BRAIN
ORIGINAL ARTICLE

The risk of secondary progressive multiple sclerosis is geographically determined but modifiable

Sifat Sharmin,[1,2] Izanne Roos,[1,2] Steve Simpson-Yap,[1,3,4] Charles Malpas,[1,2]
Marina M. Sánchez,[1,2,5] Serkan Ozakbas,[6] Dana Horakova,[7] Eva K. Havrdova,[7]
Francesco Patti,[8] Raed Alroughani,[9] Guillermo Izquierdo,[10] Sara Eichau,[10] Cavit Boz,[11]
Magd Zakaria,[12] Marco Onofrj,[13] Alessandra Lugaresi,[14] Bianca Weinstock-Guttman,[15]
Alexandre Prat,[16] Marc Girard,[16] Pierre Duquette,[16] Murat Terzi,[17] Maria Pia Amato,[18]
Rana Karabudak,[19] Francois Grand'Maison,[20] Samia J. Khoury,[21] Pierre Grammond,[22]
Jeannette Lechner-Scott,[23] Katherine Buzzard,[24] Olga Skibina,[24] Anneke van der Walt,[25]
Helmut Butzkueven,[25] Recai Turkoglu,[26] Ayse Altintas,[27] Davide Maimone,[28]
Allan Kermode,[29] Nevin Shalaby,[30] Vincent V. Pesch,[31] Ernest Butler,[32]
Youssef Sidhom,[33] Riadh Gouider,[33,34] Saloua Mrabet,[33,34] Oliver Gerlach,[35,36]
Aysun Soysal,[37] Michael Barnett,[38] Jens Kuhle,[39] Stella Hughes,[40] Maria J. Sa,[41]
Suzanne Hodgkinson,[42] Celia Oreja-Guevara,[43] Radek Ampapa,[44] Thor Petersen,[45]
Cristina Ramo-Tello,[46] Daniele Spitaleri,[47] Pamela McCombe,[48] Bruce Taylor,[49]
Julie Prevost,[50] Matteo Foschi,[51] Mark Slee,[52] Chris McGuigan,[53] Guy Laureys,[54]
Liesbeth V. Hijfte,[54] Koen de Gans,[55] Claudio Solaro,[56] Jiwon Oh,[57]
Richard Macdonell,[58] Eduardo Aguera-Morales,[59] Bhim Singhal,[60] Orla Gray,[61]
Justin Garber,[62] Bart V. Wijmeersch,[63] Mihaela Simu,[64,65] Tamara Castillo-Triviño,[66]
Jose L. Sanchez-Menoyo,[67] Dheeraj Khurana,[68] Abdullah Al-Asmi,[69] Talal Al-Harbi,[70]
Norma Deri,[71] Yara Fragoso,[72,†] Patrice H. Lalive,[73] L. G. F. Sinnige,[74] Cameron Shaw,[75]
Neil Shuey,[76] Tunde Csepany,[77] Angel P. Sempere,[78] Fraser Moore,[79] Danny Decoo,[80]
Barbara Willekens,[81,82] Claudio Gobbi,[83] Jennifer Massey,[84] Todd Hardy,[85]
John Parratt[86] and Tomas Kalincik,[1,2] on behalf of the MSBase investigators

†Deceased.

Geographical variations in the incidence and prevalence of multiple sclerosis have been reported globally. Latitude as a surrogate for exposure to ultraviolet radiation but also other lifestyle and environmental factors are regarded as drivers of this variation. No previous studies evaluated geographical variation in the risk of secondary progressive multiple sclerosis, an advanced form of multiple sclerosis that is characterized by steady accrual of irreversible disability. We evaluated differences in the risk of secondary progressive multiple sclerosis in relation to latitude and country of residence, modified by high-to-moderate efficacy immunotherapy in a geographically diverse cohort of patients with relapsing-remitting multiple sclerosis. The study included relapsing-remitting multiple sclerosis patients from the global MSBase registry with at least one recorded assessment of disability. Secondary progressive multiple sclerosis

was identified as per clinician diagnosis. Sensitivity analyses used the operationalized definition of secondary progressive multiple sclerosis and the Swedish decision tree algorithm. A proportional hazards model was used to estimate the cumulative risk of secondary progressive multiple sclerosis by country of residence (latitude), adjusted for sex, age at disease onset, time from onset to relapsing-remitting phase, disability (Multiple Sclerosis Severity Score) and relapse activity at study inclusion, national multiple sclerosis prevalence, government health expenditure, and proportion of time treated with high-to-moderate efficacy disease-modifying therapy. Geographical variation in time from relapsing-remitting phase to secondary progressive phase of multiple sclerosis was modelled through a proportional hazards model with spatially correlated frailties.

We included 51 126 patients (72% female) from 27 countries. The median survival time from relapsing-remitting phase to secondary progressive multiple sclerosis among all patients was 39 (95% confidence interval: 37 to 43) years. Higher latitude [median hazard ratio = 1.21, 95% credible interval (1.16, 1.26)], higher national multiple sclerosis prevalence [1.07 (1.03, 1.11)], male sex [1.30 (1.22, 1.39)], older age at onset [1.35 (1.30, 1.39)], higher disability [2.40 (2.34, 2.47)] and frequent relapses [1.18 (1.15, 1.21)] at inclusion were associated with increased hazard of secondary progressive multiple sclerosis. Higher proportion of time on high-to-moderate efficacy therapy substantially reduced the hazard of secondary progressive multiple sclerosis [0.76 (0.73, 0.79)] and reduced the effect of latitude [interaction: 0.95 (0.92, 0.99)]. At the country-level, patients in Oman, Tunisia, Iran and Canada had higher risks of secondary progressive multiple sclerosis relative to the other studied regions.

Higher latitude of residence is associated with a higher probability of developing secondary progressive multiple sclerosis. High-to-moderate efficacy immunotherapy can mitigate some of this geographically co-determined risk.

1 CORe, Department of Medicine, University of Melbourne, Melbourne 3050, Australia
2 Neuroimmunology Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne 3050, Australia
3 Neuroepidemiology Unit, Melbourne School of Population and Global Health, University of Melbourne, Melbourne 3050, Australia
4 Menzies Institute for Medical Research, University of Tasmania, Tasmania 7000, Australia
5 Department of Neurology, Hospital Germans Trias i Pujol, Badalona 08916, Spain
6 Faculty of Medicine, Dokuz Eylul University, Konak/Izmir 35220, Turkey
7 Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague 12808, Czech Republic
8 Department of Medical and Surgical Sciences and Advanced Technologies, GF Ingrassia, Catania 95123, Italy
9 Division of Neurology, Department of Medicine, Amiri Hospital, Sharq 73767, Kuwait
10 Multiple Sclerosis Unit, Hospital Universitario Virgen Macarena, Sevilla 41009, Spain
11 Faculty of Medicine, Karadeniz Technical University, Karadeniz Technical University Farabi Hospital, Trabzon 61080, Turkey
12 Faculty of Medicine, Ain Shams University, Cairo 11566, Egypt
13 Department of Neuroscience, Imaging, and Clinical Sciences, University G. d'Annunzio, Chieti 66013, Italy
14 Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna 40139, Italy
15 Department of Neurology, Jacobs Multiple Sclerosis Center for Treatment and Research, University at Buffalo, Buffalo 14202, USA
16 CHUM MS Center, Faculty of Medicine, Universite de Montreal, Montreal H2L 4M1, Canada
17 Faculty of Medicine, 19 Mayis University, Samsun 55160, Turkey
18 Department NEUROFARBA, University of Florence, Florence 50134, Italy
19 Department of Neurology, Hacettepe University, Ankara 6100, Turkey
20 Neuro Rive-Sud, Hôpital Charles LeMoyne, Quebec J4V 2J2, Canada
21 Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Beirut 1107 2020, Lebanon
22 Médecine spécialisée, CISSS Chaudière-Appalaches, Levis G6X 0A1, Canada
23 School of Medicine and Public Health, University of Newcastle, Newcastle 2305, Australia
24 Department of Neurology, Box Hill Hospital, Melbourne 3128, Australia
25 Department of Neurology, The Alfred Hospital, Melbourne 3000, Australia
26 Department of Neurology, Haydarpasa Numune Training and Research Hospital, Istanbul 34668, Turkey
27 Department of Neurology, School of Medicine, Koc University, Koc University Research Center for Translational Medicine (KUTTAM), Istanbul 34450, Turkey
28 Centro Sclerosi Multipla, UOC Neurologia, ARNAS Garibaldi, Catania 95124, Italy
29 Perron Institute, University of Western Australia, Nedlands 6009, Australia
30 Department of Neurology, Kasr Al Ainy MS Research Unit (KAMSU), Cairo 11562, Egypt
31 Service de Neurologie, Cliniques Universitaires Saint-Luc, Brussels 1200 BXL, Belgium

32 Monash Medical Centre, Melbourne 3168, Australia
33 Department of Neurology, Razi Hospital, Manouba 2010, Tunisia
34 Clinical Investigation Center Neurosciences and Mental Health, Faculty of Medicine, University of Tunis El Manar, Tunis 1068, Tunisia
35 Academic MS Center Zuyderland, Department of Neurology, Zuyderland Medical Center, Sittard-Geleen 5500, The Netherlands
36 School for Mental Health and Neuroscience, Department of Neurology, Maastricht University Medical Center, Maastricht 6131 BK, The Netherlands
37 Department of Neurology, Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases, Istanbul 34147, Turkey
38 Multiple Sclerosis Clinic, Brain and Mind Centre, Sydney 2050, Australia
39 Neurologic Clinic and Policlinic, Departments of Medicine and Clinical Research, University Hospital and University of Basel, Basel 4000, Switzerland
40 Department of Neurology, Royal Victoria Hospital, Belfast BT12 6BA, UK
41 Department of Neurology, Centro Hospitalar Universitario de Sao Joao, Porto 4200-319, Portugal
42 Immune tolerance laboratory Ingham Institute and Department of Medicine, University of New South Wales, Sydney 2170, Australia
43 Department of Neurology, Hospital Clinico San Carlos, Madrid 28050, Spain
44 MS centrum, Nemocnice Jihlava, Jihlava 58633, Czech Republic
45 Department of Neurology, Aarhus University Hospital, Arhus C 8000, Denmark
46 Department of Neurology, Hospital Germans Trias i Pujol, Badalona 8916, Spain
47 Centro Sclerosi Multipla, Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino 83100, Italy
48 Royal Brisbane and Women's Hospital, University of Queensland, Brisbane 4000, Australia
49 Department of Neurology, Royal Hobart Hospital, Hobart 7000, Australia
50 Département de neurologie, CSSS Saint-Jérôme, Saint-Jerome J7Z 5T3, Canada
51 Department of Neuroscience, Neurology Unit, S. Maria delle Croci Hospital of Ravenna, Ravenna 48121, Italy
52 College of Medicine and Public Health, Flinders University, Adelaide 5042, Australia
53 Department of Neurology, St Vincent's University Hospital, Dublin D04 T6F4, Ireland
54 Department of Neurology, Universitary Hospital Ghent, Ghent 9000, Belgium
55 Department of Neurology, Groene Hart Hospital, Gouda 2800 BB, The Netherlands
56 Department of Rehabilitation, CRRF 'Mons. Luigi Novarese', Moncrivello (VC) 16153, Italy
57 Barlo Multiple Sclerosis Centre, St. Michael's Hospital, Toronto M5B1W8, Canada
58 Department of Neurology, Austin Health, Melbourne 3084, Australia
59 Department of Neurology, University Hospital Reina Sofia, Cordoba 14004, Spain
60 Department of Neurology, Bombay Hospital Institute of Medical Sciences, Mumbai 400020, India
61 Department of Neurology, South Eastern HSC Trust, Belfast BT16, UK
62 Department of Neurology, Westmead Hospital, Sydney 2145, Australia
63 Rehabilitation and MS-Centre Overpelt, Hasselt University, Hasselt 3900, Belgium
64 Clinic of Neurology II, Emergency Clinical County Hospital 'Pius Brinzeu', Timisoara 300723, Romania
65 Department of Neurology, Victor Babes University of Medicine and Pharmacy Timisoara, Timisoara 300041, Romania
66 Department of Neurology, Hospital Universitario Donostia, San Sebastián 20014, Spain
67 Department of Neurology, Hospital de Galdakao-Usansolo, Galdakao 48660, Spain
68 Department of Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India
69 Department of Medicine, Sultan Qaboos University Hospital, Al-Khodh 123, Oman
70 Neurology Department, King Fahad Specialist Hospital-Dammam, Khobar 31952, Saudi Arabia
71 Hospital Fernandez, Buenos Aires 1425, Argentina
72 Department of Neurology, Universidade Metropolitana de Santos, Santos 11045-002, Brazil
73 Department of Clinical Neurosciences, Division of Neurology, Faculty of Medicine, Geneva University Hospital, Geneva 1211, Switzerland
74 Department of Neurology, Medical Center Leeuwarden, Leeuwarden 8934 AD, The Netherlands
75 Neuroscience Department, Barwon Health, University Hospital Geelong, Geelong 3220, Australia
76 Department of Neurology, St Vincents Hospital, Fitzroy, Melbourne 3065, Australia
77 Department of Neurology, Faculty of Medicine, University of Debrecen, Debrecen 4032, Hungary
78 Department of Neurology, Hospital General Universitario de Alicante, Alicante 3010, Spain
79 Department of Neurology, McGill University, Montreal H3T 1E2, Canada
80 Department of Neurology & Neuro-Rehabilitation, AZ Alma Ziekenhuis, Sijsele-Damme 8340, Belgium
81 Department of Neurology, Antwerp University Hospital, Edegem 2650, Belgium
82 Translational Neurosciences Research Group, Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk 2650, Belgium
83 Ospedale Civico Lugano, Lugano 6900, Switzerland

84 St Vincent's Hospital Sydney, Sydney 2010, Australia
85 Concord Repatriation General Hospital, Sydney 2139, Australia
86 Royal North Shore Hospital, Sydney 2065, Australia

Correspondence to: Sifat Sharmin
CORe, Department of Medicine, The University of Melbourne, Royal Melbourne Hospital
L4 East, 300 Grattan St, Melbourne 3050, Australia
E-mail: sifat.sharmin@unimelb.edu.au

Correspondence may also be addressed to: Tomas Kalincik
E-mail: tomas.kalincik@unimelb.edu.au

Introduction

It is widely accepted that the incidence and prevalence of multiple sclerosis is subject to geographical variation. In general, prevalence is higher in higher latitudes in both the northern and southern hemispheres.[1,2] Studies have linked this geographical variation to the exposure to ultraviolet (UV) B radiation and vitamin D levels.[3,4] Our recent study using data from the global MSBase registry showed that above 40°, higher latitude was associated with faster accumulation of disability.[5] It is not known if the risk of conversion to secondary progressive multiple sclerosis (SPMS), which is characterized by gradual accumulation of disability following an initial relapsing-remitting phase, is also subject to this geographical variation. Despite recent advances in the treatment of relapsing-remitting multiple sclerosis (RRMS), prognosis remains suboptimal, probably due to differential response to various therapies and substantial heterogeneity in treatment approaches across different countries due to differences in drug licensing and availability. Geographically related countries often share many environmental, lifestyle and dietary characteristics. Spatial modelling, which is a statistical approach to account for homogeneity across neighbouring regions would enable us to model geographical variations of SPMS risk.[6] This study examines the association between the place of residence and risk of SPMS in a large multi-national cohort using a spatial analysis.

Materials and methods

Ethics statement

The MSBase registry (WHO registration ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee and by the site institutional review boards. Written informed consent was obtained from all enrolled patients or guardians.

Patients

The MSBase registry is a global multiple sclerosis cohort from 151 centres in 41 countries on all populated continents. Since 2006, MSBase has prospectively collected demographic, clinical and limited radiological information from mainly tertiary specialist clinics.[7] Data for this study were extracted on 1 February 2022. Patients with confirmed diagnosis of RRMS were included conditional on the availability of at least one disability assessment with the Expanded Disability Status Scale (EDSS). Included centres had a MSBase generalizability score ≥ 10 to ensure representativeness of the study cohort of the known multiple sclerosis epidemiology and contemporary disease-modifying therapy.[8] The study excluded centres with no reported SPMS patients and countries with no data recorded after 1 January 2015, to minimize selection bias.

Primary outcome

The primary outcome of interest was the cumulative hazard of SPMS conversion over time from the diagnosis of RRMS. SPMS was diagnosed by treating clinicians based on the Lublin diagnostic criteria.[9,10]

Statistical analyses

A parametric proportional hazards frailty model was used to estimate the cumulative hazard of SPMS by patients' country of residence (latitude of centroid), adjusted for sex, age at disease onset, time from first symptom to RRMS, Multiple Sclerosis Severity Score (MSSS) at the inclusion (i.e. the time of entry to the MSBase registry) and relapse frequency during the subsequent year. National multiple sclerosis prevalence (per 100 000 population),[11] government health expenditure (% of current health expenditure),[12] and proportion of time treated with high-to-moderate efficacy disease-modifying therapy (alemtuzumab, mitoxantrone, natalizumab, ocrelizumab, ofatumumab, rituximab, cladribine, fingolimod, siponimod or daclizumab) during study follow-up were assessed as potential modifiers of the outcome. Multicollinearity was assessed using the variance inflation factor with larger values providing stronger evidence of multicollinearity.

Let, t_{ij} denote the time to SPMS conversion after diagnosis of RRMS for the i-th patient from the j-th country.

$$t_{ij} \sim Weibull\,(\lambda_{ij}, \alpha\,)$$

$$h(t_{ij}) = h_0(t_{ij})\exp(X_{ij}\beta + Z_j\gamma + U_j) \qquad (1)$$

where, $h(t_{ij})$ denotes the hazard function for the i-th patient within the j-th country, while $h_0(t_{ij})$ denotes the Weibull baseline hazard function. The X_{ij} and Z_j denote vectors of patient-level covariates and the country-level covariates (latitude, national multiple sclerosis prevalence and government health expenditure), respectively. The U_j denotes the random effect associated with the j-th country, which accounts for within-country homogeneity in the outcome. λ and α are the scale and the shape parameters of the Weibull distribution.

The difference in the effect of latitude on the hazard of SPMS conversion with varying proportion of time on high-to-moderate

efficacy disease-modifying therapy was evaluated in a secondary analysis through inclusion of an interaction term in Model (1).

Next, to investigate heterogeneity in the risk of SPMS conversion across countries, we modelled geographically referenced areal data of time to SPMS with a spatial parametric proportional hazards frailty model,[6] while accounting for patient-specific prognostic factors. The location of country of residence was incorporated through a spatially continuous, stationary latent Gaussian field Y, of which Y_j is the value of the field at the location of country j:

$$h(t_{ij}) = h_0(t_{ij}) \exp(X_{ij}\beta + Y_j) \qquad (2)$$

The exponential covariance function for Y, $\sigma^2 \exp(-d\emptyset)$, is a function of the Euclidean distance (d) between the coordinates of any two countries, marginal variance (σ^2) of the Gaussian field Y, and spatial decay parameter, $\emptyset$. The spatially correlated frailties modelled by the Gaussian stochastic process account for the unobserved spatial variation, which cannot be explained by patient-specific prognostic factors included in the model.

Spatial heterogeneity in SPMS risk is illustrated with a map of the predicted risk-exceedance probabilities ($P[\exp(Y) > 1]$) for individual countries.

To minimize the likelihood of under-reporting or delayed diagnosis of SPMS by clinicians, sensitivity analyses were performed using two different definitions of SPMS. We enriched the group with clinician-diagnosed SPMS with patients identified by the operationalized definition.[13] The operationalized definition relies on longitudinal data from relapsing-remitting phase to identify 3-month confirmed increase in EDSS in the absence of relapses in patients with EDSS ≥4 and pyramidal score ≥2.[13] The decision tree developed in the Swedish Multiple Sclerosis registry, relies on the most recent EDSS score and patient age.[14]

In two more sensitivity analyses we adjusted the primary analysis for ethnicity and different multiple sclerosis diagnostic criteria (Poser/McDonald 2010/McDonald 2017).

All the analyses were implemented within the Bayesian framework. For all regression coefficients, weakly informative prior distributions were assumed. Estimates of the parameters were obtained through Markov chain Monte Carlo simulation using the R package 'spatsurv', based on sampling chains of 350 000 iterations following the 100 000 iterations of burn-in period. To eliminate autocorrelation among samples within the chains, every 50th iteration was selected. The convergence of sampling chains was assessed with trace and density plots of the posterior distributions. All continuous covariates were standardized to mean 0 and standard deviation (SD) 1 to accelerate convergence. Modified Cox-Snell residuals and deviance residuals were used to evaluate the goodness-of-fit of the proportional hazards models.

Results

Fifty-one thousand one hundred and twenty-six patients from 27 countries were included in the analyses (Fig. 1), of which 72% were female (Table 1). Four thousand three hundred and nine patients were diagnosed with SPMS by their treating clinician. The median age at RRMS diagnosis was 32 (quartiles 26–40) years. The median time from RRMS to SPMS conversion was 39 [95% confidence interval (CI): 37 to 43] years, which means 50% of the whole study cohort converted to SPMS within 39 years from RRMS diagnosis. Among the 4309 patients with clinician-diagnosed SPMS, the median time from RRMS to SPMS conversion was 10 (quartiles

6–16) years. A description of the study cohort by country is provided in Table 2. There was a little evidence for multicollinearity of the analysed data (largest variance inflation factor of 1.3 for the national multiple sclerosis prevalence and latitude).

The posterior median hazard ratio (HR) and associated 95% credible interval (CrI) for the parameters of Model (1) are given in Table 3. Higher latitude was associated with greater hazard of SPMS conversion [HR = 1.22 (95% CrI: 1.17 to 1.28)]. The median increase in the hazard of SPMS for every 27° (1 SD) increase in latitude was 22%. It is not surprising that higher national multiple sclerosis prevalence was associated with higher conversion risk of SPMS [1.06 (1.02 to 1.10)]. The median increase in the hazard of SPMS for every additional 70 (1 SD) patients with multiple sclerosis per 100 000 population was 6%. Importantly, longer time on high-to-moderate efficacy disease-modifying therapy was associated with a substantial reduction in the hazard of SPMS conversion [0.76 (0.73 to 0.79)]. With every 42% (1 SD) increase in the time treated with high-to-moderate efficacy therapy, the median hazard of SPMS decreased by 34%. Interaction term from secondary analysis revealed a 5% decline in the effect of latitude on median hazard of SPMS for every 42% (1 SD) increase in the time treated with high-to-moderate efficacy therapy [0.95 (0.92 to 0.99)].

As expected, hazard of SPMS conversion was higher in males compared to females [1.30 (1.22 to 1.39)]. Also, older age at disease onset [1.35 (1.30 to 1.39), 35% higher hazard per 10 older years], higher MSSS [2.40 (2.34 to 2.47), 140% higher hazard per 2.5 higher MSSS decile] and more frequent relapses at study inclusion [1.18 (1.15 to 1.21), 18% higher hazard per one additional relapse] were associated with higher hazard of SPMS.

All these associations were robust to further adjustment for ethnicity and different multiple sclerosis diagnostic criteria. We did not observe any evidence for an association between ethnicity and the hazard of SPMS [Asian: ref; Black/African American: 1.15 (0.81 to 1.60); Caucasian: 1.17 (0.96 to 1.44); Middle Eastern: 0.93 (0.71 to 1.20); Others: 0.93 (0.31 to 3.08)]. Clinically definite multiple sclerosis cases diagnosed using McDonald 2010 [0.58 (0.51 to 0.67)] and 2017 diagnostic criteria [0.56 (0.36 to 0.88)] were associated with lower hazards of SPMS compared to the Poser diagnostic criteria.

To ensure that our findings were robust to under-reporting or delayed diagnosis of SPMS by clinicians, we performed two sensitivity analyses using (i) a merged cohort of clinician-diagnosed SPMS enriched with cases identified by the operationalized definition of SPMS[13]; and (ii) SPMS identified by the Swedish decision tree classifier.[14] The median survival time from RRMS to SPMS conversion was 34 (95% CI: 33 to 36) years in the former cohort and 24 (95% CI: 23 to 24) years in the latter. In both analyses, there was consistent evidence of the association of latitude with SPMS (Supplementary Table 1). Persistent treatment with high-to-moderate efficacy disease-modifying therapy was consistently associated with reduced risk of SPMS, although the narrow 95% CrI marginally cross the null value of one. Interestingly, in the analysis of SPMS identified by the decision tree classifier, the association of national multiple sclerosis prevalence with the hazard of SPMS was inverse [0.84 (0.82 to 0.86)].

The spatial parametric proportional hazards model showed that country of residence was associated with the risk of SPMS conversion. The spatial variance $\sigma^2 = [0.73 (95\% \text{ CrI: } 0.55 \text{ to } 0.96)]$ confirms presence of spatial heterogeneity in the risk of SPMS. The posterior median for the Weibull shape parameter is 1.80 (95% CrI: 1.76 to 1.84); a value >1 suggests increasing hazard of SPMS conversion over time.

Figure 2 illustrates predicted risk-exceedance probabilities for individual countries. Red colour indicates that the probability of the covariate-adjusted relative risk ('cases' relative to 'controls') of
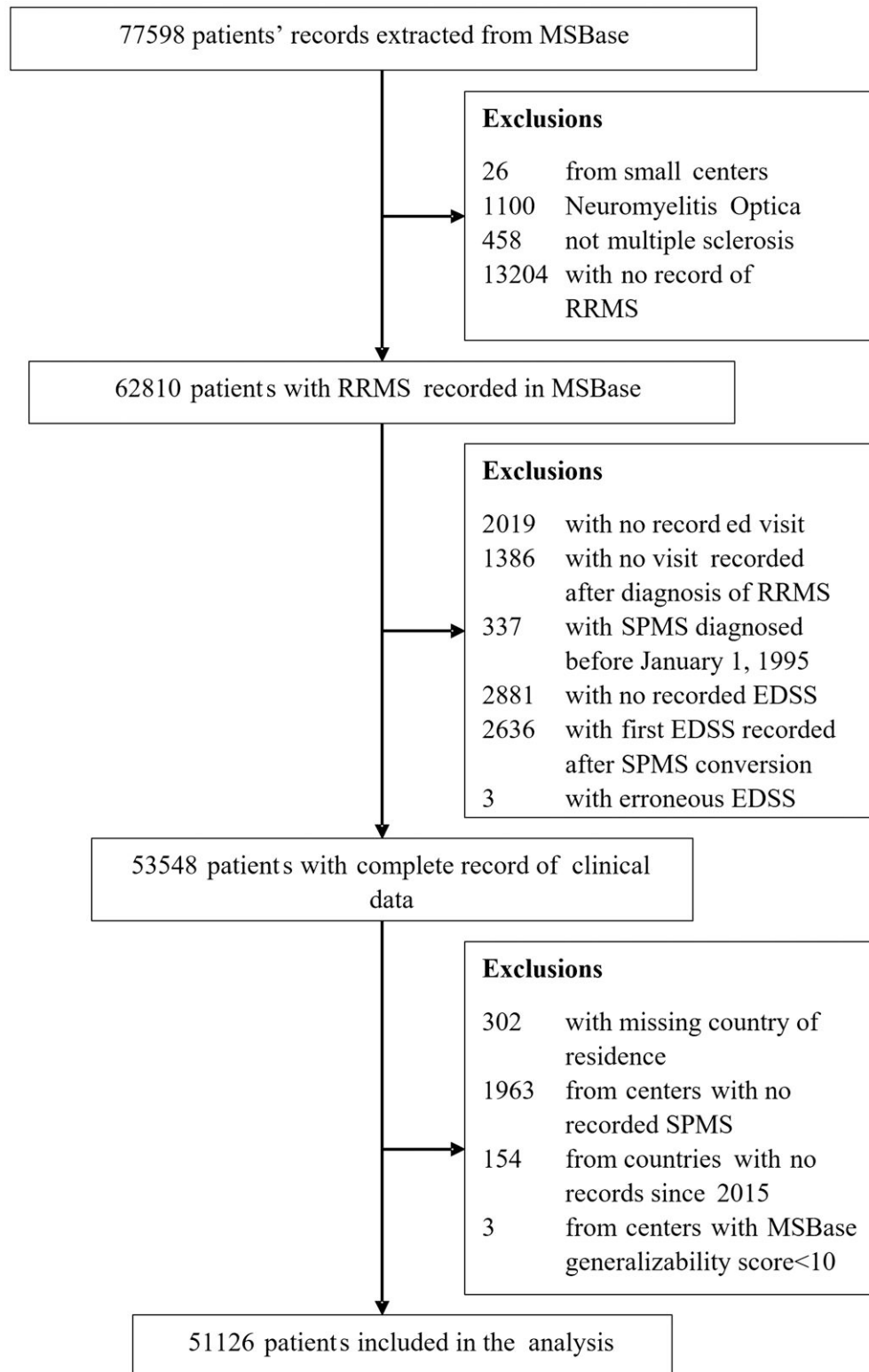
```
┌────────────────────────────────────────────────────┐
│  77598 patients' records extracted from MSBase      │
└────────────────────────────────────────────────────┘
```

Exclusions

26	from small centers
1100	Neuromyelitis Optica
458	not multiple sclerosis
13204	with no record of RRMS

```
┌────────────────────────────────────────────────────┐
│  62810 patients with RRMS recorded in MSBase        │
└────────────────────────────────────────────────────┘
```

Exclusions

2019	with no record ed visit
1386	with no visit recorded after diagnosis of RRMS
337	with SPMS diagnosed before January 1, 1995
2881	with no recorded EDSS
2636	with first EDSS recorded after SPMS conversion
3	with erroneous EDSS

```
┌────────────────────────────────────────────────────┐
│  53548 patients with complete record of clinical    │
│                     data                            │
└────────────────────────────────────────────────────┘
```

Exclusions

302	with missing country of residence
1963	from centers with no recorded SPMS
154	from countries with no records since 2015
3	from centers with MSBase generalizability score<10

```
┌────────────────────────────────────────────────────┐
│  51126 patients included in the analysis            │
└────────────────────────────────────────────────────┘
```

Figure 1 CONSORT chart of patient disposition. RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

SPMS > 1 in the given country is close to 100%. In countries coloured green, the probability that their relative risk of SPMS exceeding 1 is close to 0%. Higher exceedance probabilities therefore indicate countries where time to SPMS conversion are usually short, given the clinical and demographic characteristics of patients recorded in these countries and considering the regional risk of SPMS. In the primary analysis of clinician-diagnosed SPMS, Oman, Kuwait, Canada, Iran, Brazil, Lebanon and Tunisia had substantially higher risk of SPMS conversion than the rest of the countries. The relatively higher risks of SPMS conversion in Oman, Tunisia, Iran and Canada are

Table 1 Description of the global cohort

Characteristic	Median (quartiles)[a]
Patients (% female)	51 126 (72% female)[b]
Age at disease onset, year	29 (23–37)
Age at RRMS diagnosis, year	32 (26–40)
Time from disease onset to RRMS, month	11 (2–36)
Time from RRMS to SPMS among those who converted, years	10 (6–16)
Time from RRMS to SPMS among all patients, median survival time in years	39 (37–43)[c]
EDSS score at inclusion	2.0 (1.0–3.0)
Age at initiation of high-to-moderate-efficacy therapy, year	38 (11)[d]
Proportion of patients treated with high-to-moderate-efficacy therapy at any time during follow-up	0.30

EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.
[a]Unless otherwise indicated.
[b]Count.
[c]Median (95% confidence interval).
[d]Mean (standard deviation).

consistent in the sensitivity analyses using the two alternative SPMS definitions (Supplementary Figs 1 and 2).

Figure 3 highlights the difference in the posterior median probabilities of remaining SPMS free for four randomly selected patients of similar clinical and demographic characteristics from Australia, Turkey, Canada and Oman.

Discussion

In this large longitudinal study of 51 126 patients with multiple sclerosis from 27 countries, we have demonstrated significant geographical variation in the risk of SPMS. Higher latitude of country of residence was generally associated with increased risk of SPMS. The conversion to SPMS was further increased in certain countries, for example, in Oman, Tunisia, Iran or Canada. Importantly, persistent treatment with high-to-moderate efficacy disease-modifying therapy reduced this risk. These observations were consistent after accounting for ethnicity, differences in multiple sclerosis diagnostic criteria, and different diagnostic definitions of SPMS.

The median time to SPMS from RRMS diagnosis estimated in our study is significantly longer than previous estimates. In 2010, a study from the British Columbia, Canada, including patients with clinically

Table 2 Description of cohort by country

Country	Patients (% female)	Age at disease onset, year[a]	EDSS score at inclusion[a]	Patients diagnosed with SPMS[b] (% of total patients)	Age at SPMS among those who converted, year[a]	EDSS score at SPMS among those who converted[a]	Proportion of patients on high-to-moderate efficacy therapy at any time during follow-up
Argentina	595 (69)	30 (24–38)	2.0 (1.0–4.0)	45 (8)	50 (43–57)	6.5 (6.0–7.0)	0.11
Australia	7381 (76)	32 (26–40)	2.0 (1.0–3.5)	447 (6)	51 (43–59)	5.5 (4.0–6.5)	0.59
Belgium	1246 (73)	30 (23–38)	2.0 (1.0–3.0)	61 (5)	46 (41–52)	4.0 (3.0–5.5)	0.40
Brazil	111 (77)	32 (26–38)	3.5 (2.0–4.5)	18 (16)	45 (40–50)	4.5 (4.0–5.0)	0.42
Canada	3926 (77)	31 (25–39)	2.0 (1.0–2.5)	710 (18)	50 (43–57)	4.5 (3.5–6.0)	0.29
Czech Republic	2895 (72)	28 (23–35)	2.0 (1.5–3.0)	167 (6)	43 (37–52)	4.5 (4.0–5.5)	0.29
Denmark	404 (67)	29 (24–37)	2.5 (2.0–2.5)	7 (2)	48 (40–57)	2.0 (2.0–2.0)	0.30
Egypt	2397 (73)	25 (20–31)	2.5 (1.5–4.0)	32 (1)	33 (28–39)	6.0 (4.5–6.5)	0.03
Hungary	100 (71)	26 (21–32)	3.0 (1.5–4.0)	2 (2)	44 (39–49)	7.5 (7.0–8.0)	0.94
India	429 (69)	28 (23–36)	2.0 (1.0–4.5)	11 (3)	33 (30–37)	4.5 (4.0–5.0)	0.10
Iran	1718 (80)	28 (22–34)	2.0 (1.0–3.0)	54 (3)	49 (45–55)	6.0 (4.0–6.0)	0.14
Ireland	330 (70)	29 (24–37)	1.5 (1.0–3.0)	18 (5)	48 (44–59)	6.0 (5.0–6.0)	0.28
Italy	7245 (70)	30 (23–38)	2.0 (1.0–3.0)	737 (10)	46 (39–54)	5.5 (4.0–6.5)	0.21
Kuwait	1840 (68)	26 (21–32)	1.5 (1.0–2.5)	110 (6)	39 (33–46)	6.0 (5.0–6.5)	0.48
Lebanon	961 (65)	28 (22–35)	1.5 (1.0–2.5)	50 (5)	45 (40–50)	3.5 (3.0–6.0)	0.42
Netherlands	1762 (75)	31 (25–39)	2.5 (1.5–4.0)	201 (11)	46 (40–53)	5.5 (4.0–6.0)	0.16
New Zealand	87 (86)	33 (26–40)	2.5 (2.0–3.5)	2 (2)	52 (44–61)	5.0 (4.0–6.0)	0.55
Oman	173 (65)	26 (22–32)	1.0 (0.0–2.0)	21 (12)	36 (31–45)	6.0 (4.0–7.0)	0.50
Portugal	719 (71)	29 (23–38)	1.5 (1.0–2.5)	66 (9)	49 (42–56)	5.0 (4.0–6.0)	0.18
Romania	219 (66)	31 (24–38)	2.5 (2.0–3.5)	6 (3)	51 (44–56)	6.0 (5.5–6.0)	0.12
Saudi Arabia	129 (57)	26 (21–32)	1.5 (1.0–3.5)	1 (1)	15 (15–15)	1.0 (1.0–1.0)	0.28
Spain	4226 (68)	30 (24–38)	2.0 (1.0–2.5)	442 (10)	46 (40–53)	5.0 (4.0–6.0)	0.26
Switzerland	654 (68)	31 (24–38)	2.0 (1.5–3.0)	27 (4)	47 (42–55)	4.5 (3.5–6.5)	0.68
Tunisia	594 (72)	28 (22–35)	2.0 (1.0–3.0)	46 (8)	41 (32–47)	6.0 (5.0–6.5)	0.14
Turkey	8658 (69)	28 (22–35)	2.0 (1.0–3.0)	507 (6)	42 (34–50)	5.5 (4.5–6.0)	0.31
UK	848 (73)	30 (24–38)	2.0 (1.0–4.0)	33 (4)	48 (43–58)	6.0 (4.5–6.5)	0.09
USA	1479 (76)	32 (25–39)	2.5 (1.5–5.5)	488 (33)	53 (47–60)	6.0 (4.5–6.5)	0.13

EDSS = Expanded Disability Status Scale; SPMS = secondary progressive multiple sclerosis.
[a]Median (quartiles).
[b]Clinician-diagnosed SPMS.

definite multiple sclerosis, diagnosed according to the Poser diagnostic criteria estimated median survival time from disease onset to SPMS as 21.4 (95% CI: 20.6 to 22.2) years.[15] In 2016, the EPIC study comprising a cohort of actively treated patients from the Multiple Sclerosis Center at the University of California, San Francisco, reported a median survival time of 35 years from disease onset to SPMS.[16] In 2019, using data from the MSBase registry, we reported a median survival time from disease onset to SPMS of 32.4 (95% CI: 31.1 to 33.7) years.[17] In this study, we report 39 (95% CI: 37 to 43) years as the median time to SPMS from RRMS diagnosis. The increasing time to SPMS conversion is driven by the increasing number of patients who do not convert to SPMS during the study follow-up. Among several factors, this trend may be driven by improvement in multiple sclerosis diagnostic criteria and more persistent use of high-to-moderate efficacy disease-modifying therapies during the relapsing-remitting phase. Among the subset of patients who converted to SPMS, median time to SPMS from RRMS diagnosis is 10 (quartiles 6–16) years, which is in line with the recent estimate reported in an Italian SPMS cohort.[18]

Previous studies have documented considerable geographic variation in the incidence and prevalence of multiple sclerosis. A meta-analysis revealed a positive association between a higher latitude and the prevalence of multiple sclerosis, which peaked around 55° and reversed above 60°.[1] In Australasia, UK, Atlantic region and Central Europe, North America and Western Europe, a positive latitudinal gradient for multiple sclerosis prevalence is well established.[1] Further, our recent study among 46 128 patients from 26 countries demonstrated increased multiple sclerosis severity with increasing latitude above 40°, closely associated with the surface dose of the UV B radiation.[5] Our present study extends our knowledge of the geographic determinants of multiple sclerosis, establishing a positive latitudinal gradient in the risk of SPMS. Furthermore, for the first time, it is now shown that persistent use of high-to-moderate efficacy disease-modifying therapy can mitigate this latitudinal effect on the risk of SPMS.

Interestingly, while adjusting for potential under-reporting in clinician-diagnosed SPMS, we have identified an association between government health expenditure and SPMS conversion risk. Even though the magnitude of the observed effect size is small, our result suggests that important health disparities exist between countries, with impact on the course and outcomes of multiple sclerosis.

We observed an association between higher national multiple sclerosis prevalence and greater risk of clinician-diagnosed SPMS. This association is probably driven by greater experience of neurologists with management of multiple sclerosis and confidence in diagnosing SPMS in countries with higher disease prevalence. In contrast, in sensitivity analysis higher national prevalence of multiple sclerosis was associated with lower risk of SPMS diagnosed with the decision tree algorithm (i.e. independent from neurologists' judgement). This most likely represents the results of better management of RRMS in countries with higher disease prevalence, and thereby a delayed progression to more substantial disability.

Many studies have reported associations of male sex, older age at disease onset, higher EDSS score and greater number of relapses early in the disease course with increased risk of SPMS.[15,17–22] In our study, SPMS risk was elevated among patients with higher MSSS at the inclusion, more frequent relapses during the subsequent year, male sex, and older age at onset, in keeping with previous studies.

As expected, the more contemporary diagnostic criteria (McDonald 2010 and 2017) were associated with lower risk of SPMS than the Poser diagnostic criteria. This reflects the fact that the current diagnostic criteria enable diagnosis of less severe multiple sclerosis and facilitate

Table 3 Primary analysis: associations of geographic, demographic and clinical patient characteristics with the risk of SPMS as per clinician diagnosis

Fixed effect parameters	Median hazard ratio	95% credible interval
Latitude of residence, per 27°	1.22	1.17, 1.28
National multiple sclerosis prevalence, per 70 in 100 000 population	1.06	1.02, 1.10
Proportion of time on high-to-moderate efficacy therapy, per 42%	0.76	0.73, 0.79
Male sex	1.30	1.22, 1.39
Age at disease onset, per 10 years	1.35	1.30, 1.39
Multiple sclerosis severity score at inclusion, per 2.5 decile	2.40	2.34, 2.47
Relapse frequency at inclusion, per 1 relapse	1.18	1.15, 1.21
Government health expenditure, per 14% of current health expenditure	1.04	0.99, 1.08
Time from disease onset to RRMS, per 4 years	1.32	1.29, 1.35

The table presents parameter estimates of the parametric proportional hazards frailty Model (1) with standardized covariates. The units represent 1 SD of the standardized variable. SPMS = secondary progressive multiple sclerosis.

the diagnosis earlier in the disease course, thus giving a longer duration of relapsing-remitting course before converting to SPMS. The average shorter delay to diagnosis may also contribute to the increasingly longer median time from RRMS to SPMS.

The findings of our study are strengthened by the use of three different definitions of SPMS to demonstrate geographical variation in the risk of SPMS in a large and diverse population from 27 countries and across a broad range of latitudes. The analysis accounted for the effects of country-specific variables, such as national multiple sclerosis prevalence and government health expenditure, to serve as a proxy for the experience with diagnosis and management of multiple sclerosis and availability of resources in the national healthcare systems, respectively. Most notably, we have employed a novel statistical approach to carry out a geographically informed search for the countries with above-average risk of SPMS conversion. The two-stage analytical approach allowed us to account for heterogeneity among individuals and among countries in unobserved factors associated with the risk of SPMS.

The results of this study need to be considered in the context of its limitations. First, the data of current residence were recorded at the time of entry to the MSBase registry. The registry does not monitor changes in residence and migration during the follow-up. Registry data are subject to heterogeneity associated with variability in data sources and data entry conventions at different countries and centres. The use of Neurostatus certification helps mitigate this heterogeneity in relation to disability assessment with EDSS—the key information that was used to identify SPMS by the operationalized definition and the decision tree algorithm. The patient datasets available at different countries may not be representative of the national multiple sclerosis populations. To maximize representativeness of the study population, we followed a rigorous data quality and generalizability procedure, with a special focus on compatibility of the reported clinical and demographic information with the known epidemiology of multiple sclerosis.[8] Spatial frailty models are commonly used for modelling of spatial
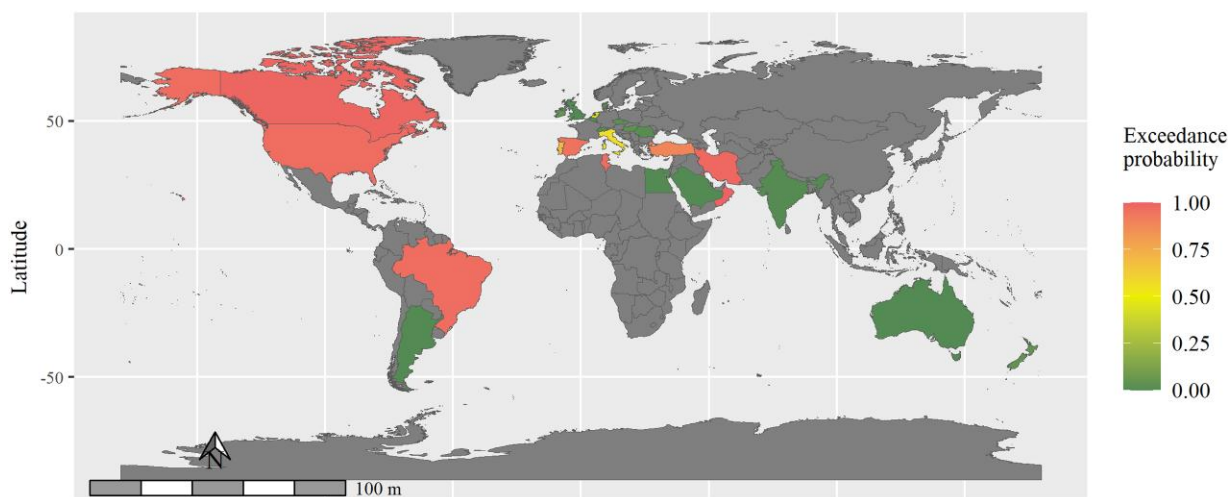
Figure 2 Map of predicted risk-exceedance probabilities. Shades of red indicate countries with substantially shorter time to secondary progressive multiple sclerosis (SPMS) conversion than those that are coloured with shades of green. Countries coloured in grey did not contribute to the MSBase registry or were excluded at the data quality assessment.
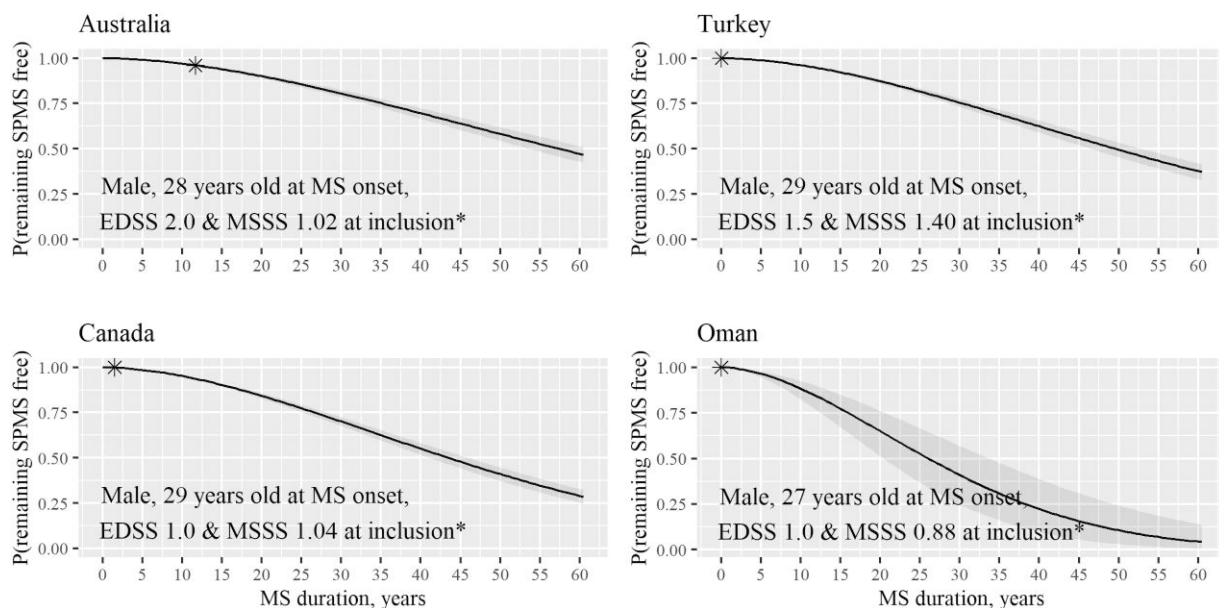

Figure 3 Posterior median probabilities of remaining SPMS-free. An example provided for four patients with similar characteristics at study inclusion (asterisk) from four countries. Grey areas represent the respective 95% credible bands. This example illustrates variability in the probability of remaining SPMS-free for patients living in four countries after accounting for patients' clinical and demographic characteristics.

data at the small area scale while assuming that populations from neighbouring regions share more features than those from distant regions. Considering the regional similarities in environments, lifestyle, diet, epidemiology, diagnostics and management of multiple sclerosis, we extended this approach to model variations at the country level. The statistical significance of the spatial variance confirms the presence of spatial heterogeneity across the studied regions. Nonetheless, we acknowledge that our analysis does not capture the heterogeneity at the sub-country regional level.

In summary, the risk of SPMS is associated with higher latitude of residence, independent of ethnicity and multiple sclerosis diagnostic criteria. This geographically determined risk of SPMS can be mitigated by persistent treatment with high-to-moderate efficacy disease-modifying therapy.

Data availability

MSBase is a data processor, and warehouses data from individual principal investigators who agree to share their datasets on a project-by-project basis. Each principal investigator will need to be approached individually for permission to access the datasets.

Acknowledgements

was provided by the MSBase administrations Ms Charlotte Sartori, Dr Sabah Quddus and Ms Eloise Hinson.

Funding

Competing interests

S.S. has received research support from the MSBase registry. I.R. served on scientific advisory boards, received conference travel support and/or speaker honoraria from Roche, Novartis, Merck, and Biogen. C.M. has received conference travel support from Merck, Novartis, and Biogen. He has received research support from the National Health and Medical Research Council, Multiple Sclerosis Research Australia, The University of Melbourne, The Royal Melbourne Hospital Neuroscience Foundation, and Dementia Australia. D.H. received speaker honoraria and consulting fees from Biogen, Merck, Teva, Roche, Sanofi Genzyme, and Novartis, as well as support for research activities from Biogen and Czech Ministry of Education (project Progres Q27/LF1). E.K.H. received honoraria/research support from Biogen, Merck Serono, Novartis, Roche, and Teva; has been member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novartis, and Sanofi Genzyme; has been supported by the Czech Ministry of Education research project Progres Q27/LF1. F.P. received speaker honoraria and advisory board fees from Almirall, Bayer, Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme, and TEVA. He received research funding from Biogen, Merck, FISM (Fondazione Italiana Sclerosi Multipla), Reload Onlus Association, and University of Catania. R.A. received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche, and Sanofi-Genzyme. G.I. received speaking honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall, and Teva. S.E. received speaker honoraria and consultant fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche, and Teva. C.B. received conference travel support from Biogen, Novartis, Bayer-Schering, Merck, and Teva; has participated in clinical trials by Sanofi Aventis, Roche, and Novartis. A.L. has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from Biogen, Merck Serono, Mylan, Novartis, Roche, Sanofi/Genzyme, Teva. Her institutions have received research grants from Novartis (last 4 yrs). B.W.-G. has participated in speaker's bureaus and/or served as a consultant for Biogen, EMD Serono, Novartis, Genentech, Celgene/Bristol Meyers Squibb, Sanofi Genzyme, Bayer, Janssen and Horizon. She also has received grant/research support from the agencies listed in the previous sentence. She serves in the editorial board for BMJ Neurology, Children, CNS Drugs, MS International and Frontiers Epidemiology. M.G. received consulting fees from Teva Canada Innovation, Biogen, Novartis, and Genzyme Sanofi; lecture payments from Teva Canada Innovation, Novartis, and EMD. He has also received a research grant from Canadian Institutes of Health Research. P.D. served on editorial boards and has been supported to attend meetings by EMD, Biogen, Novartis, Genzyme, and TEVA Neuroscience. He holds grants from the CIHR and the MS Society

of Canada and has received funding for investigator-initiated trials from Biogen, Novartis, and Genzyme. M.T. received travel grants from Novartis, Bayer-Schering, Merck, and Teva; has participated in clinical trials by Sanofi Aventis, Roche, and Novartis. M.P.A. received honoraria as consultant on scientific advisory boards by Biogen, Bayer-Schering, Merck, Teva, and Sanofi-Aventis; has received research grants by Biogen, Bayer-Schering, Merck, Teva, and Novartis. F.G. received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, Mitsubishi, and ONO Pharmaceuticals. S.J.K. received compensation for serving on advisory boards for Merck and Roche. P.G. has served in advisory boards for Novartis, EMD Serono, Roche, Biogen idec, Sanofi Genzyme, Pendopharm and has received grant support from Genzyme and Roche, has received research grants for his institution from Biogen idec, Sanofi Genzyme, EMD Serono. J.L.-S. travel compensation from Novartis, Biogen, Roche, and Merck. Her institution receives the honoraria for talks and advisory board commitment as well as research grants from Biogen, Merck, Roche, TEVA, and Novartis. K.B. received honoraria and consulting fees from Biogen, Teva, Novartis, Genzyme-Sanofi, Roche, Merck, CSL, and Grifols. A.vdW. served on advisory boards and receives unrestricted research grants from Novartis, Biogen, Merck, and Roche. She has received speaker's honoraria and travel support from Novartis, Roche, and Merck. She receives grant support from the National Health and Medical Research Council of Australia and MS Research Australia. H.B. has received institutional (Monash University) funding from Biogen, F. Hoffmann-La Roche Ltd, Merck, Alexion, CSL, and Novartis; has carried out contracted research for Novartis, Merck, F. Hoffmann-La Roche Ltd. and Biogen; has taken part in speakers' bureaus for Biogen, Genzyme, UCB, Novartis, F. Hoffmann-La Roche Ltd. and Merck; has received personal compensation from Oxford Health Policy Forum for the Brain Health Steering Committee. A.A. received personal fees and speaker honoraria from Teva, Merck, Biogen—Gen Pharma, Roche, Novartis, Bayer, Sanofi-Genzyme; received travel and registration grants from Merck, Biogen—Gen Pharma, Roche, Sanofi-Genzyme, and Bayer. D.M. received speaker honoraria for Advisory Board and travel grants from Almirall, Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. A.K. received speaker honoraria and scientific advisory board fees from Bayer, BioCSL, Biogen, Genzyme, Innate Immunotherapeutics, Merck, Novartis, Sanofi, Sanofi-Aventis, and Teva. V.V.P. received travel grants from Merck, Biogen, Sanofi, Celgene, Almirall, and Roche. His institution has received research grants and consultancy fees from Roche, Biogen, Sanofi, Celgene, Merck, and Novartis Pharma. M.B. served on scientific advisory boards for Biogen, Novartis, and Genzyme and has received conference travel support from Biogen and Novartis. He serves on steering committees for trials conducted by Novartis. His institution has received research support from Biogen, Merck, and Novartis. S.H. has received unrestricted educational grants or speaking honoraria from Biogen, Merck Serono, Novartis, Roche, and Sanofi Genzyme. S.H. received honoraria and consulting fees from Novartis, Bayer Schering, and Sanofi, and travel grants from Novartis, Biogen Idec, and Bayer Schering. C.O.-G. received honoraria as consultant on scientific advisory boards from Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme, and TEVA. R.A. received conference travel support from Novartis, Teva, Biogen, Bayer, and Merck and has participated in clinical trials by Biogen, Novartis, Teva, and Actelion. T.P. received funding from Biogen, Merck, Novartis, Sanofi-Aventis, Roche, and Genzyme. C.R.-T. received research funding, compensation for travel or speaker honoraria from Biogen, Novartis,

Supplementary material

Supplementary material is available at *Brain* online.

Appendix 1

The following contributors participated in data acquisition: Vahid Shaygannejad, From Nehme and Therese Tohme Multiple Sclerosis Center, American University of Bassem Yamout, Yolanda Blanco, Elisabetta Cartechini, Edgardo Cristiano, Maria Edite Rio, Ricardo Fernandez Bolaños, Maria Laura Saladino, Sarah Besora, Jamie Campbell, Jan Schepel, Alberto Roiguez Alfici, Elizabeth Alejana Bacile, Juan Ingacio Rojas, Mike Boggild, Ik Lin Tan, Mark Marriott, Trevor Kilpatrick, John King, Katherine Buzzard, Ai-Lan Nguyen, Chris Dwyer, Mastura Monif, Izanne Roos, Ms Lisa Taylor, Ms Josephine Baker, Marzena Fabis-Peini, Stephane Charest, Catherine Larochelle, Jose Antonio Cabrera-Gomez, Karim Kotkata, Etienne Roullet, Magdolna Simo, Tunde Erdelyi, Clara Chisari, Emanuele D'Amico, Lo Fermo Salvatore, Giovanna De Luca, Valeria Di Tommaso, Daniela Travaglini, Erika Pietrolongo, Maria di Ioia, Deborah Farina, Luca Mancinelli, Matteo Diamanti, Cees Zwanikken, Leontien Den braber-Moerland, Raymond Hupperts, Freek Verheul, Deborah Mason, Albert Saiz, Javier Olascoaga, Robert Zivadinov, Ralph Benedict. Further details are available in the Supplementary material.

References

1. Simpson S, Blizzard L, Otahal P, Van der Mei I, Taylor B. Latitude is significantly associated with the prevalence of multiple sclerosis: A meta-analysis. *J Neurol Neurosurg Psychiatry*. 2011;82: 1132-1141.

2. Simpson S, Wang W, Otahal P, Blizzard L, van der Mei IA, Taylor BV. Latitude continues to be significantly associated with the prevalence of multiple sclerosis: An updated meta-analysis. *J Neurol Neurosurg Psychiatry*. 2019;90:1193-1200.

3. Lucas R, Ponsonby A-L, Dear K, *et al*. Sun exposure and vitamin D are independent risk factors for CNS demyelination. *Neurology*. 2011;76:540-548.

4. Simpson S Jr, Van der Mei I, Lucas RM, *et al*. Sun exposure across the life course significantly modulates early multiple sclerosis clinical course. *Front Neurol*. 2018;9:16.

5. Vitkova M, Diouf I, Malpas C, *et al*. Association of latitude and exposure to ultraviolet B radiation with severity of multiple sclerosis: An international registry study. *Neurology*. 2022;98: e2401-e2412.

6. Banerjee S, Carlin BP, Gelfand AE. *Hierarchical modeling and analysis for spatial data*. Chapman and Hall/CRC; 2003.

7. Butzkueven H, Chapman J, Cristiano E, *et al*. MSBase: An international, online registry and platform for collaborative outcomes research in multiple sclerosis. *Mult Scler*. 2006;12: 769-774.

8. Kalincik T, Kuhle J, Pucci E, *et al*. Data quality evaluation for observational multiple sclerosis registries. *Mult Scler*. 2017;23: 647-655.

9. Lublin FD, Reingold SC, Cohen JA, *et al*. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology*. 2014;83:278-286.

10. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: Results of an international survey. *Neurology*. 1996; 46:907-911.

11. The Multiple Sclerosis International Federation. *Atlas of MS*, 3rd ed. The Multiple Sclerosis International Federation (MSIF); 2020.

12. World Bank. *World development indicators 2019*. The World Bank; 2019.

13. Lorscheider J, Buzzard K, Jokubaitis V, *et al*. Defining secondary progressive multiple sclerosis. *Brain*. 2016;139:2395-2405.

14. Ramanujam R, Zhu F, Fink K, *et al*. Accurate classification of secondary progression in multiple sclerosis using a decision tree. *Mult Scler*. 2021;27:1240-1249.

15. Koch M, Kingwell E, Rieckmann P, Tremlett H. The natural history of secondary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2010;81:1039-1043.

16. University of California SFMET, Cree BA, Gourraud PA, Oksenberg JR, *et al*. Long-term evolution of multiple sclerosis disability in the treatment era. *Ann Neurol*. 2016;80:499-510.

17. Fambiatos A, Jokubaitis V, Horakova D, *et al*. Risk of secondary progressive multiple sclerosis: A longitudinal study. *Mult Scler*. 2020;26:79-90.

18. Iaffaldano P, Lucisano G, Patti F, *et al*. Transition to secondary progression in relapsing-onset multiple sclerosis: Definitions and risk factors. *Mult Scler*. 2021;27:430-438.

19. Scalfari A, Neuhaus A, Daumer M, Muraro PA, Ebers GC. Onset of secondary progressive phase and long-term evolution of multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2014;85:67-75.

20. Vukusic S, Confavreux C. Prognostic factors for progression of disability in the secondary progressive phase of multiple sclerosis. *J Neurol Sci*. 2003;206:135-137.

21. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: An amnesic process. *Brain*. 2003;126:770-782.

22. Stankoff B, Mrejen S, Tourbah A, *et al*. Age at onset determines the occurrence of the progressive phase of multiple sclerosis. *Neurology*. 2007;68:779-781.