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Factors associated with time from first-symptoms to diagnosis and treatment initiation of Multiple Sclerosis in Switzerland

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Abstract

Background: Recent studies emphasise the importance of timely diagnosis and early initiation of disease-modifying treatment in the long-term prognosis of multiple sclerosis.

Objectives: The objective of this study was to investigate factors associated with extended time to diagnosis and time to disease-modifying treatment initiation in the Swiss Multiple Sclerosis Registry.

Methods: We used retrospective data (diagnoses 1996–2017) of the survey-based Swiss Multiple Sclerosis Registry and fitted logistic regression models (extended time to diagnosis $\geq$2 years from first symptoms, extended time to disease-modifying treatment initiation $\geq$1 year from diagnosis) with demographic and a priori defined variables.

Results: Our study, based on 996 persons with multiple sclerosis, suggests that 40% had an extended time to diagnosis, and extended time to disease-modifying treatment initiation was seen in 23%. Factors associated with extended time to diagnosis were primary progressive multiple sclerosis (odds ratio (OR) 5.09 (3.12–8.49)), diagnosis setting outside of hospital (neurologist (private practice) OR 1.54 (1.16–2.05)) and more uncommon first symptoms (per additional symptom OR 1.17 (1.06–1.30)). Older age at onset (per additional 5 years OR 0.84 (0.78–0.90)) and gait problems (OR 0.65 (0.47–0.89)) or paresthesia (OR 0.72 (0.54–0.95)) as first symptoms were associated with shorter time to diagnosis. Extended time to disease-modifying treatment initiation was associated with older age at diagnosis (per additional 5 years OR 1.18 (1.09–1.29)). In more recent years, time to diagnosis and time to disease-modifying treatment initiation tended to be shorter.

Conclusions: Even in recent periods, substantial and partially systematic variation regarding time to diagnosis and time to disease-modifying treatment initiation remains. With the emerging paradigm of early treatment, the residual variation should be monitored carefully.

Keywords: Registries, logistic models, disease-modifying treatment, retrospective studies, age of onset, time to diagnosis

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Introduction

The management of multiple sclerosis (MS) is evolving with revised diagnostic criteria and new treatments based on different targeting strategies approved in recent years or in the pipeline, mainly for relapsing–remitting multiple sclerosis (RRMS).[1–5] In addition, first treatments that show clinical benefits in progressive disease stages (primary-progressive multiple sclerosis (PPMS) and secondary-progressive multiple sclerosis (SPMS)) are emerging.[2,4,5] However, the risk–benefit assessment of treatments as well as the overall therapeutic decisions

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for the Swiss Multiple Sclerosis Registry (SMSR)

are gaining in complexity.[6,7] The way the disease is diagnosed and managed is frequently adapted to the most recent evidence to provide optimal treatment and care.[1]

An expert panel recently identified a timely diagnosis and treatment initiation as the most influential factors for disease control and an increased likelihood of a milder disease course.[8] The rationale behind this approach is to limit inflammatory and possibly degenerative damage to the brain tissue. Indeed, evidence suggests that for RRMS this early treatment approach seems to reduce disease progression and the conversion rate to SPMS.[9–11]

Recent studies found that time to diagnosis in MS was reduced over time, but may still be substantial.[12,13] In part, the variation in time to diagnosis may be systematic, as exemplified by a Canadian study that identified younger age at onset and PPMS as factors associated with referral delays.[14] But overall, the relevance of other factors such as first symptoms and the diagnostic setting remains elusive.

The aim of this study was to investigate driving factors associated with extended intervals between first symptoms and definite MS diagnosis as well as factors associated with extended intervals between diagnosis and disease-modifying treatment (DMT) initiation. We therefore intended to identify factors of relevance regarding early diagnosis and management of MS and potential bottlenecks in the healthcare system that could be addressed in the future.

Methods

Study population

For the present study, we analysed data of 1059 participants of the Swiss Multiple Sclerosis Registry (SMSR) who were diagnosed with MS after 1995 (introduction of the first DMT in August 1995 in Switzerland, (interferon beta-1b (Betaferon))) and having clinically definite MS (Figure 1).[15,16]

Study design

We used data of the SMSR, which is a prospective, observational, patient-centred, ongoing study including adult persons with MS (PwMS) living in Switzerland. This innovative study obtains data directly from PwMS by online and paper questionnaires but includes clinical data collection with the treating physicians for validation purposes. Between the launch of the SMSR in June 2016 and 1 November 2017, the SMSR has collected 1365 initial questionnaires. Participants are asked to submit a diagnosis confirmation signed by their treating physician to ascertain the disease status. This diagnosis confirmation is a requirement for persons to enter the regular follow-up surveys. The registry is a representative sample of the adult Swiss MS population, with a coverage of at least 12%. The study was approved by the ethics committee of the canton of Zurich (PB-2016-00894) and written informed consent was obtained from all SMSR participants.[17,18]

Outcome measures

We looked at two different outcomes. The first outcome was the time between the first symptoms and the definitive diagnosis of MS (time to diagnosis). This outcome was available for 996 PwMS of whom 990 had no missing values in the covariates and were therefore included in the analysis (Figure 1). For the purpose of interpretability, the interval was dichotomised into less than 2 and 2 or more years, with the latter henceforth being referred to as extended time to diagnosis. The cut-off of 2 years was determined a priori based on the expertise of two neurologists and not according to the available data.

The second outcome concerned the time between diagnosis and first DMT (time to DMT initiation). This outcome was only defined for PwMS with a relapsing-onset disease and a diagnosis before the year 2017 (Figure 1), with a final sample size of 872. In this analysis, time to DMT initiation was also dichotomised for better interpretability, using 1 year as a cut-off (i.e. time <1 or ≥ 1 year) according to the advice of two neurologists.

Identification of factors potentially associated with time to diagnosis and time to treatment

We used a fixed and a variable set of factors, both of which were determined a priori. The fixed set included in all models was identified by literature search as either being associated with time to diagnosis and time to DMT initiation or being demographic variables commonly used.

The following factors were included in the fixed set: disease course (relapsing-onset MS (reference level), PPMS), age at onset, year of diagnosis (5-year periods from 1996 to 2017 (1996–2000 is reference level)) and sex (female (reference level), male).[14] Furthermore, we identified a pool of potential factors, which were included in the models on the basis of statistical criteria (variable set). For the time to

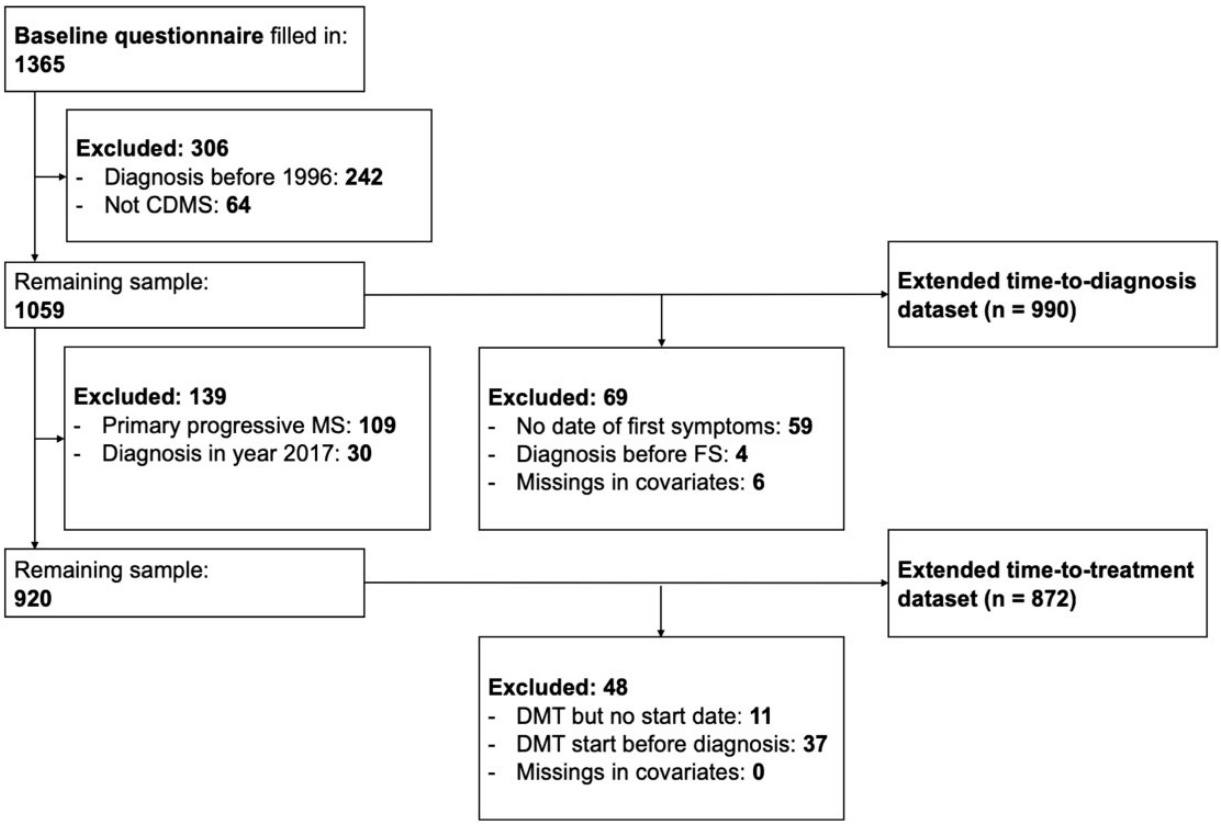

Figure 1. Flow chart showing study population. The first set concerns the time between the first symptoms and diagnosis (1365 to 990) (column 2 in Table 1). The second set is the time between diagnosis and disease-modifying treatment start (1059 to 872) (column 3 in Table 1). CDMS: clinically definite multiple sclerosis.

diagnosis outcome, the variable set consisted of the following self-reported MS symptoms occurring at the first manifestation of the disease (based on a standardised set as used, for example, by the German MS Registry and evaluated by experts):[19] visual disturbances; speech, swallowing, gait, balance, bladder, bowel and memory problems; weakness; paralysis; fatigue; paresthesia; dizziness; pain; spasms; tics; tremor; epilepsy; sexual dysfunction or depression (absence is reference level). The number of first symptoms, the number of common (based on occurrence frequencies in the SMSR ($\geq$20%) (paraesthesia, visual disturbances, fatigue, gait problems, weakness, balance problems, paralysis and dizziness/vertigo) (Supplementary Table 1) and uncommon first symptoms (the remainder), the typology of the current home residence (urban (reference level), urban to rural, rural), if the home residence is located in a mountainous area (not mountainous (reference level), mountainous), defined as living in one of the 'Gebirgskantone' (Uri, Obwalden, Nidwalden, Glarus, Graubünden, Tessin and Wallis), in the canton of Jura or the Bernese 'Oberland', language area of Switzerland (German (reference level), French, Italian), having Swiss citizenship (yes (reference level), no) and the setting of the diagnosis (neurologist in hospital (reference level), neurologist in private practice, general practitioner) were the other variables. The factors for the time to DMT initiation were identical except for disease course, due to the existing prescription guidelines and first symptoms, in which a mix of the effect of first symptoms and symptoms at diagnosis can currently not be disentangled.

Statistical analysis

We fitted logistic regression models for both outcomes using the variables of the fixed set and extended the model by including factors from the variable set on the basis of the Akaike information criterion (AIC) in a bottom-up variable selection

approach.[20] This approach was chosen to incorporate the prior evidence as well as to consider the large number of potential covariates while preventing overfitting. We coded an algorithm that added – one at a time – the potential variables and fitted each of the corresponding models. Then the AICs of the models were compared and the one with the lowest value was chosen. If this AIC was at least 2 units smaller than the AIC of the previous reference model, the corresponding model was defined as the new reference model. The added variable was consequently removed from the variable set and the procedure started anew. It was repeated until none of the remaining variables could further improve the model fit.[21,22]

The time to diagnosis model was refit using the information of the physician-signed diagnosis confirmation as a sensitivity analysis. To this end, the self-reported MS type, date of diagnosis and setting of the diagnosis were replaced by physician-reported information of the diagnosis confirmation (sample size 704). Furthermore, the time to diagnosis model was refit on a restricted dataset (diagnoses 2006–2015 (sample size 567)) as a sensitivity analysis for the healthy survivor bias. For the time to DMT initiation model the sensitivity analysis consisted of refitting the model on a dataset restricted to PwMS with a time to DMT initiation within 12 months and a cut-off of 3 months was chosen (sample size 585).

All statistical analyses were performed using R, version 3.3.3.[23]

Results

Population characteristics

The characteristics of our study population and the analysis datasets at the time of enrolment into the SMSR (during years 2016 and 2017) are displayed in Table 1. The most common type of disease course is RRMS (76%), followed by SPMS (14%) and PPMS (10%). The sex ratio is 2.7:1 (female to male), the median age 47 years (interquartile range (IQR) 38–55) and the median disease duration is 9 years (IQR 4–14). The median age at diagnosis is 38 years (IQR 29–45) (corresponding distribution shown in Supplementary Figure 1). The percentage of PwMS with Swiss citizenship is 91%.

Factors associated with extended time to diagnosis

The time to diagnosis is displayed in Figure 2. The curve has a steep increase, with 50% being diagnosed within 1.1 years and 60% after no more than 2 years (range 0–52 years). However, 13% also had a time to diagnosis of at least 10 years. The distribution of the population characteristics split by less than 2 (60%) compared to 2 or more years (40%) until diagnosis is displayed in Supplementary Table 2.

The results of the time to diagnosis model are shown in Figure 3 (numbers see Supplementary Table 3). The strongest factors for extended time to diagnosis was having PPMS (odds ratio (OR) 5.09 (3.12–8.49)). Being diagnosed by a neurologist in a private practice as opposed to in a hospital (1.54 (1.16–2.05)) and having a higher number of uncommon first symptoms (1.17 (1.06–1.30) per additional symptom) were also associated with an extended time to diagnosis.

By contrast, older age at onset (0.84 (0.78–0.90) per age increase of 5 years) or having either of two common first symptoms (gait problems (0.65 (0.47–0.89)), paresthesia (0.72 (0.54–0.95))) were associated with shorter time to diagnosis. Furthermore, the time to diagnosis tended to be extended for diagnoses between 1996 and 2000 and to become gradually shorter afterwards (1996–2000 1, 2001–2005 0.83 (0.52–1.31), 2006–2010 0.92 (0.60–1.40), 2011–2015 0.77 (0.51–1.15), 2016–2017 0.55 (0.31–0.95)).

The sensitivity analyses performed agreed well with the previous model (Supplementary Tables 3–5).

Factors associated with extended time to DMT initiation

Figure 4 shows the time to DMT initiation. Similar to the time to diagnosis curve, it has a steep increase. Over 50% of the eligible PwMS started DMT within 2 months after diagnosis, 77% within 1 year (range 0–20 years). Nevertheless, 23% initiated therapy only after 1 year or not at all (n=72, 8%). The distribution of the population characteristics split by less than 1 (77%) compared to 1 or more years (23%) until time to DMT initiation is displayed in Supplementary Table 6.

Figure 5 (numbers in Supplementary Table 7) shows that factors for taking at least 1 year until treatment start were an older age at diagnosis (OR 1.18 (1.09–1.29) per increase of 5 years) and an earlier year of diagnosis (1996–2000 1, 2001–2005 0.39 (0.24–0.64), 2006–2010 0.26 (0.16–0.42), 2011–2015 0.14 (0.09–0.23), 2016 0.20 (0.09–0.40)).

Table 1. Study populations.

	All	Time to diagnosis dataset	Time to treatment dataset
N per group	1059	990	872
Current type of MS			
RRMS	803 (76%)	753 (76%)	737 (85%)
SPMS	147 (14%)	139 (14%)	135 (15%)
PPMS	109 (10%)	98 (10%)	0 (0%)
Women	770 (73%)	719 (73%)	653 (75%)
Age (years)	47 (38–55)	47 (38–55)	46 (37–53)
Age at onset	33 (26–41)	33 (26–41)	32 (25–40)
Age at diagnosis	38 (29–45)	38 (29–45)	36.5 (28–44)
Age at DMT start	38 (29–45)	37 (29–44)	37 (29–44)
Swiss citizen	962 (91%)	896 (91%)	792 (91%)
MS in relatives			
Close relatives	80 (8%)	74 (8%)	64 (8%)
Other relatives	124 (12%)	110 (12%)	107 (13%)
DMT (ever)	914 (86%)	861 (87%)	800 (92%)
Diagnosis setting			
Neurologist (clinic)	659 (63%)	617 (62%)	553 (64%)
Neurologist (private practice)	371 (35%)	352 (36%)	296 (34%)
General practitioner	22 (2%)	21 (2%)	17 (2%)
Seen a doctor in last 12 months	954 (90%)	894 (90%)	786 (90%)
Diagnosis confirmation received	698 (66%)	652 (66%)	581 (67%)

Column 1 displays the overall dataset, column 2 the dataset for the time to diagnosis analysis and column 3 the time to treatment dataset. Shown are the absolute numbers or the median for continuous variables. In brackets for factors the percentage with the specified factor level, for continuous variables the interquartile range.
RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary-progressive multiple sclerosis; PPMS: primary-progressive multiple sclerosis; DMT: disease-modifying treatment.

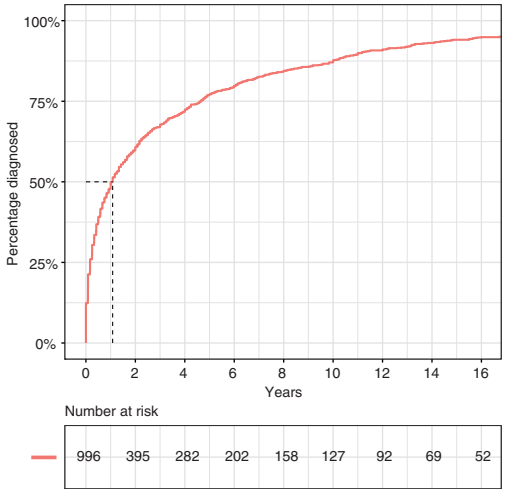

Figure 2. Cumulative incidence of multiple sclerosis diagnoses curve displaying the time between first symptoms and diagnosis. The *y* axis shows the percentage of the whole sample (n=996) that is diagnosed within a certain time frame (years on *x* axis). The table underneath the graph displays the number of people who are still 'at risk', so not yet diagnosed, at a given time after the first symptoms. The dashed line shows the median, which is at 1.1 years.

The sensitivity analysis agreed in the direction of the effects (Supplementary Tables 7 and 8).

To be consistent, the time to DMT initiation between the first symptoms and treatment initiation, which was not considered in the regression analysis is displayed in Supplementary Figure 2.

Discussion

Using patient-reported data, we observed that even in recent time periods a substantial fraction of PwMS experience an extended time to diagnosis of at least 2 years (40%). An extended time to diagnosis was associated with PPMS, a younger age at the onset of symptoms, an earlier diagnosis period, not being diagnosed in a hospital setting, not having either one of two common first symptoms (gait problems or paresthesia) and a higher number of uncommon first symptoms.

In a second step, all PwMS with a relapsing-onset MS and a diagnosis before the year 2017 were scrutinised to identify factors associated with an

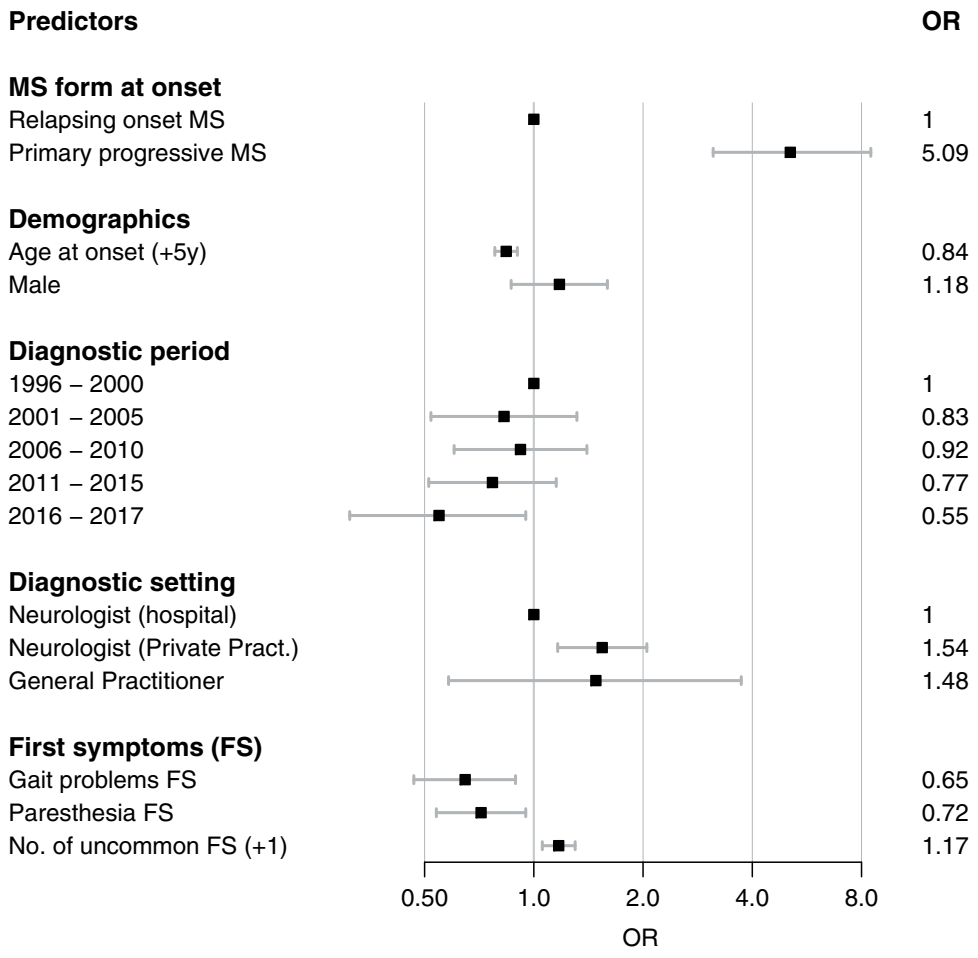

Figure 3. Extended time between first symptoms and diagnosis (≥2 years) model displayed in a forest plot. The odds ratios (ORs) and 95% confidence intervals (CIs) of the individual factors are shown on a $\log^2$ scale and the point estimates are stated at the right side of the plot. Values higher than 1 indicate an association with extended time, below 1 with shorter time. The reference levels of the factors are (from top to bottom, variable in brackets): type of MS: relapsing-onset MS (primary progressive MS), sex: female (male), diagnosis period: 1996–2000 (diagnosis period: 2001–2005, 2006–2010, 2011–2015, 2016–2017), diagnosis setting: neurologist (hospital) (neurologist (private practice), general practitioner) and absence of the stated first symptoms (gait problems first symptom, paresthesia first symptom). diag.: diagnosis; pract.: practice; FS: first symptoms. The results are displayed on a $\log^2$ scale to give the positive and negative factors the same weight.

extended time to DMT initiation of at least 1 year, which was observed for 23%. The PwMS with later or no treatment start tended to be of older age at diagnosis and were diagnosed in an earlier diagnosis period.

Overall, the time to diagnosis decreased substantially over time, which is likely to be an effect of updated diagnostic guidelines, the availability of treatment for relapsing MS forms, increased awareness and better communication of the disease.[1,12,14] However, additional individual factors could prolong the time to diagnosis. The strongest of these is having PPMS. The immediate explanation for this finding is that diagnostic guidelines for PPMS require at least 1 year of disease progression before the definite diagnosis.[1] Especially with first treatments showing positive effects in persons with PPMS, these guidelines should be critically discussed.[5] Whether additional factors such as different first symptom profiles for PPMS may have contributed to extended time to diagnosis is currently not discernible from these data.

The finding of a greater probability for extended time to diagnosis in younger persons was shown

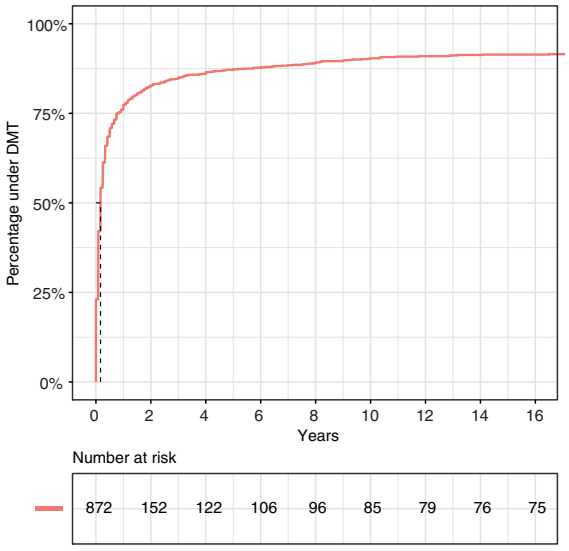

Figure 4. Cumulative incidence of disease-modifying treatment (DMT) initiation curve displaying the time between diagnosis and first DMT initiation. The *y* axis names the percentage of the whole sample (n=872) that is under DMT within a certain time frame (years on *x* axis). The table underneath the graph displays the number of people who are still 'at risk', so not yet treated with DMT, at a given time after diagnosis. The dashed line shows the median, which is at 2 months.

before and has potential implications for healthcare and the diagnostic process.[14] Because younger persons tend to seek care less frequently, this may contribute to the extended time to diagnosis.[24] The effect of diagnoses of neurologists in private practices being associated with extended times compared to their colleagues in hospitals might be related to symptom severity, which was not measured in this study. We hypothesise that mild cases of MS more frequently attend private practice neurologists or general practitioners, whereas persons who are strongly affected by their first symptoms might more often seek care in a hospital and emergency department. If true, then the observed effect may be more related to disease-specific factors rather than variations in healthcare setting.

Our findings further point to an important role of pattern differences in first symptom manifestation. In particular, we saw that having the common first MS symptoms gait problems or paresthesia were associated with shorter time to diagnosis. By contrast, an increasing number of uncommon symptoms led to extended time to diagnosis. We therefore assume that the awareness of less typical symptoms can play a key role in promoting quicker MS diagnosis. However, as the numbers of PwMS with specific uncommon first symptoms are rather low in the SMSR, this will need to be confirmed by further studies.

Evidence suggests that a rapid initiation of DMT after diagnosis positively affects MS disease course.[9–11] Therefore, we examined this aspect of the disease management. We observed that the time to DMT initiation evolved in parallel with the introduction of new diagnostic guidelines, but also with the availability of novel treatment options. On an individual level, we observed extended time to DMT initiation among older persons. It is conceivable that age might influence joint treatment decisions by altering the patients' preferences (e.g. more reluctance for initiation at an older age) or a physician's perception of the urgency of immediate DMT start (e.g. because DMT may be more effective at a younger age).[25–29] These aspects clearly warrant further investigation.

Due to the observational, self-reported nature of our study, limitations need to be considered. The date of the first symptoms is quite likely to be influenced by recall bias. However, the mostly good agreement in the sensitivity analyses regarding direction and point estimates of the effects as well as the good agreement of demographics, disease characteristics and the age at diagnosis distribution compared to other studies (except Swiss citizenship), mitigate this concern.[19,30–33] In addition, the entire SMSR project was specifically structured to reduce selection bias and warrant representativeness (e.g. layer model, form of participation, communication strategy and funding body).[17,18] The high share of PwMS with DMT uptake (87–92%) can mainly be explained by the sample which is only covering diagnoses after 1995. Considering the entire SMSR database, the share reduces to 82%, which corresponds well with other Swiss data and is representative of the generally high uptake of DMT in Switzerland.[32] Moreover, it is likely that our study did not capture all important influencing factors. In that regard, our study also reflects current limitations in our understanding of the full diagnostic cascade, as well as the individual characteristics and processes that foster a quicker diagnosis. For example, we observed that the diagnostic setting and first symptoms were important factors in time to diagnosis. However, it remains yet to uncover whether these factors were exerting their influence more on the side of patients or the health system. Furthermore, the effect of the healthy survivor bias on the time trend by missing the group of rapidly progressing PwMS in the oldest time period

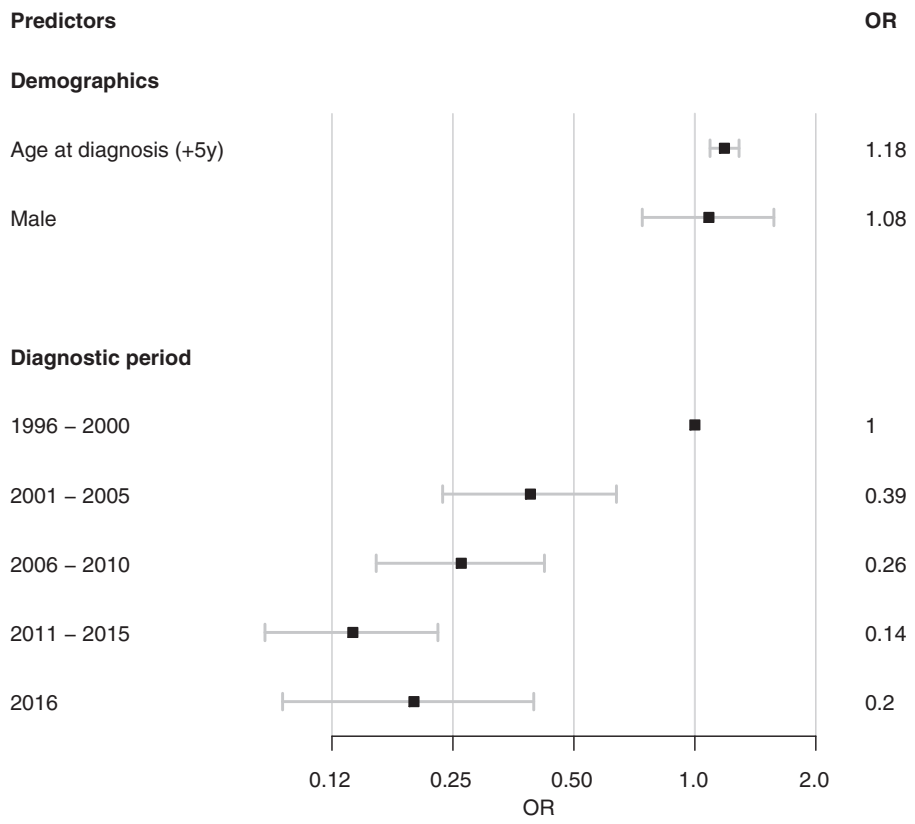

Figure 5. Extended time between diagnosis and first disease-modifying treatment (DMT) initiation (1 or more years) model displayed in a forest plot. The odds ratios (ORs) and 95% confidence intervals (CIs) of the individual factors are shown on a $\log^2$ scale and the point estimates stated at the right side of the plot. Values higher than 1 indicate an association with extended time, below 1 with shorter time. The reference levels of the factors are (from top to bottom, variable in brackets): sex: female (male), diagnosis period 1996–2000 (2001–2005, 2006–2010, 2011–2015, 2016). diag.: diagnosis; pract.: practice; FS: first symptoms. The results are displayed on a $\log^2$ scale to give the positive and negative factors the same weight.

(1996–2000) has to be considered. However, we are confident that the effect is limited because the study is structured specifically also to catch the usually underrepresented groups of newly diagnosed or highly disabled PwMS, and the sensitivity analysis on a restricted dataset (diagnoses 2006–2015) confirmed that the results are stable (see Supplementary Appendix and Supplementary Table 5). The time trend is likely still to exist even if the group of rapidly progressing PwMS was missing (calculations in Supplementary material). As a last point, it is important to note that in general an extended time to diagnosis may not necessarily be negative, because it can also be associated with a milder disease course.

We conclude that even in recent periods, substantial and partially systematic variation regarding time to diagnosis and time to DMT initiation remains. With the emerging paradigm of early treatment, the residual unexplained variation should be monitored carefully and informed decisions be made about updating guidelines and raising awareness among physicians as well as the public.

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Conflict of Interests

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Supplemental Material

Supplemental material for this article is available online.

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