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REVIEW ARTICLE

The epidemiology of multiple sclerosis in Europe

M. Pugliatti[a,b], G. Rosati[a], H. Carton[c], T. Riise[b], J. Drulovic[d], L. Vécsei[e] and I. Milanov[f]

[a]*Ist. Clinica Neurologica, Facoltà di Medicina e Chirurgia, Università di Sassari, Viale San Pietro 10, 07100 Sassari, Italy;* [b]*Department of Public Health and Primary Health Care, Section for Occupational Medicine, University of Bergen, Kalfarveien 31, 5018 Bergen, Norway;* [c]*Department of Neurology, Universitaire Ziekenhuizen, 3000 Leuven, Belgium;* [d]*Department of Neurology, School of Medicine, University of Belgrade, Dr. Subotica 6, 11000 Belgrade, Yugoslavia;* [e]*Department of Neurology, Faculty of Medicine, University of Szeged, Semmelweis u. 6, 6725 Szeged, Hungary;* [f]*IIII Neurological Clinic, University Hospital, Boulevard Tzarigradsko shosse - IV km, 1113 Sofia, Bulgaria*

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Multiple sclerosis (MS) is a chronic and potentially highly disabling disorder with considerable social impact and economic consequences. It is the major cause of non-traumatic disability in young adults. The social costs associated with MS are high because of its long duration, the early loss of productivity, the need for assistance in activities of daily living and the use of immunomodulatory treatments and multidisciplinary health care. Available MS epidemiological estimates are aimed at providing a measure of the disease burden in Europe. The total estimated prevalence rate of MS for the past three decades is 83 per 100 000 with higher rates in northern countries and a female:male ratio around 2.0. Prevalence rates are higher for women for all countries considered. The highest prevalence rates have been estimated for the age group 35–64 years for both sexes and for all countries. The estimated European mean annual MS incidence rate is 4.3 cases per 100 000. The mean distribution by disease course and by disability is also reported. Despite the wealth of epidemiological data on MS, comparing epidemiological indices among European countries is a hard task and often leads only to approximate estimates. This represents a major methodological concern when evaluating the MS burden in Europe and when implementing specific cost-of-illness studies.

Introduction

Multiple sclerosis (MS) is a chronic progressive potentially disabling disorder with considerable social impact and economic consequences despite its relatively limited prevalence. It is the major cause of non-traumatic disability in young adults [1].

The social costs of MS are high. They are higher than those for stroke and Alzheimer's disease because of the disease's long duration, the higher prevalence and incidence among young adults, the subsequent early loss of productivity because of physical disability, fatigue and comorbidity, the need for assistance in activities of daily living and the cost of immunomodulatory treatments and multidisciplinary health care [2]. Till date, no cost-of-illness studies based on consistent methodology are available for MS in Europe.

The present overview is an updated collection of the best available estimates of current prevalence and incidence rates, and of the MS distribution by course and disability in Europe. The review is specifically aimed at providing a source of epidemiological data for evaluating the current socioeconomic burden of the disease in European countries.

Corrrespondence: Maura Pugliatti, MD, Ist. Clinica Neurologica, Facoltà di Medicina e Chirurgia, Università di Sassari, Viale San Pietro 10, 07100 Sassari, Italy (tel.: + 39 079 228 231; fax: + 39 079 228 423; e-mail: maurap@uniss.it).

MS: relevant definitions

Multiple sclerosis is an acquired inflammatory and neurodegenerative immuno-mediated disorder of the central nervous system, characterized by inflammation, demyelination and primary or secondary axonal degeneration [3]. It clinically manifests with signs of multiple neurological dysfunctions (e.g. visual and sensory disturbances, limb weakness, gait problems and bladder and bowel symptoms) followed by recovery or by an increasing disability because of irreversible functional disability over time [4]. However, more aspecific symptoms can be detected, such as fatigue, which is experienced by nearly 80% patients as interfering with their quality of life and productivity, regardless of the degree of disability and course status [5,6].

Immunoprophylactic therapies have not yet proven to be highly efficacious in modifying the disease course, and are often associated with side effects further worsening patients' quality of life and productivity. The disease shows heterogeneity with respect to its patho-

genesis, clinical manifestations, prognosis and, most interestingly, with respect to its pathology [7]. The etiology of MS is unknown. It is a complex multifactorial disorder, in which environmental factors are hypothesized to interact with genetically susceptible individuals [8]. Pediatric MS and late-onset MS (i.e. clinical onset over the fifth decade) are rare.

Diagnostic criteria

There are no pathognomonic tests for the diagnosis of MS, which remains clinical despite the many paraclinical markers. Diagnostic criteria require evidence of dissemination of neurologic signs and symptoms in space and time, based on anamnestic, clinical and paraclinical evidences. The most widely used criteria in MS epidemiological research over the past two decades were the Poser Committee criteria [9]. Based on the number of relapses (attacks), clinical and paraclinical evidences (evoked potentials) and the increased number of oligoclonal bands and/or IgG patients are assigned to the following categories: (i) clinically definite MS (CDMS), (ii) laboratory-supported definite MS (LSD-MS), (iii) clinically probable MS (CPMS) and (iv) laboratory-supported probable MS (LSPMS). Subcategories are applied to (i), (ii) and (iii), which, however, are seldom taken into account in epidemiological descriptive studies of MS. Magnetic resonance imaging (MRI) has been recently integrated into new criteria for the diagnosis of MS [10]. According to these new indications, patients can receive a diagnosis of MS or possible MS. MRI findings must themselves meet specific criteria to be considered attributable to MS [11–13]. When comparing all categories of Poser Committee diagnostic criteria with McDonald's criteria, MS rates appear to be overestimated when the latter are used [14]. Finally, the lack of 'attacks' and of recurrent episodes in primary progressive forms may lead to an underestimation of such forms when the Poser Committee criteria are used [15].

Clinical course

The clinical course of MS shows heterogeneity among patients and within the same patient. The following categorization of the clinical course of MS has been reported to reduce the confusion in terminology [16]: (i) relapsing–remitting MS (RR-MS), a clearly defined disease with relapses with full recovery, or with sequelae upon recovery and periods between relapses characterized by a lack of disease progression, (ii) progressive–relapsing MS (PR-MS), progressive disease from onset, with clear superimposed relapses, with or without full recovery, and periods between relapses characterized by continuing progression; (iii) secondary-progressive MS (SP-MS), initial RR course followed by progression with or without occasional relapses, minor remissions and plateaus; (iv) primary-progressive MS (PP-MS), disease with progression from onset with plateaus and temporary minor improvements.

Because of the cross-sectional or historical design of most epidemiological studies on MS, the disease course is often more simply categorized into RR-MS, SP-MS and chronic progressive (CP)- or PP-MS [4], and it is based on prevalent cases. It is often unclear whether PR courses are lumped to RR or PP courses.

Disability

Several scales are used to measure disability in MS, with special regard to longitudinal studies aimed at evaluating the efficacy of interventional programs (the use of immunomodulatory and symptomatic drugs, rehabilitation, etc.). However, because of the retrospective or cross-sectional nature of assessments, in MS epidemiological descriptive research, the burden of disability is most frequently presented as Kurtzke's Expanded Disability Status Score (EDSS) for prevalent cases [17]. Disability because of MS can be measured within functional neurological systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, other) by assigning each a score. The distribution of the scores over the functional systems combined with their degree is then assigned to one of the 20 categories (0, 0.5, 1,…,10), which indicate the level of disability. Further lumping is often needed when precise scores cannot be assessed in historical or cross-sectional studies so that EDSS 0–3.5 refers to fully ambulatory with at most moderate disability in at least one functional system, 4.0–6.5 refers to fully ambulatory, although relatively severe disability, eventually constant bilateral assistance needed to walk 20 m, 7.0–9.5 refers to patients restricted to wheelchairs, confined to bed and totally dependent and 10 is death caused by MS.

Material and methods

The list of European countries considered was derived from the European Union (EU) website including sites for EU Member States, Applicant Countries and Other Countries [18]. For the study purposes and because of the very small population sizes, Andorra, Liechtenstein, Luxembourg, Monaco, San Marino and Vatican City were not considered in the review.

When existing, estimates from the former Yugoslavia assessed prior to 1991 were assigned to the newly formed countries, Slovenia, Croatia, Bosnia and

Herzegovina, Serbia and Montenegro and to the former Yugoslavia-Republic of Macedonia on a geographic basis.

At the time of the literature search for the present review, no epidemiological studies had been conducted, which used the diagnostic criteria of McDonald *et al.* [10] for MS.

The distribution of MS prevalence rates in Europe was recently reviewed by selecting articles published in the international scientific peer-reviewed literature and reporting on surveys conducted in the past three decades [19,20]. An extensive collection of epidemiological data on MS in Europe by Firnhaber and Lauer [21] also served as a source for the present review.

With the aim of depicting the current burden of MS in Europe, previous epidemiological information was updated and integrated by reviewing the impact of disability, disease course and incidence rates. Toward this purpose, large population-based studies (i.e. 50 000 population and over, registry-based and nation-wide surveys) were preferably considered. For those countries where multiple epidemiological assessments on MS had been carried out over time, data from the largest populations and from the most recent studies were selected. Nevertheless, reliable evidences reported in non-English scientific literature or from local small population surveys were also used when the search on international peer-reviewed literature failed to produce any result for a specific country.

Age categorization for prevalence and incidence differs from study to study. Toward the study purpose, as more pertinent to the 'burden of disease' nature of the review, the following age classification was chosen for age-specific prevalence rates: <17, 18–34, 35–49, 50–64, 65–74, ≥ 75 years. When feasible, i.e. when age-specific prevalence rates were given, the total prevalence rate was standardized using the 1966 European population [22]. The distribution of disability was categorized into mild (EDSS 0–3.5), moderate (4.0–6.5) and severe (7.0–9.5).

For practical purposes and given the heterogeneity and unclearness of the classifications used, SP-MS and RP-MS were lumped together into RP-SP-MS, so that the distribution of the disease course consisted of the three categories RR-MS, RP-SP-MS and PP-MS. As the proportion of both disability and disease course is reported based preferentially on the prevalent cases, prevalence studies were used for this specific purpose, and it was indicated otherwise if based on incidence.

Results

Nearly 200 surveys on MS epidemiology in Europe published in the past three decades were scrutinized, of which a third turned out to be informative with regard to disease burden. More recent and population-based surveys on larger population sizes were preferably considered. The distribution of the population sizes included had a mean of 523 000 and a median of 318 000, with a range of 54 000–3 100 000, and an interquartile range of 172 000–503 000 (not including nationwide surveys).

Prevalence

The UK and the Republic of Ireland

The epidemiology of MS in the British Isles in the past few decades has been characterized by three main trends, i.e. a north-to-south gradient (north-east mainland and the Scottish off-shore islands versus southern England and Wales), a marked increase of prevalence with repeated assessments over time especially in southern regions and the subsequent tendency for the latitudinal gradient to level off [23]. A prevalence rate of 187 per 100 000 was reported for the year 1995 in south-east Scotland [24], which is at least twofold that for England and Wales [25–29]. Even higher rates of nearly 200 cases per 100 000 were found for Scotland offshore islands (Shetlands and Orkneys), but they were based on the small populations and older diagnostic criteria [30,31]. The north-to-south latitudinal gradient of MS prevalence throughout Great Britain and Ireland is undisputed. By designing a prevalence study in eastern Scotland on a large population that had not been previously investigated and comparing the use of more or less inclusive diagnostic criteria (i.e. Allison and Millar [32] versus Poser *et al.* [9]), Forbes *et al.* ruled out any north-to-south gradient of MS prevalence in Scotland. Their data were consistent with those reported for south-eastern Scotland [24]. The sharp change of MS prevalence over the English border suggests that having a Scottish ancestry is a risk factor for MS [24]. Nonetheless, other surveys indicate that MS is more prevalent in northern Great Britain and Ireland than in the respective southernmost regions [33,34]. However, methodological differences between surveys must be taken into account as well as the difference in prevalence being on a regional rather than latitudinal basis [33]. The most recently reported prevalence estimate of MS for northern Ireland was 168 per 100 000, indicating a risk similar to that in Scotland, probably because of the close genetic composition and ethnicity between the Scottish and the northern Irish population [35]. In England and Wales, the prevalence reported from different areas over the last two decades has varied from 84 to 112 MS cases per 100 000 [25–29,36–38]. No latitudinal gradient between northern and southern England was disclosed by Ford *et al.* [38] by means of a

prevalence study conducted in the Leeds Health Authority in northern England for the year 1996 and showing a total crude prevalence rate of 97 per 100 000. In Great Britain, the female:male ratio for MS prevalence varied between 2.2 and 2.8 in Scotland and northern England [24,33,35,36,38].

Multiple sclerosis is more prevalent in the age group of 50–64 years for Great Britain and northern Ireland [24,33,35,36,38]. The highest annual MS incidence rates ever reported was 12.0 per 100 000 for Scotland [24], whereas mean incidence rate for England was 5.1 per 100 000 [36].

In northern England, the proportion of progressive forms SP- and RP-MS (55%) appears to be greater than RR- and PP-MS (31% and 14%, respectively) [38]. However, as most of these patients have been assessed in hospital settings, the proportion of the progressive course might be an overestimation. A study conducted in Leeds showed that, in 1999, 38% of patients had RR-MS or benign MS, 47% had SP-MS and RP-MS, and 15% had PP-MS [39]. The distribution of MS by disease course in northern Ireland shows that 48% of patients have RR-MS, 40% have SP-MS and 12% have PP-MS [35]. The PP-MS forms, demographically and clinically characterized by the same authors, showed a female:male ratio of 1.3 and a skewed EDSS distribution toward the scale higher scores [15,35]. The distribution of prevalence cases by EDSS reported for northern Ireland showed that 32% had a score of 0–3.5 and 20% of 7–9.5 [40].

As for the Republic of Ireland, MS prevalence was recently investigated by McGuigan *et al*. [34] for two different counties showing rates similar to those from the UK at comparable latitudes, i.e. between 121 and 185 cases per 100 000 in year 2001. A gradient of the female:male ratio was also observed: 1.7 in southern versus 3.4 in northern Ireland. The highest prevalence rates were found in the age group of 35–44 years in the County of Donegal, north of Ireland [34].

Incidence was 4.5/100 000/year for Ireland [34]. As for Ireland, the proportion of RR-MS is about 50%, that of SP- and RP-MS is 38%, and 12% for PP-MS [34].

Scandinavia

Scandinavian countries are not homogeneous with respect to the distribution of MS. In Norway, the highest prevalence rate ever reported was of 164 per 100 000 in the Nord-Trøndelag County in the central part [41]. However, the study was based on a small population and hospital records. A prevalence rate of 120 per 100 000 was found in Oslo for the year 1995 [42]. Such rate is higher when only the native Norwegians of Oslo are considered (136 per 100 000). Only Poser definite MS was considered in the Oslo study and the 1995 prevalence rate is therefore underestimated. No significant differences in prevalence among the Oslo patients of different areas of origin were observed, pointing to some environmental factor sustaining MS in the Oslo area [42]. These rates are higher than was previously reported in Vestfold County, Norway (86 per 100 000 in 1983) [43], but comparable with more recent Danish data (112 per 100 000) [44]. The increase in prevalence rates is hypothesized to be partly because of methodological differences in ascertainment over time, and to an increased incidence because of biological factor as well. In fact, MS clinical features also seem to change over time and an increased proportion of RR- versus PP-MS [45] or in females versus males [43] is observed. An uneven distribution of prevalence rates is observed throughout Norway. The prevalence in north Norway was around 21 per 100 000 in 1973 [46]. A recent survey in the same region showed a rate of 73 per 100 000 in 1993 but still lower than in the rest of the country [47]. Such south-to-north decreasing gradient in MS prevalence might be attributed to either Sami's genetic resistance to MS, or to the small population size, or both. The mean age of prevalent cases, mean age at onset, mean age at diagnosis, female:male ratio and the mean time from onset to diagnosis was comparable with other data from the studies conducted in Norway [43,48], Great Britain [24,28,36,38] and Switzerland [49]. South-eastern Norway appears therefore to be at especially higher risk for MS. Prevalence is higher in the age group of 50–59 years for both sexes in the south-east and western regions [41,42] and between 40 and 49 years among the Sami population [47].

Multiple sclerosis incidence rates in Norway increased from 2.6 to 4.3 per 100 000 in the western and northern regions in the past three decades [42,45,47], whereas a fluctuating pattern was reported for Vestfold with the highest rates in 1953–1957 (4/100 000/year) and a more recent peak rate of 3.8 in 1973–1977 [43], Nord-Trøndelag County [41] and Møre-Romsdal [48] with a peak of 8.1 per 100 000 in the years 1984–1988 and among women, similar to that reported for Finland [50]. The highest crude incidence of MS in Europe after that reported for Scotland was observed in south-eastern Norway with a rate of 8.7/100 000/year [42]. Again, such rate was based only on Poser definite cases and is thus underestimated when compared with other sources. Moreover, the incidence rates might be biased toward lower values because of the influx of young second-generation immigrants who contribute to the rate denominator, but are still too young to be at risk [42]. The increase of incidence in Norway over time has been more evident for RR-MS and in women, and thus for more benign cases [42,43,51].

A proportion of 85% of relapsing and 15% of progressive onset was reported for the time-period 1950–1984 in a study of prognostic factors for survival in MS in Norway [52]. The distribution of cases by EDSS shows that 77% have a score of 0–4.5 and 6% a score of 8.0–9.5 [51].

The most recent epidemiological data for Sweden are based on multiple assessments carried out in the Västerbotten County, northern Sweden, which showed an increase in the prevalence rates from 125 per 100 000 in 1990 to 154 in 1997 [53,54] with a more recent female:male ratio of 1.9. Higher prevalence rates were observed for the age group of 35–54 years for both men and women in 1997 [54]. A prevalence rate of 96 per 100 000 in 1988 was previously assessed in Göteborg, south-western Sweden, where an MS register has existed since the early 1950s [55]. An incidence rate of 5.2 per 100 000 was estimated for Västerbotten County in the time-period 1988–1997 [54]. The distribution of patients by EDSS was 0–2.5 in 36%, 3.0–5.5 in 27% and 6–9.5 in 37% of prevalent cases between 1997 and 1998 [56]. A proportion of 84% of RR-MS, 4% of progressive-relapsing MS and 13% of PP-MS was reported [53].

In Finland, the ethnic composition shows heterogeneity from the rest of Scandinavia. Data from the western province of Vaasa and the southern province of Uusimaa reveal an uneven distribution of MS in this country, with a prevalence rate of 93 per 100 000 in 1993 (only definite cases according to Poser criteria were considered) in a large population of Uusimaa, the southernmost region of Finland where the diagnostic facilities are provided by the University Hospital of Helsinki [57]. MS prevalence was investigated in the western part of Finland (Seinäjoki and Vaasa districts) for the same year but in smaller populations, and showed rates of 188 and 107 per 100 000, respectively. An increase of prevalence rates was found in Seinäjoki and Uusimaa districts for the period 1983–1993 and in Vaasa especially among women [57]. MS was nearly twofold more frequent among women than men, and in the age group of 40–59 years in women and 50–59 years in men. Incidence rates also differed from 8.7/100 000/year in the western districts to 5.1 in the south, with the highest rate of 11.6 in the Seinäjoki district in western Finland [50]. The increased incidence rate over time was clearly shown to account for the high prevalence rates in Seinäjoki district. Such rates also appear to account for the remarkable difference of MS frequency between western and southern Finland [57]. Based on the evidence of frequent familial MS occurrence in western Finland, a higher genetic susceptibility to the disease because of genetic drift phenomena related to the geographic isolation of many rural communities was hypothesized to explain the difference in the absolute high rates between regions [58], but environmental factors are probably responsible for the increase of MS over time in Seinäjoki district [57].

Data on the distribution of disease course reported based on the incident cases and modality of onset, showed that, on average, 78% of incident cases were relapsing and 22% progressive with no significant change in the proportion over the time period 1979–1993 [59].

The Danish MS Registry which was established in Denmark in 1948 based on a nationwide survey on MS has allowed the analysis of prevalence, incidence and mortality trends through a 50-year follow-up. The latest updates on MS prevalence showed a rate of 112 per 100 000 in 1990 [44] and 122 per 100 000 in 1996 (H. Brønnum-Hansen and N. Koch-Henriksen, pers. obs.). Consistently with the Norwegian and Swedish findings, these data point to a similar ethnic and environmental background for the susceptibility to the disease. Prevalence is higher in the age group of 35–59 years [44]. The average annual incidence rate was 5.0 per 100 000 in 1980–1989 and the highest ever reported for Denmark over a 40-year time interval [44]. The distribution by sex and based on the cumulative life-time incidence showed a female:male ratio of 1.4 [60].

In Iceland, recent epidemiological data on MS come from a 50-year observational period of the disease in a well-defined and stable population [61]. A threefold increase of the MS prevalence was reported from 1950 to 1999 when the rate was 119 per 100 000, with a female:male ratio of 2.2. However, such increase might be largely due to the detection of relatively more benign cases and the MS natural history in this country appears to be more favorable than elsewhere. Improved case ascertainment and the increased number of trained neurologists over time could explain such a trend. The risk is similar to that in England, Denmark, Sweden and southern Norway in the early 1990s. Interestingly, although Vikings from the west coast of Norway settled in Iceland in the ninth and 10th centuries, studies on the frequency of blood groups have shown that Icelanders are genetically closer to the British and Irish populations than to the Norwegians [62].

Fluctuating patterns of incidence rates were observed in Iceland in the time interval 1900–2000 ranging from 0 to 5/100 000/year, the latter peak rate was reported for 1981–1990 [61]. As for disease course and disability, after a 15-year disease duration, 70% have an EDSS score < 4, 20% have a score between 4 and 6.5 and 10% have a score of ≥ 7. After 30 years, 50% still have mild disability and the remaining are in the moderate-to-severe EDSS group. Progression in disability over a

15-year observational period occurs in 80% of PP- and RP-MS versus 20% in RR- and SP-MS with initial low EDSS score [61].

Germany, Switzerland and Austria

The most recent large population-based studies conducted in Germany disclosed prevalence rates of 83 in Göttingen in 1986 [63], 85 per 100 000 in southern Hesse (onset-adjusted prevalence rates; 64] and 108 for southern Lower Saxony, with no latitudinal gradient but, rather, a homogeneous distribution. A total rate of 95 per 100 000 with a female:male ratio of 1.8 was reported for the city of Bochum. More recently, based on the representative samples of MS-treated patients taken from physicians, the prevalence rate in Germany was estimated as 127 per 100 000 [65]. The highest prevalence was observed for the 40–59-year age group. Incidence rates of 4.6/100 000/year were found in south Lower Saxony [66] in the period 1975–1985 and 6.1/100 000/year in the city of Bochum in similar time interval [67], with some fluctuation over time [68]. An incidence rate of 4.2 per 100 000 was found for the period 1979–1992 (K. Lauer, Griesheim, pers. obs.). The proportion of disease course has been reported for the area of Rostock, Germany in the 1980s according to which 20% of prevalent cases were RR-MS, 45% were RP- and SP-MS and 35% were PP-MS, this last figure being significantly higher than the European average. The distribution of MS cases by disability approximately shows that 46% of patients have low EDSS scores and 15% have high EDSS scores (K. Lauer, pers. obs.).

In Switzerland, the most recent epidemiological survey reported a prevalence rate of 110 per 100 000 for the Canton of Berne in 1986, with a female:male ratio of 1.8 [69], a risk similar to that found in Germany in the early 1990s. The distribution of total rates by age indicated that the highest rates in the 40–50-year age group [69]. The estimated total mean incidence for the period 1961–1980 was 4/100 000/year, its trend showing no significant fluctuations [69].

The most updated prevalence data for Austria have been analyzed by using an extrapolation model in which the frequency of patients' visits at MS clinics was merged with findings from questioning patients [70]. A total rate of 98 per 100 000 was estimated in 1999, with a female:male ratio of 2.5. No recent data on incidence are available. The clinical course based on the clinical dataset, and therefore not fully representative of the general MS population, was RR-MS in 64% of cases, RP- and SP-MS in 28%, PP-MS in 4% and not defined in 4% [70]. The same authors reported that 69% of patients presented with a mild, 26% a moderate and 5% a severe disability.

The Netherlands, Belgium and France

In the Netherlands, MS frequency was assessed for the province of Groningen in 1992, giving a prevalence of 76 per 100 000 [71] with higher estimated rates in the age group of 50–64 years and an estimated female:male ratio of 1.7. A mean total incidence rate of 3.0 was reported for the province of Groningen for the period 1985–1990 [71]. Data on the distribution of prevalent cases from the Groningen population in 1982 showed that 24% patients had RR-MS, 47% had RP- or SP-MS and 29% had PP-MS. As for disability, 43% of cases had a mild course, whereas 18% and 39% a moderate and severe course, respectively [72]. The proportion of severe cases is the highest estimated in Europe.

In Belgium, the prevalence in southern Flanders was 88 per 100 000 in 1991, 74 for men and 101 for women, with a female:male ratio of 1.4 [73]. Probably, because of the similar Germanic descent and exposure to environmental risk factors, these rates do not appear to differ from those from similar latitudes. In the same survey, the highest total rates were estimated for the age groups of 35–49 and 50–64 years, with women contributing mostly in the first and men in the second group. No data on incidence rates are available in the recent literature. Disease course based on the incident cases showed a relapsing–remitting onset in 85% and a progressive onset in 15% [73]. The distribution of prevalent cases by disability was 54%, 23% and 23% for mild, moderate and severe MS, respectively (H. Carton, pers. comm.).

Multiple sclerosis prevalence in France is lower than in other European countries at comparable latitudes. In the 1980s, the rates reported for different French regions varied from 37 to 58 per 100 000 [74–77], and were similar to those found in Spain and mainland Italy. Higher rates were observed for Chalon sur Saône and Avignon in south-eastern France [75] and lower ones were observed for Côte-d'Or in the north-east [74] and the Pyrénées-Atlantiques in the south-west [77]. A total mean prevalence rate of about 50 per 100 000 and spatial aggregation of MS cases in the north-east were reported from the nationwide survey conducted by INSERM in 1986, which was based on the questionnaires returned by MS patients in reply to a television announcement [78]. As the response rate varied among different departments and regions, an inference bias cannot be ruled out. A female:male ratio of 2.4 is reported in the study from Pyrénées-Atlantiques [77] and of 2.5 based on the incident cases from Dijon [79]. A northeast-to-southwest gradient was found for MS mortality by Alpérovitch and Bouvier (1982) [80] and more recently by means of a survey conducted on the whole French farming population with rates varying

from 100 to 50 per 100 000 and a mean of 65 per 100 000 [81]. A mean total incidence rate of 4.3/100 000/year was reported for Dijon in the period 1993–1997 [79]. The same study shows that major differences are observed for prevalence but not for incidence, which is probably attributable to the focal distribution of MS in ethnic groups at different risk for the disease who reside in France. As for the disease course, based on EDMUS, 58% of cases were RR-MS, 27% were SP-MS and 15% PP-MS [82]. No crude recent data on prevalence distribution by age, or by disease disability are available in the recent literature.

Poland, the Czech Republic and Hungary

The most recent prevalence and incidence survey on MS in Poland was carried out for the region of Szczecin in 1995 and published in local scientific literature in Polish [83]. The author found a prevalence of 55 per 100 000 with a peak of 110 in a region southern focus. An MS prevalence was 51 per 100 000 in the Poznan area in 1982 with the highest rates in the age group of 45–59 years [84]. However, in this study, arbitrarily selected criteria of 'definite' and 'possible' were used, thus making comparisons and standardizations with other population unreliable. The mean annual incidence rate for the period 1993–1995 was 2.2 per 100 000 [83] in the Szczecin region where a rate of 3.4/100 000/year had been estimated for the time period 1960–1992 with a decreasing trend over time leading to a mean rate of 1.4 in 1987–1992 [85]. Based on the incident cases, a female:male ratio of 1.2 was reported for the Szczecin region in 1960–1992. A recent local report from Lodz shows that of 2500 patients followed at the MS center, 60% have a RR-MS, 32% an SP-MS and 8% a PP-MS [86]. No recent data are available for prevalence by age and sex, and by distribution by EDSS and disease course.

Prevalence rates for MS in the Czech Republic are unevenly distributed. The most recent surveys show a prevalence of 71 per 100 000 in western former Czechoslovakia in 1984 [87] and between 78 and 160 in smaller populations for three Bohemian districts in the northern part of the Czech Republic in 1992 [88]. A 1.5 female:male ratio has been reported [89]. Mean annual incidence rates between 4 and 8 per 100 000 were reported for the years 1985–1990 [88]. No prevalence data by age nor data on the distribution by disease severity are available, but as for the disease course local Czech data show that 55–70% are RR-, 28–35% are RP- and SP- and 2–10% are PP-MS [90,91].

The MS prevalence rates found in Hungary in the years between 1992 and 1996 ranged from 32 to 79 per 100 000, with lowest rates in Baranya County and highest rates in Fejer County [92–94]. In the Gipsies, prevalence varied between 5 per 100 000 in Baranya County and 98 in Fejer County. More recent data obtained for the the Csongrád County show a total prevalence rate of 62 per 100 000 in 1999, with a female:male ratio of 2.7 [95]. No recent data are available on the distribution of prevalence rates by age. Mean total incidence rate was estimated of 5.5/100 000 for the year 1997–1998. The distribution according to disease course was 69% for the RR-MS and benign forms, 20% for the RP- and SP-MS and 11% for PP-MS. From the same study, 58% of patients were mild cases, 22% were moderately and 20% were severely disabled patients.

The Iberian peninsula, continental and insular (Sicily, Sardinia) Italy and Malta

Prior to the late 1980s and based from information from hospital records and mortality data, Spain and Portugal had been included in the low–medium frequency zone for MS [96]. From the beginning of 1990s, along with the modernization of the public health system, multiple population-based surveys were conducted in Spain [97–103] that revealed rates ranging from 32 per 100 000 in the province of Teruel [99] to 65 in the Gijon health district [100]. The most recent prevalence investigations on larger populations were conducted for northern, eastern and central Spain. Prevalence was 58 per 100 000 in 1997 in the health district of Valladolid in the north [103], 32 in 1996 in the province of Teruel, eastern Spain [98] and 43 in 1998 in the municipality of Mostoles, central Spain [101]. The female:male ratio was 2.0, 1.7 and 1.6, respectively. Spain can be now considered a medium-risk area for MS and a latitude gradient of prevalence can be reasonably ruled out. The highest prevalence rates were observed in the age group of 35–49 years for Teruel and Mostoles and in the ages between 18 and 34 years for Valladolid. The average annual incidence rate ranged from 2.2 per 100 000 in the period 1992–1996 [99] to 3.8 in the period 1994–1998 [101]. The distribution by disease course showed that between 68% and 82% of patients have RR-MS, 9% and 12% have RP-SP-MS and between 9% and 20% have a PP-MS [101; 103]. The distribution by disease severity has been multiply assessed, 58–80% of cases being estimated to be mildly, 15–29% moderately, and 5–18% severely disabled [99,101,103].

Data on MS in Portugal have recently been published in the form of an abstract, which showed a prevalence of 47 per 100 000 in Santarem in 1998 [104], a risk similar to that in Spain.

Multiple and detailed epidemiological assessments on MS have been conducted in Italy in the past two decades. For the Italian mainland, prevalence rates range from 40 to 70 per 100 000 [105–109], with the exception

of Salerno with 35 per 100 000 in 1998 [110] and Valle d'Aosta with 90 per 100 000 [111]. The most recent population-based studies conducted on larger populations yielded different rates throughout the country. MS prevalence rates from most significant studies in northern Italy varied from 81 per 100 000 in 1999 in the province of Padova [112], 69 per 100 000 in 1993 in the province of Ferrara [107], and 53 per 100 000 in 1996 in the district of L'Aquila, central Italy [109]. As for insular Italy, a prevalence rate of 59 per 100 000 in 1995 was found for the city of Catania in Sicily [113] and of 144 and 152 in the provinces of Nuoro and Sassari, Sardinia, in 1994 and 1997, respectively [114; 115]. Female:male ratios varied from 1.2 to 2.3 and the highest prevalence rates were found in the age group of 35–49 years all throughout the country and isles. The increase of prevalence rates observed over time in all surveys considered was ascribed to the better diagnostic accuracy, the improvement of epidemiological methodology and increased survival over time. Incidence trend either remained stable [107] or its increase was concomitant to the introduction of new diagnostic procedures, i.e. oligoclonal band testing in CSF and MRI [112]. However, when comparing incidence trends among different Italian populations, better ascertainment could not fully account for the observed increased prevalence in Sardinia where rates are among the highest worldwide [115]. Because of their peculiar genetic structure and different environmental exposures, Sardinians are probably more susceptible to the disease when compared with mainland Italians or other Mediterranean populations [116].

For the whole country, the mean annual incidence tended to increase over time from 2.4 and 3.9 per 100 000 in 1990–1993 [107; 113] to 4.2 per 100 000 in 1995–1999 [112]. Incidence was significantly higher in Sardinia with a rate of 6.8 per 100 000 in 1993–1997 [115].

According to the disease course, the proportion of patients with RR-MS was 51–75%, it was 18–35% with RP-SP-MS and 5–19% with PP-MS. The distribution by EDSS showed that 62%, 15% and 24% of patients present with the mild, moderate and severe form, respectively.

Prevalence was recently updated for Malta, which disclosed a rate of 17 per 100 000 in 1999 with a female:male ratio of 1.5. The highest rates were observed for the age group of 35–49 years [117]. The prevalence increase in the Maltese-born population over time was ascribed to a change in the population age structure, the increased life expectancy in the general population and earlier diagnoses. The genetic influence from northern Africa, an area at low risk for MS, seems to account for the low absolute MS frequency among the Maltese. Mean incidence rate was 0.8/100 000/year in the period 1989–1998 [117]. No data are available for the distribution of prevalent cases by disease course and severity.

Former Yugoslavia (Slovenia, Croatia, Bosnia and Herzegovina, Serbia and Montenegro, Rep. of Macedonia) and Romania

A national survey carried out in Slovenia in 1992 revealed a prevalence rate of 83 per 100 000 [118], similar to that reported in Germany, probably because of Slovenians' strong Germanic admixture. A total incidence rate of 2.9/100 000/year was estimated in the early 1990s [118]. No data on the prevalence distribution by sex, age, disease course and severity are currently available for Slovenia.

A review of MS prevalence studies in Croatia conducted in the time period 1969–2000 and published as local reports was recently carried out [119]. The mean total prevalence rates obtained by multiple assessments in the past 10 years and with population sizes greater than 50 000 showed a range of rates from 25 to 53 per 100 000; prevalence was 50 per 100 000 in 1998 in a study conducted in Osijek-Baranya (approximately 300 000 population). An exception to these observations was the rate of 125 per 100 000 in 1999 reported for the community of Gorski Kotar (population 56 050). Germanic ethnicity, a higher rate of consanguinity and the relatively small population size, could account for such high rate in this isolated mountainous community. The distribution of prevalence by sex also varied from region to region, but a mean female:male ratio of 1.8 was estimated. The annual mean incidence in most recent studies varied from 1.3 (Northern Adriatic Islands, 1956–1998) to 3.5 (Osijek-Baranya, 1991–1998) per 100 000; an incidence rate of 4.1 was reported for Gorski Kotar in the time-period 1948–1987 [119]. No data are available on the prevalence distribution by age, and by disease course and severity.

The most recent prevalence data for Serbia were assessed for the region of Belgrade in 1996 showing a crude prevalence rate of 51 per 100 000 with a female:male ratio of 1.9 [120]. The distribution of prevalence rates by age was reported for two groups based on early versus late onset. The highest rates were reported among patients in the former group, in women and especially for the age group of 21–50 years. The distribution according to disease course showed a proportion of 51% RR-MS cases, 36% RR- and SP-MS and 13% PP-MS. No data are currently available for incidence and prevalence distribution according to disease severity.

In the Republic of Macedonia, the MS overall prevalence based on the patients treated at the Neurological Clinic of Skopje was reported as 16 per 100 000 in 1991 with a female:male ratio of 1.7 [121]. Incidence

rates were reported to range between 0.2 and 1.2 per 100 000. No other data are currently available for this country.

Only data published in local scientific literature are available for MS epidemiology in Romania. In 1984, a hospital-based epidemiologic survey conducted in a large county by means of reviewing hospital medical records in 34 Romanian counties (76% of the whole Romanian population) estimated a mean prevalence rate of 26 per 100 000 with a female:male ratio of 1.2 and the highest prevalence rates in the age group of 31–50 years for both sexes [122,123]. More recently, a rate of 21 per 100 000 was reported for the region of Transylvania in 1986, with a female:male ratio of 1.3 [124]. A mean incidence rate of 0.9/100 000/year for the time interval 1977–1986 was also found. As from a local report on the distribution of MS-treated patients by disease course, 61% of them had RR-MS, 24% had SP-MS and 15% had PP-MS [125]. No data on the distribution of prevalent cases by disease severity are currently available for Romania.

Bulgaria, Albania, Greece, Cyprus and Turkey

Several epidemiological assessments on MS in Bulgaria are reported in literature. The most recent ones are population-based studies conducted in two small communities adding up to nearly 55 000 population showing a mean total prevalence rate of 39 per 100 000 in 1995, and a female:male ratio of 2.0 [126]. In the urban area of Sofia and the rural town of Somokov, the prevalence of MS was lower in Gipsies [127], similarly to that reported for the Hungarian Baranya County [92]. The distribution of prevalent cases by age was reported in an older population-based study conducted in the Plovdiv area based on the rates in 1992, when the total prevalence was 18 per 100 000 and highest rates were in the age group of 40–49 years [128]. No updated incidence data are currently available as well as the distribution by disease severity. The disease course shows that 32%, 50% and 18% are RR-MS, RP-SP-MS and PP-MS, respectively [126].

The first survey of MS prevalence in Albania was carried out for the year 1988, but it was based on the criteria of Rose *et al.* [129] for definite and probable MS. A prevalence rate of 10 per 100 000 with a female:male ratio of 1.1 and highest rates in the age group of 40–49 years were reported [130]. The mean annual incidence rate was 0.5 per 100 000 for the period 1968–1987. No data for the distribution by disease course and severity are available for Albania.

The most recent prevalence rates of MS for Greece were of 39 per 100 000 for the provinces of Evros in 1999, with a female:male ratio of 2.8 [131]. The authors report the highest prevalence rates for the age group of 25–45 years for both sexes. The mean annual incidence rate increased from 0.7 per 100 000 in the period 1974–1978 to 2.4 per 100 000 in the period 1994–1999. According to the distribution by disease course, 63% had RR-MS, 25% had RP-SP-MS and 12% PP-MS. No data on the distribution of prevalence by severity were presented.

Multiple sclerosis prevalence rates in Cyprus vary according to whether the studies are conducted in the whole population, or in the Greek or Turkish Cypriot populations [132,133]. A total prevalence rate of 45 per 100 000 was reported for 1988 in the native Cypriots residing in the districts of Paphos and Famagusta, and in an inner montaneous area [132]. An MS prevalence in Cypriots in the Republic of Cyprus (Greek part) does not differ from northern Cyprus (Turkish part), but is considerably lower in the Turkish immigrant population of northern Cyprus. When the population of refugees was included, the prevalence rate was 39 per 100 000. A female:male ratio of 1.1 was reported whether only the native Cypriots or also the refugees were included. No crude data on the prevalence distribution by age can be extrapolated from this study; however, 93% of prevalent cases appear to be distributed between age 20 and 59. No incidence data are available. An RR-MS was estimated to be 95% of cases, the remaining being transitional forms to progressive cases. As for disease severity, 56% patients were estimated to have mild disability, 23% a moderate and 21% a severe one.

Epidemiological data on MS in Turkey have been reported recently for the metropolitan area of Edirne city, in the north-western part [134]. Prevalence was 30 per 100 000 in 2003, with a 2.3 female:male ratio and 76% of prevalent cases being RR-MS.

Estonia, Latvia, Lithuania, Belarus, Ukraine and Russia

The prevalence studies of MS carried out in Russia and other countries of the former Soviet Union after 1970 were reviewed by Boiko *et al.* [135,136]. The interpretation of such data from this vast territory is particularly difficult because of relevant differences in the population ethnicity, to the variability in the geographic and social features of the surveyed areas, to the high rate of migration and to the poor organization of the epidemiological studies. Rates within each of these countries are therefore probably to be underestimated and a simple west-to-east gradient can be ruled out.

The best estimate of the total prevalence rate in Estonia based on a mean of rates among native Estonians, Russians and other nationality and based on the mean among different counties was 51 per 100 000 in 1989 (55 in Estonians and 29 in Russians) with a 2.0 female:male ratio and highest rates observed in the age

group of 35–49 years for both sexes [137]. The Schumacher Committee diagnostic criteria were used in this study. No data on incidence, the distribution by disease course or severity, have been reported for Estonia.

For Latvia, prevalence rates were reported to range between 38 and 85 per 100 000 in the late 1960s and 55 per 100 000 in the Pskov region in 1980 [135]. No further epidemiological data are currently available in the international literature on Latvia. A prevalence rate of 35 per 100 000 was registered for Lithuania and a range from 20 to 55 per 100 000 in Belorus around the early 1980s [135].

From the recent and local epidemiological surveys, it is possible to estimate an MS prevalence rate of 41 per 100 000 for central and south-western Ukraine for year 2001 with a female:male ratio of 2.1 [138]. In a previous survey in the same area, the highest prevalence rates were reported in the age group of 30–49 years [139]. In the same study, the mean annual incidence rate for the period 1990–1994 was 0.7 per 100 000. As for the distribution by disease course, 52%, 37% and 11% presented with RR-, RP-SP, and PP-MS, respectively [138].

In Russia, prevalence rates were estimated to be around 30 per 100 000 between the 1970s and 1990s [135]. A new extended study on MS prevalence was carried out in the whole country, showing prevalence ranging from 31 in Ufa to 60 per 100 000 in Novosibirsk [140]. The same study showed incidence rates of 3/100 000/year in Iaroslavl in 1996–2001.

Summary

MS prevalence rates

The distribution of total prevalence rates for each of the country with available reliable data is reported in Fig. 1 and Table 1. Mean rates are higher in northern countries, also likely ascribed to a better degree of disease ascertainment, i.e. better accuracy in survey methodology (nationwide investigations and the use of registry systems) and repeated assessments over time. Nevertheless, a certain extent of prevalence heterogeneity was found within countries, such as in Sardinia (Italy), Scotland (UK), or southern Norway. Therefore, the role of environmental factors and their interaction with the population specific genetic susceptibility in

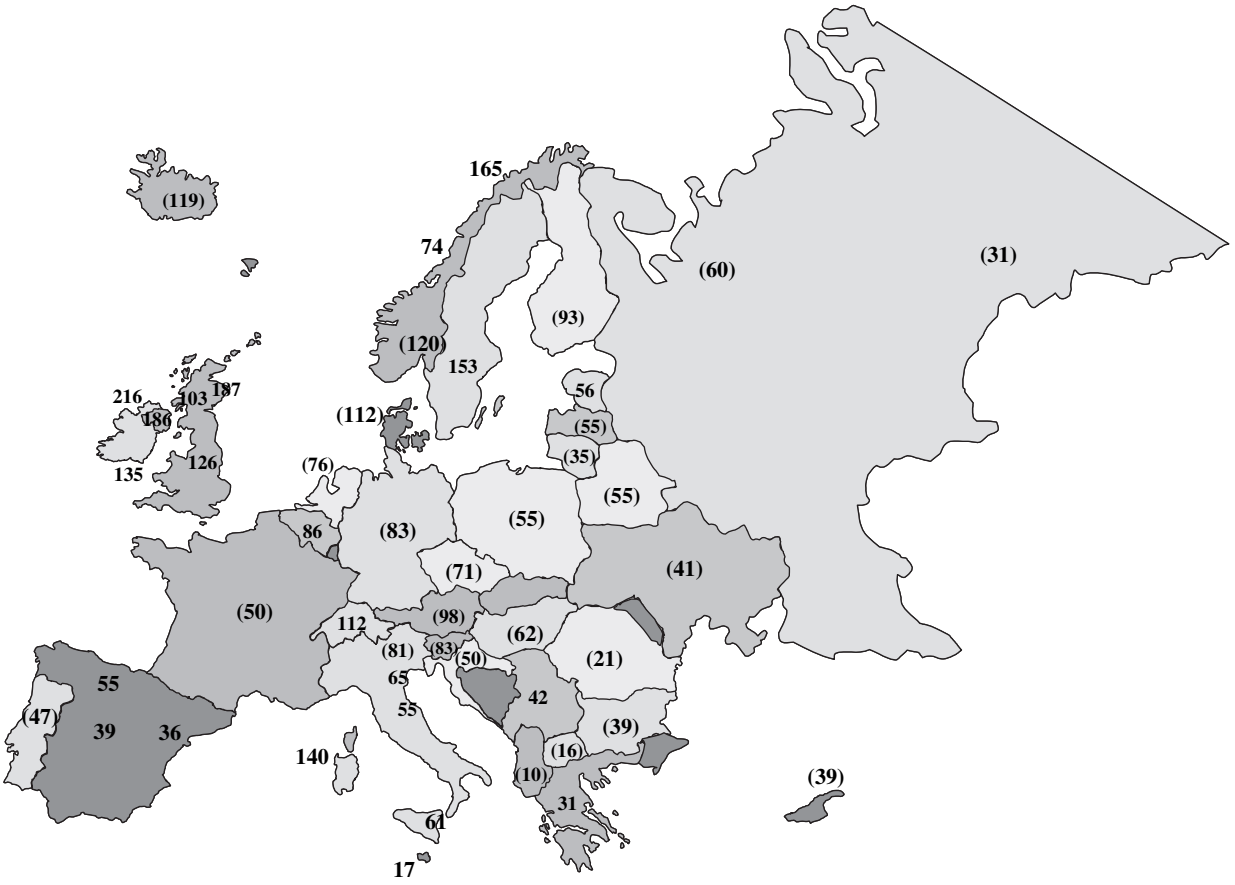

Figure 1 Multiple sclerosis prevalence rates in Europe (adjusted for the European population; in brackets crude rates when adjustment was not possible).

Table 1 Prevalence (per 100 000) of MS in Europe

Country	Country population size [18; 153]	Study population size (% of country population)	Previous year	Crude rate [95% class intervals (CIs)]	Adjusted rate [European standard population, 22]	Reference
Albania	3 130 000	3 091 400 (98.8)	1988	10 (–)*	–	130
Austria	8 100 000	Nationwide	1999	98 (92–104)	–	70
Belgium (Flanders)	10 200 000	250 393 (2.5)	1991	88 (76–99)	86	73
Bulgaria (Svoge and Trojan)	7 900 000	53 573 (0.7)	1995	39 (24–60)	–	126
Croatia (Osijek-Baranya)	4 400 000	298 600 (6.8)	1998	50 (42–59)**	–	119 (review)
Cyprus	800 000	108 600 (13.6)	1988	39 (28–52)	–	132
Czech Republic (west)	10 300 000	–	1984	71 (–)	–	87
Denmark	5 300 000	Nationwide	1996	122 (115–120)	116	Brønnum-Hansen and Koch-Henriksen, personal data
Estonia (south)	1 330 000	392 009 (29.5)	1989	51 (44–59)	56	137
Finland (Seinäjoki)	5 100 000	197 042 (3.9)	1993	188 (168–211)**	–	57
Finland (Uusimaa)	5 100 000	1 277 932 (25.1)	1993	93 (87–99)**	–	57
Finland (Vaasa)	5 100 000	179 079 (3.5)	1993	107 (91–125)**	–	57
France	60 400 000	Nationwide	1986	50 (–)***	–	78
Germany (South Lower Saxony)	82 000 000	265 746 (0.3)	1986	83 (72–95)	–	63
Germany	82 000 000	Nationwide	–	127 (–)	–	65
Greece (Evros)	10 500 000	143 752 (1.4)	1999	39 (29–51)	31	131
Hungary (Csongrad Co.)	10 200 000	400 128 (3.9)	1999	62 (55–70)	–	95
Iceland	290 000	285 000 (98.3)	1999	119 (106–133)	–	61
Ireland (Donegal Co.)	3 700 000	129 994 (3.5)	2001	185 (162–210)	216	34
Ireland (Wexford Co.)	3 700 000	104 372 (2.8)	2001	121 (101–144)	135	34
Italy (Ferrara, north)	57 600 000	358 808 (0.6)	1993	69 (62–79)	65	107
Italy (L'Aquila, central)	57 600 000	297 838 (0.5)	1996	53 (45–62)	55	109
Italy (Padua, north)	57 600 000	820 318 (1.4)	1999	81 (70–91)	–	112
Italy (Sardinia, insular)	57 600 000	454 904 (0.8)	1997	144 (134–156)	140	115
Italy (Sicily, insular)	57 600 000	337 332 (0.6)	1995	58 (51–68)****	61	113
Latvia	2 400 000	–	1980	55 (–)	–	135
Malta	400 000	378 518 (94.6)	1999	17 (13–22)	17	117
Norway (Nord-Trøndelag Co.)	4 620 000	127 108 (2.7)	2000	164 (142–188)	165	41
Norway (Oslo)	4 620 000	483 401 (10.5)	1995	120 (111–131)**	121	42
Norway (Troms and Finnmark)	4 620 000	224 724 (4.9)	1993	73 (62–85)	74	47
Poland (west)	38 600 000	2 901 170 (7.5)	1981	45 (42–48)*****	47	84
Poland (west)	38 600 000	50 000 (0.1)	1995	55 (–)	–	83
Portugal	10 800 000	61 496 (0.6)	1998	47 (30–64)	–	104
Republic of Macedonia	2 030 000		1991	16 (–)	–	121
Romania (Mures Co.)	22 400 000	615 032 (2.7)	1986	21 (18–25)**	–	124
Russia (Novosibirsk)	143 200 000	–	1991–2001 (mean)	60 (–)	–	140
Russia (Ufa)	143 200 000	–	1970s	31 (–)	–	140
Slovenia	2 000 000	–	1992	83 (–)	–	118
Spain (Mostoles, central)	39 400 000	195 979 (0.5)	1998	43 (35–54)	39	101
Spain (Teruel, east)	39 400 000	143 680 (0.4)	1996	32 (23–41)	36	99
Spain (Valladolid, north)	39 400 000	92 632 (0.2)	1997	58 (44–76)	55	103
Sweden (Västerbotten Co.)	8 900 000	259 163 (2.9)	1997	154 (139–170)	153	54
Switzerland (Canton of Berne)	7 250 000	920 000 (12.7)	1986	110 (103–117) ***	112	69
The Netherlands (Groningen)	15 800 000	560 000 (3.5)	1992	76 (–)	–	71
UK (E Scotland)	58 600 000	395 600 (0.7)	1996	184 (171–198)	184	33
UK (Leeds Health Auth.)	58 600 000	732 061 (1.2)	1996	97 (90–105) ***	103	38
UK (N Cambridgeshire)	58 600 000	378 959 (0.6)	1993	107 (98–118) ***	126	36
UK (northern Ireland)	58 600 000	151 000 (0.3)	1996	168 (148–189)	186	15
UK (South-east Scotland)	58 600 000	864 300 (1.5)	1995	187 (178–196)	185	24
Ukraine (Vinnytsya)	46 480 000	390 500 (0.8)	2001	41 (35–48)	–	138
Yugoslavia (Belgrade)	10 500 000	1 602 226 (15.2)	1996	51 (47–55)	42	120

*Rose *et al*. definite and probable MS.

**Only Poser Committee *et al*. definite MS.

***Approx.

****Onset-adjusted prevalence rate.

*****Poser Committee *et al*. definite and possible MS.

increasing MS frequency cannot be ruled out. A tendency for a decreasing variability in prevalence rates among and within countries has been observed over time, which might point to a widespread improvement of case ascertainment and survey methodology in the same time frame, rather than to biological factors accounting for such variability.

MS prevalence by gender

The estimation of prevalence rates by gender could be computed from data deriving from the following countries: Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Malta, Norway, Spain, Sweden, Switzerland, the Netherlands and UK (Table 2). Prevalence rates range from 11 to 282 per 100 000 in women and from 10 to 123 in men, with a female:male ratio between 1.1 and 3.4. Prevalence rates are higher for women in each of the countries considered. However, lower gender ratios (in the distribution first quartile, i.e. between 1.1 and 1.5) were reported for Malta, Czech Republic, Belgium, Denmark, Romania,

Table 2 Prevalence (per 100 000) of MS in Europe by gender

Country	Previous year	Women (95% CIs)	Men (95% CIs)	Women:men ratio	Reference
Albania	1988	11(–)*	10(–)*	1.1	130
Austria	1999	–	–	2.5**	70
Belgium (Flanders)	1991	101 (80–115)	74 (59–89)	1.4	73
Bulgaria (Svoge and Trojan)	1995	52 (28–87)	26 (10–54)	2.0	126
Croatia	1969–1991	–	–	1.8	119
Cyprus	1988	39 (24–59)	37 (23–57)	1.1	132
Czech Republic	1970–1978 (mean)	–	–	1.5	89
Denmark	1996	155 (145–165)	89 (84–95)	1.8	Brønnum-Hansen, personal data
Estonia (south)	1989	63 (53–75)	37 (29–47)	2.0	137
Finland (Uusimaa)	1993	123 (114–132)***	60 (54–67)***	2.3	57
Germany (South Lower Saxony)	1986	–	–	2.9	63
Greece (Evros)	1999	–	–	2.8	131
Hungary (Csongrad Co.)	1999	182 (–)	66 (–)	2.7	95
Iceland	1999	157 (136–181)	72 (59–88)	2.2	61
Ireland (Co. Donegal)	2001	282 (243–327)	85 (64–111)	3.4	34
Ireland (Co. Wexford)	2001	154 (122–191)	88 (64–117)	1.7	34
Italy (Ferrara, north)	1993	91 (78–106)	46 (36–58)	2.1	107
Italy (L'Aquila, central)	1996	68 (57–83)	37 (28–48)	2.1	109
Italy (Padua, north)	1999	111 (99–123)	50 (41–58)	2.3	112
Italy (Sardinia, insular)	1997	205 (188–224)	83 (72–95)	2.5	115
Italy (Sicily, insular)	1995	62 (51–75)****	55 (44–68)****	1.2	113
Malta	1999	20 (14–27)	13 (8–19)	1.5	117
Norway (Nord-Trøndelag Co.)	2000	205 (171–243)	123 (97–153)	1.7	41
Norway (Oslo)	1995	–	–	2.1**	42
Norway (Troms and Finnmark)	1993	89 (73–108)	58 (46–73)	1.4	47
Republic of Macedonia	1990s	–	–	1.7	121
Romania (Mures Co.)	1986	–	–	1.3	124
Spain (Mostoles, central)	1998	54 (40–70)	33 (23–47)	1.6	101
Spain (Teruel, east)	1996	41 (26–55)	24 (12–35)	1.7	99
Spain (Valladolid, north)	1997	74 (52–102)	41 (24–65)	2.0	103
Sweden (Västerbotten Co.)	1997	202 (179–228)	105 (89–125)	1.9	54
Switzerland (Canton of Berne)	1994	137 (127–148)	62 (56–69)	1.8	69
The Netherlands (Groningen)	1992	–	–	1.7	71
UK (E Scotland)	1996	262 (241–285)	100 (86–115)	2.8	33
UK (Leeds Health Auth.)	1996	141 (–)	52 (–)	2.8	38
UK (N Cambridgeshire)	1993	–	–	2.2	36
UK (northern Ireland)	1996	230 (–)	104 (–)	2.3	15
UK (South-east Scotland)	1995	257 (242–272)	112 (102–122)	2.5	24
Ukraine (Vinnytsya)	2001	–	–	2.1	138
Yugoslavia (Belgrade)	1996	54 (49–59)**	28 (24–32)**	1.9	120

*Rose *et al*. definite and probable MS.

**Only Poser Committee *et al*. definite MS.

***Age-adjusted data.

****Onset-adjusted prevalence rate.

Sicily (Italy), Albania and Cyprus. The highest gender ratio (in the distribution third quartile, i.e. between 2.3 and 3.4) was reported for northern Ireland and Ireland, UK (Scotland), Finland, Italy (north and Sardinia), Austria, Germany, Hungary and Greece.

MS prevalence by age

Prevalence rates by age have been computed based on the data from the following countries: Belgium, Denmark, Estonia, Greece, Ireland, Italy, Malta, Norway, Poland, Spain, Sweden, Switzerland and UK (Table 3). Mean total prevalence estimates by age group varied significantly within countries, ranging from 0 (Greece and Mala) to 22 (northern Spain) per 100 000 for the age group of 0–17 years, 16 (Greece) to 147 (Sardinia, Italy) for the age group of 18–34 years, 36 (Malta) to 383 (Scotland, UK) for the age group of 35–49 years, 24 (Greece) to 377 (northern Ireland, UK) for the age group of 50–64 years, 0 (Malta) to 313 (northern Ireland, UK) for age group of 65–74 years, and 0 (Malta and Sicily, Italy) to 120 (Norway) for age 75 years and above. The highest prevalence estimates have been reported for age group of 35–49 for all countries considered, with the exception of Ireland, UK (northern Ireland and Scotland) and Norway, where prevalence was higher in the age group of 50–64 years.

MS incidence estimates

The distribution of available crude total incidence rates is reported in Fig. 2 and Table 4. European total mean MS incidence rate is estimated to be four cases per 100 000/year based on the data from Albania, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Malta, Norway, Poland, Rep. of Ireland, Romania, Slovenia, Spain, Sweden, Switzerland, the Netherlands, Ukraine and UK. Total mean incidence rates are lower (below the distribution first percentile) in Albania, Malta, Poland, Republic of Macedonia, Romania, Spain and Ukraine, and higher (over the distribution third quartile) in Czech Republic, Finland, Hungary, Italy (Sardinia), Norway and UK (Scotland). For the time-period considered, peaks of incidence rates were registered in Seinajoki, Finland (11.6/100 000/year), south-eastern Scotland (9.3/100 000/year), eastern Norway (8.7/100 000/year) and northern Sardinia, Italy (6.8/100 000/year).

The distribution of MS by disease course

The distribution of prevalent cases by disease course is a hard task in that classification can be especially confusing between the RP-MS and SP-MS. Furthermore, depending on the article-specific purposes, these two

Table 3 Prevalence (per 100 000) of MS in Europe, by age

Country	Previous year	0–17 year	18–34 year	35–49 year	50–64 year	65–74 year	75+ years	Reference
Belgium (Flanders)	1991	1	61	161	157	86*	32*	73
Denmark	1996	5	51	195	236	228	112	Brønnum-Hansen, personal data
Estonia (south)	1989	1	47	141	71	17	8	137
Greece (Evros)	1999	5	59	85	41	5	5*	131
Ireland (Co. Wexford and Donegal)	2001	4	84	346	358	224	94	34
Italy (Ferrara, north)	1993	6	63	125	104	38	13	107
Italy (L'Aquila, central)	1996	10	86	103	51	7*	7*	109
Italy (Sardinia, insular)	1997	7	147	312	163	82*	61*	115
Italy (Sicily, insular)	1995	5	65	137	77	25	0	113
Malta	1999	0	26	36	28	0	0	117
Norway (Nord-Trøndelag Co.)	2000	0	102	282	349	194	122	41
Norway (Oslo)	1995	2	65	200	255	177	90	42**
Poland	1981	1	73	75	68	16*	16*	84
Spain (Mostoles, central)	1998	6	43	88	37	8*	8*	101
Spain (Teruel, east)	1996	2	51	78	33	6*	6*	99
Spain (Valladolid, north)	1997	22	91	78	57	5*	5*	103
Sweden (Västerbotten Co.)	1997	4	103	295	267	223	87	54
Switzerland (Canton of Berne)	1986	5*	55*	120–230*	220*	115–220*	40*	69
UK (East Scotland)	1996	4	91	383	358	176	89	33
UK (Leeds Health Auth.)	1996	–	15–70*	150–250*	200–250*	150*	60*	38
UK (North Cambridgeshire)	1993	–	10–75*	200–300*	250–300*	170*	75*	36
UK (northern Ireland)	1996	4	81	343	377	313	60	15
UK (South-east Scotland)	1995	7	97	356	363	261	103	24

*Approx.

**Only Poser Committee *et al.* definite MS.

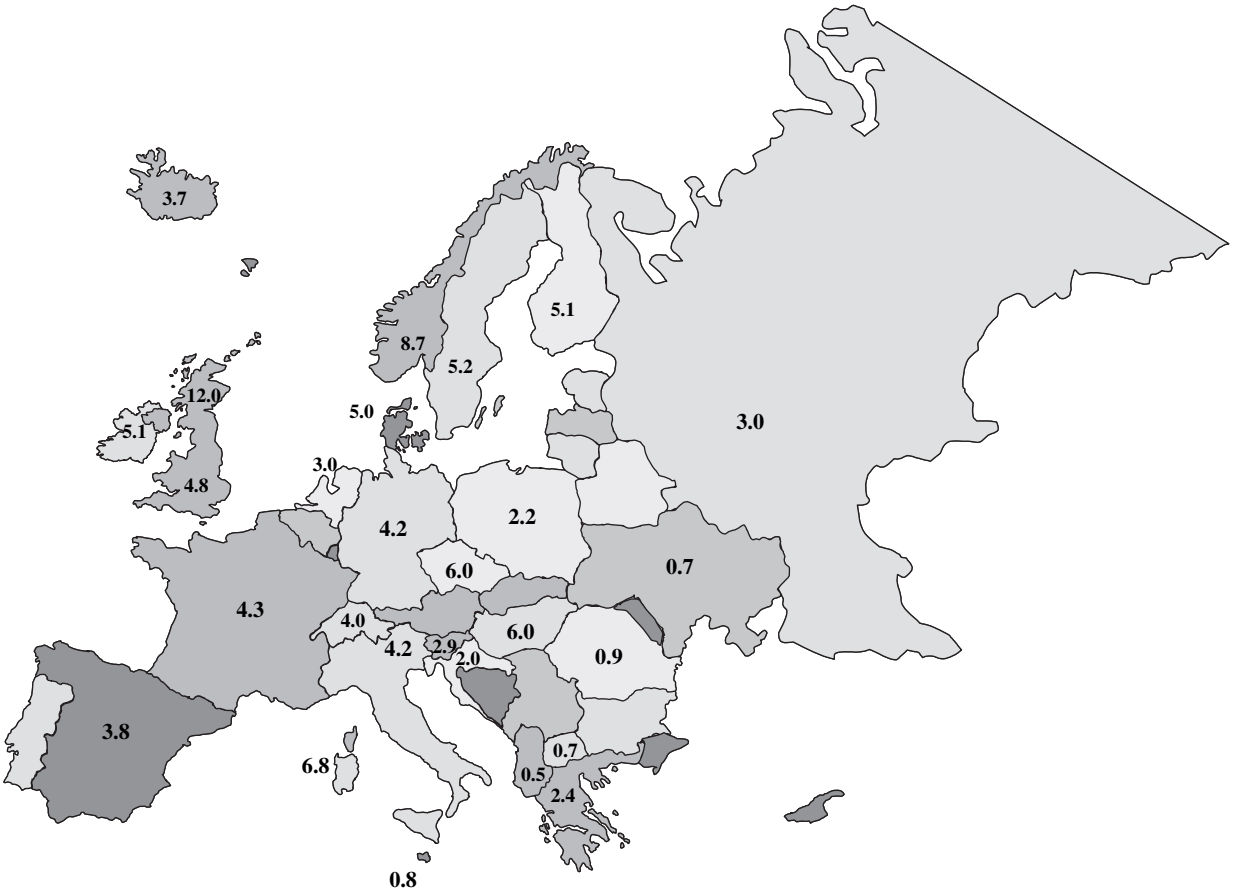

Figure 2 Multiple sclerosis crude incidence rates in Europe.

categories are sometimes omitted, or the trend during the disease early phase is only considered. RR-MS ranged from 24% (The Netherlands) to 88% (Greece) of prevalent cases. The combined proportion of RP-MS and SP-MS ranged from 4% (Sweden) to 50% (Bulgaria), whereas PP-MS ranged from 4% (Austria) to 35% (The Netherlands). The distribution of prevalent cases by disease course is reported in Fig. 3 and Table 5.

The distribution of MS by severity

In most studies, the distribution of disease severity was expressed by using the proportion of disability according to Kurtzke's EDSS in prevalent cases. The estimated proportion range for mild MS (EDSS 0–3.5) was 33% (UK) to 80% (Spain); it was between 13% (Italy) and 48% (UK) for moderate MS (EDSS 4–6.5) and between 5% (Austria) and 39% (The Netherlands) for severe MS (EDSS 7–9.5) (Fig. 4 and Table 6).

MS mortality rates and survival time

Multiple sclerosis is associated with an elevated risk for death. Multiple sclerosis mortality rates in Europe range from 0.5 to 3.6 per 100 000, within decreasing trends over time reported for Denmark, Scotland, The Netherlands, Switzerland, Germany, Austria and Portugal [141–143], increasing trends in Norway, Sweden, Bulgaria and in Italy for women [51,141,144,145]. The highest mortality rates from MS in Austria were observed for the age group of 50–69 and with a female:male ratio of 2.0 [143]. In the same study, the total median age at death from MS was 59 years between 1990 and 2001, with a 15-year shorter life expectancy than the general population. Mean survival time after onset ranges from about 30 to 45 years [142,146–148].

Discussion

Despite the wealth of data from systematic epidemiological studies on MS conducted over the past three decades, reliable information on age-specific prevalence rates, on the distribution of prevalent cases by disease severity and course, and on incidence rates is lacking for nearly two-thirds of all European countries. The attempt to redefine the geographical pattern of MS in

Table 4 Incidence (per 100 000/year) of MS in Europe

Country	Time interval	Study population size (ca.)	Rate (95% CI)	Reference
Albania	1968–1987	3 091 000	0.5 (0.4–0.6)	130
Czech Republic	1985–1990	–	6.0 (–)*	88
Denmark	1980–1989	Nationwide	5.0 (4.8–5.2)	44
Finland (Seinäjoki)	1979–1993	197 000	11.6 (10.1–13.1)**	50
Finland (Uusimaa)	1979–1993	1 278 000	5.1 (4.1–6.3)**	50
Finland (Vaasa)	1979–1993	179 000	5.2 (4.8–5.5)**	50
France	1993–1997	94 000	4.3 (2.9–7.2)	79
Germany	1979–1992	100 000	4.2 (–)	Lauer, personal data
Greece (Evros)	1994–1999	143 000	2.4 (1.4–3.7)	131
Hungary	1998	400 128	6.0 (–)	95
Iceland	1991–1995	255 000	3.7 (–)	61
Ireland (Co. Donegal)	2001	129 994	5.1 (1.6–11.7)	34
Ireland (Co. Wexford)	2001	104 372	4.5 (0.3–8.7)	34
Italy (Ferrara, north)	1990–1993	368 000	2.4 (1.6–3.4)	107
Italy (Padua, north)	1995–1999	820 000	4.2 (3.7–4.7)	112
Italy (Sardinia, insular)	1993–1997	432 000	6.8 (5.8–7.9)	115
Italy (Sicily, insular)	1990–1994	338 000	3.9 (3.0–5.0)	113
Malta	1989–1998	400 000	0.8 (–)	117
Norway (Nord-Trøndelag Co.)	1974–1998	127 000	5.3 (3.7–7.5)	41
Norway (Oslo)	1992–1996	484 000	8.7 (6.3–11.9)**	42
Norway (Troms and Finnmark)	1989–1992	225 000	4.3 (3.0–5.9)	47
Poland (west)	1993–1995	50 000	2.2 (–)	83
Republic of Macedonia	1990s	–	0.7 (–)*	121
Romania (Mures Co.)	1976–1986	600 000	0.9 (–)**	124
Russia (Iaroslavl)	1996–2001	–	3.0 (–)	140
Slovenia	1990s		2.9 (–)	118
Spain (Mostoles)	1994–1998	196 000	3.8 (2.7–5.3)	101
Spain (Teruel)	1992–1996	143 000	2.2 (–)	99
Sweden (Västerbotten Co.)	1988–1997	256 000	5.2 (4.4–6.2)	54
Switzerland (Canton of Berne)	1961–1980	920 000	4.0 (3.7–4.3)	69
UK (North Cambridgeshire)	1990–1995	379 000	4.8 (3.8–6.0)	36
UK (South-east Scotland)	1992–1995	864 000	12.0 (10.6–13.3)	24
Ukraine (Vinnytsya)	1990–1994	390 000	0.7 (–)	139

*Approx.

**Only Poser Committee *et al.* definite MS.

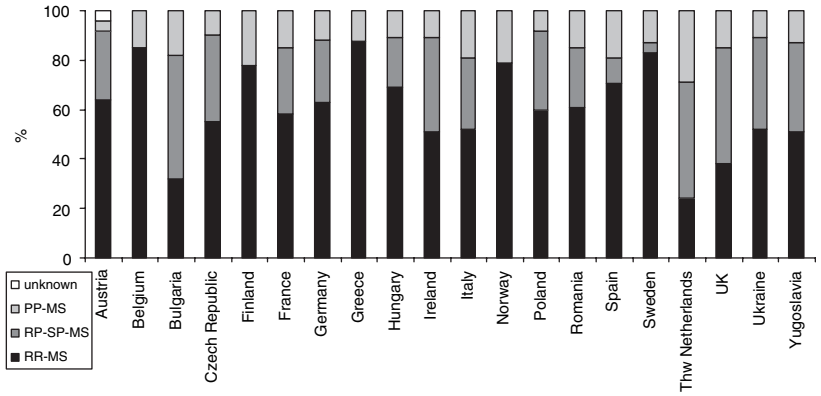

Figure 3 Estimated proportion of MS cases by disease course based on the prevalence.

Europe is a hard task because of: (i) the variability of the surveyed populations with respect to size, age structure, ethnicity; (ii) the capability to detect benign and/or early cases; (iii) the different degree of case ascertainment coverage based on the geographic and time setting, access to medical care, number of neuro-

Table 5 Proportion (%) of MS patients by disease course in Europe

Country	Year	RR (%)	RP-SP (%)	PP (%)	Reference
Austria	1999	64*	28*	4*	70
Belgium (Flanders)	1991	85**	–	15**	73
Bulgaria (Svoge and Trojan)	1995	32	50	18	127
Cyprus	1988	95	–	–	132
Czech Republic	2004	55	35	10	90
Finland	1979–1993	78	–	22	59
France	1997	58	27	15	82
Germany (South Lower Saxony)	1986	63	25	12	63
Greece (Evros)	1999	87.5**	–	12.5**	131
Hungary (Csongrad Co.)	1996	69	20	11	95
Ireland (Co. Donegal)	2001	51	38	11	34
Ireland (Co. Wexford)	2001	49	39	12	34
Italy (Ferrara, north)	1993	52	29	19	107
Italy (L'Aquila, central)	1996	75	18	7	109
Italy (Sicily, insular)	1995	51	35	5	113***
Norway (Nord-Trøndelag Co.)	2000	54	29	17	41
Norway (Oslo)	1995	78**	–	22**	42****
Norway (Troms and Finnmark)	1993	79**	–	21**	47
Poland	2004	60	32	8	86
Romania	2004	61	24	15	125
Spain (Mostoles, central)	1998	70.5	10.5	19	101
Spain (Teruel, east)	1996	82	9	9	99
Spain (Valladolid, north)	1997	68	12	20	103
Sweden	1997	84	4	13	53
The Netherlands (Groningen)	1982	24	47	29	71
UK (Leeds Health Auth.)	1996	38	47	15	39
UK (North Cambridgeshire)	1993	55	23	22	36
UK (northern Ireland)	1996	48	40	12	15
Ukraine (Vinnytsya)	2001	52	37	11	138
Yugoslavia (Belgrade)	1996	51	36	13	120

*4% Unknown.
**Initial course.
***9% unknown.
****Only Poser Committee *et al*. definite MS.

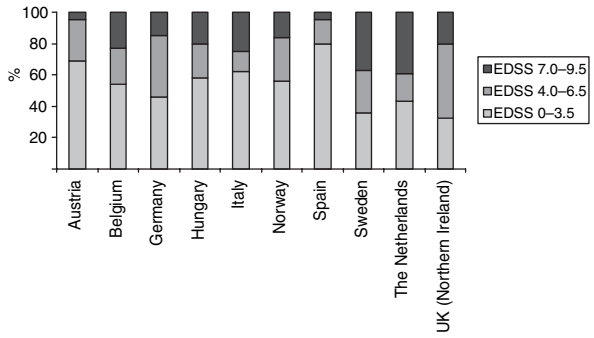

Figure 4 Estimated proportion of MS cases by disease severity (EDSS) based on the prevalence.

logists, availability of new diagnostic procedures, public awareness about MS; (iv) the impact of different diagnostic criteria used and the interobserver variability when comparing incidence and prevalence rates between studies.

A decreasing north-to-south gradient in the distribution of MS prevalence rates across Europe is observed. Although assessment biases might play a role in such distribution, biological factors, i.e. differences in environmental exposures, and/or different genetic susceptibility underlying such differences cannot be ruled out. Mean rates tend to be higher in countries where the degree of disease investigation is also higher, where a better accuracy in survey methodology is used and where assessments have been repeatedly conducted over time, often based on nationwide surveys and on the use of registry systems. In this perspective, the positive correlation between MS prevalence and degree of country socioeconomic level can be confounded by the quality and number of epidemiological assessments conducted. The tendency for a decreased variability in prevalence rates among and within countries over time and an increase of prevalence and incidence rates over time where multiple assessments have been carried out also seems to

Table 6 Proportion (%) of MS patients by disease severity (EDSS) in Europe

Country	Year	EDSS 0–3.5 (%)	EDSS 4.0–6.5 (%)	EDSS 7.0–9.5 (%)	Reference
Austria	1999	69	26	5	70
Belgium (Flanders)	1990s	54	23	23	Carton, personal data
Germany	2004	46*	39*	15*	Lauer, personal data
Hungary (Csongrad Co.)	1999	58	22	20	95
Italy (Ferrara, north)	1993	62	13	25	107
Italy (Sardinia, insular)	1997	65	20	15	115
Italy (Sicily, insular)	1995	61	16	23	113
Norway (Nord-Trøndelag Co.)	2000	56	28	16	41
Spain (Mostoles, central)	1998	80	15	5	101
Spain (Teruel, east)	1996	60	22	18	99
Spain (Valladolid, north)	1997	58	29	13	103
Sweden	1998	36*	27*	37*	56
The Netherlands (Groningen)	1980s	43	18	39	72
UK (northern Ireland)	1996	32.5	47.5	20	15

*Approx.

**Only Poser Committee *et al.* definite MS.

be pointing to a general improvement in case ascertainment and survey methodology in time.

When multiple regression models were used to predict the degree of MS prevalence according to latitude, a latitudinal gradient was found if crude prevalence rates were considered [149]. However, for prevalence and incidence rates, age-adjusted to the European (and world) population a weak correlation was found, which points to the populations age structure as a relevant factor underlying the differences in MS distribution.

Nevertheless, a certain extent of heterogeneity has been found within countries. In fact, significantly higher rates have been reported for Sardinia as opposed to mainland Italy, in Scotland as opposed to the rest of UK, and in Norwegian southern regions, which might point to a role of the interaction between specific yet unknown environmental factors and the population specific genetic susceptibility. Moreover, as incidence is reported to be increasing over time, when quantifying the burden of MS such trend should not be overlooked as it implies greater prevalence rates in the aging population in the future.

A general methodological issue encountered in reviewing the current epidemiology of MS in Europe was categorization. A great deal of variability in categorizing variables (age group, disease course, disease severity) is observed among studies, which thus yield to results that are not or just hardly comparable among each other. Sometimes, crude figures are not reported and any attempt at assigning cases to a standard referral categorization for all countries cannot but lead to 'best guesses'.

The different age group categories used in the reported studies and the frequent lack of crude data make a precise quantification of MS burden by age difficult. This especially applies to the patients in their fifth and sixth decade of life, a crucial age when investigating on the disease socioeconomic burden because of the relevant loss of productivity at this age.

Given the multiple criteria used, the remarkable heterogeneity of the course patterns and, again, the cross-sectional nature of the assessments, assigning cases to a referral classification is even more challenging than for the distribution by age groups. Specific categorization can be especially confusing for progressive relapsing MS and transitional forms. Furthermore, depending on the study-specific purposes, only the proportion of RR-MS and PP-MS is sometimes reported. As disease course categorization is mostly based on the prevalent cases, it is assessed at one point time leading to misclassification biases with respect to future outcomes (e.g. RR-MS converting into SP-MS over time). This might yield to an underestimation of the proportion of progressive courses and highly disabled cases, subsequently underestimating the impact of such cases in the global disease burden and biasing the planning of specific socioeconomic interventions.

In most studies, the distribution of disease degree of severity was expressed by using the proportion of disability according to Kurtzke's EDSS [17] in prevalent cases. Because of the historical or cross-sectional nature of most epidemiological studies scrutinized, precise scores could not be assessed and a variability in categorization has often been observed, for which only best estimates of proportions could be reported.

The disability adjusted life years (DALYs) is one of the most commonly used measures in evaluating the

burden of MS in health economics. DALYs are the sum of the present value of future years of life-time lost because of premature mortality [years of life lost (YLLs)] and of life-time adjusted for the disease severity because of mental and/or physical disability [years of life with disability (YLDs)] [150,151]. The computation of DALYs is therefore based upon epidemiological data, such as prevalence and incidence rates, age at disease onset, life expectancy at disease onset, age at death, degree and duration of disability. The total DALY for MS in Europe is 307 000 years and varies according to mortality strata, being 157 000 in the very-low-child/very-low-adult stratum, 63 000 in the low-child/low-adult and 87 000 in the low-child/high-adult mortality strata, respectively [152]. Despite diseases such as stroke-, dementia- or alcohol-related neurological disorders having the highest burden in DALYs among the brain disorders, one should, however, notice that fewer studies on measuring DALYs have been carried out so far for MS when compared with other neurological disorders. Comorbidity in MS, such as epileptic seizures, mood disturbances, urinary tract infections, or other immuno-mediated conditions frequently reported in association with MS, is often overlooked when measuring DALYs in MS.

The general decreasing trend of mortality rates over time reported for many countries and subsequent increased survival time after onset up to 45 years lead to an increased burden of the disease because of the greater number of YLDs. The mean life expectancy at birth estimated for the year 2002 in Europe is 67.5 years (65 for men and 70 for women), with Russia, Ukraine, Moldova, Belarus, Albania, Turkey, Latvia, Romania, Lithuania and the Republic of Macedonia being in the first quartile (< 63.7 years), whereas Luxembourg, Germany, Norway, France, Spain, Italy, Iceland, Switzerland and Sweden being in the third quartile (> 71.4 years) [152]. The majority of the latter countries are found to have a medium to high prevalence for MS.

Data on MS mortality rates must be taken cautiously, when they are retrospectively based on International Classification of Diseases (ICD) codes as they may reflect a change in the coding system over time. In addition, when MS patients die from other causes or from age-related diseases if they are in the older tier, misclassification deriving from the assessment through death certificates is probably to occur as MS is not mentioned. In fact, a 23% underestimation of MS mortality was reported in Scotland for the time-period 1996–1999 [39]. In the attempt at defining the burden of the disease, the results may be even more distorted because of 'MS' being omitted in death certificates of patients died from complications from an MS-related high disability (e.g. pneumonia, septicemia, urinary trait infections, etc.).

Conclusions

Despite the multiple assessments on MS epidemiology in Europe reported in the international literature in the past three decades, comparing indices among countries is still a hard task and often only leads to approximate estimates. This becomes a major methodological concern when evaluating the burden of MS in Europe and when implementing specific cost-of-illness studies. Methodological variables, represented by the different use of classification systems, inclusion criteria, the lack of standardization and of quotation of confidence intervals and the use of different population sizes, should be adequately addressed and a collaborative multicentric European project encouraged for the assessment of the current burden of MS in Europe.

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