

Supplementary Material

Figure S1: Study flowchart.

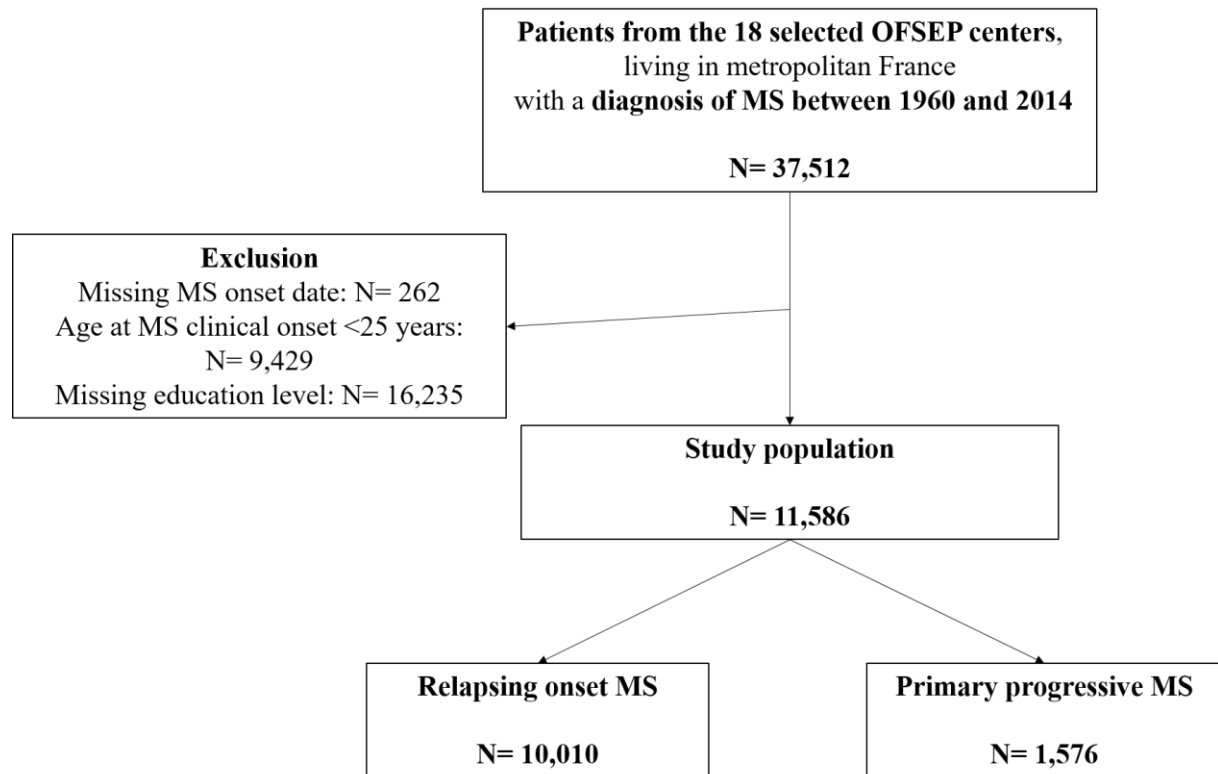
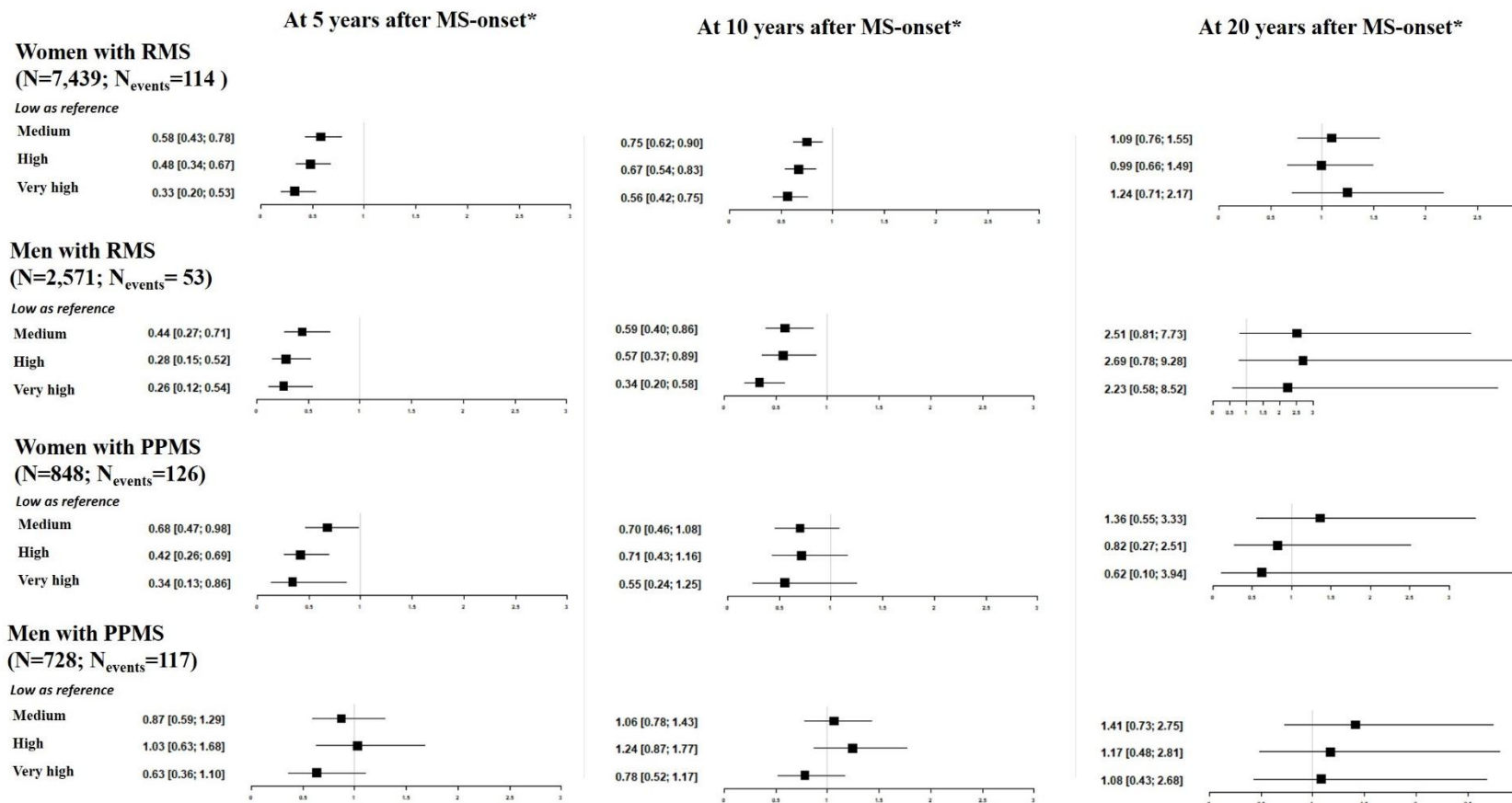


Figure S2: Hazard ratio estimates of the time before reaching the 6-month confirmed and sustained Expanded Disability Status Scale (EDSS) score of 6.0 at the indicated time points after multiple sclerosis (MS) onset in patients with Relapsing onset MS (RMS) and with Primary Progressive MS (PPMS) according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