Effect of Changes in MS Diagnostic Criteria Over 25 Years on Time to Treatment and Prognosis in Patients With Clinically Isolated Syndrome

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Abstract

Background and Objectives
To explore whether time to diagnosis, time to treatment initiation, and age to reach disability milestones have changed in patients with clinically isolated syndrome (CIS) according to different multiple sclerosis (MS) diagnostic criteria periods.

Methods
This retrospective study was based on data collected prospectively from the Barcelona-CIS cohort between 1994 and 2020. Patients were classified into 5 periods according to different MS criteria, and the times to MS diagnosis and treatment initiation were evaluated. The age at which patients with MS reached an Expanded Disability Status Scale (EDSS) score ≥3.0 was assessed by Cox regression analysis according to diagnostic criteria periods. Last, to remove the classic Will Rogers phenomenon by which the use of different MS criteria over time might result in a changes of prognosis, the 2017 McDonald criteria were applied, and age at EDSS score ≥3.0 was assessed by Cox regression.

Results
In total, 1,174 patients were included. The median time from CIS to MS diagnosis and from CIS to treatment initiation showed a 77% and 82% reduction from the Poser to the McDonald 2017 diagnostic criteria periods, respectively. Patients of a given age diagnosed in more recent diagnostic criteria periods had a lower risk of reaching an EDSS score ≥3.0 than patients of the same age diagnosed in earlier diagnostic periods (reference category Poser period): adjusted hazard ratio (aHR) 0.47 (95% confidence interval 0.24–0.90) for McDonald 2001, aHR 0.25 (0.12–0.54) for McDonald 2005, aHR 0.30 (0.12–0.75) for McDonald 2010, and aHR 0.07 (0.01–0.45) for McDonald 2017. Patients in the early-treatment group displayed an aHR of 0.53 (0.33–0.85) of reaching age at EDSS score ≥3.0 compared to those in the late-treatment group. Changes in prognosis together with early-treatment effect were maintained after the exclusion of possible bias derived from the use of different diagnostic criteria over time (Will Rogers phenomenon).

Discussion
A continuous decrease in the time to MS diagnosis and treatment initiation was observed across diagnostic criteria periods. Overall, patients diagnosed in more recent diagnostic criteria periods displayed a lower risk of reaching disability. The prognostic improvement is maintained after the Will Rogers phenomenon is discarded, and early treatment appears to be the most likely contributing factor.

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Data arising from recent decades suggest that disability accrual in multiple sclerosis (MS) is shifting toward a milder form. Early studies evaluating long-term outcomes reported that after 15 to 20 years of follow-up, half of the patients studied needed to use a cane to walk. These figures contrast with those derived from recent studies such as the MS-Expression, Proteomics, Imaging, Clinical Study (EPIC) and the Barcelona inception cohort, which report rates of 4.7% and 7% of patients with MS requiring a cane at 10 years, respectively. Although no specific cause has been found to independently contribute to this apparent improvement in prognosis, epidemiologic, genetic, and changing environmental factors (i.e., fatty acid or vitamin intake) have been the main ones proposed beyond treatment-related effects.

Overall, the establishment of different MS criteria over the past decades has enabled the diagnosis of patients in earlier stages of the disease, thereby offering these patients more opportunities to benefit from disease-modifying drugs (DMDs) at an earlier time, which could imply better disease control in terms of disability. Although a recent study has shown a decrease in the risk of reaching disability milestones in recent years, others did not find this shifting trajectory over time. Furthermore, information in previous studies was collected at the time of MS diagnosis but not at the time of the first episode, the so-called clinically isolated syndrome (CIS). We hypothesized that changes in MS diagnostic criteria and treatment initiation could be associated with an improvement in long-term disability accrual in a large cohort of patients with CIS.

In the present study, we aimed to explore whether the course of MS has been altered over the past 25 years in a large cohort of patients with CIS. Specifically, we sought to address the following: (1) whether changes have occurred in the proportion of patients diagnosed and the time to diagnosis, (2) whether changes have occurred in the proportion of treated patients and the time to treatment initiation across periods in which the disease started, and (3) whether there has been a change in the risk of disability accrual according to the period in which the patients were diagnosed with the use of different diagnostic criteria.

**Methods**

**Patients**

This is a retrospective study based on patients included in the Barcelona-CIS cohort from the Multiple Sclerosis Center of Catalonia (Cemcat) between January 1994 and March 2020. Patients were <50 years of age at the time of CIS that was suggestive of CNS demyelination not attributable to other diseases and were prospectively enrolled from 1994. The information collected included demographics (sex, date of birth, and date of CIS onset), clinical data (CIS topography and baseline disability collected within 3 months from the CIS according to the Expanded Disability Status Scale [EDSS]), and oligoclonal band analysis of CSF and serum based on agarose gel isoelectric focusing combined with immunoblotting. Patients were evaluated every 3, 6, or 12 months to assess relapses and disability according to EDSS score. Patients were also assessed at the time of the relapse, which was defined as the occurrence of new symptoms or exacerbation of existing symptoms persisting for at least 24 hours in the absence of fever and infection.

The exclusion criteria for the present study were (1) age <18 years at the time of CIS, (2) only 1 clinical visit, (3) lack of demographic information, and (4) a diagnosis other than CIS.

The DMD initiation date and type of DMD were also collected. Treatment status was defined as early or late treatment initiation according to whether treatment was initiated before or after the second demyelinating episode, respectively.

**Radiologic Protocol**

Patients with CIS underwent baseline brain MRI within 5 months of the diagnosis of CIS, at 12 months, and every 5 years thereafter. Baseline MRIs of the whole spinal cord have been systematically performed since 2007 regardless of the CIS topography. MRI scans were evaluated during daily clinical practice. Number and topography of T2 and contrast-enhancing lesions of the type seen in MS at baseline and the number of active lesions (new/enlarged T2 and contrast-enhancing lesions) at follow-up MRIs of the brain and spinal cord were recorded.

Brain MRI was performed with a 1.5T or 3.0T magnet and included the following sequences: transverse proton density and T2-weighted conventional or fast spin echo, transverse and sagittal T2 fluid-attenuated inversion recovery, and unenhanced and contrast-enhanced T1-weighted spin echo. Having a normal brain MRI is not an exclusion criterion because patients are included solely on the basis of their clinical features if they were suggestive of MS (i.e., patients with optic neuritis and normal baseline brain MRI are included). Spinal...
cord sequences included sagittal dual echo proton density/T2-weighted fast spin echo, sagittal short-tau inversion recovery, and, in patients with brain gadolinium T1-weighted sequences or spinal cord lesions, a gadolinium-enhanced sagittal T1-weighted spin echo. Axial T2-weighted sequences covered segments showing abnormalities on the sagittal images or with suspected clinical involvement. All sequences were obtained with a contiguous 3- to 5-mm slice thickness covering the entire brain or spinal cord.

**Diagnostic Criteria Period Definition**

Five different periods were generated according to the different MS diagnostic criteria established over time: 1994 to 2000 (Poser period), 2001 to 2004 (McDonald 2001 period), 2005 to 2009 (McDonald 2005 period), 2010 to 2016 (McDonald 2010 period), and 2017 to March 2020 (McDonald 2017 period).

The diagnostic criteria corresponding to the CIS period were applied to diagnose MS. However, if a given patient was not diagnosed with MS during the same diagnostic criteria period as the CIS diagnosis, this patient was diagnosed later on the basis of the newest available criteria, and the term catch-up patient was applied. For these patients, the year of publication of the criteria was considered the time of diagnosis. This methodology reflects routine diagnosis in daily clinical practice. An example clarifying this concept is presented in Figure 1.

**Statistical Analysis**

For descriptive statistics, quantitative variables are expressed as medians (ranges or interquartile ranges [IQRs]) and categorical variables as percentages. For group comparisons, parametric (t test or $\chi^2$) or nonparametric (Wilcoxon, exact Fisher) tests were performed as appropriate.

Statistical analyses were classified into 3 analyses.

**Analysis 1**

Analysis 1 was done to evaluate changes in the proportion of patients diagnosed and time to diagnosis across periods and changes in the proportion of treated patients and the time to treatment initiation across periods in which the disease started. We included patients with CIS regardless of MS diagnostic confirmation. Patients were classified according to the diagnostic criteria periods in which CIS occurred, called the CIS period. First, descriptive analyses of the baseline features at the time of CIS were performed. Second, the proportion of patients with an MS diagnosis and the time elapsed from the CIS event to the MS diagnosis were compared across CIS periods. Last, the proportion of treated patients and the time elapsed from CIS to treatment initiation were compared across CIS periods.

In analysis 1, the risk of attaining an MS diagnosis or treatment initiation among CIS periods was examined using the Cox proportional hazards model. Two different sensitivity analyses were performed as part of analysis 1 to allow the same window of opportunity to reach outcomes. A first sensitivity analysis excluding catch-up patients was performed to allow the same window of opportunity to diagnose MS across diagnostic criteria periods. A second sensitivity analysis was performed including only patients whose time to treatment...
initiation was shorter than the median follow-up time of patients in McDonald 2017 period. This approach enables the same opportunity of being treated across diagnostic criteria periods.

**Analysis 2**
In this analysis, we evaluated the risk of disability accrual according to the period in which patients were diagnosed using different diagnostic criteria. We included only patients diagnosed with MS and evaluated whether changes in diagnostic criteria over time altered the prognosis of MS. For this, we generated Kaplan-Meier heat maps to assess the proportion of patients reaching age at EDSS score ≥3.0, using colors as a scoring gradient. Because patients were left-censored at the age at CIS, they were classified according to the diagnostic criteria periods in which they were diagnosed with MS, which was called the MS diagnostic criteria period. Cox proportional hazard models were performed to assess whether the MS diagnostic criteria period has an association with age at EDSS score ≥3.0. We used age at EDSS score ≥3.0 (instead of time to EDSS score ≥3.0) as a survival time to better balance the shorter follow-up time of the more recent diagnostic criteria periods and because age is suggested to be a more important determinant of disability than disease duration. Age can also be used as the timescale whereby patients enter the analysis at the age at MS diagnosis (left truncation) and exit at their event/censoring age, loss to follow-up, or last clinical visit.

**Analysis 3**
The aim of this analysis was to remove changes in prognosis that may result from the use of different classifying tools over time. The use of different criteria for classifying patients could imply the classic Will Rogers phenomenon. When a given disease is categorized into several stages with different definitions, the prognosis of each category may change, even though the disease course itself is not modified.

Regardless of the diagnostic criteria period, we applied the 2017 McDonald criteria to a cohort of treated patients after excluding catch-up patients. Thus, the cohort was preselected to include in the analysis those patients with similar features among periods.

First, baseline features of this preselected cohort were described. Second, a comparison of the age at EDSS score ≥3.0 was performed, and the effect of early treatment across periods was analyzed.

All variables with a cutoff value of \( p < 0.2 \) in univariate analyses and variables with a potential high impact on prognosis (sex, age at MS diagnosis, CIS topography, baseline EDSS score, number of visits, number of brain T2 lesions, and early and late treatment) were considered for the multivariate model. The results of univariate analyses are expressed as hazard ratios (HRs) and those of multivariate analyses as adjusted HRs (aHRs) with 95% confidence intervals (CIs).

A value of \( p = 0.05 \) was considered statistically significant. All statistical analyses were performed with STATA-12 software (64 bit, StataCorp, College Station, TX) and R Core team (2013, R Foundation Statistical Computing, Vienna, Austria).

**Standard Protocol Approvals, Registrations, and Patient Consents**
Databases have been developed according to national and international standards on ethics aspects (Declaration of Helsinki and Tokyo), and these data may be used in accordance with the regulations in force regarding the protection of personal data (European Union 2016/679; April 27, 2016, General Data Protection Regulation). The study protocol was evaluated by the ethics committee of Vall d’Hebron Hospital, and all patients signed the corresponding informed consent form.

**Data Availability**
The data that support the findings of this study are available from the corresponding author on reasonable request.

**Results**

**Baseline Features of the Total Cohort at the Time of CIS**
Among the 1,327 patients registered within the CIS-Barcelona cohort, a total of 1,174 patients fulfilled the inclusion criteria for the present study (eFigure 1, doi.org/10.5061/dryad.0gb5km1c). At the time of the CIS, the median (IQR) age was 31.6 (24.2–35.6) years, and 799 (68%) of the patients were female. There was a progressive increase in the median age at CIS over the diagnostic periods (Kruskal-Wallis test, \( p < 0.001 \)). The baseline features of the cohort of patients with CIS are described in Table 1.

**MS Diagnosis and Time to Diagnosis**
After a median (IQR) follow-up of 9.1 (3.9–15.0) years, 735 (62.6%) of the 1,174 patients with CIS had a diagnosis of MS at any time. The proportion with an MS diagnosis increased progressively from 25.2% in Poser to 55.1% in McDonald 2017, according to different diagnostic criteria periods (Table 1).

The median (IQR) time to reach the diagnosis of MS was 11.1 (3.8–25) months and decreased across CIS periods (Figure 2). Overall, from the Poser to McDonald 2017 periods, there was a 77% reduction in the median time from CIS to MS diagnosis. Because recent diagnostic criteria periods had shorter follow-up times, sensitivity analyses excluding catch-up patients were performed, which showed a 62.6% reduction between the Poser and McDonald 2017 periods (eTable 1, doi.org/10.5061/dryad.0gb5km1c)

**Treated Patients and Time to Treatment Initiation**
Overall, 618 (52.6%) patients did not receive any treatment, 264 (22.5%) received early treatment, and 292 (24.9%)

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received late treatment. The median (IQR) time from CIS to initiating treatment was 5.9 (3.4–8.5) months in the early-treatment group and 23.8 (10–44.5) months in the late-treatment group.

At baseline, treated patients displayed a more active clinical and radiologic disease than did untreated patients. Baseline features according to treatment category are presented in eTable 2 (doi.org/10.5061/dryad.0gb5mkm1c).

The median (IQR) time from CIS to treatment initiation showed a sustained decrease across diagnostic criteria periods: 35.8 (15.5–85) months in Poser, 18.2 (6.2–53.6) in McDonald 2001, 7.1 (5.0–11.8) in McDonald 2005, 7.6 (4.3–12.9) in McDonald 2010, and 6.6 (4.7–8.6) in McDonald 2017 (Figure 3). Overall, there was an 82% reduction in the median time to treatment initiation from Poser to McDonald 2017. Moreover, sensitivity analyses performed considering the first 14 months after CIS (the median follow-up time of patients in McDonald 2017 period) indicated an overall reduction of 17% in the median time to treatment initiation (eTable 3, doi.org/10.5061/dryad.0gb5mkm1c).

A sustained increase in the proportion of both diagnosed and treated patients was found across diagnostic criteria periods after the exclusion of catch-up patients (eTables 1 and 3, doi.org/10.5061/dryad.0gb5mkm1c).

**MS Prognosis According to Diagnostic Criteria Periods**

The baseline features of the 735 patients with MS are provided in eTable 4 (doi.org/10.5061/dryad.0gb5mkm1c). The median (IQR) age at MS diagnosis was 32.9 (27.2–40.1) years, with a sustained increase across diagnostic criteria periods from a median (IQR) of 29.3 (25.6–34.6) years in Poser to 36.4 (29.2–44.4) years in McDonald 2017. However, the female/male ratio remained constant over the periods.

Among patients with MS, we found a constant increase in age at EDSS score ≥3.0 throughout the diagnostic criteria periods.
Because the progressive increase in age at CIS observed in the cohort could contribute to final disability according to the age-based analysis, we performed a sensitivity disease duration analysis evaluating time to reach an EDSS score of 3.0 from the CIS event (eFigure 3). A final model including only treated patients analyzing the impact of the different MS diagnostic criteria periods on prognosis for age at EDSS score ≥3.0 was performed. The adjusted multivariate analyses (Table 2) showed that patients diagnosed in more recent diagnostic criteria periods were at a lower risk of reaching EDSS score ≥3.0 at different ages (Poser period as the reference category): aHR 0.47 (95% CI 0.24–0.90) for McDonald 2001, aHR 0.25 (95% CI 0.12–0.54) for McDonald 2005, aHR 0.30 (95% CI 0.12–0.75) for McDonald 2010, and aHR 0.07 (95% CI 0.01–0.45) for McDonald 2017. Baseline EDSS score was also an independent predictor of age at EDSS score ≥3.0 (aHR 2.46 [95% CI 1.91–3.16]). Men were at higher risk of reaching an EDSS score ≥3.0 at an early age (aHR 1.62 [95% CI 1.07–2.47]), as were patients with polyregional location (aHR 1.99 [95% CI 1.05–3.76]) CIS. Last, early treatment was independently related to a lower risk of reaching an EDSS score ≥3.0 compared to late treatment (HR 0.53 [95% CI 0.33–0.85]).

The effect of diagnostic criteria periods on prognosis was maintained after the Will Rogers phenomenon was discarded.

In evaluations of the effect of different diagnostic criteria periods on prognosis with the same criteria (McDonald 2017), a lower risk of reaching age at EDSS score ≥3.0 was globally maintained in recent periods. In Figure 4, Kaplan-Meier curves and multivariate Cox regression analyses show the effect of different diagnostic criteria periods on prognosis by application of the McDonald 2017 criteria. Once the Will Rogers phenomenon was overcome (the possibility that MS prognosis might change due to the application of different MS criteria over time), early-treated patients were at lower risk of reaching age at EDSS score ≥3.0 than late-treated patients. Baseline features of the preselected cohort are depicted in eTable 5 (doi.org/10.5061/dryad.0gb5km1c).
Discussion

In the present study evaluating the association of different diagnostic and treatment periods on disease course in a largely deeply phenotyped longitudinal cohort of patients with CIS, the following important findings were identified: (1) a higher proportion of patients diagnosed with MS and treated was found in more recent diagnostic criteria periods; (2) a sustained decrease in the time from CIS to MS diagnosis and to treatment initiation was observed throughout diagnostic criteria periods; (3) patients diagnosed in more recent diagnostic criteria periods displayed a lower risk of reaching disability milestones; (4) the improvement seen in prognosis is maintained after the Will Rogers phenomenon is ruled out; (5) early initiation of DMD appears to decrease long-term accrual disability; and (6) a continuous increase in the age at CIS and MS diagnosis was observed across periods.

One of the main objectives of refining MS criteria over time is to provide clinicians with sensitive tools to diagnose patients at early stages of the disease, whereby patients would be diagnosed with milder symptoms and treated faster to eventually prevent long-term disability. The present CIS cohort reflects an achievement of such a purpose with a decrease in the time of both outcomes: time to diagnosis and time to treatment initiation. MRI is known to be a major contribution in the McDonald criteria,\textsuperscript{10,12,13} and its integration within the diagnostic scheme likely reflects the dramatic decrease in the time to diagnose MS between clinically based and more MRI-based criteria. Accordingly, we found that patients initiated treatment earlier across diagnostic criteria periods, and this finding was even maintained in the sensitivity analysis when the follow-up of patients in every period was limited by the median follow-up of patients included in the McDonald 2017 period. We also consider that these changing patterns can be partially explained by more relaxed criteria adopted by the Catalan public health insurance for the approval of MS-DMD and the availability of different drugs in recent periods.

Here, we clearly found an impact of the MS diagnostic criteria developed over time on prognosis: patients diagnosed under the scope of the more recent MS criteria displayed a better...
prognosis. These observations are in line with a recent retrospective study showing a robust trend toward a lower risk of disability with increased calendar year of diagnosis, regardless of the time to treatment initiation. Other studies have attributed changes in treatment patterns to a positive effect on disability in recent years, although they did not directly adjust by treatment in statistical analyses. Because the decrease in the time to MS diagnosis across diagnostic criteria periods partially explained an increase in DMD use and an earlier treatment initiation, we accounted for time from CIS to treatment initiation to mitigate any possible confounding effect. Indeed, we found that both the strength of the association and the significance between the MS diagnostic criteria periods and disability were not substantially modified when adjusted by treatment. In addition, we found that early treatment initiation was related to a decrease in the risk of further disability accrual; this finding stresses the importance of initiating treatment in the inflammatory phase of the disease.

An important concept that may influence the impact of different diagnostic periods on prognosis is the Will Rogers phenomenon. This classic bias shows that changes in the criteria used to establish a specific disease diagnosis might result in an improvement of disease prognosis. In the MS field, an earlier MS diagnosis based on the application of more accurate tools (i.e., brain MRI) could change prognosis compared with a later MS diagnosis based only on clinical grounds. Therefore, because the Will Rogers phenomenon may skew the effect attributed to the diagnostic criteria periods per se, we evaluated the risk of disability after applying McDonald 2017 in a preselected cohort with similar clinical activity and follow-up (after excluding catch-up patients). By using this approach, we found that patients diagnosed in more recent periods have a lower risk of reaching age at EDSS score ≥3.0, regardless of the diagnostic criteria period applied. In addition, the effect of early treatment on long-term accrual disability remained significant. However, we could not exclude that some hidden factors may also contribute to this

Table 2 Cox Regression Analysis Assessing Age at EDSS Score of 3.0

| Baseline variables | Univariate | Multivariate |
|--------------------|------------|--------------|
|                    | HR (95% CI) | p Value      | aHR (95% CI) | p Value |
| Diagnostic criteria periods |          |              |          |         |
| 1994–2000          | Ref        | Ref          | Ref        | Ref     |
| 2001–2004          | 0.58 (0.40–0.85) | 0.005       | 0.47 (0.24–0.90) | 0.023 |
| 2005–2009          | 0.42 (0.27–0.65) | <0.001      | 0.25 (0.12–0.54) | <0.001 |
| 2010–2016          | 0.35 (0.22–0.56) | <0.001      | 0.30 (0.12–0.75) | 0.010 |
| 2017–2020          | 0.16 (0.1–0.45) | <0.001      | 0.07 (0.01–0.45) | 0.005 |
| Age at diagnosis   | 1.01 (0.97–1.04) | 0.685       | 1.01 (0.96–1.06) | 0.716 |
| Male               | 1.52 (1.14–2.04) | 0.005       | 1.62 (1.07–2.47) | 0.024 |
| Topography at onset |           |              |          |         |
| Optic neuritis     |            |              |          |         |
| Spinal cord        | 1.47 (1.02–2.13) | 0.041       | 1.42 (0.79–2.53) | 0.241 |
| Brainstem          | 1.24 (0.84–1.84) | 0.283       | 1.08 (0.59–1.95) | 0.812 |
| Polyregional       | 1.66 (0.01–2.14) | 0.044       | 1.99 (1.05–3.76) | 0.036 |
| Baseline EDSS score| 2.16 (1.87–2.49) | <0.001      | 2.46 (1.91–3.16) | <0.001 |
| No. of visits      | 1.02 (1.02–1.03) | <0.001      | 1.01 (0.99–1.02) | 0.128 |
| Oligoclonal bands  | 1.32 (0.89–1.98) | 0.170       | 0.76 (0.42–1.39) | 0.368 |
| Baseline brain T2 lesions ≥9 | 1.94 (1.39–2.71) | <0.001      | 1.42 (0.87–2.32) | 0.160 |
| Patients with baseline CEL | 1.38 (0.99–1.92) | 0.058       | 0.98 (0.63–1.51) | 0.923 |
| MS-DMD             |            |              |          | 0.008  |
| Late treatment     | Ref        | Ref          | Ref        | Ref     |
| Early treatment    | 0.55 (0.39–0.79) | <0.001      | 0.53 (0.33–0.85) |         |

Abbreviations = aHR = adjusted hazard ratio; CI = confidence interval; CEL = contrast-enhancing lesion; EDSS = Expanded Disability Status Scale; HR = hazard ratio; MS-DMD, multiple sclerosis disease-modifying drugs.
better prognosis such as a widespread accessibility to more recent diagnostic tools (i.e., molecular biomarkers or genetic analysis), new health behaviors (diet, smoking exposition), or other environmental factors (vitamin D levels, smoking, other).

Age at MS diagnosis exhibited a progressive shift by increasing from the earliest to the most recent periods, a trend that has already been described for other MS cohorts. A consistent increase in the female/male ratio over the last decades driven mainly by an older age at onset in women has also been proposed. In our study, despite a more significant increase in age at CIS and MS diagnosis across diagnostic criteria periods in women (data not shown), the female/male ratio remained constant and thus alone did not explain this pattern. Last, and consistent with other cohorts, we observed a delay in age at disability milestones over time. Indeed, a given patient 40 years of age and diagnosed in the Poser period presented 77% higher chances of reaching an EDSS score ≥3.0 compared to a patient diagnosed in the McDonald 2017 period.

Some limitations must be addressed. First, we cannot exclude whether competing or combination effects of ascertainment or the preferential enrollment of more affected cases during the first year of database inception affected our results. Second, the increase in age at CIS or MS diagnosis in more recent diagnostic criteria periods could be considered a potential bias when evaluating disability and using age instead of time on study as the timescale. However, after performing a disease-duration sensitivity analysis, we obtained a similar trend on prognosis, thus supporting the robustness of the methodologic approach. The increase in the age at CIS over time may lead to an older age to reach disability in recent diagnostic criteria periods, thus implying a better outcome in patients recently diagnosed. However, an adjustment by age at CIS (data not shown) did not modify the effect of periods. Third, type of treatment in each diagnostic criteria period is lacking, and time
on treatment is missing when performing the analysis, which could play an important role in changes in MS prognosis. Last, we highlight that results derived from the present study are not applicable to pediatric patients or patients >50 years of age.

A continuous decrease in the time to MS diagnosis and treatment initiation was observed across diagnostic criteria periods. Overall, patients diagnosed in more recent diagnostic criteria periods displayed a lower risk of reaching disability. It is important to note that the prognostic improvement is maintained after the Will Rogers phenomenon is discarded, and early treatment appears to be the most likely contributing factor.

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**Appendix Authors**

| Name                  | Location                                  | Contribution                                                                 |
|-----------------------|-------------------------------------------|------------------------------------------------------------------------------|
| Mar Tintore, MD, PhD  | Department of Neurology/Neuroimmunology, Hospital Universitari Vall d’Hebron, Barcelona, Spain | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data |
| Alvaro Cobo-Calvo, MD, PhD | Department of Neurology/Neuroimmunology, Hospital Universitari Vall d’Hebron, Barcelona, Spain | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
Appendix (continued)

| Name                      | Location                                                                 | Contribution                                                                 |
|---------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Pere Carbonell            | Department of Neurology/Neuroimmunology, Hospital Universitari Vall d’Hebron, Barcelona, Spain | Analysis or interpretation of data                                           |
| Georgina Arrambide, MD, PhD | Department of Neurology/Neuroimmunology, Hospital Universitari Vall d’Hebron, Barcelona, Spain | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data |
| Susana Otero-Romero, MD, PhD | Department of Neurology/Neuroimmunology, Hospital Universitari Vall d’Hebron, Barcelona, Spain | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data |
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Appendix (continued)

| Name                      | Location                                                                 | Contribution                                                                 |
|---------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Annalaura Salerno, MD     | Department of Radiology (IDI), Hospital Universitari Vall d’Hebron, Barcelona, Spain | Major role in the acquisition of data                                         |
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| Xavier Montalban, MD, PhD | Department of Neurology/Neuroimmunology, Hospital Universitari Vall d’Hebron, Barcelona, Spain | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data |

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