, and job type, among others. Additional data on these variables were not available for the population studied and thus could not be included as covariates. However, it is unlikely that most of these would follow such a striking south–north gradient, although the possibility that these variables intrinsically influence the strength of the UVB–MS association cannot be ruled out.

There are several possible mechanisms through which UVB radiation could be mediating the effect on MS risk. The most attractive explanation is UVB-induced synthesis of cutaneous vitamin D, which is the principal source of this metabolite. However, concentrations of vitamin D were not measured in this cohort and therefore potential mechanisms related to vitamin D can only be speculative. Interestingly, previous studies have shown gender differences in vitamin D metabolism and concentrations in patients with MS.[35,36] Seasonal effects on MS risk have been shown previously.[27,37,38] The relationship between UVB levels and MS prevalence was slightly stronger in the winter months. Levels of 25(OH)D in the French population are relatively low during the winter period[39] and extension of the present study to investigate variability in population levels of 25(OH)D among the 22 MSA regions would be useful. In addition, vitamin D may be operative through a gene–environment route. Recent findings show regulation of HLA-DRB1*1501, the most significantly associated MS gene, via vitamin D–responsive element in its promoter region.[40]

The current results indicate that UVB radiation influences MS prevalence rates in France. There was a significant gradient of increasing prevalence with decreasing UVB and the trend was slightly stronger in winter, as well as in females. The findings suggest UVB is likely an important environmental factor in MS susceptibility and it may influence gender-specific differences in disease risk.

DISCLOSURE

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REFERENCES

1. Pugliatti M, Sotgiu S, Rosati G. The worldwide prevalence of multiple sclerosis. Clin Neurol Neurosurg 2002;104:182–191.
2. Alonso A, Hernan MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology 2008;71:129–135.
3. McLeod JG, Hammond SR, Hallpike JF. Epidemiology of multiple sclerosis in Australia: with NSW and SA survey results. Med J Aust 1994;160:117–122.
4. Koch-Henriksen N. The Danish Multiple Sclerosis Registry: a 50-year follow-up. Mult Scler 1999;5:293–296.
5. Barnett MH, Williams DB, Day S, Macaskill P, McLeod JG. Progressive increase in incidence and prevalence of multiple sclerosis in Newcastle, Australia: a 35-year study. J Neurol Sci 2003;213:1–6.
6. Wallin MT, Page WF, Kurtzke JF. Multiple sclerosis in US veterans of the Vietnam era and later military service: race, sex, and geography. Ann Neurol 2004;55:65–71.
7. Granieri E, Economou NT, De Gennaro R, et al. Multiple sclerosis in the province of Ferrara: evidence for an increasing trend. J Neurol 2007;254:1642–1648.
8. 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;13:962–967.
9. Larsen JP, Kvaale G, Riise T, Nyland H, Aarli JA. An increase in the incidence of multiple sclerosis in western Norway. Acta Neurol Scand 1984;70:96–103.
10. Noonan CW, Kathman SJ, White MC. Prevalence estimates for MS in the United States and evidence of an increasing trend for women. Neurology 2002;58:136–138.
11. Orton SM, Herrera BM, Yee IM, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol 2006;5:932–936.
12. Confavreux C, Darchy P, Alperovitch A, Aimard G, Devic M. [South-Eastern France, a high risk area for multiple sclerosis?] Presse Med 1987;16:622–623.
13. Fender P, Megnigbeto C. [Morbidity estimates of beneficiaries of national health insurance for seven chronic conditions.] Rev Epidemiol Sante Publique 1997;45:193–202.
14. Pugliatti M, Rosati G, Carton H, et al. The epidemiology of multiple sclerosis in Europe. Eur J Neurol 2006;13:700–722.
15. Vukusic S, Van Bockstael V, Gosselin S, Confavreux C. Regional variations in the prevalence of multiple sclerosis in French farmers. J Neurol Neurosurg Psychiatry 2007;78:707–709.
16. Alperovitch A, Bouvier MH. Geographical pattern of death rates from multiple sclerosis in France: an analysis of 4912 deaths. Acta Neurol Scand 1982;66:454–461.
17. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004;80:1678S–1688S.
18. SoDa SSflaR. SoDa Online documents and references. Available at: www.soda-is.com. Accessed 2008–2009.
19. Gschwind B, Ménard L, Albuisson M, et al. Converting a successful research project into a sustainable service: the case of the SoDa Web service. Environ Modelling Software 2006;21:1555–1561.
20. Kift R, Webb AR, Page J, Rimmer J, Janjai S. A Web-based tool for UV irradiance data: predictions for European and Southeast Asian sites. Photochem Photobiol 2006;82:579–586.
21. Remund JP. Advanced parameters WP 5.2b: chain of algorithms: short- and long-wave radiation with associated temperature prediction resources. IN Report to the European Commission. Available at: http://www.soda-is.com/doc/d5–2-2_v3.pdf. Accessed 2008.
22. Wald L, Albuisson M, Best C, et al. SoDa: a project for the integration and exploitation of networked solar radiation databases, part 2. In: Pillmann W, ed. International Society for Environmental Protection. Vienna, Austria: 2002;713–720.
23. SPSS. Statistical Package for the Social Sciences, version 16.0. Chicago: SPSS; 2006.
24. A Language and Environment for Statistical Computing. Vienna: Foundation for Statistical Computing; 2004.
25. Sloka JS, Pryse-Phillips WE, Stefanelli M. The relation of ultraviolet radiation and multiple sclerosis in Newfoundland. Can J Neurol Sci 2008;35:69–74.
26. van der Mei IA, Ponsonby AL, Blizzard L, Dwyer T. Regional variation in multiple sclerosis prevalence in Australia and its association with ambient ultraviolet radiation. Neuroepidemiology 2001;20:168–174.
27. Willer CJ, Dyment DA, Sadovnick AD, Rothwell PM, Murray TJ, Ebers GC. Timing of birth and risk of multiple sclerosis: population based study. BMJ 2005;330:120.
28. Alter M, Kahana E, Zilber N, Miller A. Multiple sclerosis frequency in Israel's diverse populations. Neurology 2006;66:1061–1066.
29. Kampman MT, Brustad M. Vitamin D: a candidate for the environmental effect in multiple sclerosis: observations from Norway. Neuroepidemiology 2008;30:140–146.
30. Kurtzke JF, Beebe GW, Norman JE Jr. Epidemiology of multiple sclerosis in US veterans: 1: race, sex, and geographic distribution. Neurology 1979;29:1228–1235.
31. Skegg DC, Corwin PA, Craven RS, Malloch JA, Pollock M. Occurrence of multiple sclerosis in the north and south of New Zealand. J Neurol Neurosurg Psychiatry 1987;50:134–139.
32. Harbo HF, Utsi E, Lorentzen AR, et al. Low frequency of the disease-associated DRB1*15-DQB1*06 haplotype may contribute to the low prevalence of multiple sclerosis in Sami. Tissue Antigens 2007;69:299–304.
33. 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;22:163–165.
34. Kampman MT, Wilsgaard T, Mellgren SI. Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. J Neurol 2007;254:471–477.

35. Carnevale V, Modoni S, Pileri M, et al. Longitudinal evaluation of vitamin D status in healthy subjects from southern Italy: seasonal and gender differences. Osteoporos Int 2001;12:1026–1030.
36. Barnes MS, Bonham MP, Robson PJ, et al. Assessment of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D3 concentrations in male and female multiple sclerosis patients and control volunteers. Mult Scler 2007;13:670–672.
37. Tremlett H, van der Mei IA, Pittas F, et al. Monthly ambient sunlight, infections and relapse rates in multiple sclerosis. Neuroepidemiology 2008;31:271–279.
38. Embry AF, Snowdon LR, Vieth R. Vitamin D and seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. Ann Neurol 2000;48:271–272.
39. Malvy DJ, Guinot C, Preziosi P, et al. Relationship between vitamin D status and skin phototype in general adult population. Photochem Photobiol 2000;71:466–469.
40. 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:e1000369.