	Frequency of first-symptom
Paresthesia	60%
Visual disturbances	39%
Fatigue	33%
Gait problems	31%
Weakness	30%
Balance problems	26%
Paralysis	25%
Dizziness / Vertigo	21%
Pain	13%
Depression	12%
Bladder problems	10%
Bowel problems	8%
Memory problems	8%
Spasms	8%
Sexual dysfunction	6%
Speech problems	6%
Tremor	6%
Tics	5%
Swallowing problems	2%
Epilepsy	1%

Table S1: Occurrence frequencies of first-symptoms. The symptoms are ordered by frequency. The numbers are rounded and refer to the percentage in the analysis sample.

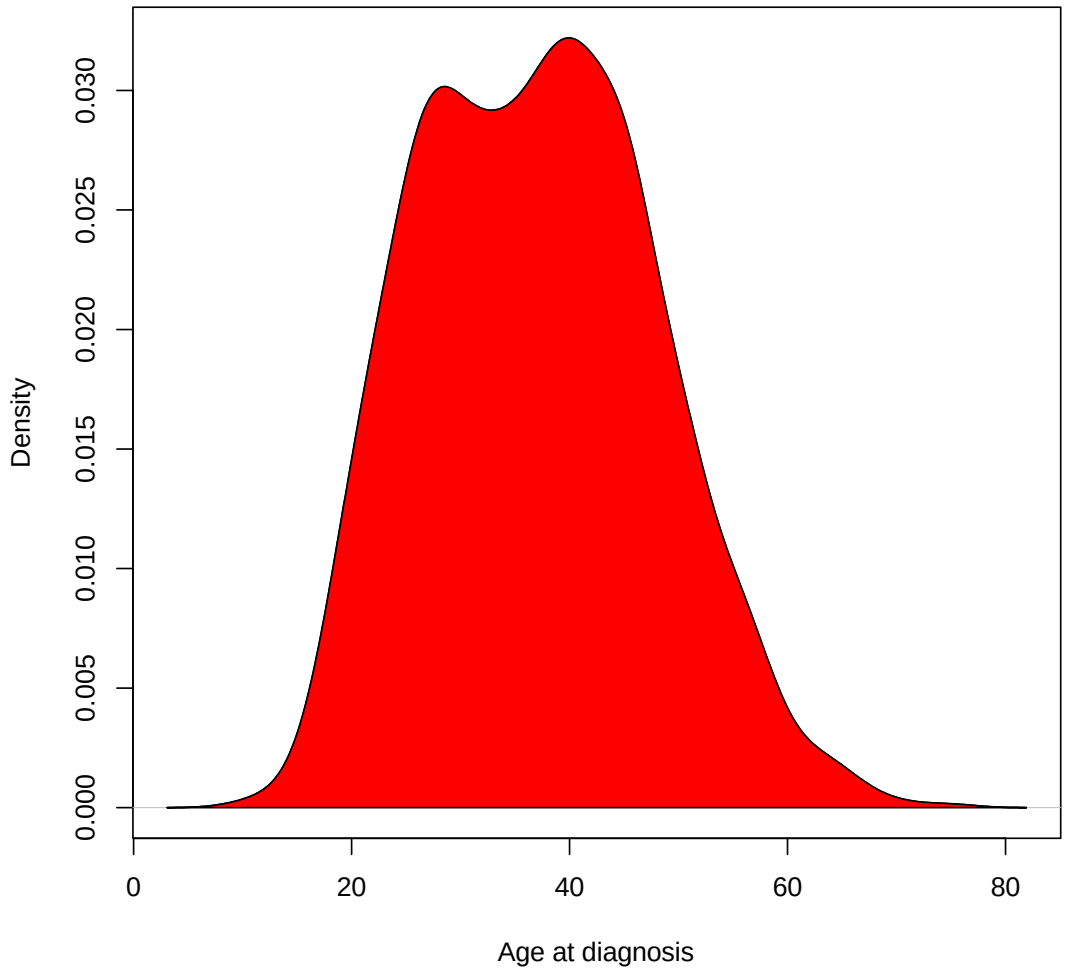

Figure S1: Distribution (kernel density) of the age-at-diagnosis. Sample size 1313. Median age-at-diagnosis is 38, inter-quartile range 29 to 45.

	Less than 2 years	2 or more years
N per group	598 (60%)	392 (40%)
Current type of MS		
RRMS	503 (84%)	250 (64%)
SPMS	63 (11%)	76 (19%)
PPMS	32 (5%)	66 (17%)
Female	442 (74%)	277 (71%)
Age	44 (35 - 52)	51 (43 - 58)
Age-at-onset	34 (27 - 42)	32 (25 - 40)
Age-at-diagnosis	35 (27 - 43)	41 (34 - 49)
Age-at-DMT-start	35 (28 - 43)	40 (33 - 47)
Swiss citizen	536 (90%)	360 (92%)
MS in relatives		
Close relatives	45 (8%)	29 (8%)
Other relatives	64 (11%)	46 (12%)
DMT (ever)	536 (90%)	325 (83%)
Diagnosis setting		
Neurologist (Clinic)	395 (66%)	222 (57%)
Neurologist (Private Practice)	192 (32%)	160 (41%)
General Practitioner	11 (2%)	10 (3%)
Seen a doctor in last 12 months	544 (91%)	350 (89%)
Diagnosis confirmation received	386 (65%)	266 (68%)

Table S2: Study population in the two groups (Less than 2 years, 2 or more years) from first-symptoms to diagnosis. 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 inter-quartile range. RRMS stands for relapsing-remitting MS, SPMS for secondary-progressive MS and PPMS for primary-progressive MS. DMT stands for disease-modifying treatment.

	OR (95% CI)
Primary-progressive MS	5.09 (3.12-8.49)
Age-at-onset (+5y)	0.84 (0.78-0.90)
Male	1.18 (0.87-1.59)
Diag. period: 2001 - 2005	0.83 (0.52-1.31)
Diag. period: 2006 - 2010	0.92 (0.60-1.40)
Diag. period: 2011 - 2015	0.77 (0.51-1.15)
Diag. period: 2016 - 2017	0.55 (0.31-0.95)
Neurologist (Private Pract.)	1.54 (1.16-2.05)
General Practitioner	1.48 (0.58-3.73)
Gait problems FS	0.65 (0.47-0.89)
Paresthesia FS	0.72 (0.54-0.95)
Number of uncommon FS	1.17 (1.06-1.30)

Table S3: Model output of the time-to-diagnosis model.

	OR (95% CI)
Primary-progressive MS	4.16 (1.98-9.09)
Age-at-onset (+5y)	0.84 (0.77-0.92)
Male	1.41 (0.95-2.08)
Diag. period: 2001 - 2005	0.82 (0.46-1.47)
Diag. period: 2006 - 2010	1.22 (0.71-2.12)
Diag. period: 2011 - 2015	0.74 (0.44-1.24)
Diag. period: 2016 - 2017	0.62 (0.30-1.25)
Neurologist (Private Pract.)	1.59 (1.13-2.24)
General Practitioner	0.81 (0.11-3.95)
Gait problems FS	0.71 (0.47-1.06)
Paresthesia FS	0.82 (0.58-1.17)
Number of uncommon FS	1.14 (1.00-1.30)

Table S4: Model output of the sensitivity analysis time-to-diagnosis model (with diagnosis confirmation diagnosis dates).

	OR (95% CI)
Primary-progressive MS	5.69 (3.05-11.03)
Age-at-onset (+5y)	0.84 (0.77-0.92)
Male	1.28 (0.84-1.93)
Diag. period: 2001 - 2005	
Diag. period: 2006 - 2010	
Diag. period: 2011 - 2015	0.82 (0.58-1.18)*
Diag. period: 2016 - 2017	
Neurologist (Private Pract.)	1.25 (0.86-1.82)
General Practitioner	1.37 (0.44-4.11)
Gait problems FS	0.64 (0.42-0.97)
Paresthesia FS	0.77 (0.53-1.12)
Number of uncommon FS	1.17 (1.02-1.34)

*Table S5: Model output of the sensitivity analysis time-to-diagnosis model restricted to diagnoses between 2006 and 2015. * This coefficient is only displayed for completeness reasons, as it cannot be directly compared (reference level changed).*

	Less than 1 year	1 or more years
N per group	673 (77%)	199 (23%)
Current type of MS		
RRMS	587 (87%)	150 (75%)
SPMS	86 (13%)	49 (25%)
PPMS	0 (0%)	0 (0%)
Female	510 (76%)	143 (72%)
Age	45 (36 - 52)	51 (42 - 57)
Age-at-onset	32 (25 - 40)	33 (25 - 43)
Age-at-diagnosis	36 (28 - 43)	38 (30 - 46)
Age-at-DMT-start	36 (28 - 43)	39 (32 - 48)
Swiss citizen	608 (90%)	184 (92%)
MS in relatives		
Close relatives	53 (8%)	11 (6%)
Other relatives	83 (13%)	24 (13%)
DMT (ever)	673 (100%)	127 (64%)
Diagnosis setting		
Neurologist (Clinic)	420 (63%)	133 (67%)
Neurologist (Private Practice)	234 (35%)	62 (31%)
General Practitioner	13 (2%)	4 (2%)
Seen a doctor in last 12 months	622 (92%)	164 (82%)
Diagnosis confirmation received	451 (67%)	130 (65%)

Table S6: Study population in the two groups (Less than 1 year, 1 and more years) from diagnosis to DMT start. 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 inter-quartile range. RRMS stands for relapsing-remitting MS, SPMS for secondary-progressive MS and PPMS for primary-progressive MS. DMT stands for disease-modifying treatment.

	OR (95% CI)
Age-at-diagnosis (+5y)	1.18 (1.09-1.29)
Male	1.08 (0.74-1.57)
Diagnosis period: 2001 - 2005	0.39 (0.24-0.64)
Diagnosis period: 2006 - 2010	0.26 (0.16-0.42)
Diagnosis period: 2011 - 2015	0.14 (0.09-0.23)
Diagnosis period: 2016	0.20 (0.09-0.40)

Table S7: Model output of the time-to-DMT-initiation model.

	OR (95% CI)
Age-at-diagnosis (+5y)	1.16 (1.06-1.28)
Male	0.98 (0.63-1.50)
Diagnosis period: 2001 - 2005	0.72 (0.35-1.52)
Diagnosis period: 2006 - 2010	0.64 (0.33-1.28)
Diagnosis period: 2011 - 2015	0.56 (0.30-1.08)
Diagnosis period: 2016	0.28 (0.11-0.68)

Table S8: Model output of the sensitivity analysis time-to-DMT-initiation model (with diagnosis confirmation diagnosis dates).

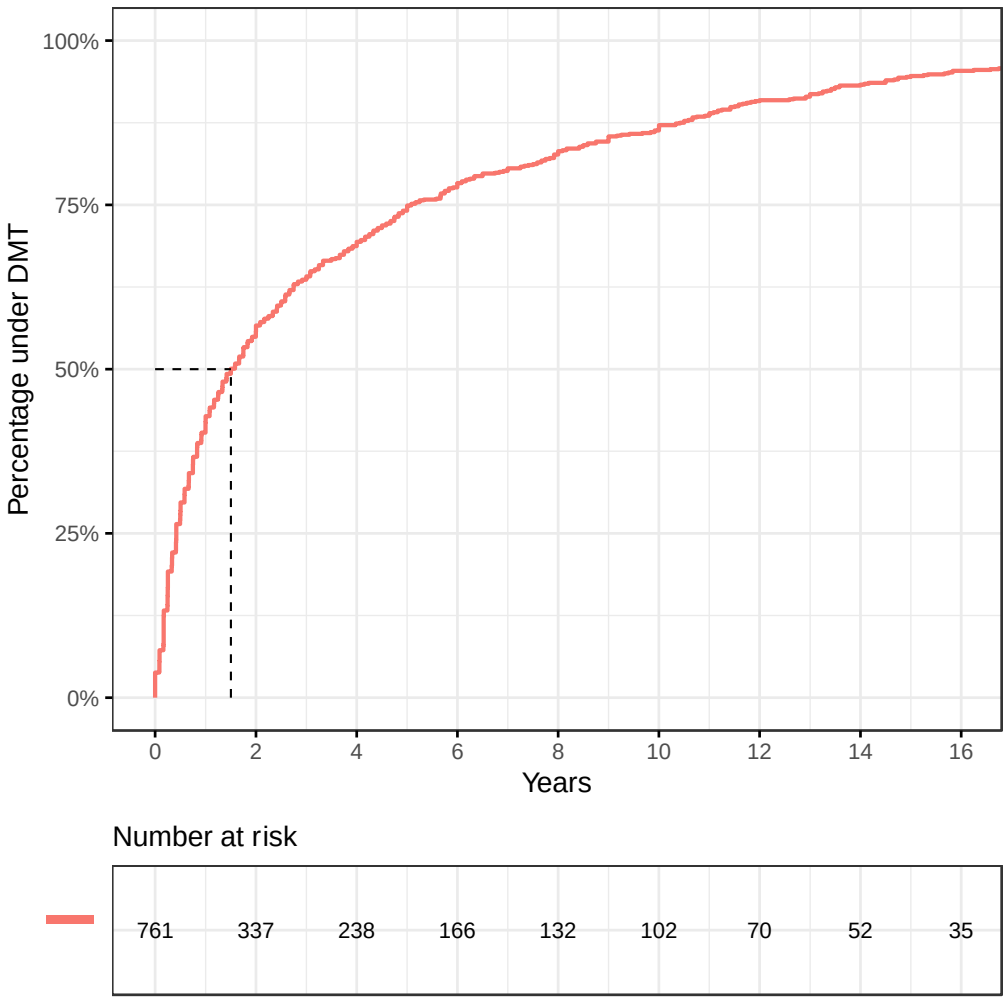

Figure S2: Cumulative incidence of DMT initiation curve displaying the time between first symptoms and DMT initiation. The y-axis names the percentage of the whole sample (n = 761) that is under DMT within a certain time frame (years on x-axis). The table underneath the graph displays the number of people that is still "at risk", so not yet treated, at a given time after first symptoms. The dashed line shows the median, which is at 1.5 years. Persons with a primary-progressive MS were excluded in this analysis.

Calculation regarding healthy survivor bias and the potentially missing group of rapidly progressing PwMS:

Time-to-diagnosis	**1996-2000 N=162**	**2001-2005 N=164**	**2006-2010 N=247**	**2011-2015 N=323**	**2016-2017 N=100**
<2 years	52.5%	61%	57.1%	62.9%	72%
>=2 years	47.5%	39%	42.9%	37.1%	28%

Table S9: Time-to-diagnosis (<2 years vs. ≥2 years) in the different time periods of diagnosis.

Table S8 shows the percentages in each time period with <2 compared to ≥2 years until diagnosis. An increase in percentage of participant with less than 2 years from the first time period (1996-2000) to the next time period can be seen. Then 2001 to 2015 are relatively stable or at least no extreme time trend is visible and after 2015 there appears to be another increase. The increase in the time period after 2015 is likely not due to missing participants with extended times, because we analyzed the data retrospectively. However, the increase should be considered carefully at this point in time because it only covers fewer participants than the other time periods.

The healthy survivor bias would most likely be visible in the time periods of 1996 to 2000 and maybe still in the period of 2001 to 2005. But as the period of 2001 to 2005 corresponds approximately well with the following two, we refrain from diving deeper into this (we inspected the decrease in 2006-2010 but could not find any concluding differences in characteristics).

For the 1996 to 2000 period, as we cannot distinguish between highly active and "normal" disease course with the current questionnaire, we decided to do a sensitivity analysis with an extreme case scenario. Therefore, we used the definition for rapidly-progressing disease course of reaching an EDSS of ≥6 within 5 years after onset which was suggested to correspond to 5-6% of a big Canadian database (Menon et al. (2013) (2017)). As this definition has been criticized to be too restrictive, we extended the percentage of the population that has a rapidly-progressing disease and is potentially missing to 10%. Using this definition, around 75% of them have a relapsing-onset disease course, whereas 25% have a primary-progressive MS. In the stated extreme case scenario, we assume indeed 10% of the 1996-2000 subgroup are missing and that the RRMS patients are diagnosed within 2 years and the PPMS patients in more than 2 years. As a consequence, we arrive at the number of an additional 16 persons with MS in this group (10% of 162) of which we count 12 to the time-to-diagnosis of less than 2 years and 4 to the time of 2 or more years groups. This results in 97 (85 + 12) in the <2 years and 81 (77 + 4) in the >=2 years group. Finally, the groups have a share of 54.5% <2 years (97 / 178) and 45.5% >=2 years (81 / 178). Comparing the 54.5% to the groups after 2000, a reasonable increase in the <2 years percentages is still visible.

References:

Menon S, Shirani A, Zhao Y, Oger J, Traboulsee A, Freedman MS, Tremlett H. Characterising aggressive multiple sclerosis. J Neurol Neurosurg Psychiatry 2013; 84:1192-1198. 10.1136/jnnp-2013-304951.
Menon S, Zhu F, Shirani A, Oger J, Freedman MS, Tremlett H. Disability progression in aggressive multiple sclerosis. Mult Scler. 2017 Mar;23(3):456-463. 10.1177/1352458516653273.