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Association between education level and access to disease-modifying treatment in patients with multiple sclerosis in France

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Abstract

Background: We hypothesized that differences in access to disease-modifying treatments (DMT) could explain the association between socioeconomic status and disability progression in Multiple Sclerosis (MS).

Objective: To analyze the association between education level and DMT use in France.

Methods: All patients from OFSEP network with MS onset over 1996-2014 and aged ≥ 25 years at onset were included. Three time-to-event outcomes were investigated using flexible parametric survival regression models: time from MS onset to first DMT (any) and to platform therapy, and time from platform therapy to switch to high-efficacy therapy.

Results: Overall, 7,563 patients were included (mean follow-up 12.6 \pm 5.9 years). The percentages of patients aged less than 40 years at MS onset and who initiated treatment before the age of 40 were significantly higher in the groups with a higher education level. The time-to-event outcomes showed no major difference in DMT practices according to education level, except for women who had a significantly shorter time to DMT initiation in medium to very high education level groups versus low, at 5 years from MS clinical onset.

Conclusion: Our results suggest that the association between education level and MS disability progression does not solely reflect different therapeutic practices, particularly in men.

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Introduction

Multiple Sclerosis (MS) is a chronic neurological disease that often starts in early adulthood (20-40 years), and affects more women than men (ratio: 3/1)¹. Two different initial phenotypes can be distinguished: relapsing-onset MS (RMS) and primary progressive MS². Both lead to disability over time, and most patients with RMS will transition to secondary progressive MS. Literature data support a potentially major effect of social determinants in MS³. Several studies reported a link between socioeconomic status and MS disability progression⁴⁻⁷, including from our group (Lefort, submitted). Indeed, in patients with RMS, we found a gradient in the risk of disability progression after MS onset according to the education level. This risk was reduced by almost 50% in patients with very high education level compared with patients with low education level. Several hypotheses can be proposed to explain it, especially the difference in access to care, particularly to disease-modifying treatments (DMT).

Inequalities in access to care can be characterized using three dimensions: physical accessibility, financial accessibility, and acceptability⁸. In France, the universal healthcare system is largely financed by the government with limited out-of-pocket costs. However, financial accessibility also includes associated costs, such as transport, sickness leave, childcare, etc. Acceptability includes other factors implicated in the decision to use care and may be related to knowledge about and acculturation to the care offer. These two dimensions are directly linked to the patient's social status. Economic, insurance-related, and geographic factors appear to limit access to neurologists⁹ who are the only healthcare professionals allowed to prescribe MS-specific treatments. Among the studies on MS treatment access¹¹⁻¹⁴, two (one from Norway¹¹ and one from the United Kingdom¹²) did not show any difference in treatment according to socioeconomic status, whereas the other two (one from Mexico¹⁴ and one from France¹³) found a link between lower socioeconomic status and reduced access to DMT. The

French study was based on a monocentric cohort using a contextual socioeconomic indicator (European deprivation index, measured at the area of residence).

Therefore, to determine whether differences in access to care/DMT could explain the reported association between education level and MS disability progression, we analyzed the association between education level and therapeutic practices in patients with RMS in France.

Methods

Data source

Prospective standardized data from the French network of MS expert centers (Observatoire Français de la Sclérose en Plaques; OFSEP www.ofsep.org)¹⁵ were extracted from the European Database for Multiple Sclerosis (EDMUS)¹⁶.

Eligibility criteria

All patients from 18 OFSEP centers, living in metropolitan France, with a diagnosis of RMS^{17,18}, and MS clinical onset between 1960 and 2014 were included. Age ≥ 25 years at MS onset was an additional inclusion criterion to avoid reverse causation (i.e. the fact that MS might influence the education level). Patients whose education level was unknown were excluded. As the present study focused on DMTs, patients with MS clinical onset before 1996 (the date when the first specific MS treatment, interferon- β , was approved in France) were excluded.

Treatments

Three DMT groups were defined: 1. platform therapies (i.e. interferon- β , glatiramer acetate, teriflunomide and dimethyl fumarate); 2. high-efficacy therapies subcategorized into three subgroups when needed: second-line (i.e. natalizumab and fingolimod), anti CD-20 antibodies (i.e. rituximab and ocrelizumab), third-line (i.e. mitoxantrone and alemtuzumab); and 3. off-label (i.e. treatments not approved in MS care in France during the study period: azathioprine,

cyclophosphamide, daclizumab, laquinimod, methotrexate, mycophenolate mofetil, ponesimod, siponimod).

Variables

The main variable of interest was the education level, based on the highest diploma. Four categories were defined: i) low (i.e. primary and junior secondary school); ii) medium (i.e. senior secondary school); iii) high (i.e. undergraduate degree); and iv) very high level (i.e. master/doctoral degrees). Other covariates of interest were sex, age at and year of MS clinical onset, and center. Moreover, in the group of patients who received platform therapies, additional variables were collected at platform therapy initiation: age, MS duration, MS-related disability measured with the Expanded Disability Status Scale (EDSS; ranges from 0, normal, to 10, death due to MS)¹⁹, and number of relapses in the preceding year.

Outcomes

The main outcome was the time from MS clinical onset to first DMT (any) initiation, right-censored at the date of outcome attainment, the date of 15 years after MS onset, or the last visit entered in the database at the extraction date (December, 2020) if the follow-up duration was <15 years. The secondary outcomes were: i) the time from MS onset to platform therapy start, right-censored at the earliest date among: the date of outcome attainment, the date of other treatment category initiation, the date of 15 years after MS onset, or the last visit; and ii) among patients who initiated a platform therapy as first treatment, the time from platform therapy start to the switch to a high-efficacy therapy. This time was right-censored at the date of outcome attainment, the date of 15 years after MS onset, or the last visit.

Statistical analysis

The patients' characteristics at MS onset were described for the whole sample and by sex. Among patients who initiated a platform therapy as first treatment, their characteristics at DMT start were described for the whole sample, by sex, and by education level. Annual DMT

exposure was described by education level for 10 years of follow-up from MS onset. In case of several DMTs in a given year, only the longest treatment was considered, except for mitoxantrone and alemtuzumab that were systematically considered. In parallel, the number of annual relapses was described by year and by education level. Then, flexible parametric survival regression models were used to study the time-to-event outcomes²⁰. These models were defined from restricted cubic splines (i.e. functions defined by piecewise polynomials, joined at points called knots). The most appropriate knot number was chosen based on the best-fitting model, using the Akaike information criterion that when minimized, denotes the better fit to the data. Models were adjusted for age at MS clinical onset, period of MS clinical onset (1996-1999, 2000-2004, 2005-2009, and 2010-2014) and center, and stratified by sex or age at MS clinical onset. Stratification allows to have separate results and see if the association between education and use of DMT is different between sub-groups. Our hypothesis is that the level of education does not necessarily have the same effect on men and women, or according to age at MS onset. For the second secondary outcome, models were also adjusted for age at platform therapy start (instead of age at MS onset), MS duration at platform therapy start, disability level and number of relapses in the preceding year. Statistical analyses were performed with the R software (R 4.0.3). The flexible survival regression analysis using the Royston-Parmar spline model was performed with the `rstpm2` R package^{21,22}.

Standard Protocol Approvals, Registrations, and Patient Consents

All patients enrolled in the OFSEP database provided informed consent for participation and their data be stored and used for research. Data confidentiality and safety were ensured according to the French recommendations (CNIL). OFSEP received approval for storing clinical, biological and imaging data for research purposes (CNIL; request 914.066; authorization decision DR-2014-110). The study did not require any additional procedures in

accordance with French legislation. OFSEP was registered at clinicaltrials.gov under NCT02889965.

Results

Characteristics of the study population

Overall, 7,563 patients were included (eFigure 1), with a mean follow-up of 12.6 ± 5.9 years from MS onset. Table 1 shows the characteristics of the whole sample and by sex (75% of women). Approximately 46% of women and 42% of men had a high or very high education level. Overall, 5,703 patients (75%) initiated a platform therapy as first treatment. Table 2 shows the characteristics at MS onset and at platform therapy start for the whole sample and by sex and by level of education. The percentages of patients who were younger than 40 years at MS onset ($p < 10^{-4}$) and who initiated a DMT before 40 years ($p < 10^{-4}$) were higher in the higher education level groups (eTable 1, eTable 2). Time from MS clinical onset to DMT start decreased over the study period, whatever the education level (eFigure 2).

Treatments and clinical disease activity in the 10 years following MS onset

The annual treatment exposure rates were similar whatever the education level (Figure 2). Untreated patients represented 88%, 85%, 87% and 87% of patients in the low, medium, high and very high education level groups, respectively, in the first year and 37%, 33%, 35% and 34% in year 10 of follow-up. Likewise, the percentages of patients with platform therapy were similar in all education level groups (low: 9%, medium: 12%, high: 11%, and very high: 11% in the first year; and low: 40%, medium: 40%, high: 41%, and very high: 44% in year 10 of follow-up). The number of relapses was also not significantly different in the four groups (Table 3, eTable 3). Conversely, the percentage of patients who transitioned into secondary progressive MS was higher in the low education level group.

Association between education level and treatment initiation

Stratification by sex. As shown in Figure 1, the probability of not having received any DMT since MS onset was little influenced by education level, in women and men. The biggest difference was observed for the main outcome, in women, between the 5th and the 10th year after MS onset. Comparison of the hazard ratios (Table 4) indicated that in women, this probability decreased with the increasing education level after 5 years of follow-up. Indeed, hazard ratios at 5 years were 0.70 [0.55; 0.89] for women with medium education level, 0.65 [0.50; 0.85] for women with high education level and 0.60 [0.44; 0.81] for women with very high education level, women with low education level being the reference group. It reflects a significant shorter time from MS onset to DMT initiation in women with medium, high or very high education level, compared with the low education level group, which is consistent with Figure 1. At 1 year, hazard ratios were closer to 1 and not significant. Similar associations were observed regarding the time from MS onset to platform therapy start. In men, no difference was observed. Lastly, no difference was observed in the time from platform therapy start to treatment switch towards high-efficacy therapy in function of the education level in both women and men (Figure 1, Table 4).

Stratification by age at MS clinical onset. Among patients who were younger than 40 years at MS onset, the time from MS onset to first DMT and to platform therapy start, and the time from platform therapy start to treatment switch at 5 years decreased when the education level increased (Table 4; HR<1). Among patients older than 40 years at MS onset, same findings were observed for patients with high and very high education level at 1 year. However, the difference was not significant at 5 years, except for patients with very high education level (Table 4).

Discussion

In the present work, no difference was found in DMT practices in function of the education level among men with MS, in accordance with similar levels of MS clinical activity among these groups. However, among women, a significant decrease in the time to DMT initiation in function of education level was shown, i.e. women with higher education were treated earlier than women with lower education. This difference did not occur from MS onset but rather appeared after 5 years up to 10 years of disease duration. We can ask ourselves whether women with a low level of education have more fears or doubts about the safety or efficacy of treatment than others, or whether they need more time to accept the diagnosis of the disease and therefore its therapeutic management. Other reasons, such as less accessibility to neurologists, a more deteriorated state of health, or priorities other than health, cannot be ruled out. In addition, we also found that patients with the lowest education level were older at MS clinical onset and at treatment start.

In Europe, a French study showed a difference in access to treatment in favor of higher socioeconomic levels¹³, whereas two studies from the UK¹² and Norway¹¹ found no difference in access to treatment according to the socioeconomic status. The French study focused on one OFSEP center in Western France. Using a contextual socioeconomic indicator, this study demonstrated that patients with RMS living in a more deprived area were more likely to delay switching to a more effective DMT than patients living in a less deprived area¹³. Nevertheless, the analyses were not adjusted for disease activity, although the decision to start or switch to another DMT is influenced by relapses, MRI data, and disability progression. In UK, no difference was found in DMT prescribing patterns (moderate, high, and very high) in function of the education level and income¹², but the study population included only treated patients. Conversely, previous studies in the UK that included both treated and untreated patients with MS found that individuals with a more deprived background were less likely to obtain treatment

^{12,23}. Recently, Flemmen and colleagues showed that in Norway, patients with the lowest degree of education had more frequently high efficacy DMTs as first treatment¹¹. In the present study, we did not find any significant difference in access to high efficacy treatment as first treatment (data not shown).

We observed that patients with the lowest education level were older at MS onset. The association between time to diagnosis and socioeconomic variables was previously studied by Flemmen and colleagues through the parents' education level²⁴. They found that high maternal education level (not available in our dataset) was significantly associated with younger age at MS onset. Our study focused on patients from OFSEP registry, who are mainly followed in MS expert centers. This could have led to a potential selection bias that might affect the results because referral to an expert center may be related to the disease severity²⁵, the geographical situation, but also to the socioeconomic status. Therefore, we cannot exclude that the inclusion of patients with the lowest level of education was associated with the disease severity. Moreover, a previous French study that compared patients from a MS expert center and patients followed by a private neurologist or in a general hospital found a significant difference in age at MS onset (31.2 ± 10.2 years for patients from the MS expert center and 33.0 ± 11.1 years for the others, $p < 10^{-4}$)²⁵. Several hypotheses can be suggested to explain this difference. For instance, the perception of the first symptoms and the referral to neurologist may differ according to the socioeconomic status. Similarly, the ability to rapidly act upon symptom appearance may differ according to the socioeconomic status. Priorities other than health or more limited access to healthcare facilities/providers (may be linked to rural or deprived areas of residence) can also be mentioned.

In the present study, we observed few differences in treatment exposure in the first 10 years of MS. The percentage of patients receiving off-label treatments was higher in the group with lower education level. Although there was no major difference in the distribution of patients by

education level in function of the MS onset period, the percentage of patients who transitioned into secondary progressive MS was higher in the group with lower education level and this could explain the higher proportion of off-label treatments. In addition, the doctor-patient communication also could have a role to explain such result. Indeed, previous works (outside MS) highlighted that the patients' socioeconomic status influences the health professionals' decision-making. For instance, simpler information is given, the discourse is less interactive, and the doctor advice/instruction is limited for patients from lower socioeconomic categories²⁶⁻²⁸.

Lastly, the present study suffered from some limitations, the main one being the lack of MRI data at treatment start due to the high number of missing values. Moreover, this work suffered from a high proportion of missing data on education level (Lefort et al, submitted). In addition, education was measured as the highest diploma obtained by the patient, and not through the number of effective years of education as this information was not collected. It would have been more suitable, notably to consider people who almost completed high school or university, but did not obtain the title.

To conclude, we previously showed that lower education level is associated with higher MS disability progression. Based on the results of the present study, it seems that different DMT practices are not the main or the unique explanatory factor, at least in men with MS. In women with MS, further work is needed but special attention should be paid by neurologists to ensure equitable access to DMT. However, patients with lower education level were older at MS clinical onset, a well-known bad prognostic factor of disability progression. Without a first consultation with a neurologist and an established diagnosis of MS, access to treatment is impossible. Therefore, the loss of chance may occur from the disease onset and the time to get the diagnosis. An exploration of the factors involved in the diagnosis delay might help to prevent this. In addition, other factors (e.g. lifestyle factors, and comorbidities), not measured

in this study, may affect the previously observed relationship between education level and MS disability²⁹. Indeed, we can assume that the impact of the socioeconomic status on health events is a consequence of complex interactions among biological mechanisms, lifestyles, and healthcare system³⁰. Regarding the healthcare system, in France, the universal health care system provides a universal service to each citizen irrespective of wealth, age or social status. However, it does not prevent social or territorial inequalities in access. A well-defined subgroup of patients from OFSEP, called OFSEP High-Definition (<https://www.ofsep.org/en/hd-cohort>), will give the opportunity to further explore the links between socioeconomic factors (education, as well as income and residence area), lifestyle factors (eg tobacco and alcohol consumption, physical exercise), comorbidity and disability progression. A better understanding of this association would help to adapt care in order to limit social disparities in disease progression, for instance using targeted therapeutic education sessions.

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Authors' contributions: M. Lefort designed the study, analysed data, interpreted the results and drafted the manuscript. O. Dejardin contributed to the study design, to the interpretation of the results and to the writing of the manuscript. E. Berger, J.P. Camdessanché, J. Ciron, P. Clavelou, J. De Sèze, M. Debouverie, O. Heinzlef, P. Labauge, D.A. Laplaud , L. Michel, C. Lebrun-Frény, T. Moreau, J. Pelletier, A. Ruet , E. Thouvenot, S. Vukusic, and H. Zephir contributed to data collection and the final version of the manuscript. G. Defer contributed to data collection, to the study design, to the interpretation of the results and to the writing of the manuscript. E. Leray designed and directed the study and drafted the manuscript

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References

1. Filippi M, Or AB-, Piehl F, et al. Multiple sclerosis. *Nat Rev*. 2018;4:1–27.
2. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology*. 2014;83:278–286.
3. Dobson R, Rice DR, D’hooghe M, et al. Social determinants of health in multiple sclerosis. *Nat Rev Neurol*. Springer US; 2022;18:723–734.
4. D’hooghe MB, Haentjens P, Van Remoortel A, De Keyser J, Nagels G. Self-reported levels of education and disability progression in multiple sclerosis. *Acta Neurol Scand*. 2016;134:414–419.
5. Briggs FBS, Thompson NR, Conway DS. Prognostic factors of disability in relapsing remitting multiple sclerosis. *Mult Scler Relat Disord* [online serial]. Elsevier B.V.; 2019;30:9–16. Accessed at: <https://doi.org/10.1016/j.msard.2019.01.045>.
6. Harding KE, Wardle M, Carruthers R, et al. Socioeconomic status and disability progression in multiple sclerosis. *Neurology* [online serial]. Epub 2019 Feb 22.:10.1212/WNL.00000000000007190. Accessed at: <http://www.neurology.org/lookup/doi/10.1212/WNL.00000000000007190>.
7. Calocer F, Dejardin O, Kwiatkowski A, et al. Socioeconomic deprivation increases the risk of disability in multiple sclerosis patients. *Mult Scler Relat Disord* [online serial]. Elsevier B.V.; 2020;40:101930. Accessed at: <https://doi.org/10.1016/j.msard.2020.101930>.
8. Chambaud L. Accès aux soins : éléments de cadrage. *Regards*. 2018;53:19–28.
9. Minden SL, Hoaglin DC, Hadden L, Frankel D, Robbins T, Perloff J. Access to and utilization of neurologists by people with multiple sclerosis. *Neurology*. 2008;70:1141–1149.
10. Roux J, Guilleux A, Lefort M, Leray E. Use of healthcare services by patients with multiple sclerosis in France over 2010–2015: a nationwide population-based study using health administrative data. *Mult Scler J - Exp Transl Clin*. 2019;5:205521731989609.

11. Flemmen HØ, Simonsen CS, Broch L, et al. The influence of socioeconomic factors on access to disease modifying treatment in a Norwegian multiple sclerosis cohort. *Mult Scler Relat Disord*. 2022;61.
12. Reyes S, Suarez S, Allen-Philbey K, et al. Socioeconomic status and disease-modifying therapy prescribing patterns in people with multiple sclerosis. *Mult Scler Relat Disord* [online serial]. Elsevier B.V.; 2020;41:102024. Accessed at: <https://doi.org/10.1016/j.msard.2020.102024>.
13. Calocer F, Dejardin O, Droulon K, Launoy G, Defer G. Socio-economic status influences access to second-line disease modifying treatment in Relapsing Remitting Multiple Sclerosis patients. Ramagopalan S V, editor. *PLoS One*. Public Library of Science ({PLoS}); 2018;13:e0191646.
14. Gómez-Figueroa E, de Saráchaga AJ, García-Estrada C, et al. Socioeconomic status and access to multiple sclerosis treatment in Mexico. *Mult Scler Relat Disord*. 2021;52.
15. Vukusic S, Casey R, Rollot F, et al. Observatoire Français de la Sclérose en Plaques (OFSEP): A unique multimodal nationwide MS registry in France. *Mult Scler J*. Epub 2018.:1–5.
16. Confavreux C, Compston DAS, Hommes R, McDonald WI, Thompson AJ. EDMUS, a European database for multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1992;55:671–676.
17. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria”. *Ann Neurol*. Free University, Amsterdam, the Netherlands; National Multiple Sclerosis Society and Scientific and Clinical Review Associates, LLC, New York, NY; Centre Hospitalier Regional Universitaire Rennes, Rennes, France; Neuroimaging Research Unit, Department of ; 2005;58:840–846.
18. Poser CM, Paty DW, Scheinberg L, et al. New Diagnostic Criteria for Multiple Sclerosis : Guidelines for Research Protocols. *Ann Neurol*. 1983;13:227–231.
19. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33:1444–1452.

20. Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med. England*; 2002;21:2175–2197.
21. Clements M. *Rstpm2 : a Simple Guide*.
22. Clements M. *Introduction to the rstpm2 package*. Epub 2003.
23. Owens T, Evangelou N, Whynes DK. Rationing and deprivation: Disease-modifying therapies for multiple sclerosis in the United Kingdom. *Eur J Heal Econ*. 2013;14:315–321.
24. Flemmen HØ, Simonsen CS, Broch L, et al. Maternal education has significant influence on progression in multiple sclerosis. *Mult Scler Relat Disord*. 2021;53.
25. Debouverie M, Laforest L, Van Ganse E, et al. Earlier disability of the patients followed in Multiple Sclerosis centers compared to outpatients. *Mult Scler*. 2009;15:251–257.
26. Arpey NC, Gaglioti AH, Rosenbaum ME. How socioeconomic status affects patient perceptions of health care: A qualitative study. *J Prim Care Community Heal*. 2017;8:169–175.
27. Willems S, De Maesschalck S, Deveugele M, Derese A, De Maeseneer J. Socio-economic status of the patient and doctor-patient communication: Does it make a difference? *Patient Educ Couns*. 2005;56:139–146.
28. Job C, Adenipekun B, Cleves A, Samuriwo R. Health professional’s implicit bias of adult patients with low socioeconomic status (SES) and its effects on clinical decision-making: A scoping review protocol. *BMJ Open*. 2022;12.
29. Marrie RA, Fisk JD, Fitzgerald K, Kowalec K, Maxwell C, Rotstein D, Salter A, Tremlett H. Etiology, effects and management of comorbidities in multiple sclerosis: recent advances. *Front Immunol*. 2023 May 30;14:1197195. doi: 10.3389/fimmu.2023.1197195.
30. Harper S, Lynch J. Measuring Health inequalities. *Methods Soc Epidemiol*. 2006. p. 134–168.

Table 1: Baseline characteristics of patients with Relapsing-onset Multiple Sclerosis (MS) between 1996 and 2014. Data are presented for the whole population and according to sex.

	All N=7563	Women N=5669	Men N=1904
Age at MS onset (years)^a	36.3±8.1	36.4±8.1	36.0±8.0
Age at MS onset (years)^b			
[25; 30]	2444 (32.3%)	1811 (32%)	633 (33.2%)
[31; 40]	3094 (40.9%)	2292 (40.5%)	802 (42.1%)
[41; 50]	1610 (21.3%)	1239 (21.9%)	371 (19.5%)
[51; max=80]	415 (5.5%)	317 (5.6%)	98 (5.1%)
MS clinical onset period^b			
[1996-1999]	1339 (17.7%)	981 (17.3%)	358 (18.8%)
[2000-2004]	1880 (24.9%)	1410 (24.9%)	470 (24.7%)
[2005-2009]	2171 (28.7%)	1589 (28.1%)	582 (30.6%)
[2010-2014]	2173 (28.7%)	1679 (29.7%)	494 (25.9%)
Education level^b			
Low	643 (8.5%)	506 (8.9%)	137 (7.2%)
Medium	3492 (46.2%)	2531 (44.7%)	961 (50.5%)
High	2329 (30.8%)	1832 (32.4%)	497 (26.1%)
Very high	1099 (14.5%)	790 (14%)	309 (16.2%)

^a mean± standard deviation, ^b N (%)

Table 2: Characteristics of patients with Relapsing-onset Multiple Sclerosis (MS) who initiated a platform therapy as first treatment between 1996 and 2014, according to sex and education level.

	All N=5703	Women N=4271	Men N=1432	p ^b	Low education level N=453	Medium education level N=2648	High education level N=1778	Very high education level N=824	p ^b
Age at MS onset (years)^a				0.196					<10 ⁻⁴
[25; 30]	1932 (33.9%)	1419 (33.2%)	513 (35.8%)		76 (16.8%)	779 (29.4%)	720 (40.5%)	357 (43.3%)	
[31; 40]	2391 (41.9%)	1793 (42%)	598 (41.8%)		187 (41.3%)	1146 (43.3%)	718 (40.4%)	340 (41.3%)	
[41; 50]	1118 (19.6%)	859 (20.1%)	259 (18.1%)		132 (29.1%)	591 (22.3%)	285 (16%)	110 (13.3%)	
[51; max=80]	262 (4.6%)	200 (4.7%)	62 (4.3%)		58 (12.8%)	132 (5%)	55 (3.1%)	17 (2.1%)	
MS clinical onset period^a				0.009					<10 ⁻⁴
[1996-1999]	979 (17.2%)	717 (16.8%)	262 (18.3%)		102 (22.5%)	496 (18.7%)	271 (15.2%)	110 (13.3%)	
[2000-2004]	1490 (26.1%)	1090 (25.5%)	370 (25.8%)		124 (27.4%)	689 (26%)	445 (25%)	202 (24.5%)	
[2005-2009]	1734 (30.4%)	1271 (29.8%)	463 (32.3%)		134 (29.6%)	778 (29.4%)	546 (30.7%)	276 (33.5%)	
[2010-2014]	1530 (26.8%)	1193 (27.9%)	337 (23.5%)		93 (20.5%)	685 (25.9%)	516 (29%)	236 (28.6%)	
Age at platform therapy start (years)^a				0.224					<10 ⁻⁴
≤40	3385 (59.4%)	2515 (58.9%)	870 (60.8%)		180 (39.7%)	1445 (54.6%)	1179 (66.3%)	581 (70.5%)	
>40	2318 (40.6%)	1756 (41.1%)	562 (39.2%)		273 (60.3%)	1203 (45.4%)	599 (33.7%)	243 (29.5%)	
MS duration at platform therapy start (years)^a				0.017					0.174
One year	2026 (35.5%)	1561 (36.5%)	465 (32.5%)		152 (33.6%)	969 (36.6%)	610 (34.3%)	295 (35.8%)	
Two years	1065 (18.7%)	792 (18.5%)	273 (19.1%)		77 (17%)	482 (18.2%)	364 (20.5%)	142 (17.2%)	
More than two	2612 (45.8%)	1918 (44.9%)	694 (48.5%)		224 (49.4%)	1197 (45.2%)	804 (45.2%)	387 (47%)	
EDSS at platform therapy start (years)^a				0.847					<10 ⁻⁴
[0;3.5]	3005 (52.7%)	2258 (52.9%)	747 (52.2%)		209 (46.1%)	1352 (51.1%)	974 (54.8%)	470 (57%)	
[4.0; 10.0]	337 (5.9%)	254 (5.9%)	83 (5.8%)		46 (10.2%)	178 (6.7%)	80 (4.5%)	33 (4%)	
Missing	2361 (41.4%)	1759 (41.2%)	602 (42%)		198 (43.7%)	1118 (42.2%)	724 (40.7%)	321 (39%)	
Number of relapses before platform therapy start^a				0.021					0.592
None	1025 (18%)	738 (17.3%)	287 (20%)		88 (19.4%)	461 (17.4%)	336 (18.9%)	140 (17%)	
One	3002 (52.6%)	2239 (52.4%)	763 (53.3%)		220 (48.6%)	1419 (53.6%)	935 (52.6%)	428 (51.9%)	
Two	1323 (23.2%)	1018 (23.8%)	305 (21.3%)		112 (24.7%)	611 (23.1%)	396 (22.3%)	204 (24.8%)	
Three and more	353 (6.2%)	276 (6.5%)	77 (5.4%)		33 (7.3%)	157 (5.9%)	111 (6.2%)	52 (6.3%)	

^a N (%) ^b chi-square test

EDSS, Expanded Disability Status Scale

Table 3: Clinical disease activity over the 10 years of follow-up from MS clinical onset in patients with Relapsing onset MS (RMS)

	Year 1 N=7,563	Year 2 N=7,444	Year 3 N=7,340	Year 4 N=7,214	Year 5 N=7,050	Year 6 N=6,852	Year 7 N=6,509	Year 8 N=6,096	Year 9 N=5,655	Year 10 N=5,184
Low education level	643	636	630	620	608	597	574	549	523	486
<i>Number of relapses</i>										
No relapse	0 (0%)	446 (70.1%)	458 (72.7%)	452 (72.9%)	441 (72.5%)	447 (74.9%)	449 (78.2%)	436 (79.4%)	420 (80.3%)	402 (82.7%)
One relapse	408 (63.5%)	134 (21.1%)	128 (20.3%)	136 (21.9%)	118 (19.4%)	121 (20.3%)	109 (19%)	93 (16.9%)	83 (15.9%)	71 (14.6%)
More than one relapse	235 (36.5%)	56 (8.8%)	44 (7%)	32 (5.2%)	49 (8.1%)	29 (4.9%)	16 (2.8%)	20 (3.6%)	20 (3.8%)	13 (2.7%)
<i>Transition into SPMS</i>	10 (1.6%)	19 (3%)	36 (5.7%)	53 (8.5%)	63 (10.4%)	84 (14.1%)	100 (17.4%)	121 (22%)	138 (26.4%)	144 (29.6%)
Medium education level	3,492	3,441	3,401	3,347	3,264	3,179	3,018	2,837	2,627	2,427
<i>Number of relapses</i>										
No relapse	0 (0%)	2333 (67.8%)	2382 (70%)	2399 (71.7%)	2367 (72.5%)	2434 (76.6%)	2365 (78.4%)	2218 (78.2%)	2058 (78.3%)	1930 (79.5%)
One relapse	2173 (62.2%)	826 (24%)	767 (22.6%)	732 (21.9%)	688 (21.1%)	589 (18.5%)	536 (17.8%)	494 (17.4%)	449 (17.1%)	420 (17.3%)
More than one relapse	1319 (37.8%)	282 (8.2%)	252 (7.4%)	216 (6.5%)	209 (6.4%)	156 (4.9%)	117 (3.9%)	125 (4.4%)	120 (4.6%)	77 (3.2%)
<i>Transition into SPMS</i>	30 (0.9%)	70 (2%)	111 (3.3%)	153 (4.6%)	222 (6.8%)	267 (8.4%)	321 (10.6%)	364 (12.8%)	407 (15.5%)	454 (18.7%)
High education level	2,329	2,286	2,248	2,205	2,166	2,099	1,987	1,845	1,695	1,551
<i>Number of relapses</i>										
No relapse	0 (0%)	1547 (67.7%)	1561 (69.4%)	1612 (73.1%)	1610 (74.3%)	1636 (77.9%)	1566 (78.8%)	1463 (79.3%)	1319 (77.8%)	1229 (79.2%)
One relapse	1452 (62.3%)	546 (23.9%)	527 (23.4%)	439 (19.9%)	437 (20.2%)	364 (17.3%)	330 (16.6%)	312 (16.9%)	316 (18.6%)	256 (16.5%)
More than one relapse	877 (37.7%)	193 (8.4%)	160 (7.1%)	154 (7%)	119 (5.5%)	99 (4.7%)	91 (4.6%)	70 (3.8%)	60 (3.5%)	66 (4.3%)
<i>Transition into SPMS</i>	6 (0.3%)	18 (0.8%)	44 (2%)	61 (2.8%)	93 (4.3%)	123 (5.9%)	151 (7.6%)	177 (9.6%)	202 (11.9%)	226 (14.6%)
Very high education level	1,099	1,081	1,061	1,042	1,012	977	930	865	810	720
<i>Number of relapses</i>										
No relapse	0 (0%)	737 (68.2%)	775 (73%)	755 (72.5%)	754 (74.5%)	756 (77.4%)	740 (79.6%)	694 (80.2%)	636 (78.5%)	578 (80.3%)
One relapse	668 (60.8%)	264 (24.4%)	222 (20.9%)	220 (21.1%)	204 (20.2%)	184 (18.8%)	165 (17.7%)	138 (16%)	145 (17.9%)	114 (15.8%)
More than one relapse	431 (39.2%)	80 (7.4%)	64 (6%)	67 (6.4%)	54 (5.3%)	37 (3.8%)	25 (2.7%)	33 (3.8%)	29 (3.6%)	28 (3.9%)
<i>Transition into SPMS</i>	5 (0.5%)	9 (0.8%)	14 (1.3%)	20 (1.9%)	31 (3.1%)	41 (4.2%)	50 (5.4%)	58 (6.7%)	72 (8.9%)	82 (11.4%)
<i>p</i> *	0.7106	0.660	0.298	0.476	0.230	0.517	0.145	0.854	0.438	0.318

between 1996 and 2014, according to education level.

Table 4: Hazard ratio estimates of the time to the indicated outcomes according to education level and stratified by sex and age at multiple sclerosis (MS) clinical onset.

	Time from MS clinical onset to first treatment ^{a,b}		Time from MS clinical onset to first platform therapy ^{a,b}		Time from platform therapy start date to treatment switch ^{a,c}	
	All patients N= 7,563		All patients N= 7,563		All patients who received a platform therapy as first treatment N=5,703	
	At one year	At five years	At one year	At five years	At one year	At five years
Women (Low education level as reference)						
Medium	0.84 [0.65; 1.08]	0.70 [0.55; 0.89]	1.01 [0.82; 1.24]	0.87 [0.7; 1.09]	1.23 [0.78; 1.93]	0.97 [0.6; 1.55]
High	0.74 [0.57; 0.96]	0.65 [0.50; 0.85]	0.94 [0.76; 1.16]	0.78 [0.62; 0.98]	1.02 [0.64; 1.63]	1.08 [0.67; 1.75]
Very high	0.77 [0.57; 1.04]	0.6 [0.44; 0.81]	0.95 [0.75; 1.21]	0.74 [0.57; 0.96]	0.92 [0.54; 1.56]	0.85 [0.48; 1.51]
Men (Low education level as reference)						
Medium	0.87 [0.6; 1.26]	0.94 [0.61; 1.46]	1.01 [0.67; 1.51]	0.97 [0.62; 1.52]	0.78 [0.38; 1.61]	0.74 [0.42; 1.29]
High	0.73 [0.5; 1.08]	0.74 [0.46; 1.19]	0.81 [0.53; 1.23]	0.81 [0.5; 1.32]	0.87 [0.41; 1.86]	0.76 [0.42; 1.36]
Very high	0.8 [0.52; 1.22]	0.7 [0.41; 1.21]	0.89 [0.57; 1.4]	0.89 [0.53; 1.51]	0.95 [0.43; 2.1]	0.62 [0.33; 1.17]
Patients ≤40 years at MS clinical onset (Low education level as reference)						
Medium	1.02 [0.8; 1.3]	0.73 [0.57; 0.95]	1.18 [0.93; 1.51]	0.8 [0.62; 1.04]	1 [0.61; 1.62]	0.68 [0.49; 0.94]
High	0.98 [0.76; 1.26]	0.60 [0.46; 0.79]	1.15 [0.9; 1.48]	0.68 [0.52; 0.89]	0.92 [0.56; 1.51]	0.66 [0.48; 0.93]
Very high	0.97 [0.74; 1.28]	0.60 [0.45; 0.82]	1.18 [0.9; 1.54]	0.68 [0.50; 0.92]	0.84 [0.49; 1.42]	0.64 [0.45; 0.92]
Patients >40 years at MS clinical onset (Low education level as reference)						
Medium	0.89 [0.69; 1.14]	0.74 [0.53; 1.03]	0.85 [0.66; 1.1]	0.99 [0.72; 1.37]	1.05 [0.54; 2.04]	1.65 [0.96; 2.83]
High	0.64 [0.47; 0.86]	0.79 [0.55; 1.12]	0.63 [0.47; 0.84]	0.98 [0.69; 1.39]	1.1 [0.55; 2.21]	1.26 [0.69; 2.29]
Very high	0.65 [0.45; 0.96]	0.62 [0.4; 0.96]	0.64 [0.44; 0.92]	0.86 [0.56; 1.33]	1.2 [0.46; 3.14]	1.19 [0.56; 2.52]

^aThe hazard ratios over time were estimated using a flexible parametric survival regression model that considered the interaction between time and education level.

^bHazard ratios were estimated with other variables fixed in the models: (1) stratified by sex, age at MS onset: [25;30], MS onset period: [1990-1999], OFSEP center: center 1; and (2) stratified by age at MS clinical onset, sex: Women, age at MS onset: [25;30] for ≤40 and [41; 50] for >40, MS onset period: [1990-1999], OFSEP center: center 1.

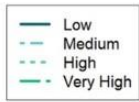
^cHazard ratios were estimated with other variables fixed in the models: (1) stratified by sex, age at platform therapy start: ≤40 years, number of relapse: none, EDSS score: [0; 3.5], treatment initiation from MS onset: within the first year, MS onset period: [1990-1999], OFSEP center: center 1; and (2) stratified by age at MS clinical onset, sex: Women, age at MS onset: [25;30] for ≤40 and [41; 50] for >40, number of relapse: none, EDSS score: [0; 3.5], treatment initiation from MS onset: within the first year, MS onset period: [1990-1999], OFSEP center: center 1.

Note: Bold highlights significant results.

Figure legend

Figure 1: Adjusted estimates of the probability of being free from the indicated outcomes at different time points during the follow-up in women (upper left panel) and men (lower left panel) with relapsing onset MS (RMS) between 1996 and 2014, according to their education level.

Figure 2: Distribution of patients according to their annual treatment exposure in the 10 years after MS clinical onset, stratified by education level.

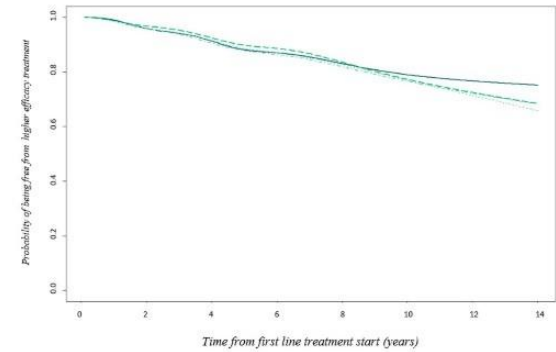
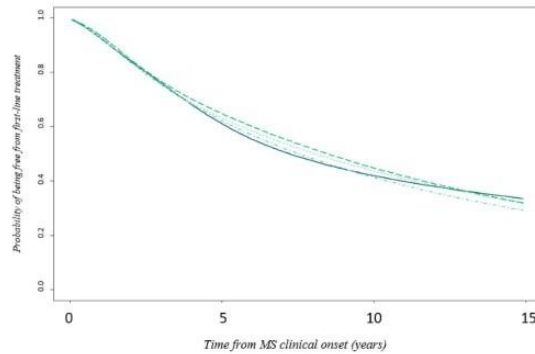
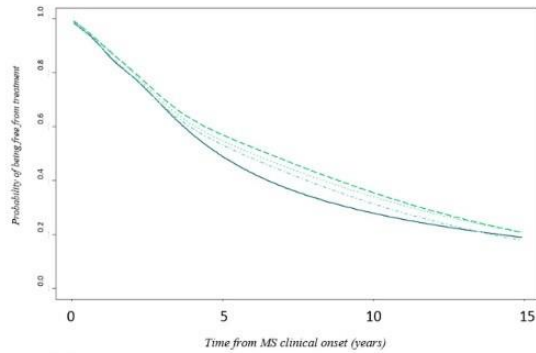


Time from MS clinical onset to first treatment

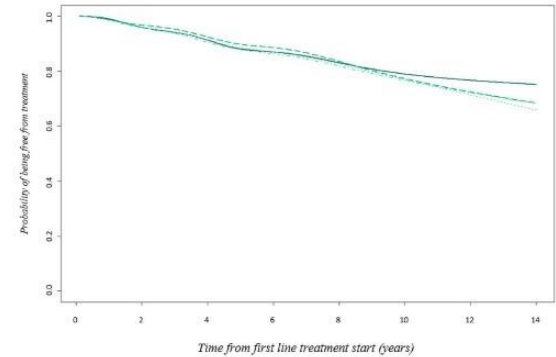
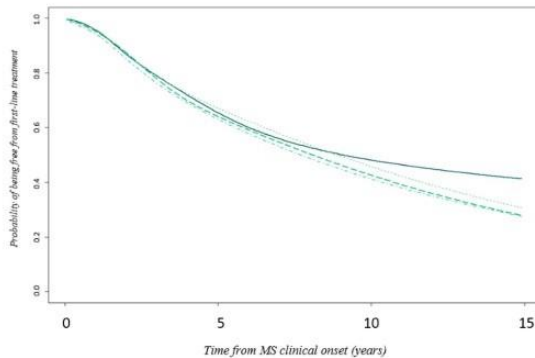
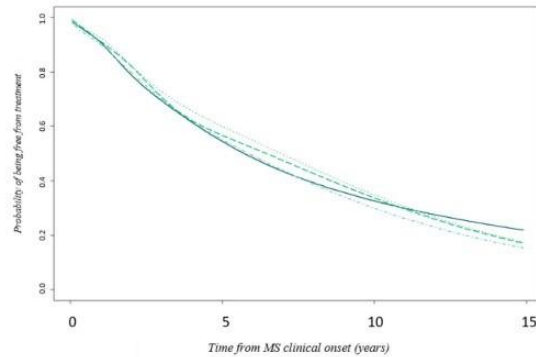
Time from MS clinical onset to first platform therapy

Time from platform therapy start to treatment switch

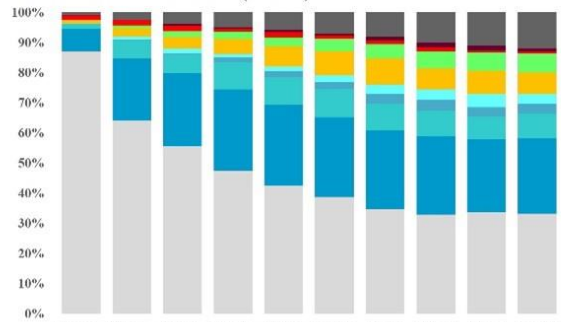
A. Women with RMS



B. Men with RMS

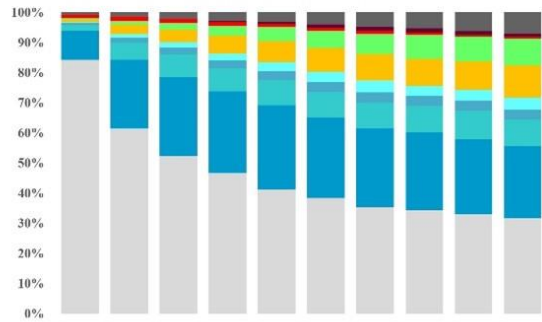


A. Low level of education (N=643)



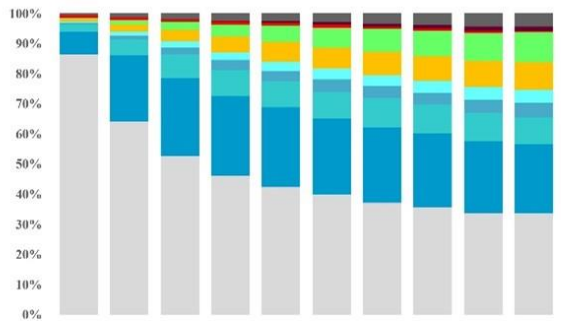
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
N	643	636	630	620	608	597	574	549	523	486
Untreated (%)	88.0	66.4	58.1	50.3	45.6	41.9	38.3	35.9	37.7	37.0
Platform therapy ^a (%)	9.2	27.8	32.5	38.6	39.6	40.4	41.3	41.5	39.2	39.7
High efficacy therapy ^b (%)	2.8	5.5	8.1	8.9	12.2	13.7	15.9	15.7	16.1	15.2

B. Medium level of education (N=3,492)



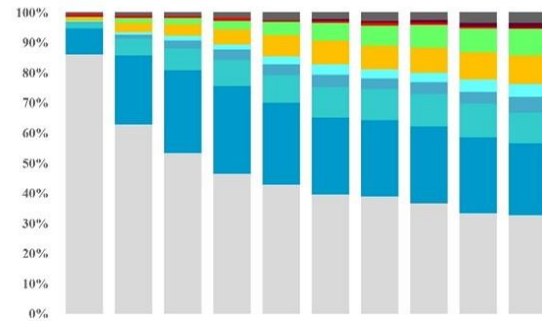
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
N	3,492	3,441	3,401	3,347	3,264	3,179	3,018	2,837	2,627	2,427
Untreated (%)	85.0	62.6	53.7	48.4	42.6	40.0	37.0	35.8	34.6	33.5
Platform therapy ^a (%)	12.5	31.4	37.8	39.6	42.4	41.9	42.0	41.3	41.3	40.1
High efficacy therapy ^b (%)	2.5	5.7	7.8	10.9	13.4	15.7	17.9	19.1	19.4	21.3

C. High level of education (N=2,329)



	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
N	2,329	2,286	2,248	2,205	2,166	2,099	1,987	1,845	1,695	1,551
Untreated (%)	87.0	65.3	54.1	47.4	43.5	40.9	38.3	36.9	34.8	34.8
Platform therapy ^a (%)	10.9	29.8	38.1	41.0	41.6	41.9	42.3	42.0	42.0	41.0
High efficacy therapy ^b (%)	2.2	4.7	7.4	10.6	13.5	15.4	17.2	18.6	20.1	21.1

D. Very high level of education (N=1,099)



	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
N	1,099	1,081	1,061	1,042	1,012	977	930	865	810	720
Untreated (%)	86.6	63.6	54.2	47.7	44.1	40.3	40.0	37.7	34.8	34.0
Platform therapy ^a (%)	11.2	30.7	39.0	43.0	42.6	43.3	42.2	43.4	44.4	43.6
High efficacy therapy ^b (%)	2.2	5.6	6.6	8.8	12.1	14.9	16.3	17.6	19.0	20.3



Supplementary Material

	All N=7563	≤40 years at MS clinical onset N=5538	>40 years at MS clinical onset N=2025
Age at MS onset (years)^a			
[25; 30]	2444 (32.3%)	2444 (56.5%)	0 (0%)
[31; 40]	3094 (40.9%)	3094 (71.6%)	0 (0%)
[41; 50]	1610 (21.3%)	0 (0%)	1610 (116.7%)
[51; max=80]	415 (5.5%)	0 (0%)	415 (30.1%)
MS clinical onset period^a			
[1996-1999]	1339 (17.7%)	1033 (23.9%)	306 (22.2%)
[2000-2004]	1880 (24.9%)	1429 (33.1%)	451 (32.7%)
[2005-2009]	2171 (28.7%)	1576 (36.5%)	595 (43.1%)
[2010-2014]	2173 (28.7%)	1500 (34.7%)	673 (48.8%)
Education level^a			
Low	643 (8.5%)	352 (8.1%)	291 (21.1%)
Medium	3492 (46.2%)	2462 (57%)	1030 (74.6%)
High	2329 (30.8%)	1829 (42.3%)	500 (36.2%)
Very high	1099 (14.5%)	895 (20.7%)	204 (14.8%)

^a N (%)

eTable 1: Baseline characteristics of patients with Relapsing onset Multiple Sclerosis (MS) between 1996 and 2014 according to age at MS clinical onset.

	All N=5703	≤40 years at MS clinical onset N=4323	>40 years at MS clinical onset N=1380
MS clinical onset period^a			
[1996-1999]	979 (17.2%)	789 (18.3%)	190 (13.8%)
[2000-2004]	1490 (26.1%)	1152 (26.6%)	308 (22.3%)
[2005-2009]	1734 (30.4%)	1283 (29.7%)	451 (32.7%)
[2010-2014]	1530 (26.8%)	1099 (25.4%)	431 (31.2%)
Age at platform therapy start (years)^a			
≤40	3385 (59.4%)	3385 (78.3%)	0 (0%)
>40	2318 (40.6%)	938 (21.7%)	1380 (100%)
MS duration at platform therapy start (years)^a			
One year	2026 (35.5%)	1521 (35.2%)	505 (36.6%)
Two years	1065 (18.7%)	784 (18.1%)	281 (20.4%)
More than two	2612 (45.8%)	2018 (46.7%)	594 (43%)
EDSS at platform therapy start (years)^a			
[0;3.5]	3005 (52.7%)	2338 (54.1%)	667 (48.3%)
[4.0; 10.0]	337 (5.9%)	202 (4.7%)	135 (9.8%)
Missing	2361 (41.4%)	1783 (41.2%)	578 (41.9%)
Number of relapses before treatment start^a			
None	1025 (18%)	736 (17%)	289 (20.9%)
One	3002 (52.6%)	2277 (52.7%)	725 (52.5%)
Two	1323 (23.2%)	1020 (23.6%)	303 (22%)
Three or more	353 (6.2%)	290 (6.7%)	63 (4.6%)

^a N (%)

EDSS, Expanded Disability Status Scale

eTable 2: Characteristics of patients with Relapsing onset Multiple Sclerosis (MS) who initiated a platform therapy as first treatment between 1996 and 2014, according to age at MS clinical onset.

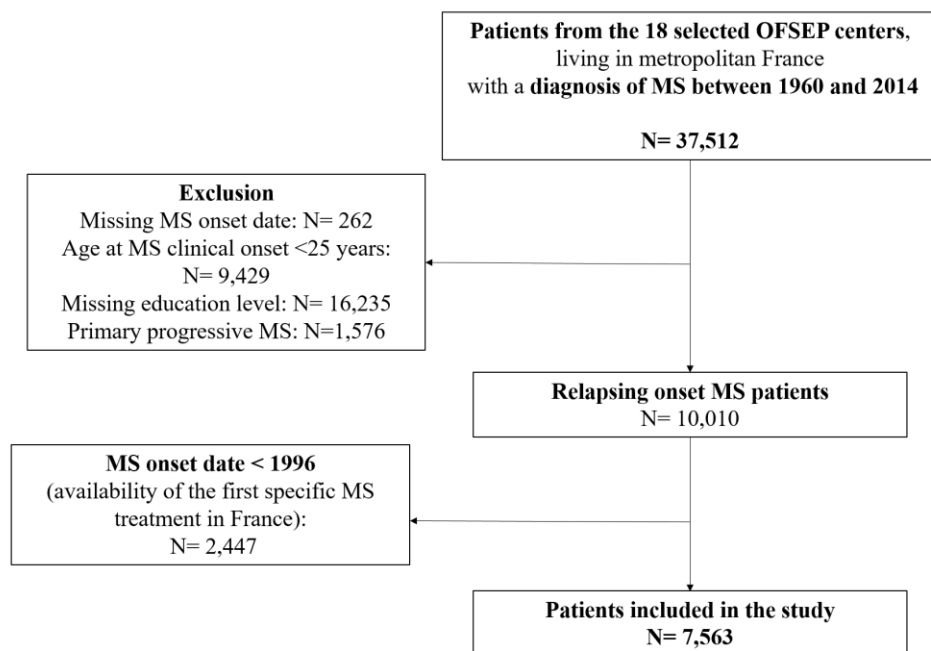
	≤40 years at MS clinical onset					>40 years at MS clinical onset				
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
	4323	4225	4125	3992	3841	1380	1322	1290	1252	1218
Low ducation level	263	258	253	246	237	190	182	175	171	170
<i>Number of relapses</i>										
No relapse	152 (57.8%)	183 (70.9%)	178 (70.4%)	184 (74.8%)	174 (73.4%)	112 (58.9%)	139 (76.4%)	135 (77.1%)	132 (77.2%)	150 (88.2%)
One relapse	72 (27.4%)	57 (22.1%)	58 (22.9%)	44 (17.9%)	45 (19%)	60 (31.6%)	36 (19.8%)	38 (21.7%)	35 (20.5%)	18 (10.6%)
More than one relapse	39 (14.8%)	18 (7%)	17 (6.7%)	18 (7.3%)	18 (7.6%)	18 (9.5%)	7 (3.8%)	2 (1.1%)	4 (2.3%)	2 (1.2%)
<i>Transition to SPMS</i>	1 (0.4%)	4 (1.5%)	10 (4.0%)	17 (6.9%)	22 (9.3%)	9(4.7%)	15(8.2%)	26(14.8%)	36(21.0%)	41(24.4%)
Medium ducation level										
<i>Number of relapses</i>	1925	1886	1835	1773	1715	723	690	672	655	643
No relapse	1154 (59.9%)	1277 (67.7%)	1327 (72.3%)	1305 (73.6%)	1304 (76%)	476 (65.8%)	510 (73.9%)	503 (74.9%)	515 (78.6%)	527 (82%)
One relapse	507 (26.3%)	449 (23.8%)	376 (20.5%)	374 (21.1%)	336 (19.6%)	185 (25.6%)	140 (20.3%)	138 (20.5%)	120 (18.3%)	97 (15.1%)
More than one relapse	264 (13.7%)	160 (8.5%)	132 (7.2%)	94 (5.3%)	75 (4.4%)	62 (8.6%)	40 (5.8%)	31 (4.6%)	20 (3.1%)	19 (3%)
<i>Transition to SPMS</i>	13(0.7%)	30(1.6%)	53(2.9%)	76(4.3%)	105(6.1%)	17(2.6%)	40(5.8%)	58(8.6%)	77(11.8%)	117(18.2%)
High ducation level										
<i>Number of relapses</i>	1438	1409	1380	1332	1279	340	329	323	310	295
No relapse	866 (60.2%)	984 (69.8%)	1012 (73.3%)	1010 (75.8%)	968 (75.7%)	231 (67.9%)	246 (74.8%)	254 (78.6%)	248 (80%)	246 (83.4%)
One relapse	388 (27%)	314 (22.3%)	279 (20.2%)	252 (18.9%)	239 (18.7%)	77 (22.6%)	65 (19.8%)	54 (16.7%)	46 (14.8%)	42 (14.2%)
More than one relapse	184 (12.8%)	111 (7.9%)	89 (6.4%)	70 (5.3%)	72 (5.6%)	32 (9.4%)	18 (5.5%)	15 (4.6%)	16 (5.2%)	7 (2.4%)
<i>Transition to SPMS</i>	2(0.1%)	7(0.5%)	20(1.5%)	31(2.3%)	51(4.0%)	4(1.2%)	11(3.3%)	24(7.4%)	30(9.7%)	42(14.2%)
Very high ducation level										
<i>Number of relapses</i>	697	672	657	641	610	127	121	120	116	110
No relapse	442 (63.4%)	485 (72.2%)	496 (75.5%)	485 (75.7%)	475 (77.9%)	90 (70.9%)	98 (81%)	101 (84.2%)	94 (81%)	93 (84.5%)
One relapse	177 (25.4%)	144 (21.4%)	130 (19.8%)	132 (20.6%)	110 (18%)	24 (18.9%)	17 (14%)	15 (12.5%)	17 (14.7%)	13 (11.8%)
More than one relapse	78 (11.2%)	43 (6.4%)	31 (4.7%)	24 (3.7%)	25 (4.1%)	13 (10.2%)	6 (5%)	4 (3.3%)	5 (4.3%)	4 (3.6%)
<i>Transition to SPMS</i>	0(0.0%)	1(0.1%)	3(0.5%)	5(0.8%)	9(1.5%)	5(3.9%)	8(6.6%)	11(9.1%)	15(12.9%)	22(20.0%)
P*	<i>0.503</i>	<i>0.448</i>	<i>0.367</i>	<i>0.241</i>	<i>0.268</i>	<i>0.192</i>	<i>0.708</i>	<i>0.075</i>	<i>0.372</i>	<i>0.504</i>

*p value of the Fisher's exact test to compare the number of relapses per year in function of the education level, from MS clinical onset to year 5 of follow-up.

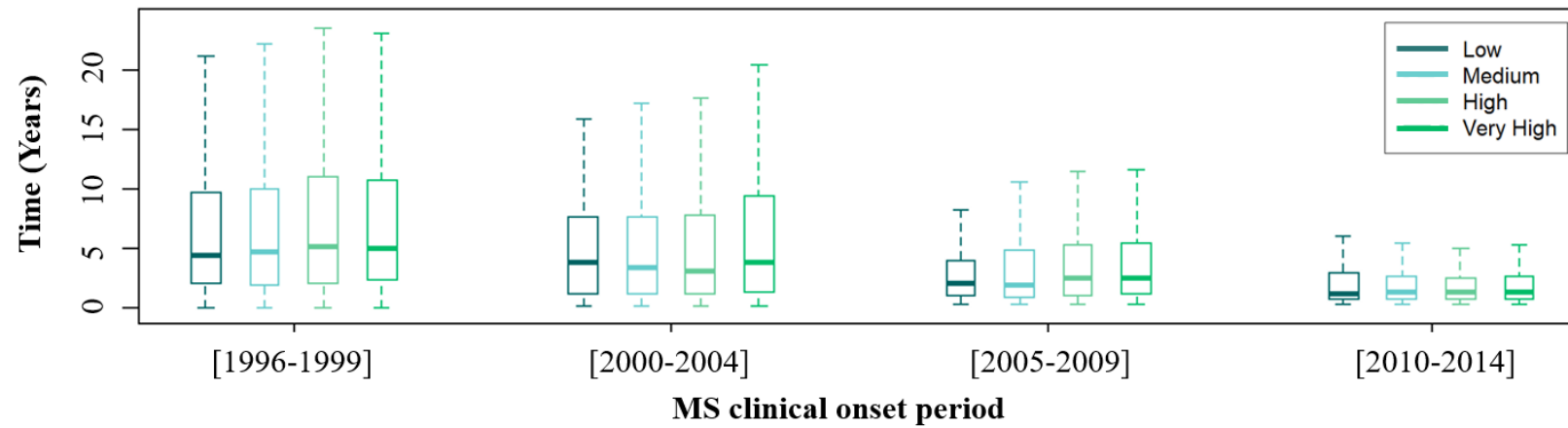
SPMS, secondary progressive multiple sclerosis.

eTable 3: Clinical disease activity (relapses and transition into secondary progressive multiple sclerosis, SPMS) during the 5 years from the first platform therapy in patients with Relapsing onset MS (RMS), according to education level and age at MS clinical onset.

eFigure1: Study flowchart.



eFigure 2: Time from multiple sclerosis (MS) clinical onset to first treatment initiation in function of the MS onset period and education level.



Comparison of time from MS clinical onset to first treatment initiation according to level of education for each MS onset period

$p^*=0.553$

$p^*=0.132$

$p^*=0.003$

$p^*=0.633$

**p value of the Kruskal-Wallis test by period*