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Apparent changes in the epidemiology and severity of multiple sclerosis

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Abstract | Multiple sclerosis (MS) is an immunological disease that causes acute inflammatory lesions and chronic inflammation in the CNS, leading to tissue damage and disability. As awareness of MS has increased and options for therapy have come into use, a large amount of epidemiological data have been collected, enabling studies of changes in incidence and disease course over time. Overall, these data seem to indicate that the incidence of MS has increased, but the course of the disease has become milder, particularly in the 25 years since the first disease-modifying therapies (DMTs) became available. A clear understanding of these trends and the reasons for them is important for understanding the factors that influence the development and progression of MS, and for clinical management with respect to prevention and treatment decisions. In this Review, we consider the evidence for changes in the epidemiology of MS, focusing on trends in the incidence of the disease over time and trends in the disease severity. In addition, we discuss the factors influencing these trends, including refinement of diagnostic criteria and improvements in health-care systems that have increased diagnosis in people with mild disease, and the introduction and improvement of DMT.

Clinical, scientific and public awareness of multiple sclerosis (MS) has increased substantially over the past five decades. In the mid-1990s, the first disease-modifying therapies (DMTs) for MS became available, contributing to increases in the numbers of specialized MS clinics, health-care professionals who specialize in the management of MS, and research units that focus on MS. The annual number of scientific publications on MS in the PubMed database has increased exponentially from 295 in 1970 to 6,786 in 2020. Increasing awareness of the value of real-world data collected in clinical practice has also led to an increasing number of MS databases and registers that have stimulated MS research in many disciplines. Commercial interests in the treatment of MS have also increased, facilitating knowledge sharing and stimulating interest in MS among clinicians and researchers.

The expansion of research into MS has generated a large amount of epidemiological data, enabling us to track changes in the incidence of the disease and the expected outcomes over time. In general, these data seem to indicate that the incidence of MS has increased[1,2], and that the course of relapsing–remitting MS has become milder over time[3]. These apparent trends could be a true reflection of changes in the natural history of the disease, but a variety of factors could contribute — for example, changing exposure to risk factors, diagnostic criteria and ascertainment probability, improvements in neurological services and improved treatment.

In this Review, we consider the trends in incidence and disease course of MS and discuss the contributing factors with the aim of estimating to what extent these trends are true and independent. We first review trends in the incidence of MS; we focus on incidence rather than prevalence because prevalence reflects a combination of cumulated incidence over many years and survival time, which can change independently. We discuss factors that contribute to an increase in the incidence of MS, which are important to inform policies and approaches for prevention and modulation of risk factors. We then discuss trends in MS disease course, including the influence of DMT and changing diagnostic criteria. Understanding the changes in prognosis is important to make informed treatment decisions.

Trends in incidence

Many studies have been done to investigate the incidence of MS, and comparisons between time periods have produced a variety of evidence for and against an increase in incidence over time. In the discussion of this evidence below, all incidence estimates are the number of incident cases per 100,000 person-years in the population.

Evidence for increasing incidence. Several longitudinal studies conducted over the past several decades have shown an increase in the incidence of MS. These trends have been replicated worldwide, as demonstrated by studies from different global regions.

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Key points

- Most studies of multiple sclerosis (MS) in the same population over time have shown that the incidence has increased.
- At least a part of the increase in incidence can be attributed to improved public awareness, better health care, more MS specialists and MRI scanners, and changing diagnostic criteria.
- In parallel with the increase in incidence, the disease course of MS has also changed; time to disability has lengthened and survival has improved in patients with relapsing–remitting MS.
- Changes in disease course are likely to have resulted from more complete diagnosis of benign MS, disease-modifying therapies and lifestyle-driven changes in the natural history of the disease.
- Understanding the reasons for the changing epidemiology of MS is important and provides insight into factors that influence development and progression of MS and for clinical management.

In Oslo, Norway, the average annual incidence rate for each 5-year period between 1972 and 1996 increased from 3.7 in 1972–1976 to 8.7 in 1992–1996 based on 671 patients[4]. In a region of southern Norway, the incidence was 10.2 for the period 2003–2007 and increased to 13.1 in the period 2008–2012 (REF.[5]), and in a region of northern Norway, the incidence of MS increased from 3.9 to 5.6 during the period 1974–1999 (REF.[6]). In Hordaland County, Norway, the incidence of MS increased from 1.8 in 1953–1957 to 3.0 in 1998–2002 based on 878 patients[7]. Further north in Norway, the incidence of MS increased from 0.9 in 1970–1974 to 10.7 in 2005–2009 based on 497 patients[8].

Similar trends have been found in other countries across Europe and worldwide. In Finland, the incidence of relapsing–remitting MS increased from 4.2 in 1981–1990 to 9.7 in 2001–2010 based on 1,419 patients[9]. In eastern France, the incidence of MS almost doubled from 3.7 in 1990 to 7.0 in 2000 based on 1,658 patients[10]. In northeast Italy, the incidence increased from 0.9 in 1960–1965 to 6.5 in 2011–2015 (REF.[11]). In western Greece, the incidence increased from 2.7 in 1984–1989 to 10.7 in 2002–2006 based on 834 patients[12]. In Newcastle, Australia, the incidence increased from 2.14 in 1971–1981 to 6.70 in 2001–2011, and the proportion of women affected increased[13]. In Alberta, Canada, an already high incidence of 20.9 in 1990 increased to 23.9 in 2004 based on 9,307 patients, which was a statistically insignificant increase[14]. These figures are the highest ever recorded.

Several studies conducted in the Middle East have also indicated strongly increasing incidence[15–22]. In one study conducted in Tehran, Iran, that included 7,501 patients with MS, the age-adjusted and sex-adjusted incidence of MS increased from 0.68 in 1989 to 4.03 in 2007 (REF.[17]). In another study conducted in Isfahan, Iran, that included 3,522 patients with MS, the incidence of MS increased from 3.64 in 2005 to 9.1 in 2009 (REF.[18]), although the investigators acknowledged that this increase could have been at least partly due to more accurate and earlier diagnosis of the disease, better availability of MRI and paraclinical tests, an increase in the number of neurologists and increased awareness.

In general, increases in incidence are greater for relapsing–remitting MS than for primary progressive MS, and the incidence has increased more in women than in men. In the Møre and Romsdal region in the far north of Norway, the age-adjusted incidence of MS increased from 2.2 in 1950–1954 to 14.8 in 2015–2017 (REF.[23]), and this increase occurred almost entirely among women. Similarly, a nationwide incidence survey conducted in Denmark since 1950 has shown an increase in the incidence of MS from 5.38 in 1950–1959 to 9.43 in 2000–2009 based on 19,536 patients, with the increase being particularly pronounced among women and also greatest among patients with an older age at onset[24].

The majority of studies of MS incidence have focused on relapsing–remitting MS and few have been done to investigate the incidence of primary progressive MS. These studies suggest that, in contrast to relapsing–remitting MS, the incidence of primary progressive MS seems to be stable or declining[4,9,25,26].

Evidence against increasing incidence. The apparent increase in incidence of MS has not been observed in all studies. Many studies conducted across the world have indicated that incidence has been stable or has even decreased over prolonged periods.

In a study conducted in Sweden, no increase in incidence was observed between 2001 and 2008 on the basis of 7,400 patients with MS[27]. Likewise, in a study conducted in British Columbia, Canada, that included 4,222 patients with MS, incidence did not increase between 1996 and 2007 (REF.[28]). In Olmsted County, Minneapolis, USA, the epidemiology of MS has been followed for nearly a century, and the incidence seemed to remain stable between 1905 and 2000, although the statistical power was limited because the total number of patients with MS that were included was only 338 (REF.[29]). In a study conducted in Bavaria, Germany, based on insurance claims, 18,105 incident cases of MS were registered between 2006 and 2015, and the incidence was stable throughout this period at a level of 16–18 (REF.[30]). In Saskatoon, Saskatchewan, Canada, the incidence of MS did not increase between 1970 and 2004 (REF.[31]).

In Ontario, Canada, the incidence of MS remained relatively stable over the period 1996–2013 except for a spike in 2010 that was followed by a decline in 2011–2013, particularly among young people and men[32]. The investigators attributed this spike to disproportionate public attention to an unproven and now abandoned theory that MS is caused by chronic cerebrospinal venous insufficiency[33] — the attention was thought to have hastened diagnosis of MS in individuals who already had symptoms.

Some studies have also suggested that the incidence of MS has declined. In Hungary, the direct age-standardized incidence of MS declined significantly from 6.7 in 2010 to 5.1 in 2015 (REF.[34]), although differences in the methods of case ascertainment could explain some of apparent decrease. In Hordaland County, Norway, incidence seems to have stabilized after the 1980s and declined in the period 1993–1997 (REF.[35]). Finally, in Nova Scotia, Canada, the incidence of MS fluctuated but the incidence curves showed that it declined overall from ~13.1 in 1995 to 5.05 in 2010 (REF.[36]).
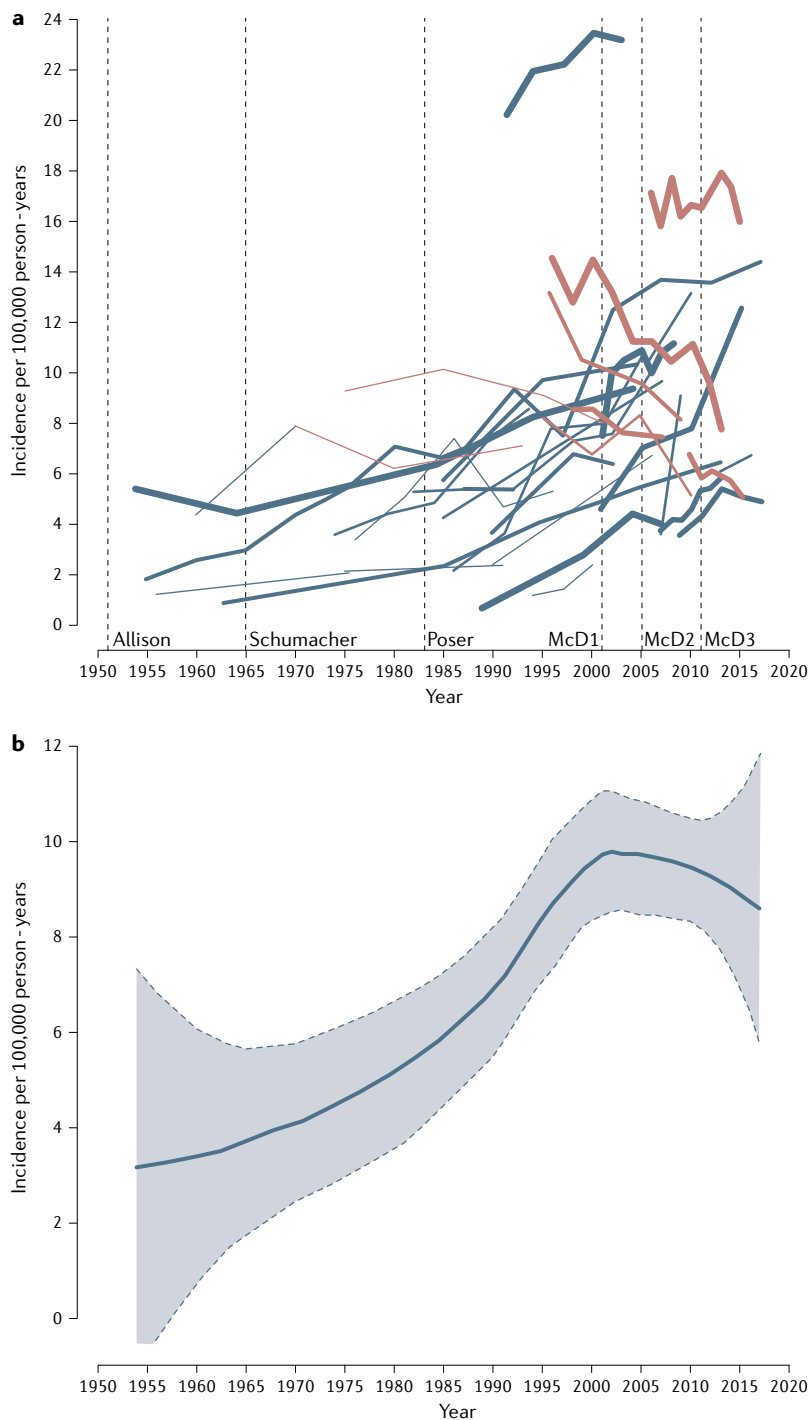
Fig. 1 | **Trends in incidence of MS. a** | Results from studies showing the changing incidence of multiple sclerosis (MS) over time. Each line represents the findings from repeated surveys in the same population. The thickness of the lines is proportional to the square root of the number of patients in the population. Blue lines represent surveys that demonstrated an increase in incidence. Red lines represent surveys that demonstrated stable or declining incidence. The vertical dashed lines indicate the publication years of different diagnostic criteria. A lag is likely between publication of these criteria and their implementation in the individual studies. The extraordinarily high incidence values are from Alberta, Canada[14]. Data from REFS[4–6,8–17,23,24,19,21,27–32,34–36,38,41]. **b** | Locally estimated scatterplot smoothing curve based on the data in part **a**. The curve indicates a marked increase in MS incidence during the second half of the twentieth century, followed by a period of stable incidence after the year 2000, with an apparent but non-significant decrease in incidence. The shaded area indicates 95% confidence intervals. McD1, original McDonald criteria; McD2, McDonald criteria 2005 revision; McD3, McDonald criteria 2010 revision.

Disparate trends in incidence. Comparison of the findings from studies of MS incidence reveals disparate findings, but a dominant upward trend (FIG. 1a). However, combining the data from these studies suggests that incidence peaked around the year 2000 (FIG. 1b), which could indicate that estimates in studies that have been conducted since are close to a hypothetical ceiling defined by the true incidence. We conducted a linear regression analysis of the published incidence data from after the year 2000 on which FIG. 1 is based, weighted by the square root of the number of patients per data point. The incidence tended to decrease by 1.1 per 10 years but without statistical significance ($P = 0.36$).

Different absolute values and trends between studies could result from different methods of case ascertainment. In many studies, case ascertainment was based on administrative data from claims for medical services. This measure can vary between periods of time and is a trade-off between sensitivity and specificity[37]. A systematic review of MS incidence and prevalence published in 2013 illustrates the point that the use of different algorithms to analyse administrative data can lead to different results[28]. In this study, incidence estimates were not age-standardized, and this might be more important because of the dynamic changes in the population of British Columbia by ancestry and age due to immigration. However, analysis in the study of incidence in Nova Scotia, Canada[36], showed that the decline in incidence was true irrespective of which case definition was used from the administrative claims databases. Underestimation of incidence could be caused by time lags between disease onset or diagnosis and entry into databases, resulting in incomplete data for the years immediately before the time of follow-up.

Even when these possible sources of variation in incidence data are taken into account, some disparate findings remain difficult to explain. One example is the opposing trends in neighbouring counties in Norway after 1995. In Hordaland, the incidence of MS decreased[35], whereas in Møre and Romsdal to the north, the incidence increased[23]. In both studies, cases were ascertained from neurological hospital case records based on current diagnostic criteria and follow-up from earlier studies and were not defined from administrative data. One possible reason for the disparity is that incidence estimates were age-standardized in the study from Møre and Romsdal but not in the study from Hordaland.

Despite the shortcomings of incidence data and the disparities between studies, the evidence overall indicates that the incidence of MS truly increased from the mid-1950s to the turn of the century. From this time onwards, incidence seems to have stabilized or even tended to decrease back to levels similar to those around 1995. However, few nationwide studies have been conducted, and such broader studies with larger cohorts and standardized methodology could provide clearer, more reliable results.

Sex ratio. Several studies of MS incidence have indicated that the ratio of women to men among patients with MS has increased over time[5,7,8,10,13,23,24,38–41], though other studies have not produced the same finding[14,28,30,32,34,35].

For example, the steep increase in MS incidence observed in Tehran, Iran, was not accompanied by an increase in the sex ratio[16]. In some studies that showed an overall increase in the ratio of women to men, this ratio also increased with year of birth among patients with relapsing–remitting MS[24,42,43] but not among those with primary progressive MS[42,43]. In one of these studies, the sex ratio decreased significantly with increasing age at onset[24]. The apparent increase in the ratio of women to men raises the question of whether this observation reflects a true increase in the incidence of MS among women or incomplete registration of women with MS in the past that has improved.

Early in the twentieth century, MS was considered to be a disease that predominantly affects men[44], although this way of thinking might have reflected the fact that men were more likely to have health insurance through their work and, therefore, better access to medical services, making it more likely that they would be diagnosed with MS than women[45]. This effect has weakened because many women in most western countries are now economically active, and health care is free in many countries. Almost all surveys conducted after 1960 have shown that the ratio of women to men among people with MS is higher than one[2].

Another explanation for low case ascertainment probability among women in older studies is that the disease is milder in women and was therefore more likely to go undetected[46]. However, we know that the time to conversion from clinically isolated syndrome (CIS) to clinically definite MS is no longer for women than for men, and that women with MS have higher relapse rates than men[46] and reach disability milestones no later than men[47], so this explanation seems unlikely.

With these observations in mind, the increase in MS incidence among women during the first six decades of the twentieth century seems most likely to have been the result of changes in women's social position. After that period, the increase could be attributed to an increase in the ascertainment probability for reasons discussed, in combination with a true rise owing to lifestyle factors, such as smoking[48–50], obesity early in life[51] and, possibly, reproductive history[52].

Effects of changing diagnostic criteria. The sensitivity and specificity of diagnostic criteria for MS are important for the completeness and validity of registers and databases on which incidence studies are based. Therefore, as criteria have become more sensitive in recent decades, hitherto undiagnosed or rejected cases have become diagnosable.

Older diagnostic criteria for MS incorporated only clinical information[53,54], and those of Schumacher et al.[54] even excluded patients with an age at onset of >50 years, probably owing to the risk of misdiagnosis in elderly people before the MRI era. From 1983, oligoclonal bands or an increased IgG index in the CSF and evoked potentials were included[55], and since the initial McDonald criteria were published in 2001, MRI findings have also been included[56]. The McDonald criteria were updated in 2005 to give MRI lesions in the spinal cord more weight[57], and the sensitive 2010 revision of the McDonald criteria[58] enabled diagnosis of MS in patients with CIS and no clinical signs of dissemination in time if MRI revealed lesions of different ages in the same scan. In the latest 2017 revision of the McDonald criteria, the presence of oligoclonal bands in the CSF can replace other signs of dissemination in time in some patients with CIS[59,60], but the increase in sensitivity is at the expense of lower specificity[61,62].

The most important change that has occurred with successive revisions of the diagnostic criteria is the distinction between CIS and MS; the updated criteria have enabled more patients with CIS to be diagnosed with MS. However, CIS is a phase in the development of relapsing–remitting MS between the first and second clinical attacks, so for many patients, the newer criteria have enabled the time of diagnosis to be brought forward. This effect was demonstrated in one study in which patients were assessed with the 2010 and 2017 revisions of the McDonald criteria[63]. In this study, 82% of patients whose disease did not meet the 2010 McDonald criteria for MS at the time of their first demyelinating event could be diagnosed with MS according to the 2017 criteria. After a mean follow-up of 3.8 years, however, 85% also met the 2010 criteria for MS.

Nevertheless, progression from CIS to clinical MS does not always occur. For example, one study has shown that one-third of patients with CIS (classified according to the 2010 McDonald Criteria) had no or minimal disability after 15–20 years, although half eventually developed secondary progressive MS[64]. On this basis, more sensitive criteria could, therefore, not only bring diagnosis forward but also increase the number of people who are diagnosed with the disease. Follow-up studies in people who have experienced a first clinical attack can provide insight into the number of patients who do not go on to have a second attack and would therefore not have been diagnosed on the basis of previous criteria. Survival analysis of the Gothenburg database showed that the lifetime cumulative probability of remaining with CIS was 17.8%[65]. Among 244 patients with a first demyelinating event who were followed up prospectively, 30% did not progress beyond CIS over 10 years[66]. In an international study that included 1,047 patients with CIS, 59.5% had converted to clinically definite MS within a median observation time of 4.3 years[67]. Several risk factors for conversion from CIS to clinically definite MS have been identified, the strongest of which is the presence and number of MRI lesions at the time of the CIS diagnosis[66–68].

These data suggest that a substantial proportion of individuals who were diagnosed with CIS with older diagnostic criteria would fulfil the latest criteria for a diagnosis of MS, thereby increasing the number of people diagnosed with MS. However, predicting this proportion is not straightforward. Among earlier incidence cohorts, 50–70% of patients who presented with CIS had multiple asymptomatic brain lesions and might have fulfilled the latest McDonald criteria. In 20% of these patients, the disease might remain clinically silent for 20 years[64], in which case 12% of all patients with true relapsing–remitting MS might have been lost from the earlier incidence cohorts. However, we do not know

the denominator, which is the pool of all patients with relapsing-onset MS, which the people diagnosed with CIS were part of. The proportion of this pool who are classified as having CIS is difficult to estimate, as it depends on variable factors such as the time between first symptom onset and first admission. If we assume that 30% of an old incidence cohort of patients with relapsing–remitting MS were classified as having CIS, only 3–4% of this cohort would be permanently missing. However, according to the follow-up of the Gothenburg Register[65], the proportion missing could be considerably higher. Thus, the term CIS is an indistinct epidemiological and prognostic notion.

Combined data from studies of MS incidence (FIG. 1a) do not suggest that diagnostic criteria strongly influence estimated trends in incidence. No obvious changes in incidence align with changes in criteria. However, new criteria can take time to be implemented in clinical practice, and the criteria have been formulated primarily for use as inclusion criteria in treatment trials rather than for epidemiology studies. In addition, in many incidence studies, particularly those conducted in Canada, the case definition depends on administrative health and insurance data determined by the number of claims for medical services under a diagnosis of MS, and these claims might not strictly and immediately be in keeping with changes in diagnostic criteria. We conclude that the Poser diagnostic criteria[55] and the original McDonald criteria[56] are likely to have permanently overlooked some patients with true MS with a long-term clinically silent course.

Discussion — trends in incidence. In general, the data demonstrate an increase in the frequency of recorded cases of MS over time until the beginning of the twenty-first century. This increase could partly be a reflection of increased public knowledge about MS and improved access to neurological services, particularly in countries that have developed recently, such as Iran. For example, the number of neurologists has increased in many countries; in the USA, the number of neurologists increased from 2,200 in 1970 to ~15,000 in 2010 (REF.[69]). The number of MRI machines has also increased — in Canada, the number of MRI scanners was 6.0 per million people in 2007 and increased to 9.9 per million by 2014 (REF.[70]), and in UK, the number increased from 4.9 per million people in 2000 to 6.8 per million in 2014 (REF.[71]). The possibility that awareness and availability of treatment and care have influenced apparent MS incidence is also indicated by the lack of increase in incidence of primary progressive MS. Interest in primary progressive MS has been lower because no treatments have been available until recently. As treatments become available for progressive forms of MS, the apparent incidence of these conditions may be expected to also increase.

Nevertheless, the increase in MS incidence could, at least to some extent, be a true reflection of increased exposure to known lifestyle risk factors for MS, such as obesity in childhood[51,72]. In the UK, the proportion of children classified as overweight increased from ~10% in 1974 to ~23% in 2003 and the prevalence of obesity increased from ~1.5% to ~6.3% in the same period[73].

Each one unit increase in BMI is known to be associated with a hazard ratio for MS of ~1.19 (REF.[51]), so in combination, these data indicate that the increases in children who are overweight or obese could have contributed to the increasing incidence of MS.

Cigarette smoking is also a risk factor for MS[74,75]. One case–control study showed that smoking was associated with MS with an odds ratio of 1.4, which is equivalent to a risk ratio of 1.2. On this basis, a change in the proportion of the population who smoke could have a substantial impact on the incidence of MS. However, after a rise in the first half of the twentieth century, cigarette consumption peaked in the USA in 1964 and subsequently halved by 2000 (REF.[76]), so smoking is unlikely to explain the increase in incidence of MS.

Other possible risk factors for MS include passive smoking in childhood[77,78], fewer childbirths in women[79], and infectious mononucleosis and Epstein–Barr virus infection[80,81]. Some evidence suggests that the incidence of these infections has been increasing since 2000, at least in the UK[82], with possible implications for the incidence of MS. Another factor that could have contributed to an increase in incidence is a worldwide tendency for populations to move from rural areas to cities over the past 70 years, with multiple effects on lifestyle. Few studies have addressed the effects of this urbanization. One study conducted in Crete suggested an associated between urbanization and an increased incidence of MS in women[39], an effect that could theoretically be associated with lower sunlight exposure or higher exposure to air pollutants[83]. However, another study found no associations between small-scale clustering of MS and urbanization[84].

In summary, on the basis of the available evidence, we conclude that more complete ascertainment of MS cases played a substantial role in the increase in incidence of MS observed during the second half of the twentieth century, but that changing lifestyles and exposures to risk factors may also have contributed to a true increase in incidence. No evidence enables the relative or absolute importance of these factors to be determined. In addition, even strong risk factors for MS will not have a substantial impact on MS incidence if exposure to these risk factors in the background population is low, and their impact cannot be quantified at all if this background exposure is unknown.

Trends in disease course

Disability progression. Progression of disability in MS is measured with the Expanded Disability Status Scale (EDSS)[85], and a common measure used to standardize assessment of disability is the time from onset to an EDSS score of 6. This score means a patient can still walk but needs walking canes or a walking frame with wheels. To consider trends in MS disease course, we have focused on studies that have used this measure (FIG. 2); in all cited studies, the time of clinical onset was used as the baseline rather than the time of diagnosis.

The earliest data from large natural history cohorts were collected before the advent of DMTs. In a subset of 197 patients seen from onset from among consecutive patients with MS followed from 1972 to 1984 in the

London, Ontario, database, the median time to a score of 6 on the Disability Status Scale (the predecessor of the EDSS, in which a score of 6 is equivalent to an EDSS score of 6) was 9.4 years[86]. In a prospective study using the Gothenburg register, a defined cohort of 255 patients with MS whose disease onset was during 1950–1964 were followed up over 25 years. The median time to an EDSS score of 6.0 (approximated on the basis of the published life-table curve from this study) was 16 years[87]. In a Norwegian study of 220 patients who were followed up until 1995, the median time to an EDSS score of 6 (also approximated from the published life-table curve) was 19 years[88].

More recent studies have spanned the introduction of DMTs and others have been conducted largely since the introduction of DMTs, and these studies indicated changes in the disease course. A study of the Lyon EDMUS database[89] was completed in 1997, so of the 1,844 patients included, only 3.9% had received treatment with interferons, and these individuals were treated only in the last year of observation. In this study, patients were followed up for up to 30 years and the median time from onset to an irreversible EDSS score of 6 was 20.1 years (23.1 years in patients with relapsing–remitting MS and 7.1 years in those with primary progressive MS)[90,91]. The median age at which an EDSS score of 6 was reached was 54.7 years[92]. Similarly, a study conducted in Rennes, France, involved follow-up of a total of 2,054 patients with MS between 1976 and 2004, a period that spanned the introduction of DMTs. The median time from onset to an irreversible EDSS score of 6 was 18.0 years[93]. However, these median times might have been inflated by immortal time bias (BOX 1) because the first onset of MS occurred 29 years before the database was established.

In a study of patients in the British Columbia database, 2,837 patients with MS were followed up until 2003 for 22,723 person-years. The time from onset to a sustained EDSS score of 6 was considerably longer than in the previous studies. The median time was 27.9 years, at a median age of 59.5 years[94]. Comparison of these results with those from the original London, Ontario, database[86] supported the conclusion that disability progression was slower, although with several caveats. The proportion of women was higher in this study than in the previous study, and the proportion of patients with primary progressive MS was lower. In addition, disease onset in some patients included in this study might have been several years before entry into the study, creating an immortal time bias (BOX 1).

In a study conducted in Nova Scotia, Canada, 1,752 patients with definite MS were followed up before and after treatment with DMTs[95], enabling a comparison of the pretreatment and treatment eras. Before 1998, when the DMT programme started, the median time from onset to an EDSS score of 6 was 14.4 years, whereas after July 1998, the median time was 18.6 years. In 2001, a national MS register was established in Sweden[96], which formed the basis of an analysis of MS disease course in 2017 (REF.[97]). This database was a combination of data from established local registers that continued to be updated with new cases from all regions of Sweden using the same online registration system. Analyses of this register showed that the median time from onset to a sustained EDSS score of 6 was 30.4 years at a median age of 63.4 years[97], though as a consequence of the way the register was formed, the proportions of the cohort who were originally prevalence defined and who were followed up from onset are unclear.

Studies completed even more recently, and therefore deeper into the treatment era, further indicate a slowing of MS disease progression over time. In a retrospective study of 197 patients with relapsing–remitting MS in Brazil, published in 2013, the median time to a sustained EDSS score of 6 was 25.8 years[98]. In a study of 7,331 patients from the Swedish MS Registry who were diagnosed with MS between 1995 and 2010, the cumulative risk of reaching a sustained EDSS score of 6 decreased according to the calendar year of diagnosis — the risk decreased at a rate of 7% per year[3]. The authors addressed the issue of left censoring and left truncation in this study (BOX 1).

Comparisons of time periods also indicate slowing of MS disease course over time. In a comparison of patients diagnosed with MS in the period 2006–2010 and those diagnosed in the period 1991–1995, an EDSS score of 6 was reached at a higher age among those diagnosed in the period 2006–2010 (REF.[99]). In another study of patients in the MSBase database, patients who were enrolled into the database with an EDSS score of
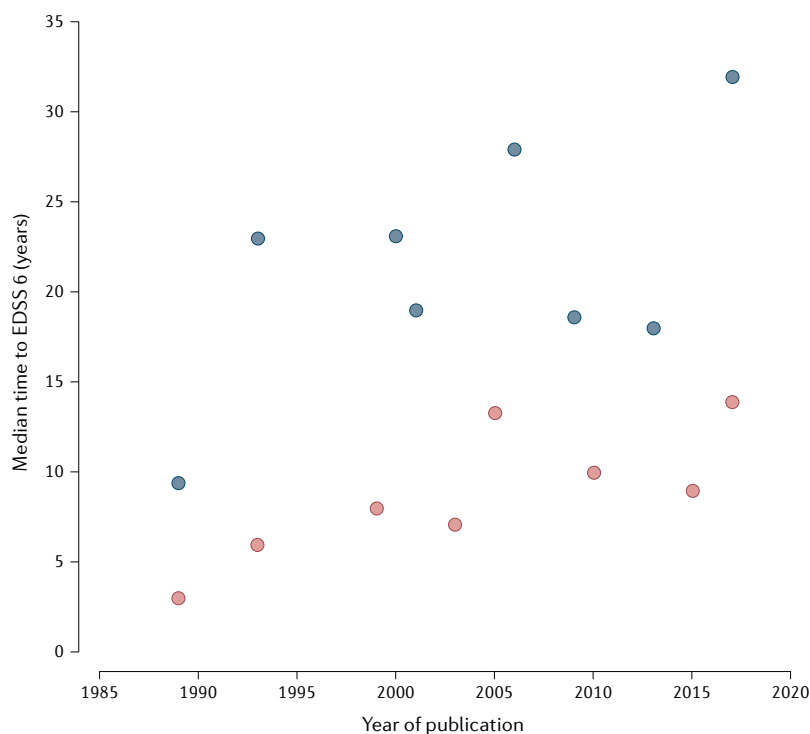

Fig. 2 | **Trend in MS progression rate.** Points indicate the median time to reach an Extended Disability Status Scale (EDSS) score of 6 in relapsing–remitting multiple sclerosis (MS; blue) and primary progressive MS (red) in individual studies. The data indicate a trend towards slower disease progression over time. Data are from studies published in each year, as follows: 1989 (REF.[86]), 1993 (REF.[87]), 1999 (REF.[103]), 2000 (REF.[90]), 2001 (REF.[88]), 2003 (REF.[91]), 2005 (REF.[104]), 2006 (REF.[94]), 2009 (REF.[95]), 2010 (REFS[93,102]), 2013 (REF.[98]) and 2017 (REF.[97]).

Bias-free follow-up of a cohort of patients with MS requires consideration of several sources of bias.

1. All patients should be observed from the time of onset, or at least the time of diagnosis, to prevent immortal time bias[148]. This bias is caused by left truncation or left censoring[149], because patients are selected by having survived from onset or diagnosis to the start of observation. The only permitted retrospective component should be the backwards time from diagnosis to onset. This bias often occurs when studying mixed prevalence and incidence cohorts.

2. Censoring should be non-differential, meaning that cessation of observation is independent of the end points.

3. Selection bias should be avoided. This form of bias arises when data are predominantly collected from tertiary MS clinics. Patients who attend these clinics differ from patients with MS who do not attend such clinics, in that they are generally younger, have a lower burden of comorbidities, have lower rates of hospitalization, and are more likely to receive disease-modifying therapy. Consequently, these patients are not representative of the wider MS populations[150].

6.0–6.5 were a mean of 4.5 years older at the end of the 1996–2010 enrolment period than at the start[100], even when controlling for the immortal time bias. However, an important study conducted in British Columbia, Canada, contradicts the hypothesis that MS disease course is slowing with time. In this study, disease progression was compared over a longer time span using four cohorts with different onset periods: 1976–1979, 1980–1984, 1985–1989 and 1990–1994 (REF.[101]). The proportions of patients who reached an EDSS score of 6 within 15 years from onset in the four cohorts were 28.5%, 26.4%, 27.7% and 22.3%, respectively, and these proportions were not significantly different.

Some studies have also provided insights into the disease course in primary progressive MS. A study conducted in Calgary, Canada[102], included 500 patients with primary progressive MS with onset between 1976 and 2012. The median time to an EDSS score of 6 was 9 years, though the median age at which this score was reached was 55 years, which does not deviate much from what is found in relapsing–remitting MS. In a study published in 2000, the median time from onset to an irreversible Disability Status Scale score of 6 in patients with PPMS was 7.1 years[90]. In a study from Rennes, France, the median time from onset to an EDSS score of 6 in patients with primary progressive MS was 10.0 years[93], and in the London, Ontario, register the median time was 8 years[103]. A study in 352 patients with primary progressive MS from the British Columbia register showed a median time to an EDSS score of 6 of 13.3 years (95% CI 11.0–15.5 years)[104]. In an analysis of the cumulative risk of reaching EDSS score milestones according to calendar year of diagnosis, no trend was seen in primary progressive MS over time[3]. On the basis of these findings, the prognosis in primary progressive MS is worse than that in relapsing–remitting MS when considered from time of disease onset, but the prognosis with respect to the age at which an EDSS score of 6 is reached is much the same[92].

Survival. Patients with MS have a shorter average life expectancy than the general population. Many survival studies have been done to compare mortality among MS patients with that in the background population. The following are examples from the past 15 years in which survival among patients with MS was compared with that of the background population and/or in which trends in survival were investigated. In a study conducted in France and published in 2007, the cumulative survival probability at 15 years after onset was 95.8%, and the standardized mortality ratio (SMR) among patients with MS compared with the general population was 1.3 (REF.[105]). In a study of 442 patients with MS in Oslo, Norway, published in 2009, the SMR was 2.47 compared with the general population[106], and in a study of US Department of Defense administrative claims, all-cause mortality was 2.9-fold higher among patients with MS than among a comparable cohort without MS[107]. In a review of the literature published in 2008, analysis of 33 studies showed that that mortality is only slightly higher among patients with MS than among the general population[108], although a meta-analysis was not possible owing to heterogeneity between studies. In a more recent review and meta-analysis, published in 2016 (REF.[109]), 22 studies fulfilled the inclusion criteria and analysis produced an overall SMR of 2.81 with no trend over time.

To determine whether survival in MS is improving, comparison of survival over time is needed. This type of comparison has been done in four studies in which the SMR has been tracked over time by studying successive onset cohorts from the same population. In one of these studies, three consecutive onset cohorts from the British Columbia MS cohort were analysed[110]. The cohorts included a total of 4,109 individuals with MS and 351 deaths, with onset periods of 1980–1985, 1986–1991 and 1992–1997. The SMRs within 10 years of follow-up in these cohorts were 2.6 (95% CI 2.2–3.1), 2.16 (95% CI 1.75–2.66) and 2.42 (95% CI 2.05–2.86), respectively, indicating stable mortality and no trend. Conversely, a similar study conducted in Haukeland County, Norway, showed that excess mortality in MS cohorts decreased with time[111]. This study included 1,388 patients with 291 observed deaths, with onset periods of 1953–1974, 1975–1996 and 1997–2012. The SMRs for these periods were 3.1 (95% CI 2.6–3.6), 2.6 (95% CI 2.2–3.1) and 0.7 (95% CI 0.3–1.5), respectively. Likewise, in a study conducted over six decades in Denmark that included 18,847 patients and in which 6,102 deaths occurred, the excess all-cause mortality within 15 years of MS onset decreased over five consecutive onset cohorts[112]. For cohorts with onset periods of 1950–1959, 1960–1969, 1970–1979, 1980–1989 and 1990–1999, the SMRs were 4.5 (95% CI 4.1–4.9), 3.3 (95% CI 2.9–3.7), 2.7 (95% CI 2.4–3.0), 2.3 (95% CI 2.1–2.6) and 1.8 (95% CI 1.6–2.0), respectively.

A study conducted in Sweden also demonstrated a substantial improvement in survival in patients with MS over time[113]. This study included 29,617 patients with MS compared with a matched cohort of patients without MS, and 9,563 deaths occurred. The adjusted hazard ratio for death decreased from 6.52 (95% CI 5.79–7.34) in the period 1968–1980 to 2.08 (95% CI 1.95–2.22) in the period 2001–2012. Patients in the 1968–1980 cohort were included on the basis of being hospital inpatients,

whereas the 2001–2012 cohort also included patients from outpatient clinics, and this difference could have exaggerated the change in survival. However, the study conducted in Denmark was based on the nationwide MS register with multiple sources of notification since ~1950. The trends in mortality in the three Scandinavian studies strongly suggest that excess mortality in MS has reduced over many decades, although the reasons for this trend are unclear. Improvements in health care are likely to have contributed substantially.

The influence of benign MS. The term 'benign MS' has been used to describe a disease course in which patients remain minimally disabled (EDSS score ≤3.0) at 10–15 years after onset. This entity is important when considering changes in disease course over time because patients with benign MS are more likely to be diagnosed and registered as having MS as diagnostic criteria and sensitivity improve. Therefore, greater inclusion of people with benign MS in study cohorts could contribute to some extent to the apparent slowing of disease progression over time. An important question to answer in this context is the proportion of patients in whom the disease course remains benign over time. Some evidence suggests this proportion is small — among a cohort of 496 patients who were followed up prospectively for 10 years, just 51 (10.3%) had benign MS (EDSS ≤3.0) and the disease course remained benign for just 35 (7%) after 20 years[114], although the number of deceased or otherwise censored patients was not reported. However, the study of benign MS is problematic for several reasons.

First, the term 'benign' has been criticized because the usual definition is heavily weighted towards low physical disability and does not take into account non-motor symptoms, such as cognitive dysfunction and fatigue[115–117]. In addition, apparently benign MS does often progress eventually. For example, a study published in 2007 showed that only ~52% of patients with apparent benign MS at 10 years after onset were also classified as having benign MS at 20 years after onset; among the remaining 48%, 21% had progressed to an EDSS score of 6, and 23% had developed secondary progressive MS[118]. Similarly, a follow-up study conducted in Wales showed that among patients whose MS was classified as benign in 1985, the disease remained benign in only 19% 20 years later[119].

Another difficulty with the study of benign MS is that findings differ according to the definition used. For example, in one study conducted in Wales and published in 2019, MS remained benign in only 2.3% of the total cohort after 15 years when impaired cognition and effects on employment were taken into account[120]. In a study of patients from the Gothenburg incidence register with MS onset between 1950 and 1964, the definition used for benign MS was evasion of the secondary progressive phase. Over a follow-up period of up to 50 years, the cumulative probability of non-progressive disease was 22% after 40 years and 14% after 50 years[121]. In a nationwide study from Denmark, the economic activity of individuals was used as a measure of benign MS. Linking the Danish MS Registry to registers under

Statistics Denmark showed that the cumulative probability of being economically active or working at 25 years after onset of MS was 20%[122].

This variability suggests that the measures of benign MS are too liberal and need to be reassessed. The use of an EDSS score of ≤3 to define benign MS was analysed in a study published in 2020 based on data from the German MS registry. The findings indicated that an EDSS score of ≤3 alone is insufficient to define benign MS[123], as ~25% of people with MS and an EDSS score of ≤3 were unemployed compared with just 5% in the background population, demonstrating that quality of life is affected even in patients with a low EDSS score. On the basis of these findings, the investigators suggested that the definition of benign MS should be an EDSS score of ≤1 and a retained ability to work after 15 years from onset.

Whether detection of more benign cases of MS explains the apparent reduction in excess mortality associated with the disease is unclear — studies have not been done to address this question. In a thought experiment to address this question, we reanalysed the results from the Danish survival study[112] by comparing the 1960–1969 onset cohort, in which the 15-year SMR was high, with the 1990–1999 onset cohort, in which the SMR was much lower. We enriched the 1960–1969 onset cohort with 2,463 hypothetical patients with undiagnosed benign MS to match the number of patients with benign MS in the 1990–1999 onset cohort. We assumed that mortality among these hypothetical patients would be the same as that of a matched background population in the first 15 years after onset. The original observed 15-year SMR for the 1960–1969 cohort was 3.25, but in our thought experiment, it was 1.90 — very close to the observed 15-year SMR for the 1990–1999 cohort (1.80). With similar hypothetical enrichment of the 1970–1979 cohort, the SMR was 1.89, compared with the original observed SMR of 2.68, again close to the SMR in the 1990–1999 cohort. These hypothetical calculations indicate that the observed reduction in excess mortality over time in this study could be explained numerically by better ascertainment of benign MS in the 1990–1999 cohort. However, other factors are likely to be relevant, particularly the fact that 50% of the 1990–1999 cohort had received DMTs, compared with 0% of the earlier cohorts.

The influence of DMT. A large number of studies have been published on the effects of DMT in MS. To review how DMT has influenced trends in disease course, we viewed all abstracts in the PubMed database on the effects of DMT and selected studies in which patients who received DMT were compared with patients who received no treatment or with patients from pretreatment cohorts in observational studies.

DMTs are primarily targeted against relapses in patients with relapsing–remitting MS, and many have modest or strong effects on this aspect of the disease. However, the relationship between relapses and accumulation of disability is still a matter of controversy[124–128]. Randomized controlled trials of DMTs have largely not been sufficiently powered to detect differences in

worsening of EDSS scores because the worsening among patients who receive the placebo within the typical study duration of 2 years was too small for a statistically significantly difference to be detected with active treatment. Longer study periods are not possible because randomization cannot be maintained longer for ethical and practical reasons. Consequently, post-marketing studies and registers based on real-world treatment of patients are crucial to understanding how DMTs influence the later course of MS. Long-term studies in which early and late initiation of DMTs are compared and different classes of DMTs are compared are informative if the groups are comparable in all other respects. In addition, a true difference between arms provides real-world confirmation that at least one of the regimens is effective.

In many studies of disease course, cohorts from the DMT era are compared with cohorts from before the DMT era, either from databases or from historically published data. As a result, these studies can be confounded not only by known factors that can be adjusted for but also by unknown factors or known factors of unknown value. In one such study conducted in Nova Scotia, Canada, the risk of progression to an EDSS score of 6 after 1998 (when the local DMT programme started) was lower than before this time (HR 0.40, 95% CI 0.31–0.52)[95]. In a similar study, a contemporary cohort from the Swedish MS Registry was compared with a historical cohort from the Gothenburg cohort[129]. A strong effect was observed — the time to transition to the secondary progressive phase was longer in the contemporary cohort, and the investigators concluded that this effect was at least partly due to long-term use of DMT among the contemporary cohort. Similarly, in a comparison of patients diagnosed with MS in the periods 1991–1995 and 2006–2010 — before and after the introduction of DMTs — the risk of progressing to an EDSS score of 6 was lower among cohorts diagnosed in the DMT era than among patients diagnosed in the earlier period[99]. In a study conducted in the UK, EDSS data from 72 sites across the country were analysed[130] with Markow models and multilevel models. The time to EDSS score changes in patients who were treated with interferon-β and glatiramer acetate were compared with that in historical, untreated controls from the British Columbia database[131]. With DMTs, worsening of EDSS score was reduced by 31% in the multilevel model and by 14% with the Markow model.

In other studies, patients who have received DMT have been compared with untreated patients from the same cohorts. In a study conducted in Florence, Italy, 1,504 patients with MS who were treated with interferon-β were compared with 401 untreated patients using propensity score weighting. The untreated patients were people who met the treatment criteria but voluntarily refused treatment for various reasons. DMT reduced the risk of transition to secondary progressive MS (HR 0.36, 95% CI 0.23–0.56) and of reaching an EDSS score of 6 (HR 0.60, 95% CI 0.38–0.95)[132]. By contrast, a study conducted in British Columbia, Canada, in which a cohort of 868 patients who were treated with interferon-β (median follow-up 5.1 years) were compared with a contemporary untreated cohort of 829 patients (median follow-up 4.0 years) and a historical cohort of 959 patients (median follow-up 10.8 years), treatment with interferon-β was not associated with a statistically significant reduction in disease progression. The hazard ratio for reaching an EDSS score of 6 was 1.30 (95% CI 0.92–1.83) when compared with a contemporary untreated control cohort and 0.77 (95% CI 0.58–1.02) when compared with a historical control cohort[101].

Another approach to the study of how DMT affects disease progression is to compare the time to worsening in patients who started DMT early or late after onset. In a study published in 2009, treatment with interferon-β within the first year after onset reduced the likelihood of reaching an EDSS score of 4 compared with later onset of treatment (HR 0.63, 95% CI 0.40–1.01) after propensity score adjustment[133]. Similarly, in a study published in 2018, analysis of a nationwide database of patients who had been treated with DMT showed that starting treatment 2–8 years after MS onset increased the risk of reaching an EDSS score of 6 relative to initiation of treatment within the first 2 years after onset (HR 1.42, 95% CI 1.18–1.70) after adjustment for stabilized inverse probability of treatment weights[134]. In addition, a follow-up study in patients who participated in the original trial of interferon-β_{1b} (REF.[135]) demonstrated that all-cause mortality over 21 years was significantly lower among the patients who were originally assigned to receive interferon-β_{1b} than among patients who originally received placebo (HR 0.532, 95% CI 0.314–0.902)[136].

A long-term benefit of DMT beyond the immediate reduction in relapse rate has been strongly supported by two studies published in the past 2 years. The first of these studies, published in 2020, was an analysis of data from the Italian iMedWeb network[137]. Among 9,567 patients, the risk of reaching different EDSS end points was statistically significantly higher among patients who had not received DMT than among those who had received treatment. Furthermore, among the patients who were treated, the time of treatment had a clear effect on the risk, and this effect was stronger among patients with early adult onset MS than in those with late onset MS. The second study, published in 2021, included 14,717 patients from the MSBase database[138], 1,085 of whom had been followed up for at least 15 years, with periods of treatment and periods without treatment. The risk of disability worsening was lower when receiving treatment than when not receiving treatment (HR 0.81), as was the risk of reaching an EDSS score of 6 (HR 0.33, 95% CI 0.19–0.59). Known confounders, including time-variant covariates, were controlled for by the use of marginal structural models. The advanced design of the study mitigated many of the inherent methodological problems of observational studies, so it provides the strongest evidence to date that DMT has long-term effects on disability accumulation.

Other factors could contribute to the improved long-term outcomes in patients who receive DMT. For example, interferon-β treatment could improve survival independently of its effect on MS, as it could protect

against the development of cancer. However, one study published in 2014 did not provide evidence to support this hypothesis[139]. In addition, individuals who do well with DMT might also have had a relatively mild disease course without treatment, so that the ultimate course is a result of intrinsic disease activity and DMT. Nevertheless, evidence from studies of the long-term outcomes after DMT suggests that treatment contributes to a lower risk of higher disability scores and longer times for these scores to be reached, as well as a lower risk of conversion to secondary progressive MS.

Effects of changing diagnostic criteria. As discussed above, the diagnostic criteria for MS have changed multiple times and their sensitivity has progressively increased. This progression raises the possibility of the 'Will Rogers phenomenon'[140,141], a serious bias in epidemiological research in which prognosis changes only as a result of changes in diagnostic criteria or the sensitivity of diagnostic tests. In MS, many patients with CIS can now be diagnosed with MS, not because of a second attack but only because the diagnostic criteria enable diagnosis on the basis of subclinical MRI pathology suggestive of dissemination in time. Consequently, the population of people with MS includes a higher proportion of people with milder disease because patients who have already experienced a second attack tend to have a worse prognosis.

The effect of changes in diagnostic criteria was demonstrated in a study that quantified the effect of changing from the Poser[55] criteria to the 2001 McDonald criteria[142]. Among patients with CIS, use of the McDonald criteria led to diagnosis of MS in three times as many people as the Poser criteria, representing a substantial effect. However, 80% of patients who fulfilled the McDonald criteria went on to have a second attack, so only the minority who never experienced a second attack or progression would have been lost for registration in the Poser era compared with the McDonald era.

Discussion — trends in disease course. Several factors can independently influence the apparent trend in MS disease course. First, improvement in ascertainment is likely to have enriched MS cohorts with patients with mild disease that would previously have remained undiagnosed and/or would not have triggered referral to MS clinics. Second, DMT is likely to have improved long-term outcomes for many patients, particularly when initiated early after onset. In addition, the natural history of the disease itself could have changed owing to decreased exposure to prognostic factors. For example, smoking also seems to increase the risk of progression to secondary progressive MS[143,144] and cigarette consumption has decreased markedly in the USA[76] and globally[145].

Other lifestyle factors that are normally associated with an increased risk of cardiovascular disease have also been shown to accelerate brain volume loss, and a poor diet has been associated with accrual of T2 lesion volume in MS[146]. Healthier diets and lifestyles could, therefore, contribute to a milder course. Similarly, recommendations for vitamin D supplementation, such as

in Canada[147], could influence the course of MS, although this development might be too recent to be reflected in the published literature. These effects of lifestyle factors on disease course means that patients with MS can be advised to make lifestyle choices that are likely to improve their long-term outcomes.

Conclusions

We conclude that, in general, the incidence of diagnosed and registered MS increased substantially until the past two decades, after which the incidence has stabilized or possibly declined. Probable contributory reasons for the increase in incidence are increased public awareness, an increase in the numbers of neurologists and MRI scanners in combination with general improvements in health services and welfare, and improved diagnosis of so-called benign MS that would previously have gone undetected. The awareness of MS and interest in its management have partly been driven by the advent of DMT. In addition to these factors, increasingly sensitive diagnostic criteria have enabled diagnosis of MS in people who would previously have been diagnosed only with CIS, thereby also increasing the proportion of patients with relatively mild disease. However, this effect might not be as important as it initially seems because the McDonald criteria simply enable earlier diagnosis of MS in patients who would eventually also have met the Poser criteria.

With respect to the disease severity of MS, prognosis seems to have improved in relapsing–remitting MS. The trend could be exaggerated by selection bias, as most data originated from tertiary MS clinics. In addition, many studies are affected by immortal time bias, which can improve the apparent prognosis of the cohort. Nevertheless, possible reasons for the improvements in disease course include the detection of more patients with so-called benign MS, who have a good prognosis, and the introduction and improvement in DMT. Reappraisal of data from a survival study that indicated a decrease in excess mortality over time showed that inclusion of more patients with benign MS in older cohorts reduces the excess mortality in these cohorts to match that in the most recent onset cohort, suggesting that inclusion of more patients with benign MS substantially influences the apparent disease course. The latest evidence strongly indicates that DMT improves long-term outcomes in addition to shorter-term effects on relapses, suggesting that DMT contributes substantially to improvements in disease course and prognosis. However, improved survival can also be attributed to some extent to better health care overall, with multidisciplinary care groups and better treatment of comorbidities.

Acknowledging the apparent changes in the epidemiology and disease course of MS and understanding the reasons for these changes is important for health-care planners, for MS neurologists and for the individual patients. Health-care planners can incorporate this knowledge into estimations of future needs for MS specialists and physiotherapists. Neurologists can take knowledge of these changes into account when assessing patients and making treatment decisions, and should be

particularly aware of patients with mild and/or early disease who need monitoring to predict and prevent future activity and worsening. For the patients, knowledge of these trends demonstrates that treatment is effective and that the disease is not always serious — the disease can be mild and even when it is not, improvements in care and effective treatments are enabling patients to live normal lives for longer.

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Author contributions

Competing interests

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