Systematic literature review and meta-analysis of the prevalence of secondary progressive multiple sclerosis in the USA, Europe, Canada, Australia, and Brazil

Vijayalakshmi Vasanthaprasad¹, Vivek Khurana², Sreelatha Vadapalle¹, Jackie Palace³ and Nicholas Adlard⁴*

Abstract

Background: Secondary progressive multiple sclerosis (SPMS) is a subtype of multiple sclerosis (MS), which is a chronic neurological disease, characterised by inflammation of the central nervous system. Most of MS patients eventually progress to SPMS. This study estimates the prevalence of SPMS in the United States of America, Europe, Canada, Australia, and Brazil.

Methods: A systematic literature search of the Medline and Embase databases was performed using the OVID™ SP platform to identify MS epidemiological studies published in English from database inception to September 22, 2020. Studies reporting the prevalence of MS and proportion of SPMS patients in the included population were selected. The pooled prevalence of SPMS was calculated based on the proportion of SPMS patients. The Loney quality assessment checklist was used for quality grading. A meta-analysis of the proportions was conducted in RStudio.

Results: A total of 4754 articles were retrieved, and prevalence was calculated from 97 relevant studies. Overall, 86 medium- and high-quality studies were included in the meta-analysis. Most studies were conducted in European countries (84 studies). The estimated pooled prevalence of SPMS was 22.42 (99% confidence interval: 18.30, 26.95)/100,000. The prevalence of SPMS was more in the North European countries, highest in Sweden and lowest in Brazil. A decline in SPMS prevalence was observed since the availability of oral disease-modifying therapies. We also observed a regional variation of higher SPMS prevalence in urban areas compared with rural areas.

Conclusion: High variability was observed in the estimated SPMS prevalence, and the quality of the studies conducted. The influence of latitude and other factors known to affect overall MS prevalence did not fully explain the wide range of inter-country and intra-country variability identified in the results.

Keywords: Meta-analysis, Multiple sclerosis, Prevalence, Secondary progressive multiple sclerosis

Background

Multiple sclerosis (MS) has affected approximately 2.2 million people worldwide till 2016 [1]. MS epidemiological studies have consistently reported that 85% of MS patients start with relapsing-remitting MS (RRMS), of which the majority eventually develop secondary progressive MS (SPMS), often with superimposed relapses that tend to decline over time [2]. A systematic literature review of 92 studies reported that approximately 25% of patients with RRMS progress to SPMS by 10 years, 50% progress by 20 years, and over 75% progress by 30 years, with most studies reporting a mean age of 40 years at
conversion to SPMS [3]. SPMS is usually diagnosed retrospectively by a history of gradual worsening of disability outside of relapses [2]. Evidence suggests that MS is more prevalent in women than in men [4]. Most MS patients experience clinical disease onset between 20 and 40 years of age [4]. Several epidemiological studies have reported an increasing MS prevalence with increasing latitude. North European countries and North America constitute the high-risk MS prevalence zone, with a high MS prevalence of more than 100 cases per 100,000 population. Low MS risk areas are centred around the equator, with less than 30 cases per 100,000 population. Medium MS risk areas are located in between with prevalence within a similar range [5].

Observational studies have consistently demonstrated a higher clinical and economic burden owing to SPMS among all subtypes of MS [6, 7]. However, epidemiological data for SPMS are not available, and there is a great need to better understand the approximate prevalence of SPMS to estimate the true SPMS disease burden. In a consensus paper, Lublin et al. revised the definitions of the clinical course of MS by using refined descriptors that include consideration of disease activity and encourage differentiation between the relapsing and progressive forms of MS, but they also acknowledged that to date, there are no clear clinical, imaging, immunologic, or pathologic criteria to determine the transition point when RRMS converts to SPMS and that the transition is usually gradual [2]. With more clarity on the MS disease classification, researchers are currently attempting to explore epidemiological aspects by MS subtype [2, 8]. Khurana et al. reported a wide variation in the estimated prevalence of SPMS within and across countries but with uncertainty related to methodology and consequent results [9]. The objective of the current study was to estimate the prevalence of SPMS in the United States of America (USA), Europe, Canada, Australia, and Brazil based on the data collected from a systematic literature review. These countries were selected based on the availability and quality of MS prevalence data [10].

**Methods**

**Data sources and search strategy**

A systematic literature search of the Medline and Embase databases was performed using the OVID™ SP platform. Major European conference abstracts between 2016 and 2018 were also searched. The search strings used were “(Multiple sclerosis AND (Epidem* OR Inciden* OR Prevalen*).ti,ab. AND (Europe OR Europ* OR Albania OR Andorra OR Armenia OR Austria OR Azerbaijan OR Belarus OR Belgium OR Bosnia OR Herzegovina OR Bulgaria OR Croatia OR Cyprus OR Czech Republic OR Denmark OR Estonia OR Finland OR France OR Georgia OR Germany OR Greece OR Hungary OR Iceland OR Ireland OR Northern Ireland OR Eire OR Italy OR Kazakhstan OR Kosovo OR Latvia OR Liechtenstein OR Lithuania OR Luxembourg OR Macedonia OR Malta OR Moldova OR Monaco OR Montenegro OR Netherlands OR Norway OR Poland OR Portugal OR Romania OR Russia OR San Marino OR Serbia OR Slovakia OR Slovenia OR Spain OR Sweden OR Switzerland OR Turkey OR Ukraine OR United kingdom OR UK OR England OR Scotland OR Wales OR US OR United states OR Canada OR Australia OR Brazil)).mp.” To validate the search further, bibliographies of all relevant reviews and primary studies were screened.

**Inclusion and exclusion criteria**

Studies published in English from database inception up to September 22, 2020, reporting the prevalence and/or incidence of adult MS (aged >18 years) and the proportion of SPMS patients were included. Studies presenting paediatric MS data or MS epidemiological studies that did not include the proportion of SPMS patients were excluded. The study design was not a criterion for exclusion.

**Screening strategy and data extraction**

After removing duplicates across the databases, the search result from the OVID platform was exported into an automated Excel file for screening. Two reviewers (VV and VK) independently screened the titles and abstracts that did not include the proportion of SPMS patients were included. Studies presenting paediatric MS data or MS epidemiological studies that did not include the proportion of SPMS patients were excluded. The study design was not a criterion for exclusion.

**Quality assessment**

The Loney quality assessment checklist, developed specifically for prevalence studies, was used for the quality grading of the included studies [11]. The Loney tool evaluates the methods of sampling, sample size, outcome measurement, outcome assessment, response rate, statistical reporting, and interpretation of study results. The overall single quality scores range from 0 to 8, with scores from 0 to 3 indicating poor, scores from 4 to 5 indicating moderate, and scores from 6 to 8 indicating higher methodological quality.
Data analysis
Only moderate- and high-quality studies (i.e., scores from 4 to 8) were included in the meta-analysis. The meta-analysis was conducted using meta-analysis of proportions using “meta,” “metafor,” and “weightr” packages in the R software (version 3.5.2) [12, 13]. A random effects model was considered more appropriate for the present analysis owing to the heterogeneous study populations from diverse geographies. A binary outcome was assigned to each study based on the number of prevalent SPMS cases across the entire population. A pooled effect size estimate was evaluated for the studies by considering a weighted average of effect sizes, wherein weights were assigned proportionally to the sample size of each study. The Q, $T^2$, and $I^2$ statistics were measured to assess heterogeneity among the studies. The Q statistic is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies. The $T^2$ statistic is an estimate of between-study variance, whereas the $I^2$ statistic is expressed as the percentage of the total variability in a set of effect sizes owing to true heterogeneity. If the Q, $T^2$, and $I^2$ values fell outside their 95% confidence interval (CI), 99% CI was used instead. The raw prevalence rates were transformed using the Freeman-Tukey (double arcsine) transformation to normalise their sampling distribution and stabilise their variance. A back transformation on the effect size was implemented using the same method to obtain the prevalence of SPMS.

Further, studies considered as outliers and influential on the summary effect size were identified by conducting tests such as studentised residuals test and leave-one-out analysis, presented in the Baujat plot [14]. Additionally, a diagnostic test was conducted to identify the influential studies. If substantial heterogeneity remained after excluding the outliers, a moderator analysis or subgroup analysis was conducted to discover other possible sources of heterogeneity. As meta-analysis of proportions includes observational and noncomparative studies, publication bias is not pertinent. However, the funnel plot and Egger test [15] were conducted to examine if the distribution of effect size estimates followed the usual pattern of less variation with higher number of studies and if the small-study effect was present.

Ethical statement
The study did not require informed consent or institutional review board approval as no identifiable patient information was extracted. This systematic review was conducted and reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [16, 17]. The review protocol is available with the corresponding author.

Results
A total of 4754 articles were retrieved from the search, of which 97 relevant studies were included and reviewed for their quality using the Loney score. Following quality assessment, 86 moderate- and high-quality studies were included in the meta-analysis (Fig. 1). Most included studies were retrospective chart reviews that followed the Poser or McDonald criteria for diagnosis (75 studies). Most studies were conducted in European countries (84 studies), especially Italy (19 studies) and Spain (13 studies). None of the epidemiological studies from the USA reported the proportion of SPMS patients; hence, they were not included in this review (Table 1). The average Loney score for all the 97 included studies was 4.6 and ranged from 1 to 8. A total of 86 studies scored ≥4 on the Loney scale and were included in the meta-analysis (Additional file 1, Table 1). Only one study reported the proportion of SPMS patients according to its subtypes. The estimated prevalence of SPMS with progression but without activity was 3.4/100,000 and without progression or activity was 6.9/100,000 [18].

Australia
Two moderate-quality studies from Newcastle were included in this meta-analysis [104, 105]. The pooled prevalence of SPMS in Australia was 10.32 (99% CI: 5.84, 15.99)/100,000 (Fig. 2). The MS prevalence has increased by 110% between 1996 and 2011 in Newcastle. However, the SPMS prevalence has increased by only 22%. Different diagnostic criteria were used in these studies [104, 105] (Additional file 1, Fig. 1).

Brazil
Six moderate-quality studies were included in this meta-analysis [106–111]. All studies reported a very low MS prevalence and proportion of SPMS patients. The pooled prevalence of SPMS was 1.68 (99% CI: 0.53, 3.31)/100,000 [106–111] (Table 1 and Fig. 2).

Canada
Three moderate-quality studies were included in this meta-analysis [112–114]. Only the Poser diagnostic criteria were used in all the studies. Two studies conducted in the early 90s in the counties of Westlock and Barrhead reported a very high MS and SPMS prevalence [113, 114]. Another study published in 2005 reported a low SPMS prevalence in the region of Newfoundland and Labrador.
The pooled prevalence of SPMS was 55.02 (99% CI: 6.37, 150.00)/100,000 (Table 1 and Fig. 2).

Europe
The pooled SPMS prevalence in European countries was 24.74 (99% CI: 19.25, 30.90)/100,000 (Fig. 2). Among the European countries, the estimated pooled prevalence of SPMS was highest in Sweden and lowest in Portugal. North European countries such as Sweden, Norway, United Kingdom (UK), and Ireland reported a higher SPMS prevalence than the rest of the European countries. The only exception was a study conducted in Croatia and Slovenia, which reported a higher prevalence equivalent to that in the North European countries in these two countries despite being South European countries (Fig. 3). Low-quality studies from Greece, Kosovo, Netherlands, and Romania were not included in this meta-analysis.

Bosnia and Herzegovina
Two moderate-quality studies were included in this meta-analysis [19, 20]. Both studies used the McDonald diagnostic criteria. The pooled prevalence of SPMS was 10.32 (99% CI: 5.84, 15.99)/100,000 (Fig. 3). Between 2003 and 2006, the MS prevalence increased by 15%, while the SPMS prevalence decreased by 2% (Table 1) [19, 20].

Bulgaria
Only one moderate-quality study was included in this meta-analysis [21]. Even though MS patients were more prevalent in the Sofia region than in the Samokov region, the prevalence of SPMS was higher in the Samokov region compared with the Sofia region (Table 1) [21]. The pooled prevalence of SPMS was 18.55 (99% CI: 9.60, 30.29)/100,000 (Fig. 3).

Croatia and Slovenia
Two MS epidemiological studies reported the proportion of SPMS patients [22, 23]. The study conducted by Perkovic et al. in Croatia did not meet the quality standards required for inclusion in this meta-analysis [22], while the study conducted by Peterlin et al. in Croatia and Slovenia was of moderate quality and was included in this meta-analysis [23]. This study reported a very high MS prevalence and a proportion of SPMS patients almost similar to that in the North European countries (Table 1 and Fig. 3).

Finland
One moderate-quality study conducted in 2018 was included in this meta-analysis [24]. The estimated SPMS prevalence was 25.81/100,000 (Table 1 and Fig. 3) [24].
| Studies       | Region                              | Study year / prevalence day | Lonely score | Diagnostic criteria          | General population denominator | SPMS prevalent cases | SPMS prevalence (per 100,000) | MS prevalence (per 100,000) |
|--------------|-------------------------------------|-------------------------------|--------------|-----------------------------|--------------------------------|----------------------|-------------------------------|-----------------------------|
| Europe       |                                     |                               |              |                             |                                |                      |                               |                             |
| **Bosnia and Herzegovina** |                                     |                               |              |                             |                                |                      |                               |                             |
| 1 Klupka-Saric et al., 2007 [19] | Western Herzegovina               | Dec 31, 2003                  | 5            | McDonald criteria            | 300,746                        | 29                   | 9.6                           | 26.9                        |
| 2 Klupka-Saric and Galic, 2010 [20] | Western Herzegovina Canton and Herzegovina-Neretva Canton | Dec 31, 2006                  | 5            | McDonald criteria            | 309,712                        | 29                   | 9.4                           | 31                          |
| **Bulgaria** |                                     |                               |              |                             |                                |                      |                               |                             |
| 3 Milanov et al., 1999 [21] | Sofia                               | Mar 31, 1998                  | 5            | Poser criteria               | 44,616                         | 10                   | 22.4                          | 38.1                        |
| 4 Milanov et al., 1999 [21] | Samokov                             |                               | 12           | 16.1                         | 4387                           | 3                    | 59.5                          | 205.7                       |
| **Croatia**  |                                     |                               |              |                             |                                |                      |                               |                             |
| 4 Perkovic et al., 2010 [22] | The town of Cabar                  | Dec 31, 2001                  | 3            | NR                          | 44,616                         | 10                   | 22.4                          | 38.1                        |
| **Croatia, Slovenia** |                                     |                               |              |                             |                                |                      |                               |                             |
| 5 Peterlin et al., 2006 [23] | Gorski Kotar, Croatia and Koc’evje, Slovenia | Jun 1, 1999                  | 5            | Poser criteria               | 57,258                         | 35                   | 61.8                          | 151.9                       |
| **Finland**  |                                     |                               |              |                             |                                |                      |                               |                             |
| 6 Laakso et al., 2019 [24] | Helsinki and Uusimaa, Southwest Finland, Tavastia Proper, Northern Savonia, and Central Finland | Dec 31, 2018                  | 5            | McDonald criteria            | 2,804,616                      | 723                  | 25.8                          | 191.3                       |
| **France**   |                                     |                               |              |                             |                                |                      |                               |                             |
| 7 Ber et al., 1989 [25] | Hautes-Pyrenees                    | Jun 1, 1983                   | 2            | Poser criteria               | 227,942                        | 5                    | 2.2                           | 40.0                        |
| 8 Debouverie, 2009 [26] | Lorraine                           | 2002                          | 4            | Diagnosed by a neurologist  | 2,310,376                      | 933                  | 40.4                          | 109.0                       |
| **Germany**  |                                     |                               |              |                             |                                |                      |                               |                             |
| 9 Farbender and Kolmel, 2008 [27] | Urban Area of Erfurt, Thuringia | Jan 31, 2006                  | 4            | Poser criteria               | 201,267                        | 97                   | 48.3                          | 127.2                       |
| 10 Hoer et al., 2014 [28] | Bavaria                             | 2009                          | 2            | Diagnosed by a neurologist  | 10,400,000                     | 1363                 | 13.1                          | 174.8                       |
| **Greece**   |                                     |                               |              |                             |                                |                      |                               |                             |
| 11 Papathanasopoulos et al., 2008 [29] | Rion-Patras                      | Dec 31, 2006                  | 2            | Poser and McDonald criteria | 652,108                        | 172                  | 26.4                          | 119.61                      |
| 12 Piperidou et al., 2003 [30] | Province of Evros                  | Dec 31, 1999                  | 1            | Poser criteria               | 143,752                        | 14                   | 9.7                           | 38.9                        |
| Studies | Region | Study year/prevalence day | Loney score | Diagnostic criteria | General population denominator | SPMS prevalent cases | SPMS prevalence (per 100,000) | MS prevalence (per 100,000) |
|---------|--------|---------------------------|-------------|---------------------|------------------------------|---------------------|-----------------------------|-----------------------------|
| **Hungary** | | | | | | | | |
| 13 Bencsik et al., 1998 [31] | Szeged city, Csongrad County | 1997 | 4 | Poser criteria | 198,682 | 5 | 2.6 | 65.0 |
| 14 Bencsik et al., 2001 [32] | Csongrad County | Jul 1, 1999 | 4 | Poser criteria | 400,128 | 48 | 12.0 | 62.0 |
| 15 Zsiros et al., 2014 [33] | Csongrad County | Jan 1, 2013 | 4 | McDonald criteria | 421,827 | 52 | 12.3 | 89.8 |
| 16 Biernacki et al., 2020 [34] | Csongrad County | Jan 1, 2019 | 4 | McDonald criteria | 399,012 | 102 | 25.6 | 105.3 |
| **Ireland** | | | | | | | | |
| 17 McDonnell and Hawk- ins, 1998 [35] | Ballymena, Coleraine, Ballymoney, and Moyle districts spanning the counties of Antrim and Derry in Northern Ireland | July 1, 1996 | 5 | Poser criteria | 151,000 | 111 | 73.5 | 190.0 |
| 18 McGuigan et al., 2004 [36] | Wexford | Jan 1, 2001 | 5 | Poser criteria | 104,372 | 49 | 46.6 | 120.7 |
| 19 Gray et al., 2008 [37] | Donegal | Jan 1, 2004 | 6 | Poser/McDonald criteria | 160,446 | 112 | 69.8 | 230.6 |
| 20 Lonergan et al., 2011 [38] | Donegal County | Dec 31, 2007 | 6 | McDonald criteria | 113,347 | 124 | 109.1 | 290.3 |
| | Wexford | | | | 119,442 | 75 | 62.6 | 144.8 |
| | Southeast Dublin city | | | | 101,721 | 51 | 50.1 | 127.8 |
| | All three areas | | | | 334,510 | 251 | 75.0 | 188.9 |
| **Italy** | | | | | | | | |
| 21 Bellantonio et al., 2013 [39] | Campobasso, chief town of Molise region | Sep 30, 2009 | 5 | Diagnosed by a neurologist | 51,633 | 17 | 32.9 | 91.0 |
| 22 Bergamaschi et al, 2020 [40] | Pavia, Northern Italy | Dec 31, 2016 | 5 | McDonald criteria | 547,251 | 295 | 53.9 | 169.4 |
| 23 Caniglia-Tenaglia et al, 2018 [41] | Republic of San Marino | Dec 31, 2014 | 5 | Diagnosed by a neurologist | 32,789 | 12 | 36.8 | 204.3 |
| 24 Cavalietti et al, 1994 [42] | Province of Modena, Northern Italy | Dec 31, 1990 | 5 | McAlpine and Confavreux | 603,989 | 53 | 8.8 | 38.9 |
| 25 Granieri et al, 1996 [43] | Ferrara | Dec 31, 1993 | 5 | Poser criteria | 358,808 | 73 | 203 | 69.4 |
| 26 Granieri et al., 2007 [44] | Province of Ferrara, Northern Italy | Dec 31, 2004 | 5 | Poser criteria | 349,777 | 147 | 41.9 | 120.9 |
| 27 Granieri et al, 2008 [45] | Republic of San Marino | Dec 31, 2005 | 4 | Poser criteria | 29,999 | 5 | 16.7 | 166.7 |
Table 1 (continued)

| Studies | Region | Study year/prevalence day | Loney score | Diagnostic criteria | General population denominator | SPMS prevalent cases | SPMS prevalence (per 100,000) | MS prevalence (per 100,000) |
|---------|--------|---------------------------|------------|---------------------|-------------------------------|---------------------|-------------------------------|----------------------------|
| 28      | Granieri et al., 2018 [46] | Province of Ferrara, Northern Italy | Dec 31, 2016 | 4 | McDonald 2010 criteria | 351,436 | 162 | 45.9 | 197.5 |
| 29      | Grimaldi et al., 2007 [47] | Caltanissetta (Sicily), Southern Italy | Dec 31, 2002 | 4 | Poser criteria | 60,919 | 16 | 26.3 | 165.8 |
| 30      | Guidetti et al., 1995 [48] | Provinces of Reggio Emilia and Modena | Dec 31, 1990 | 4 | McAlpine criteria | 1,024,223 | 30 | 2.9 | 40.2 |
| 31      | Iuliano et al., 2014 [49] | Salerno (Southern Italy) | Dec 31, 2010 | 5 | McDonald criteria | 366,025 | 79 | 21.6 | 85.2 |
| 32      | Millefiorini et al., 2010 [50] | Province of Frosinone | Jan 1, 2007 | 5 | Poser criteria | 491,548 | 85 | 17.2 | 95.0 |
| 33      | Nicoletti et al., 2001 [51] | Catania, Sicily | Jan 1, 1995 | 5 | Poser criteria | 333,075 | 68 | 20.4 | 58.5 |
| 34      | Nicoletti et al., 2005 [52] | Catania, Sicily | Dec 31, 1999 | 5 | Poser criteria | 313,110 | 77 | 24.6 | 92.0 |
| 35      | Nicoletti et al., 2011 [53] | Catania, Sicily | Dec 31, 2004 | 5 | Poser criteria | 313,110 | 90 | 28.7 | 127.1 |
| 36      | Patti et al., 2019 [54] | Sicily | Dec 31, 2018 | 4 | McDonald criteria and Thompson criteria | 23,948 | 5 | 209 | 292.3 |
| 37      | Solano et al., 2005 [55] | Province of Genoa | Dec 31, 1997 | 5 | Poser criteria | 913,218 | 150 | 16.4 | 94.0 |
| 38      | Totaro et al., 2000 [56] | LAquila | Dec 31, 1996 | 5 | Poser criteria | 297,828 | 29 | 9.7 | 53.0 |
| Kosovo | Zekiraj et al., 2014 [57] | Pristina | 2003–2012 | 2 | McDonald criteria | 2,102,041 | 93 | 4.4 | 19.6 |
| Netherlands | Minderhoud et al., 1988 [58] | Groningen | NR | 2 | Poser criteria | 560,000 | 108 | 19.3 | 61.1 |
| Norway | Dahl et al., 2004 [59] | Nord-Trøndelag County | Jan 1, 2000 | 6 | Diagnosed by a neurologist | 127,108 | 59 | 46.4 | 163.6 |
| 40      | Gronning and Mellgren, 1985 [60] | Troms and Finnmark | Jan 1, 1983 | 3 | Rose criteria | 225,073 | 23 | 104 | 31.5 |
| 41      | Risberg et al., 2011 [61] | Oppland County hospitals, Gjøvik, and Lillehammer | Jan 1, 2002 | 4 | Poser criteria | 183,235 | 95 | 51.8 | 174.1 |
| Poland | Broda et al., 2016 [62] | Swietokrzyskie Province | Dec 31, 2014 | 5 | McDonald criteria | 1,263,176 | 317 | 25.1 | 115.7 |
| Studies          | Region                                      | Study year/prevalence day | Loney score | Diagnostic criteria               | General population denominator | SPMS prevalent cases | SPMS prevalence (per 100,000) | MS prevalence (per 100,000) |
|------------------|---------------------------------------------|---------------------------|-------------|-----------------------------------|-------------------------------|----------------------|-------------------------------|-------------------------------|
| 45 Brola et al., 2017 [63] | Swietokrzyskie Province                       | Dec 31, 2015              | 5           | McDonald criteria                 | 1,257,179                     | 360                  | 28.6                          | 121.3                         |
| 46 Kapica-Topczewska et al., 2018 [64] | Central Poland, Northeastern Poland          | Dec 31, 2013              | 5           | McDonald criteria                 | 1,268,239                     | 311                  | 24.6                          | 109.1                         |
| 47 Kulakowska et al., 2017 [65]       | Northeastern Poland (Podlaskie voivodeship)   | NR                        | 3           | McDonald criteria                 | 750,460                       | 200                  | 26.6                          | 108.6                         |
| 48 Potemkowski and Jasinska, 2015 [66] | Kielce, Central Poland                       | NR                        | 4           | McDonald criteria                 | 200,938                       | 71                   | 35.4                          | 98.53                         |
| Portugal         |                                             |                           |             |                                   |                               |                      |                               |                               |
| 49 Branco et al., 2020 [67]         | Entre Douro e Vouga region                   | Jul 1, 2014               | 5           | McDonald criteria                 | 274,859                       | 36                   | 13.1                          | 64.4                          |
| 50 De Sa et al., 2006 [68]          | District of Santarém                         | Nov 1, 1998               | 6           | Poser criteria                    | 62,621                        | 6                    | 9.6                           | 46.3                          |
| 51 Figueiredo et al, 2015 [69]      | Braga                                       | Dec 31, 2009              | 5           | Diagnosed by a neurologist        | 866,012                       | 49                   | 5.7                           | 39.8                          |
| 52 Lopes et al., 2020 [70]          | Sao Miguel                                   | Jul 1, 2019               | 4           | McDonald criteria                 | 137,150                       | 4                    | 2.9                           | 34.3                          |
| 53 Ruano et al., 2014 [71]          | Entre Douro-e-Vouga                         | Jan 1, 2013               | 4           | McDonald criteria                 | 274,859                       | 34                   | 1.23                          | 58.6                          |
| Romania           |                                             |                           |             |                                   |                               |                      |                               |                               |
| 54 Becus and Popovicu, 1994 [72]    | Mures County                                | Dec 31, 1986              | 2           | Diagnosed by a neurologist        | 615,032                       | 8                    | 1.3                           | 21.0                          |
| 55 Cornea et al., 2016 [73]         | Timis County                                | Aug 16, 2016              | 3           | McDonald criteria                 | 486,420                       | 45                   | 9.3                           | 69.1                          |
| Serbia            |                                             |                           |             |                                   |                               |                      |                               |                               |
| 56 Pekmezovic et al, 2019 [74]      | Belgrade                                    | Dec 31, 2018              | 4           | McDonald criteria                 | 1,685,673                     | 586                  | 34.7                          | 136.8                         |
| 57 Toncev et al., 2011 [75]         | Sumadija                                    | Dec 31, 2006              | 4           | McDonald criteria                 | 298,778                       | 62                   | 20.8                          | 64.9                          |
| Spain             |                                             |                           |             |                                   |                               |                      |                               |                               |
| 58 Aladro et al., 2005 [76]         | Las Palmas, Canary Islands                  | Dec 31, 2002              | 5           | Poser criteria/McDonald criteria  | 82,623                        | 12                   | 14.5                          | 73.8                          |
| 59 Benito-Leon et al, 1998 [77]     | Mostoles                                    | Feb 1, 1998               | 5           | Poser criteria                    | 195,979                       | 9                    | 46                            | 43.4                          |
| 60 Bufill et al., 1995 [78]         | Region of Osona in northern Catalonia       | Dec 31, 1991              | 4           | Poser criteria                    | 71,985                        | 6                    | 83                            | 58.0                          |
| 61 Candeliere-Merlicco et al, 2016 [79] | Health District III, Murcia                 | Dec 13, 1999              | 5           | McDonald criteria                 | 171,040                       | 27                   | 15.8                          | 71.9                          |
| 62 Casquero et al, 2001 [80]        | Menorca (Balearic Islands)                  | Dec 31, 1996              | 5           | Poser criteria                    | 67,009                        | 9                    | 13.4                          | 68.6                          |
| Studies | Region | Study year/prevalence day | Lower score | Diagnostic criteria | General population denominator | SPMS prevalent cases | SPMS prevalence (per 100,000) | MS prevalence (per 100,000) |
|---------|--------|--------------------------|-------------|---------------------|--------------------------------|---------------------|-----------------------------|-----------------------------|
| 63      | Costa Arpin et al., 2020 [81] | Santiago de Compostela | Dec 31, 2015 | 5 | McDonald criteria | 95,612 | 24 | 25.1 | 152 |
| 64      | Hernandez, 2002 [82] | Island of La Palma, Canary Islands | Dec 15, 1998 | 4 | Poser criteria | 81,507 | 11 | 13.5 | 41.7 |
| 65      | Izquierdo et al., 2015 [83] | Northern Seville | Dec 31, 2011 | 5 | Poser criteria | 163,324 | 24 | 14.7 | 90.2 |
| 66      | Modrego Pardo et al., 1997 [84] | Province of Teruel | Mar 1, 1996 | 5 | Poser criteria | 143,680 | 4 | 2.8 | 32.0 |
| 67      | Modrego and Pina, 2003 [83] | Bajo Aragon, province of Teruel, Northeastern Spain | Jan 1, 2003 | 5 | Poser criteria | 58,666 | 5 | 8.5 | 75.0 |
| 68      | Perez-Carmona et al., 2017 [18] | San Vicente del Raspeig | Apr 10, 2017 | 3 | 2010 McDonald criteria - MS diagnosis, Lublin criteria (2013 revisions) – MS subtypes | 56,696 | NR | SPMS with progression but without activity: 3.4%; SPMS without progression or activity: 6.9% | 102.3 |
| 69      | Perez-Carmona et al., 2019 [86] | San Vicente del Raspeig | Dec 31, 2018 | 5 | McDonald criteria | 1,685,673 | 586 | 34.7 | 136.8 |
| 70      | Pina et al., 1998 [87] | Sanitary District of Calatauyd | Apr 1, 1995 | 5 | NR | 58,591 | 18 | 30.7 | 58.0 |
| 71      | Tola et al., 1999 [88] | Valladolid | Mar 1, 1997 | 5 | Poser criteria | 92,632 | 6 | 6.5 | 58.3 |
| **Sweden** | | | | | | | | | |
| 72      | Bostrom et al., 2009 [89] | County of Värmland in Western Sweden | Dec 31, 2002 | 4 | Poser criteria | 273,419 | 205 | 75.0 | 170.1 |
| **Turkey** | | | | | | | | | |
| 73      | Akdemir et al., 2017 [90] | Middle Black Sea Region | Aug 2010–May 2011 | 4 | McDonald criteria | 3,666,667 | 74 | 2.0 | 43.2 |
| 74      | Çelik et al., 2011 [91] | Edirne Gty | 2003 | 5 | McDonald criteria | 119,298 | 8 | 6.7 | 33.9 |
| 75      | Çelik et al., 2011 [91] | Edirne Gty | 2004 | 119,298 | 8 | 6.7 | 36.5 |
| 76      | Gokce et al., 2019 [92] | Sivas Province | Apr 2017–Jan 2018 | 7 | McDonald criteria | 6595 | 4 | 60.7 | 288 |
| 77      | Turk Boruet al, 2006 [93] | Maltepe, Istanbul | Nov 2002–May 2003 | 7 | Poser criteria | 32,531 | 11 | 3.38 | 101.4 |
| 77      | Turk Boruet al, 2011 [94] | Three areas of the Black Sea coast of Turkey (Kandira, Geyve, Erbaa) | 2006 and 2010 | 8 | Poser criteria | 53,364 | 9 | 16.9 | 50.6 |
Table 1 (continued)

| Studies          | Region                                | Study year/prevalence day | Loney score | Diagnostic criteria                         | General population denominator | SPMS prevalent cases | SPMS prevalence (per 100,000) | MS prevalence (per 100,000) |
|------------------|---------------------------------------|---------------------------|-------------|---------------------------------------------|-------------------------------|---------------------|-------------------------------|-------------------------------|
| 78 Turk Boru et al, 2018 [95] | Gazipasa (Mediterranean coast)        | Apr–May 2012              | 7           | McDonald 2010 criteria                      | 13,451                        | 1                   | 7.4                           | 52.0                           |
|                  | Artvin (Black sea coast)              | May–Jun 2012              |             |                                             |                               |                     |                               |                               |
|                  | Ordu (Black sea coast)                | Nov–Dec 2012              |             |                                             |                               |                     |                               |                               |
| 79 Turk Boru et al, 2020 [96] | Eregli                                | May–Oct 2018              | 7           | McDonald criteria                           | 32,261                        | 5                   | 15.5                          | 96.1                           |
| Turk Boru et al, 2020 [96] | Devrek                                |                           |             |                                             | 21,963                        | 2                   | 9.1                           | 45.5                           |
| **United Kingdom**|                                       |                           |             |                                             |                               |                     |                               |                               |
| 80 Ford et al, 1998 [97] | Leeds                                 | Apr 30, 1996              | 4           | Poser criteria                             | 732,061                       | 225                 | 30.7                          | 97.3                           |
| 81 Ford et al, 2002 [98] | Leeds                                 | Oct 31, 1999              | 5           | Poser criteria                             | 732,061                       | 244                 | 33.3                          | 108.7                          |
| 82 Fox et al, 2004 [99] | Devon                                 | Jun 1, 2001               | 5           | Poser criteria                             | 341,796                       | 121                 | 35.3                          | 117.6                          |
| 83 Gajofatto et al, 2013 [100] | Verona                                | Dec 31, 2001              | 5           | McDonald criteria                          | 253,208                       | 59                  | 23.4                          | 106.0                          |
| 84 Robertson et al, 1995 [101] | Cambridgeshire                        | Jul 1, 1993               | 5           | Poser, Allison, and Millar criteria        | 378,959                       | 85                  | 22.4                          | 118.0                          |
| 85 Simpson et al, 2015 [102] | Isle of Man                           | 2006, 2011                | 5           | McDonald criteria                          | 80,058                        | 56                  | 69.9                          | 153.6                          |
| 86 Visser et al, 2012 [103] | Aberdeen, Orkney, Shetland            | Sep 24, 2009              | 5           | Poser and McDonald criteria                | 24,8102                       | 237                 | 95.5                          | 238.0                          |
| **Australia**    |                                       |                           |             |                                             |                               |                     |                               |                               |
| 87 Barnett et al, 2003 [104] | Newcastle                             | 1996                      | 5           | Diagnosed by a neurologist                 | 133,686                       | 13                  | 9.7                           | 59.1                           |
| 88 Ribbons et al, 2017 [105] | Newcastle                             | Aug 9, 2011               | 5           | McDonald criteria                          | 148,535                       | 17                  | 11.8                          | 124.2                          |
| **Brazil**       |                                       |                           |             |                                             |                               |                     |                               |                               |
| 89 Callegaro et al, 2001 [106] | Sao Paulo                             | Jul 1, 1997               | 4           | Poser criteria                             | 9,380,000                     | 23                  | 0.2                           | 15.8                           |
| 90 Calmon et al, 2016 [107] | Volta Redonda                         | Nov 2012                  | 5           | Poser criteria/McDonald criteria           | 260,180                       | 1                   | 0.4                           | 15.4                           |
| 91 Negreiros et al, 2015 [108] | Joao Pessoa, Paraiba                  | Jul 2013                  | 4           | Diagnosed by a neurologist                 | 723,515                       | 19                  | 2.6                           | 12.0                           |
| 92 Lana-Peixoto et al, 2012 [109] | Belo Horizonte                        | July 1, 2001              | 4           | Poser criteria                             | 2,238,526                     | 78                  | 3.5                           | 18.1                           |
Table 1 (continued)

| Studies       | Region                          | Study year/prevalence day | Loney score | Diagnostic criteria          | General population denominator | SPMS prevalent cases | SPMS prevalence (per 100,000) | MS prevalence (per 100,000) |
|---------------|---------------------------------|---------------------------|-------------|------------------------------|--------------------------------|----------------------|-----------------------------|-----------------------------|
| 93 Ribeiro et al., 2011 [110] | Uberaba, Minas Gerais          | Aug–Dec 2008              | 4           | Poser and McDonald criteria | 287,760                        | 2                    | 0.7                         | 12.5                        |
| 94 Ribeiro et al., 2019 [111]  | Goiânia                        | Dec 31, 2015              | 4           | Poser or McDonald criteria  | 1,430,697                      | 27                   | 1.9                         | 22.2                        |
| **Canada**    |                                 |                           |             |                              |                                |                      |                             |                             |
| 95 Sloka et al., 2005 [112]    | Newfoundland and Labrador      | Dec 31, 2001              | 5           | Poser criteria               | 521,986                        | 94                   | 18.0                        | 94.4                        |
| 96 Warren and Warren, 1992 [113] | County of Barrhead, Alberta    | Jan 1, 1990               | 5           | Poser criteria               | 9720                           | 9                    | 92.6                        | 196.0                       |
| 97 Warren and Warren, 1993 [114] | Westlock county                | Jan 1, 1991               | 5           | Poser criteria               | 11,510                         | 9                    | 78.2                        | 200.0                       |

*As this is the sub-group analysis, not included in the meta-analysis*

MS Multiple sclerosis, NR Not Reported, SPMS Secondary progressive multiple sclerosis
France
One moderate-quality study was included in this meta-analysis [26]. This study reported an SPMS prevalence of 40.38/100,000 [26]. Another study was excluded from the meta-analysis owing to low quality [25]. In France, over a period of 19 years, the SPMS prevalence has increased by 18.4 times, while the MS prevalence has increased only by 2.7 times (Table 1 and Fig. 3).

Germany
Two MS epidemiological studies reported the proportion of SPMS patients [27, 28], one among them was of moderate quality and was included in this meta-analysis [27]. In 2006, the SPMS prevalence was 48.19/100,000 and MS prevalence was 127.2/100,000 in the urban area of Erfurt (Table 1 and Fig. 3).

Hungary
Four moderate-quality studies conducted in Csongrad County were included in this meta-analysis [31–34]. The pooled prevalence of SPMS was 11.26 (99% CI: 2.19, 26.66)/100,000 (Fig. 3). The prevalence of SPMS was 4.6 times greater in Csongrad County compared with the Szeged region of Hungary [31, 32]. Over a period of 14 years, the SPMS prevalence has remained almost same in Csongrad County, while the MS prevalence has increased by 45% [32, 33]. A recent study conducted in Csongrad County in early 2019 showed a two times increase in the SPMS prevalence and a 1.2 times increase in the MS prevalence since 2013 [34] (Additional file 1, Fig. 2).

Ireland
A total of four moderate- and high-quality studies were included in this meta-analysis [35–38]. The pooled prevalence of SPMS was 68.69 (99% CI: 53.44, 85.84)/100,000 (Fig. 3). The prevalence of SPMS was highest in Donegal County in the year 2007 and lowest in Wexford County in the year 2001 (Table 1). Over a period of 6 years, the SPMS prevalence has increased by 34% and 55% in the Wexford and Donegal counties, respectively. The increase in SPMS prevalence was in line with that of overall
MS prevalence in Donegal County but not in Wexford County (Additional file 1, Fig. 3) [36, 38].

**Italy**
A total of 18 MS moderate-quality studies reported the proportion of SPMS patients and thus were included in this meta-analysis [39–56]. The pooled prevalence of SPMS was 22.49 (99% CI: 14.97, 31.48)/100,000 (Fig. 3). Multiple studies conducted in the province of Ferrara, Republic of San Marino, and Catania showed an increase in the SPMS prevalence over time. Between 2001 and 2011, a gradual increase in the SPMS prevalence was observed in Catania, while the increase in MS prevalence was more pronounced [51–53]. In the Republic of San Marino, between 2005 and 2014, the SPMS prevalence increased by 120%, while the MS prevalence increased by 22.5% [41, 45]. In the province of Ferrara, between 1993 and 2004, the SPMS prevalence increased by 106%, while the MS prevalence increased by 74% [43, 44]. In the same region, between 2004 and 2016, the SPMS prevalence increased only by 9.5%, while the MS prevalence increased by 63% [44, 46] (Table 1 and Additional file 1-Fig. 4).

**Norway**
Two of three studies were of moderate quality and were included in this meta-analysis [59, 61]. The pooled prevalence of SPMS was 49.26 (99% CI: 39.47, 60.12)/100,000 (Fig. 3).

**Poland**
Four of five studies were of moderate quality and were included in this meta-analysis [62–64, 66]. The pooled prevalence of SPMS was 26.46 (99% CI: 22.87, 30.31)/100,000 (Fig. 3). During the 1-year period in the Swietokrzyskie Province, the MS prevalence increased by
5% and SPMS prevalence increased by 14% (Additional file 1-Fig. 5) [62, 63].

**Portugal**
Five moderate-quality studies were included in this meta-analysis [67–71]. The pooled prevalence of SPMS was 7.88 (99% CI: 3.33, 14.16)/100,000. The SPMS prevalence increased with increase in MS prevalence (Fig. 3).

**Serbia**
Two moderate-quality studies were included in this meta-analysis [74, 75]. The pooled prevalence of SPMS was 27.04 (99% CI: 12.01, 47.89)/100,000 (Fig. 3 and Table 1).

**Spain**
A total of 14 MS epidemiological studies reported the proportion of SPMS patients [18, 76–88]. Of these, 13 were of moderate and high quality and thus were included in this meta-analysis [76–88]. The pooled prevalence of SPMS was 11.89 (99% CI: 7.04, 17.93)/100,000. The prevalence of SPMS varied between 2.8 and 34.7 cases per 100,000 and was the highest in San Vicente del Raspeig (Table 1 and Fig. 3).

**Sweden**
One moderate-quality study was included in this meta-analysis [89]. The estimated SPMS prevalence was 75.0/100,000, which was the highest among the included studies (Table 1 and Fig. 3).

**Turkey**
All seven studies were of moderate and high quality and were included in this meta-analysis [90–96]. The pooled prevalence of SPMS was 13.00 (99% CI: 4.91, 24.68)/100,000 (Table 1 and Fig. 3).

**United Kingdom**
A total of seven moderate-quality studies were included in this meta-analysis [97–103]. The pooled prevalence of SPMS was 47.66 (99% CI: 25.10, 77.26)/100,000 (Fig. 3). In Leeds, between 1996 and 1999, the MS prevalence increased by 12%, while the SPMS prevalence increased by 8.5% [97, 98]. In the Isle of Man, between 2006 and 2011, the SPMS prevalence increased by 7%, while the MS prevalence increased by 17% [102] (Additional file 1-Fig. 6).

**Worldwide**
The overall pooled prevalence of SPMS was 22.42 (99% CI: 18.30, 26.95)/100,000 with substantial heterogeneity (Fig. 4). Publication bias assessed by constructing a funnel plot showed heterogeneity or small-study effect; however, the effect was not significant ($p = 0.334$) (Additional file 1-Fig. 7). Brazil reported the lowest pooled prevalence, followed by Australia, Europe, and Canada (Fig. 2). Overall, the prevalence of SPMS correlated with that of MS (Pearson’s correlation coefficient: 0.89).

The SPMS prevalence varied widely among different regions within each country. In Hungary, between 1997 and 1999, the prevalence of SPMS increased by 4.6 times in the entire Csongrad County compared with that in the Szeged region of Csongrad County [31, 32]. Multiple studies conducted in the same regions over time have shown an increase in the prevalence of SPMS. The only exception was the study conducted in Bosnia and Herzegovina, which showed a slight reduction of 2% in the SPMS prevalence between 2003 and 2006 [19, 20]. The extent of increase in the SPMS prevalence varied based on the diagnostic criteria used. Studies using the same diagnostic criteria reported a moderate increase in the SPMS prevalence ranging between 7% and 20.5% [51–53, 62, 63, 97, 98, 102]. The only exceptions were two Italian studies conducted in the province of Ferrara between 1993 and 2004 that used the Poser diagnostic criteria, which showed a very high increase of 106% in the prevalence of SPMS [43, 44].

The overall prevalence of SPMS statistically correlated with the prevalence of MS. However, this correlation hypothesis was not consistent when focusing on the extent of correlation. Only in Donegal County, Ireland, the SPMS prevalence increased proportionately with that of MS [36, 38]. The proportion of increase in the SPMS prevalence was lower than that of MS prevalence in Newcastle, Australia [104, 105]; Csongrad County, Hungary [32, 33]; Catania, Italy [51–53]; Ferrara, Italy [44, 46]; Swietokrzyskie Province, Poland [62, 63]; and Isle of Man, UK [102]. The proportion of increase in the SPMS prevalence was higher than that of MS prevalence in the Republic of San Marino, Italy [41, 45]; Ferrara, Italy [43, 44]; and Leeds, UK [97, 98].

Access to oral disease-modifying therapies (DMTs) may have contributed to a decline in the SPMS prevalence. The estimated SPMS pooled prevalence in studies conducted before access to DMTs was 24.54 (CI: 17.50, 32.74)/100,000 in studies conducted between 1996 and 2010. The SPMS pooled prevalence in studies conducted after access to oral DMTs since 2011 was 18.24/100,000 (CI: 11.27, 26.82). Most studies used the Poser or McDonald diagnostic criteria (75 studies). The pooled SPMS prevalence in studies that used the Poser (22.55 [99% CI: 14.88, 31.76]/100,000) and McDonald (24.96 [99% CI: 16.38, 35.28]/100,000) diagnostic criteria was comparable.

Using various statistical tests mentioned earlier, a Brazilian study by Callegaro et al. 2001 [106], an Irish study
by Lonergan et al. 2011 [38], and a UK study by Visser et al. 2012 [103] were identified as the most influential studies (Additional file 1-Table 2, Additional file 1-Figs. 8–9). The prevalence of SPMS after removing these three influential studies was 21.17 (99% CI: 17.90, 25.90)/100,000 compared with the previous result of 22.42 (99% CI: 18.30, 26.95)/100,000.

The subgroup analysis showed that the moderators such as world region (European vs. non-European countries) (Additional file 1-Fig. 10), introduction of oral DMTs (before 2010 vs. after 2010) (Additional file 1-Fig. 11), and sample size (≤100 vs. ≥100 and ≥1000) (Additional file 1-Fig. 12) were significantly (all p < 0.000001) associated with the overall pooled prevalence of SPMS. World region contributed to 10.95%, introduction of oral DMTs contributed to 0.81%, and sample size contributed to 22.13% of the total between-study variance. The moderator diagnostic criteria (McDonald or Poser criteria vs. others) (Additional file 1-Fig. 13) did not significantly influence the overall pooled prevalence of SPMS (p = 0.278) and contributed to only 0.21% of the total between-study variance.

**Discussion**

Several MS epidemiological studies have been published across geographies. However, the same research interest has not been observed for the MS subtypes. A total of 92 countries accounting for 79% of the world population provided MS data for the Atlas of MS 2013 updates. On the contrary, studies from only 20 countries accounting for less than 10% of the world population contributed to the current SPMS prevalence systematic review [5]. This systematic literature review is an attempt to understand the epidemiology of SPMS in Australia, Brazil, Canada, European countries, and the USA. Our study was designed to reduce the uncertainty of outputs using a robust systematic methodology and the Loney quality grading of publications.

Most studies included in this review were of moderate quality, with publication bias per the Loney et al. checklist. However, statistically, no publication bias was observed. It is interesting to note that none of the MS epidemiological studies reported the prevalence of SPMS despite the large number of studies published. Hence, we have estimated the prevalence of SPMS based on the proportion of SPMS patients reported in the MS epidemiological studies. None of the MS epidemiological studies conducted in the USA reported the proportion of SPMS patients. Most studies were conducted in European countries, especially Italy and Spain.

In line with the prevalence of MS reported in the previous studies, the estimated SPMS prevalence varied widely across geographies and was the highest in Sweden (75/100,000) and lowest in Brazil (1.35/100,000) [5, 38, 106, 115, 116]. These results are similar to the findings of MS Atlas 2013, which reported that the highest prevalence of MS in Europe was in Sweden (189/100,000) [5]. Factors considered as possible modifiers of prevalence are differences in actual prevalence by population demographics, in latitude or longitude, in healthcare resourcing such as number of neurologists per 100,000 population, in definitions of SPMS or reimbursement, and in audit of DMTs across countries leading to different levels of diagnostic moral hazard for SPMS.

Our systematic review did not find any demographical data on SPMS, possibly due to lack of focus on the SPMS population in MS research. However, population density had no influence on the SPMS prevalence pattern across countries [117]. Only one study reported the proportion of SPMS patients without disease progression two times that of SPMS patients with disease progression [18]. However, these data need further investigation.

Geographical region, such as European countries and non-European countries, significantly (p < 0.000001) influenced the overall pooled prevalence of SPMS. One of the reasons for this influence was latitude; epidemiological studies have established variations in MS prevalence with latitude, and similar patterns were also observed in SPMS populations across continents [5]. The analysis from this review found that Brazil reported a seven times lower pooled prevalence of SPMS than Australia, a 19 times lower pooled prevalence of SPMS than Europe, and a 42 times lower pooled prevalence of SPMS than Canada. Within Europe, latitudinal influence was observed among northern countries like Sweden, Norway, UK, and Ireland and the remaining European countries. The only exceptions were Croatia and Slovenia, which reported a higher prevalence despite being South European countries. However, because only one study was conducted together in Croatia and Slovenia, this finding needs further investigation. Similarly, longitudinal influence on the prevalence among the West European countries was
Fig. 4 (See legend on previous page.)
also observed. Portugal being the extreme West European country had the lowest SPMS prevalence among the European countries. The prevalence increased by 70.4% than that of Spain in France and by 126.3% than that of France in Germany. However, these observations are inconclusive, as they cannot be generalised across other European countries; some results directly conflict with any interpretation of the results based on latitude or longitude.

The overall SPMS prevalence has increased since the 1990s till the introduction of oral DMTs in the year 2010. This may be due to the possibility of the real SPMS prevalence being more than the reported prevalence, as no separate treatment interventions for SPMS patients were available until recently. The introduction of oral DMTs significantly influenced the overall pooled prevalence of SPMS ($p < 0.000001$). The prevalence of SPMS statistically correlated with that of MS. However, the extent of increase in the SPMS prevalence did not correlate with that of MS.

In the current review, the availability of medical resources, especially neurosurgeons and neurologists per 100,000 population, had no apparent effect on the differences in the SPMS prevalence across countries [118]. However, between different regions of some countries, medical resources may have a direct influence. In Germany, the prevalence of SPMS in the urban area of Erfurt in 2006 was 3.7 times higher than that in Bavaria in 2009 [27, 28]. In contrast, in the Republic of Ireland, high-income counties with better healthcare facilities such as Dublin and Wexford had a lower prevalence of SPMS compared with Donegal, which is a county with the lowest regional per capita [36, 38, 119].

MS research has evolved significantly since 2000 with the introduction of different diagnostic criteria and DMTs. However, these evolutions did not reflect in the prevalence pattern in this study. The use of well-accepted diagnostic criteria, such as the McDonald or Poser criteria, did not influence the overall pooled prevalence of SPMS statistically. Even the quality of the studies did not seem to have an impact on prevalence. Finally, a sample size of below 100 compared with above 100 and below 1000 also significantly influenced the overall pooled prevalence of SPMS ($p < 0.000001$).

Our literature search was limited to English-language publications; however, we manually screened the bibliography of the included publications and found no additional references from other languages. Hence, we believe that the possibility of missing prevalence data is low. Despite including higher-quality studies, the possibility of publication bias cannot be ruled out considering the variability in the quality of the studies included. In summary, this study provides information on the epidemiology of SPMS. To the best of our knowledge, no studies specifically report the epidemiology of SPMS. Our review found high variability in the estimated SPMS prevalence and the quality of the studies conducted with no obvious explanation for variability based on what is known of the SPMS disease physiology. Quality grading of SPMS prevalence studies does not appear to reduce the uncertainty associated with the results. These variations may therefore be due to the differences across healthcare systems in the reporting of SPMS and audit of treatments. It may be important to consider this context in the design of future epidemiological studies of SPMS. Focus on MS subtypes such as SPMS is warranted in high-quality MS epidemiological studies like the MS Atlas project and the Global Burden of Disease project for a better understanding of the prevalence of SPMS.

Conclusions
The estimated prevalence of SPMS and the quality of the studies varied widely. Common confounding factors like latitude that are known to affect MS prevalence did not fully explain the wide range of inter-country and intra-country variability identified in the results.

Abbreviations
CI: Confidence interval; DMT: Disease-modifying therapy; MS: Multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; UK: United Kingdom; USA: United States of America.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12883-022-02820-0.

Acknowledgements
Authors would like to thank Subhashini Subramanian (Novartis Healthcare Pvt. Ltd., Hyderabad) for helping in executing R-code.

Authors’ contributions
Study concept and design: VV and NA; acquisition and preparation of the data: VV and VK; analysis and interpretation of the data: VV, JV, JR and NA; risk of bias assessment: VV and VK; first draft of the manuscript: VV. SV was an employee of Novartis Healthcare Pvt. Ltd., Hyderabad, India, at the time of study; however, she had moved out of the organisation when this manuscript was submitted to the Journal. All authors critically reviewed the manuscript and approved the final version of the manuscript to be published. All authors have read and approved the manuscript.
**Funding**
This study was initiated and completely funded by Novartis AG, Switzerland.

**Availability of data and materials**
All data generated or analysed during this study are included in this published article [and its supplementary information files].

**Declarations**

**Ethics approval and consent to participate**
The study did not involve human participants; hence, the need for approval is not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
Authors have no competing interests.

**Author details**
1 Novartis Healthcare Pvt Ltd, Value & Access, NBS CONEXTS, Hyderabad, India.
2 Novartis Corporation (Malaysia) Sdn. Bhd, Kuala Lumpur, Selangor, Malaysia.
3 Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK.
4 Novartis Pharma AG, Basel, Switzerland.

Received: 14 June 2021    Accepted: 1 July 2022
Published online: 17 August 2022

**References**

1. Collaborators GBDMS. Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18:269–85.
2. Lublin FD, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83:278–86.
3. Khurana V, Medin J, Time to, and rate of secondary progression in patients with multiple sclerosis: results of a systematic search in ECTRIMS. 2017. https://onlinelibrary.wiley.com/doi/abs/10.1111/ectr.12800.
4. Sadovnick AD, et al. Age of onset in concordant twins and other relative pairs with multiple sclerosis. Am J Epidemiol. 2009;170:289–96.
5. Atlas of MS database. https://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf. Accessed 2 Apr 2020.
6. Gross HJ, Watson C. Characteristics, burden of illness, and physical functioning of patients with relapsing-remitting and secondary progressive multiple sclerosis: a cross-sectional US survey. Neuropsychiatr Dis Treat. 2017;13:1349–57.
7. Purmonen T, et al. Impact of multiple sclerosis phenotypes on burden of disease in Finland. J Med Econ. 2020;23:156–65.
8. Rojas J, et al. A systematic review about the epidemiology of primary progressive multiple sclerosis in Latin America and the Caribbean. Mult Scler Relat Disord. 2018;22:1–7.
9. Khurana V, Sharma H, Medin J. Estimated prevalence of secondary progressive multiple sclerosis in the USA and Europe: results from a systematic literature search. Neurology. 2018;90(Suppl 15):P2.380.
10. Walton C, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Mult Scler. 2020;26:1816–21.
11. Loney PL, et al. Critical appraisal of the health research literature: prevalence or incidence of a health problem. Chronic Dis Can. 1998;19:170–6.
12. Miller J. The inverse of the Freeman-Tukey double arc sine transformation. Am Stat. 1978;32:138.
13. How to Conduct a Meta-Analysis of Proportions in R: A Comprehensive Tutorial. 2018. https://www.researchgate.net/publication/325486099_How_to_Conduct_a_Meta-Analysis_of_Proportions_in_R_A_Comprehensive_Tutorial. Accessed 2 Apr 2020.
14. Bujat B, et al. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. Stat Med. 2002;21:2641–52.
15. Egger M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.
16. Liberati A, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
17. Stroup DF, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008–12.
18. Perez-Carmona N, et al. Prevalence of multiple sclerosis in San Vicente del Raspeig, Spain: a population-based study. Mult Scler. 2017;23(Suppl 2):171.
19. Klupka-Saric I, et al. Epidemiology of multiple sclerosis in western Herzegovina. Clin Neurol Neurosurg. 2007;109:779–83.
20. Klupka-Saric I, Galic M. Epidemiology of multiple sclerosis in western Herzegovina and Herzegovina-Neretva Canton, Bosnia and Herzegovina. Coll Antropol. 2010;34(Suppl 1):189–93.
21. Milanov IN, Topalov KT. Prevalence of multiple sclerosis in Bulgaria. Neuroepidemiology. 1998;18:218–22.
22. Perkovic O, et al. The town of Cabar, Croatia, familiar pseudocluster for multiple sclerosis— descriptive epidemiological study. Coll Antropol. 2010;34(Suppl 2):141–4.
23. Peterlin B, et al. Region with persistent high frequency of multiple sclerosis in Croatia and Slovenia. J Neurol Sci. 2006;247:169–72.
24. Laakso SM, et al. Multiple sclerosis in Finland 2018: Data from the national register. Acta Neurol Scand. 2019;140:303–11.
25. Beir C, et al. Risk factors in multiple sclerosis: a population-based case-control study in Hauts-Pyrenees, France. Acta Neurol Scand. 1989;80:46–50.
26. Debovenere M. Gender as a prognostic factor and its impact on the incidence of multiple sclerosis in Lorraine, France. J Neurol Sci. 2009;286:14–7.
27. Fasbender P, Kolmil HW. Incidence of multiple sclerosis in the urban area of Erfurt, Thuringia, Germany. Neuroepidemiology. 2008;30:147–51.
28. Hoer A, et al. Multiple sclerosis in Germany: data analysis of administrative prevalence and healthcare delivery in the statutory health system. BMJ Health Serv Res. 2014;14:381.
29. Papathanasiopoulos P, et al. Prevalence and incidence of multiple sclerosis in western Greece: a 23-year survey. Neuroepidemiology. 2008;30:167–73.
30. Piperidou GN, et al. Epidemiological data of multiple sclerosis in the province of Evros, Greece. Eur Neurol. 2003;49:498–12.
31. Bencsik K, et al. The prevalence of multiple sclerosis in the Hungarian city of Szeged. Acta Neurol Scand. 1998;97:315–9.
32. Bencsik K, et al. The prevalence of multiple sclerosis, distribution of clinical forms of the disease and functional status of patients in Csorgo County, Hungary. Eur Neurol. 2001;46:206–9.
33. Zsirös V, et al. Prevalence of multiple sclerosis in Csorgo County, Hungary. Acta Neurol Scand. 2014;130:277–82.
34. Biernacki T, et al. Epidemiology of multiple sclerosis in Central Europe, update from Hungary: Brain Behav. 2020;10:e01598.
35. McDonnell GV, Hawkins SA. An epidemiologic study of multiple sclerosis in Northern Ireland. Neurology. 1998;50:423–8.
36. McGuigan C, et al. Latitudinal variation in the prevalence of multiple sclerosis in Ireland, an effect of genetic diversity. J Neurol Neurosurg Psychiatry. 2004;75:572–6.
37. Gray OM, McDonnell GV, Hawkins SA. Factors in the rising prevalence of multiple sclerosis in the north-east of Ireland. Mult Scler. 2008;14:880–6.
38. Lonergan R, et al. Multiple sclerosis prevalence in Ireland: relationship to vitamin D status and HLA genotype. J Neurol Neurosurg Psychiatry. 2011;82:317–22.
39. Bellantonio P, et al. Prevalence and incidence of Multiple Sclerosis in Campobasso (Molise region: chietino, southern Italy). Clin Neuroepidemiology. 2013;115:1806–8.
40. Bergamaschi R, et al. Increased prevalence of multiple sclerosis and clusters of different disease risk in Northern Italy. Neurol Sci. 2020;41:1089–95.
41. Caniglia-Tenaglia M, et al. Multiple sclerosis in the Republic of San Marino, Italian peninsula: an incidence and prevalence study from a high-risk area. Neurol Sci. 2018;39:1231–6.
42. Cavalluti S, et al. Frequency of MS in the province of Modena, 1970-1990. Acta Neurol Scand. 1994;90:377–81.
43. Granieri E, et al. Multiple sclerosis in Italy: A reappraisal of incidence and prevalence in Ferrara. Arch Neurol. 1996;53:793–8.
44. Granieri E, et al. Multiple sclerosis in the Republic of San Marino: a prevalence and incidence study. Mult Scler. 2008;14:325–9.
45. Granieri E, et al. Multiple sclerosis in Italy: a 20-year follow-up of the prevalence in Ferrara. Neuroepidemiology. 2018;51:158–65.
46. Grimaldi LM, et al. High prevalence and fast rising incidence of multiple sclerosis in Caltanissetta, Sicily, Southern Italy. Neuroepidemiology. 2007;28:28–32.
47. Guidetti D, et al. Epidemiological survey of multiple sclerosis in the provinces of Reggio Emilia and Modena, Italy. Neuroepidemiology. 1995;14:7–13.
48. Iuliano GR, Napoletano CM. Multiple sclerosis: updated prevalence and incidence in Salerno (Southern Italy) and its province. Eur J Neurol. 2014;21(Suppl. 1):S88–93.
50. Milleforini E, et al. The prevalence of multiple sclerosis in central Italy. Milt Scler. 2010;16:1432–6.
51. Nicolotti A, et al. Prevalence and incidence of multiple sclerosis in Catania, Sicily. Neurology. 2001;56:62–6.
52. Nicolotti A, et al. Possible increasing risk of multiple sclerosis in Catania, Sicily. Neurology. 2005;65:1259–63.
53. Nicolotti A, et al. Increasing frequency of multiple sclerosis in Catania, Sicily: a 30-year survey. Mult Scler. 2011;17:273–80.
54. Patti F, et al. Prevalence and Incidence of Multiple Sclerosis in the City of Biancavilla. Neuroepidemiology. 2019;53:108–14.
55. Solaro C, et al. The prevalence of multiple sclerosis in the north-west Italian province of Genoa. J Neurol. 2005;252:436–40.
56. Totaro R, et al. Prevalence of multiple sclerosis in the L'Aquila district, central Italy. J Neurol Neurosurg Psychiatry. 2000;68:349–52.
57. Zerqaq K, et al. Epidemiological characteristics and functional disability of multiple sclerosis patients in Kosovo. Med Arch. 2014;68:274–81.
58. Minderhoud JM, van der Hoeven JH, Prange AJ. Course and prognosis of chronic progressive multiple sclerosis. Results of an epidemiological study. Acta Neurol Scand. 1988;78:10–5.
59. Dahl OP, et al. Multiple sclerosis in Nord-Trondelag County, Norway: a prevalence and incidence study. Mult Scler Relat Disord. 2016;9:3–7.
60. Gronning M, Mellgren SI. Multiple sclerosis in the two northernmost counties of Norway. Acta Neurol Scand. 1985;72:321–7.
61. Risberg G, et al. Increasing prevalence of multiple sclerosis in the province of Teruel, Spain. J Neurol. 1997;244:182–5.
62. Modrego Pardo PJ, et al. Prevalence of multiple sclerosis in San Vicente del Raspeig, Spain. Mult Scler Relat Disord. 2019;33:78–81.
63. Costa Arpin E, et al. Epidemiology of multiple sclerosis in Santiago de Compostela (Spain). Acta Neurol Scand. 2020;142:267–74.
64. Hernandez MA. Epidemiology of multiple sclerosis in the Canary Islands (Spain): a study on the island of La Palma. J Neurol. 2002;249:1378–81.
65. Izquierdo G, et al. Long-term epidemiology of multiple sclerosis in the Northern Seville District. Acta Neurol Scand. 2015;132:111–7.
66. Aladro Y, et al. Prevalence of multiple sclerosis in Bajo Aragon, northern Spain. J Neurol. 1999;261(Suppl 1):S162.
67. Vincenzi F, et al. Prevalence of multiple sclerosis in Belgrade (Serbia): a 34-year follow-up study. MSJ. 2015;21(Suppl 1):S89.
68. Marzec M, et al. Prevalence of multiple sclerosis in the Serbian district of Varvarin, Serbia. J Neurol Neurosurg Psychiatry. 2005;76:114–8.
69. Benito-Leon J, et al. Multiple sclerosis in Mostoles, central Spain. Acta Neurol Scand. 1998;98:118–23.
70. Pekmezovic T, et al. Prevalence of multiple sclerosis in the city of Sarajevo (Bosnia and Herzegovina). J Neurol Neurosurg Psychiatry. 2004;75:56–60.
71. Aladro Y, et al. Prevalence and incidence of multiple sclerosis in the city of Malaga. J Neurol Neurosurg Psychiatry. 2006;77:113–7.
72. Becs T, Popovic L. Epidemiologic survey of multiple sclerosis in Timisoara, Romania. Rom J Neurol Psychiatry. 1994;32:115–22.
104. Barnett MH, et al. Progressive increase in incidence and prevalence of multiple sclerosis in Newcastle, Australia: a 35-year study. J Neurol Sci. 2003;213:1–6.
105. Ribbons K, et al. Ongoing increase in incidence and prevalence of multiple sclerosis in Newcastle, Australia: A 50-year study. Mult Scler. 2017;23:1063–71.
106. Callegaro D, et al. The prevalence of multiple sclerosis in the city of Sao Paulo, Brazil, 1997. Acta Neurol Scand. 2001;104:208–13.
107. Calmon AB, et al. Prevalence of multiple sclerosis in the City of Volta Redonda - Rio De Janeiro, Brazil using the capture-recapture method. Neuroepidemiology. 2016;46:88–95.
108. Negreiros AA, et al. Clinical and epidemiological profile of patients diagnosed with multiple sclerosis in Joao Pessoa, Paraiba, Brazil. Arq Neuropsiquiatr. 2015;73:741–5.
109. Lana-Peixoto MA, et al. The prevalence of multiple sclerosis in Belo Horizonte, Brazil. Arq Neuropsiquiatr. 2012;70:102–7.
110. Ribeiro SB, et al. Clinical and epidemiological profile of patients with multiple sclerosis in Uberaba, Minas Gerais, Brazil. Arq Neuropsiquiatr. 2011;69:184–7.
111. Ribeiro TAGJ, et al. Prevalence of multiple sclerosis in Goiânia, Goiás, Brazil. Arquivos de Neuro-Psiquiatria. 2019;77:352–6.
112. Sloka JS, Pryse-Phillips WE, Stefanelli M. Incidence and prevalence of multiple sclerosis in Newfoundland and Labrador. Can J Neurol Sci. 2005;32:37–42.
113. Warren S, Warren KG. Prevalence of multiple sclerosis in Barhead County, Alberta, Canada. Can J Neurol Sci. 1992;19:72–5.
114. Warren S, Warren KG. Prevalence, incidence, and characteristics of multiple sclerosis in Westlock County, Alberta, Canada. Neurology. 1993;43:1760–3.
115. Howard JS, Trevick YDS. Epidemiology of Multiple Sclerosis. Neurol Clin. 2016;34:919–39.
116. Leray E, et al. Epidemiology of multiple sclerosis. Rev Neurol (Paris). 2016;172:3–13.
117. Demographics of European countries, Demographics of European countries. https://en.wikipedia.org/wiki/Europe. Accessed 2 Apr 2020.
118. WHO, WHO mental health evidence_Europe region, 2001. https://www.who.int/mental_health/evidence/Country_profiles_Europe.pdf. Accessed 2 Apr 2020.
119. Ireland CSO, County incomes and regional GDP, 2012. http://cdn.thejournal.ie/media/2012/01/20120126countyincomes.pdf. Accessed 02 Apr 2020.

**Publisher’s Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.