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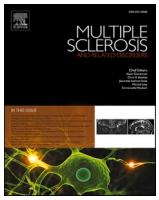

Original article

The age at onset of relapsing-remitting multiple sclerosis has increased over the last five decades

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ABSTRACT

Background: Patients with relapsing-remitting multiple sclerosis (RRMS) most commonly experience their first symptoms between 20 and 40 years of age. The objective of this study was to investigate how the age at which the first symptoms of RRMS occur has changed over the past decades.
Methods: Patients who were followed up in our unit after an initial diagnosis of RRMS using the Poser or McDonald criteria and who experienced their first symptoms between January 1970 and December 2019 were included in the study. The cohort was divided into five groups according to the decade in which the first symptoms appeared. The age at disease onset was compared across decades. Changes in age were also determined after excluding patients with early-onset disease (<18 years of age) and those with late-onset disease (>50 years of age) to avoid bias.
Results: The cohort included 1,622 patients with RRMS, 67.6% of whom were women. Among them, 5.9% and 4% had early-onset and late-onset disease, respectively. The mean age ± standard deviation at onset was 31.11 ± 9.82 years, with no differences between men and women. The mean ages at onset were 23.79 ± 10.19 years between 1970 and 1979, 27.86 ± 9.22 years between 1980 and 1989, 30.07 ± 9.32 years between 1990 and 1999, 32.12 ± 9.47 between 2000 and 2009, and 34.28 ± 9.83 years between 2010 and 2019. The ages at disease onset were progressively higher in the later decades; this trend was statistically significant ($p < 0.001$), with a Pearson linear correlation coefficient R of 0.264 and R^2 of 0.070 ($p < 0.001$). The results were similar when analysing men and women separately. We conducted an analysis of 1,460 patients (mean age at onset: 31.10 ± 7.99 years), after excluding patients with early-onset and late-onset disease. In this specific subgroup, the mean ages at disease onset were 28.38 ± 8.17 years between 1970 and 1979, 29.22 ± 7.51 years between 1980 and 1989, 30.06 ± 8.02 years between 1990 and 1999, 31.46 ± 7.77 years between 2000 and 2009, and 33.37 ± 7.97 years between 2010 and 2019. The trend was also statistically significant ($p < 0.001$), with a Pearson linear correlation coefficient R of 0.193 and R^2 of 0.037 ($p < 0.001$).
Conclusion: Our data showed that the age at RRMS onset has increased over the past decades.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system, and its most common type manifests with a relapsing-and-remitting phenotype (Klineova and Lublin, 2018). Patients with relapsing-remitting MS (RRMS) usually experience their first symptoms between the ages of 20 and 40 years (Oh et al., 2018); however, RRMS may manifest at any age. Patients with early-onset MS (EOMS) are usually defined as those who are under 18 years when they experience their first symptoms, whereas patients with late-onset MS (LOMS) are those who experience their first symptoms when over 50 years of age. Reportedly, of all the patients with MS, 5–10% have EOMS (Alroughani and Boyko, 2018; Yeshokumar et al., 2017) and approximately 5% have LOMS (Naseri et al., 2021).

Epidemiological studies have shown that the incidence rate of MS

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Abbreviations

EBV	Epstein-Barr virus
EOMS	early-onset multiple sclerosis
LOMS	late-onset multiple sclerosis
MRI	magnetic resonance imaging
MS	multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis

has been increasing over the past decades (Dobson and Giovannoni, 2019). A recent study from a Danish cohort showed that the rising incidence rate of MS was mainly attributed to an increase in the number of diagnoses among women and older individuals (Koch-Henriksen et al., 2018). Several studies have found that the female-to-male ratio has been increasing over recent years; this was attributed to environmental and social changes (Boström and Landtblom, 2015; Magyari, 2015). Although not many long-term incidence studies have been conducted in the same population, the few that have been performed have provided preliminary evidence that the age at MS onset has been increasing in recent decades (Koch-Henriksen et al., 2018; Ribbons et al., 2017). This, together with the increasing longevity in the general population as well as longer survival of individuals with MS, may be contributing to the increasing prevalence of older persons with MS (Vaughn et al., 2019).

To verify whether this trend is real requires specific studies aimed at investigating the changes in the age at MS onset over time. Accordingly, the objective of the present study was to analyse the changes in the age at initial symptoms of RRMS over the last five decades, from 1970 to 2019, in a large cohort of patients.

2. Methods

2.1. Study participants

This study included patients who were followed at the MS clinic of Bellvitge University Hospital, which is the reference centre for demyelinating diseases in the *Gerència Territorial Barcelona Metropolitana Sud* region of Catalonia, northeast Spain, an area with more than 1,300,000 inhabitants. Patients diagnosed with MS at our institution according to the Poser et al. (1983) or McDonald (Polman et al., 2011; Thompson et al., 2018) criteria and who initially exhibited the RR phenotype, were eligible for the study. Among them, those who had experienced their first symptoms between January 1970 and December 2019 were included in the study.

Our MS clinic is the only centre for demyelinating disease in our health district. This district had a population of 206,040 on 31 December 2019. We evaluated the hospital-based prevalence of MS in our centre in 2019 to determine if it was representative of the population-based prevalence. For this purpose, we considered all patients treated in our centre during 2019 belonging to our health district and diagnosed with MS according to the aforementioned criteria. We also analysed a subgroup of the cohort consisting of only those living in our health district.

2.2. Study design

We performed a longitudinal observational retrospective study, with the cohort divided into five groups according to the decade of MS onset: 1970–1979, 1980–1989, 1990–1999, 2000–2009, and 2010–2019. The ages of the patients at disease onset were compared across decades. The age at onset of the disease was defined as the age at which the patients experienced their first symptoms of relapse. A relapse was always considered as a new neurological symptom lasting at least 24 h accompanied by neurological signs and in the absence of fever or infection.

We performed the same analyses after excluding patients who experienced their first symptoms before 18 years of age (i.e. those with EOMS) and those who experienced their first symptoms after 50 years of age (i.e. those with LOMS) to avoid bias. We also calculated the interval between the initial symptom onset and first examination at our MS unit and analysed the subgroup of patients with an interval of 1 year or less.

The correlation between the age at onset and the date of onset was also determined for the subgroup of patients living in our health district.

2.3. Data collection

Patients were registered prospectively in the European Database for Multiple Sclerosis (Confavreux et al., 1992), which was first used by our unit in 1995. Only patients whose follow-up commenced before 1995 were registered retrospectively using data collected from clinical records.

2.4. Statistical analyses

Univariate analyses using Pearson's chi-square test and Student's t-test were performed as appropriate. A one-way analysis of variance was used to compare the mean age at onset within each decade. A linear regression model was performed to analyse the relationship between age at onset and date of onset. Statistical analyses were performed using the SPSS statistical software version 25 (IBM Corp., Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

2.5. Protocol approvals

The Clinical Research Ethics Committee of *Hospital Universitari de Bellvitge* approved this study (PR044/22). The requirement for informed consent was waived by the ethics committee. Data were collected in an anonymised fashion.

3. Results

The cohort included 1,622 patients with RRMS who experienced their first MS symptoms between January 1970 and December 2019. The mean age ± standard deviation at onset was 31.11 ± 9.82 years. The mean age at onset was 31.10 ± 9.94 years among men (who comprised 32.6% of the cohort), and 31.12 ± 9.76 years among women (67.4% of the cohort); the difference was not significant ($p = 0.968$).

The mean ages at MS onset during each decade from 1970 to 2019 are shown in Table 1. The age at disease onset increased progressively with each passing decade; this trend was statistically significant ($p < 0.001$) with a Pearson linear correlation coefficient R of 0.264 and R^2 of 0.070 ($p < 0.001$) (Fig. 1). The trends remained significant when analysing the data of men and women separately (Supplementary Fig. 1).

Additionally, of all patients, 5.9% had EOMS and 4% had LOMS. The proportion of patients with LOMS increased in later decades, while the proportion of those with EOMS decreased (Fig. 2).

After excluding patients with EOMS and LOMS, the data of the 1,460 remaining patients were analysed; the ages at RRMS onset in this

Table 1
Age at onset of relapsing-remitting multiple sclerosis during each of the past five decades.

Decade of disease onset	Number of subjects	Age at onset (years)
1970–1979	65	23.79 ± 10.19
1980–1989	218	27.86 ± 9.22
1990–1999	440	30.07 ± 9.32
2000–2009	561	32.12 ± 9.47
2010–2019	338	34.28 ± 9.83
Total	1,622	31.11 ± 9.82

Ages are shown as means ± standard deviations, $p < 0.001$.

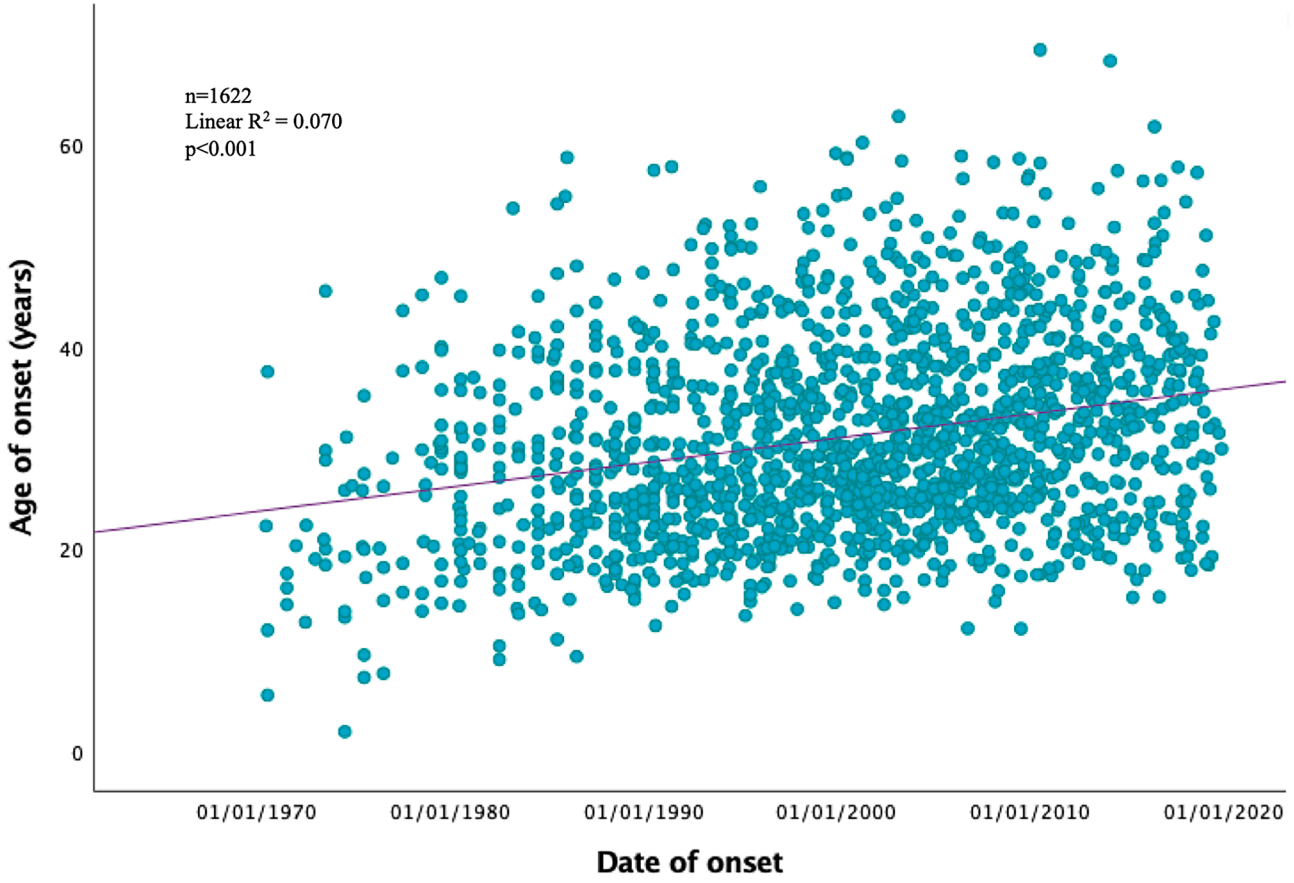

Fig. 1. Age at onset of relapsing-remitting multiple sclerosis in the entire cohort in relation to the date of onset.

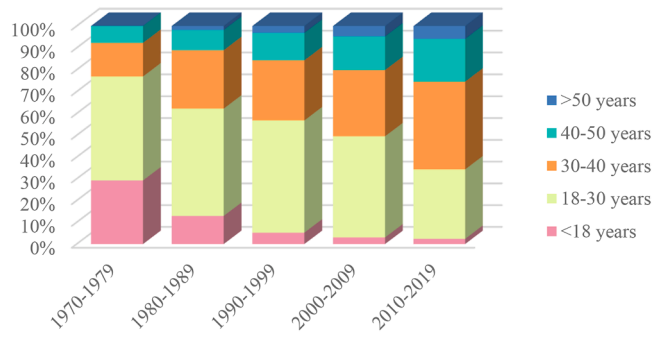

Fig. 2. Proportions of patients in the indicated relapsing-remitting multiple sclerosis onset age groups in the examined decades.

subgroup are shown in Table 2. Again, the ages at disease onset were progressively higher as the decades progressed, and this trend was statistically significant ($p < 0.001$). The Pearson linear correlation coefficient R was 0.193, and R^2 was 0.037 ($p < 0.001$) (Fig. 3). We also analysed the sexes separately in this subgroup (Supplementary Fig. 2).

Table 2
Age at onset of relapsing-remitting multiple sclerosis during each of the past five decades excluding patients with early- and late-onset disease.

Decade of disease onset	Number of subjects	Age at onset (years)
1970–1979	46	28.38 ± 8.17
1980–1989	185	29.22 ± 7.51
1990–1999	403	30.06 ± 8.02
2000–2009	517	31.46 ± 7.77
2010–2019	309	33.37 ± 7.97
Total	1,460	31.10 ± 7.99

Ages are shown as means ± standard deviations, $p < 0.001$.

The mean duration from the development of initial symptoms to the first visit to our centre was 3.44 ± 5.58 years. This interval was shorter among patients whose first MS-related symptoms occurred more recently (Pearson linear correlation coefficient R = 0.549 and R^2 = 0.290 [$p < 0.001$]) and who were older at disease onset (R = 0.193 and $R^2 = 0.037$ [$p < 0.001$]). We found that 840 patients were seen within 1 year from disease onset; their ages at onset as a function of dates of onset mirrored those of the entire cohort (Supplementary Figs. 3 and 4).

The hospital-based prevalence of MS in our MS centre in 2019 was 103.86 per 100,000 inhabitants, as 214 patients diagnosed with MS and living in our health district were seen during 2019. We found 219 patients who lived in our health district with onset between January 1970 and December 2019 and whose initial phenotype was relapsing-remitting. The mean age ± standard deviation at onset was 32.16 ± 10.81 years. The mean age at onset among men (who comprised 32.4% of the cohort) was 32.55 ± 10.57 years, while that among women (67.6% of the cohort) was 31.97 ± 10.95 years; the difference was not significant ($p = 0.713$). The age at disease onset, as in the whole cohort, increased progressively with each passing decade (Supplementary Table 1); this trend was statistically significant ($p < 0.001$), with a Pearson linear correlation coefficient R of 0.299 and an R^2 of 0.089 ($p < 0.001$) (Supplementary Fig. 5).

4. Discussion

In this observational study, we found that the age at MS onset has increased over the last five decades among men and women living in our geographical region. The increase was more marked when including patients with EOMS and LOMS, although the differences in the ages at

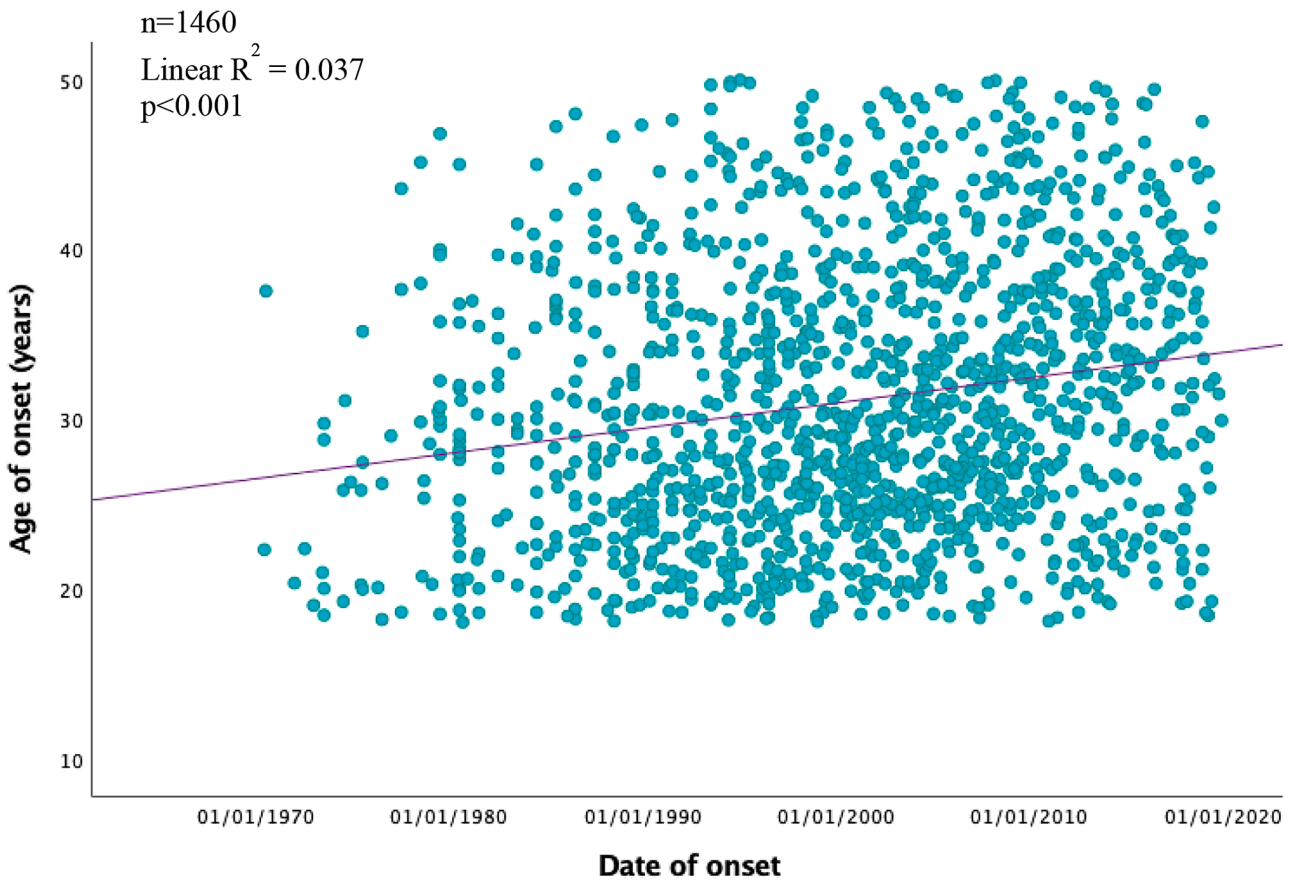

Fig. 3. Age at onset of relapsing-remitting multiple sclerosis in relation to the date of onset in the cohort, excluding patients with early-onset and late-onset disease.

onset remained significant even when excluding these two groups. Our results are consistent with those of several epidemiological studies in which increasingly higher ages at onset were observed, even though analysing the age at onset was not in the objectives of these studies (Koch-Henriksen et al., 2018; Ribbons et al., 2017). Other studies have found that age at onset decreased over time (Boström and Landtblom, 2015; Cocco et al., 2004), but these findings may have been influenced by follow-up bias given that patients were compared by year of birth. We previously showed that, when adjusting our cohort analysis to allow for equal follow-up intervals, an apparent anticipation of age at onset disappeared (Alonso-Magdalena et al., 2010).

Changes in diagnostic criteria may have contributed to the reported increase in the incidence of MS as well as the increase in age at disease onset. The diagnostic methods to confirm the disease have improved in recent decades, overcoming the limited diagnostic accuracy of previous criteria in elderly patients (Gafson et al., 2012; Koch-Henriksen and Magyari, 2021). In a recent study in northwest Spain, the age at disease onset was found not to be significantly higher in 2015 than in 2003 after the same diagnostic criteria were applied to all patients (Costa-Arpín et al., 2021). Concurrently, the increasing use of magnetic resonance imaging (MRI), especially in elderly patients, may explain the reported higher ages at onset to some extent. However, after excluding patients with EOMS and LOMS in our study, our data still showed that the age at onset increased over time; hence, the diagnostic criteria, varying use of MRI, and the higher prevalence of EOMS in the early years might not suffice to explain our results. The prevalence of EOMS in our cohort in the decade of the 1970s was strikingly high. Our hospital was inaugurated 50 years ago, in 1972, and the Department of Neurology in 1974. Consequently, we assumed that the hospital-based prevalence of neurological diseases during those initial years of the 1970s could not be as representative of the general population as it was for the rest of our cohort. We analysed the cohort excluding patients who had their onset in the decade of 1970–1979, and the results were the same as in the whole cohort (data not shown). Another potential reason for the higher age at onset in recent decades could be the ageing of the general population in our area. However, the changes in the population of the different age-at-onset groups over the past decades did not correspond to the observed variations in the general population of Catalonia according to the *Instituto Nacional de Estadística* (https://www.ine.es).

There have been remarkable lifestyle changes in recent decades, and the relationship between these changes and the age at RRMS onset warrants investigation. Increase in outdoor activities over time as well as the adoption of sunbathing could potentially explain the older age at which the first symptoms manifest. A study performed on United States veterans provided evidence of an association between low sun exposure during childhood/early adolescence and an early age at MS onset (McDowell et al., 2011). Another study using the Danish Multiple Sclerosis Treatment Registry also found that the first symptoms occurred earlier among patients who had low exposure to summer sun during adolescence (Laursen et al., 2016). Furthermore, a large study from the MSBase global dataset found an association between higher latitudes and an earlier age at MS onset (Tao et al., 2016), reinforcing the evidence of a relationship between greater exposure to ultraviolet radiation and an older age at disease onset.

In Spain, the consumption of cigarettes has decreased over the past decades (Villalbí et al., 2019), and there have been controversial findings of an association between age at MS onset and smoking. In a Swedish study that found that smoking is a risk factor for MS, the age at disease onset was found to be higher among smokers than among non-smokers (Hedström et al., 2013); the same was found in an Australian multicentre case-control study (Tao et al., 2018). However, a more recent study found an association of smoking with an earlier age at

onset (Briggs et al., 2019). Regardless, the changes in smoking patterns in our area could have influenced the changes in age at MS onset.

As is the case in other Mediterranean countries, authorities in our area are increasing their efforts to tackle the prevalence of childhood and adolescent obesity (Garrido-Miguel et al., 2019). There is an established association between a high body mass index in the early years of life and the risk of MS (Hedström et al., 2014). However, the relationship between body mass index and age at onset is not clear given the conflicting findings reported in the literature (Kavak et al., 2015; Siokas et al., 2021).

Additionally, hormone levels are hypothesised to be associated with the age at MS onset. Women have postponed childbearing in recent decades, and a recent study showed that women with previous pregnancies have higher ages at disease onset, although reverse causality could not be ruled out (Nguyen et al., 2020). A lower age at menarche was associated with an earlier age at MS onset in several studies (Bove et al., 2016; Chitnis et al., 2016); however, given that the mean age at menarche has decreased in recent decades, our findings that the age at MS onset increased over time contradict prior observations regarding menarche. Notably, our data showed an increase in age at MS onset in both men and women.

A plausible explanation for our findings is the evolution of the epidemiology of Epstein-Barr virus (EBV) infection, which is a well-known environmental risk factor for MS. In recent years, primary EBV infections have been occurring at later ages in developed countries, likely owing to improved socioeconomic conditions (Dunmire et al., 2018; Fourcade et al., 2017). In a research among American individuals, the EBV antibody prevalence decreased in those aged 6–19 years from 2003–2004 to 2009–2010, mainly because of the decrease in prevalence among non-Hispanic white participants aged 6-11 years (Balfour et al., 2013). In the studies performed by the group from Harvard, it was evidenced that EBV infection not only precedes by several years the first clinical manifestation of MS but also the elevation of serum neurofilament levels in the preclinical phase of the disease (Bjornevik et al., 2022; Levin et al., 2010). Therefore, the delay in EBV seroconversion could influence the older age of MS onset.

The human leukocyte antigen haplotype *DRB1*15* is frequently associated with a higher risk of MS; we found a similar finding in our previous study (Romero-Pinel et al., 2011). Several studies have also found an association between this allele and an earlier age at MS onset (Bove et al., 2016; Briggs et al., 2019; Ramagopalan et al., 2009); however, such an association was not found in our cohort. Nonetheless, genetic changes would not be expected to occur during the time span of our study, as they are unlikely to have played a role in our results.

A limitation of our study is that follow-up bias may have played a role in our conclusions, as we observed a shorter interval between the manifestation of initial symptoms and first visit to our centre among patients who had a more recent disease onset as well as those who were older. This delay from onset to diagnosis could explain the downshift in the number of patients in the last decade as well as the higher age at onset in recent years. To adjust for this and avoid recall bias, we repeated the analyses, including only patients who were seen at our centre within the 1st year of symptom onset and found that the patterns observed in the entire cohort (i.e. an older age at onset over time) were the same for this subgroup.

Moreover, to mitigate a possible referral bias, we could identify and select a subgroup of patients living in our health district, where we have the only MS centre. The hospital-based prevalence of MS observed in 2019 was representative of the epidemiological population-based studies performed in our area. A study carried out in Catalonia demonstrated that the crude prevalence of MS was 79.9 (95% CI: 66.3–95.6) per 100,000 inhabitants (Otero-Romero et al., 2013), while in another recently published paper from southeast Spain, the non-adjusted prevalence of MS was 111.9 (95% CI: 87.7–142.9) cases per 100.000 inhabitants (Perez-Carmona et al., 2019). Considering these results, we can assume that our hospital-based prevalence was very similar to our expected population-based prevalence. Therefore, with this analysis, we could minimize the referral bias. The results in this subgroup analysis were the same as in the whole cohort.

A strength of our study was that we analysed a large population over a very long period. Moreover, most patients who visited our MS centre were followed from the time of disease onset, which allowed for greater data accuracy.

5. Conclusion

Our findings indicate that the age at RRMS onset has increased over the past decades among both men and women. The same significant trend of increasing age at onset persisted when excluding patients with early-onset and late-onset disease and when analysing only those patients followed from disease onset.

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Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Lucía Romero-Pinel: Conceptualization, Methodology, Data curation, Writing – original draft, Visualization. **Laura Bau:** Methodology, Data curation. **Elisabet Matas:** Resources, Data curation. **Isabel León:** Resources, Data curation. **Albert Muñoz-Vendrell:** Resources, Data curation. **Pablo Arroyo:** Resources, Data curation. **Cristina Masuet-Aumatell:** Methodology, Formal analysis. **Antonio Martínez-Yélamos:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision. **Sergio Martínez-Yélamos:** Conceptualization, Methodology, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

Lucía Romero-Pinel, Laura Bau, Elisabet Matas, Isabel León, Albert Muñoz-Vendrell, Pablo Arroyo, Antonio Martínez-Yélamos, and Sergio Martínez-Yélamos received honoraria for participating on advisory boards and for collaborations as consultants and scientific communications; they also received research support as well as funding for travel and congress-attending expenses from Roche, Biogen Idec, Novartis, TEVA, Merck, Genzyme, Sanofi, Bayer, Almirall, and Celgene. Cristina Masuet-Aumatell received honoraria for participating on advisory boards and for collaborations as a consultant and scientific communications and has received research support as well as funding for travel and congress-related expenses from GlaxoSmithKline, Pfizer, Seqirus, Emergent and Sanofi Pasteur.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104103.

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