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► To cite this version:

Mathilde Lefort, Olivier Dejardin, Eric Berger, Jean-Philippe Camdessanché, Jonathan Ciron, et al.. Association between education level and disability progression in patients with multiple sclerosis in France. *Multiple Sclerosis Journal*, 2024, 31 (1), pp.59-68. 10.1177/13524585241289274 . hal-04814408

HAL Id: hal-04814408

<https://hal.science/hal-04814408v1>

Submitted on 18 Feb 2025

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Association between education level and disability progression in patients with multiple sclerosis in France

Authors: Mathilde Lefort, PhD ⁽¹⁾, Olivier Dejardin, PhD ⁽²⁾, Eric Berger, MD ⁽³⁾, Jean-Philippe Camdessanché, MD, PhD ⁽⁴⁾, Jonathan Ciron, MD ⁽⁵⁾, Pierre Clavelou, MD, PhD ⁽⁶⁾, Jerome De Sèze, MD, PhD ⁽⁷⁾, Marc Debouverie, MD, PhD ⁽⁸⁾, Olivier Heinzlef, MD ⁽⁹⁾, Pierre Labauge, MD, PhD ⁽¹⁰⁾, David Axel Laplaud, MD, PhD ⁽¹¹⁾, Emmanuelle Le Page, MD ⁽¹²⁾, Christine Lebrun-Frény, MD, PhD ⁽¹³⁾, Thibault Moreau, MD, PhD ⁽¹⁴⁾, Jean Pelletier, MD, PhD ⁽¹⁵⁾, Aurélie Ruet, MD, PhD ⁽¹⁶⁾, Eric Thouvenot, MD, PhD ⁽¹⁷⁾, Sandra Vukusic, MD, PhD ⁽¹⁸⁾, Hélène Zephir, MD, PhD ⁽¹⁹⁾, Gilles Defer, MD ⁽²⁰⁾, Emmanuelle Leray, PhD ⁽¹⁾

⁽¹⁾ Univ Rennes, EHESP, CNRS, Inserm, Arènes - UMR 6051, RSMS (Recherche sur les Services et Management en Santé) - U 1309 – F-35000 Rennes, France

⁽²⁾ UNICAEN, CHU de Caen, INSERM U1086 ANTICIPE, Pôle de Recherche, Normandie University, Caen 14000, France

⁽³⁾ CHU de Besançon, Service de Neurologie 25 030 Besançon, France

⁽⁴⁾ CHU de Saint-Étienne, Hôpital Nord, Department of Neurology, F-42000 Saint-Étienne, France

⁽⁵⁾ CHU de Toulouse, CRC-SEP, department of Neurology, F-31059 Toulouse Cedex 9, France; Université Toulouse III, Infinity, INSERM UMR1291 - CNRS UMR5051, F-31024 Toulouse Cedex 3, France

⁽⁶⁾ CHU Clermont-Ferrand, Department of Neurology, F-63000 Clermont-Ferrand ; Université Clermont Auvergne, Inserm, Neuro-Dol, F-63000 Clermont-Ferrand, France

⁽⁷⁾ CHU de Strasbourg, Department of Neurology and Clinical Investigation Center, CIC 1434, INSERM 1434, F-67000 Strasbourg, France

⁽⁸⁾ Nancy University Hospital, Department of Neurology, Nancy, France. Université de Lorraine, APEMAC, F-54000 Nancy, France.

⁽⁹⁾ Hôpital de Poissy, Department of Neurology, F-78300 Poissy, France

⁽¹⁰⁾ CHU de Montpellier, MS Unit, F-34295 Montpellier Cedex 5, France; University of Montpellier (MUSE), F-34000 Montpellier, France

⁽¹¹⁾ Nantes Université, CHU Nantes, INSERM, Center for Research in Transplantation and Translational Immunology, UMR 1064, CIC INSERM 1413, Service de Neurologie, F-44000, Nantes, France

⁽¹²⁾ CHU Pontchaillou, CIC1414 INSERM, F-35000 Rennes France.

⁽¹³⁾ Neurology, UR2CA_URRIS, Centre Hospitalier Universitaire Pasteur2, Université Nice Côte d'Azur, Nice, France

⁽¹⁴⁾ CHU de Dijon, Department of Neurology, EA4184, F-21000 Dijon, France

⁽¹⁵⁾ Aix Marseille Univ, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, 13005 Marseille, France.

⁽¹⁶⁾ Univ. Bordeaux, F-33000 Bordeaux ; INSERM U1215, Neurocentre Magendie, F-33000 Bordeaux ; CHU de Bordeaux, Department of neurology, CIC Bordeaux CIC1401, F-33000 Bordeaux, France.

⁽¹⁷⁾ Department of Neurology, Nimes University Hospital, F-30029 Nimes Cedex 9, France ; Institut de Génomique Fonctionnelle, UMR5203, INSERM 1191, Univ. Montpellier, F-34094 Montpellier Cedex 5, France

⁽¹⁸⁾ Hospices Civils de Lyon, Service de Neurologie, sclérose en plaques, pathologies de la myéline et neuro-inflammation, Bron, France, 69677 Observatoire Français de la Sclérose en Plaques, Centre de Recherche en Neurosciences de Lyon, INSERM 1028 et CNRS UMR 5292, Lyon, France, 69003

Université de Lyon, Université Claude Bernard Lyon 1, Lyon, France, 69000 Eugène Devic EDMUS Foundation Against Multiple Sclerosis (a government approved foundation) Bron, France, 69677

⁽¹⁹⁾ CHU Lille, CRCSEP Lille, Univ Lille, U1172, F-59000 Lille, France

⁽²⁰⁾ UNICAEN, Normandie University, MS Expert Center, Department of Neurology, CHU de Caen Normandie, Caen 14000, France

Corresponding author:

Dr Emmanuelle Leray

15 avenue du professeur Léon Bernard, 35043 Rennes, France

Mail: emmanuelle.leray@ehesp.fr

Keywords: multiple sclerosis, social inequities, observational study, disability progression

Abstract

Background Studies have reported an association between socioeconomic status and disability progression in Multiple Sclerosis, but findings using the pre-MS individual socioeconomic status are missing.

Objective To investigate the association between education level and disability progression.

Methods All OFSEP patients with MS clinical onset over 1960-2014, and aged ≥ 25 years at MS onset were included. Education level was classified into four categories from low (primary/secondary school) to very high (master/doctoral degree). Time from MS onset to EDSS 4.0 was studied using flexible parametric survival models adjusted for age, period, center, and stratified by phenotype (relapsing (RMS) and primary progressive (PPMS)) and sex.

Results 11,586 patients were included (women/men ratio=2.5; age=36.7 \pm 8.6 years; follow-up duration 16.7 \pm 9.3 years; 86.4% RMS). For women with RMS, the risk of reaching the outcome at 5 years was inversely associated with the education level (Hazard Ratio medium: 0.74[0.63; 0.87], high: 0.51[0.43; 0.62], very high: 0.39[0.30; 0.50] versus low). Results were similar for men. In PPMS, the risk was significantly different between the extreme groups for women (0.45[0.28; 0.75]) and men (0.54 [0.32; 0.91]), but no gradient was evident.

Conclusion Our study showed a strong association between education level and disability progression, regardless of sex and phenotype.

Funding Research grant from Eugène Devic EDMUS Foundation against multiple sclerosis, in partnership with the ARSEP Foundation

Introduction

Multiple Sclerosis (MS) is a chronic neurological disease that starts in early adulthood, and affects more women than men¹. Two initial phenotypes may be distinguished: Relapsing onset MS (RMS) and Primary Progressive MS (PPMS)², both leading to disability over time.

It is often shown that better health is closely associated with social advantages³. Understanding the links between socioeconomic measures and health is a major objective of social epidemiology with the ultimate aim of improving equity in health. Several socioeconomic indicators can be considered (e.g. education, occupation, income)⁴.

In MS, the literature supports a potential effect of social determinants⁵. Several studies have reported a link between socioeconomic status and disability progression. In Belgium, the risk of needing unilateral walking aid) was lower in patients with >12 years of education than in patients with less⁶. The assessment of prognostic factors in patients with RMS at Cleveland Clinic (USA) showed a lower median income (at the ZIP code level) was associated with slower walking speed and higher perceived global disability, as measured using the Performance Scale⁷, a self-reported measure of MS-associated disability in eight functional domains⁸. In a cohort of patients with MS from Canada and UK, lower neighborhood-level average income, measured at MS symptom onset (± 3 years), was associated with higher risk of disability progression⁹. In France, the only study on this topic involved three MS centers and showed that the risk of disability progression was higher in patients living in a more socioeconomically deprived area than in a less socioeconomically deprived area¹⁰. Only one of these studies considered the individual socioeconomic status (i.e. education level)⁶. Socioeconomic indicators may have been measured after MS onset, which could lead to reverse causation because MS may cause a decline in socioeconomic status¹¹. Using education level, an individual characteristic that can reflect social status in early adulthood (i.e. before or at the time of MS onset), could allow reducing reverse causation issues. Indeed, a recent systematic review

suggested that education level in patients with MS is not different from the general population¹². Accordingly, our aim was to assess the association between education level and disability progression in patients with MS.

Methods

Data source

Data on patients with MS were obtained from the French network of MS expert centers (Observatoire Français de la Sclérose en Plaques; OFSEP www.ofsep.org)¹³ using the European Database for Multiple Sclerosis (EDMUS) software to collect prospective standardized data¹⁴.

Eligibility criteria

Eighteen OFSEP centers were selected because they have been following patients for several decades, thus allowing sufficient follow-up to study long-term outcomes¹⁵. All patients, living in metropolitan France, with a diagnosis of MS^{16,17}, and MS onset between 1960 and 2014 were eligible. Age at MS onset ≥ 25 years was an additional inclusion criterion to avoid reverse causation. Patients without known education level were excluded.

Variables

The main variable of interest was education level, assessed by the highest diploma. Four categories were defined: i) low (primary/junior secondary school); ii) medium (senior secondary school); iii) high (undergraduate degree); and iv) very high level (master/doctoral degree). Other covariates measured at MS onset were sex, age, year, phenotype (RMS or PPMS), and center.

Outcomes

The main outcome was the time from MS onset to the 6-month confirmed and sustained Expanded Disability Status Scale (EDSS) score of 4.0. The secondary outcome was the equivalent for EDSS 6.0. Both times were right-censored at the date of outcome attainment, or

at 20 years after MS onset, or the last visit at the extraction date (December, 2020) if the follow-up duration was <20 years. In an exploratory analysis, the number of relapses in patients with RMS during the three years following MS onset was analyzed (Supplement 1).

Statistical analysis

The characteristics of the included and excluded patients were described for the whole sample and according to phenotype. Then, flexible parametric survival regression models were used¹⁸, as they allow a greater flexibility in the specification of the baseline log cumulative survival function and in dealing with non-proportional hazards. Therefore, they provide a better fit to the data than the standard Cox models^{19,20}, as they can include interactions between time and education and estimate the hazard ratios over time. They also allow a graphical representation of the adjusted survival estimates¹⁹⁻²¹. They 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 (AIC) that, when minimized, denotes the better fit to the data. Models were adjusted for age at MS clinical onset, period (1960-1989, 1990-1999, 2000-2004, 2005-2009, and 2010-2014) and center, and stratified by MS phenotype and sex. Stratification allows to have separate results and see if the association between education and progression 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 MS phenotype, since these groups have different characteristics. Statistical analyses were performed with R software (R 4.0.3). The flexible survival regression analysis using the Royston-Parmar spline model was performed with the `rstpm2` R package^{19,21}.

Secondary analysis

Associations between education level and disability progression were also studied by stratifying patients in five groups according to MS onset period. To avoid different follow-up durations

and a different chance to observe outcomes, the time before reaching EDSS 4.0 in the five years following MS onset was studied using a flexible parametric survival model, adjusted for sex, age and center, stratified by phenotype, without time interaction (i.e a constant hazard ratio over time).

Standard Protocol Approvals, Registrations, and Patient Consents

All patients enrolled in the OFSEP database provided informed consent for participation and that their data be stored and used for research. Data confidentiality and safety were ensured according to the French recommendations (CNIL; May 6, 2014; request 914.066; authorization decision DR-2014-110).

Results

Characteristics of the study population

Education level was missing for 16,235 patients (58%) who were excluded (eFigure S1), Thus, 11,586 MS patients were included. Table 1 shows the comparison of baseline characteristics of the included and excluded patients. Although significant differences were detected due to the high number of patients (high statistical power), the differences did not appear as clinically significant (women/men ratio: 2.5 and 2.3; mean age: 36 and 37 years). The biggest discrepancy was the MS onset period because education level was more frequently reported in the recent period, which reflects better data collection over time (less missing values)¹³. The mean follow-up duration was 16.7±9.3 years for the included patients and 14.5±10.0 years for the excluded patients ($p < 10^{-4}$). When looking at the occurrence of the outcomes over follow-up duration, the two groups had very similar curves.

Baseline characteristics according to the initial MS phenotype

Overall, 10,010 patients had RMS (86%) and 1,576 (14%) had PPMS (Table 2). As expected, patients with RMS were mainly women while in patients with PPMS, the sex ratio was close to

one. In the RMS group, approximately 43% of women and 40% of men had a high or very high education level. In the PPMS group, 28% of women and 31% of men had a high or very high education level.

Association between education level and MS disability progression

Patients with RMS. Among women, the adjusted survival curves (Figure 1A – left panels) showed that the probability of being free from EDSS 4.0 decreased over time for all education level groups. Nevertheless, the outcome was reached later in patients with very high education level compared with the low education group (-15% in the probability). The right panels show the magnitude of the differences between the extreme groups. Comparison of the hazard ratios (Figure 2) indicated that the risk of reaching EDSS 4.0 progressively decreased with the increasing education level. This significant gradient was observed at 5 and 10 years after MS onset. At 20 years, results were no more significant, probably due to the lack of statistical power. Similar findings were observed for men at 5 years (Figure 2). At 10 years, the gradient of risk was no more observed, although the difference in the probability of being free from EDSS 4.0 between very high and low education level groups persisted (-25%) (Figures 1B and 2). For the secondary outcome (EDSS 6.0), similar findings were observed for men and women (eFigure S2). It can be noted that the frequency of follow-up visits was slightly lower in patients with lower education level (median annual number of visits: 0.7 in low vs 0.9 in medium, high and very high, eTable S1). The exploratory analysis about the risk of relapse in the first three years according to the level of education did not show any association (Incidence Rate Ratio [95% CI] medium: 0.99[0.95; 1.04], high: 0.99[0.94; 1.04], very high: 0.97[0.91; 1.02] versus low; eTable S2).

Patients with PPMS. The difference in the probability of being free from EDSS 4.0 between the very high and low education level groups persisted in women and men (Figure 1C-D), but no gradient was demonstrated, as indicated by the absence of significant differences between

the medium and high education level groups and the low education level group (Figure 2). Here again, the frequency of visits was slightly lower in patients with lower education level (0.7 in low vs 0.8 in medium, high and very high; eTable S1).

Secondary analysis

The proportion of patients with high to very high education level was higher in patients with a more recent MS onset (eTable S3). Analysis according to the period showed that in the RMS group (Figure 3), the differences in disability progression according to the education level increased (i.e. stronger gradient over time). In the PPMS group, results were not statistically significant.

Discussion

The present study confirmed the higher risk of disability progression in people with MS having lower socioeconomic status, as measured by level of education^{6,8-10}. We found, in the RMS group, a gradient in the risk of disability progression after MS onset according to the level of education: a reduction of almost 50% in patients with very high education level compared to patients with low education level. This effect was stronger in women. On the other hand, no association was found between early clinical activity (relapses in the first three years) and education level. Moreover, for the first time, our study showed that this social gradient became stronger for patients with a more recent diagnosis. In patients with PPMS, no gradient was detected, although differences were observed between the extreme groups.

Among previous studies on the topic, only one used the patients' level of education⁶ and showed that in RMS, the risk of reaching the EDSS score of 6.0 was reduced by 32% in patients who reported >12 years of education compared with patients who reported <12 years of education.

Conversely, it did not find any association in patients with PPMS⁶. Based on contextual socioeconomic factors, Harding and colleagues⁹, in Canada, showed that a higher average income was associated with a lower risk of reaching the EDSS scores of 6.0 (-10%) and 4.0 (-7%). Calocer and colleagues¹⁰ found that the risk of reaching EDSS scores of 4.0 and 6.0 was higher in more socioeconomically deprived areas than in the less socioeconomically deprived area in France. Our findings, obtained using different indicators and statistical methods, highlighted the existence of social inequalities in MS disability progression.

Education is widely considered a proxy of cognitive reserve, and higher cognitive reserve was shown to be associated with higher neuropsychological performance among people with MS²². So our findings may be in favor of a relation between cognitive reserve and EDSS-related disability progression, which mainly reflects physical decline. Moreover, we do think that using the education level gives the opportunity to capture the patients' knowledge level and their ability to communicate with health services and understand information about their health⁴. It may be a good proxy of health literacy (i.e. the capacity to obtain, process, and understand the health information needed to make more effective use of information and make appropriate health decisions²³). An integrative review explored findings on the mediating role of health literacy in the relationship between socioeconomic and health disparities²⁴. They confirmed that a disadvantaged social position contributes to lower health literacy, which is strongly influenced by the educational attainment. However, cognitive skills and performance do not depend solely on the highest diploma obtained, and there are educational opportunities outside school²⁵. In addition, we cannot exclude that brain damage in MS (that may start before clinical onset) might affect cognitive performances and thus education²⁶, although a recent systematic review showed that the education level in patients with MS was not different compared with the general population¹². Also, it has been reported that the time between MS onset and diagnosis was shorter in patients whose mothers had >12 years of education than in patients whose mothers

had a lower education level²⁷. This is important because delayed diagnosis leads to delayed treatment which is associated with a higher risk of disability progression²⁸⁻³⁰. Therefore, education level seems to be a good indicator to study the effect of the socioeconomic status on MS, but is not flawless. First, the results would have been strengthened if we could have completed the analysis using additional indicators related to occupation/work and income. However, these data were not available. Second, collection of education level might be difficult, as indicated by the high proportion of missing data. The comparison of patients with and without education level suggests that excluded patients had more often older MS onset date. The use of imputation methods was considered; however, the high proportion of missing data and the restricted numbers of available variables for imputation would have led to a complex interpretation of the results. Two subgroups were considered to study the impact of missing data: i) only centers with the largest number of available data; and ii) only patients with MS onset over 2005-2014, and results were similar to what obtained with the main analysis (not shown).

It is important to keep in mind that the average education level can vary over time⁴. In France, the proportion of people with high education level has increased over time. Specifically, in 2019, the proportions of 55 to 64-year-old and of 25 to 34-year-old French people with at least a bachelor degree were 40.1% and 72.6% for women and 35.6% and 66.2% for men, respectively³¹. This difference is probably linked to changes in education opportunities, particularly easier access to higher education in France. Thus, people who did not reach a bachelor degree in recent years were probably more disadvantaged at other levels (family, social history...), even before attending school, than people with a comparable level of education at the beginning of our study period (in the 1960s)³². This difference is probably even stronger in women who represent 75% of people with MS. In agreement, the secondary analysis showed that the social gradient became stronger in patients with more recent disease onset. This result may mirror the widening disparities among socioeconomic levels over time. We did not define

specific education categories according to the period of MS onset because this would have been complex to put in place and could have led to complex interpretations.

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 system³³. In France, the universal health care system provides a universal service to each citizen irrespective of wealth, age or social status. One limitation of our study is that confounders, such as lifestyle factors (eg smoking status, obesity, etc), comorbidity and lifecourse data (e.g. family health history) were not measured. They were not available for the entire OFSEP cohort. A well-defined subgroup of patients from OFSEP, called OFSEP High-Definition (<https://www.ofsep.org/en/hd-cohort>), recently included additional data. In the future, this cohort will give the opportunity to adjust for the lifestyle factors and comorbidity and to include other socioeconomic indicators such as income and residence area, which will provide a better understanding of mechanisms behind our findings. We did not include time-dependent variables in the modeling strategy, which means that effects of MRI and disease-modifying therapies were not examined.

We also observed a lower frequency of follow-up visits among patients with lower education level, which can lead to a decreased chance of collecting outcomes. It can also reflect a risk of inappropriate care and/or therapeutic management or a decreased adherence. In addition, to limit reverse causation bias, we excluded patients <25 years old. However, we cannot exclude that patients with a master/doctoral degree got it after 25 years old or after MS onset.

Regarding methodology, we used a flexible parametric survival regression. This gives considerable flexibility in the construction of the linear predictor, with possible interactions between time and covariates. Such model allowed highlighting that the education level effect was stronger in the first years after MS onset. After several years, disability progression seems to become unavoidable and the education level may not have a significant effect any longer.

Education seems to act on disability progression only in the first years of the disease course (at 5 years for both sexes, and at 10 years for women).

To conclude, our study showed a gradient in the risk of disability progression according to the level of education: the risk progressively decreased from low to very high education level. These findings highlight the importance of considering the education level in MS care and management. Besides demographic and clinical factors, the social background should be an integral part of the decision-making process between healthcare professionals and patient to adapt the level of information and to offer a more equitable care. Moreover, as MS might increase socioeconomic disparities¹² (for instance due to negative consequences of occupational trajectories), preventive measures should be put in place as early as possible to limit social inequalities and deprivation accumulation. Future work on that dataset will evaluate the impact of the education level on access to treatment, by studying the time between MS onset and first treatment or therapeutic escalation.

Acknowledgments

Disclosure of potential conflicts of interest: M. Lefort, O. Dejardin, M. Debouverie, C. Lebrun-Frény and J. Pelletier had nothing to disclose. E. Berger disclosed honoraria and consulting fees from Novartis, Sanofi Aventis, Biogen, Genzyme, Roche and Teva Pharma. J.P. Camdessanché disclosed consulting and lecturing fees from Akcea, Alexion, Alnylam, Argencx, Biogen, Bristol Myers Squibb, CSL-Behring, Genzyme, Grifols, Laboratoire Français des Biotechnologies, Merck-Serono, Natus, Novartis, Pfizer, Pharmalliance, UCB Pharma, Teva, SNF-Floerger; travel grants from Akcea, Alexion, Alnylam, Argencx, Biogen, CSL-Behring, Genzyme, Grifols, Laboratoire Français des Biotechnologies, Merck-Serono, Natus, Novartis, Pfizer, Teva, SNF-Floerger. J Ciron disclosed consulting, serving on a scientific advisory board, speaking, or other activities with Biogen, Novartis, Merck, Sanofi-Genzyme, Roche, Celgene-BMS, Alexion. P. Clavelou disclosed consulting and lecturing fees, travel grants and unconditional research support from Biogen, Janssen, Medday, Merck, Novartis, Roche,

Sanofi-Genzyme and Teva Pharma. J. De Sèze disclosed consulting and lecturing fees, travel grants and unconditional research support from Biogen, Genzyme, Novartis, Roche, Sanofi Aventis and Teva Pharma. O. Heinzlef disclosed consulting and lecturing fees from Bayer Schering, Merck, Teva, Genzyme, Novartis, Almirall and BiogenIdec, travel grants from Novartis, Teva, Genzyme, Merck Serono and Biogen Idec and research support from Roche, Merck and Novartis. P. Labauge disclosed consulting and lecturing fees, travel grants and unconditional research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, and Teva Pharma. D.A. Laplaud disclosed served on scientific advisory boards for Alexion, BMS, Roche, Sanofi, Novartis, Merck, Janssen and Biogen, received conference travel support and/or speaker honoraria from Alexion, Novartis, Biogen, Roche, Sanofi, BMS, Teva Pharma and Merck and received research support from Fondation ARSEP, Fondation EDMUS and Agence Nationale de la Recherche. E. Le Page disclosed consulting or lectures, and invitations for national and international congresses from Biogen, Merck, Teva, Sanofi-Genzyme, Novartis Alexion, research support from Teva and Biogen academic research grants from PHRC and LFSEP, and travel grant from ARSEP Foundation. T. Moreau disclosed fees as scientific adviser from Biogen, Medday, Novartis, Genzyme, Sanofi. A. Ruet disclosed Consultancy fees, speaker fees, research grants (non-personal), and/or honoraria approved by the institutions from Novartis, Biogen Idec, Genzyme, Roche, and Merck. E. Thouvenot disclosed consulting and lecturing fees, travel grants or unconditional research support from the following pharmaceutical companies: Actelion, Biogen, Celgene, Genzyme, Merck Serono, Novartis, Roche, Teva pharma; has a patent pending for biomarkers of neurodegeneration and neuroregeneration and a patent pending for a diagnosis method of multiple sclerosis (EP18305630.8) ; and received academic research support from PHRC and ARSEP Foundation. S. Vukusic disclosed lecturing fees, travel grants and research support from Biogen, BMS-Celgene, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme, Teva. H. Zephir disclosed consulting or lectures, and invitations for national and international congresses from Biogen, Merck, Teva, Sanofi-Genzyme, Novartis and Bayer, as well as research support from Teva and Roche, and academic research grants from Académie de Médecine, LFSEP, FHU Imminent and ARSEP Foundation. G. Defer disclosed Consulting and lecturing fees for Biogen, Novartis, Genzyme, Merck-Serono, Roche and Teva and funding for travel from Merck Serono, Biogen, Sanofi-Genzyme, Novartis and Teva. Institution granted for research supporting from Merck Serono, Biogen, Genzyme and Novartis. E. Leray disclosed consulting and lecture fees or travel grants

from Biogen, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Sanofi Aventis and Roche

Authors' contributions: M. Lefort designed the study, analysed data, interpreted the results and drafted the manuscript. O. Dejardin contributed to the design of the study, 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, E. Le Page, C. Lebrun-Fréney, 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 design of the study, to the interpretation of the results and to the writing of the manuscript. E. Leray designed and directed the study and drafted the manuscript

Funding: Research grant from Eugène Devic EDMUS Foundation against multiple sclerosis, in partnership with the ARSEP Foundation

Data Availability Statement: Data collection has been supported by a grant provided by the French State and handled by the "Agence Nationale de la Recherche," within the framework of the "France 2030" and Eugène Devic EDMUS Foundation against multiple sclerosis. M. Lefort had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The individual data from the present study can be obtained upon request to the OFSEP Scientific Board and after validation by the OFSEP Steering Committee (<https://www.ofsep.org/en/data-access>).

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Table 1: Comparison of baseline characteristics in patients with Multiple Sclerosis (MS) eligible for inclusion (N=27,821), according to the availability of data on their education level.

	Education level Available 11,586 (43.3%)	Education level Missing 16,235 (58.3%)	P value
Sex			
Female/Male ratio	2.5	2.3	
Females	8287 (71.5%)	11328 (69.8%)	0.002
Males	3299 (28.5%)	4907 (30.2%)	
Age at MS onset (years)	36±8.6	37±8.8	<10 ⁻⁴
MS clinical onset period			
[1960-1989]	1290 (11.1%)	4215 (26.0%)	10 ⁻⁴
[1990-1999]	3047 (26.3%)	5356 (33.0%)	
[2000-2004]	2245 (19.4%)	2994 (18.4%)	
[2005-2009]	2564 (22.1%)	2368 (14.6%)	
[2010-2014]	2440 (21.0%)	1302 (8.0%)	
MS phenotype			
Relapsing MS	10010 (86.4%)	13553 (83.5%)	<10 ⁻⁴
Primary progressive MS	1576 (13.6%)	2682 (16.5%)	
Follow-up (From MS onset to last visit)	16.7±9.3	14.5±10.0	<10 ⁻⁴

Table 2: Baseline characteristics of patients with Multiple Sclerosis (MS) (N=11,586) in function of their MS phenotype [Relapsing onset MS (RMS) and primary progressive MS (PPMS)] and sex.

	Patients with RMS			Patients with PPMS		
	All N=10,010	Women N=7,439	Men N=2,571	All N=1,576	Women N=848	Men N=728
Age at onset (years)^a	35±7.8	35±7.8	35±7.8	44±9.8	44±9.6	43±9.9
Age at onset (years)^b						
[25; 30]	3,544 (35.4%)	2,589 (34.8%)	955 (37.1%)	150 (9.5%)	65 (7.7%)	85 (11.7%)
[31; 40]	4,120 (41.2%)	3,068 (41.2%)	1,052 (40.9%)	466 (29.6%)	240 (28.3%)	226 (31%)
[41; 50]	1,908 (19.1%)	1,445 (19.4%)	463 (18%)	562 (35.7%)	318 (37.5%)	244 (33.5%)
[51; max=80]	438 (4.4%)	337 (4.5%)	101 (3.9%)	398 (25.3%)	225 (26.5%)	173 (23.8%)
MS clinical onset period^b						
[1960-1989]	1,139 (11.4%)	810 (10.9%)	329 (12.8%)	151 (9.6%)	82 (9.7%)	69 (9.5%)
[1990-1999]	2,647 (26.4%)	1,951 (26.2%)	696 (27.1%)	400 (25.4%)	212 (25%)	188 (25.8%)
[2000-2004]	1,880 (18.8%)	1,410 (19%)	470 (18.3%)	365 (23.2%)	206 (24.3%)	159 (21.8%)
[2005-2009]	2,171 (21.7%)	1,589 (21.4%)	582 (22.6%)	393 (24.9%)	212 (25%)	181 (24.9%)
[2010-2014]	2,173 (21.7%)	1,679 (22.6%)	494 (19.2%)	267 (16.9%)	136 (16%)	131 (18%)
Education level^b						
Low	1,065 (10.6%)	831 (11.2%)	234 (9.1%)	305 (19.4%)	193 (22.8%)	112 (15.4%)
Medium	4,704 (47%)	3,401 (45.7%)	1,303 (50.7%)	807 (51.2%)	420 (49.5%)	387 (53.2%)
High	2,888 (28.9%)	2,267 (30.5%)	621 (24.2%)	327 (20.7%)	184 (21.7%)	143 (19.6%)
Very high	1,353 (13.5%)	940 (12.6%)	413 (16.1%)	137 (8.7%)	51 (6%)	86 (11.8%)

^a mean± standard deviation, ^b N (%)

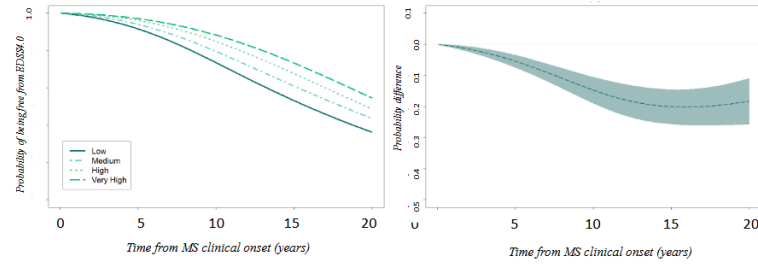
Figure legends

Figure 1: Adjusted estimates of the probability of not having a 6-month confirmed and sustained Expanded Disability Status Scale (EDSS) score of 4.0 at different time points after Multiple Sclerosis (MS) onset (left panels), according to the level of education; and difference in probability and 95% confidence interval between patients with very high and low level of education (right panels) in women and men with Relapsing onset MS (RMS) (A and B) and with Primary Progressive MS (PPMS) (C and D).

Figure 2: Hazard ratio estimates of the time before reaching the 6-month confirmed and sustained Expanded Disability Status Scale (EDSS) score of 4.0 at the indicated time points after multiple sclerosis (MS) onset in patients with Relapsing onset MS (RMS) and with Primary Progressive MS (PPMS) according to their level of education, and stratified by sex.

Figure 3: Hazard ratio estimates of the time before reaching the 6-month confirmed and sustained Expanded Disability Status Scale (EDSS) score of 4.0 within five years after multiple sclerosis (MS) onset in patients with Relapsing onset MS (RMS) and with Primary Progressive MS (PPMS) according to their level of education, and stratified by MS onset period.

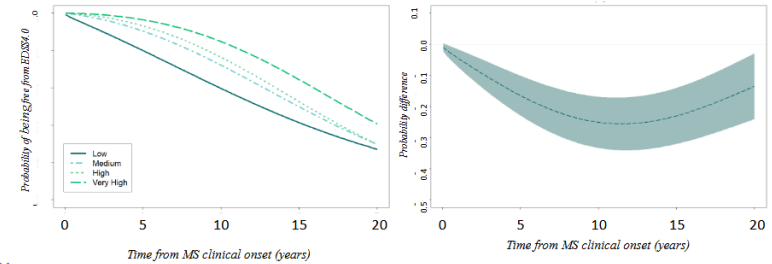
A. Women with RMS



Number at risk

	0	5	10	15	20
Low	831	717	533	374	204
Medium	3401	2936	2054	1285	705
High	2267	1979	1344	760	365
Very high	940	824	544	303	147

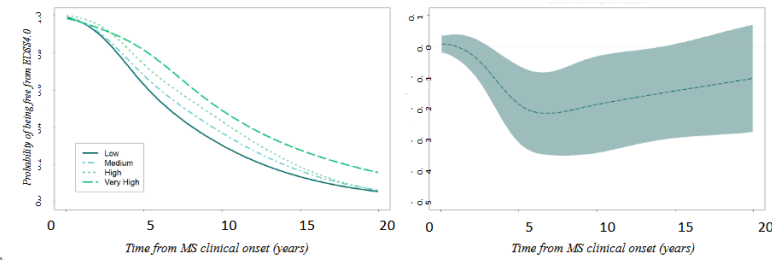
B. Men with RMS



Number at risk

	0	5	10	15	20
Low	234	195	133	95	62
Medium	1303	1110	758	461	235
High	621	541	347	183	89
Very high	413	367	258	156	80

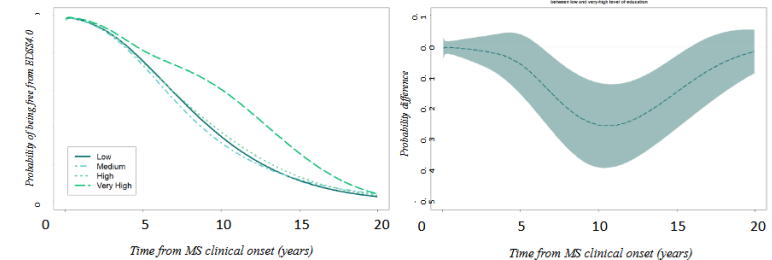
C. Women with PPMS



Number at risk

	0	5	10	15	20
Low	193	106	55	30	16
Medium	420	325	129	62	27
High	184	108	54	21	9
Very high	51	38	20	8	5

D. Men with PPMS



Number at risk

	0	5	10	15	20
Low	112	69	34	17	6
Medium	387	226	101	45	23
High	143	77	41	20	8
Very high	86	57	38	14	3

At 5 years after MS-onset*

At 10 years after MS-onset*

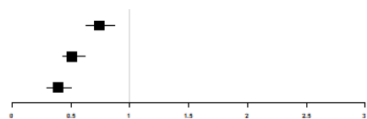
At 20 years after MS-onset*

Women with RMS

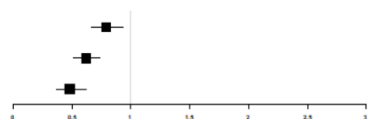
(N=7,439; N_{events}=490)

Low as reference

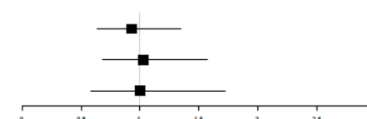
Medium 0.74 [0.63; 0.87]
 High 0.51 [0.43; 0.62]
 Very high 0.39 [0.30; 0.50]



0.79 [0.66; 0.93]
 0.62 [0.51; 0.74]
 0.48 [0.37; 0.62]



0.93 [0.64; 1.35]
 1.03 [0.68; 1.57]
 1.00 [0.58; 1.72]

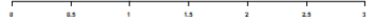


Men with RMS

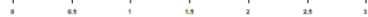
(N=2,571; N_{events}=196)

Low as reference

Medium 0.63 [0.50; 0.80]
 High 0.50 [0.38; 0.66]
 Very high 0.29 [0.20; 0.43]



0.89 [0.71; 1.12]
 0.84 [0.65; 1.09]
 0.58 [0.44; 0.78]



1.49 [1.00; 2.22]
 1.82 [1.17; 2.84]
 1.63 [0.95; 2.80]

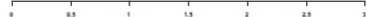


Women with PPMS

(N=848; N_{events}=338)

Low as reference

Medium 0.80 [0.60; 1.05]
 High 0.72 [0.51; 1.01]
 Very high 0.45 [0.28; 0.75]



0.91 [0.66; 1.25]
 0.86 [0.59; 1.25]
 0.76 [0.43; 1.32]



1.20 [0.53; 2.71]
 1.59 [0.58; 4.35]
 0.62 [0.11; 3.49]



Men with PPMS

(N=728; N_{events}=441)

Low as reference

Medium 1.14 [0.80; 1.61]
 High 1.02 [0.68; 1.53]
 Very high 0.54 [0.32; 0.91]



0.99 [0.70; 1.40]
 0.88 [0.59; 1.33]
 0.50 [0.32; 0.77]



0.63 [0.22; 1.84]
 0.99 [0.29; 3.35]
 2.00 [0.57; 7.05]



*Taking into account the interaction between time and education level, flexible parametric survival regression estimates the hazard ratios over time. Hazard ratios are estimated with other variables fixed in the models: Age at MS onset: [25;30]; MS onset period: [1990-1999]; OFSEP center: center 1

Number of patients by education level group:

Women with RMS: N_{low}=831, N_{medium}=3401, N_{high}=2267, N_{very high}=940. Men with RMS: N_{low}=234, N_{medium}=1303, N_{high}=621, N_{very high}=413.
 Women with PPMS: N_{low}=193, N_{medium}=420, N_{high}=184, N_{very high}=51. Men with PPMS: N_{low}=112, N_{medium}=387, N_{high}=143, N_{very high}=86.

A. Patients with RMS

Low as reference

1960-1995 (N=2,447, N_{events}=60)

Medium 0.60 [0.33; 1.09]

High and Very high 0.46 [0.23; 0.93]

1996-2005 (N=3,219, N_{events}= 211)

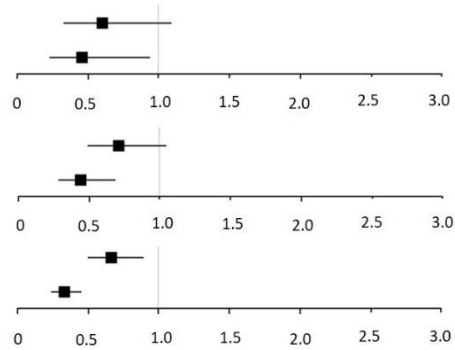
Medium 0.71 [0.49; 1.04]

High and Very high 0.44 [0.29; 0.68]

2006-2014 (N=4,344, N_{events}=415)

Medium 0.66 [0.50; 0.89]

High and Very high 0.33 [0.24; 0.45]



B. Patients with PPMS

Low as reference

1960-1995 (N=350, N_{events}=52)

Medium 0.53 [0.28; 0.99]

High and Very high 0.47 [0.22; 1.01]

1996-2005 (N=566, N_{events}=188)

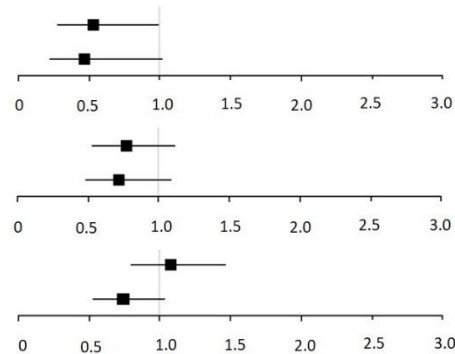
Medium 0.77 [0.53; 1.11]

High and Very high 0.72 [0.48; 1.09]

2006-2014 (N=660, N_{events}=275)

Medium 1.08 [0.80; 1.46]

High and Very high 0.74 [0.53; 1.03]



Hazard ratios are adjusted for sex, age at MS clinical onset and center; education level was not estimated with time interaction.

Supplementary Material

Figure S1: Study flowchart.

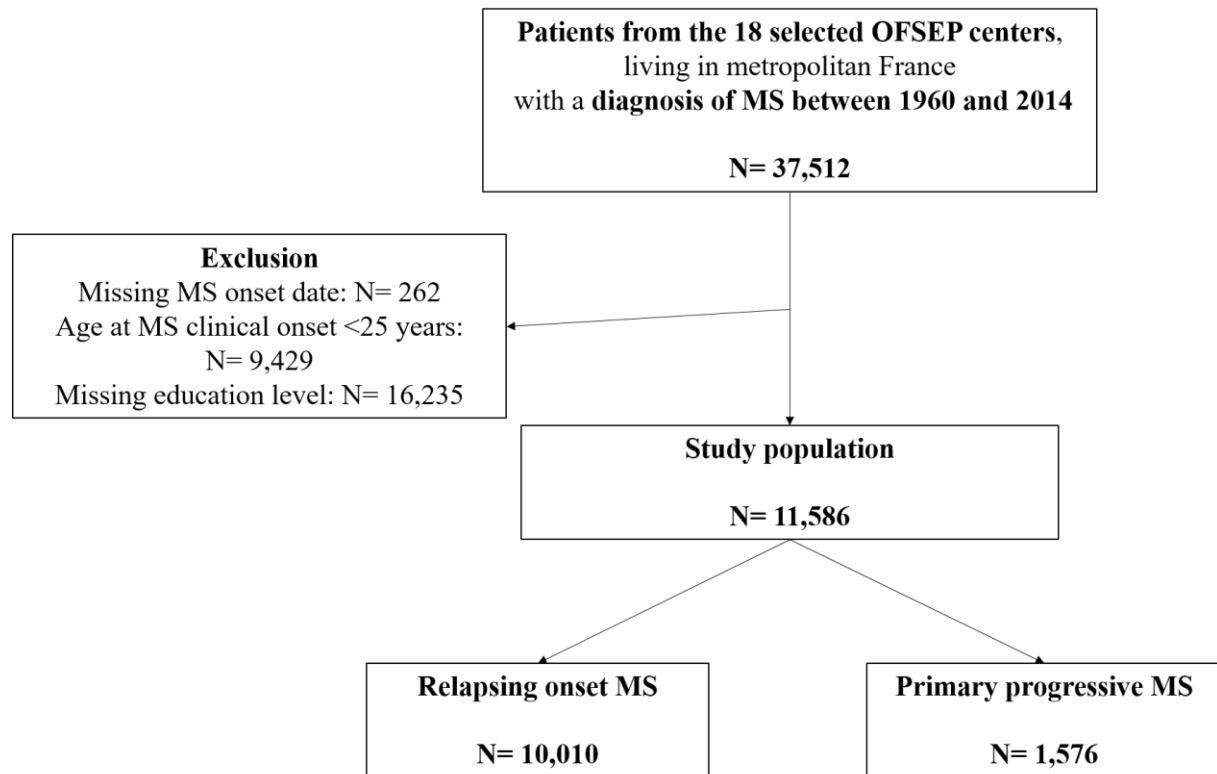
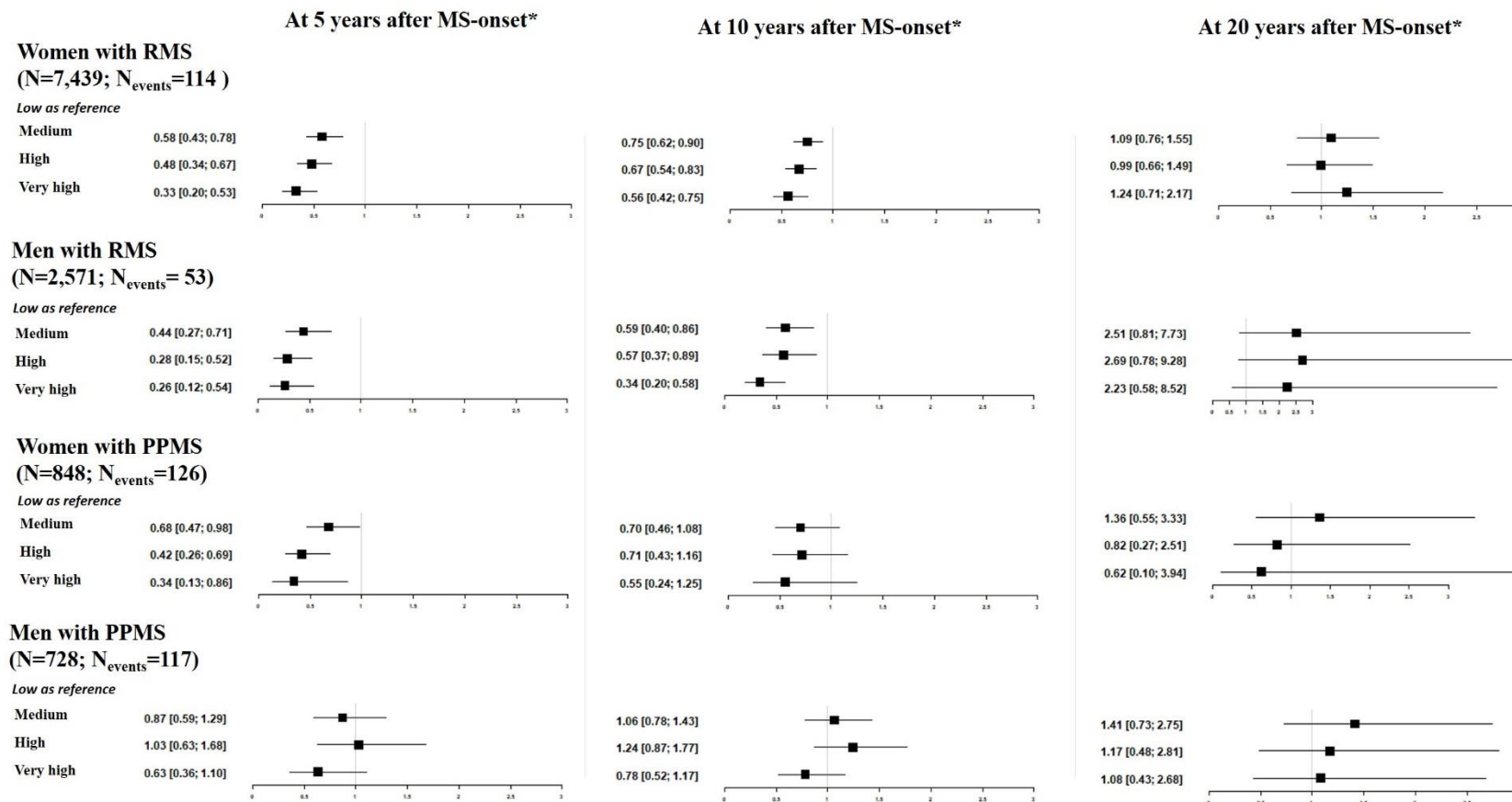


Figure S2: Hazard ratio estimates of the time before reaching the 6-month confirmed and sustained Expanded Disability Status Scale (EDSS) score of 6.0 at the indicated time points after multiple sclerosis (MS) onset in patients with Relapsing onset MS (RMS) and with Primary Progressive MS (PPMS) according to their level of education, and stratified by sex.



*Taking into account the interaction between time and education level, flexible parametric survival regression estimates the hazard ratios over time. Hazard ratios are estimated with other variables fixed in the models: Age at MS onset: [25;30]; MS onset period: [1990-1999] ; OFSEP center: center 1

Table S1: Median annual number of visits [Q1 – Q3] according to level of education, stratified on sex and MS phenotype

Level of education	Low	Medium	High	Very high	p-value*
Relapsing-onset MS	0.7 [0.4-1.3]	0.9 [0.5-1.4]	0.9 [0.5-1.4]	0.9 [0.5-1.5]	< 10 ⁻⁴
Primary progressive MS	0.7 [0.4-1.1]	0.8 [0.5-1.2]	0.8 [0.4-1.2]	0.8 [0.5-1.2]	< 0.05
Women with RMS	0.7 [0.4-1.3]	0.9 [0.5-1.4]	0.9 [0.5-1.4]	0.9 [0.5-1.5]	< 10 ⁻⁴
Men with RMS	0.6 [0.4-1.2]	0.9 [0.5-1.4]	0.9 [0.5-1.4]	0.9 [0.5-1.4]	< 10 ⁻⁴
Women with PPMS	0.7 [0.4-1.0]	0.8 [0.4-1.3]	0.8 [0.5-1.2]	0.8 [0.5-1.2]	< 0.05
Men with PPMS	0.7 [0.4-1.1]	0.8 [0.5-1.2]	0.7 [0.4-1.2]	0.8 [0.5-1.2]	0.60

*Kruskal-Wallis test

Table S2: Adjusted incidence rate ratio (IRR) of MS relapse in the first three years after MS clinical onset in patients with Relapsing onset MS (RMS) (N=10,010).

	<i>IRR</i>	<i>95% confidence interval</i>
Education level (reference Low)		
Medium	0.99	[0.95; 1.04]
High	0.99	[0.94; 1.04]
Very high	0.97	[0.91; 1.02]
Sex (reference Women)		
Men	0.94	[0.91 ; 0.97]
Age at onset as categorical variable (reference [25; 30])		
[31; 40]	0.94	[0.92; 0.97]
[41; 50]	0.88	[0.85; 0.91]
[51; max=80]	0.80	[0.74; 0.86]
MS clinical onset period (reference [1960-1989])		
[1990-1999]	1.32	[1.25; 1.39]
[2000-2004]	1.48	[1.40; 1.57]
[2005-2009]	1.56	[1.48; 1.65]
[2010-2014]	1.58	[1.49; 1.67]

Centre - variance of random effect = 0.005

Table S3: Baseline characteristics of the patients with Multiple sclerosis (MS) included in this study (N=11,586) in function of their MS phenotype [(Relapsing onset MS (RMS) and primary progressive MS (PPMS))] and MS onset period.

	Patients with RMS			Patients with PPMS		
	1960-1995	1996-2005	2006-2014	1960-1995	1996-2005	2006-2014
	N=2,447	N=3,219	N=4,344	N=350	N=566	N=660
Sex^b						
Women	1,780 (72.7%)	2,391 (74.3%)	3,268 (75.2%)	182 (52.0%)	318 (56.2%)	348 (52.7%)
Men	667 (27.3%)	828 (25.7%)	1,076 (24.8%)	168 (48.0%)	248 (43.8%)	312 (47.3%)
Age at onset (years)^a	33 ± 6.3	36 ± 7.4	37 ± 8.5	39 ± 8.3	44 ± 9.4	47 ± 9.7
Age at onset (years)^b						
[25; 30]	1,100 (45.0%)	1,052 (32.7%)	1,392 (32.0%)	60 (17.1%)	53 (9.4%)	37 (5.6%)
[31; 40]	1,026 (41.9%)	1,410 (43.8%)	1,684 (38.8%)	158 (45.1%)	158 (27.9%)	150 (22.7%)
[41; 50]	298 (12.2%)	639 (19.9%)	971 (22.4%)	97 (27.7%)	214 (37.8%)	251 (38%)
[51; max=80]	23 (0.9%)	118 (3.7%)	297 (6.8%)	35 (10%)	141 (24.9%)	222 (33.6%)
Education level^b						
Low	422 (17.2%)	335 (10.4%)	308 (7.1%)	86 (24.6%)	123 (21.7%)	96 (14.5%)
Medium	1,212 (49.5%)	1,564 (48.6%)	1,928 (44.4%)	171 (48.9%)	284 (50.2%)	352 (53.3%)
High	559 (22.8%)	907 (28.2%)	1,422 (32.7%)	61 (17.4%)	104 (18.4%)	162 (24.5%)
Very high	254 (10.4%)	413 (12.8%)	686 (15.8%)	32 (9.1%)	55 (9.7%)	50 (7.6%)

^a mean ± standard deviation, ^b N (%)