RESEARCH ARTICLE

Association of Latitude and Exposure to Ultraviolet B Radiation With Severity of Multiple Sclerosis

An International Registry Study

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Abstract

Background and Objectives

The severity of multiple sclerosis (MS) varies widely among individuals. Understanding the determinants of this heterogeneity will help clinicians optimize the management of MS. The aim of this study was to investigate the association between latitude of residence, UV B radiation (UVB) exposure, and the severity of MS.

Methods

This observational study used the MSBase registry data. The included patients met the 2005 or 2010 McDonald diagnostic criteria for MS and had a minimum dataset recorded in the registry (date of birth, sex, clinic location, date of MS symptom onset, disease phenotype at baseline and

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MSBase Study Group members are listed at http://links.lww.com/WNL/B957.

Glossary

DMT = disease-modifying therapy; **EBV** = Epstein-Barr virus; **EDSS** = Expanded Disability Status Scale; **MS** = multiple sclerosis; **MSSS** = Multiple Sclerosis Severity Score; **TOMS** = Total Ozone Mapping Spectrometer; **UVB** = UV B radiation.

censoring, and ≥1 Expanded Disability Status Scale score recorded). The latitude of each study center and cumulative annualized UVB dose at study center (calculated from National Aeronautics and Space Administration's Total Ozone Mapping Spectrometer) at ages 6 and 18 years and the year of disability assessment were calculated. Disease severity was quantified with Multiple Sclerosis Severity Score (MSSS). Quadratic regression was used to model the associations between latitude, UVB, and MSSS.

Results

The 46,128 patients who contributed 453,208 visits and a cumulative follow-up of 351,196 patient-years (70% women, mean age 39.2 ± 12 years, resident between latitudes 19°35′ and 56°16′) were included in this study. Latitude showed a nonlinear association with MS severity. In latitudes <40°, more severe disease was associated with higher latitudes (β = 0.08, 95% CI 0.04–0.12). For example, this translates into a mean difference of 1.3 points of MSSS between patients living in Madrid and Copenhagen. No such association was observed in latitudes <40° (β = −0.02, 95% CI −0.06 to 0.03). The overall disability accrual was faster in those with a lower level of estimated UVB exposure before the age of 6 years (β = − 0.5, 95% CI −0.6 to 0.4) and 18 years (β = − 0.6, 95% CI −0.7 to 0.4), as well as with lower lifetime UVB exposure at the time of disability assessment (β = −1.0, 95% CI −1.1 to 0.9).

Discussion

In temperate zones, MS severity is associated with latitude. This association is mainly, but not exclusively, driven by UVB exposure contributing to both MS susceptibility and severity.

The etiology of multiple sclerosis (MS) is being elucidated, with a complex interplay between genetic and environmental factors believed to underpin the majority of the risk of disease.[1] Of the environmental factors, the positive latitudinal gradient of prevalence rates has been noted as a consistent feature of MS epidemiology.[2] Because latitude is strongly inversely related to solar UV radiation, a substantial body of research has postulated that increasing risk of MS in countries further from the equator may be linked to decreased sunlight and UV exposure.[3-5]

While a lot is known about the latitudinal gradient of MS prevalence, less attention has been paid to the effect of latitude on disease severity. A few studies to date have reported conflicting findings.[6-9]

The primary objective of this MSBase study was to estimate the association between latitude of place of residence and MS severity. The secondary objective was to study whether such a latitudinal gradient in MS severity can be explained by UV exposure at childhood (before age 6 years), adolescence (before age 18 years), or adulthood (before the latest disability assessment). Last, we explored the effect of migrating between latitudes on the severity of MS.

Methods

Standard Approvals

MSBase, an international MS registry,[10] was approved by the Melbourne Health Human Research Ethics Committee. Participants have provided written informed consent as required.

Study Population

Data from 63,583 patients from 161 centers in 74 countries were extracted from the registry in April 2019. Standard data quality procedures were followed[11] (eTable 1, links.lww.com/WNL/B952). Patients included in this study met the 2005 or 2010 McDonald diagnostic criteria for MS and had a minimum dataset available (date of birth, sex, clinic location, date of MS symptom onset, disease phenotype at baseline and censoring, and ≥1 Expanded Disability Status Scale [EDSS] score recorded). Centers in the lowest quintiles of data quality or generalizability scores[11] and centers with no record of patients with progressive-onset MS were excluded (eFigure 1, links.lww.com/WNL/B948). Patients disposition per center is shown in eTable 2 (links.lww.com/WNL/B953).

Variables of Interest

Age at disease onset was defined as the age at first symptoms consistent with MS. Patients were divided into relapsing-onset and progressive-onset MS.

Disease severity was assessed with the EDSS[12] and converted into the Multiple Sclerosis Severity Score (MSSS) to compare disability at different times from disease onset. The MSBase study protocol stipulates that a Neurostatus-certified rater is present at every center.[13] EDSS scores recorded within 30 days of a relapse onset were excluded. The rate of disability accrual differs between groups with different disease courses; therefore, we used the original MSSS for all patients with relapsing onset of MS[14] and the updated MSSS with normative data for patients with progressive onset of MS.[15]

The latitude of each study center was derived from LatitudeLongitude.Org.[16] We assumed that patients resided within the vicinity of their study center. The analyses used absolute latitude and the hemisphere of residence.

Furthermore, several analyses used the latitude of birth when known. For countries spanning <5° latitude, the latitude of the capital was used. For countries with a greater latitudinal span, we used the latitude of the city of birth if available. Those born in countries with a large latitudinal span (e.g., Australia), with no information about their birthplace, were excluded.

Satellite-derived UV B radiation (UVB) data were obtained from National Aeronautics and Space Administration's (NASA's) Total Ozone Mapping Spectrometer (TOMS), which provides an estimate of daily doses (J/m^2) of erythemal UVB reaching the earth's surface in 1.25° × 1.00° grids for most of the planet.[17] First, annual UVB doses for each calendar year and each city were calculated by averaging daily values over the given year. Exposure estimates were based on both latitude and longitude to account for variability in UVB level within latitudinal bands. TOMS accounts for cloud conditions, ozone thickness, length of day, solar zenith angle, and surface albedo. The NASA TOMS data showed that average UV irradiance reaching the Earth's surface has consistently increased since 1979 at all latitudes except the equatorial zone, following linear trends at the included locations.[18] For years in which no TOMS data were recorded, values were extrapolated from the available data with linear regression models. Next, the cumulative lifetime dose of UVB was estimated for each person as the sum of the UVB doses for each previous lived year and annualized by dividing the sum by age at each visit. In addition, we calculated cumulative UVB dose at the age of 6 and 18 years for each person after excluding patients whose age at symptom onset was <6 or <18 years, respectively. The UVB dose is therefore an estimate based on gross geographic data that does not account for individual factors (occupation, average time spent outdoors, cultural factors, habits, use of sunscreen, and others).

Information about the prevalence of MS in the represented countries was derived from World Health Organization-Multiple Sclerosis International Federation Atlas of MS 2013.[19]

The percentage of cases treated with any disease-modifying therapy (DMT) and with high-efficacy DMTs (natalizumab, alemtuzumab, cladribine, rituximab, ocrelizumab, fingolimod, mitoxantrone, daclizumab, ofatumumab) at the time of censoring was calculated for each study center.

Information about self-assigned ethnicity was recorded by treating neurologists for approximately two-thirds of the patients.

Statistical Analysis

All analyses were performed with R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria). Demographic and clinical characteristics were described for the whole sample and separately for the sample stratified by latitude.

Primary Analysis

Primary analysis was carried out with a mixed-effects linear regression model of the association between latitude and MSSS (the latter being the modeled outcome), adjusted for sex, age at MS onset, disease phenotype, hemisphere of study center, prevalence of MS in the country of residence (a proxy for regional experience with MS), and proportions of cases on any DMT and high-efficacy DMTs per center (to account for local treatment practices). The selection of covariates was based on a correlation matrix. To account for center-specific effects and within-person interdependence among multiple recorded MSSS observations, center and case identifiers were modeled as random intercepts. After inspecting the relationship between latitude of residence and MSSS, we explored the regression models with latitude defined as first-, second-, and third-order polynomials. Akaike and Bayesian information criteria were used to determine the best-fitted model. Furthermore, we have examined the distribution of residuals. When a nonlinear relationship between latitude and MSSS was observed, models were stratified into the relevant ranges of latitudes as determined by visual inspection of the interpolated regression curve and by use of differential calculus.

To evaluate consistency of the observed associations, the models were also fitted separately for the Northern and the Southern Hemispheres.

Secondary Analyses

The model used in the primary analysis was then extended to include cumulative UVB dose at the age of 6 and 18 years and annualized UVB dose at the date of the MSSS assessment. This analysis excluded patients for whom the latitudes of their place of birth and MS center differed by >5° because the information about the age at which they migrated was not available. The models were assessed for multicollinearity using variance inflation factor and tolerance statistic.

Furthermore, we explored the final model adjusted for ethnicity in the cohort for whom data on ethnicity were available (with White used as the reference).

Among patients with information about their place of birth available, we analyzed independent contributions of the latitude of residency and latitude of birthplace to the MS severity in a group of nonmigrant individuals, in whom the difference in the latitude of residence and the latitude of birthplace was ≤5°, and in a group of migrants, in whom the latitudes of birthplace and residence differed by >5° (equivalent to a distance of ≈555 km). Similar to the primary analysis, multivariable mixed-effect regression models with random intercepts for center and case were used.

Data Availability

Data were obtained from the international MSBase cohort study. Information on data availability can be obtained online.[20]

Table 1 Characteristics of the Study Population

	All (N = 46,128)	Low latitude (≤40°) (n = 25,714)	High latitude (>40°) (n = 20,414)
Female, n, %	32,474, 70.4	18,020, 70.0	14,451, 70.7
Age at censoring, mean (SD), median, y	39.2 (12.0), 38.1	37.2 (12.1), 36.9	40.9 (12.1), 39.4
Interquartile range (range), y	30.0–47.4 (1–85.9)	29.0–45.8 (1–85.9)	31.5–49.2 (6.8–85.6)
Age at MS onset, mean (SD), median, y	32.0 (10.5), 31	31.2 (10.6), 30	33.0 (10.6), 31
Interquartile range (range), y	24–39 (1–83)	24–38 (1–82)	25–40 (1–83)
MS onset phenotype, n, %			
ROMS	42,860, 93.0	24,103, 93.8	18,757, 91.9
POMS	3,268, 7.0	1,611, 6.2	1,657, 8.1
EDSS score at censoring, mean (SD), median	2.5 (2.0), 2.0	2.5 (2.0), 2.0	2.6 (2.0), 2.0
Interquartile range (range)	1.0–3.5 (0–10)	1.0–3.5 (0–10.0)	1.5–3.5 (0–9.5)
MS duration at censoring, mean (SD), median, y	7.2 (8.3), 4.0	6.6 (7.6), 4.0	7.8 (8.9), 4.0
Interquartile range (range)	1–10.5 (0–63.4)	1–9.7 (0–60.8)	1–12 (0–63.5)
MSSS at censoring, mean (SD), median	3.9 (2.4), 3.7	3.9 (2.7), 3.7	4.0 (2.6), 3.6
Interquartile range (range)	1.5–5.8 (0–10)	1.5–5.9 (0–10)	1.7–5.9 (0–10)
Ethnicity information available, n , %	31,214, 67.7	16,666, 53.4	14,548, 71.3
White	27,749, 89.1	13,482, 80.8	14,267, 98.0
Middle East	2,715, 8.7	2,694, 16.1	21, 0.1
African/Hispanic	541, 1.7	363, 2.2	178, 1.3
Asian	92, 0.2	65, 0.4	27, 0.2
Other	117, 0.3	62, 0.4	55, 0.4
Northern Hemisphere, n	39,439	20,090	19,349
Southern Hemisphere, n	6,689	6,365	324
Latitude of residence, mean (SD), median, degrees	41.4 (6.8), 40.1	36.4 (3.9), 37.4	47.6 (3.8), 45.7
Interquartile range (range), degrees	37.5–45.5 (19.4–56.1)	33.9–38.4 (19.3–41.3)	44.6–51.8 (41.4–56.2)
Northern Hemisphere, mean (SD), median, degrees	42.4 (6.7), 41.4	36.8 (4.0), 37.4	47.7 (3.7), 45.5
Interquartile range (range), degrees	37.5–46.8 (19.4–56.1)	33.9–40.4 (19.4–41.2)	44.6–50.8 (41.4–56.2)
Southern Hemisphere, mean (SD), median, degrees	35.6 (3.6), 37.8	35.3 (3.3), 37.8	42.8[a]
Interquartile range (range), degrees	34.0–37.8 (24.0–42.8)	34.0–37.8 (24.0–38.2)	
Country MS prevalence, mean (SD), median, n patients per 100,000 population	106 (67), 100	77.4 (8.4), 95.6	162 (73.9), 113
Interquartile range (range)	55–113 (14–291)	55–100 (14–135)	113–164 (30–291)
Place of birth			
Patients with available data, n	21,127	15,500	5,627
Latitude of birth, mean (SD), median, degrees	39.2 (6.0), 40.4	37.6 (5.9), 39.9	42.7 (4.6), 41.9
Interquartile range (range), degrees	35.7–42.2 (0.3–60.2)	33.9–41.9 (0.3–60.2)	41.9–41.9 (0.3–60.2)
Proportion of DMT-treated patients/center			
Mean (SD), median	45.5 (20.3), 39	49.2 (2.6), 46	40.8 (19), 36
Interquartile range (range)	28–62 (15–92)	32–65 (15–89)	26–59 (21–92)
Proportion of patients on high-efficacy drugs[b]/center			

Continued

Table 1 Characteristics of the Study Population *(continued)*

	All (N = 46,128)	Low latitude (≤40°) (n = 25,714)	High latitude (>40°) (n = 20,414)
Mean (SD), median	26.1 (12.6), 24	29.9 (13.8), 30	21.4 (8.8), 23
Interquartile range (range)	18–30 (1–58)	23–58 (1–58)	18–24 (1–55)
Migration			
>5° Difference in latitude between place of birth and place of residence, n	1,198	862	336

Abbreviations: DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; MSSS = Multiple Sclerosis Severity Score; POMS = progressive-onset multiple sclerosis; ROMS = relapsing-onset multiple sclerosis.
[a] Single center lies in the Southern Hemisphere >40°.
[b] High-efficacy therapies: natalizumab, alemtuzumab, cladribine, rituximab, ocrelizumab, fingolimod, mitoxantrone, daclizumab, ofatumumab.

Results

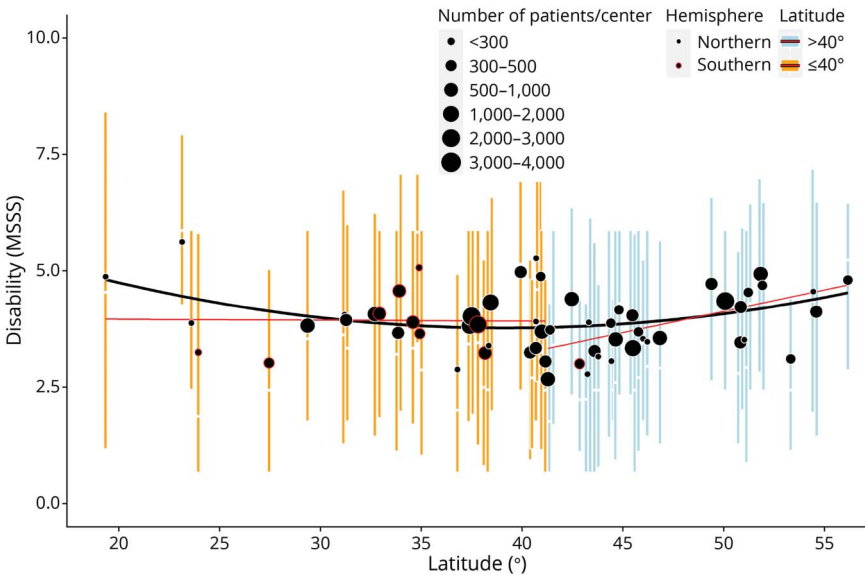
From the 77 study centers across 26 countries included in the analysis, 46,128 patients (70% women, mean age 39.2 ± 12 years, mean MSSS 2.9 ± 3.4, resident between latitudes 19°35′ and 56°16′) contributing 453,208 visits with a cumulative follow-up 351,196 person-years were included. Table 1 describes the demographic and clinical characteristics of the study cohort, and eFigure 2 (links.lww.com/WNL/B949) shows the map of cities included in the study.

Latitude and MS Severity

The distribution and variability of MSSS are reflected by the SD of random intercept within centers of 2.25 (95% CI 2.24–2.27) and SD of random intercept between centers of 0.61 (95% CI 0.52–0.74). Visual inspection of the distribution of MSSS at centers ordered by latitude revealed a nonlinear relationship between latitude and MSSS (Figure 1), with the local minimum at ≈40° of latitude. This observation was confirmed by the use of differential calculus, which has shown the local minimum of the curve to be at 40.16° of latitude. We have modeled this relationship with multivariable mixed-effects regression models of MSSS with latitude represented by first-, second-, or third-degree polynomials. The quadratic model was the best-fitting parsimonious model (eTable 3, links.lww.com/WNL/B954); latitude was therefore modeled as a second-degree polynomial in the subsequent analyses.

The multivariable mixed-effects model with a quadratic term confirmed that there was a significant nonlinear relationship between latitude and MSSS that was independent of the adjustment variables (Table 2). The results of 2 separate models in the Northern and the Southern Hemispheres confirmed the results of the overall primary model (eTable 4, links.lww.com/WNL/B955).

Figure 1 Association Between Latitude and Multiple Sclerosis Severity



Mean Multiple Sclerosis Severity Scores (MSSS) plotted by the latitude of each MSBase center are shown. Number of patients per center is indicated by circle size. Color of circle margin denotes location of centers in Northern/Southern Hemisphere. Interpolated curve represent the overall quadratic model (black) and 2 linear models split by 40° latitude (red).

Table 2 Associations Between Latitude and MSSS Modeled With Mixed-Effects Models With a Quadratic Term for Latitude Adjusted for Potential Confounders

	All (N = 46,128)		High latitude (>40°) (n = 20,414)		Low latitude (≤40°) (n = 20,414)	
	β Value (95% CI)	*p* Value	β Value (95% CI)	*p* Value	β Value (95% CI)	*p* Value
Latitude, degrees	−0.22 (−0.35, −0.07)	0.003	0.08 (0.041, −0.12)	<0.001	−0.02 (−0.06, 0.03)	0.4
Latitude^2 (quadratic term)	0.003 0.001, −0.004	0.003	—	—	—	—
Hemisphere (southern)	−0.002 (−0.4, 0.4)	1.0	−0.01 (−1.3, 1.1)	0.9	−0.02 (−0.6, 0.3)	0.5
Sex (male)	0.31 (0.25, 0.34)	<0.001	0.24 (0.11, 0.29)	<0.001	0.33 (0.28, 0.41)	<0.001
Age at MS onset, y	0.050 (0.052, 0.056)	<0.001	0.059 (0.056, 0.061)	<0.001	0.053 (0.051, 0.056)	<0.001
MS onset phenotype (POMS)	0.18 (0.07, 0.25)	<0.001	0.22 (0.10, 0.36)	<0.001	0.51 (0.4, 0.7)	<0.001
Prevalence of MS, 1/100,000	−0.003 (−0.005, −0.001)	0.02	−0.002 (−0.005, 0.0004)	0.1	−0.005 (−0.01, 0.003)	0.2
DMT-treated patients per center, %	−0.005 (−0.012, 0.004)	0.2	−0.002 (−0.012, 0.004)	0.7	−0.005 (−0.01, 0.01)	0.3
Patients on high-efficacy[a] drugs per center, %	−0.007 (−0.018, 0.004)	0.2	−0.008 (−0.018, 0.004)	0.3	−0.003 (−0.02, 0.02)	0.7

Abbreviations: DMT = disease-modifying treatment; MS = multiple sclerosis; MSSS = Multiple Sclerosis Severity Score; POMS = progressive-onset multiple sclerosis.
Results are shown for the model with the quadratic term in the full cohort and the 2 models with only linear terms stratified by 40° of latitude.
[a] High-efficacy therapies: natalizumab, alemtuzumab, cladribine, rituximab, ocrelizumab, fingolimod, mitoxantrone, daclizumab, and ofatumumab.

On the basis of the observed nonlinear association, we have developed 2 multivariable linear mixed-effect models that we applied separately to subpopulations within latitudes >40° and ≤40° (Table 2). The latitude of residence was associated with disease severity in the high-latitude group. MSSS increased by 0.08 (95% CI 0.04–0.12) points for every degree of latitude. This translates into a predicted difference of ≈1.3 points of MSSS between patients living in Madrid (40°) and those in Copenhagen (56°). No evidence of association between latitude and MSSS was found in the lower-latitude group (β = −0.02, 95% CI −0.06 to 0.03).

Among the covariates, older age at onset, male sex, and progressive-onset multiple sclerosis phenotype were associated with greater MSSS (Table 2). The model confirmed our expectation that the higher prevalence of MS in the country of residence is related to less severe disease (β = −0.003, 95% CI −0.005 to 0.001), but this association is of marginal clinical

Table 3 Associations Between Annualized Cumulative UVB Doses and MSSS Score, Evaluated at the Time of MSSS, 6 and 18 Years of Age

	β Value (95% CI) *p* Value		
	All (N = 44,931)	Patients with disease onset ≥6 y of age (n = 44,894)	Patients with disease onset ≥18 y of age (n = 42,366)
Latitude of residence	−0.3 (−0.5, −0.1) <0.001	−0.3 (−0.5, −0.2) <0.001	−0.3 (−0.5, −0.2) <0.001
Latitude of residence^2 (quadratic term)	0.003 (0.001, 0.005) 0.002	0.003 (0.001, 0.005) 0.002	0.004 (0.001, 0.005) 0.001
Annualized cumulative UVB dose at the age of 6 y	—	−0.5 (−0.6, −0.4) <0.001	—
Annualized cumulative UVB dose at the age of 18 y	—	—	−0.6 (−0.7, −0.4) <0.001
Annualized cumulative UVB dose at the time of visit	−1.0 (−1.1, −0.9) <0.001	—	—

Abbreviations: MSSS = Multiple Sclerosis Severity Score; UVB = UV B radiation.
Only the variables of interests from the multivariable-adjusted quadratic mixed regression models (see Table 2) are shown.

Table 4 Associations Between the Latitude of Residence and the Latitude of Birth Place With MSSS Score Among Patients Native to Their Place of Residence and Migrants

	β Value (95% CI) *p* Value	
	Patients followed up at MS centers ≤5° from their latitude of birth (n = 19,929)	**Patients followed up at MS centers >5° from their latitude of birth (n = 1,198)**
Latitude of residence, degrees	−0.2 (−0.5, −0.03) 0.02	−0.2 (−0.5, 0.2) 0.4
Latitude of residence^2 (quadratic term)	0.002 (0.0001, 0.004) 0.04	0.002 (−0.001, 0.004) 0.4
Latitude of birth	−0.2 (−0.3, −0.02) 0.02	−0.007 (−0.05, 0.04) 0.7
Latitude of birth^2 (quadratic term)	0.002 (0.0001, 0.004) 0.03	0.0001 (−0.001, 0.001) 0.7

Abbreviations: MS = multiple sclerosis; MSSS = Multiple Sclerosis Severity Score.
Only the variables of interest from the multivariable-adjusted quadratic mixed regression models (see Table 2) are shown. Each multivariable model included only terms for latitude of residence or latitude of birth but not both because the 2 variables are strongly collinear.

importance (0.03 points of MSSS per 10 of 100,000 prevalence change).

Secondary Analyses: UVB Exposure, Ethnicity, and Migration

The role of exposure to UVB in the detected association between latitude and MS severity was examined in a cohort of 44,931 eligible patients. Table 3 and eFigure 3 (links.lww.com/WNL/B950) show a linear decrease of disease severity with increasing levels of annualized cumulative UVB dose (β = −1.0, 95% CI −1.1 to 0.9). This association was independent of the association of MSSS with latitude and tended to plateau above the annualized UVB dose of 4 kJ/m^2 (corresponding to the mean latitude of 35.38°, median latitude of 37.50°, eFigure 4, links.lww.com/WNL/B951). If the annual UVB exposure increased by 1 kJ/m^2 (corresponding to, for instance, a difference in average annual UVB dose between Barcelona and Dublin or between Hobart and Brisbane), the severity of disease decreased by 1.0 MSSS point. An association in the same direction but with a smaller magnitude was observed for annualized cumulative UVB exposure at the age of 6 years (β = −0.5, 95% CI −0.6 to 0.4) and 18 years (β = −0.6, 95% CI −0.7 to 0.4). The correlation between latitude and annual UVB exposure in our sample was moderately strong (Pearson correlation coefficient = −0.81, adjusted R^2 = 0.80). Due to the large study cohort, inclusion of both latitude and UVB in the same model did not result in model overfitting or multicollinearity. The mean variance inflation factor for UVB in our final model was 1.31, and the tolerance statistic was 0.76. These results show that latitude and UVB exposure were not critically correlated with respect to their prediction of MS severity.

Information about ethnicity was available for a subgroup of 31,214 patients. Among these patients, models adjusted for ethnicity confirmed the associations of MSSS with latitude and UVB exposure at the 3 studied time points. In all models, African and Hispanic ethnicity was associated with more severe disease compared to White ethnicity (eTable 5, links.lww.com/WNL/B956).

A series of analyses assessed the interplay between the latitude of residence and the latitude of birthplace with regard to MS severity. In the group of nonmigrants (n = 19,929 with no substantial difference between the latitude of their birthplace and place of residence), the results were consistent between the models that included both the latitude of residence and the latitude of birthplace and with the primary overall model (Table 4). On the other hand, while the latitude of residence and the latitude of birth showed similar trends among those who migrated by >5° latitude from their birthplace, the models did not find statistical evidence for these associations.

Discussion

In this international, multicenter observational study, latitude of current place of residence demonstrated a significant nonlinear association with the severity of MS. A positive latitudinal gradient of disease severity is observed in geographic areas >40° of latitude. In these higher latitudes, the magnitude of the association corresponds to a clinically significant difference of 1.3 deciles of the MSSS between Madrid and Copenhagen (with those in Copenhagen with more severe disease). In lower latitudes, no similar gradient is seen. Accrual of disability is faster in people with MS with lower levels of UVB exposure at the ages of 6 and 18 years, as well as with lower lifetime UVB exposure at the time of disability assessment. This pattern is consistent between the Northern and the Southern Hemispheres and when ethnicity of the participants is taken into account.

In all previous studies that explored the effect of latitude on MS severity, the association of latitude with disease outcomes was considered to be linear.[6-8] The results of these studies have been inconclusive. A recently published study observed an association of latitude with MS severity in 2 multicenter cohorts (43°N–51°N and 48°N–54°N) and showed that lower latitude was associated with lower disease severity and lower disability accumulation.[9] This is in line with the results of our

study, which showed that, in latitudes >40°, MS severity decreases linearly with decreasing latitude. Similar results were reported by a study of almost 2,500 self-selected responders living mostly between 35° and 49° of latitude in both hemispheres, which showed that those residing at a higher latitude were more likely to experience higher self-reported disability.[7] The study did not analyze the association of latitude with MS severity separately in latitudes >40° or <40°. A study in 434 patients in Japan reported an inverse relationship between latitude and disability, with those from the south of Japan (38°N) having a greater MS severity than those from the north (46°N).[8] However, the authors reported phenotypic differences between the northern and the southern subgroups, which raises the possibility that the group in the south was potentially enriched with an opticospinal form of MS, which may overlap with neuromyelitis optica spectrum disorders and is recognized to have a more severe course than more common MS phenotypes.[21] This could explain the contrasting findings reported by our present work and their study. Last, a study among 2,422 patients from New Zealand found no evidence of an association between latitude and MS severity between 35°S and 46°S of latitude.[6] The variability of the results may be driven by the fact that the nature of the latitude-MSSS association differs in the 2 latitudinal bands (stratified by ≈40° latitude). We observed that MS severity decreases with the increasing distance from the poles up to ≈40° latitude. No such effect was detected in latitudes <40°. This observation implies an existence of a ceiling effect for the benefit of living in lower latitudes for reducing MS severity.

Studies of MS prevalence have suggested that variation of UVB exposure is the most dominant driver of the latitudinal gradient of susceptibility to MS.[22,23] Our present study describes such a relationship for disease severity. It is interesting to observe that the association of MS severity with UVB, unlike that with latitude, is linear. Higher estimated average cumulative UVB dose at the time of disability assessment is associated with less severe MS course. On average, MSSS decreases by 1.0 to 1.2 deciles for each 1 –kJ/m^2 increase in annual UVB dose. These associations, although of a relatively smaller magnitude, are already present at 6 and 18 years of age with respect to all future MSSS. This suggests that exposure to UVB during the early stages of life may be critical for defining future severity of the disease.[24] Experimental models have shown that immunomodulation by UVB is mediated through both vitamin D–dependent and vitamin D–independent pathways.[5,25] Several studies used mendelian randomization with polymorphism of genes to codetermine serum concentration of vitamin D and to eliminate reverse causation and establish a causal role for vitamin D in susceptibility to MS.[26,27] On the other hand, independently from vitamin D, a genetic polymorphism encoding the melanocortin-1 receptor, which is also a codeterminant of skin tone, seems to be associated with MS severity.[28] Human clinical trials are underway to analyze the effects of UVB light[29] and vitamin D[30] on the progression of MS.

The association of latitude with disease severity observed in our study was partly independent from the estimated UVB exposure. This suggests that factors other than UVB dose could also underpin the latitudinal gradient of MS severity. Most notably, UVB exposure is modified by behavioral factors, which are in turn determined by a patient's disability, comorbid conditions, and cultural factors. Epstein-Barr virus (EBV) is another potential candidate determinant. EBV seroprevalence is substantially greater in higher latitudes in both patients with MS and healthy controls.[31] In some studies, the serologic response against EBV correlated with clinical[32] and MRI disease activity.[33,34] Systematic differences in the genomic composition of populations in different regions could also play a role. We found no evidence to support the effect of latitude of birthplace and latitude of residence on MS severity among persons who migrated between countries with markedly different latitudes. This finding could be explained by the fact that these people moved between latitudes at various ages, and therefore, they adopted variable composites of the risk characteristics of their latitude of origin and latitude of residence. This view is based on studies of MS prevalence, which showed that people who migrated after the age of 15 years retained the risk within their country of origin, whereas those who migrated before the age of 15 years adopted a combination of the risks, within their country of origin and their new country of residence.[35] Because the information on age at migration was not available in the present cohort, we were unable to test this hypothesis directly.

The limitations of the present study revolve mainly around the nature of the available data. First, this is a study based on a large cohort, and our results cannot be directly translated into predictions of individual outcomes. Lifetime UVB exposure did not take into account individual behaviors such as occupation, intentional sun exposure, or cultural habits. In addition, we did not have access to information about other confounders of susceptibility to MS such as body mass index or history of EBV infection. However, we have substituted for some of these effects by estimating individual UVB exposure as the sum of satellite UVB data during the years from birth to the time of disability assessment for each EDSS time point. In addition, we have estimated models with UVB exposure at 2 different early milestones: ages 6 and 18 years. Furthermore, for time points (46%) outside the operating years of the TOMS project (before 1979, 1994–1995, after 2004), we have resorted to linear extrapolation of the values. There are a number of geographically dependent codeterminants of disease severity that we did not explore in this study. These include regional diagnostic and therapeutic practices, dietary and cultural factors, and others. While we were unable to adjust the models for these confounders directly, the models are adjusted for MS center and ethnicity (in a subgroup), with center serving as a group term for a number of local influences and a proxy for the genetic constitution of the studied populations.

Both the prevalence of MS and MS severity are subject to a highly internally consistent latitudinal gradient. In latitudes <40°, the underlying environmental determinants of MS severity reach saturation, and a ceiling effect is observed, with no

further systematic shift in the disease severity. It is important to note that UVB exposure is not exclusively associated with susceptibility to MS; it also shows an association with MS severity. Further research is needed to identify other environmental factors that could play a role in geographic variation of disease severity.

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Continued

Appendix 1 *(continued)*

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