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ORIGINAL COMMUNICATION

Effect of late-onset on multiple sclerosis phenotype and outcome: evidence from a multi-national registry

Amira Souissi · Francesco Patti · Tim Spelman · Clara Chisari · Amina Gargouri · Nevin John, et al. ***[full author details at the end of the article]***

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Abstract

Background Multiple Sclerosis (MS) severity is influenced by several factors. Understanding the impact of age at disease onset may help to better characterize clinical and disease features across age groups. This study aimed to characterize the clinical features and disability outcomes of late-onset MS (LOMS) and very late-onset MS (vLOMS), compared to adult-onset MS (AOMS).

Methods We conducted an observational study using data from the MSBase registry and categorized patients based on age at MS onset: AOMS (18–39 years), transition onset (40–49 years), LOMS (50–59 years), and vLOMS (≥ 60 years). Disease progression was assessed using the 24 week confirmed disability progression, EDSS4 and 6 milestones, conversion to secondary progressive MS(SPMS), and the first progression independent of relapse activity (PIRA) event. Cox proportional hazard regression models were used to determine unadjusted hazard ratios(HR), and propensity score inverse probability of treatment weighting(PS-IPTW) balanced covariate distributions.

Results Among 81,236 patients, 5.2% had LOMS and 1% had vLOMS. Primary progressive MS was more frequent in LOMS and vLOMS (21.7 and 24%, respectively). Patients with LOMS and vLOMS had a significantly increased risk of 24 week confirmed disability progression (HR:LOMS = 1.39, vLOMS = 1.80), EDSS 4 (HR:LOMS = 2.14, vLOMS = 2.95), EDSS 6 (HR:LOMS = 2.33, vLOMS = 6.33), SPMS (HR:LOMS = 1.62, vLOMS = 2.38), and first PIRA event (HR:LOMS = 2.12, vLOMS = 2.93).

Conclusion LOMS and vLOMS exhibited a more progressive disease onset and higher disability milestones compared with AOMS.

Keywords Multiple Sclerosis · Prognosis · Aging · Progression · Immunosenescence

Background

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system (CNS) that is likely to occur in adult patients (AOMS) aged under 40 years. However, a proportion of individuals develop initial disease manifestations after the age of 50 years, which refers to late-onset MS (LOMS) or even after the age of 60 years, which refers to very late-onset MS (vLOMS) [1]. LOMS and vLOMS present their own challenges due to diagnostic uncertainties, and potential overlap with other neurodegenerative disorders and nutritional deficiencies [2].Aging is associated with a higher prevalence of cerebrovascular diseases, which might induce increased diagnostic delay, accelerated disability progression, increased mortality and reduced quality of life [3]. Older people with MS are more likely to develop motor relapses and to experience an accelerated disability [4, 5]. In terms of imaging features, older patients had less MRI activity and more frequent lesions in the spinal cord with possible vascular white matter-associated lesions [6, 7]. The absence of knowledge regarding the safety and efficacy of disease-modifying therapies (DMTs) in this particular age group is attributable to the lack of clinical trials focusing on them. Indeed, the cut-off age for MS trials typically falls below 55 years [8]. Few studies tried to identify the characteristics of LOMS and vLOMS compared with AOMS. However, a large-scale study is still needed to highlight the impact of aging on the different age groups.

This article aims to identify the epidemiological and clinical hallmarks of LOMS and vLOMS compared with AOMS in a multinational/multicentric cohort and to compare disability outcomes between patients from these different age groups.

Methods

Patients and inclusion criteria

Longitudinal data from 90,097 MS patients treated in 48 countries were extracted from MSBase in August 2023. For inclusion, patients needed to be classified as having a clinically definite MS and to have a complete MSBase minimum data set (sex, date of birth, date of MS onset, clinical visits and disability assessment). This observational cohort study examined patients according to their age of disease onset, which was defined as the age at first initial symptoms consistent with MS. Patients were divided into 4 groups according to age at MS onset:

- **Age of onset ≥ 18 and < 40 years:** AOMS group
- **Age of onset ≥ 40 and < 50 years:** Transition onset age group—This group was isolated to better understand the age-related modifications, as patients moved from adulthood to a more advanced age.
- **Age of onset ≥ 50 and < 60 years:** LOMS group
- **Age of onset ≥ 60 years:** vLOMS group

Clinical data are presented as documented by the patient's attending physicians and recorded in the MSBase registry database. This includes age at onset, sex, first symptoms (optical pathways involvement, supratentorial symptoms, brainstem or spinal cord relapse), MS phenotype, and first recorded EDSS score (recorded at first visit in the registry). In addition to these data, first brain MRI characteristics were also extracted.

Study outcomes

To qualify for the analysis of disease activity and disability outcomes, patients in the different age groups were evaluated for:

- **Annualized relapse rate (ARR):** Total number of post-baseline relapses divided by the years of post-baseline follow-up.
- **Time to first relapse:** Time from the baseline date (first visit date, regardless of whether a patient had initiated treatment on this date or not) to the date of the first recorded post-baseline visit, or the end of the follow-up period.
- **Time to first 24 week confirmed disability progression:** Time from the initial assessment to the occurrence of the first confirmed instance of disability progression, as determined during a subsequent evaluation conducted at least 24 weeks later.
- **Time to EDSS4:** Time from the disease onset to EDSS4.
- **Time to EDSS 6:** Time from the disease onset to EDSS6.
- **Time to secondary progressive MS (SPMS):**Time from the disease onset to reach secondary progression as it was assessed by the principal investigator of each site.
- **Progression independent of relapse activity (PIRA):** was defined as an episode of confirmed disability progression with no relapse during the 90 days before the EDSS increase and during the 6 months between the EDSS increase and the confirmation of disability progression.

Standard protocol approvals, registrations, and patient consents

The study of the MSBase registry (WHO CTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee and local ethics committees in all centers.

Statistical analyses

All analyses were conducted using Stata version 18 (StataCorp. 2023. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC). Data were summarized as means, standard deviations (SD), medians, and interquartile ranges (IQR) for continuous variables and as numbers and percentages for categorical variables. Pairwise differences in time-to-event variables (time to first relapse, time to first 24 week confirmed disability progression, time to EDSS4 and 6, time to SPMS and time to first PIRA event) were analyzed using Cox proportional hazards regression models to calculate unadjusted hazard ratios (HR) and associated 95% CI in the unweighted cohorts. To adjust for potential confounding, weighted analyses were performed. Confounders for the weighted analysis were sex, baseline EDSS, first symptoms, baseline brain MRI lesion counts and time to initiate DMTs. Propensity scores (PS) weighted separately to each of the different age groups were generated using a logistic regression to estimate the predicted probability of age at MS onset on time-to-event variables. Propensity Score Inverse Probability of Treatment Weighting (PS-IPTW) was used to balance the distribution of covariates between pairs of age groups. Separate propensity score weights were derived for each of the three key age group comparisons: (1) AOMS vs LOMS; (2) AOMS vs vLOMS: and (3) AOMS vs the transition onset age group. These three comparisons were run as three separate PS-IPTW adjusted analyses. Pre

and post-weighting confounder balance was assessed via the derivation of unweighted and weighted standardized differences. Results were summarized by age at MS onset based on the Kaplan–Meier survival and failure curves for each of the three weighted cohorts compared with the AOMS group. The baseline epoch was categorized as before 2000, 2001–2005, 2006–2010, 2011–2015 and 2016 and later, based on treatment paradigms and the introduction of new classes of DMTs to examine how the changing availability of treatments influenced the progression of MS categorized by age.

Results

Of the 90,097 patients in the MSbase registry, 81,236 were enrolled: 62,503 (76.9%) had AOMS, 13,730 (16.9%) were in the transition onset group, 4188 (5.2%) had LOMS and 815 (1%) had vLOMS (Fig. 1). The AOMS group showed a higher female predominance with a female-to-male ratio of 2.45 vs 2.37 in the transition onset MS group, 1.95 in the LOMS ($p < 0.0001$) and 1.88 in the vLOMS group ($p < 0.0001$). This sex ratio was comparable beyond an onset age of 50 years. The AOMS group exhibited a higher proportion of optical (24.2%) and supratentorial pathways (21.5%) involvement in the first relapse compared with the LOMS and vLOMS groups ($p < 0.0001$).The LOMS and vLOMS groups were characterized by a higher proportion of patients exhibiting spinal cord symptoms as a first demyelinating event (LOMS: 32%—vLOMS: 33% vs AOMS: 24.8%; $p < 0.0001$). Radiological signs of activity tend to decrease as the age at MS onset increases, as does the lesion load on T2 brain MRI (Table 1).

Median time between onset and first/baseline EDSS was 3.64 years. LOMS and vLOMS groups exhibited a higher mean and median first recorded EDSS score than the AOMS ($p < 0.0001$). This difference was also significant between the LOMS (mean EDSS = 3.54 ± 2.23) and vLOMS (mean EDSS = 4.08 ± 2.18) groups, with higher results observed in the latter one ($p < 0.0001$). During AOMS, RRMS was found in 67.8% of cases compared to 44.4% during LOMS and 40.5% during vLOMS. However, the frequency of PPMS

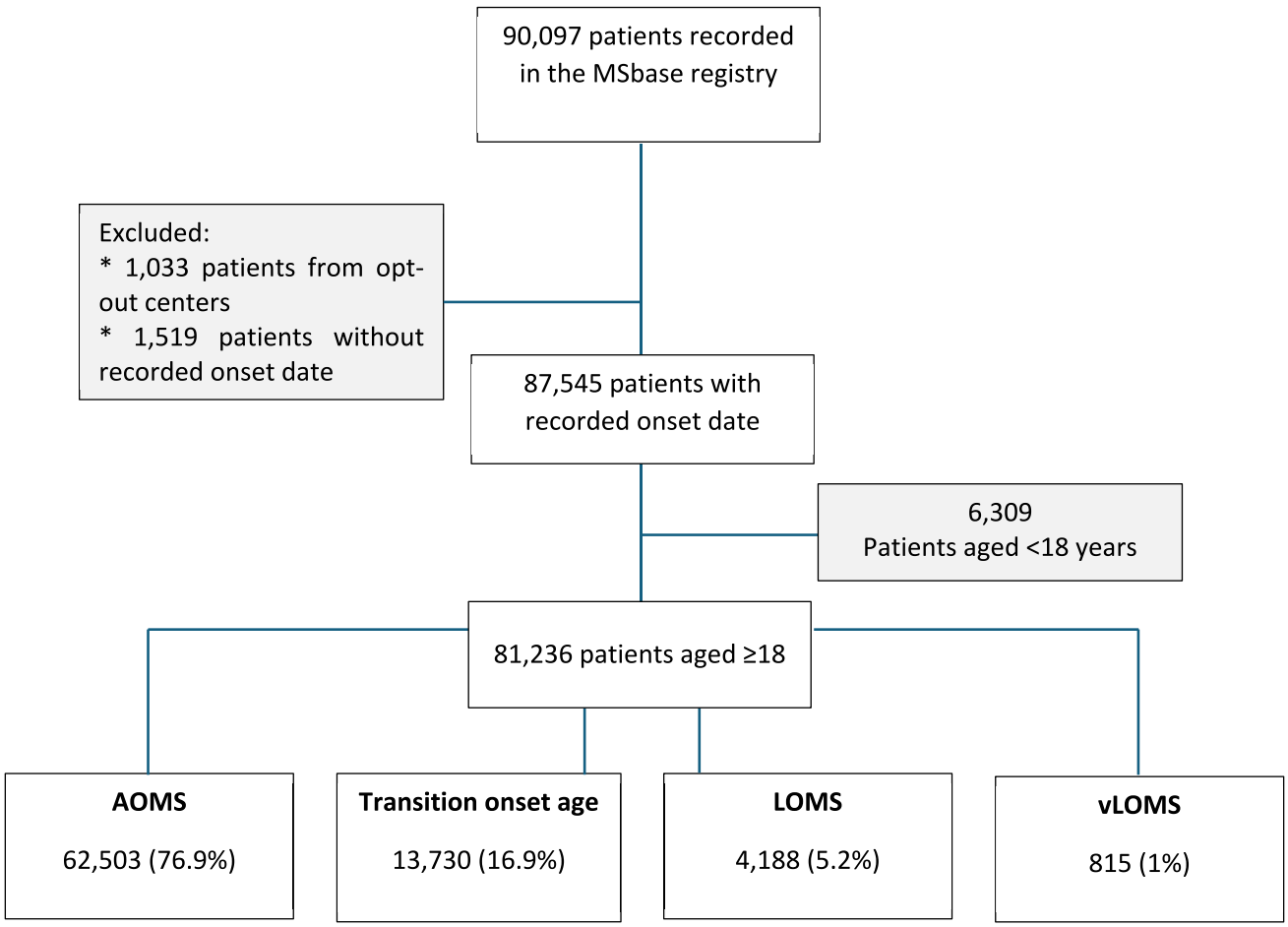


Fig. 1 Patient flow diagram by age at MS onset

Table 1 Demographics and baseline characteristics of patients according to age of MS onset

Characteristics at onset	Category/metric	AOMS ($n=62,503$)	Transition onset age ($n=13,730$)	LOMS ($n=4188$)	vLOMS ($n=815$)	AOMS vs LOMS p value	AOMS vs vLOMS p value	LOMS vs vLOMS p value	Standardised difference (weighted)[#] AOMS vs LOMS	Standardised difference (weighted)[#] AOMS vs vLOMS
Age at onset (years)	Mean (SD)	28.62 (5.89)	44.27 (2.83)	53.83 (2.74)	64.59 (4.49)	< 0.0001	< 0.0001	< 0.0001	N/A	N/A
	Median (IQR)	28.33 (23.79, 33.42)	43.96 (41.77, 46.54)	53.34 (51.44, 55.92)	63.27 (61.54, 66.11)					
Sex—*n* (%)	Female	44,404 (71.0)	9659 (70.3)	2768 (66.1)	532 (65.3)	< 0.0001	< 0.0001	0,652	− 0.107	− 0.093
	Male	18,097 (29.0)	4071 (29.7)	1420 (33.9)	283 (34.7)					
	Not recorded	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)					
Time to MS diagnosis (years)	Median (IQR)	1.00 (0.19, 4.00)	1.00 (0.22, 3.11)	1.00 (0.25, 3.00)	1.00 (0.20, 2.80)	0.0008	0.0029	0.1473	− 0.058	− 0.009
First symptoms—*n* (%)[a]	Optical pathways	15,118 (24.2)	2321 (16.9)	502 (12.0)	90 (11.0)	< 0.0001	< 0.0001	< 0.0001	− 0.321	− 0.156
	Supratentorial	13,429 (21.5)	2796 (20.4)	778 (18.6)	131 (16.1)	< 0.0001	< 0.0001	0,090	− 0.073	− 0.05
	Brainstem	12,759 (20.4)	2635 (19.2)	812 (19.4)	156 (19.1)	0,111	0,370	0,870	− 0.026	0.041
	Spinal cord	15,502 (24.8)	3913 (28.5)	1340 (32.0)	269 (33.0)	< 0.0001	< 0.0001	0,572	0.160	0,140
First recorded EDSS[b]	Mean (SD)	2.60 (2.10)	3.09 (2.13)	3.54 (2.13)	4.08 (2.18)	< 0.0001	< 0.0001	< 0.0001	0,447	0,177
	Median (IQR)	2 (1. 4)	2.5 (1.5, 4.5)	3 (2, 5.5)	4 (2.5, 6)					
First brain MRI[c]—T1 Gd + lesions	0	12,285 (19.7)	2970 (21.6)	856 (20.4)	153 (18.8)	< 0.0001	0,004	0,001	− 0,047	0,018
	1 +	4036 (6.5)	703 (5.1)	202 (4.8)	28 (3.4)					
	MRI performed, lesions not reported	33,925 (54.3)	7675 (55.9)	2502 (59.7)	469 (57.6)					
	No first MRI	12,257 (19.6)	2382 (17.4)	628 (15.0)	165 (20.3)					
First brain MRI[c]—T2 hyperintense lesions	0	980 (1.6)	247 (1.8)	72 (1.7)	26 (3.2)	< 0.0001	< 0.0001	< 0.0001	− 0,036	− 0,031
	1–2	1224 (2.0)	260 (1.9)	70 (1.7)	22 (2.7)					
	3–8	6667 (10.7)	1508 (11.0)	472 (11.3)	63 (7.7)					
	9 +	11,352 (18.2)	2306 (16.9)	686 (16.4)	132 (16.2)					
	MRI performed, lesions not reported	30,020 (48.0)	7015 (51.1)	2260 (54.0)	407 (49.9)					
	No first MRI	12,257 (19.6)	2382 (17.4)	628 (15.0)	165 (20.3)					

Table 1 (continued)

Characteristics at onset	Category/metric	AOMS ($n=62,503$)	Transition onset age ($n=13,730$)	LOMS ($n=4188$)	vLOMS ($n=815$)	AOMS vs LOMS p value	AOMS vs vLOMS p value	LOMS vs vLOMS p value	Standardised difference (weighted)[#] AOMS vs LOMS	Standardised difference (weighted)[#] AOMS vs vLOMS
MS course at baseline[d]	RRMS	42,470 (67.8)	7599 (55.4)	1861 (44.4)	330 (40.5)	< 0.0001	< 0.0001	< 0.0001	0.044	0.106
	SPMS	3420 (5.5)	765 (5.6)	193 (4.6)	23 (2.8)					
	PPMS	1852 (3.0)	1451 (10.6)	830 (19.8)	170 (20.9)					
	PRMS	504 (0.8)	206 (1.5)	78 (1.9)	25 (3.1)					
	CIS	12,071 (19.3)	3133 (22.8)	1018 (24.3)	200 (24.5)					
	Not recorded	2186 (3.5)	576 (4.2)	208 (5.0)	67 (8.2)					

RRMS relapsing MS, *SPMS* Secondary progressive MS, *PPMS* Primary progressive MS, *PRMS* Progressive relapsing MS, *CIS* Clinically isolated syndrome

[a]individual patients can record multiple first-symptom entries

[b]Only applies to a subset of patients who recorded an EDSS

[c]Only applies to a subset of patients who recorded an MRI. The first recorded MRI date is not necessarily the same as the date of onset

[d]baseline = first recorded registry visit

[#]weighted on propensity score, propensity score derived on sex, EDSS, first symptoms, baseline MRI lesions and time to DMT initiation

was higher during LOMS (21.7%) and vLOMS (24%) compared to AOMS (3.8%) and to the transition phase group (12.1%) ($p<0.0001$) (Table 1).

The ARR decreases as the age of MS onset increases within the 18–50 age range ($p<0.0001$). Once individuals reach 50 years of age, which refers to the LOMS (ARR = 0.0949; CI 0.0908, 0.09913) and the vLOMS groups (ARR = 0.0841; CI 0.0741, 0.0950), this rate becomes comparable ($p=0.0679$) (Table 2). Patients with LOMS and vLOMS are significantly less likely to experience a new relapse after baseline assessment than patients with AOMS (HR < 1; $p<0.001$). Moreover, they exhibited a significantly higher risk of reaching time to first 24 week confirmed disability progression, to EDSS4, to EDSS6 and to SPMS compared with the AOMS patients (Figs. 2, 3). These results were also highlighted in the weighted analysis, indicating that the effect of age on these outcomes is independent of sex, EDSS, first symptoms, baseline MRI lesion counts, and treatment initiation. LOMS and vLOMS presented a also shorter time to the first PIRA event compared with the AOMS (Fig. 4).

Subgroup analysis by baseline epoch showed a reduction in the relapse rate in the LOMS and vLOMS relative to AOMS (Supplementary Table 1). Conversely, both the increases in the time to the first 24 week confirmed disability progression and SPMS conversion rates in the LOMS and vLOMS compared to the AOMS become progressively larger over time (Supplementary tables 2, 3). This difference is notably pronounced, especially concerning the risk of conversion to SPMS among patients with vLOMS compared to AOMS (PS-IPTW HR = 12.59; $p<0.001$). Moreover, the comparison of patients with AOMS, LOMS and vLOMS has highlighted a shorter time to reach the first PIRA event in all analyzed epochs, in particular for vLOMS than LOMS groups (Supplementary Table 4).

Discussion

In this largest observational study retrospectively analyzing records of patients with LOMS and vLOMS, we identified several hallmarks associated with aging. LOMS was described in 5.2% of cases and vLOMS in 1%. This aligns with the results of a recent meta-analysis, which estimated the proportion of LOMS at 5% and vLOMS at a range of 0.6–3.6% [9]. Recent reports have highlighted a rising occurrence of MS onset beyond the age of 40–45 years across various populations [10]. The expanding availability of MRI with improvements in technical aspects and updated diagnostic criteria has enhanced the ability to differentiate between demyelinating, vascular, and nonspecific lesions [11].

Table 2 Patient annualized relapse rate

Onset group	Count of post-baseline relapses	Cumulative post-baseline follow-up years	ARR (95% CI)	AOMS vs LOMS *p* value	AOMS vs vLOMS *p* value	LOMS vs vLOMS *p* value	AOMS vs Transition *p* value	LOMS vs Transition *p* value	vLOMS vs transition *p* value
AOMS ($n=62,503$)	76,682	379,930,80	0.2018 (0.2004, 0.2033)	< 0.0001	< 0.0001	0,0679	< 0.0001	< 0.0001	< 0.0001
Transition onset age ($n=13,730$)	10,233	78,568,79	0.1302 (0.1277, 0.1328)						
LOMS ($n=4188$)	2017	21,254,01	0.0949 (0.0908, 0.09913)						
vLOMS ($n=815$)	256	3044,72	0.0841 (0.0741, 0.0950)						

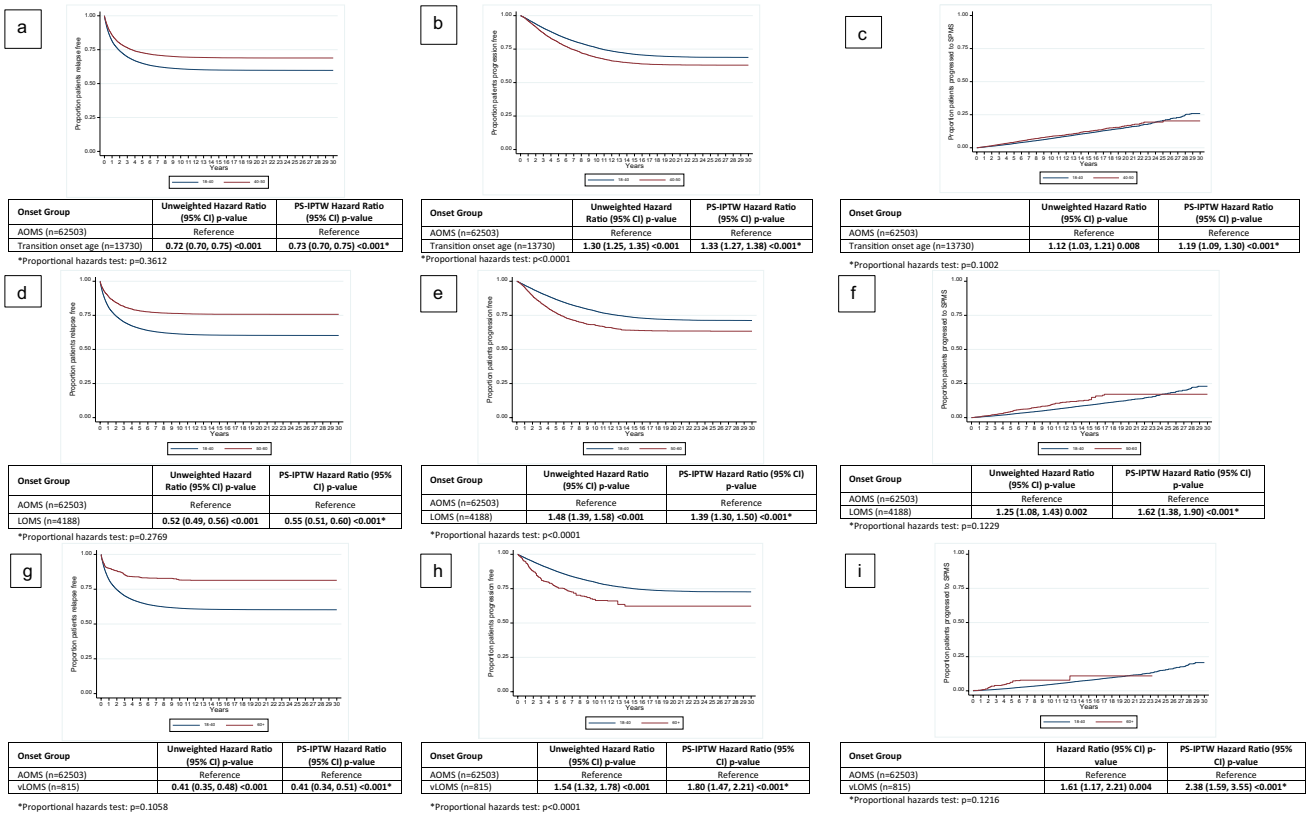
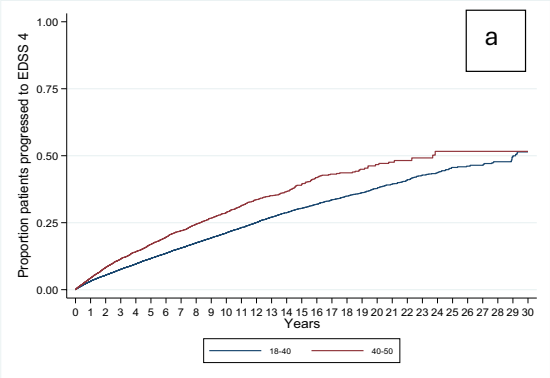


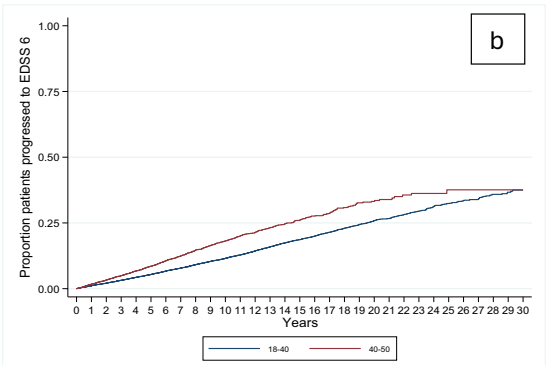
Fig. 2 Kaplan–Meier graphs for probability for disease activity (relapse free) or progression (24 week confirmed disability progression and reaching SPMS) over time according to the age of MS onset—(**a**, **b**, **c**) Transition onset MS group; (**d**, **e**, **f**) LOMS; (**g**, **h**, **i**) (vLOMS)

Although MS was more prevalent in females across all age groups, the female-to-male ratio tends to decline with increasing age. In a meta-analysis about LOMS, female cases (64.46%) were also more important than males, with a trend toward an increasing proportion of males with aging [9]. Some authors have suggested that the female gender might be a risk factor for an earlier MS onset [12]. During the early years, testosterone and estrogen exert a protective effect on the CNS by reducing the production of inflammatory cytokines and protecting neuronal cells from glutamate toxicity and oxidative stress [13]. Nonetheless, their levels decline as individuals age, potentially contributing to the



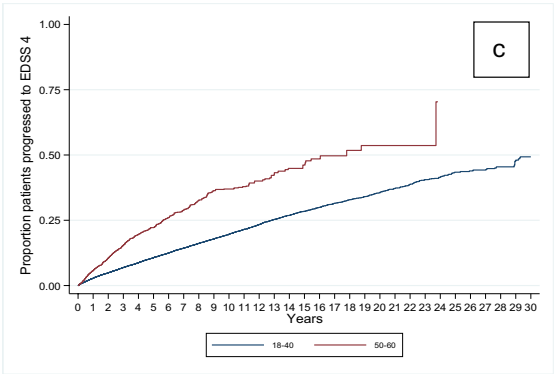
Onset Group	Unweighted Hazard Ratio (95% CI) p-value	PS-IPTW Hazard Ratio (95% CI) p-value
AOMS (n=42673)	Reference	Reference
Transition onset age (n=8327)	**1.41 (1.34, 1.50) <0.001**	**1.42 (1.34, 1.51) <0.001***

*Proportional hazards test: p=0.1009



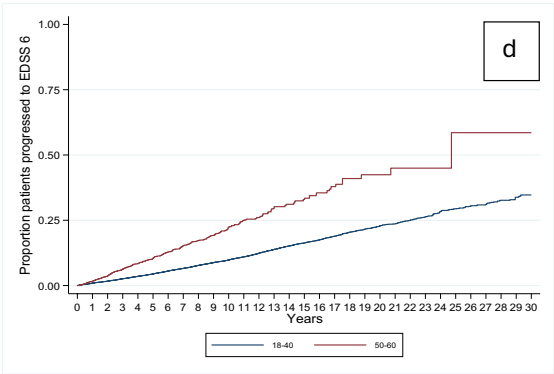
Onset Group	Unweighted Hazard Ratio (95% CI) p-value	PS-IPTW Hazard Ratio (95% CI) p-value
AOMS (n=49772)	Reference	Reference
Transition onset age (n=10367)	**1.51 (1.41, 1.61) 0.001**	**1.52 (1.43, 1.63) <0.001***

*Proportional hazards test: p=0.0933



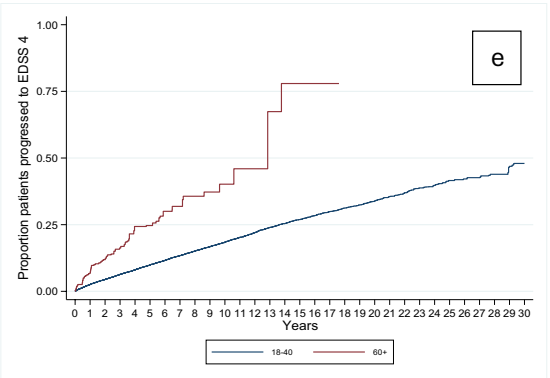
Onset Group	Unweighted Hazard Ratio (95% CI) p-value	PS-IPTW Hazard Ratio (95% CI) p-value
AOMS (n=42673)	Reference	Reference
LOMS (n=2171)	**2.06 (1.88, 2.26) <0.001**	**2.14 (1.92, 2.37) <0.001***

*Proportional hazards test: p=0.1121



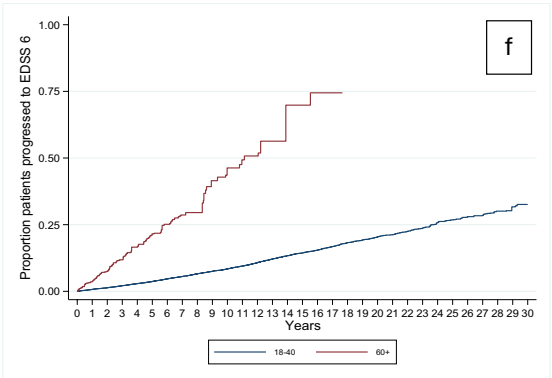
Onset Group	Unweighted Hazard Ratio (95% CI) p-value	PS-IPTW Hazard Ratio (95% CI) p-value
AOMS (n=49772)	Reference	Reference
LOMS (n=2912)	**2.20 (1.99, 2.43) <0.001**	**2.33 (2.08, 2.61) <0.001***

*Proportional hazards test: p=0.1178



Onset Group	Unweighted Hazard Ratio (95% CI) p-value	PS-IPTW Hazard Ratio (95% CI) p-value
AOMS (n=42673)	Reference	Reference
vLOMS (n=329)	**2.60 (2.04, 3.30) <0.001**	**2.95 (2.26, 3.84) <0.001***

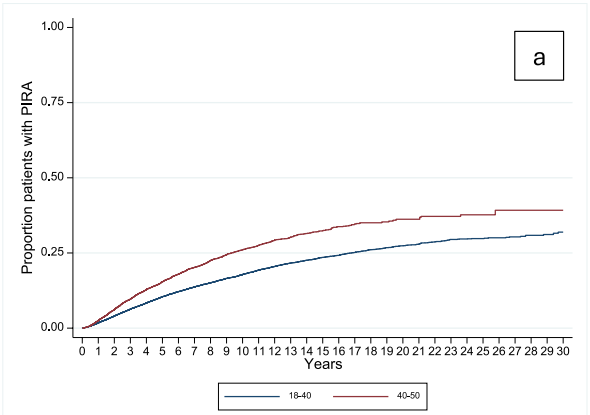
*Proportional hazards test: p=0.5535



Onset Group	Unweighted Hazard Ratio (95% CI) p-value	PS-IPTW Hazard Ratio (95% CI) p-value
AOMS (n=49772)	Reference	Reference
vLOMS (n=508)	**4.73 (3.91, 5.71) <0.001**	**6.33 (5.03, 7.97) <0.001***

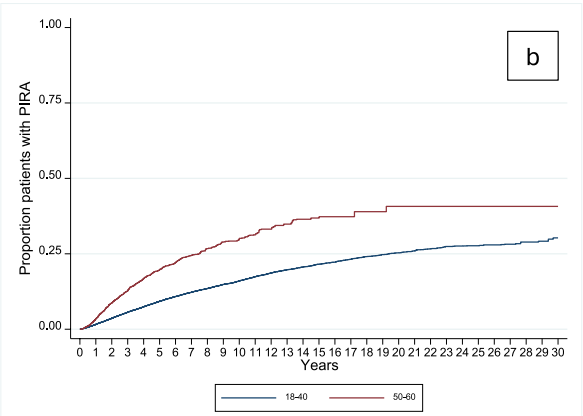
*Proportional hazards test: p=0.6770

Fig. 3 Kaplan–Meier graphs for probability of reaching EDSS4 and EDSS6 over time according to the age of MS onset—(**a**, **b**) Transition onset MS group; (**c**, **d**) LOMS; (**e**, **f**) (vLOMS)



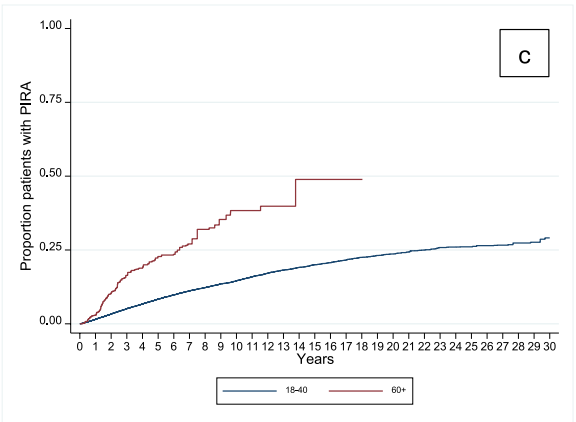
Onset Group	Unweighted Hazard Ratio (95% CI) p-value	PS-IPTW Hazard Ratio (95% CI) p-value
AOMS (n=62503)	Reference	Reference
Transition onset age (n=13730)	**1.47 (1.40, 1.55) <0.001**	**1.51 (1.43, 1.59) <0.001***

*Proportional hazards test: p=0.0171



Onset Group	Unweighted Hazard Ratio (95% CI) p-value	PS-IPTW Hazard Ratio (95% CI) p-value
AOMS (n=62503)	Reference	Reference
LOMS (n=4188)	**1.94 (1.80, 2.10) <0.001**	**2.12 (1.93, 2.32) <0.001***

*Proportional hazards test: p<0.0001



Onset Group	Unweighted Hazard Ratio (95% CI) p-value	PS-IPTW Hazard Ratio (95% CI) p-value
AOMS (n=62503)	Reference	Reference
vLOMS (n=815)	**2.44 (2.05, 2.91) <0.001**	**2.93 (2.34, 3.66) <0.001***

*Proportional hazards test: p=0.6383

Fig. 4 Kaplan–Meier graphs for probability for reaching the first PIRA event over time according to the age of MS onset—(**a**) Transition onset MS group; (**b**) LOMS; (**c**) (vLOMS)

rising trends of MS among elderlies. Males might be more vulnerable to this phenomenon, which explains the increased frequency of MS with age [14].

AOMS was associated with optic nerve and supratentorial involvement, while older patients presented with more frequent spinal cord symptoms. In the British Columbia cohort, motor symptoms were more prevalent among older people with MS, while optic nerve involvement was more frequent in the AOMS [6]. Moreover, spinal cord involvement was more prevalent in the LOMS and vLOMS groups [7, 15–17]. MS first relapse plays a critical role in determining the prognosis of the disease [18]. Older people with MS experienced more frequent spinal cord relapses at disease onset, which was associated with higher baseline disability, as reflected by higher EDSS scores. Gadolinium-enhancing lesions and MRI lesion load decreased with increasing age. The same trend was reported among French and Italian patients [19, 20]. The clinicopathological paradox—where significant CNS inflammation and damage can occur without clinical signs—may become more pronounced with age, suggesting that routine imaging markers may underestimate silent pathological processes which contribute to long-term neurodegeneration and disability in older people with MS [21]. We observed a progressive decrease in relapse activity with increasing age of onset. This trend can be attributed to a decline in CNS reserve and repair mechanisms with age. Consequently, in the AOMS group, inflammatory activity is more noticeable with frequent relapses. Conversely, in LOMS and vLOMS, the frequency of relapses diminishes as neurodegeneration becomes more pronounced. Preventing

relapses in older individuals is paramount, as even a single relapse at an advanced age could lead to a substantial disability due to diminished recovery capacity [22, 23].

Older onset cohorts were associated with higher levels of disability. Indeed, one of the main risk factors for additional disability accumulation is advanced age. The older the MS onset age is, the shorter the survival time for reaching EDSS4 and 6 and for transition to SPMS will be [5, 17]. Additionally, older individuals with or without MS might demonstrate significantly higher disability on the EDSS assessment [24]. During MS, immunosenescence, a major determinant of increased disability, occurs prematurely and continues to progress over the years [1]. The shortening of telomere length is also notably more significant and is associated with an increased risk of clinical progression over time [25]. There is an elevated proportion of T lymphocytes expressing markers associated with activation and cytotoxicity, which are linked to the aging process [26]. This compromised immune system induces a chronic low-grade inflammatory condition referred to as "inflammaging", marked by elevated levels of inflammatory cytokines [27]. The latter heightens the risk of morbidity in older individuals, especially the cardiovascular one [28]. On the other hand, the presence of vascular comorbidities, whether detected at symptom onset, diagnosis, or later stages of the disease, is linked to a significantly higher risk of disability accrual in MS, reaching more than 200% in participants with 2 comorbidities [3]. Hormonal factors impact the severity of the disease, particularly in older women given that emerging evidence suggests higher disability levels and more severe neurodegenerative aspects among postmenopausal women with MS [29].

Our study confirmed that MS phenotype distribution varied according to the age at disease onset, showing a notably higher occurrence, approximately 5–6 times more, of the PPMS in patients aged over 50 years. Higher proportions of PPMS were described in cases of LOMS and vLOMS [9]. These phenomena are closely correlated with immunosenescence and early neurodegeneration [30].

LOMS and vLOMS were associated with a shorter time to reach a first PIRA event. According to the study of Tur et al., [31] older age at the first attack was the only predictor of PIRA and patients aged more than 60 years were more susceptible to the development of PIRA. Moreover, early presence of PIRA has been demonstrated to negatively impact disease outcomes. People with MS who exhibit PIRA had an 8-fold greater risk of reaching EDSS6 than those without PIRA [32]. A growing body of evidence suggests that PIRA represents the most common form of disability accumulation across the full spectrum of MS phenotypes [32]. Older patients with MS would present a predisposition to PIRA due to enhanced mitochondrial dysfunction, oxidative stress, and impaired synaptic plasticity [33]. These results reflect the limitations of the concept that "MS is a 2-stage disease, starting with inflammation and followed by a neurodegenerative phase" and highlight that MS is better considered as a continuum with a predominance of the degenerative component with increasing age [34].

Subgroup analysis by baseline epoch highlighted that, while the initial differences in relapse rates between onset groups decrease over time, the differences in time to 24-confirmed disability worsening, SPMS and PIRA increase with time, suggesting a worsening disease trajectory in LOMS and vLOMS compared to AOMS. This may, in part, reflect better management of AOMS over time toward an earlier diagnosis compared to older patients with MS. The increasing use of paraclinical assessments, especially imaging and cerebrospinal fluid analysis, to complement clinical findings has enabled earlier, more sensitive, and more specific diagnosis in patients aged younger than 50 years [35].

A major strength of this study is the large sample size providing a representative sample of patients with MS across various age groups. PS-IPTW was used to generate a pseudopopulation in which confounders are equally distributed across treated and untreated patients. However, several limitations need to be mentioned. Firstly, the retrospective design of this study introduces potential biases into data collection practices. Moreover, the availability of baseline MRI scans was very limited, and spinal cord MRI data have not been detailed, which may restrict our understanding of disease characteristics in the different age groups. The lack of comorbidity data represents a limitation, as age-related comorbidities may confound clinical presentation and disability assessments, especially in older-onset MS. Then, despite the effectiveness of PS, this approach is constrained by limitations arising from nonrandom missing data and the potential influence of unmeasured confounders on outcomes. Finally, we have not addressed the therapeutic aspects, which could be crucial in influencing the progression of disability according to age. The treatment options for MS have greatly expanded over the past decade, especially for RRMS and younger patients. This likely contributes to the increasing contrast in disease progression between MS that starts in adulthood and MS that begins later in life. Addressing these limitations through prospective designs could enhance the robustness and applicability of future research in this domain.

Conclusion

In this international study, disease prognosis was markedly influenced by the age of MS onset, with older patients experiencing more rapid disease progression and shorter survival times to reach disability milestones. It also emphasized the impact of PIRA on disability accumulation. Overall, this

study has shown the complex interplay of age and clinical characteristics in shaping the trajectory of MS. Further research is warranted to explain the underlying mechanisms and risk factors associated with LOMS and vLOMS.

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Authors and Affiliations

Amira Souissi[1,2] · Francesco Patti[3] · Tim Spelman[4,5] · Clara Chisari[3] · Amina Gargouri[1,2] · Nevin John[6] · Allan G. Kermode[7,8,9] · Tomas Kalincik[10,11] · Helmut Butzkueven[12,13] · Seyed Aidin Sajedi[14,15] · Jeannette Lechner-Scott[16,17] · Izanne Roos[10,11] · Guy Laureys[18] · Bruce Taylor[19,20] · Raed Alroughani[21] · Samia J. Khoury[22] · Richard Macdonell[23] · Bianca Weinstock-Guttman[24] · Eva Kubala Havrdova[25] · Davide Maimone[26] · Stephen Reddel[27] · Marzena Fabis-Pedrini[28,29] · Barbara Willekens[30] · Abdorreza Naser Moghadasi[31] · Patrice Lalive[32] · Alessandra Lugaresi[33] · Serkan Ozakbas[34] · Claudio Solaro[35] · Simón Cárdenas-Robledo[36,106] · Vahid Shaygannejad[37] · Masoud Etemadifar[38,39] · Cavit Boz[40] · Sara Eichau[41] · Valentina Tomassini[42,43] · Murat Terzi[44] · Alexandre Prat[45] · Mario Habek[46] · Yolanda Blanco[47] · Ayse Altintas[48] · Oliver Gerlach[49,50] · Recai Turkoglu[51] · Katherine Buzzard[52] · Olga Skibina[53,54,55] · Aysun Soysal[56] · Anneke van der Walt[57,58] · Stella Hughes[59] · Vincent van Pesch[60,61] · Matteo Foschi[62,63] · Andrea Surcinelli[64] · Julie Prevost[65] · Cristina Ramo-Tello[66] · Chris McGuigan[67,68] · Maria Jose Sa[69,70] · Jens Kuhle[71,72] · Daniele Spitaleri[73] · Bhim Singhal[74] · Radek Ampapa[75] · Koen de Gans[76] · Thor Petersen[77] · Mihaela Simu[78] · Emmanuelle Lapointe[79] · Jose Luis Sanchez-Menoyo[80,81] · Orla Gray[82] · Justin Garber[83] · Eduardo Aguera-Morales[84,85] · Katrin Gross-Paju[86] · Tamara Castillo-Triviño[87] · Abdullah Al-Asmi[88] · Nikolaos Grigoriadis[89,90] · Jihad Inshasi[91] · Talal Al-Harbi[92] · Todd A. Hardy[28,29] · Sudarshini Ramanathan[93,94,95] · Melissa Cambron[96,97] · Neil Shuey[98] · Angel Perez sempere[99,100] · Tunde Csepany[101] · Irene Treviño-Frenk[102] · Csilla Rozsa[103] · Marija Cauchi[104] · Rana Karabudak[105] · Saloua Mrabet[1,2] · Riadh Gouider[1,2]

✉ Francesco Patti
francesco.patti@unict.it

✉ Riadh Gouider
riadh.gouider@gnet.tn

[1] Neurology Department, LR18SP03 and Clinical Investigation Center Neurosciences and Mental Health, university hospital center Razi-Mannouba, Tunis, Tunisia

[2] Faculty of Medicine of Tunis, Tunis El Manar University, Tunis, Tunisia

[3] Department of Medical and Surgical and Advanced Technologies, G F Ingrassia, University of Catania, UOS Sclerosi Multipla, AOU Policlinico "G Rodolico-San Marco", University of Catania, Catania, Italy

[4] Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

[5] MSBase Foundation, Melbourne, VIC, Australia

[6] Department of Neurology, Monash Health, Clayton, Australia

[7] Sir Charles Gairdner Hospital, Perron Institute for Neurological and Translational Science, QEIIMC, University of Western Australia, Nedlands, Australia

[8] Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Perth, Australia

[9] Institute for Immunology and Infectious Diseases, Murdoch University, Perth, WA, Australia

[10] Department of Neurology, Neuroimmunology Centre, Royal Melbourne Hospital, Melbourne, Australia

[11] CORe, Department of Medicine, University of Melbourne, Melbourne, Australia

[12] Department of Neurology, The Alfred Hospital, Melbourne, Australia

[13] Department of Neuroscience, School of Translational Medicine, Monash University, Melbourne, Australia

[14] Department of Neuroscience, School of Translational Medicine, Monash University, Melbourne, Australia

[15] Neuroscience Research Center, Golestan University of Medical Sciences, Gogan, Iran

[16] Hunter Medical Research Institute, University Newcastle, Newcastle, Australia

[17] Hunter New England Health, John Hunter Hospital, Newcastle, NSW, Australia

[18] Department of Neurology, Universitary Hospital Ghent, Ghent, Belgium

[19] Royal Hobart Hospital, Hobart, Australia

[20] Menzies Institute for Medical Research University of Tasmania, Hobart, Australia

[21] Division of Neurology, Department of Medicine—Amiri Hospital, Sharq, Kuwait

[22] Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Beirut, Lebanon

[23] Austin Health, Melbourne, Australia

[24] Department of Neurology, Jacobs MS Center for Treatment and Research, New York, USA

[25] Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic

[26] Centro Sclerosi Multipla, UOC Neurologia, Azienda Opsedaliera Per L'Emergenza Cannizzaro, Catania, Italy

[27] Department of Neurology, Concord Repatriation General Hospital, Sydney, Australia

[28] Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Perth, Australia

[29] Perron Institute for Neurological and Translational Science, The University of Western Australia, Perth, Australia

[30] Department of Neurology, Laboratory of Experimental Hematology, Vaccine & Infectious Disease Institute (VAXINFECTIO)- Translational Neurosciences Research Group, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

[31] Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

[32] Department of Clinical Neurosciences, Division of Neurology, Unit of Neuroimmunology—Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

[33] Dipartimento Di Scienze Biomediche E Neuromotorie, IRCCS Istituto delle Scienze Neurologiche di Bologna, Università di Bologna, Bologna, Italia

[34] Izmir University of Economics, Medical Point Hospital, Multiple Sclerosis Research Association, Izmir, Turkey

[35] Neurology Unit, Galliera Hospital, Genoa, Italy

[36] Hospital Universitario Nacional de Colombia Bogota, Bogotá, Colombia

[37] Isfahan University of Medical Sciences, Isfahan, Iran

[38] MS Institute, Isfahan University Of Medical Sciences, Isfahan, Iran

[39] Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

[40] Department of Neurology, Medical Faculty, Karadeniz Technical University, Trabzon, Turkey

[41] Department of Neurology, Hospital Universitario Virgen Macarena, Seville, Spain

[42] University G. d'Annunzio of Chieti-Pescara, Chieti, Italy

[43] Department Neurosciences, Imaging and Clinical Sciences MS Centre, Clinical Neurology—SS, Institute for Advanced Biomedical Technologies (ITAB), Annunziata University Hospital, Chieti, Italy

[44] Medical Faculty, Mayis University, Samsun, Turkey

[45] CHUM and Universite de Montreal, Montreal, Canada

[46] Department of Neurology, University Hospital Center Zagreb, Zagreb, Croatia

[47] Center of Neuroimmunology, Service of Neurology, Hospital Clinic de Barcelona, Barcelona, Spain

[48] Department of Neurology, School of Medicine and Koc University Research Center for Translational Medicine (KUTTAM), School of Medicine, Koc University, Istanbul, Turkey

[49] Academic MS Center Zuyd, Department of Neurology, Zuyderland Medical Center, Sittard-Geleen, Heerlen, Netherlands

[50] School for Mental Health and Neuroscience, Department of Neurology, Maastricht University Medical Center, 6131 BK Maastricht, Netherlands

[51] Department of Neurology, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey

[52] Department of Neurosciences, Eastern Health Clinical School, Box Hill Hospital, Monash University, Box Hill, Australia

[53] Department of Neurology, Box Hill Hospital, Box Hill, Australia

[54] Department of Neurosciences, Eastern Health Clinical School, Monash University, Melbourne, Australia

[55] Department of Neurology, The Alfred Hospital, Melbourne, Australia

[56] Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases, Istanbul, Turkey

[57] Department of Neurology, The Alfred Hospital, Melbourne, Australia

[58] Department of Neuroscience, School of Translational Medicine, Monash University, Melbourne, Australia

[59] Royal Victoria Hospital, Belfast, UK

[60] Department of Neurology, Cliniques Universitaires Saint-Luc, Brussels, Belgium

[61] Université Catholique de Louvain, Neuve, Belgium

[62] Department of Neuroscience, MS Center, Neurology Unit, S. Maria Delle Croci Hospital, AUSL Romagna, Ravenna, Italy

[63] Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

[64] Department of Neuroscience, MS Center, Neurology Unit, S. Maria Delle Croci Hospital, AUSL Romagna, Ravenna, Italy

[65] CSSS Saint-Jérôme, Saint-Jerome, Canada

[66] Department of Neuroscience, Hospital Germans Trias I Pujol, Badalona, Spain

[67] St Vincent's University Hospital, Dublin, Ireland

[68] School of Medicine, University College Dublin, Dublin, Ireland

[69] Department of Neurology, Centro Hospitalar Universitario de Sao Joao, Porto, Portugal

[70] Rede de Investigação Em Saúde, FP-I3ID, Instituto de Investigação, FCS-UFP, Faculdade de Ciências da Saúde; RISE-UFP, Universidade Fernando Pessoa, Inovação E Desenvolvimento Fernando Pessoa, Porto, Portugal

[71] Department of Neurology, University Hospital and University of Basel, Basel, Switzerland

[72] Multiple Sclerosis Centre and Research Center for Clinical Neuroimmunology and Neuroscience (RC2NB), Departments of Biomedicine and Clinical Research, University Hospital and University of Basel, Basel, Switzerland

[73] Azienda Ospedaliera Di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino, Italy

[74] Bombay Hospital Institute of Medical Sciences, Mumbai, India

[75] Nemocnice Jihlava, Jihlava, Czech Republic

[76] Groene Hart Ziekenhuis, Gouda, Netherlands

[77] Aarhus University Hospital, Arhus C, Denmark

[78] University of Medicine and Pharmacy Victor Babes Timisoara, Timisoara, Romania

[79] Medicine, Division of Neurology, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Canada

[80] Department of Neurology, Usansolo University Hospital, Osakidetza-Basque Health Service, Galdakao, Spain

[81] Biocruces-Bizkaia Health Research Institute, Galdakao, Spain

[82] South Eastern HSC Trust, Belfast, UK

[83] Department of Neurology, Westmead Hospital, Sydney, Australia

[84] Department of Medicine and Surgery, University of Cordoba, Cordoba, Spain

[85] Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Cordoba, Spain

[86] Multiple Sclerosis Centre, West-Tallinn Central Hospital, Multiple Sclerosis Centre, Tallinn, Estonia

[87] Hospital Universitario Donostia and IIS Biodonostia, San Sebastián, Spain

[88] College of Medicine & Health Sciences, Sultan Qaboos University, Al-Khodh, Oman

[89] Department of Neurology, AHEPA University Hospital, Thessaloniki, Greece

[90] Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

[91] Rashid Hospital, Dubai, United Arab Emirates

[92] Neurology Department, King Fahad Specialist Hospital-Dammam, Dammam, Saudi Arabia

[93] University of Sydney, Sydney, Australia

[94] Translational Neuroimmunology Group, Kids Neuroscience Centre and Brain and Mind Centre, Faculty of Medicine and Health, University of Sydney, Sydney, Australia

[95] Department of Neurology, Concord Clinical School, Concord Hospital, Sydney, Australia

[96] Neurology, Az Sint-Jan Brugge, Bruges, Belgium

[97] Ghent University, Ghent, Belgium

[98] Vincents Hospital, Fitzroy, Melbourne, Australia

[99] Neurology Unit, Hospital General Universitario de Alicante, Angel Perez Sempere, Alicante, Spain

[100] University Miguel Hernandez, Spain –ISABIAL, Alicante, Spain

[101] Department of Neurology, Faculty of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

[102] Department of Neurology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

[103] Jahn Ferenc Teaching Hospital, Budapest, Hungary

[104] Neurosciences Department, Mater Dei Hospital, Birkirkara, Malta

[105] Department of Neurological Sciences, Faculty of Medicine, Clinical Neuroimmunology & MS Unit, Koşuyolu Hospital, Yeditepe University, Istanbul, Turkey

[106] Centro de Esclerosis Múltiple (CEMHUN), Departamento de Neurología, Departamento de Medicina Interna, Facultad de Medicina, Universidad Nacional de Colombia, Bogotá, Colombia