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Aging in multiple sclerosis: From childhood to old age, in women and men

Edited by
Alessandra Lugaresi, Kristen Marie Krysko and Vilija Jokubaitis

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Aging in multiple sclerosis: From childhood to old age, in women and men

Topic editors

Alessandra Lugaresi — University of Bologna, Italy
Kristen Marie Krysko — St Michael's Hospital, Canada
Vilija Jokubaitis — Monash University, Australia

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EDITED AND REVIEWED BY
Robert Weissert,
University of Regensburg, Germany

*CORRESPONDENCE
Alessandra Lugaresi
✉ alessandra.lugaresi2@unibo.it

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Editorial: Aging in multiple sclerosis: from childhood to old age, in women and men

Alessandra Lugaresi[1,2]*, Vilija G. Jokubaitis[3,4] and Kristen M. Krysko[5,6]

[1]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, [2]Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy, [3]Department of Neuroscience, School of Translational Medicine, Monash University, Melbourne, VIC, Australia, [4]Department of Neurology, Alfred Health, Melbourne, VIC, Australia, [5]Division of Neurology, Department of Medicine, BARLO MS Centre, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada, [6]Li Ka Shing Knowledge Institute, Toronto, ON, Canada

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Editorial on the Research Topic
Aging in multiple sclerosis: from childhood to old age, in women and men

This Research Topic is dedicated to our dear friend Prof Yara Fragoso, the fourth member of our editorial team who passed away unexpectedly during the compilation of this work. Yara was a well-respected researcher and physician who specialized both in Migraine and Multiple Sclerosis. She was the president of the Brazilian Congress of Headache and Orofacial Pain at the time of her passing. She was a leader in women's health research in multiple sclerosis, and an active contributor to the international MSBase Registry, where she helped to develop a pregnancy, neonatal outcomes and women's health registry (1). We miss her deeply.

Multiple sclerosis (MS) is the most common inflammatory disease of the central nervous system and the main cause of non-traumatic disability in young adults, affecting more than 2.8 million people worldwide (2). Although it is typically diagnosed in people aged between 20–40 years, MS onset can be earlier (pediatric onset MS, POMS) or after the age of 55 (late onset MS, LOMS).

The Research Topic "*Aging in multiple sclerosis: from childhood to old age, in women and men*" consists of 12 articles providing insight into several of these aspects of MS, including aging, menopause, reproductive issues, and providing considerations on treatment, working impairment, socio-economic burden, and frailty. Assessment of the role of aging, sex hormones, diet, and infections, has enhanced our understanding in many research areas, from immunology to imaging techniques to psychology; topics further explored in the context of multiple sclerosis in this issue.

In their extension of the 2019 reviews on neurological disorders (3) and MS (4) global, regional and national burden, Qian et al. address the issue of changes reported in the incidence, mortality, disability-adjusted life years (DALYs), in people with MS all of which have increased. Whereas, age-standardized rates, calculated from the available GBD 2019 data have decreased.

With improvement of diagnostic and treatment algorithms and consequently of outcomes, the epidemiology of MS has shifted to an older than previously described population, with a peak prevalence in the 55–65 years age group. Around 50-years of age there is a consistent peak of disability accrual. Macaron et al. provide thoughtful aging related treatment considerations, taking into account confounders linked to

aging, comorbidities and consequent frailty. They suggest, in the setting of aging, to monitor concomitant symptomatic treatment and to switch to safer DMTs or to de-escalate treatment through administration interval extension, depending on individual characteristics.

The impact of MS on working ability and productivity have been studied by Moccia et al. through a cross-sectional study. They have found that in MS working ability is decreased compared to matched controls, with an impact of fatigue and cognitive dysfunction, leading to lower quality of life.

The socio-economic consequences of physical and mental disability later in life have been extensively studied in Denmark, where elderly persons with MS (PwMS) face unemployment, reduced income, and increased dependence on social care (Wandall-Holm et al.).

In their narrative review Capasso et al. highlight the importance of a timely diagnosis both in POMS and LOMS, to overcome challenges encountered along the whole course of MS, including improving communication and active involvement of PwMS and caregivers.

As both mental and physical disability progress steadily in the secondary progressive phase of MS, the timely identification of patients at risk might positively impact further disease course. Tartaglia et al. suggest use of the frailty index, which correlates with the neurophysiological index and neurodegenerative rather than inflammatory processes, to predict conversion to progression.

Along this line the systematic review by Tokarska et al. highlights the use of magnetic resonance imaging (MRI) in investigating the neurobiological aging process, including physical and cognitive deterioration in PwMS, addressing questions such as (1) how does brain structure (e.g., volume, white matter microstructure) differ or change with age in PwMS? Studies show an accelerated whole brain and gray matter atrophy in PwMS; (2) Are there specific structural MRI findings in older PwMS compared to younger PwMS? This issue is still controversial, due to the lack of sufficient data available, but there is some evidence that aging may have differential effects on brain atrophy in PwMS across the lifespan as compared to normal aging; (3) Are there structural differences in the brain as a function of sex in aging PwMS? Despite the insufficient number of studies investigating this issue, the evidence to date suggests that males have greater brain atrophy than females with age, corresponding to more rapid disability accumulation and cognitive decline in males than in females; it has also been suggested that menopause may affect brain atrophy patterns in aging females with MS.

Further, the multicenter retrospective study conducted in China on 208 PwMS investigated the sex-related differences in connectivity strength and time variability within large-scale networks in relapsing remitting (RR) MS, showing alterations in connectivity strength only in male PwMS and time variability in female PwMS, suggesting that sex-related mechanisms may play an important role in the functional impairment and reorganization of cerebral activity in RRMS (Wang et al.).

With aging many PwMS present with co-morbidities which might decrease the performance of the central vein sign (CVS) in the diagnosis of MS. Lapucci et al. investigated this issue in 5,303 lesions selected for the CVS assessment in 120 MS patients stratified into 4 age groups. They found that age and migraine have a relevant impact in reducing the percentage of perivenular lesions, particularly in the deep/subcortical WM. They suggest use of the Spherical Mean Technique (SMT) diffusion model, as a helpful tool to differentiate perivenular lesions, characterized by higher inflammation, demyelination and fiber disruption, from non-perivenular lesions secondary to a different pathophysiology, especially in the deep/subcortical white matter of older patients (Lapucci et al.).

Regarding women with MS (WwMS), strategies to manage pregnancy planning have significantly changed in the last 30 years. A Delphi survey conducted in Italy led to the formulation of 21 statements in relation to optimizing "time to pregnancy". Statements dealt with fertility considerations, treatment strategies to be adopted in case of assisted reproductive technologies and consideration for oocyte cryopreservation in women with reduced ovarian reserve, who require unpredictable time to complete diagnostic workup and achieve control of their MS (Carbone et al.).

Lorefice et al. investigated the possible role of menopause in influencing MS from clinical and neuroradiological perspectives, with special attention on brain atrophy. They found that menopause may facilitate cortical GM atrophy, probably due to a decline in the neuroprotective effects of estrogen.

The incidence of cancer in MS and the effects of treatment have not been thoroughly investigated and available results are conflicting. More specifically, there are limited data on the effect of DMTs on cervical cancer risk in WwMS. In their review Bridge et al. report the different risks associated with low, moderate and high efficacy drugs, according to different modes of action. They also take into account the possible positive effects of cervical screening programs and HPV vaccination against the barriers which preclude preventative health assessments in more advanced cases.

We hope to have provided readers with new insight in the complexities of aging with MS.

Topics still needing consideration include the impact of diagnosis on personal and sexual relationships; the role of pre-puberty and puberty in pediatric onset MS; the role of sex hormones during childbearing age (in particular hormone therapy and changes in pregnancy and postpartum); the interplay between menopause and aging; MRI techniques to investigate sexual dysfunction in male and female patients; cognition across different age groups in POMS, adult-onset MS and LOMS; immune-senescence in MS, amongst others.

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AL: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. VJ: Writing – review & editing. KK: Writing – review & editing.

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Conflict of interest

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EDITED BY
Alessandra Lugaresi,
University of Bologna, Italy

REVIEWED BY
Bahia Hakiki,
IRCCS Don Carlo Gnocchi Firenze, Italy
Giampaolo Brichetto,
Associazione Italiana Sclerosi Multipla, Italy

*CORRESPONDENCE
Marcello Moccia
marcello.moccia@unina.it

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Determinants of early working impairments in multiple sclerosis

Marcello Moccia[1,2]*, Luca Fontana[3], Raffaele Palladino[4,5], Fabrizia Falco[6], Ferdinando Finiello[3], Mauro Fedele[3], Roberta Lanzillo[2,6], Liberata Reppuccia[3], Maria Triassi[4], Vincenzo Brescia Morra[2,6] and Ivo Iavicoli[3]

[1]Department of Molecular Medicine and Medical Biotechnology, Federico II University of Naples, Naples, Italy, [2]Multiple Sclerosis Clinical Unit, Federico II University Hospital, Naples, Italy, [3]Occupational Health Unit, Department of Public Health, Federico II University of Naples, Naples, Italy, [4]Department of Public Health, Federico II University of Naples, Naples, Italy, [5]Department of Primary Care and Public Health, Imperial College, London, United Kingdom, [6]Department of Neuroscience, Reproductive Science and Odontostomatology, Federico II University of Naples, Naples, Italy

Introduction: Unemployment can directly affect social status and identity. Assessing and adjusting determinants of early working impairments in a chronic disease can thus reduce its long-term burden. Hereby, we aim to evaluate differences in occupational history and early working impairments between people with multiple sclerosis (MS) and healthy workers.

Methods: This is a cross-sectional study comparing 71 workers with MS [age 41.7 ± 9.4 years; females 59.1%; EDSS 2.0 (1.0–6.0)] and 71 controls (age 42.6 ± 11.9 years; females 33.8%). All participants filled in Work Ability Index (WAI), Work Productivity and Activity Impairment (WPAI), European Questionnaire for Quality of Life (EuroQoL), Beck Depression Inventory II (BDI-II), and Pittsburgh Sleep Quality Index (PSQI). In MS, we further collected expanded disability status scale (EDSS), MS Questionnaire for Job difficulties (MSQ-Job), Fatigue severity scale (FSS), and the Brief International Cognitive Assessment for MS (BICAMS).

Results: Workers with MS were more working disabled ($p < 0.01$), less exposed to workplace risks ($p < 0.01$), and more limited in fitness to work ($p = 0.01$), compared with controls. On linear regression models adjusted by age, sex, education, and type of contract, people with MS had worse WAI (Coeff = −5.47; 95% CI = −7.41, −3.53; $p < 0.01$), EuroQoL (Coeff = −4.24; 95% CI = −17.85, −6.50; $p < 0.01$), BDI-II (Coeff = 3.99; 95% CI = 2.37, 7.01; $p < 0.01$), and PSQI (Coeff = 4.74; 95% CI = 3.13, 7.61; $p < 0.01$), compared with controls, but no differences in WPAI ($p = 0.60$). EuroQoL, BDI-II, and PSQI were equally associated with both WAI and WPAI in MS and controls (all $p < 0.01$). In MS, worse MSQJob was associated with higher EDSS (Coeff = 5.22; 95% CI = 2.24, 7.95; $p < 0.01$), progressive disease (Coeff = 14.62; 95% CI = 5.56, 23.69; $p < 0.01$), EuroQoL (Coeff = 4.63; 95% CI = 2.92, 6.35; $p < 0.01$), FSS (Coeff = 0.55; 95% CI = 0.38, 0.72; $p < 0.01$), and cognitive impairment (Coeff = 4.42; 95% CI = 0.67, 8.22; $p = 0.02$).

Discussion: Early factors associated with working difficulties in MS include disability, fatigue, depression, and cognitive dysfunction. Early

identification of clinical features potentially causing working difficulties should be considered to enhance job retention, along with targeted prevention and protection measures.

KEYWORDS

multiple sclerosis, working, job, disability, fatigue, mood, cognitive

Introduction

Multiple sclerosis (MS) is a chronic and potentially highly-disabling disease of the central nervous system, which can lead to physical and cognitive impairment, including walking difficulties, fatigue, poor balance, bladder and bowel dysfunction, reduced visual acuity, mood changes, and impaired cognition, (1). Symptoms can present in the form of relapses, followed by a recovery period [relapsing-remitting MS (RRMS)], or as gradual progression of disability, either preceded by relapses [secondary progressive MS (SPMS)] or not [primary progressive MS (PPMS)] (2). The MS natural history has changed thanks to the use of disease modifying treatments (DMTs), which primarily target relapses, but also affect disability outcomes in the long term (3).

MS holds significant psychological, physical, financial and social burden on patients, their caregivers, and healthcare services (4–6). The heavy financial burden of MS is related to young age at onset (usually around 30 years of age), variety of chronic symptoms, and subsequently high unemployment rates (7). Indeed, about 50% of workers with MS suffer from reduced working abilities from disease onset (e.g., scaling down from full-time to part-time work), and will eventually lose (or quit) their job (8–11). Exclusion from the workplace is responsible for worsening social status and finances, thus affecting health outcomes in MS (12). The main factors potentially associated with unemployment are progressive disease course, motor disability, fatigue, mood changes, and cognitive impairments (9, 11, 13–17). Nevertheless, data on work ability and occupational difficulties related to MS are rather limited. Also, most studies compared demographic and clinical variables between employed and unemployed people with MS, with potential bias coming from largely different populations (e.g., disease duration, disability) (12). As such, in the present study, we specifically focused on workers with MS to evaluate differences in occupational history and early working impairments (e.g., ability, productivity and activity), when compared with healthy workers as controls, and to define clinical correlates of MS-related perceived working difficulties. Identifying determinants of early working impairments in employed people with MS can direct work retention strategies, ultimately reducing the long-term burden of this chronic disease.

Methods

Study design

This is a cross-sectional study comparing workers with MS and healthy workers as controls. The study was conducted at the MS Unit and at the Occupational Health Unit, of the Federico II University Hospital, Naples, Italy. The study was approved by Ethics Committee, at Federico II University Hospital, Naples, Italy (355/19), and all recruited subjects signed informed consent authorizing the use of anonymized data, in line with data protection regulation (GDPR EU2016/679). The study was performed in accordance with good clinical practice and Declaration of Helsinki.

Study setting and participants

We included people with MS, consecutively recruited from Feb 2021 (until the reaching of the recruitment target, as from power calculation), according to the following inclusion criteria: (1) diagnosis of MS (18); (2) employment age (18–65 years); (3) employment in the previous 6 months; and exclusion criteria: (1) any concomitant condition, disease or treatment potentially affecting employment; (2) relapses in the previous 3 months.

We also recruited consecutively a group of healthy controls within the same age range (with a case:control matching ratio of 1:1), from Feb 2021 (until the reaching of the recruitment target, as from power calculation), while attending the same hospital within the same period for their scheduled visit at the Occupational Health Unit, in accordance with Italian legislation (Legislative Decree n. 81/2008) on the protection of health and safety in the workplace. The Occupational Health Unit regularly sees healthy workers from a number of public and private institutions, thus providing heterogeneous case mix.

Data collection was conducted by MS specialists with the support of Occupational Health specialists and neuropsychologists, as appropriate.

Main variables of interest

To measure work ability and work productivity and activity impairment, people with MS and controls were required to fill in the following questionnaires:

- Work Ability Index questionnaire (WAI) (19), with higher scores indicating better work ability;
- Work Productivity and Activity Impairment Questionnaire: General Health questionnaire (WPAI) (20), with higher scores indicating better work productivity and activity.

To measure MS-related perceived difficulties in work-related tasks, people with MS were required to fill in the following questionnaire:

- MS Questionnaire for Job difficulties (MSQ-Job) (7), with higher percent scores indicating worse perception of difficulties in work-related tasks;

Endpoints in people with MS and controls

We collected demographics (age, sex), education (highest educational attainment), and occupational history, using a structured questionnaire, as from the clinical practice at the Occupational Health Unit, in people with MS and controls. In detail, occupational history included the following variables: formal acknowledgment of working disability status, percent of disability status (with higher scores indicating higher disability), type of contract (e.g., permanent, temporary, self-employed), occupational risk factors (e.g., physical, ergonomic, biological, chemical, etc.), and formal limitations in the fitness to work (depending on both working disability status and exposure to specific occupational risk factors). We also classified working activity using the Italian Institute of Statistics classification (ISTAT – Nomenclatura e classificazione delle Unità Professionali), which includes: (1) law makers, businessmen, and managers; (2) intellectual, scientific and high-specialization work; (3) technical work; (4) office executive work; (5) qualified work in commercial activities and services; (6) craftsmen, skilled workers, and farmers; (7) System operators, workers of fixed and mobile machinery, and vehicle drivers; (8) Unqualified work; (9) armed forces.

Also, people with MS and controls were required to fill in the following questionnaires:

- European Questionnaire for Quality of Life – 5 Domains (EuroQoL) (21), for evaluating impairments in daily activities and percent rating of quality of life (we collected only the latter in controls, who would have had no significant impairments);
- Beck Depression Inventory II (BDI-II) (22), with higher scores indicating worse depression;
- Pittsburgh Sleep Quality Index (PSQI) (23), with higher scores indicating worse sleep quality.

MS specialists, MS nurses, and Occupational Health specialists were available to people with MS and controls while filling in the questionnaires, as needed.

Endpoints in people with MS

In people with MS, we collected disease duration (time from reported disease onset to baseline assessment), expanded disability status scale (EDSS), clinical subtype (RRMS, SPMS and PPMS; for statistical purposes SPMS and PPMS were grouped), and DMTs (grouped into first and second line DMTs). EDSS was categorized into <3.5 and >4.0 to identify people with MS without and with walking impairment. Moreover, workers with MS were also administered the following questionnaire and neuropsychological tests:

- Fatigue severity scale (FSS) (24), with higher scores indicating worse fatigue;
- Brief International Cognitive Assessment for MS(BICAMS) neuropsychological battery, which includes the following tests: the Symbol Digit Modalities Test (SDMT), evaluating attention and information processing speed; the California Verbal Learning Test-II (CVLT-II), evaluating memory and verbal learning; and the Brief Visuospatial Memory Test-Revised (BVMTR), evaluating visuo-spatial learning (25). Results were corrected for age, sex, and education, according to the Italian normative values. We then calculated the corresponding cerebral functional system (FS) score (0 corresponds to normal BICAMS tests, ≥ 1 corresponds to at least one impaired BICAMS test), as from previous studies (26).

Study size and power analysis

Considering a normal distribution of variables to be analyzed in regression model (including one dependent variable and four covariates), given a 10% minimum detectable effect size, a two-sided tail and a 5% α error, a sample of 142 individuals (71 cases and 71 controls) would be able to achieve 98% power.

Statistical methods

Results are presented as mean (standard deviation), median (range), or number (percent), as appropriate. Differences in demographics and occupational history in people with MS and

controls were evaluated using *t*-test, chi-square test and Fisher's exact test, as appropriate.

Differences between MS cases and controls were evaluated using linear regression models including each scale (WAI, WPAI, EuroQoL, BDI-II, PSQI), in turn, as dependent variable, and disease status as independent variable (people with MS vs. controls). Then, correlates of working ability (WAI), productivity and activity impairment (WPAI) were evaluated using linear regression models including each of these scales (WAI, WPAI), in turn, as dependent variable, and potential correlates (EuroQoL, BDI-II, PSQI), in turn, as independent variable; we also included an interaction term between disease status (people with MS vs. controls) and potential correlates (EuroQoL, BDI-II, PSQI), in turn, to evaluate changes in these associations between people with MS and controls.

Correlates of MS-related perceived difficulties in work-related tasks were evaluated using linear regression models including MSQJob as dependent variable, and each additional clinical variable (disease duration, EDSS, walking impairment on EDSS, clinical subtype, DMT, EuroQoL, FSS, SDMT, CVLT, BVMRT, cerebral functional system), in turn, as independent variable.

Univariate linear regression models were preliminarily run to evaluate associations between main variables of interests and study endpoints, in turn. We selected age, sex, education, and type of contract as covariates, that were included in all statistical models.

Distribution of variables and residuals was checked using both graphical and statistical methods. Results are reported as coefficients (Coeff), 95% confidence intervals (95% CI), and *p*-values, as appropriate. Statistical analyses were performed using Stata 17.0.

Result

We included 71 people with MS and 71 controls. Demographics and occupational history in subjects with MS

TABLE 1 Demographics and occupational history in people with MS and controls.

		People with MS ($n = 71$)	Controls ($n = 71$)	*p*-value
Age, mean ± SD		41.7 ± 9.4	42.6 ± 11.9	0.61
Sex, females (%)		42 (59.1%)	24 (33.8%)	<0.01
Education	Degree	36 (50.7%)	53 (74.6%)	0.01
	High school	33 (46.5%)	16 (22.6%)	
	Primary school	2 (2.8%)	2 (2.8%)	
Working disability status, *n*		68 (95.7%)	1 (1.4%)	<0.01
Working disability, percent		43.7 ± 35.1%	1.0 ± 8.4%	<0.01
Contract	Permanent	48 (67.6%)	40 (56.3%)	0.08
	Temporary	11 (15.5%)	22 (31.0%)	
	Self employed	12 (16.9%)	9 (12.7%)	
Work classification*	Law makers, businessmen, and managers	13 (18.3%)	10 (14.1%)	0.69
	Intellectual, scientific and high-specialization work	9 (12.7%)	7 (9.9%)	
	Technical work	9 (12.7%)	5 (7.0%)	
	Office executive work	3 (4.2%)	3 (4.2%)	
	Qualified work in commercial activities and services	18 (25.3%)	19 (26.8%)	
	Craftsmen, skilled workers, and farmers	15 (22.6%)	24 (33.8%)	
	System operators, workers of fixed and mobile machinery, and vehicle drivers	0 (0%)	0 (0%)	
	Unqualified work	3 (4.2%)	3 (4.2%)	
	Armed forces	0 (0%)	0 (0%)	
Occupational risks	Physical	15 (21.2%)	9 (12.7%)	<0.01
	Ergonomic	17 (23.9%)	23 (32.4%)	
	Biological/Chemical	3 (4.2%)	30 (42.2%)	
	None	36 (50.7%)	9 (12.7%)	
Limitations in fitness for work		11 (15.5%)	2 (2.8%)	0.01

P-values are shown from t-test, chi-square test and Fisher's exact test, as appropriate. MS, multiple sclerosis; SD, standard deviation.
*Work classification refers to the Italian Institute of Statistics (ISTAT – Nomenclatura e classificazione delle Unità Professionali).

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TABLE 2 Working impairment in people with MS and controls, and their associations with clinical features.

	People with MS ($n = 71$)	Controls ($n = 71$)	Coeff.	95% CI		p-value
				Lower	Upper	
WAI	37.5 ± 6.4	43.7 ± 4.7	−5.47	−7.41	−3.53	<0.01
WPAI	4.6 ± 12.6	3.9 ± 14.0	−1.62	−7.82	4.57	0.60
EuroQoL, percent	73.5 ± 16.9	85.5 ± 14.2	−4.24	−17.85	−6.50	<0.01
Association with WAI			0.15	0.10	0.21	<0.01
Interaction term WAI			0.15	0.04	0.25	<0.01
Association with WPAI			−0.32	−0.49	−0.14	<0.01
Interaction term WPAI			−0.99	−0.53	0.18	0.32
BDI-II	8.3 ± 7.5	3.1 ± 5.0	3.99	2.37	7.01	<0.01
Association with WAI			−0.47	−0.6 0	−0.35	<0.01
Interaction term WAI			−0.18	−0.28	0.23	0.85
Association with WPAI			0.75	0.30	1.20	<0.01
Interaction term WPAI			−0.80	−1.31	0.55	0.42
PSQI	9.5 ± 6.5	4.7 ± 5.7	4.74	3.13	7.61	<0.01
Association with WAI			−0.48	−0.61	−0.35	<0.01
Interaction term WAI			−0.10	0.41	−0.35	0.14
Association with WPAI			1.09	0.65	1.54	<0.01
Interaction term WPAI			−0.05	−0.92	0.87	0.95

Coefficients (Coeff), 95% confidence intervals (95% CI), and p-values are shown from linear regression models adjusted by age, sex, education, and type of contract. First, we evaluated differences between people with MS and controls; then associations between WAI/WPAI and EuroQoL/BDI-II/PSQI; and, finally, changes in these associations between people with MS and controls on an interaction term. BDI-II, Beck Depression Inventory II; EuroQoL, European Questionnaire for Quality of Life; MS, multiple sclerosis; PSQI, Pittsburgh Sleep Quality Index; WAI, Work Ability Index questionnaire; WPAI, Work Productivity and Activity Impairment Questionnaire.

and controls are reported in Table 1. MS workers had similar age, when compared with controls ($p = 0.61$), but were more frequently females ($p < 0.01$), less educated ($p = 0.01$), more working disabled ($p < 0.01$), less exposed to occupational risk factors ($p < 0.01$), and more limited in fitness to work ($p = 0.01$) (Table 1).

Working impairment (e.g., ability, productivity and activity) of people with MS and controls, and their associations with clinical features (e.g., quality of life, depression, quality of sleep) are reported in Table 2. People with MS had worse WAI (Coeff = −5.47; 95% CI = −7.41, −3.53; $p < 0.01$), EuroQoL (Coeff = −4.24; 95% CI = −17.85, −6.50; $p < 0.01$), BDI-II (Coeff = 3.99; 95% CI = 2.37, 7.01; $p < 0.01$), and PSQI (Coeff = 4.74; 95% CI = 3.13, 7.61; $p < 0.01$), compared with controls, while no difference in WPAI was found (Coeff = −1.62; 95% CI = −7.82, 4.57; $p = 0.60$). EuroQoL, BDI-II, and PSQI were associated with both WAI and WPAI (all $p < 0.01$); however, when evaluating differences between people with MS and controls in these associations using interaction terms, only the association between EuroQoL and WAI was less strong in people with MS, when compared with controls ($p < 0.01$) (Table 2).

Clinical features of workers with MS, and their associations with perceived work-related difficulties (MSQJob) are reported in Table 3. Worse MSQJob was associated with higher EDSS (Coeff = 5.22; 95% CI = 2.24, 7.95; $p < 0.01$), walking impairment (EDSS > 4.0) (Coeff = 5.59; 95% CI = 7.20, 23.97; $p < 0.01$), progressive disease subtype (Coeff = 14.62; 95% CI = 5.56, 23.69; $p < 0.01$), EuroQoL (Coeff = 4.63; 95% CI = 2.92, 6.35; $p < 0.01$), FSS (Coeff = 0.55; 95% CI = 0.38, 0.72; $p < 0.01$), CVLT (Coeff = −0.31; 95% CI = −0.52, −0.09; $p < 0.01$), and MS-related cerebral functional system involvement (Coeff = 4.42; 95% CI = 0.67, 8.22; $p = 0.02$) (Table 3).

Discussion

In the present study, we showed that, working ability, productivity and activity impairment are associated with quality of life, depressive symptoms, and sleep quality in both MS and age-matched controls, though overall working ability is lower in people with MS. In particular, determinants of perceived work-related difficulties in MS are disability, walking impairment, progressive symptoms, lower quality of life, fatigue and cognitive dysfunction. Of note, we specifically focused on employed people with MS, rather than on unemployment, and, thus, our work aims at increasing awareness on determinants of early working impairments, and at considering medications, rehabilitation, and specific working adaptations to tackle employability in clinical practice (16). The baseline level of work productivity is associated with work productivity trajectories

TABLE 3 Clinical features of people with MS and associations with MSQJob.

		People with MS ($n = 71$)	Coeff.	95% CI		p-value
				Lower	Upper	
MSQJob, percent		17.0 ± 12.6	n/a	n/a	n/a	n/a
Disease duration, years		10.5 ± 7.4	0.01	−0.59	0.68	0.98
EDSS, median (range)		2.0 (1.0–6.0)	5.22	2.24	7.95	<0.01
<3.5		59 (83.1%)	15.59	7.20	23.97	<0.01
>4.0		12 (16.9%)				
Clinical subtype	RRMS	61 (85.9%)	Ref.			
	Progressive (SPMS and PPMS)	10 (14.1%)	14.62	5.56	23.69	<0.01
DMT						
1st line	Dimethyl fumarate	10 (14.2%)	Ref.			
	Glatiramer acetate/Interferon	6 (8.4%)				
	Teriflunomide	1 (1.4%)				
2nd line	Alemtuzumab	8 (11.3%)	3.55	−3.71	10.83	0.33
	Fingolimod	11 (15.5%)				
	Natalizumab	28 (39.4%)				
	Ocrelizumab	7 (9.8%)				
EuroQoL, score		2.0 ± 1.6	4.63	2.92	6.35	<0.01
FSS		29.6 ± 14.5	0.55	0.38	0.72	<0.01
SDMT, adjusted score		50.0 ± 12.5	−0.15	−0.42	0.11	0.25
CVLT, adjusted score		48.6 ± 14.5	−0.31	−0.52	−0.09	<0.01
BVMRT, adjusted score		52.1 ± 13.5	−0.09	−0.33	0.15	0.45
Cerebral FS	0	57 (80.3%)				
	≥1	14 (19.7%)	4.42	0.67	8.22	0.02

Coefficients (Coeff), 95% confidence intervals (95% CI), and p-values are shown from linear regression models adjusted by age, sex, education, and type of contract. BVMRT, Brief Visuospatial Memory Test-Revised; CVLT, California Verbal Learning Test; DMT, disease modifying treatment; EDSS, expanded disability status scale; EuroQoL, European Questionnaire for Quality of Life; FS, functional system; MS, multiple sclerosis; MSQJob, multiple sclerosis questionnaire for job difficulties; PPMS, primary progressive MS; RRMS, relapsing remitting MS; SDMT, symbol digit modalities test; SPMS, secondary progressive multiple sclerosis.

over time (11), and, thus, variables associated with working difficulties should be identified and targeted as soon as possible during the course of the disease.

We showed that employed people with MS have lower working ability, when compared with controls, but are able to keep up with requested working productivity and activity, possibly thanks to the acknowledgment of working disability and subsequent arrangements (e.g., reduced or modified exposure to selected occupational risk factors). In previous studies, there was poor awareness on the tools to assist people with MS in retaining employment (27), while this does not seem the case in our population. Over the disease course, there is a progressive reduction of occupational activities, with up to 50% patients with MS being unemployed within 10 years from disease onset (8, 9, 27–29). As such, the employability of workers with MS should be preserved by adaptation and prevention of working conditions (e.g., ergonomic and technical aspects of the workplace) based on the individual clinical manifestations of the disease (11). In a recent survey, Italian occupational physicians reported on difficulties in rating fitness to work in people with MS (30), and, thus, we hope that our study will raise awareness on the opportunity to design and implement special and reasonable accommodations for MS workers in order to meet their individual needs, according to their clinical features.

Among the novelties of our study, we included both people with MS and controls, and showed that quality of life, depressive symptoms and quality of sleep were worse in people with MS, when compared with controls, but were equally associated with working activity and capacity (productivity and ability). These results suggest that, though quantitatively different, people with MS and controls share qualitatively similar correlates of working impairment. As such, early identification and clinical management of worsening quality of life, depression and sleep, along with subsequent working adaptations, may contribute to improve productivity and to retain employment in individuals with MS, as well as in otherwise healthy workers (10, 11).

Looking at MS-specific factors, in our study, self-perceived difficulties in work-related tasks were associated with higher disability (especially walking impairment), progressive disease subtype, fatigue and cognitive dysfunction, especially in relation to verbal learning and memory. These results are in line with previous studies showing associations between unemployment

and mood changes (11, 13), fatigue (8, 13, 28), motor disability (8, 13, 28, 31, 32), and cognitive dysfunction (32). Intriguingly, we specifically focused on workers with MS, and decided to evaluate determinants of perceived working difficulties, which were ultimately not different from actual correlates of unemployment. In keep with this, previous studies showed associations between work difficulties and mood changes (14, 33, 34), fatigue (11, 14, 34), motor disability (11, 14, 33), and cognitive dysfunction (11, 14, 35). In a previous study also using the BICAMS, attention and processing speed (SDMT) was associated with working ability (35), while we found an association for verbal learning and memory (CVLT). While we acknowledge that the SDMT is a marker of overall cognitive function in MS (36), in our study, we computed the cerebral FS score based on overall BICAMS results, which also reflects cognitive impairment (26), and was associated with working difficulties. Not least, working difficulties can be associated with a variety of cognitive deficits based on the actual tasks. We cannot exclude a similar association in controls as well, but unfortunately did not have availability of cognitive variables.

Our study is limited by the single-center design and the relatively small sample size, though sufficiently powered to show consistently significant associations. Controls were recruited based on the age range, which is a main determinant of employability; however, cases and controls were not balanced in sex and education, which were included as covariates in the statistical models. As such, notwithstanding statistical adjustments, we have to acknowledge the risk of bias coming from sex and education differences. Also, our cross-sectional design does not allow causal inference, nor the evaluation of longitudinal changes in working difficulties, also in relation to treatments (20). Generalizability of our results is definitely limited to countries with similar working retention policies and universal healthcare coverage (e.g., Europe, Canada) (17, 37).

In conclusion, our study encourages the early identification and management of clinical features potentially causing an impairment of working ability in people with MS, along with the implementation of individually targeted prevention and protection measures on the workplace. Based on our results, MS specialists should primarily consider disability, fatigue, depression, and cognitive impairment, and liaise with occupational physicians to identify the most suitable arrangements, counseling programs and strategies to support workers with MS. In the future, multidisciplinary patient/worker management teams, including MS specialists, occupational physicians and other healthcare professionals (38, 39), should be considered to protect the health and the employment of vulnerable people with MS.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Federico II University Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MM and LF contributed to data collection, data analysis and interpretation, manuscript preparation, and revision. VB and II contributed to data interpretation, manuscript revision, and coordination. RP and MT contributed to data analysis and interpretation and manuscript revision. FFa, FFi, MF, RL, and LR contributed to data collection, database preparation, and manuscript revision.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Zsolt Illes,
University of Southern Denmark, Denmark

REVIEWED BY
Cecilia Rajda,
University Szeged, Hungary
Luanne Metz,
University of Calgary, Canada

*CORRESPONDENCE
Francesca Bridge
✉ Francesca.bridge@monash.edu

†These authors have contributed equally to this work

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Risk of cervical pre-cancer and cancer in women with multiple sclerosis exposed to high efficacy disease modifying therapies

Francesca Bridge[1,2]*, Julia M. L. Brotherton[3,4], Yi Foong[1,2,5], Helmut Butzkueven[1,2], Vilija G. Jokubaitis[1,2†] and Anneke Van der Walt[1,2†]

[1]Department of Neuroscience, Central Clinical School, Monash University, Melbourne, VIC, Australia, [2]Department of Neurology, Alfred Health, Melbourne, VIC, Australia, [3]Australian Centre for the Prevention of Cervical Cancer (Formerly Victorian Cytology Service), Carlton South, VIC, Australia, [4]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia, [5]Department of Neurosciences, Eastern Health, Melbourne, VIC, Australia

There is a growing need to better understand the risk of malignancy in the multiple sclerosis (MS) population, particularly given the relatively recent and widespread introduction of immunomodulating disease modifying therapies (DMTs). Multiple sclerosis disproportionately affects women, and the risk of gynecological malignancies, specifically cervical pre-cancer and cancer, are of particular concern. The causal relationship between persistent human papillomavirus (HPV) infection and cervical cancer has been definitively established. To date, there is limited data on the effect of MS DMTs on the risk of persistent HPV infection and subsequent progression to cervical pre-cancer and cancer. This review evaluates the risk of cervical pre-cancer and cancer in women with MS, including the risk conferred by DMTs. We examine additional factors, specific to the MS population, that alter the risk of developing cervical cancer including participation in HPV vaccination and cervical screening programs.

KEYWORDS

cervical cancer, disease modifying therapy (DMT), autoimmune disease (AID), multiple sclerosis (MS), human papilloma virus (HPV)

1. Introduction

There is growing need to better understand the risk of cancer in the multiple sclerosis (MS) population, particularly with the recent and widespread introduction of highly effective immunomodulatory or immunosuppressive disease modifying therapies (DMTs) (1, 2). MS is a chronic inflammatory autoimmune disease of the central nervous system that is three times more prevalent in women and usually diagnosed between the ages of 20–40 years (3). Treatment with DMTs is usually commenced at diagnosis and continued life-long, leading to significant long-term exposure (4).

A recent scoping review highlighted gynecological cancer risk, including cervical cancer, as an important knowledge gap in the MS literature (1). The risk of cervical cancer may be altered in women with MS (wwMS). It remains unclear whether this is the result of the autoimmune condition or secondary to the DMTs used in the treatment of MS. Additionally, wwMS may be underrepresented in primary and secondary prevention programs (5–9), further contributing to the risk of cancer in this vulnerable patient population.

Almost all cervical cancer is due to an underlying persistent infection with oncogenic types of human papillomavirus (HPV) (10, 11), a very common double stranded DNA virus, that is transmitted *via* sexual contact (12–14). HPV is usually cleared by the immune system without symptoms within 1–2 years. Persistent infection with one of the 13 oncogenic HPV types (including the most oncogenic types, HPV 16 and HPV 18, which are associated with 70% of cervical cancers globally) increases the risk of developing cervical pre-cancerous abnormalities. Cervical pre-cancerous abnormalities are classified as cervical intraepithelial neoplasia (CIN) grade 2 or 3 (CIN3 is synonymous with carcinoma in situ), or adenocarcinoma in situ (AIS). These abnormalities also referred to as High-grade squamous intraepithelial lesions (HSIL). Pre-cancerous lesions are at risk of progression to cancer of the cervix (see Figure 1) (12, 13). Co-factors for the development of cervical cancer in the presence of persistent oncogenic HPV include smoking, high parity, oral contraceptive use, and immunocompromise. An intact immune system is necessary for adequate clearance of HPV. HPV clearance is impaired in patients who are severely immunocompromised, including patients with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), solid-organ transplant recipients and some autoimmune conditions (4, 15–17). The immunocompromised population are at risk of infection with multiple HPV types along with a greater diversity of HPV types (18–20).

Here we review the literature relating to the risk of cervical cancer in people with a cervix, hereby referred to as women with MS. We consider the role that immunotherapies play in altering this risk. Furthermore, we explore other factors, specific to the MS population, that may impede access to HPV vaccination and cervical screening programs and further increase patients' risk of developing cervical cancer.

2. Methodology

2.1. Literature search

We searched the PubMed database for peer-reviewed articles published in English from 1990 through October 2022 on multiple sclerosis and cervical cancer risk, using the following search strategy:

> ((((((“multiple sclerosis”[MeSH Terms] OR (“multiple”[All Fields] AND “sclerosis”[All Fields]) OR “multiple sclerosis”[All Fields]) AND (“uterine cervical neoplasms”[MeSH Terms] OR (“uterine”[All Fields] AND “cervical”[All Fields] AND “neoplasms”[All Fields]) OR “uterine cervical neoplasms”[All Fields] OR (“cervical”[All Fields] AND “cancer”[All Fields]) OR “cervical cancer”[All Fields])) AND (fft[Filter])) OR (((“neoplasms”[MeSH Major Topic] OR “uterine cervical neoplasms”[MeSH Major Topic]) AND “multiple sclerosis”[MeSH Major Topic]) AND ((fft[Filter]) OR ((viral)) AND (cancer)) AND (multiple sclerosis)) AND (1990:2022[pdat])))

In addition, we hand-searched reference lists from the articles identified by the search and key review articles. We also reviewed the pivotal pharmaceutical trials for each DMT.

2.2. Selection criteria

We reviewed titles, abstracts to identify studies examining the risk of cervical abnormalities in wwMS, including the risk conferred by DMTs.

3. Risk of cervical cancer in wwMS

There is limited literature on the risk of cervical abnormalities and cancer in wwMS (see Table 1). The reported incidence of cervical cancer in wwMS ranges from 0.1–1.1 per 1,000 person years (21, 23, 24, 27, 28, 36). The heterogeneity in incidence estimates is likely due to the differences in the way the MS population was identified, study sample sizes, methods for reporting cancers, observation periods, and variation in DMT use across these studies (36, 37).

Two retrospective observational studies, one Finnish and the other Australian, evaluated the risk of cervical abnormalities in wwMS (4, 31). Women with MS were found not to be at increased risk of cervical cancer or high-grade histological and cytological abnormalities, respectively. However, it is important to consider important limitations of both studies which could impact their generalizability. Firstly, the cohorts were identified through hospital administration data (4, 31). Hospitalization is atypical for the MS population, and could represent patients with more severe disease, or significant medical comorbidities. Secondly, neither study examined the impact of DMT use, either due to lack of information, or insufficient power (4, 31).

The finding that cervical cancer risk in the MS population is not increased was supported by population-based registry studies. Again, the impact of DMTs, particularly high-efficacy therapies was not accounted for in many of these studies.

In contrast, a Norwegian nationwide cohort study found that, although the risk of female genital organ cancer was not different between wwMS and population-based controls between the years 1953–1995, the risk increased significantly from 1996–2017 (4, 21–35). They hypothesized that this may reflect the introduction of highly effective DMTs over this period (34). Again, the study did not directly explore this hypothesis.

Population-wide cohort studies have shown an increased risk of cervical abnormalities in females with autoimmune conditions including inflammatory bowel disease (IBD), systematic lupus erythematosus (SLE), and rheumatoid arthritis (RA), especially if treated with immunomodulatory therapy (4, 38). However, these conditions are not directly comparable with MS, as the diseases have different risk profiles for cervical cancer and most commonly are treated with different DMTs. While most studies in the MS population have found the incidence of cervical cancer to be equal to or less than the general population (4, 21–33, 35), there is growing concern that long-term exposure to DMTs may increase risk.

4. Risk of persistent HPV infection and cervical cancer attributable to disease modifying therapies in wwMS

The treatment of multiple sclerosis has been revolutionized over the past two decades with the introduction of highly effective DMTs (2). These therapies have transformed MS disease trajectories

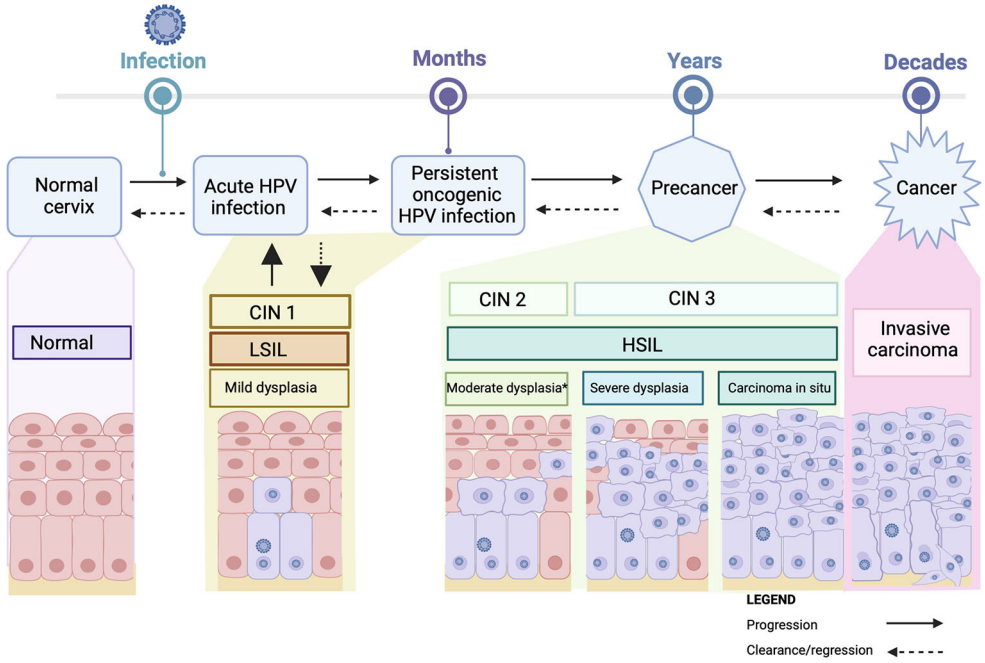

FIGURE 1
Cervical carcinogenesis. Acute Infection with HPV may cause mild cervical abnormalities [CIN I (mild dysplasia/LSIL)], which usually clear spontaneously. Persistent infection with oncogenic HPV can result in cervical pre-cancerous lesions [CIN 2 (moderate dysplasia), CIN3 (severe dysplasia or carcinoma *in situ*/HSIL)] which can progress over time to invasive cancer. Progression is not inevitable, with regression possible at any stage. *sometimes acute infections/infections with lower risk HPV types can produce an appearance that is identified as moderate disease (CIN2). CIN2 is a heterogeneous entity likely comprising "severe CIN1 cases" and "mild CIN2" cases rather than a single disease state with a uniform prognosis. HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions. Created with BioRender.com.

by significantly reducing disease activity, relapse rates and disability progression (37). Natalizumab was the first highly effective DMT to receive US Food and Drug Administration (FDA) approval in 2004, and since then there has been successive introductions of new agents, all of which target the immune system in varying ways.

While the benefit of these therapies should be emphasized, they are not without risk. High-efficacy DMTs have been found to increase the risk of opportunistic infections and, theoretically, can reduce immune surveillance and increase cancer risk (2, 39). There is potential for the impact of DMTs to be significant, given that these medications are often commenced at a young age and continued indefinitely (40).

4.1. DMTs and the risk of HPV infection

DMTs increase the risk of opportunistic infections within the MS population (39). However, there is currently insufficient data to draw conclusions on the risk of HPV infection (41).

HPV enters the basal keratinocytes of the cervical epithelium through micro-abrasions (42). As keratinocytes migrate to the upper epidermis there is increasing viral replication (14, 43). New infectious HPV is released from the surface of the epithelium. As HPV is essentially an intracellular pathogen, there is minimal HPV viraemia or lymphatic infection. This results in minimal exposure of HPV to the circulating immune system (14). However, in most cases, activation of the innate and adaptive immune systems does occur, leading to viral clearance in the majority of women (12–14, 44). DMTs alter the immune response *via* several mechanisms which may limit immune surveillance and clearance of the virus (Figure 2). During persistent infections oncogenic types may integrate into the host DNA, disrupting expression of the E6 and E7 viral oncogenes, which may inactivate critical cell cycle checkpoints and increase genetic instability in the host, which over time may lead to cervical cancer (45).

Few studies have investigated the risk of DMTs on HPV infection. Fingolimod has been identified in a small number of case report series as being associated with a risk of HPV infection (39, 46–48). However, this finding has not been validated by higher quality evidence.

4.2. Disease modifying therapies and risk of cervical cancer

There is limited data on the effect of DMTs on cervical cancer risk in the MS population (see Supplementary Table 1). At present, studies are limited by sample size, duration of follow-up, difficulty capturing representative population-based samples and complete and accurate data. Additionally, there is likely underreporting of this outcome in part due to under-participation in screening programs in the MS population (6–8, 49). Importantly cervical cancer outcomes may not be captured in the pharmaceutical safety trials, as these trials are often conducted over a shorter duration (1–2 years), and oncogenesis secondary to HPV is known to occur over decades.

Studies to date have found conflicting results regarding the risk of overall cancer associated with DMTs. Most studies have reported

TABLE 1 Summary of studies that evaluate cervical cancer risk in patients with multiple sclerosis.

Authors	Type of study	Country	MS sample size	Index period	Data source for MS patients	Results risk of cervical cancer		Interpretation
						N (%)	SIR/HR/AHR	
Studies which found decreased risk cervical abnormalities								
Moller et al. (21)	Cohort study	Denmark	5,359 MS patients 3,165 women	1977–1987	Registry data linkage: Danish hospital discharge register, Danish cancer register	Cervical cancer MS 5	RR 0.9, $p \leq 0.05$	Risk of cervical cancer reduced in wwMS
Moisset et al. (22)	Case-control study	France	1,107 MS patients 1,568 controls	2014–2015	"MS patients' network in Auvergne" association members	Gynecological cancers MS 13 (1.17%) Controls 28 (2.93%)	NR	Risk of cervical cancer not increased in wwMS
Studies which found cervical abnormality risk same as general population								
Nielsen et al. (23)	Cohort study	Denmark	11,817 MS patients 7,188 women	1968–1997	Registry data linkage (Danish MS register, Danish cancer register)	Cervical cancer 40	SIR 1.11 (0.81–1.51)	No difference in cervical cancer incidence in wwMS
Bahmanyar et al. (24)	Cohort study	Sweden	20,276 MS (13,218 wwMS) 203,951 non-MS controls (132,638 women)	1958–2005	Data linkage registry data: Swedish MS register and national inpatient register), patients with MS matched to age, sex, area controls	Cervical cancer 63	HR 0.83 (95% CI 0.64-1.07)	No difference in cervical cancer risk in wwMS compared with controls
Fois et al. (25)	Observational study	United Kingdom	4,250 MS patients 2,812 women	1963–1999	Oxford record linkage study (ORLS)	Cervical cancer 6	Adjusted rate ratio 1.3 (95% CI 0.5–2.8, $p = 0.75$)	No increased risk of cervical cancer in wwMS
Lebrun et al. (26)	Descriptive study	France	20,993 MS patients 15,220 women	1995–2009	Registry data: European database for MS, French national cancer registry	Gynecological (ovarian, cervix, uterine) cancer 28	SIR 1.2 (0.8–1.9)	No difference in cervical cancer incidence in wwMS
Kingwell et al. (27)	Retrospective cohort study	Canada	6,820 MS patients 4,998 women	1980–2004	Registry data linkage: British Columbia MS database, British Columbia cancer registry, British Columbia ministry of health's registration and premium billing files, British Columbia vital statistics death database	Cervical cancer 8	SIR 0.84 (0.36–1.65)	No difference in cervical cancer incidence in wwMS compared with controls
Hemminki et al. (28)	Observational study	Sweden	185,014 wwMS	1964 (some regions) 1986–2008	Linkage of national datasets: Swedish hospital discharge register, Swedish cancer registry	Cervical cancer 18 Cervical cancer deaths 8	Cervical cancer SIR 0.92 (95%CI 0.54–1.45) Cervical cancer deaths HR 1.81 (95% CI 0.91–3.62)	Incidence of cervical cancer and cervical cancer deaths in wwMS the same as the general population
Dugué et al. (29)	Cohort study	Denmark	14,403 wwMS	1977–2010	Registry data linkage: Danish national patient register, Danish national prescription registry, Danish cancer register	Cervical cancer 1977–2010: 46 1995–2010: 28	1977–2010: SIR 1.2 (0.9–1.6) 1995–2010: SIR 1.2 (0.8-1.8)	No difference in cervical cancer incidence in wwMS

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TABLE 1 (Continued)

Authors	Type of study	Country	MS sample size	Index period	Data source for MS patients	Results risk of cervical cancer		Interpretation
						N (%)	SIR/HR/AHR	
Ajdacic-Gross et al. (30)	Case-control study	Switzerland	5,489 MS patients number of women NR	1969–2007	Data linkage from medical records and hospital coding	Cervical cancer 20	SMR 1.11 (chi2 lCI-uCI 1.03–1.46, $p > 0.1$)	Cervical cancer mortality not increased in the MS population
Hongell et al. (31)	Case-control study	Finland	1,974 MS patients 10,740 controls	2004–2012	Hospital administrative data	Cervical cancer MS 1 (0.1%) Controls 5 (0.0%)	OR 2.0 (95% CI 0.2–16.4, $p = 0.519$)	No increased risk of cervical cancer in MS population
Grytten et al. (32)	Prospective cohort study	Norway	6,883 MS patients (4597 wwMS) 27,919 population controls (25,265 women)	1952–2016	Registry data linkage: Norwegian MS registry, cancer registry of Norway	Female genital organ cancer MS 94 (12.1%) Controls 459 (11.4%)	HR 1.18 (0.94–1.47)	No increased risk of female genital organ cancer in wwMS compared to controls
Foster et al. (4)	Retrospective cohort study	Australia	1,426 wwMS 985,383 non-MS controls	2000–2013	Data linkage: Victorian emergency minimum dataset, victorian cervical cytology register	High grade histology 40 High grade cytology 77 Low grade cytology 251	High-grade histological abnormalities: 3.07 vs. 3.76 per 1,000 person-years, AHR = 0.78, $p = 0.124$ High-grade cytological abnormalities (5.98) vs. 6.26 per 1,000 person-years, AHR = 0.98, $p = 0.836$ Low-grade histological abnormalities: 20.45 vs. 19.99 per 1,000 person-years, AHR = 1.10, $p = 0.139$	No difference in risk of cervical abnormalities (high or low-grade) in wwMS compared with controls
Johnson et al. (33)	Observational study	North America	7,277 MS patients 7,277 controls	1997-NR	Health record database used to identify cases of MS and age, race, and gender matched controls	Anal/vaginal/cervical cancer MS 11 (0.2%) Controls 13 (0.2%)	NR	No difference in cervical cancer incidence in wwMS
Grytten et al. (34)	Cohort study	Norway	6,949 MS patients (4,638 wwMS) 37,922 controls (2,513 women)	1953–2017	Registry data linkage	Female genital organ cancer 1953–1995: 6 1996–2017: 68	Female genital organ cancer: 1953–1995: IRR 0.78 (95% CI 0.48–1.27) 1996–2017: IRR 1.40 (95% CI 1.09–1.80, $p < 0.05$)	1953–1995 no difference in cervical cancer frequency in MS patients 1996–2017 increased frequency of female genital organ cancer in wwMS
Marrie et al. (35)	Retrospective matched cohort study	Canada	53,983 MS cases 269,915 controls	1998–2017	Population-based administrative databases: manitoba population research data repository, institute for clinical evaluative sciences (ICES)	NR	Cervical cancer crude IRR 1998–2007 0.85 (95% CI 0.5–1.45) 2008–2017 0.85 (95% CI 0.55–1.31) Age-standardized IRR 1998–2007 0.92 (0.52–1.63) 2008–2017 0.84 (0.53–1.33)	Cervical cancer incidence not increased in the MS population

(Continued)

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TABLE 1 (Continued)

Authors	Type of study	Country	MS sample size	Index period	Data source for MS patients	Results risk of cervical cancer		Interpretation
						N (%)	SIR/HR/AHR	
Studies which found increased risk cervical abnormalities								
Grytten et al. (34)	Cohort study	Norway	6,949 MS patients (4,638 wwMS) 37,922 controls (2,513 women)	1953–2017	Registry data linkage: Norwegian MS registry, cancer registry of Norway	Female genital organ cancer 953–1995: 6, 1996–2017: 68	Female genital organ cancer: 1953–1995: IRR 0.78 (95% CI 0.48–1.27) 1996–2017: IRR 1.40 (95% CI 1.09–1.80, $p < 0.05$)	1953–1995 no difference in cervical cancer frequency in MS patients 1996–2017 Increased frequency of female genital organ cancer in MS patients

AHR, adjusted hazard ratio; CI, confidence interval; DMT, disease modifying therapy; HR, hazard ratio; IRR, incidence rate ratio; MS, multiple sclerosis; NR, not reported; OR, odds ratio; RR, relapse rate; SIR, standardized incidence ratio; SMR, standardized mortality ratio; wwMS, women with MS.

no increased risk of cancer (22, 50–55), while others have found an increased cancer risk (22, 50–56). Individual classes of DMTs have also been associated with an increased (26, 57), or a reduced risk of cancer (58). The discrepancy is likely in part explained by study design, with many observational studies grouping therapies, for example as immunomodulating vs. immunosuppressing, in order to improve statistical power. However, many of these therapies have different mechanisms of action and thus different risk profiles. Across studies there is also a lack of uniformity as to which therapies are included. Several studies have included therapies such as azathioprine and cyclophosphamide in the analysis for immunosuppressive therapies (22, 26, 50, 51, 53, 55, 56). These therapies have been widely reported to increase the risk of cancer (59, 60), and are seldom used in the modern-day treatment of MS, thereby likely skewing results.

A further challenge is that patients with MS often switch DMTs throughout their life. This makes quantifying the risk attributable to individual DMTs difficult. Additionally, it poses challenges for calculating the risk for an individual who may have been exposed to several different therapies. The cumulative risk is likely the product of the combination of therapies used, along with the duration of exposure to each therapy (26, 50, 51).

Age at exposure to DMT also likely impacts risk. Similar to the general population, cancer risk in patients with MS increases with advancing age, likely in part due to weakening of the immune system (50, 61). Evidence suggests an additive effect from DMT exposure with several DMTs including cladribine, anti-CD20, alemtuzumab and sphingosine-1-phosphate modulators increasing the risk of malignancy with age (61). However, while aging increases cancer risk more broadly, cervical cancer incidence is highest in younger populations (25–50 years) (62). The impact of aging on cervical cancer risk in the MS population remains unclear but may have implications for long-term malignancy surveillance, and DMT counseling.

Despite the lack of definitive evidence to confirm the role of DMTs in the development of cancer, DMTs including cladribine, fingolimod, natalizumab, alemtuzumab, and ocrelizumab all carry a warning for potential cancer risk (34, 63). It is a requirement that all patients treated with these medications undergo cancer surveillance (40).

The cancer incidence among patients treated in the modern-DMT era was examined in a French study that identified 9,269 patients with MS who had been exposed to DMTs from two population-based disease registers and these were linked to patient records in the French National Cancer Register (26). DMTs were categorized into two groups: immunomodulatory drugs and immunosuppressive drugs. Interferons and glatiramer acetate were considered immunomodulatory therapies, whereas azathioprine, mitoxantrone, mycophenolate mofetil, natalizumab, methotrexate, fingolimod, cladribine and teriflunomide were classified as immunosuppressive therapies. For this analysis, all gynecological cancers, including ovarian, cervical, and uterine were grouped together. WwMS treated with DMTs had a non-significantly increased risk of gynecological cancers (SIR 1.2; CI 0.8–1.9). The risk of "all cancer" was increased if the patient had been exposed to more than three types of immunosuppressive drugs, or more than two types of immunomodulatory drugs. The risk of cancer was increased with increased duration of exposure to DMTs ($P < 0.001$). The mean duration of treatment with

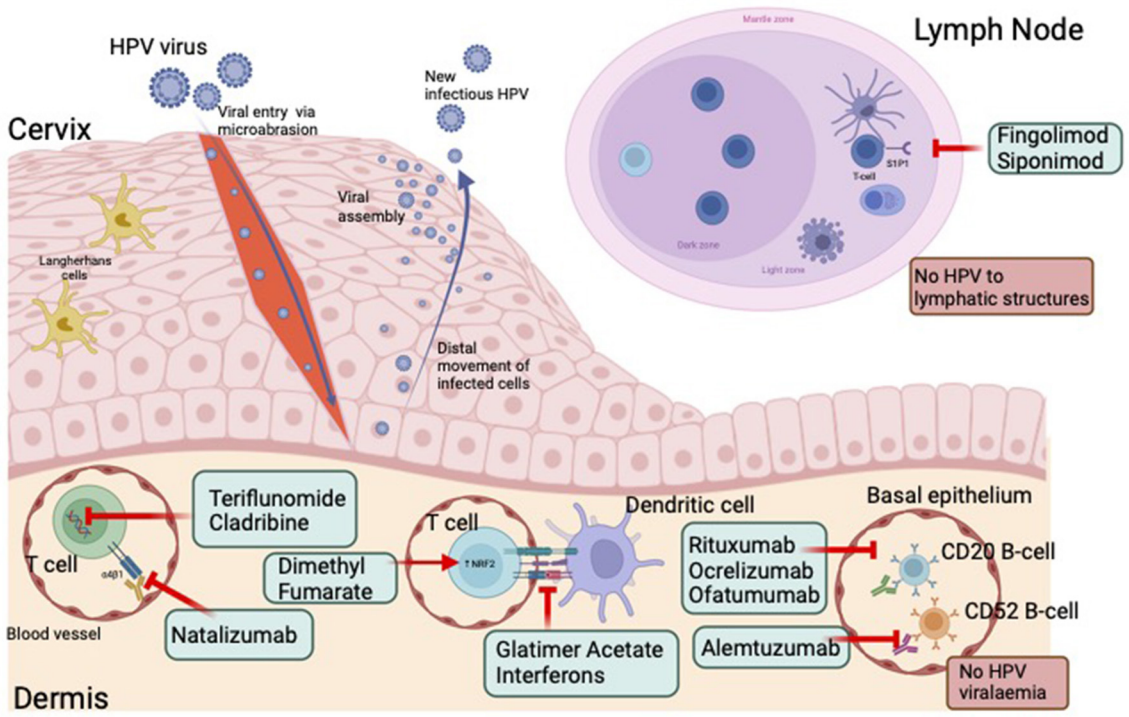

FIGURE 2
HPV infection, immune response and effect of disease modifying therapies. HPV enters the basal keratinocytes of the cervical epithelium through micro-abrasions. As keratinocytes migrate to the upper epidermis there is increasing viral replication. New infectious HPV is released from the surface of the epithelium. The absence of HPV viraemia or lymphatic infection, results in minimal exposure of HPV to the circulating immune system. DMTs alter the immune response *via* several mechanisms which may further limit immune surveillance and clearance of the virus. HPV, human papillomavirus. Created with BioRender.com.

immunosuppressive drugs was 4.9 +/- 4.5 years for patients with MS and cancer and 3.6 +/- 4.5 years for patients with MS and no cancer. This observation period is arguably too short to see long-term implications from DMT exposure. Individual DMT analyses, identified only azathioprine and cyclophosphamide as increasing the risk of cancer (RR 1.9, CI 1.7–3.4, $p = 0.4$; RR = 1.9, CI 1.3–2.6, $p = 0.5$, respectively) (26).

5. Individual disease modifying therapies and risk of cervical abnormalities

5.1. Low efficacy DMTs

5.1.1. Interferons and glatiramer acetate

Glatiramer acetate and the interferon-beta preparations were the first available MS DMTs and were introduced in the 1990's. These therapies are now considered low-efficacy, relative to newer treatments. Interferons exert their effect on the immune system by shifting cytokine profiles toward an anti-inflammatory state and inhibition of leucocyte migration across the blood-brain barrier (64). The mechanism of action of glatiramer acetate is not fully understood, however, it is thought to inhibit T cell responses to several myelin antigens and cause a shift toward Th2 immunity (65, 66).

To date, these therapies have not been associated with an increased cervical cancer incidence in wwMS (67–73).

5.2. Moderate to high efficacy DMTs

5.2.1. Dimethyl fumarate

Dimethyl fumarate has been used in the treatment of MS since 2013 due to its proposed anti-inflammatory, immunomodulatory and oxidant properties. While the mechanism by which it exerts its effect is not fully understood, it is thought to suppress the transcription of nuclear factor-kappa B and activate the transcription of the nuclear (erythroid-derived2)-related factor (Nrf2) (74).

DEFINE, a phase three randomized control study found no increased risk of malignancy associated with the use of dimethyl fumarate, one case of cervical cancer was reported in the treatment arm, with no cases reported in the placebo arm (75). This finding was supported by a prospective observational study conducted in Spain over a 5 year period. Again they found no increased risk of malignancy, and only one case of cervical LSIL was reported (76).

5.2.2. Inhibition of lymphocyte migration: Natalizumab and sphingosine-1-phosphate receptor antagonists

5.2.2.1. Natalizumab

Natalizumab was one of the first high-efficacy DMTs and was approved by the FDA in 2004. It is a monoclonal antibody that inhibits alpha4beta1-integrin, thereby preventing T-cells from egressing from the circulation across the blood-brain barrier and into the central nervous system (77). Alpha4beta1 integrins are also located on the surface of the cervix (78) and it is postulated that alpha4beta1 inhibition prevents T-cells from being able to enter the genital mucosa resulting in impaired antimicrobial clearance (79, 80).

A possible association between natalizumab and cervical abnormalities has been described in case reports (79, 81, 82). One case series described four patients treated with natalizumab for 9–45 months who developed high-grade cervical pre-cancer. Three were diagnosed with CIN 2 and one was diagnosed with CIN 3. All four women were positive for HPV (81).

Larger studies have not supported a possible association between natalizumab and cervical cancer (83–86). A Swedish population-based registry study identified no significant risk of pre-cancer (CIN 3+) or cancer in patients treated with natalizumab compared with the general population. However, average duration of follow-up for women treated with natalizumab in this study was 3.94 years. This short duration of surveillance may not have been sufficient to capture cervical cancer outcomes (87).

AFFIRM, a stage 3 randomized, placebo-controlled trial evaluated the safety and efficacy of 627 MS patients treated with natalizumab over a 2-year period. This study identified one case of cervical carcinoma *in situ* in the natalizumab treatment arm (88).

5.2.2.2. Sphingosine 1-P receptor modulators: Fingolimod and siponimod

Fingolimod is a sphingosine-1-phosphate receptor modulator that blocks lymphocyte egress from lymph nodes, limiting the number of circulating T-cells in the peripheral circulation (89). Reductions in the number of circulating T-cells may have implications for immune surveillance, which is a possible mechanism for cancer development (2).

Small case series have found an increase in HPV associated lesions in patients treated with fingolimod (46, 47, 90). A case series of 16 MS patients without a previous history of HPV found that 11 women and 5 men developed HPV lesions following fingolimod initiation (46). The lesions were identified on average 4 years after commencement of fingolimod. Of the nine women who developed cervical abnormalities, five had LSIL and four had HSIL. Oncogenic HPV-16 was identified in three patients. An important limitation of this series was that most patients had been exposed to other immunomodulating therapies prior to the commencement of fingolimod (46).

A Swedish population registry-based cohort study found a borderline significant increased risk of invasive cancer in patients treated with fingolimod compared to the general population (HR 1.53, 95% CI 0.98–2.38) (87). Notably, however, they found no difference in the rates of high-grade cervical pre-cancer (CIN 3) in the fingolimod treated population compared with healthy controls. It is important to note that the average follow-up period was 3.96 years, which may not have been long enough to see an effect on cancers with a long oncogenic lag, such as HPV associated cervical cancer (87).

LONGTERMS, a phase IIIb open-label extension trial, of patients treated with fingolimod for up to 14 years identified seven cases of cervical pre-cancer (0.2%, IR 0.04) (91).

5.2.2.3. Siponimod

Similar to fingolimod, Siponimod is a sphingosine-1-phosphate receptor modulator, which prohibits the egress of immune cells from the lymph nodes into the peripheral circulation (92). It is also thought to exert anti-inflammatory and neuroprotective effects in secondary progressive MS patients (SPMS) (92). It has been FDA approved for both RRMS and SPMS (2).

The stage III randomized, placebo controlled EXPAND trial did not find a difference between the frequency of malignancies in the Siponimod cohort compared to the placebo cohort. There were 11 cases of basal cell carcinoma associated with treatment, however, this did not significantly differ from the placebo arm (93).

5.2.3. Inhibitors of DNA synthesis: Teriflunomide and cladribine

5.2.3.1. Teriflunomide

Teriflunomide inhibits the mitochondrial enzyme dihydroorotate dehydrogenase which is necessary for the synthesis of pyrimidines. This causes inhibition of DNA and RNA synthesis and affects actively dividing cells including immune T and B cells, resulting in less circulating lymphocytes (2). This may reduce immune surveillance, allowing tumorigenesis to go unchecked.

The frequency of malignancy, including cervical cancer, has not been found to be significantly increased in patients treated with teriflunomide (94–96). 9-year follow-up from the TEMSO trial, which evaluated safety and efficacy of teriflunomide, identified one case of cervical carcinoma *in situ* in the teriflunomide treatment arm (97).

5.2.3.2. Cladribine

Cladribine has been newly licensed for the treatment of RRMS and SPMS. It was approved by the FDA in 2019. Cladribine is a nucleoside analog that inhibits DNA synthesis and repair. This results in sustained reduction of circulating B and T lymphocytes (98).

The pharmaceutical safety trials for Cladribine identified one case of cervical carcinoma *in situ* (99, 100). Of note, HPV 16 was identified 3 years prior and the patient was prescribed the higher strength dose of 5.25 mg/kg (101). However, the combined safety data from three previously reported Phase III studies (CLARITY, CLARITY extension and ORACLE-MS), as well as the prospective observational PREMIERE registry for patients prescribed 3.5 mg/kg dose of cladribine, did not identify any cases of cervical pre-cancer or cancer in the cladribine cohort. Two cases of cervical carcinoma *in situ* were identified in the placebo group (102).

5.2.4. Monoclonal antibodies: Rituximab, ocrelizumab, ofatumumab, and alemtuzumab

5.2.4.1. Anti-CD20: Rituximab, ocrelizumab, and ofatumumab

Anti-CD20 monoclonal antibody therapies, including Rituximab, Ocrelizumab, and Ofatumumab, target CD 20 on B cells causing B cell depletion (103). B cells have an important role in the regulatory immunological response to cancer. Tumor metabolites can attract B

cells to tumor sites, resulting in detection and lysis of proliferating tumor cells (104). In the absence of B cells, cancer growth may proceed unchecked (2).

Anti-CD20 therapies have not been associated with an increased incidence of invasive cancer (105–109). Class III evidence to support the safety profile of ocrelizumab was obtained by an analysis of pooled safety data from 11 clinical trials including controlled treatment, open-label extension periods of the phase II and III trials and the phase IIIb trials of ocrelizumab in patients with RRMS and SPMS. This data included 5680 patients with MS who received ocrelizumab in clinical trials. There were 18, 218 patient-years of exposure. The rate of malignancy was calculated to be 0.46 (0.37–0.57) per 100 patient-years, which is consistent with the ranges reported in epidemiologic data (110). One case of stage II cervical carcinoma was identified (110).

5.2.4.2. Alemtuzumab

Alemtuzumab is a humanized monoclonal anti-CD-52 antibody which targets B and T lymphocytes, resulting in peripheral lymphocyte depletion, along with a reduction of natural killer cells, dendritic cells, granulocytes and monocytes (111). Pharmaceutical safety trials have not found a statistically significant increased rate of malignancy compared to controls (108, 112–116). One case of cervical cancer has been reported in association with Alemtuzumab (117).

6. Other factors that may increase cervical cancer risk in wwMS

6.1. HPV vaccination

The development of HPV vaccinations and the introduction of population-wide vaccination programs have become the fundamental pillar of the WHO Global Strategy to accelerate the elimination of cervical cancer as a public health problem (118). There is emerging evidence for cancer prevention in higher Development Index countries with organized population-based vaccination programs (119–123). However, globally rates have yet to fall as the greatest disease burden remains in low-and middle-income countries with the highest populations, where vaccination programs are yet to be implemented (124–126).

HPV vaccines [including the bivalent (HPV 16, 18), quadrivalent (HPV 6, 11, 16, 18), and nonavalent (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58)] are inactive and therefore safe and immunogenic for the immunocompromised population (43, 127–129). Immunocompromised women will likely benefit from vaccination, even if they have already been exposed to the virus, as vaccine induced antibodies can prevent any new infection, reinfection with previously cleared types or spread of infection throughout the genital tract in cases of reactivation of a previously controlled HPV infection. The vaccines will not, however, clear any existing HPV infection, and do not reduce the need for screening (130, 131). The relatively recent introduction of the HPV vaccination program and age criteria (in Australia, women aged younger than 27 in 2007), has meant that many women have not had access to vaccination and would likely benefit from a "catch-up" vaccine. This would preferably be administered prior to the introduction of immunomodulating therapy (46). However, in Australia this is not routinely funded, and is cost-prohibitive for many.

Current Australian guidelines recommend a two-dose schedule of the nonavalent vaccine for immunocompetent people aged 11–14 years (WHO recommends a global primary target age range for HPV vaccination of 9–14 years) (132). Three doses are advised for those who are severely immunocompromised at the time of vaccination and those aged 15 years or older at the time of the first dose (133). To our knowledge, there is no data specifically examining the MS populations response to HPV vaccination. On the basis of extrapolation from other immunocompromised patient populations, the current recommendation is that wwMS on DMTs should be treated as immunocompromised and offered a three-dose schedule (134).

6.2. Cervical screening programs

Cervical screening programs remain fundamental for cervical cancer prevention, regardless of HPV vaccination status (128, 135). Screening programs ensure early detection of pre-cancerous cervical abnormalities so that intervention can occur before progression to cervical cancer (42). The current recommendations for the Australian general population is for 5-yearly cervical screening tests (CST) for women aged 25–74 years. A CST comprises a HPV test followed by a liquid based cytology (LBC) test if oncogenic HPV is detected (133).

Many countries with organized population-based screening programs, including Australia, Canada, Sweden and North America, recommend more frequent screening for immunocompromised women compared to the general population (136–141). However, whether wwMS exposed to immunomodulating therapy are included in this recommendation is often unclear. The Cancer Council Australia's Cervical Cancer Screening guideline lists women treated with immunosuppression for autoimmune diseases as a "group that require special consideration." They state that this group of women could be considered for screening on a 3-yearly interval, but there is no definitive recommendation for wwMS (142). No studies have specifically addressed this question.

WwMS may have reduced participation in preventative health assessments including cervical cancer screening (5–9). The risk of non-participation increases with increasing physical disability (5, 141, 143). Additionally, MS has the potential to impact cognition and mood which may negatively affect a patient's ability to access preventative health care (7).

Other barriers include physical and environmental barriers such as inaccessible medical offices, lack of transportation and difficulty with patient positioning and discomfort; time limitations as procedures such as CSTs may take longer in patients with physical limitations; and attitudinal barriers for both patients and clinicians. Physicians may hold misconceptions about the value of preventative health care due to an incorrect beliefs that physical disability precludes sexual activity, or that wwMS have a reduced life expectancy and therefore preventative screening is not required. WwMS bring their own attitudes about participation in cervical screening programs. Women may have had previous negative experiences with health care visits leading to reluctance to participate.

It is important that clinicians maintain awareness of current guidelines for immunocompromised patients and cervical screening and of new opportunities. For example, Australia's screening program now offers all people with a cervix the option of self-collection (a low-mid vaginal sample is collected by the patient or their clinician to

screen for HPV, replacing the need for cervical specimen collection. This test is as accurate for the detection of CIN2+ as a clinician collected sample) (144).

It is likely that any reduced participation in screening will negatively impact on cervical cancer outcomes. A Canadian retrospective cohort study of 6,820 patients with MS found that, although the incidence of cancer was lower in the MS population, patients had a larger tumor size at diagnosis (27). They argued that increased tumor size may reflect a later cancer stage at diagnosis, possibly as a result of reduced engagement with preventative health care.

7. Conclusion

There is insufficient data regarding the risk of HPV infection and progression to cervical pre-cancer and cancer in wwMS treated with DMTs. This is particularly evident for women treated with high-efficacy DMTs. Many studies are underpowered to detect cervical pre-cancer and cancer, particularly due to insufficient follow up time to capture this serious outcome. This represents an important knowledge gap in the MS literature and understanding the risk is imperative for the health and safety of wwMS.

Establishing whether DMTs increase the risk of cervical abnormalities will allow individualized counseling for patients regarding their risk profile. It will also guide international primary and secondary prevention strategies including HPV vaccination and cervical screening programs.

More research is needed to identify and address the barriers to participation in vaccination and screening programs for wwMS. Patients and clinicians need to be aware that wwMS are vulnerable to poor participation in these programs so they can better utilize strategies to optimize engagement.

Addressing these factors will significantly impact the rates of cervical abnormalities in the MS population and will help to advance the target of eliminating cervical cancer as a public health problem globally.

Author contributions

FB: conceptualization, methodology, writing original draft, reviewing and editing, and visualization. JB and YF: writing—reviewing and editing. HB: writing—reviewing and editing and supervision. VJ and AV: conceptualization, writing—reviewing and editing, and supervision. All authors contributed to the article and approved the submitted version.

Conflict of interest

FB has received travel support from Biogen and a travel grant from the European Committee for Treatment and Research in Multiple Sclerosis. YF has received travel support from Biogen and receives grant support from MS Research Australia, National Health and Medical Research Council of Australia, Australia and New Zealand Association of Neurologists, and Avant Foundation. HB served on scientific advisory boards for Biogen, Novartis and Sanofi-Aventis and received conference travel support from Novartis, Biogen and Sanofi Aventis, and serves on steering committees for trials conducted by Biogen and Novartis received research support from Merck, Novartis, and Biogen. VJ receives research grant support from MS Research Australia and the National Health and Medical Research Council of Australia (NHMRC 1156519). AV has received travel support and served on advisory boards for Novartis, Biogen, Merck Serono, Roche and Teva, and receives grant support from the National Health and Medical Research Council of Australia.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1119660/full#supplementary-material

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EDITED BY
Alessandra Lugaresi,
University of Bologna, Italy

REVIEWED BY
Bruno Colombo,
University of Milan, Italy
Francesco Patti,
University of Catania, Italy

*CORRESPONDENCE
Kunliang Qiu
✉ qkl@jsiec.org
Mingzhi Zhang
✉ zmz@jsiec.org

†These authors have contributed equally to this work

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Global, regional, and national burden of multiple sclerosis from 1990 to 2019: Findings of global burden of disease study 2019

Zhen Qian[1†], Yuancun Li[1†], Zhiqiang Guan[1†], Pi Guo[2], Ke Zheng[1], Yali Du[1], Shengjie Yin[1], Binyao Chen[1], Hongxi Wang[1], Jiao Jiang[1], Kunliang Qiu[1*†] and Mingzhi Zhang[1*†]

[1]Department of Ophthalmology, Joint Shantou International Eye Center of Shantou University and The Chinese University of Hong Kong, Shantou University Medical College, Shantou, China, [2]Department of Preventive Medicine, Shantou University Medical College, Shantou, Guangdong, China

Background: The global rising prevalence and incidence of multiple sclerosis (MS) has been reported during the past decades. However, details regarding the evolution of MS burden have not been fully studied. This study aimed to investigate the global, regional, and national burden and temporal trends in MS incidence, deaths, and disability-adjusted life years (DALYs) from 1990 to 2019 using the age-period-cohort analysis.

Methods: We performed a secondary comprehensive analysis of incidence, deaths, and DALYs of MS by calculating the estimated annual percentage change from 1990 to 2019 obtained from the Global Burden of Disease (GBD) 2019 study. The independent age, period, and birth cohort effects were evaluated by an age-period-cohort model.

Results: In 2019, there were 59,345 incident MS cases and 22,439 MS deaths worldwide. The global number of incidences, deaths, and DALYs of MS followed an upward trend, whereas the age-standardized rates (ASR) slightly declined from 1990 to 2019. High socio-demographic index (SDI) regions had the highest ASR of incidences, deaths, and DALYs in 2019, while the rate of deaths and DALYs in medium SDI regions are the lowest. Six regions which include high-income North America, Western Europe, Australasia, Central Europe, and Eastern Europe had higher ASR of incidences, deaths, and DALYs than other regions in 2019. The age effect showed that the relative risks (RRs) of incidence and DALYs reached the peak at ages 30–39 and 50–59, respectively. The period effect showed that the RRs of deaths and DALYs increased with the period. The cohort effect showed that the later cohort has lower RRs of deaths and DALYs than the early cohort.

Conclusion: The global cases of incidence, deaths, and DALYs of MS have all increased, whereas ASR has declined, with different trends in different regions. High SDI regions such as European countries have a substantial burden of MS. There are significant age effects for incidence, deaths, and DALYs of MS globally, and period effects and cohort effects for deaths and DALYs.

KEYWORDS

multiple sclerosis, burden, global, regional, national, age-period-cohort effects

Key messages

- What is already known on this topic:

We searched PubMed for articles published until September 2022 focusing on the incidence, deaths, and overall burden of multiple sclerosis (MS), using the terms "global burden," "incidence," "deaths," "disability-adjusted life years," "epidemiology," "multiple sclerosis," and "age–period–cohort analysis". A previous study reported the global burden of MS, and its time range is from 1990 to 2016. However, an assessment of the global MS disease burden, trends, and age-period-cohort effects based on the new estimates from GBD 2019 has not been done.

- What this study adds:

This study provided a comprehensive assessment of the burden of MS at the global, regional, and country-specific levels, which included incidence, deaths, and DALYs, by age, sex, and SDI from 1990 to 2019. There are significant age effects for incidence, deaths, and DALYs of MS globally, and period effects and cohort effects for deaths and DALYs.

- How this study might affect research, practice, or policy:

High SDI regions such as European countries have a substantial burden of MS, indicating that health policymakers should take appropriate measures to reduce the MS burden. The age-period-cohort analysis contributes to interpreting temporal changes in epidemiological rates and to further analyzing the risk factors of MS.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system that may cause neurological dysfunction in young adults (1–3). It has been reported that MS ranked the 10th leading cause of disease burden (4). Previous studies have shown that MS has a genetic susceptibility and is also associated with several environmental risk factors including Epstein-Barr virus infection, vitamin D insufficiency, smoking, and childhood obesity (5–8). However, the exact etiology of the disease is still not fully understood.

The distribution of MS varies substantially among regions. Studies have shown that Western Europe and North America have the highest prevalence, followed by Central and Eastern Europe, the Balkans, Australia, and New Zealand, while Asia, Africa, and the Middle East have the lowest prevalence (9, 10). During the past decades, previous studies have reported the increasing incidence and prevalence of MS globally (9–13). More importantly, the significantly increasing trend of MS incidence and prevalence was observed in regions considered low-prevalence areas such as India (14), Latin America (15, 16), Iran (10, 17), Japan (18), the Greater Hobart cohort of Tasmania, and Australia (19).

Over recent decades, there have been changes in the risk factors of MS contributing to the increase in MS incidence and prevalence. Previously, significant period and cohort effects have been reported for the increasing female incidence in Danish and Swiss populations (20, 21). However, evidence regarding the interactions between the effects of age, period, and cohort in MS globally is limited. Age-period-cohort (APC) analysis is an important model to investigate how and why disease trends change over time. It is a tool for interpreting temporal variables in epidemiological rates (22). The age effect represents the variations in different age groups. Period effects reflect changes over the period that affect people of all age groups simultaneously. Cohort effects are the discriminations between early and later birth cohort groups that experience the same initial exposure environment (23).

Previously, by using the 2016 GBD data, the global and regional MS burden has been reported (23). However, an assessment of the global MS disease burden, trends, and age-period-cohort effects based on the new estimates from GBD 2019 has not been done. In the current study, we aimed to demonstrate the global and regional temporal trends in MS incidence, deaths, and disability-adjusted life years from 1990 to 2019. We further investigated the effects of age, period, and cohort by using the age-period-cohort analysis.

Method

Study population and data resource

Annual estimates of global, regional, and national incidence, deaths, and DALYs data of MS from 1990 to 2019 were extracted from the database of the 2019 Global Burden of Diseases, Injuries, and Risk Factors (GBD) study (http://ghdx.healthdata.org/gbd-results-tool) (3). For the 2019 GBD, there are 195 countries and territories that can be categorized into five regions based on SDI quintiles from 0 (less developed) to 1 (most developed) (24): high SDI, high-middle SDI, middle SDI, low-middle SDI, and low SDI, and 21 GBD regions in terms of birth status, education, income, etc. To analyze the effect of age on incidence, death, and DALYs rate, we extracted the data of the 10 different age groups from 1 to 99 years. To compare the disease burden of MS with the other neurological disorders, we also collected data on Parkinson's disease, headache disorders, Alzheimer's disease, idiopathic epilepsy, and motor neuron disease from 2019 GBD.

Age-standardized rates (ASR) and estimated annual percentage change (EAPC)

Age-standardized rate of incidence (ASIR), death (ASDR), and DALYs in MS were available in 2019 GBD and can be used to calculate EAPC, which can identify temporal trends of ASR relative changes of MS from 1990 to 2019 (25). We first constructed a regression linear model about ASR, i.e., $ln\ (ASR) = \alpha + \beta x + \varepsilon$, where α represents intercept, β represents the slope of the fitted line, x refers to calendar year, and ε is the error term. Then we calculated EAPC as $100 \times (e^{\beta} - 1)$ (26). ASR is considered an increasing trend if both EAPC and its lower limit of 95% confidence interval > 0; conversely, ASR is considered a decreasing trend if both EAPC and its upper limit of 95% confidence interval < 0; ASR is considered to be stable along with year otherwise (27). R software (R Foundation for Statistical Computing, Vienna, Austria, version 4.1.0) was used to perform the EAPC calculation. A p-value of <0.05 was considered to be statistically significant.

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TABLE 1 Incidence number and ASR of multiple sclerosis in 1990 and 2019, and EAPC of ASR from 1990 to 2019.

	1990		2019		1990–2019
	Incidence number No. (95 UI%)	ASR per 100,000 No. (95 UI%)	Incidence number No. (95 UI%)	ASR per 100,000 No. (95 UI%)	EAPC No. ×100% (95 CI%)
Global	41,854 (36,306.1–47,444.9)	0.8 (0.7–0.9)	59,345.4 (51,817.8–66,942.6)	0.7 (0.6–0.8)	−0.19 (−0.24 to −0.13)
Sex					
Male	15,614.5 (13,454.4–17,819)	0.6 (0.5–0.7)	22,329.6 (19,289.5–25,332.6)	0.6 (0.5–0.6)	−0.23 (−0.27 to −0.2)
Female	26,239.5 (22,894.8–29,645.2)	1 (0.9–1.1)	37,015.8 (32,431.3–41,581.9)	0.9 (0.8–1)	−0.16 (−0.22 to −0.09)
SDI region					
High SDI	20,100.6 (17,823.9–22,507.9)	2.3 (2–2.6)	24,240.3 (21,899.9–26,506.6)	2.5 (2.3–2.8)	0.4 (0.37–0.43)
High-middle SDI	10,581.3 (9,261.5–11,867.5)	0.9 (0.8–1)	12,329.8 (10,846.4–13,773.1)	0.8 (0.7–0.9)	−0.27 (−0.31 to −0.22)
Middle SDI	5,964.6 (4,919.8–7,066.4)	0.4 (0.3–0.4)	11,344 (9,469.3–13,171)	0.4 (0.4–0.5)	0.76 (0.71–0.81)
Low-middle SDI	3,647.3 (2,952.3–4,399)	0.4 (0.3–0.4)	7,448.4 (6,087.8–8,850.2)	0.4 (0.3–0.5)	0.43 (0.39–0.46)
Low SDI	1,542 (1,237.4–1,874.4)	0.4 (0.3–0.4)	3,951.4 (3,191.7–4,744.9)	0.4 (0.3–0.5)	0.32 (0.26–0.37)
GBD region					
Central Europe	2,246.8 (1,986.3–2,482.2)	1.8 (1.6–2)	1,840.6 (1,648.3–2,036.3)	1.7 (1.5–1.9)	−0.12 (−0.17 to −0.06)
Eastern Europe	2,920.4 (2,483.8–3,329.9)	1.3 (1.1–1.4)	2,151.7 (1,832.3–2,468.4)	1.1 (0.9–1.2)	−0.52 (−0.58 to −0.47)
Western Europe	10,253.6 (9,116–11,453.9)	2.6 (2.3–2.9)	12,497.3 (11,105.6–13,902.6)	3.2 (2.8–3.6)	0.7 (0.68–0.72)
Central Sub-Saharan Africa	93.3 (72.7–116.1)	0.2 (0.2–0.3)	243.5 (188.5–301.8)	0.2 (0.2–0.3)	0.11 (0.07–0.16)
Eastern Sub-Saharan Africa	370.3 (288.7–459.1)	0.3 (0.2–0.3)	876.2 (680.7–1,087.4)	0.3 (0.2–0.3)	0 (−0.08–0.08)
Western Sub-Saharan Africa	554.4 (445.7–668.9)	0.4 (0.3–0.4)	1,549.4 (1,264.5–1,846.1)	0.4 (0.3–0.5)	0.4 (0.39–0.42)
Southern Sub-Saharan Africa	174.2 (138.5–212.5)	0.4 (0.3–0.4)	302.2 (239.9–365.3)	0.4 (0.3–0.5)	0.08 (−0.02–0.18)
North Africa and Middle East	4,189.5 (3,598.1–4,785.4)	1.3 (1.1–1.5)	9,217.9 (7,878.6–10,525.5)	1.4 (1.2–1.6)	0.3 (0.25–0.35)
East Asia	2,100 (1,695.6–2,542.2)	0.2 (0.2–0.2)	3,119.5 (2,554.9–3,722.3)	0.2 (0.1–0.2)	−0.14 (−0.23 to −0.04)
High-income Asia Pacific	655 (528–787.4)	0.3 (0.3–0.4)	727.1 (596.5–872.5)	0.4 (0.3–0.4)	0.12 (0.09–0.16)
South Asia	3,559.5 (2,839.2–4,324)	0.4 (0.3–0.4)	7,446.5 (5,987.3–8,964.7)	0.4 (0.3–0.5)	0.33 (0.29–0.37)
Southeast Asia	724.9 (571.4–890.6)	0.2 (0.1–0.2)	1,251.5 (1,010.3–1,503.5)	0.2 (0.1–0.2)	−0.05 (−0.06 to −0.04)
Central Asia	887.5 (778.6–999.1)	1.5 (1.4–1.7)	1,351.6 (1,176.2–1,536.5)	1.4 (1.2–1.6)	−0.36 (−0.39 to −0.32)
Australasia	336.1 (300.6–373.9)	1.5 (1.4–1.7)	592.8 (519.8–664.4)	2.1 (1.8–2.3)	1.21 (0.91–1.5)
Oceania	7.5 (5.8–9.2)	0.1 (0.1–0.2)	15.8 (12.3–19.2)	0.1 (0.1–0.2)	−0.15 (−0.16 to −0.14)

(Continued)

TABLE 1 (Continued)

	1990		2019		1990–2019
	Incidence number No. (95 UI%)	ASR per 100,000 No. (95 UI%)	Incidence number No. (95 UI%)	ASR per 100,000 No. (95 UI%)	EAPC No. ×100% (95 CI%)
Caribbean	147.7 (118.9–176.4)	0.4 (0.4–0.5)	230.3 (188.7–270.6)	0.5 (0.4–0.6)	0.26 (0.22–0.29)
Andean Latin America	85.5 (67.6–104.2)	0.3 (0.2–0.3)	206.4 (164.8–243.6)	0.3 (0.3–0.4)	0.63 (0.57–0.7)
Central Latin America	454 (361.2–548.4)	0.3 (0.3–0.4)	1,041.9 (855.9–1,222.1)	0.4 (0.3–0.5)	0.72 (0.62–0.82)
Southern Latin America	445.5 (370.4–519.2)	0.9 (0.8–1.1)	657 (550.2–760)	0.9 (0.8–1.1)	0.12 (0.12–0.13)
Tropical Latin America	1,040.6 (857.5–1,222.7)	0.7 (0.6–0.9)	1,968.4 (1,637.5–2,320.2)	0.8 (0.7–0.9)	0.25 (0.16–0.33)
High-income North America	10,607.8 (9,353.4–11,936.2)	3.5 (3.1–3.9)	12,057.8 (11,089.5–12,990.1)	3.6 (3.3–3.8)	0.24 (0.18–0.29)

ASR, age-standardized rates; EAPC, estimated annual percentage change; UI, uncertainty interval; CI, confidence interval.

Age–period–cohort model

The APC model was used to analyze the impact of three types of time-related variations—age, period, and cohort—on global incidence, death, and DALYs rate of MS. To construct the APC model, we first used the number of cases as the dependent variable and assumed that the number follows a Poisson distribution. For the incidence rate, we can construct a log-linear regression form as follows:

$$\text{Log}\left(E_{ij}\right) = \log\left(P_{ij}\right) + \mu + \alpha_i + \beta_j + \gamma_k, \quad (1)$$

where E_{ij} represents the expected incidence number in the cell (i, j) of MS; P_{ij} is the total exposed population for the same period; μ is the intercept or adjusted average incidence rate; α_i represents the coefficient of i_{th} age group; β_j represents the coefficient of the j_{th} period group; and γ_k represents the coefficient of the k_{th} cohort group (28).

Since there is multicollinearity between the age, period, and cohort, i.e., a linear correlation between any two variables, we used the intrinsic estimator (IE) method to calculate the relative coefficient. Then, the relative risks (RRs) are obtained in the exponential form of the coefficient to analyze the incidence, death, and DALYs rate of each age, period, and cohort group to the total groups (29). We used the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) to evaluate the goodness of model fit, with lower AIC-value and BIC-value indicating less information loss and better goodness of fit (30, 31).

As the 95% confidence interval (CI) of parameters was unreasonably small due to the large sample size (global population) according to GBD 2019 study, to obtain a reasonable 95% confidence interval, normal distribution was used instead of Poisson distribution. The model used "rate" as the dependent variable, which was obtained by simply dividing the number of a specific group of patients by the number of exposure of the corresponding group, and presumed to follow a normal distribution with a log link function. The "apc_ie" command in STATA version 16.0 software (Stata Corp., College Station, TX, USA) was used to perform the APC analysis.

Results

The global incidence, deaths, and DALYs of MS and other neurological disorders

At the global level, the incidence, deaths, and DALYs number increased 41.8 [from 41,854 (95% uncertainty interval [UI] 36,306.1–47,444.9) to 59,345.4 (51,817.8–66,942.6)], 68.0 [from 13,356 (11,903.5–17,571.1) to 22,439 (20,226–27,791.5)], and 59.7% [from 726,065.6 (621,892.3–867,796) to 1,159,831.8 (1,001,179.9–1,381,870.2)] from 1990 to 2019, respectively (Tables 1–3, Figures 1A–C). The incidence rate showed a relatively stable trend from 1990 to 2019, while mortality and DALYs rates presented an upward trend slightly in the same period (Figures 1D–F). However, the ASIR, ASDR, and age-standardized DALYs rates all have decreased trends in the same period, with EAPC being −0.19 (95% CI, −0.24 to −0.13), −0.62 (−0.67 to −0.56) and −0.56 (−0.6 to −0.52) (Tables 1–3, Figures 1G–I), respectively. With regard to other neurological disorders, a consistent increase both for counts and age-standardized DALYs rates was observed for Parkinson's disease [EAPC = 0.1 (95% CI, 0.04–0.16)], headache disorders [EAPC = 0.04 (0.03–0.05)], Alzheimer's disease, and other dementias [EAPC = 0.15 (0.13–0.16)] from 1990 to 2019, whereas a decrease both for counts and age-standardized DALYs rate was observed for idiopathic epilepsy [EAPC = −0.78 (−0.82 to −0.73)] and motor neuron disease [EAPC = −0.24 (−0.28 to −0.19)] (Supplementary Table 2, Supplementary Figure 1A). Overall, DALYs of MS contributed to 1.30% of all neurological disorders (Supplementary Figure 1B). Women have higher global morbidity, mortality, and, DALYs than men (Figure 2). We found that female to male ratio with MS in 2019 was greatest in the 25–29 age group and then decreased gradually for both incidence number and rate. The incidence rate peaked at the 25–29 age group in 2019 ahead of peaking at 30–34 in 1990 (Figures 2A, B).

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TABLE 2 Deaths number and ASR of multiple sclerosis in 1990 and 2019, and EAPC of ASR from 1990 to 2019.

	1990		2019		1990–2019
	Death number No. (95 UI%)	ASR per 100,000 No. (95 UI%)	Death number No. (95 UI%)	ASR per 100,000 No. (95 UI%)	EAPC No. ×100% (95 CI%)
Global	13,356 (11,903.5–17,571.1)	0.3 (0.3–0.4)	22,439 (20,226–27,791.5)	0.3 (0.2–0.3)	−0.62 (−0.67 to −0.56)
Sex					
Male	5,454.3 (4,452.4–7,679.8)	0.3 (0.2–0.4)	9,116.9 (7,670.8–12,350.5)	0.2 (0.2–0.3)	−0.66 (−0.71 to −0.61)
Female	7,901.8 (6,898–11,139.9)	0.4 (0.3–0.5)	13,322.1 (10,675–16,760.9)	0.3 (0.2–0.4)	−0.59 (−0.65 to −0.53)
SDI region					
High SDI	5,854.7 (5,226.9–8,068.1)	0.6 (0.5–0.8)	9,866.9 (6,992.5–11,411.2)	0.6 (0.4–0.7)	0.06 (0–0.12)
High-middle SDI	4,088.2 (3,665.6–5,644.1)	0.4 (0.3–0.5)	4,854.6 (3,918.9–7,676.4)	0.2 (0.2–0.4)	−1.72 (−1.85 to −1.59)
Middle SDI	1,791.8 (1,544.4–2,281)	0.1 (0.1–0.2)	3,839.6 (3,288.8–4,967.9)	0.1 (0.1–0.2)	−0.06 (−0.1 to −0.03)
Low-middle SDI	1,160.4 (806.4–1,666.7)	0.2 (0.1–0.2)	2,755.8 (2,319.1–3,359.2)	0.2 (0.2–0.2)	0.32 (0.27–0.38)
Low SDI	454.6 (267.8–713.3)	0.2 (0.1–0.3)	1,110.2 (829–1,461.3)	0.2 (0.1–0.2)	0.26 (0.24–0.27)
GBD region					
Central Europe	1,249.8 (1,052–1,548.1)	0.9 (0.7–1.1)	1,147.8 (872.5–1,844.8)	0.6 (0.5–1.1)	−1.27 (−1.35 to −1.2)
Eastern Europe	1,522.1 (1,299.8–2,260.3)	0.6 (0.5–0.9)	1,421.2 (941.8–2,847.5)	0.5 (0.3–1)	−1.31 (−1.58 to −1.04)
Western Europe	3,721.6 (3,358.6–5,327.4)	0.7 (0.6–1)	5,235.4 (3,829.1–6,538.4)	0.7 (0.5–0.9)	0 (−0.04 to 0.04)
Central Sub-Saharan Africa	30.6 (17.6–51.5)	0.1 (0.1–0.2)	78.6 (50.2–122.7)	0.1 (0.1–0.2)	0.06 (−0.02 to 0.13)
Eastern Sub-Saharan Africa	102.6 (51.3–174.8)	0.1 (0.1–0.2)	236.8 (136.1–347.9)	0.1 (0.1–0.2)	0 (−0.06 to 0.07)
Western Sub-Saharan Africa	183.6 (133–292.7)	0.2 (0.1–0.3)	559.4 (439.3–740.2)	0.2 (0.2–0.3)	1.05 (0.96–1.13)
Southern Sub-Saharan Africa	42.2 (34.9–47.8)	0.1 (0.1–0.1)	87.1 (71.4–103.7)	0.1 (0.1–0.2)	0.16 (−0.02 to 0.33)
North Africa and Middle East	580.7 (435.3–778.4)	0.3 (0.2–0.4)	1,436.3 (1,175.7–1,813.7)	0.3 (0.2–0.3)	0.16 (0.14–0.19)
East Asia	1,274.3 (923.4–1,543.1)	0.1 (0.1–0.2)	1,887.6 (1,526.7–2,506.3)	0.1 (0.1–0.1)	−1.44 (−1.59 to −1.3)
High-income Asia Pacific	237.4 (210.4–350.8)	0.1 (0.1–0.2)	321.3 (265.7–498.4)	0.1 (0.1–0.1)	−0.75 (−0.78 to −0.71)
South Asia	1,190.1 (765.7–1,753.6)	0.2 (0.1–0.3)	2,915.3 (2,386.8–3,671.7)	0.2 (0.2–0.2)	0.19 (0.11–0.26)
Southeast Asia	389.7 (324.9–536.9)	0.1 (0.1–0.2)	770.8 (592.7–1,106.5)	0.1 (0.1–0.2)	−0.36 (−0.41 to −0.3)
Central Asia	101 (81.1–121.6)	0.2 (0.2–0.2)	146.4 (117.2–222.7)	0.2 (0.2–0.3)	−0.14 (−0.29 to 0.02)
Australasia	108.7 (94.3–160)	0.5 (0.4–0.7)	214.5 (155.7–276)	0.5 (0.4–0.6)	0 (−0.08 to 0.08)
Oceania	3.7 (2.3–5.1)	0.1 (0.1–0.1)	8 (5.5–11.5)	0.1 (0.1–0.1)	−0.42 (−0.48 to −0.36)

(Continued)

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TABLE 2 (Continued)

	1990		2019		1990–2019
	Death number No. (95 UI%)	ASR per 100,000 No. (95 UI%)	Death number No. (95 UI%)	ASR per 100,000 No. (95 UI%)	EAPC No. ×100% (95 CI%)
Caribbean	59.1 (49.2–72.2)	0.2 (0.2–0.3)	122.8 (92.4–155.8)	0.2 (0.2–0.3)	0.54 (0.48–0.61)
Andean Latin America	30.6 (25.5–39.5)	0.1 (0.1–0.2)	78.7 (58.7–101)	0.1 (0.1–0.2)	0.3 (0.19–0.41)
Central Latin America	154 (132.9–240.2)	0.2 (0.1–0.2)	532.9 (414.2–682.6)	0.2 (0.2–0.3)	1.31 (1.18–1.45)
Southern Latin America	131.1 (117–185.8)	0.3 (0.3–0.4)	185 (149.9–314.7)	0.2 (0.2–0.4)	−0.82 (−0.96 to −0.69)
Tropical Latin America	158.3 (138–240.8)	0.2 (0.1–0.2)	420.6 (362.1–598.7)	0.2 (0.1–0.2)	−0.05 (−0.28 to 0.18)
High-income North America	2,084.7 (1,886.4–2,911.9)	0.6 (0.6–0.9)	4,632.5 (3,115.6–5,134.1)	0.8 (0.6–0.9)	0.69 (0.48–0.91)

ASR, age-standardized rates; EAPC, estimated annual percentage change; UI, uncertainty interval; CI, confidence interval.

The incidence, deaths, and DALYs in SDI regions and countries of MS

Regions and countries with higher SDI had a higher number and ASR of incidence, death, and DALYs both in 1990 and 2019, while EAPC of countries from 1990 to 2019 had a low correlation with SDI (Tables 1–3, Supplementary Table 1, Figures 3, 4). ASIR increased over time in most SDI regions except the high-middle SDI region, where there was a stable decreasing trend in ASIR with EAPC is −0.27 (95% CI, −0.31 to −0.22). Among them, the ASIR of middle SDI had the highest increasing speed with EAPC being 0.76 (95% CI, 0.71–0.81) (Table 1, Figure 4). The ASDRs and ASR of DALYs of MS in medium SDI region had the lowest value in both 1990 (ASDRs = 0.1 (95% UI, 0.1–0.2)/100,000 persons, ASR of DALYs = 7 (6–8.5)/100,000 persons) and 2019 (ASDRs = 0.1 (0.1–0.2)/100,000 persons, ASR of DALYs = 7.5 (6.3–9.1)/100,000 persons). High-middle SDI had the fastest decreasing trend in ASDRs and ASR of DALYs with EAPC being −1.72 (95% CI, −1.85 to −1.59) and −1.33 (−1.42 to −1.23), respectively, while low-middle SDI had the most increasing trend with EAPC being 0.32 (0.27–0.38) and 0.4 (0.35–0.44) (Tables 2, 3, Figure 4).

The incidence, deaths, and DALYs in GBD regions of MS

For the GBD region, the top two regions with the highest incidence number of MS were Western Europe [12,497.3 (95% UI, 11,105.6–13,902.6)] and high-income North America [12,057.8 (11,089.5–12,990.1)]. High-income North America [3.6 (95% UI, 3.3–3.8) per 100,000], Western Europe [0.7 (0.68–0.72) per 100,000], Australasia [1.21 (0.91–1.5) per 100,000], Central Europe [1.7 (1.5–1.9) per 100,000], and Eastern Europe [1.1 (0.9–1.2) per 100,000] had the highest ASIR of MS in 2019 than other regions. Australasia [EAPC = 1.21 (95% CI, 0.91–1.5)] and Eastern Europe [EAPC = −0.52 (−0.58 to −0.47)] had the most increase and decrease in ASIRs from 1990 to 2019, respectively (Table 1, Figures 3A, 5A, B). Regarding deaths and DALYs, absolute numbers of MS cases increased in most regions except Central Europe [1,249.8 (95% UI, 1,052–1,548.1) to 1,147.8 (872.5–1,844.8) for deaths] [57,785.2 (50,040.5–67,952.8) to 51,364 (40,324.7–75,257.2) for DALYs] and Eastern Europe [1,522.1 (1,299.8–2,260.3) to 1,421.2 (941.8–2,847.5) for deaths] [77,450.5 (65,376.4–106,470.8) to 69,170.3 (48,216.6–125,154.3) for DALYs] from 1990 to 2019. High-income North America [0.8 (95% UI, 0.6–0.9) per 100,000 persons for deaths] [49.3 (40.2–57.4) per 100,000 persons for DALYs] and Western Europe [0.7 (0.5–0.9) per 100,000 persons for deaths] [43.5 (35.8–52.7) per 100,000 persons for DALYs] were the top two regions with the highest ASDRs and ASR of DALYs in 2019. The EAPCs of ASDRs varied in different GBD regions: the most significant increasing trend was detected in Central Latin America (EAPC = 1.31, 95% CI 1.18–1.45), while East Asia (EAPC = −1.44, −1.59 to −1.3) had the most significant decrease trend. Trends in DALYs by region were broadly consistent with changes in deaths (Tables 2, 3, Figures 3B, C, 5C–F).

Age–period–cohort analysis of MS incidence, deaths, and DALYs

Table 4 shows the results of age–period–cohort analysis for incidence, death, and DALYs rates globally. Figure 6 shows the coefficient of MS incidence, death, and DALYs rates globally from 1990 to 2019 due to age, period, and cohort effects. After controlling for the period and cohort effects, the age effect significantly impacts the MS incidence, death, and DALYs rates. The RRs for incidence rate rise until age 30–39, then decline and plateaus after age 50–59, and the RRs for death rate and DALYs peak at 50–59 years and keep stable or decline slightly thereafter, respectively. Regarding period effect, the risk value in the death rate and DALYs had an increasing trend over time, while the incidence rate had a relatively small period effect. In terms of cohort effect, we observed decreasing trends in the risk of deaths and DALYs in later birth cohorts (Table 4, Figure 6).

Under the influence of three temporal risk factors, the rates of incidence, death, and DALYs changed accordingly as shown in Figure 7. The incidence rate of MS in all periods increased over

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TABLE 3 DALYs number and ASR of multiple sclerosis in 1990 and 2019, and EAPC of ASR from 1990 to 2019.

	1990		2019		1990–2019
	DALYs number No. (95 UI%)	ASR per 100,000 No. (95 UI%)	DALYs number No. (95 UI%)	ASR per 100,000 No. (95 UI%)	EAPC No. ×100% (95 CI%)
Global	726,065.6 (621,892.3–867,796)	16.1 (13.8–19.3)	1,159,831.8 (1,001,179.9–1,381,870.2)	14 (12–16.6)	−0.56 (−0.6 to −0.52)
Sex					
Male	446,134.5 (375,656.9–557,397.5)	19.5 (16.4–24.4)	716,487.8 (603,116.4–866,743.5)	17 (14.3–20.5)	−0.54 (−0.58 to −0.5)
Female	279,931.1 (234,138.2–361,106.2)	12.6 (10.5–16.2)	443,344 (378,482.1–554,817.1)	10.8 (9.3–13.6)	−0.6 (−0.64 to −0.57)
SDI region					
High SDI	328,086 (277,413.6–398,197.8)	34.6 (29.2–41.9)	500,325.1 (411,436.1–581,040.5)	35.4 (29.1–41.5)	0.1 (0.05–0.16)
High-middle SDI	216,664.5 (189,121.2–269,159.3)	18.9 (16.5–23.6)	260,398.5 (207,342.4–359,882.4)	14 (11.1–19.4)	−1.33 (−1.42 to −1.23)
Middle SDI	96,587.2 (81,861.5–116,209.9)	7 (6–8.5)	199,666.1 (168,751.2–241,140.8)	7.5 (6.3–9.1)	0.21 (0.18–0.24)
Low-middle SDI	60,369.1 (44,772.5–83,402.9)	7.5 (5.6–10.2)	138,239.2 (116,847.9–167,903.7)	8.5 (7.2–10.3)	0.4 (0.35–0.44)
Low SDI	24,026.4 (16,430.2–36,047.5)	7.3 (5–10.9)	60,580.2 (47,505.3–77,711.9)	8.1 (6.4–10.2)	0.32 (0.31–0.34)
GBD region					
Central Europe	57,785.2 (50,040.5–67,952.8)	41.5 (35.9–48.7)	51,364 (40,324.7–75,257.2)	32.7 (25.6–48.1)	−0.95 (−1 to −0.91)
Eastern Europe	77,450.5 (65,376.4–106,470.8)	30.5 (25.9–41.6)	69,170.3 (48,216.6–125,154.3)	26.2 (18.3–47.6)	−1.14 (−1.36 to −0.91)
Western Europe	192,347 (162,402.8–237,882.1)	40.5 (34.1–49.9)	271,038.6 (222,001.5–324,345.6)	43.5 (35.8–52.7)	0.27 (0.26–0.29)
Central Sub-Saharan Africa	1,526.7 (1,033.3–2,369.3)	4.7 (3.1–7.2)	4,031.4 (2,877.9–5,786.6)	4.9 (3.5–7.1)	0.09 (0.02–0.16)
Eastern Sub-Saharan Africa	5,352.2 (3,377.6–8,358.8)	5 (3.1–7.7)	12,716.8 (8,611.1–17,088.6)	5.1 (3.4–6.9)	−0.01 (−0.07 to 0.06)
Western Sub-Saharan Africa	9,036.5 (6,974.5–13,288.5)	7.7 (6–11.4)	28,344 (22,716–35,169.6)	9.9 (8–12.5)	1 (0.93–1.07)
Southern Sub-Saharan Africa	2,379.7 (2,005.5–2,770.4)	6.5 (5.5–7.5)	4,686.1 (3,927.2–5,552.7)	6.6 (5.6–7.8)	0.06 (−0.02 to 0.14)
North Africa and Middle East	47,116.1 (36,127.9–60,785.3)	18.8 (14.7–23.2)	115,885.8 (93,053.4–144,757.9)	19.9 (16.1–24.7)	0.27 (0.24–0.3)
East Asia	54,947.3 (40,126.2–66,523.5)	5 (3.6–6)	75,174.9 (62,164.2–95,959.6)	3.8 (3.1–4.8)	−1.35 (−1.52 to −1.17)
High-income Asia Pacific	12,485 (10,440.7–16,555.6)	6.1 (5.1–8.1)	15,515.8 (12,323.7–20,968.3)	5.6 (4.4–7.7)	−0.39 (−0.42 to −0.35)
South Asia	61,498 (43,487.9–87,447.7)	7.8 (5.5–10.8)	144,077.3 (119,712.1–177,475.5)	8.6 (7.1–10.5)	0.29 (0.24–0.35)
Southeast Asia	18,650.9 (15,589.4–24,836.8)	5.1 (4.3–6.7)	32,509.9 (25,887.3–44,139.2)	4.5 (3.6–6.1)	−0.58 (−0.65 to −0.5)
Central Asia	7,574.3 (6,135.4–9,190.8)	14.4 (11.7–17.5)	12,221 (9,340.7–15,780.9)	13.8 (10.7–17.6)	−0.15 (−0.19 to −0.1)
Australasia	5,483.4 (4,570.8–7,033.5)	24.5 (20.4–31.4)	11,116 (9,023.6–13,401)	28.9 (23.3–35.3)	0.59 (0.4–0.78)
Oceania	167.7 (115.4–226.3)	3.8 (2.6–5.2)	363.2 (263.6–502.5)	3.5 (2.5–4.8)	−0.39 (−0.44 to −0.34)

(Continued)

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TABLE 3 (Continued)

	1990		2019		1990–2019
	DALYs number No. (95 UI%)	ASR per 100,000 No. (95 UI%)	DALYs number No. (95 UI%)	ASR per 100,000 No. (95 UI%)	EAPC No. ×100% (95 CI%)
Caribbean	2,979 (2,563.7–3,604.5)	10 (8.7–12.1)	5,729.5 (4,626.6–7,077.6)	11.3 (9.1–14)	0.45 (0.4–0.49)
Andean Latin America	1,494.2 (1,246.4–1,836.8)	5.7 (4.8–7)	3,734.9 (2,951.9–4,623.3)	6.1 (4.9–7.6)	0.33 (0.26–0.41)
Central Latin America	7,920.3 (6,629.8–11,288.2)	7 (5.8–10)	24,524 (20,014.5–29,813.9)	9.6 (7.9–11.7)	1.22 (1.1–1.35)
Southern Latin America	7,247.9 (6,031.8–9,269.3)	15.4 (12.8–19.7)	10,638.5 (8,314–15,021)	14 (11–19.8)	−0.42 (−0.5 to −0.35)
Tropical Latin America	10,529.2 (8,439.1–13,679.2)	9.1 (7.4–11.9)	25,311.8 (20,304.9–31,970.6)	10.1 (8.1–12.7)	0.29 (0.2–0.39)
High-income North America	142,094.4 (116,994.6–171,097.7)	45.3 (37.3–54.5)	241,677.9 (195,635–278,600.5)	49.3 (40.2–57.4)	0.29 (0.19–0.4)

DALYs, disability-adjusted life years; ASR, age-standardized rates; EAPC, estimated annual percentage change; UI, uncertainty interval; CI, confidence interval.

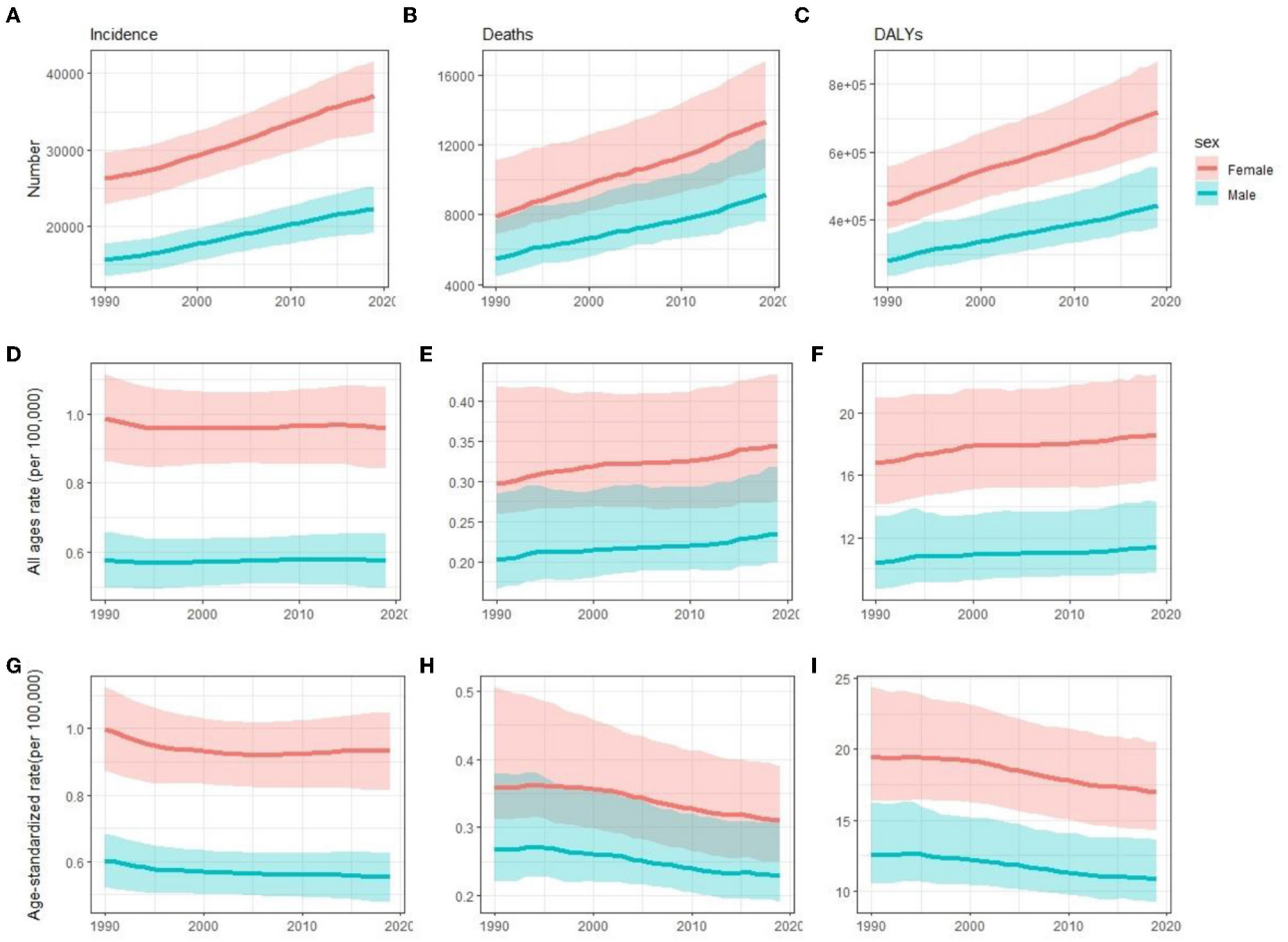

FIGURE 1
Comparison of time trends between women and men in incidence **(A, D, G)**, deaths **(B, E, H)**, and DALYs **(C, F, I)** number, all-age rate, and ASR of multiple sclerosis globally for 1990–2019, respectively. Error bars represented the 95% confidence intervals. DALYs, disability-adjusted life years; ASR, age-standardized rates.

age and peaked at age 30–39, which then decreased and dropped to its lowest level at 60–69 (Figures 7A, D). For all periods, the death rate increased with age (Figures 7B, E), and the DALYs rate peaks at age 50–59 (Figures 7C, F). The distribution by period according to cohorts did not show significant variation (Figures 7A–C, G–I). Cohorts from 1960 to 1989 had the highest incidence rate

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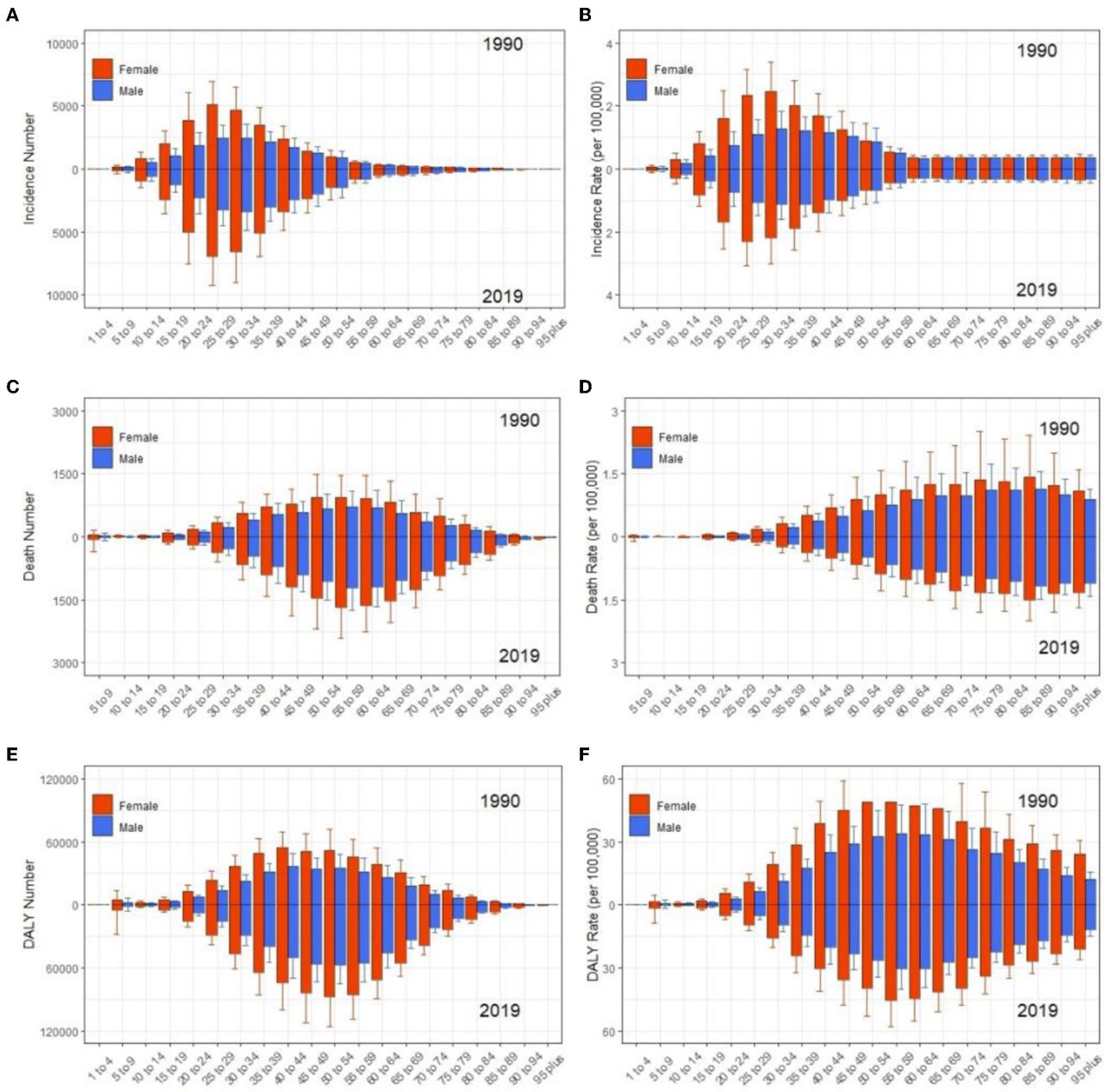

FIGURE 2
Comparison of age trends between women and men in incidence **(A, B)**, deaths **(C, D)**, and DALYs **(E, F)** number and rate of MS globally from 1990 to 2019, respectively. Error bars represented the 95% confidence intervals. DALYs, disability-adjusted life years.

and dropped fast afterward (Figure 7G). Death rates and DALYs rates were lower for younger generations than they were for older generations for all periods (Figures 7H, I).

Discussion

In the current study, we evaluated the most recent examination of the global, regional, and national burden and temporal trends in MS by using the age–period–cohort analysis. From 1990 to 2019, we found that the global number of incidences, deaths, and DALYs of MS increased while the ASR decreased. The incidence rate remained relatively stable, whereas death and DALYs rates increased somewhat. Regions and countries with a higher SDI had a greater number and ASR of incidence, death, and DALYs. High-income North America and Western Europe were the top two regions with the highest ASIRs, ASDRs, and age-standardized DALYs. The age effect showed that the RRs of incidence and DALYs reached the peak at ages 30–39 and 50–59, respectively. The period effect showed that the RRs of deaths and DALYs increased with the period. The cohort effect showed that the later cohort has lower RRs of deaths and DALYs than the early cohort.

Previous studies have shown a relatively stable or slightly increasing incidence rate of MS in whites over the past four or five decades (32, 33). Our data from GBD 2019 showed that the

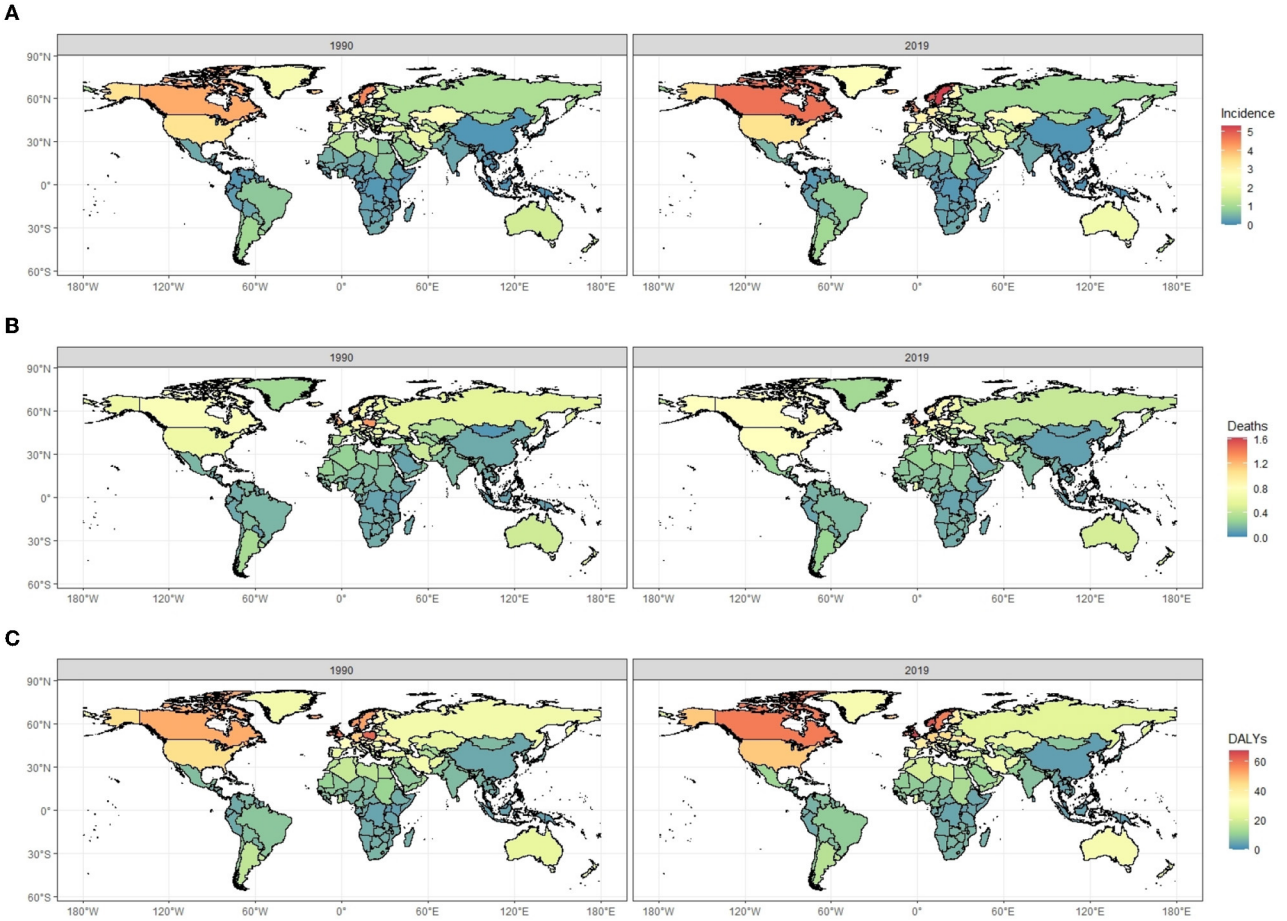

FIGURE 3
The comparisons of age-standardized incidence rates **(A)**, death rates **(B)**, and DALYs rates **(C)** of multiple sclerosis (per 100,000 population) between 1990 and 2019 for both sexes, by location. DALYs, disability-adjusted life years.

number of incidences is increasing globally, however, the rate is flat or mildly decreasing. The combined estimate of the total MS incidence in 75 countries was 2.1 (95% CI, 2.09–2.12) per 100,000 persons/year (12), which differs from our estimate of 0.7 (95% UI, 0.6–0.8) per 100,000 persons in 2019. The lack of incidence data in some regions contributes to the discrepancy in global estimates of total incidence. We found that DALYs of MS made up 1.30% of all neurological disorders in 2019. Although the burden of MS is less than other neurological disorders such as headache disorders, Alzheimer's disease, and other dementias, the early age of MS onset and the significant impact on life quality and productivity cause a considerable non-fatal burden (11). The decreasing burden of MS, idiopathic epilepsy, and motor neuron disease observed since 1990 is partly in line with a rapidly improving quality of care, whereas an increasing burden of Parkinson's disease, Alzheimer's disease, and other dementias, which reflects increasing longevity and declining birth rates (34, 35). Several previous studies have reported a much higher crude death rate and ASDR in people with MS compared with the general population (36–38).

A positive correlation between age-standardized DALYs and SDI has been reported previously by using the GBD 2016 data (11). In agreement with the previous studies, we also detected a similar positive association between age-standardized DALY and SDI. Moreover, we found that ASIR and age-standardized DALYs in the high-medium SDI region declined significantly from 1990 to 2019 and the general improvement of clinical care and the abundance of medical resources in the regions may be the underlying causes. Our study found that ASIR from 1990 to 2019 in high SDI regions was the highest and that ASIR was moderately correlated with SDI levels, which confirmed that developed countries have a higher incidence of MS than developing countries (39). In high SDI regions, patients with MS are more likely to be treated and reported due to the availability of a robust healthcare system and adequate healthcare resources. Whereas, in low SDI regions, medical resources are so scarce that mild MS may go undetected. The significant ASIR in high SDI regions may account for its high DALYs rates. At the same time, the overall burden of MS may be much heavier than we estimated, given that data collection is limited to areas with underdeveloped health systems. The reason for the increased incidence trend of MS in most SDI regions may be that the immune system has undergone inappropriate changes over the past few decades in developed countries through the increasing use of healthy vaccinations and antibiotics, leaving people more vulnerable to autoimmune diseases (40).

Our results are consistent with some previous reports on the burden of MS in various regions (10, 11). The Atlas of MS has shown that Europe has the highest incidence, followed by the United States;

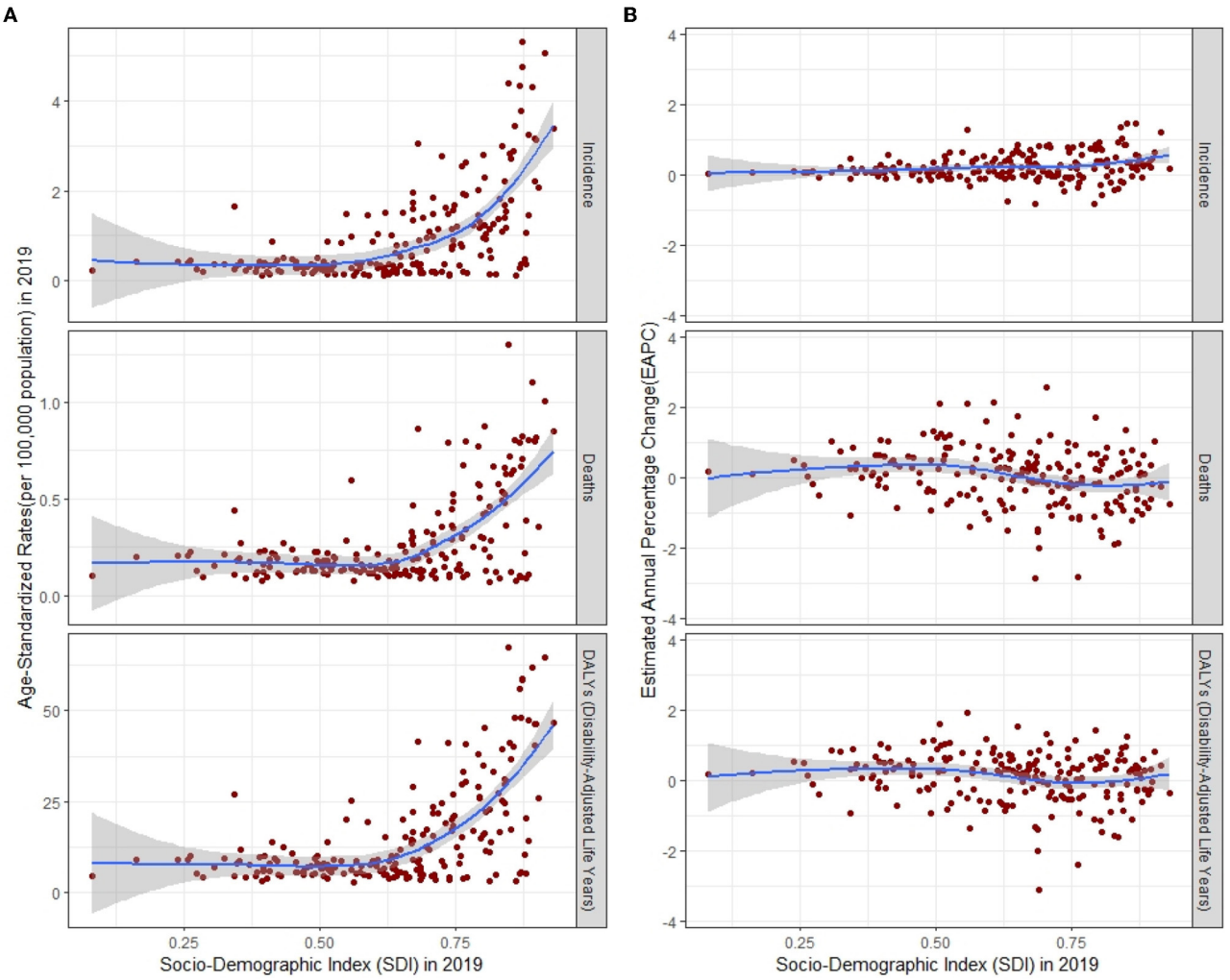

FIGURE 4
ASR **(A)** and its EAPC **(B)** of incidence, deaths, and DALYs for multiple sclerosis by SDI, 1990–2019, expected value-based SDI. The blue line represents the average expected relationship between SDI and corresponding disease burden indicator values. ASR, age-standardized rates; EAPC, estimated annual percentage change; DALYs, disability-adjusted life years; SDI, Socio-demographic Index.

South-Central Asia and Africa have the lowest incidence (12). An analysis of data from the Danish Multiple Sclerosis Registry showed that the incidence doubled in women between 1950 and 2009, while the increase in men was more modest. In contrast, the excess death rate among MS patients in Denmark has declined since 1950 (41). The incidence has been rising sharply in Iran between 1990 and 2017, possibly due to the growth of urbanization, which leads to changes in lifestyle, exposure to more weather pollutants, more stress, and consumption of fast food. DALYs are lower in the Middle East and Northern Africa, possibly due to the more benign course of MS disease (10). On the other hand, a study by Mansouri et al. indicated Latin America and the Caribbean showed increasing trends of incidence in recent years. Lack of vitamin D intake and genetic risk factors have been cited as the possible causes of this increasing trend (40).

Discrepancies in MS burden were also found across different age groups and genders. From 1990 to 2019, across all age groups, women had higher ASIR, ASDR, and ASR of DALYs due to MS. This result was consistent with those of previous studies carried out in Italy (42), Denmark (41), France (43), Australia (19, 44), and Norway (45), which similarly showed an increase in female incidence rates (46, 47). Gonadal hormones, lifestyle changes, lactation patterns, oral contraceptives, reduced physical activity, and increased stress may be the basis of this phenomenon (11, 47). Moreover, we found an earlier onset age for women in 2019 compared to 1990, indicating that more effort should be invested in women to combat MS.

There is an evident age effect on MS incidence and mortality as expected. Age effects explain the variation of indicators of interest in disease with age and reflect the nature of age changes (23, 48). The global high-risk age group for MS is 30–39 years old, which shows a similar age at MS onset patterns in published MS literature (9, 43, 49). Several countries, such as Kuwait (49), Newcastle, and Australia (44), show an age-specific bimodal distribution at MS onset during 1986–2011, indicating the existence of at least two age population segments at risk for MS. MS develops during the prime of life, and with the increasing aging of the global population (50), the burden on people living with MS will increase further, and the cost to society may soar in future. This finding broadly supports the previous study in this area that DALYs of MS globally peaked in the sixth decade (11). Higher life

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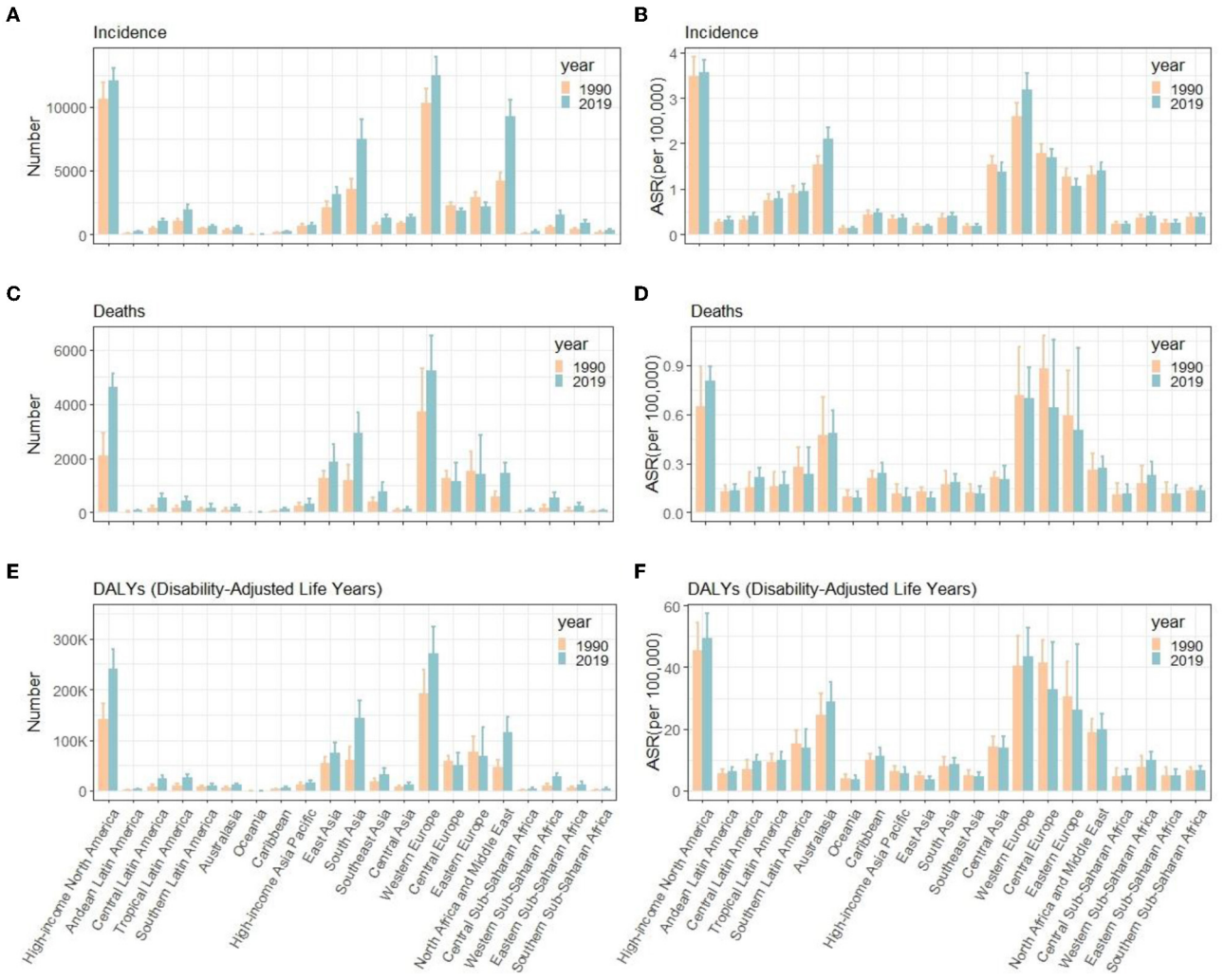

FIGURE 5
Number and ASR of incidence **(A, B)**, deaths **(C, D)**, and DALYs **(E, F)** of multiple sclerosis in different GBD countries, 1990 and 2019. ASR, age-standardized rates; DALYs, disability-adjusted life years; GBD, global burden of diseases, injuries, and risk factors study.

expectancy and early onset age have resulted in a high number of DALYs.

Although the global period effect and cohort effect of MS incidence have not been reported, the period effect and cohort effect have been evaluated in different regions previously. The period effect and cohort effect showed no significant change in the incidence of MS globally among the RRs of the different period groups and the same results showed in Lorraine, France between 1996 and 2015 (43), implying that genetic and environmental factors (5–8) that influence the disease's risk have not changed significantly or that factors that mitigate the disease's onset have emerged that have not yet been detected. On the other hand, Denmark and Kuwait show a significant period effect and cohort effect in incidence (41, 49). Moreover, a study in Norway found that the period effect on mortality was stable in men in the last three decades but increased for women (45). However, the period effect of mortality in Spain is decreasing from 1951 to 1997, probably due to an increasing life expectancy, while the risk of the birth cohort showed an increasing trend (51). A cohort effect analysis of MS-related mortality in North America and several European countries also showed a decline after the 1910–1930 generations (52). In the current study, the period effect showed that the RRs of deaths and DALYs increased with the period. The cohort effect showed that the later cohort has lower RRs of deaths and DALYs than the early cohort. Over the birth cohorts covered in our dataset, changes in lifestyle and environmental factors may have changed the risk of one cohort group over another. The late birth cohort, in comparison to the early birth cohort, received greater education, had a higher degree of awareness about health and illness prevention, and was more actively involved in treatment (22, 53). Furthermore, increasing risk factors for MS were discovered over time, raising public awareness of the disease. In APC analyses, birth cohort effects were largely unaffected by period effects due to changes in diagnostic criteria. In general, such changes are more likely too vague underlying birth cohort patterns than to emerge by chance (54).

One limitation of our current study is that the accuracy of our findings depends on the integrity and reliability of the GBD. However, insufficient diagnosis of diseases due to limited medical care in less developed regions and few national incidence and prevalence studies in high-income countries have led to the lack of partial data on the GBD, which in turn has resulted in biased models for predicting

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TABLE 4 The age, period, and cohort effect on the global incidence, death, and DALYs rate of multiple sclerosis.

Variable	Incidence			Deaths			DALYs		
	Coefficient (95% CI)	Relative risk (95% CI)	*p*-value	Coefficient (95% CI)	Relative risk (95% CI)	*p*-value	Coefficient (95% CI)	Relative risk (95% CI)	*p*-value
Constant	−9.36 (−9.39, −9.34)	0 (0, 0)	<0.01	−10.0 (−10.17, −10.01)	0 (0, 0)	<0.01	−6.09 (−6.14, −6.04)	0 (0, 0)	<0.01
Age									
0–9	−2.79 (−2.95, −2.62)	0.06 (0.05, 0.07)	<0.01	−2.23 (−2.61, −1.86)	0.11 (0.07, 0.16)	<0.01	−2.21 (−2.47, −1.96)	0.11 (0.08, 0.14)	<0.01
10–19	0.07 (0.03, 0.12)	1.08 (1.03, 1.12)	<0.01	−2.64 (−3, −2.27)	0.07 (0.05, 0.1)	<0.01	−1.9 (−2.06, −1.75)	0.15 (0.13, 0.17)	<0.01
20–29	1.32 (1.29, 1.36)	3.75 (3.62, 3.88)	<0.01	−0.86 (−1.02, −0.71)	0.42 (0.36, 0.49)	<0.01	−0.21 (−0.29, −0.12)	0.81 (0.75, 0.88)	<0.01
30–39	1.41 (1.38, 1.44)	4.09 (3.97, 4.22)	<0.01	0.16 (0.03, 0.28)	1.17 (1.03, 1.33)	0.013	0.64 (0.57, 0.7)	1.89 (1.77, 2.02)	<0.01
40–49	1.02 (1, 1.05)	2.78 (2.71, 2.85)	<0.01	0.8 (0.71, 0.9)	2.23 (2.03, 2.45)	<0.01	1.04 (0.99, 1.1)	2.84 (2.7, 2.99)	<0.01
50–59	0.36 (0.34, 0.38)	1.43 (1.4, 1.46)	<0.01	1.05 (0.98, 1.11)	2.86 (2.68, 3.05)	<0.01	1.09 (1.06, 1.13)	2.99 (2.88, 3.1)	<0.01
60–69	−0.35 (−0.37, −0.33)	0.7 (0.69, 0.72)	<0.01	1.06 (1.01, 1.1)	2.88 (2.76, 3)	<0.01	0.88 (0.86, 0.91)	2.42 (2.36, 2.48)	<0.01
70–79	−0.34 (−0.35, −0.32)	0.71 (0.7, 0.72)	<0.01	1 (0.96, 1.04)	2.72 (2.62, 2.83)	<0.01	0.56 (0.54, 0.58)	1.76 (1.72, 1.79)	<0.01
80–89	−0.34 (−0.35, −0.33)	0.71 (0.7, 0.72)	<0.01	0.95 (0.89, 1.01)	2.58 (2.43, 2.74)	<0.01	0.22 (0.19, 0.25)	1.25 (1.21, 1.29)	<0.01
Period									
1990–1999	0 (−0.01, 0)	1 (0.99, 1)	0.17	−0.19 (−0.22, −0.15)	0.83 (0.8, 0.86)	<0.01	−0.13 (−0.14, −0.11)	0.88 (0.87, 0.9)	<0.01
2000–2009	0 (−0.01, 0)	1 (0.99, 1)	<0.01	0 (−0.01, 0)	1 (0.99, 1)	<0.01	0 (0, 0)	1 (1, 1)	0.933
2010–2019	0.01 (0, 0.02)	1.01 (1, 1.02)	<0.01	0.19 (0.16, 0.22)	1.21 (1.17, 1.25)	<0.01	0.13 (0.11, 0.14)	1.13 (1.11, 1.15)	<0.01
Cohort									
1900–1909	0.19 (0.15, 0.22)	1.2 (1.17, 1.24)	<0.01	1.2 (1.09, 1.31)	3.33 (2.99, 3.71)	<0.01	0.89 (0.83, 0.95)	2.42 (2.28, 2.58)	<0.01
1910–1919	0.15 (0.13, 0.18)	1.17 (1.14, 1.2)	<0.01	1.09 (1, 1.17)	2.96 (2.73, 3.22)	<0.01	0.76 (0.71, 0.81)	2.14 (2.03, 2.24)	<0.01
1920–1929	0.13 (0.11, 0.16)	1.14 (1.11, 1.17)	<0.01	0.94 (0.87, 1)	2.56 (2.4, 2.73)	<0.01	0.63 (0.59, 0.67)	1.88 (1.8, 1.96)	<0.01
1930–1939	0.1 (0.08, 0.13)	1.11 (1.08, 1.14)	<0.01	0.7 (0.64, 0.76)	2.02 (1.91, 2.15)	<0.01	0.45 (0.41, 0.49)	1.57 (1.51, 1.64)	<0.01
1940–1949	0.07 (0.04, 0.1)	1.07 (1.04, 1.1)	<0.01	0.51 (0.43, 0.58)	1.66 (1.54, 1.78)	<0.01	0.32 (0.27, 0.37)	1.37 (1.31, 1.44)	<0.01
1950–1959	0.01 (−0.02, 0.04)	1.01 (0.98, 1.04)	0.691	0.3 (0.2, 0.39)	1.35 (1.22, 1.48)	<0.01	0.19 (0.13, 0.24)	1.2 (1.14, 1.28)	<0.01
1960–1969	−0.06 (−0.09, −0.02)	0.94 (0.91, 0.98)	<0.01	−0.01 (−0.13, 0.12)	0.99 (0.88, 1.12)	0.933	−0.02 (−0.09, 0.05)	0.98 (0.91, 1.05)	0.559
1970–1979	−0.14 (−0.17, −0.1)	0.87 (0.84, 0.9)	<0.01	−0.37 (−0.52, −0.22)	0.69 (0.59, 0.8)	<0.01	−0.28 (−0.36, −0.19)	0.76 (0.69, 0.82)	<0.01
1980–1989	−0.11 (−0.15, −0.06)	0.9 (0.86, 0.94)	<0.01	−0.64 (−0.82, −0.46)	0.53 (0.44, 0.63)	<0.01	−0.43 (−0.53, −0.33)	0.65 (0.59, 0.72)	<0.01
1990–1999	−0.12 (−0.16, −0.07)	0.89 (0.85, 0.93)	<0.01	−0.93 (−1.14, −0.72)	0.39 (0.32, 0.49)	<0.01	−0.61 (−0.73, −0.49)	0.54 (0.48, 0.61)	<0.01

(Continued)

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TABLE 4 (Continued)

Variable	Incidence			Deaths			DALYs		
	Coefficient (95% CI)	Relative risk (95% CI)	*p*-value	Coefficient (95% CI)	Relative risk (95% CI)	*p*-value	Coefficient (95% CI)	Relative risk (95% CI)	*p*-value
2000–2009	−0.12 (−0.17, −0.06)	0.89 (0.85, 0.94)	<0.01	−1.26 (−1.73, −0.79)	0.28 (0.18, 0.45)	<0.01	−0.84 (−1.07, −0.61)	0.43 (0.34, 0.54)	<0.01
2010–2019	−0.12 (−0.43, 0.19)	0.89 (0.65, 1.21)	0.455	−1.52 (−2.27, −0.78)	0.22 (0.1, 0.46)	<0.01	−1.05 (−1.59, −0.52)	0.35 (0.2, 0.59)	<0.01
AIC	−25.31799			−26.30645			−18.13016		
BIC	−27.20958			−27.20958			−27.20958		

DALYs, disability-adjusted life years.

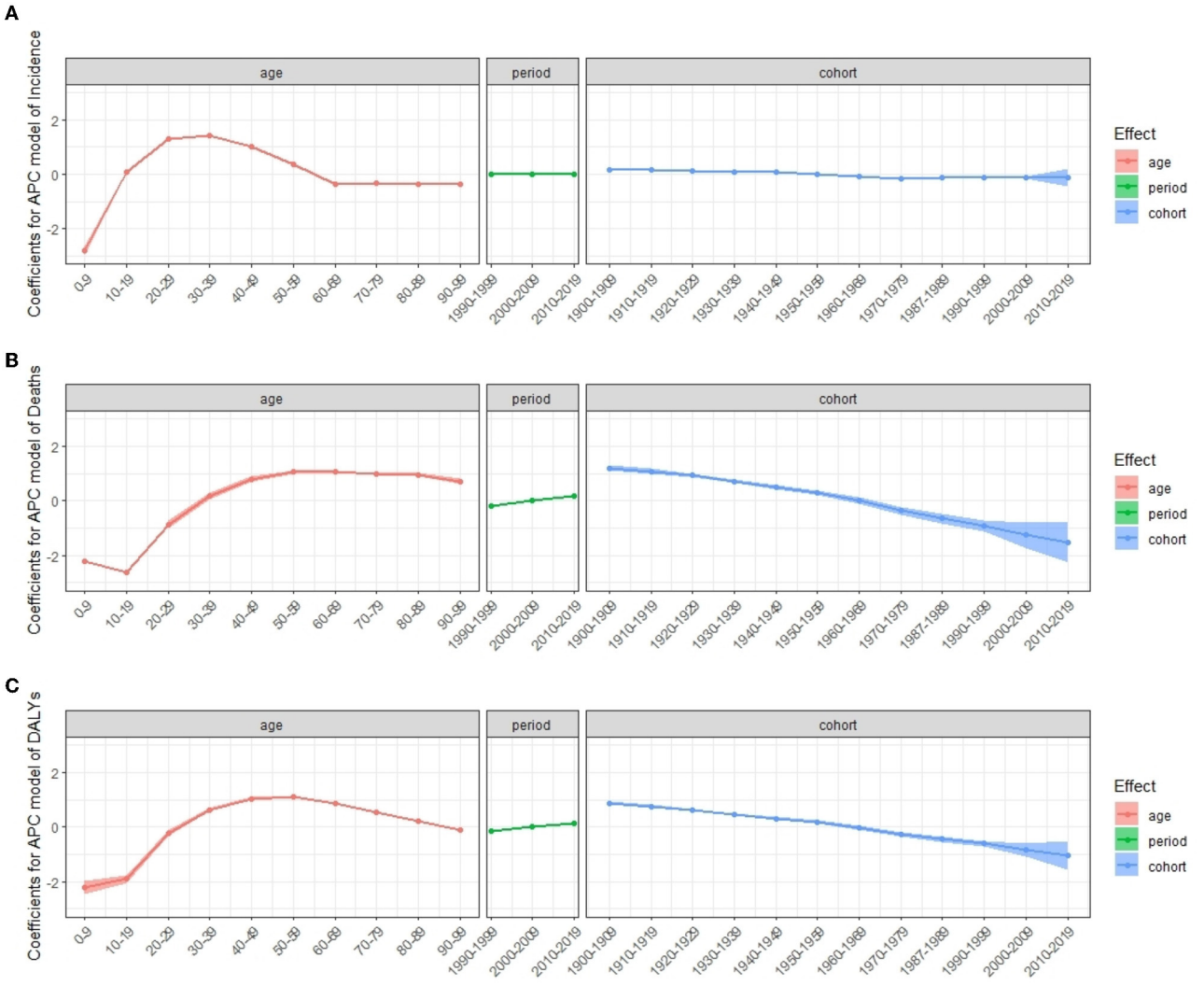

FIGURE 6
Coefficients for APC model of multiple sclerosis incidence **(A)**, deaths **(B)**, and DALYs **(C)** from 1990 to 2019. Error bars represented the 95% confidence intervals. APC, age–period–cohort; DALYs, disability-adjusted life years.

rates. In addition, the disease prediction models used in the database lack robust covariates for a more reliable risk assessment of the population (11). A second major limitation is that models are based on superimposed assumptions of age, period, and cohort effects. This not only creates identification problems but also led to a poor approximation of how social change occurs. Therefore, additional new models and methods are needed to test other theories of social change (23).

In conclusion, the cases of incidence, deaths, and DALYs of MS globally have all increased, whereas ASR has declined, with different

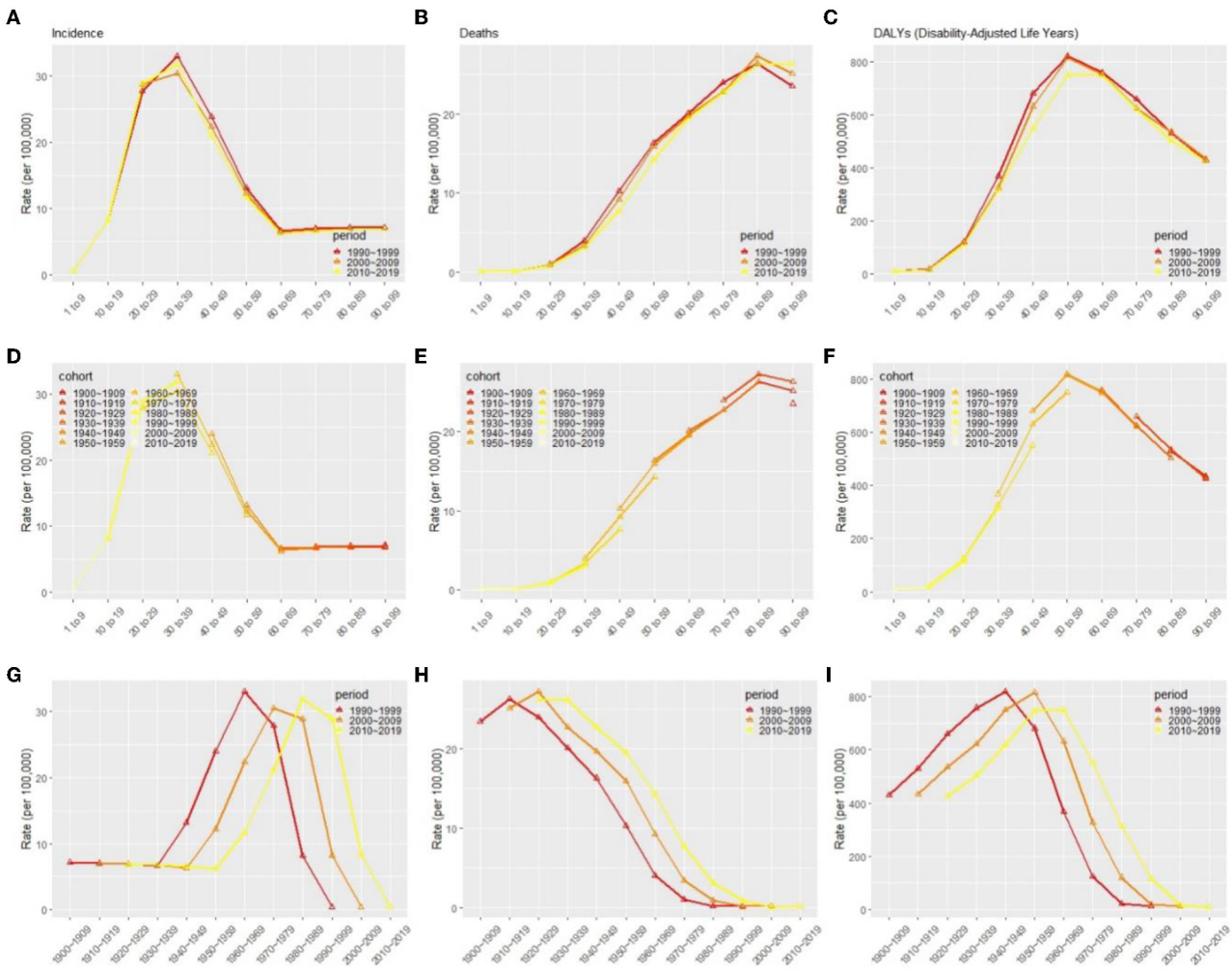

FIGURE 7
Effects of age **(A–C)**, period **(D–F)**, and cohort **(G–I)** on incidence rate, death rates, and DALYs in patients with multiple sclerosis globally, respectively. DALYs, disability-adjusted life years.

trends in different regions. High SDI regions have a substantial burden of MS. Furthermore, we found significant age effects for incidence, deaths, and DALYs of MS globally, and period effects and cohort effects for deaths and DALYs. Health promotion, disease prevention, and rehabilitation should all receive significant attention, especially in high-risk areas.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

ZQ: study design and manuscript drafting. YL: data collection, data analysis, and drawing graphs. KZ, YD, SY, BC, HW, and JJ: data collection and data analysis. KQ, ZG, and MZ: study design, data analysis, results interpretation, and manuscript reviewing. All authors contributed to the review of manuscript and the final version of paper.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1073278/full#supplementary-material

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EDITED BY
Alessandra Lugaresi,
University of Bologna, Italy

REVIEWED BY
Russell Ouellette,
Karolinska Institutet (KI), Sweden
Massimiliano Calabrese,
University of Verona, Italy

*CORRESPONDENCE
Matilde Inglese
✉ m.inglese@unige.it

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Central vein sign and diffusion MRI differentiate microstructural features within white matter lesions of multiple sclerosis patients with comorbidities

Caterina Lapucci[1,2], Francesco Tazza[2], Silvia Rebella[3], Giacomo Boffa[2], Elvira Sbragia[2], Nicolò Bruschi[2], Elisabetta Mancuso[2], Nicola Mavilio[4], Alessio Signori[5], Luca Roccatagliata[4,5], Maria Cellerino[2], Simona Schiavi[2] and Matilde Inglese[2,6]*

[1]HNSR, IRRCS Ospedale Policlinico San Martino, Genoa, Italy, [2]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy, [3]University of Genoa, Genoa, Italy, [4]Department of Neuroradiology, IRCCS Ospedale Policlinico San Martino, Genoa, Italy, [5]Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy, [6]IRCCS Ospedale Policlinico San Martino IRCCS, Genoa, Italy

Introduction: The Central Vein Sign (CVS) has been suggested as a potential biomarker to improve diagnostic specificity in multiple sclerosis (MS). Nevertheless, the impact of comorbidities on CVS performance has been poorly investigated so far. Despite the similar features shared by MS, migraine and Small Vessel Disease (SVD) at T2-weighted conventional MRI sequences, *ex-vivo* studies demonstrated their heterogeneous histopathological substrates. If in MS, inflammation, primitive demyelination and axonal loss coexist, in SVD demyelination is secondary to ischemic microangiopathy, while the contemporary presence of inflammatory and ischemic processes has been suggested in migraine. The aims of this study were to investigate the impact of comorbidities (risk factors for SVD and migraine) on the global and subregional assessment of the CVS in a large cohort of MS patients and to apply the Spherical Mean Technique (SMT) diffusion model to evaluate whether perivenular and non-perivenular lesions show distinctive microstructural features.

Methods: 120 MS patients stratified into 4 Age Groups performed 3T brain MRI. WM lesions were classified in "perivenular" and "non-perivenular" by visual inspection of FLAIR* images; mean values of SMT metrics, indirect estimators of inflammation, demyelination and fiber disruption (EXTRAMD: extraneurite mean diffusivity, EXTRATRANS: extraneurite transverse diffusivity and INTRA: intraneurite signal fraction, respectively) were extracted.

Results: Of the 5303 lesions selected for the CVS assessment, 68.7% were perivenular. Significant differences were found between perivenular and non-perivenular lesion volume in the whole brain ($p < 0.001$) and between perivenular and non-perivenular lesion volume and number in all the four subregions ($p < 0.001$ for all). The percentage of perivenular lesions decreased from youngest to oldest patients (79.7%–57.7%), with the deep/subcortical WM of oldest patients as the only subregion where the number of non-perivenular was higher than the number of perivenular lesions. Older age and migraine were independent predictors of a higher percentage of non-perivenular lesions ($p < 0.001$ and $p = 0.013$ respectively). Whole brain perivenular lesions showed higher inflammation, demyelination and fiber disruption than non perivenular lesions ($p = 0.001$, $p = 0.001$ and $p = 0.02$ for EXTRAMD, EXTRATRANS and INTRA respectively). Similar

findings were found in the deep/subcortical WM ($p = 0.001$ for all). Compared to non-perivenular lesions, (i) perivenular lesions located in periventricular areas showed a more severe fiber disruption ($p = 0.001$), (ii) perivenular lesions located in juxtacortical and infratentorial regions exhibited a higher degree of inflammation ($p = 0.01$ and $p = 0.05$ respectively) and (iii) perivenular lesions located in infratentorial areas showed a higher degree of demyelination ($p = 0.04$).

Discussion: Age and migraine have a relevant impact in reducing the percentage of perivenular lesions, particularly in the deep/subcortical WM. SMT may differentiate perivenular lesions, characterized by higher inflammation, demyelination and fiber disruption, from non perivenular lesions, where these pathological processes seemed to be less pronounced. The development of new non-perivenular lesions, especially in the deep/subcortical WM of older patients, should be considered a "red flag" for a different -other than MS- pathophysiology.

KEYWORDS

multiple sclerosis, comorbidities, MRI, central vein sign, diffusion

Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterized by a relapsing or progressing clinical course. Although focal hyperintensities on T2-weighted magnetic resonance imaging (MRI) detected within the brain and spinal cord represent the radiological hallmarks of the disease (1), they lack histopathological specificity and may hide heterogeneous pathological substrates.

The perivenular location of MS lesions has been known for more than a century. From a histopathological point of view, MS lesions are characterized by cellular infiltrates that rise around small-to-medium-sized parenchymal venules (2), the so-called "perivascular cuffs", mainly characterized by mononuclear cells that enter CNS by damaging the blood-brain barrier (BBB) as waves of inflammatory invasion (3). The essential transition from the histopathological evidence to the "*in vivo*" demonstration of the presence of a central venule within MS lesions has been made possible by advanced gradient-echo MRI techniques (4, 5). Thus, this "Central Vein Sign" (CVS) has been suggested as a potential biomarker to improve diagnostic specificity in MS (6–8).

Nevertheless, the presence of cardiovascular comorbidities, which are particularly frequent in older patients with progressive MS, introduces an extra challenge in the conventional radiological setting, where advanced and specific MRI biomarkers may be needed to distinguish whether a new T2-weighted lesion is due to MS or age-related comorbidities. The prevalence of small vessel disease (SVD)-related white matter (WM) hyperintensities increases from approximately 5% for people aged 50 years to nearly 100% for people aged 90 years (9). In addition to age, arterial hypertension (HT) (10), current and former smoking, and diabetes mellitus (11) are considered modifiable risk factors (RFs) for SVD.

However, data about the impact of age and, more generically, of other RFs for SVD on CVS performance in patients with MS are still scarce. In a recent study, performed on a relatively small cohort of patients with MS, the percentage of CVS+ (from now on "%CVS+") lesions significantly decreased in older and hypertensive patients with MS (12).

Besides SVD, migraine is a frequent comorbidity in patients with MS (13). It is well-known that WM T2-weighted hyperintensities are frequently detected in patients with migraine and persist over time (14), with the deep/subcortical WM of the frontal lobes typically involved (15). Although previous studies explored how to differentiate MS from migraine by using MRI (16) and how migraine may be associated with a more symptomatic MS course (17), the impact of migraine as a comorbidity in MS diagnosis and radiological monitoring has not yet been deeply investigated.

Despite the similar features shared by MS, migraine, and SVD-related WM T2-weighted hyperintensities on conventional MRI, *ex vivo* studies showed the heterogeneity of the underlying histopathological substrates (18, 19). Nevertheless, the microstructural features differentiating WM lesions due to MS from WM lesions due to comorbidities have not yet been investigated by using *in vivo* MRI.

To overcome the limited pathological specificity of conventional MRI, several advanced MRI techniques have been developed and applied to characterize microstructural alterations due to tissue disruptions caused by MS (20, 21). Among all the proposed multicompartment models, the spherical mean technique (SMT) has been successfully applied to characterize the brain (22) and the spinal cord (23) of patients with MS. Nevertheless, to the best of our knowledge, whether CVS+ lesions

Abbreviations: BBB, Blood Brain Barrier; BMI, Body Mass Index; CNS, Central Nervous System; CVS, Central Vein Sign; EDSS, Expanded Disability Status Scale; EXTRAMD, Extraneurite Mean Diffusivity; EXTRATRANS, Extraneurite Transverse Diffusivity; FDR, False Discovery Rate; FLIRT, FMRIB's Linear Image Registration Tool; FSL, FMRIB Software Library; GEE, Generalized Estimating Equation; HT, Arterial Hypertension; INTRA, Neurite Signal Fraction; MS, Multiple Sclerosis; NAWM, Normal Appearing White Matter; NMOSD, Neuromyelitis Optica Spectrum Disorder; PMS, Progressive Multiple Sclerosis; PP, Primary Progressive; RFs, Risk Factors; RRMS, Relapsing Remitting Multiple Sclerosis; SMT, Spherical Mean Technique; SP, Secondary Progressive; SVD, Small Vessel Disease; WM, White Matter.

show distinctive microstructural features compared to CVS− lesions has not yet been investigated.

Therefore, the aims of our study were a) to investigate the impact of risk factors for SVD and migraine on the global and subregional brain CVS assessment in a large cohort of patients with MS as a whole and stratified according to age; b) to investigate the pathological substrate of CVS+ and CVS− lesions using advanced diffusion metrics (SMT); and c) to determine whether the use of SMT-derived metrics can differentiate perivenular lesions, typical of MS, from no perivenular lesions, possibly associated with different pathophysiological mechanisms related to comorbidities.

Materials and methods

Subjects

In this prospective study, 120 patients with a diagnosis of MS (24) [84 with relapsing-remitting (RRMS), 36 with progressive (Primary Progressive, PP and Secondary Progressive, SP, from now on "PMS") disease course (25)] were consecutively enrolled between January 2019 and September 2020 at the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (University of Genoa). Inclusion criteria were as follows: (I) age >18 years and (II) MS diagnosis according to revisions of McDonald's criteria (24). Exclusion criteria were as follows: (i) absence of capability to sign the informed consent and (ii) suboptimal MRI quality.

Moreover, we stratified the included subjects as follows: (i) Group 1: 18–30 years ($n = 30$); (ii) Group 2: 31–44 years ($n = 30$); (iii) Group 3: 45–55 years ($n = 30$); (iv) Group 4: 56–77 years ($n = 30$).

All patients underwent neurological examination with the assessment of the Expanded Disability Status Scale (EDSS). In addition, the following RFs for SVD were recorded: body mass index (BMI; measured as a weight-to-height ratio, cut-off ≥25 kg/m^2), smoking (at the time of MRI examination or in the past), diagnosis of HT (at the time of MRI examination or in the past) and its medications, diabetes or glucose intolerance (at the time of MRI examination or in the past) and its medications, and hypercholesterolemia (at the time of MRI examination or in the past) and its medications. The cumulative number of RFs was calculated for each patient. Furthermore, the presence of migraine (or history of migraine) with or without aura (from now on simply "migraine") was also recorded.

MRI acquisition

All patients underwent MRI on a 3T Siemens MAGNETOM Prisma (Siemens Healthcare, Erlangen, Germany) with a 64-channel head and neck coil.

The MRI protocol included (i) 3D sagittal T2-FLAIR (repetition time/inversion time/echo time (TR/TI/TE): 5,000/1,800 ms/393 ms; resolution 0.4 × 0.4 × 1 mm^3); (ii) 3D sagittal T1 MPRAGE (TR/TI/TE: 2300 ms/919 ms/2.96 ms; resolution 1 × 1 × 1 mm^3) before and after intravenous contrast injection of 10 ml of 0.5 mmol/ml gadoteric acid contrast agent; (iii) twice-refocused spin echo echo-planar imaging sequence for multi-shell diffusion-weighted images (TR/TE: 4,500 /75 ms; 107 diffusion directions distributed in 5 shells with b-value up to 3,000 s/mm^2 plus 7 non weighted images acquired with both anterior-posterior and posterior-anterior phase encoding directions; spatial resolution 1.8 × 1.8 × 1.8 mm^3); (iv) 3D sagittal segmented echo-planar imaging (EPI) providing T2* magnitude and phase contrasts (TR/TE: 64 ms/35 ms; resolution 0.65 × 0.65 × 0.65 mm^3) after intravenous contrast injection of 10 ml of 0.5 mmol/ml gadoteric acid contrast agent.

Lesion segmentation and CVS assessment

Central vein sign assessment was performed on FLAIR* images obtained by rigid co-registration (26) and voxel-wise multiplication of the high-resolution 3D T2* EPI and the 3D T2-FLAIR, as previously described (27).

FLAIR* images were reformatted in the axial plane maintaining the native section thickness of 0.65 mm to improve the visualization of vessels within MS lesions and were used for the assessment of the presence of the CVS. For each patient, brain WM matter lesions were selected for the assessment of CVS according to NAIMS guideline (28). The presence or absence of the CVS (CVS+ lesions or "perivenular" and CVS− lesions or "non-perivenular", respectively) was blindly and independently evaluated by two assessors (neurologists with expertise in neuroimaging of MS), according to the NAIMS guidelines (28). In the case of disagreement between assessors, lesions were reviewed by a third assessor (with great expertise in neuroimaging) and a consensus was reached. Gadolinium enhancing lesions were excluded from the analysis to avoid the possible contamination of FLAIR* images due to the leakage of contrast agent within lesions with evidence of BBB disruption. Then, selected CVS+ and CVS− lesions were manually segmented on native FLAIR* images using Jim software (Jim 7.0, Xinapse System; http://www.xinapse.com), creating CVS+ and CVS− lesion masks, respectively.

In addition, patients with MS were classified into "perivenular positive" vs. "perivenular negative" according to the previously proposed criteria: the 40% CVS proportion-based diagnostic thresholds (29–31), the "6-lesion rule" (8), and the "3-lesion rule" (32).

An in-house algorithm based on priors about tissues segmentation was used to automatically subdivide CVS+ and CVS− lesions according to their location: (i) deep/subcortical WM, (ii) periventricular, (iii) juxtacortical, and (iv) infratentorial. To avoid mislabelling, a quality check on the resulting classification was then made by a neurologist with more than 5 years of experience.

Finally, whole brain and subregion-specific CVS+ and CVS− lesion masks were registered on T1- weighted images using the automated FMRIB's Linear Image Registration Tool (FLIRT) with boundary-based registration (33).

Diffusion processing

Diffusion MR images were first denoised using the Marchenko-Pastur principal component analysis algorithm (34) available in MRtrix3 (35). Then they were corrected for movement artifacts and susceptibility induced distortions using eddy and top-up commands from FMRIB Software Library (FSL) (36–39). As the last step of pre-processing, we also performed B1 field inhomogeneity correction to all the dMRI volumes (40). To compute the microstructural maps derived from the SMT model, we used the open-source code available at (https://github.com/ekaden/smt). To register the different lesion masks on the SMT maps, first, the diffusion weighted images were registered on T1-weighted images using FLIRT with boundary-based registration (33), then the resulting transformations were inverted and applied to the lesion masks to register them in the diffusion weighted image space. Similar to the study by Inglese et al. (41), to compensate for the variable partial volume effects caused by the different resolutions between the images, only lesions larger than three voxels after registration on diffusion space were included in the final data analysis. All the registrations were visually checked by a trained professional with more than 5 years of experience in neuroimaging. Finally, we extracted the mean values inside each type of lesions of the following SMT microstructural maps, namely intraneurite signal fraction (INTRA), extraneurite transverse diffusivity (EXTRATRANS), and extraneurite mean diffusivity (EXTRAMD), that describe the fraction of signal coming from the intra-axonal compartment as well as the properties of the anisotropic extraneurite compartment *via* its transverse microscopic diffusivity and mean diffusion outside the axons, respectively (42, 43).

Statistical analysis

Results were reported as mean with standard deviation (SD) or median with range. Differences in lesion volume and lesion location frequencies were compared between CVS+ and CVS− using a generalized estimating equation (GEE) model to take into account multiple lesions from the same patients. The association of demographic and clinical characteristics of patients on the percentage of CVS lesions was assessed using the Mann-Whitney test for binary variables or the Kruskal-Wallis test for categorical variables. Spearman's rank correlation was used for continuous characteristics such as age, disease duration, and BMI. All significant ($p < 0.05$) characteristics at the univariable analyses were included in a multivariable linear regression model. Single lesions microstructural metrics comparisons between CVS+ and CVS− and according to age groups were performed using the GEE model for the same reasons reported above. The mean and SD of each microstructural metric were estimated from a multivariable GEE model also including age, gender, and MS type. EDSS scores were correlated with lesional and normal appearing white matter (NAWM) SMT-derived metrics by using Spearman's test. *P*-values were adjusted for multiple comparisons using the false-discovery rate (FDR) approach. Stata (v.16; Statacorp) was used for the computation.

Approval for this study was received from the Local Ethic Committee of the IRCCS Ospedale Policlinico San Martino (Genoa), and written informed consent was obtained from all subjects.

Data availability

The 3T brain MRI images used were obtained from the IRCCS Ospedale Policlinico San Martino of Genoa and could be made available from the corresponding author upon reasonable request.

Results

Demographic and clinical data

In our cohort, 66 patients with MS were women (55%), the mean (±SD) age was 43.8 ± 14.4 years, and the mean disease duration was 13.4 ± 10.6 years. A more detailed summary of the demographic and clinical features of the enrolled subjects is reported in Table 1. No differences were present in terms of gender distribution. Disease duration was different between age Group 4 vs. age Group 1 and age Group 2 ($p < 0.001$ for both, >in age Group 4) and between age Group 3 vs. age Group 1 ($p = 0.001$, >in age Group 3) and age Group 2 (p <0.001, >in age Group 3). No differences in disease duration were present between age Group 1 vs. age Group 2 and age Group 3 vs. age Group 4. MS phenotype was different between age Group 1 vs. Age Group 3 and age Group 4 [RRMS >PMS, $p < 0.001$ for both] and between age Group 2 vs. age Group 4 (RRMS>PMS, $p = 0.002$). HT was more prevalent in age Group 4 vs. age Group 3 ($p = 0.04$), age Group 2, and age Group 1 ($p < 0.001$ for both). A difference in the prevalence of hypercholesterolemia was observed between age Group 4 vs. age Group 1 ($p = 0.021$). No differences in terms of prevalence of migraine, smoke, diabetes or glucose intolerance were observed among age groups.

CVS assessment: Global data and inter-assessor agreement

A total of 7,445 brain WM lesions were analyzed with a median of 27.3 (range: 4–51) lesions per patient. Among the 7,445 lesions, 5,303 (71.2%) were selected for CVS assessment. Of the 5,303 lesions, 3,645 (68.7%) were CVS+. The median frequency of CVS+ lesions per patient was 73.5% (range: 27.7–100%). The inter-assessor agreement for the percentage of CVS+ lesions was "substantial/good" with a Cohen's κ of 0.7 and an agreement of 89%.

Lesion volume was different between CVS+ and CVS– lesions (median = 1,292 mm^3, range: 26–7,969 mm^3 vs. 224 mm^3, range: 17–1,713 mm^3, respectively; $p < 0.001$). CVS+ lesions had a significantly higher volume and number compared to CVS− lesions in all the four brain regions analyzed [deep/subcortical WM, periventricular, juxtacortical, and infratentorial; ($p < 0.001$ for all, both for volume and number), Table 2].

TABLE 1 Baseline demographic and clinical characteristics.

Demographic and MS clinical data	
Patients, *n*	120
Female, %	55
Age, years, mean (*SD*)	43.8 (14.4)
EDSS score, median (*range*)	2 (1–7)
MS phenotype, *n* (%)	
RRMS	84 (70)
SPMS	21 (17.5)
PPMS	15 (12.5)
Disease duration, years, mean (*SD*)	13.4 (10.6)
Comorbidities clinical data	
Age Groups, *n*	4
Age Group 1, *n*. patients (range, years)	30 (18–30 years)
Age Group 2, *n*. patients (range, years)	30 (31–44 years)
Age Group 3, *n*. patients (range, years)	30 (45–55 years)
Age Group 4, *n*. patients (range, years)	30 (56–77 years)
HT, *n* (%)	17 (*14.2*)
Diabetes or glucose intolerance, *n* (%)	2 (1.7)
Smoke, *n* (%)	63 (52.5)
BMI ≥25 kg/m^2, *n* (%)	10 (8.3)
Hypercholesterolemia, *n* (%)	21 (17.5)
Cumulative number of RFs for SVD, median (*range*)	1 (0–4)
Migraine, *n* (%)	34 (28.3)
Demographic and clinical features according to age Groups[a]	
Disease duration	1 vs. 4 (**$p < 0.001$**)
	2 vs. 4 (**$p < 0.001$**)
	1 vs. 3 (**$p = 0.001$**)
	2 vs. 3 (**$p < 0.001$**)
	(> in age Group 4 and age Group 3)
MS phenotype*	1 vs. 3 (**$p < 0.001$**)
	1 vs. 4 (**$p < 0.001$**)
	2 vs. 4 (**$p = 0.002$**)
	(RRMS > PMS in age Group 1)
HT	1 vs. 4 (**$p < 0.001$**)
	2 vs. 4 (**$p < 0.001$**)
	3 vs. 4 (**$p = 0.04$**)
	(>HT in age Group 4)
Hypercholesterolemia	1 vs. 4 (**$p = 0.021$**)
	(>hypercholesterolemia in age Group 4)

EDSS, Expanded Disability Status Scale; RRMS, Relapsing Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis; PPMS, Primary Progressive Multiple Sclerosis; HT, arterial hypertension; BMI, Body Mass Index; RFs, risk factors; SVD, Small Vessel Disease.

[a]Only significant comparisons among age groups were reported.

*All PPMS patients were included in age Groups 3 and 4.

TABLE 2 Volume and topography of CVS+ and CVS− lesions in the whole cohort and according to age groups.

	CVS+	CVS−	*p*-value
Total lesions, *n* (%)	3,645 (68.7)	1,658 (31.3)	–
Whole cohort, Lesion volume (mm^3), median (*range*)			
Periventricular	1,292 (26–7,969)	224 (17–1,713)	**<0.001**
Infratentorial	296 (110–555)	45 (13–88)	**<0.001**
Juxtacortical	161 (75–273)	34 (16–54)	**<0.001**
Deep/subcortical WM	283 (72–526)	74 (29–255)	**<0.001**
	596 (158–1,229)	141 (56–270)	**<0.001**
Whole cohort, Lesion location, *n* (%)			
Periventricular	584 (80)	146 (20)	**<0.001**
Infratentorial	527 (85.6)	89 (14.4)	**<0.001**
Juxtacortical	640 (61.3)	404 (38.7)	**<0.001**
Deep/subcortical WM	1894 (65.1)	1019 (34.9)	**<0.001**
Age Group 1 (18–30), Lesion location, *n* (%)			
Periventricular	136 (84.5)	25 (15.5)	**<0.001**
Infratentorial	112 (85.5)	19 (14.5)	**<0.001**
Juxtacortical	171 (67.6)	82 (32.4)	**<0.001**
Deep/subcortical WM	411 (72.1)	159 (27.9)	**<0.001**
Age Group 2 (31–44), Lesion location, *n* (%)			
Periventricular	178 (84)	34 (16)	**<0.001**
Infratentorial	161 (88.5)	21 (11.5)	**<0.001**
Juxtacortical	187 (64.9)	101 (35.1)	**<0.001**
Deep/subcortical WM	570 (73.4)	207 (26.6)	**<0.001**
Age Group 3 (45–55), Lesion location, *n* (%)			
Periventricular	123 (75.9)	39 (24.1)	**<0.001**
Infratentorial	113 (85)	20 (15)	**<0.001**
Juxtacortical	161 (59.2)	111 (40.8)	**0.033**
Deep/subcortical WM	558 (67.1)	273 (32.9)	**<0.001**
Age Group 4 (56–77), Lesion location, *n* (%)			
Periventricular	147 (75.4)	48 (24.6)	**<0.001**
Infratentorial	141 (82.9)	29 (17,1)	**<0.001**
Juxtacortical	121 (52.4)	110 (47.6)	0.19
Deep/subcortical WM	355 (48.3)	380 (51.7)	0.085

CVS, Central Vein Sign.

CVS proportion-based diagnostic thresholds vs. simplified algorithms

Based on the 35% and the 40% of CVS proportion-based diagnostic thresholds (29–31), 119 of the 120 included patients were perivenular positive for both thresholds. In one patient, %CVS+ lesions was 28% (age Group 4, secondary progressive phenotype, and history of migraine); in the other patient, it was 39% (age Group 2, secondary progressive phenotype, smoke, and migraine). When

applying the simplified algorithms, 6-lesion (8) and 3-lesion rules (32), 119 and 111 of the 120 included patients were perivenular positive, respectively.

CVS relationship with MS phenotype, RFs for SVD, and migraine

Patients with relapsing-remitting multiple sclerosis showed a higher percentage of CVS+ lesions compared to patients with PMS (76.9%, range 40–100 vs. 67.3%, range 27.7–100%; $p = 0.002$).

The median percentage of CVS+ lesions decreased from age Group 1 to age Group 4 (for age Group 1: median 79.7%, range 60.3–100%; for age Group 2: median 79.1%, range 39.1–100%; for age Group 3: median 71.8%, range 40–100%; for age Group 4: median 57.7%, range 27.7–100%). Differences in the median percentage of CVS+ lesions were observed among all age groups, except for age Group 2 vs. age Group 3 (Table 3).

When patients with MS were stratified according to age groups, we found that, in all age groups and brain subregions, CVS+ lesion number was higher than CVS− lesions [$p < 0.001$ for all, except for (i) juxtacortical area in age Group 3 ($p = 0.033$) and (ii) juxtacortical area in age Group 4 where the difference was not significant], excluding the deep/subcortical WM in age Group 4, where CVS− lesion number was higher than CVS+ lesions, although not reaching statistical significance (Table 2, Figure 1).

Patients with HT showed a lower percentage of CVS+ lesions (median: 61.9%, range 43.3–100%) compared to patients not diagnosed with HT (median: 74.7%, range 27.7–100%; $p = 0.031$). Patients with migraine had a lower percentage of CVS+ lesions (median: 65.8%, range 27.7–100%) compared to patients without migraine (median: 76.4%, range 40–100%; $p = 0.032$). A trend was observed between patients with hypercholesterolemia and no hypercholesterolemia (median: 68%, range 43.1–100% vs median 74.7%, range 27.7–100% respectively; $p = 0.078$). For the variables: smoking/no smking, BMI $\geq$ 25/BMI $\leq$ 25, diabetes or glucose intolerance/ no diabetes or glucose intolerance, and cumulative number of RFs for SVD, no differences in terms of CVS+ vs CVS− lesion median percentage were observed in terms of CVS+ vs CVS− lesion median percentage (Table 3).

A negative correlation was found between %CVS+ lesions and age ($r = -0.46$; $p < 0.001$, Figure 2) and between %CVS+ lesions and disease duration ($r = -0.24$; $p = 0.008$), while a trend was observed with BMI ($r = -0.17$; $p = 0.058$).

In the multivariable model, including age, migraine, the cumulative number of RFs for SVD, HT, MS phenotype, and disease duration, age and migraine were independently associated with the %CVS+ lesions (model R^2 0.25; $p < 0.001$ for age and $p = 0.013$ for migraine).

TABLE 3 CVS+ lesions percentage comparisons among age groups, MS phenotype, RFs for SVD, and migraine.

	CVS+ (% lesions), median (range)	p-value
Age		
Age Group 1: 18–30 ($n = 30$)[1]	79.7 (60.3–100)	1 vs 2 $\mathbf{p = 0.026}$
Age Group 2: 31–44 ($n = 30$)[2]	79.1 (39.1–100)	1 vs 3 $\mathbf{p < 0.001}$ 2 vs 3 0.088
Age Group 3: 45–55 ($n = 30$)[3]	71.8 (40–100)	1 vs 4 $\mathbf{p < 0.001}$
Age Group 4: 56–77 ($n = 30$)[4]	57.7 (27.7–100)	2 vs 4 $\mathbf{p < 0.001}$
		3 vs 4 $\mathbf{p = 0.017}$
MS type		
RR ($n = 84$)	76.9 (40–100)	**0.002**
PMS ($n = 36$)	67.3 (27.7–100)	
HT		
No ($n = 103$)	74.7 (27.7–100)	**0.031**
Yes ($n = 17$)	61.9 (43.3–100)	
Diabetes or glucose intolerance		
No ($n = 118$)	74.0 (27.7–100)	0.33
Yes ($n = 2$)	60.8 (49.2–72)	
Smoke		
No ($n = 57$)	72.4 (27.7–100)	0.84
Yes ($n = 63$)	75 (39.1–100)	
BMI		
18–24.9 ($n = 79$)	75 (27.7–100)	0.27
$\geq$25 ($n = 41$)	72 (40–100)	
Hypercholesterolemia		
No ($n = 99$)	74.7 (27.7–100)	0.07
Yes ($n = 21$)	68 (43.1–100)	
Cumulative RFs number		
0 ($n = 31$)	74.7 (40–100)	0.55
1 ($n = 52$)	77.1 (27.7–100)	
2 ($n = 20$)	65.8 (39.1–93.3)	
3–4 ($n = 17$)	66.7 (43.5–88.1)	
Migraine (with or without aura)		
No ($n = 86$)	76.4 (40–100)	**0.032**
Yes ($n = 34$)	65.8 (27.7–100)	

CVS, Central Vein Sign.

Microstructural features of CVS+ and CVS− lesions evaluated by the SMT diffusion model

Compared to CVS− lesions, CVS+ lesions showed higher EXTRAMD ($p = 0.001$), higher EXTRATRANS ($p = 0.001$), and lower INTRA ($p = 0.02$). In the deep/subcortical WM, juxtacortical, and infratentorial areas, EXTRAMD was higher in CVS+ lesions compared to CVS− lesions ($p = 0.001$, 0.01, and 0.05, respectively), while in the periventricular region, we observed the opposite result ($p = 0.001$). In the deep/subcortical WM and infratentorial areas, EXTRATRANS was higher in CVS+ lesions compared to CVS− lesions ($p = 0.001$ and $p = 0.04$, respectively), while in periventricular and juxtacortical regions, no differences were observed. In the deep/subcortical WM and periventricular areas, INTRA was lower in CVS+ lesions compared to CVS−

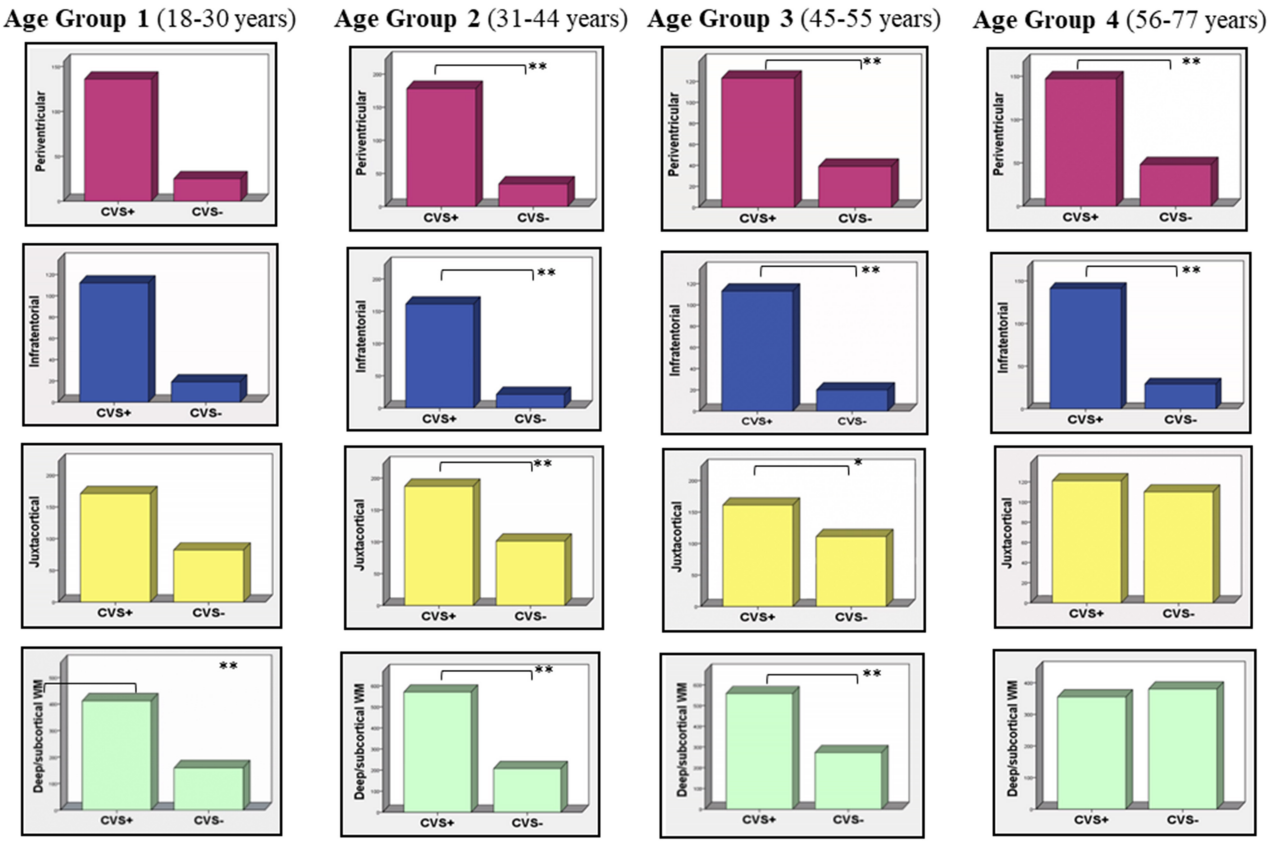

FIGURE 1
CVS+ and CVS− distribution according to age groups and brain subregions. In all age groups and brain subregions, CVS+ lesion number is higher than CVS− lesions (**$p < 0.001$; *$p = 0.033$), except for the juxtacortical area in age Group 4 where the difference is not significant. Note that in the deep/subcortical WM in age Group 4 (57–77 years) CVS− lesion number rises and becomes higher than CVS+ lesions, although not statistically significant. CVS, Central Vein Sign.

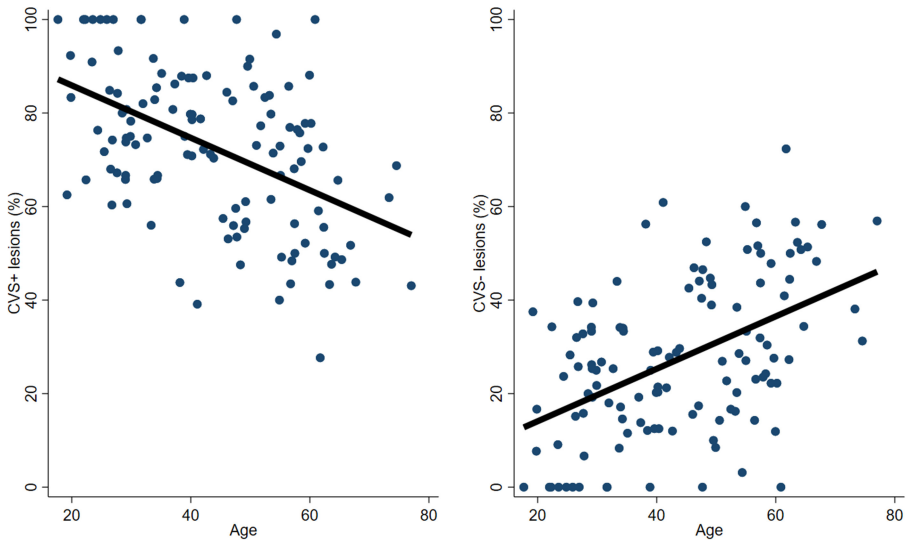

FIGURE 2
Association between patient's age and the frequency of CVS+ and CVS− lesions. An inverse correlation was found between %CVS+ lesions and age ($r = -0.46$; $p < 0.001$), while a positive correlation was found between %CVS− lesions and age ($r = 0.46$; $p < 0.001$). CVS, Central Vein Sign.

TABLE 4 SMT metrics comparisons between CVS+ and CVS− lesions.

	CVS+	CVS−	*p*-value*	*p*-value adjusted for m.c.^
EXTRAMD (inflammation), mean (*SD*) mm²/s	0.00144 (0.000245)	0.00139 (0.000228)	**<0.001**	**0.001**
Deep/subcortical WM	0.00139 (0.000128)	0.00135 (0.000114)	**<0.001**	**0.001**
Periventricular	0.00154 (0.000226)	0.00163 (0.000301)	**<0.001**	**0.001**
Juxta	0.00132 (0.000175)	0.00129 (0.000190)	**0.007**	**0.01**
Infratentorial	0.00141 (0.000251)	0.00134 (0.000260)	**0.035**	**0.05**
EXTRATRANS (demyelination), mean (*SD*) mm²/s	0.00117 (0.000288)	0.00111 (0.000252)	**<0.001**	**0.001**
Deep/subcortical WM	0.00109 (0.000182)	0.00105 (0.000145)	**<0.001**	**0.001**
Periventricular	0.00131 (0.000252)	0.00135 (0.000333)	0.13	0.15
Juxta	0.00114 (0.000176)	0.00112 (0.000194)	0.08	0.11
Infratentorial	0.00103 (0.000293)	0.000952 (0.000296)	**0.027**	**0.04**
INTRA (fiber disruption), mean (*SD*)	0.399 (0.129)	0.409 (0.124)	**0.012**	**0.02**
Deep/subcortical WM	0.425 (0.113)	0.449 (0.0976)	**<0.001**	**0.001**
Periventricular	0.341 (0.0969)	0.378 (0.109)	**<0.001**	**0.001**
Juxta	0.309 (0.0932)	0.301 (0.0894)	0.17	0.19
Infratentorial	0.507 (0.122)	0.530 (0.138)	0.11	0.14

m.c., multiple comparisons.
**P*-value obtained from the GEE model and adjusted for age, MS phenotype, and gender; ^Adjustment for multiple comparisons using the false-discovery rate approach. CVS, Central Vein Sign; SMT, Spherical Mean Technique.

lesions ($p = 0.001$ for both), while in infratentorial and juxtacortical regions, no differences were observed (Table 4).

SMT-metrics maps within representative CVS+ and CVS−lesions (at the top) and their graphical representation by violin plots (at the bottom) are shown in Figure 3.

EDSS scores correlations with SMT metrics

The EDSS scores were correlated with SMT metrics extracted from CVS+ and CVS− lesions but no significant results were observed, while a significant negative correlation was detected between SMT-intra of the NAWM and EDSS ($p = 0.014$ $r = -0.226$).

Discussion

In this study, we investigated the impact of RFs for SVD and migraine on the global and subregional brain CVS assessment in a large cohort of patients with MS stratified according to age and thus applied the SMT diffusion model to evaluate whether perivenular lesions show distinctive microstructural features compared to non-perivenular lesions. We focused on the different risk factors for SVD (age, BMI, smoking, HT, diabetes or glucose intolerance, hypercholesterolemia) and migraine, due to their high prevalence in the common population, including patients with MS (13, 44). Unlike MS, histopathological studies in SVD revealed that the anatomical target of tissue damage is mostly represented by the arteriolar side of vascular microcirculation (19, 45), where vessel lumen restriction and chronic hypoperfusion mainly occur. Although the pathophysiology of migraine-related deep WM hyperintensities is poorly understood, both ischemic and inflammatory mechanisms have been proposed, as there is increased cerebral vulnerability to ischemia in migraineurs, as well as evidence of BBB disruption during migraine attacks (18).

Among the RFs for SVD, age was the strongest inverse predictor of the percentage of CVS+ lesions, while HT, although associated with a higher prevalence of CVS− lesions, did not survive as a significant predictor in the regression analysis. The low percentage of MS patients with HT in our sample (as for patients with diabetes, higher BMI, and smokers) may explain these findings. One of the most novel aspects of our study was the investigation of migraine impact on the percentage of CVS+ lesions. MS patients with migraine showed a higher percentage of CVS− lesions compared to MS patients without migraine. Furthermore, migraine also survived as an inverse predictor of the percentage of perivenular lesions in the regression analysis. Interestingly, analyzing the demographic and clinical features of patients with MS who did not fulfill the 40% thresholds approach in our sample, we observed that both MS patients had suffered or suffered from migraine. Although our data confirmed that the previously proposed CVS proportion-based thresholds (29–31) remain valid for differential diagnosis, they may suggest that migraine, as well as aging, could be able to affect CVS performance and, thus, it should be carefully considered in the radiological workflow of patients with high clinical suspicion of MS.

Furthermore, in order to investigate whether older age has a more preferential impact on the CVS assessment in some brain subregions than in others, we considered the distribution of the CVS+ and CVS− lesions in brain areas considered specific (periventricular, infratentorial, and juxtacortical) and not specific

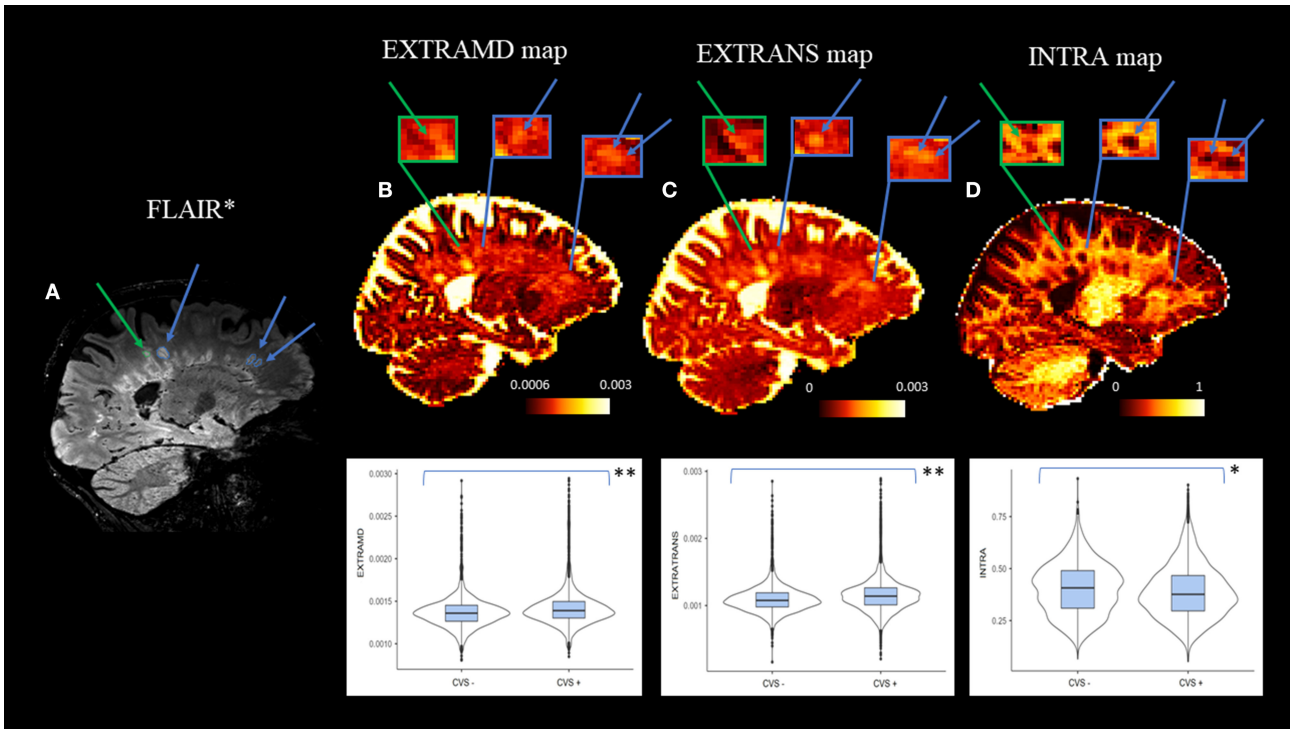

FIGURE 3
Selected sagittal FLAIR* **(A)** and SMT-derived EXTRAMD **(B)**, EXTRATRANS **(C)** and INTRA **(D)** maps of a 62-year-old patient diagnosed with multiple sclerosis. At the top: the color bar expresses each SMT-metric: adimensional unit for INTRA (intraneurite signal fraction, corresponding to fiber disruption), mm^2/sec for EXTRAMD (extraneurite mean diffusivity, corresponding to inflammation severity), and EXTRATRANS (extraneurite transverse diffusivity, corresponding to the degree of demyelination) measures. Arrows and zoomed-in boxes indicate the presence of representative CVS+ lesions (blu arrows) and CVS− lesion (green arrows) to highlight the differences in SMT metrics among them. At the bottom: violin plots showed higher inflammation, demyelination, and fiber disruption in CVS+ lesions compared to CVS− lesions (**$p = 0.001$; *$p = 0.02$). CVS, Central Vein Sign.

(deep/subcortical WM) for MS. CVS+ lesion volume was higher than CVS–lesion volume, both considering the global brain and the four subregions analyzed, where CVS+ lesions were also numerically prevalent. In a recent study (12), it was reported that CVS+ lesion volume in the whole brain and CVS+ lesion number in the deep/subcortical WM were higher than CVS− lesion volume and CVS− lesion number in the global brain and deep/subcortical WM, respectively, although there was no statistical significance between them. The larger sample size and the higher number of lesions analyzed in our study may partially explain these different findings. Nevertheless, conflicting results emerged also in the juxtacortical area, where Guisset et al. (12) found that CVS− lesions were numerically prevalent compared to CVS+ lesions. CVS evaluation in the juxtacortical area may be challenging due to the possible effect of distortion artifacts intrinsic to EPI-T2* images. To improve the detection rate of CVS+ lesions, we decided to perform EPI-T2* images after contrast agent administration, following the suggestion of previous studies (46–48). It is possible that T1 shortening, due to gadolinium administration, may lead to an increase in the phase effects around blood vessels, thus improving the visibility of the central vein (47, 49). In our study, the CVS assessment in gadolinium enhanced susceptibility images could have helped to optimize the detection of perivenular lesions on the whole brain but also in challenging areas.

After having stratified MS patients according to age to evaluate the CVS in the different brain subregion, we found that in brain subregions considered typical of MS (periventricular, infratentorial, and juxtacortical), the relationship between CVS+/CVS− lesion number showed a clear prevalence of CVS+ on CVS− lesions in all age groups, except for juxtacortical areas in the 56–77 years group. An overestimation of CVS− lesions in the juxtacortical area throughout all age groups due to the abovementioned technical issues, despite our attempt to improve CVS detection by acquiring EPI-T2* images after contrast injection, may partially explain our findings. Furthermore, despite both SVD and migraine-related WM T2-weighted hyperintensities being mostly located in the deep/subcortical WM, different studies showed that juxtacortical areas may also be involved (50, 51). Interestingly, we found that in age Group 4 (56–77 years) CVS− lesion number increased to become higher than CVS+ lesions in the deep/subcortical WM, although no statistical significance was found.

Therefore, driven by our findings about the impact of age and migraine on the percentage of CVS+ lesions and the inversion of CVS+/CVS− lesions prevalence in deep/subcortical WM in older patients with MS, we decided to use the SMT model to investigate the pathological substrate of CVS+ and CVS− lesions. The choice to use SMT relied on its interesting basic assumptions and its encouraging recent results in MS (20, 23, 43). Overcoming the issue represented by the fixed intrinsic diffusivity

of other multicompartment models (20), SMT considers WM as a two-compartment (intra- and extra-axonal) tissue and provides signal fraction and diffusion metrics per axon without confounds from fiber direction, crossing, or dispersion (43). Histopathologic validation of SMT has been performed in the animal model of tuberous sclerosis, where the absence of neuroinflammation makes the detection of CNS axonal injury and demyelination more suitable. Thus, although obtained with a different disease model, the provided validation against axonal histology is fundamental. It applies to any condition affecting myelin and axonal integrity and supports the ability of SMT to quantify axonal content without artifactual effects from fiber-crossing and orientation dispersion (18). This is particularly important in MS because many WM voxels contain complex fiber configurations, and fiber arrangements widely vary within MS lesions. Thus, these fiber orientation-independent diffusion metrics may provide more accurate estimates of axon integrity. SMT has been already applied in different *in vivo* studies focusing on the brain (22) and spinal cord (23) of patients with MS, demonstrating to be helpful in differentiating MS lesions damage from the NAWM as well as the NAWM of patients with MS from that of healthy controls (20) and in characterizing pathological features within MS lesions (52). Furthermore, it has been demonstrated that DTI, neurite orientation dispersion and density imaging (NODDI), and SMT concur on the direction of tissue changes in MS, providing consistent descriptors of tissue microstructure useful in monitoring MS in clinical trials and practice (53). In this study, we demonstrated that SMT was able to investigate the pathological substrates of CVS+ and CVS− lesions and detect distinctive features capable of differentiating them from each other. Compared to CVS− lesions, perivenular lesions showed higher EXTRAMD, indirectly reflecting higher free water content, higher EXTRATRANS, indirect expression of a decrease in myelin content, and lower INTRA, suggestive of a higher degree of axonal damage and fiber disruption. Thus, we could suggest that perivenular lesions, typical of MS, were characterized by a more severe degree of inflammation, demyelination, and fiber disruption than non-perivenular lesions, possibly associated with different pathophysiological mechanisms. Similar strong evidence was found comparing all SMT metrics within CVS+ and CVS− lesions clustered in the deep/subcortical WM. Fiber disruption seemed to also be higher in perivenular lesions located in periventricular areas, while cerebrospinal fluid (CSF) contamination could have affected extraneurite compartment metrics (EXTRAMD >in CVS− lesions; no difference was found between CVS+ and CVS− lesions in EXTRATRANS). Similar, although weaker, differences were found in juxtacortical and infratentorial areas. Indeed, compared to CVS− lesions, a higher inflammatory component was detected in CVS+ lesions located in both regions and a more pronounced degree of demyelination was found in infratentorial CVS+ lesions. Technical issues may have affected these findings. Because the voxel signal is a sum of all tissue signals within the voxel, finite image resolution inevitably causes a mixture of signals at the interface of two tissues. This phenomenon, known as partial volume effect (PVE), may obscure small lesions near the interface between tissues (54) and, quantitatively, may cause errors in volumetric measurements using structural MRI or region-of-interest (ROI) measurements using diffusion-weighted imaging (55). Thus, this limitation in SMT metrics extraction cannot be disregarded in periventricular and juxtacortical areas, where CSF contamination and the different tissue cytoarchitecture of gray matter characterize the corresponding WM interfaces. Furthermore, the lower mean volume of juxtacortical and infratentorial T2-weighted hyperintensities compared to the deep/subcortical WM may also contribute to explain why SMT metrics seem to perform worse in differentiating perivenular from non-perivenular lesions in these areas.

Finally, we found a correlation between EDSS score as a clinical parameter and SMT metrics extracted from the NAWM but not between EDSS scores and SMT metrics obtained from CVS+ and CVS− lesions. The pathological, and, thus, microstructural, heterogeneity of FLAIR hyperintense lesions, ranging from early lesions to T1-hypointense "black holes" and the exclusion of a considerable amount of FLAIR lesions from the CVS assessment, whose SMT metrics were thus not extracted in our study, might explain our findings. Conversely, the correlation we found between the NAWM microstructural damage and the ESSS is in line with that shown in a recent paper (53), suggesting that the greater the widespread axonal damage, the poorer the clinical status. These findings may indicate initial hints about the clinical potential of SMT diffusion derived metrics in explaining disability in MS *in vivo*.

This study is not without limitations. First, the presence of a comparison group including non-MS patients suffering from RFs for SVD and/or migraine would have been very helpful to investigate whether CVS− lesions in MS and non-MS patients possibly share microstructural features, thus potentially contributing to validating our findings. Moreover, the cross-sectional design of this study does not allow us to evaluate how and where the new T2-weighted hyperintensities develop over time and their temporal relationships with aging and other comorbidities in patients with MS. The relatively low incidence of MS patients with RFs for SVD in our sample may have underestimated the role of HT, above all, in reducing the percentage of CVS+ lesions and thus affecting CVS performance. Finally, we did not include other potential causes of WM lesions, such as a macroangiopathic disease, i.e., lacunar infarcts-, hemodynamic changes, and abnormalities of heart rhythm (i.e., atrial fibrillation) or structure (i.e., patent foramen ovale), that could increase the prevalence of CVS− lesions within the brains of patients with MS.

In conclusion, this study demonstrated that aging has a relevant impact on reducing the percentage of CVS+ lesions in patients with MS. This effect is already clear when the whole brain is considered but becomes even more evident when the deep/subcortical WM, a region not typical of MS, is specifically analyzed. Indeed, in this site, non-perivenular lesions become more prevalent than perivenular lesions in older patients with MS. Although the use of three periventricular lesions instead of 1, as required by current MS criteria for DIS (24), surely helps in reducing the risk of misdiagnosis or wrong interpretation of disease activity in older and comorbid patients with MS (56), it lacks a pathophysiological basis. Furthermore, vascular leukoaraiosis is typically extended around ventricles and its differentiation from confluent MS lesions may be very challenging.

Our findings suggest that thanks to the use of MRI biomarkers closely linked to MS pathophysiology -as the CVS-, also "non-DIS" regions may become very informative and help to prevent diagnostic misinterpretation.

Among the other comorbidities, for the first time, we showed that migraine may also play a significant role in increasing the amount of non-perivenular lesions in younger patients with MS. Furthermore, we demonstrated that SMT-derived metrics may provide a deep characterization of microstructural features within WM lesions and, for the first time, that these metrics seem to be able to differentiate perivenular lesions, characterized by higher levels of inflammation, demyelination, and fiber disruption, from non-perivenular lesions, for which other pathophysiological mechanisms could be suggested.

Therefore, in our opinion, the development of a new non-perivenular T2-weighted hyperintensity, especially if located in the deep/subcortical WM in older patients with MS, should be considered a "red flag" for a pathophysiology other than MS disease activity. A careful evaluation of comorbidities during CVS assessment for the diagnosis and monitoring of MS should be mandatory, to avoid misleading interpretations and potentially inappropriate therapeutic strategies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Local Ethic Committee of the IRCCS Ospedale Policlinico San Martino (Genoa). The patients/participants provided their written informed consent to participate in this study.

Author contributions

CL: designed and conceptualized study, major role in the acquisition and analysis of data, and drafted the manuscript for intellectual content. FT: major role in the acquisition and analysis of data and revised the manuscript for intellectual content. SR and AS: major role in the analysis of data. GB and ES: major role in the acquisition of data and revised the manuscript for intellectual content. NB, EM, and NM: major role in the acquisition of data. LR: major role in the acquisition of data and study conceptualization and revised the manuscript for intellectual content. MC: revised the manuscript for intellectual content. SS: major role in the analysis of data and revised the manuscript for intellectual content. MI: design and conceptualized study, analyzed the data, and revised the manuscript for intellectual content.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Kristen Marie Krysko,
St Michael's Hospital, Canada

REVIEWED BY
Mirta Fiorio,
University of Verona, Italy
Caterina Lapucci,
San Martino Hospital (IRCCS), Italy

*CORRESPONDENCE
Antonella Conte
✉ antonella.conte@uniroma1.it

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Neurophysiological and clinical biomarkers of secondary progressive multiple sclerosis: A cross-sectional study

Matteo Tartaglia[1], Marco Canevelli[1], Leonardo Malimpensa[2], Daniele Belvisi[1,2], Viola Baione[1], Gina Ferrazzano[1], Giorgio Leodori[1,2], Alfredo Berardelli[1,2] and Antonella Conte[1,2]*

[1]Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy, [2]Department of Neurophysiology, IRCCS Neuromed, Pozzilli, Italy

Timely diagnosis of secondary progressive multiple sclerosis (SPMS) represents a clinical challenge. The Frailty Index, a quantitative frailty measure, and the Neurophysiological Index, a combined measure of sensorimotor cortex inhibitory mechanism parameters, have recently emerged as promising tools to support SPMS diagnosis. The aim of this study was to explore the possible relationship between these two indices in MS. MS participants underwent a clinical evaluation, Frailty Index administration, and neurophysiological assessment. Frailty and Neurophysiological Index scores were found to be higher in SPMS and correlated with each other, thus suggesting that they may capture similar SPMS-related pathophysiological mechanisms.

KEYWORDS

multiple sclerosis, frailty, neurophysiology, disease progression, biomarkers, transcranial magnetic stimulation

1. Introduction

Secondary progressive multiple sclerosis (SPMS) develops after a relapsing-remitting form of multiple sclerosis (RRMS). SPMS diagnosis is retrospectively based on worsening of the Expanded Disability Status Scale (EDSS) scores, without substantial changes in magnetic resonance imaging (MRI). There is evidence that a high EDSS score at MS diagnosis is a risk factor for RRMS-to-SPMS conversion (1). However, EDSS assessment is affected by significant inter-rater variability and a substantial frequency of rating errors depending on the examiner's experience (2).

The identification of possible objective markers of RRMS-to-SPMS conversion is therefore needed. A neurophysiological marker to identify SPMS has been recently proposed, which consists of an index derived from the objective assessment of a neurophysiological and a psychophysical variable. The first is short intracortical inhibition (SICI), which tests inhibitory interneuron excitability in the motor cortex. The second is the somatosensory temporal discrimination threshold (STDT), which tests inhibitory interneuron excitability in the primary sensory cortex (3, 4).

The neurophysiological index combining SICI and STDT also included age as a factor in the formula predicting SPMS. This observation is in line with previous evidence suggesting that chronological aging may play a role in the RRMS-to-SPMS transition (5). Besides chronological aging, however, also biological aging, as measured by Frailty Index (FI), seems to be associated with SPMS (6). The FI is a quantitative frailty indicator based on clinical

and laboratory data that assesses an individual's global vulnerability to stressors and may represent a useful multidimensional tool to evaluate biological aging in MS. FI is able to discriminate SPMS from RRMS and has been proposed as a possible clinical marker for SPMS (6). Intriguingly, the association between frailty and SPMS is lost in the advanced phases of the disease (7), thus suggesting that frailty should be considered a factor implied in the conversion from RRMS to SPMS rather than a long-term feature of SPMS. From this perspective, FI could be considered a quantitative clinical marker of SPMS at its early stages.

Both the neurophysiological index and FI correlate with chronological aging in MS but it is unknown whether a relationship between these potential biomarkers for MS is present.

The aim of this study was to investigate the neurophysiological index and the FI comparing RRMS and SPMS patients and explore possible correlations between these two measures.

2. Materials and methods

2.1. Subjects

For this purpose, 19 patients with MS (13 RRMS, mean age 41.2 ± 9.0 years, median EDSS 1.0 [0–4.0]; 6 SPMS, mean age 53.3 ± 5.2 years, median EDSS 6.0 [2.5–7.5]) were enrolled at the Multiple Sclerosis Outpatient Clinic, Department of Human Neurosciences, Sapienza University of Rome. MS diagnosis was defined accordingly to the latest revised McDonald criteria (8), while disease course was identified based on Lublin definition (9). Inclusion criteria were age over 18 years, RRMS or SPMS diagnosis, absence of contraindications to TMS (such as epilepsy or head trauma). SPMS enrolled patients were not in an active phase as defined by Lublin et al. (9), while RRMS patients had to be free from relapses and from corticosteroid intake in the 30 days preceding the assessments. All study participants gave a written informed consent. The study was approved by the Ethical Committee of our Institution and was conducted according to the Declaration of Helsinki. All patients underwent clinical and neurophysiological examination.

2.2. Neurophysiological index

All neurophysiological assessments were performed in a random order while patients were comfortably sitting on an armchair. The neurophysiological index was calculated for each patient using the following formula obtained in a previous work (3):

$$P(X=1) = \frac{e^{-5.95503+0.00056*SICI(\%)*Age+0.00073*STDT*Age}}{1+e^{-5.95503+0.00056*SICI(\%)*Age+0.00073*STDT*Age}}$$

This score computes the probability that a patient (X) has to be assessed as SPMS (class 1) using three variables: age, SICI (%), and STDT.

2.2.1. Short intracortical inhibition (SICI)

We delivered single and paired-pulses through a Magstim Bistim2 magnetic stimulator (The Magstim Company, Ltd., Whitland, South West Wales, UK) connected to a figure-of-eight coil. Motor evoked potentials (MEPs) from the first dorsal interosseous muscle were elicited delivering transcranic magnetic stimulation (TMS) to the contralateral M1 motor area. Coil was handled tangentially to the scalp, while tail was placed backward at 45° respect of the median line. Minimum single-pulse intensity able to elicit a 50 μV of amplitude MEP was defined as resting motor threshold (RMT). Consequently, conditioning stimulus intensity was set as 80% of RMT while TMS intensity able to evoke a 1 mV of average amplitude MEP was used as test stimulus. To assess SICI, a 3 ms interstimulus interval (ISI) between conditioning and test stimulus was used. SICI effects were then computed as the percentage ratio between the conditioned MEP amplitude and the test MEP amplitudes [SICI (%)].

2.2.2. Somatosensory temporal discrimination threshold (STDT)

To test STDT we used procedures explained in previous studies (3, 10, 11). Briefly, pairs of square-wave electric stimuli were delivered with an increasing ISI of 10 ms starting from a couple of simultaneous stimuli. Electric stimulation was performed through a stimulator (Digitimer DS7AH) connected to AgCl electrodes placed on the volar face of the right index finger. Stimulation intensity was increased, starting from 2 mA, by 1 mA for each step to reach the minimum intensity at which patients perceived 10 out of 10 stimuli. STDT was defined as the first of three consecutive ISIs when patients could temporally discriminate the stimuli. During the experiment "catch trials" were performed to reduce persevering answers and to check patient's attention level.

2.3. Frailty index (FI)

The FI was assessed through 42 clinical and laboratory health items as previously described (6). During the outpatient visit, subjects were questioned about each item and a score of 1 was assigned if a deficit was present and of 0 if absent. The FI score was then computed for each participant as a ratio between the total number of deficits and the total number of items ($n = 42$).

2.4. Statistical analysis

Mann-Whitney U test for independent samples was used to evaluate differences in the neurophysiological and frailty indices between RRMS and SPMS patients. Spearman's correlation

Abbreviations: EDSS, expanded disability status scale; FI, frailty index; ISI, interstimulus interval; MEP, motor evoked potential; MRI, magnetic resonance imaging; RMT, resting motor threshold; RRMS, relapsing-remitting multiple sclerosis; SICI, short intracortical inhibition; STDT, somatosensory temporal discrimination threshold; SPMS, secondary progressive multiple sclerosis; TMS, transcranic magnetic stimulation.

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TABLE 1 Patients' demographic, neurophysiological and frailty characteristics.

ID	Age (years)	Sex	Clinical phenotype	EDSS (score)	Disease duration (years)	Neurophysiological index (score)	Frailty index (score)
1	49	F	RR	0	21	0.06	0.14
2	34	M	RR	0	1	0.31	0.07
3	51	F	RR	2	11	0.65	0.19
4	30	F	RR	0	5	0.05	0.05
5	30	F	RR	1	1	0.01	0.19
6	55	M	RR	1.5	28	0.21	0.26
7	52	F	RR	1.5	9	0.52	0.11
8	48	F	RR	1	6	0.11	0.14
9	38	F	RR	2	4	0.15	0.38
10	40	M	RR	4	13	0.07	0.07
11	38	M	RR	1	8	0.09	0.05
12	29	M	RR	1.5	6	0.02	0
13	42	F	RR	1	11	0.18	0.12
14	49	M	SP	3.5	26	0.78	0.19
15	52	M	SP	6	18	0.96	0.29
16	46	F	SP	7.5	21	0.94	0.33
17	59	F	SP	2.5	35	0.95	0.12
18	57	F	SP	7	22	0.99	0.33
19	57	F	SP	6	24	0.92	0.33
RRMS mean (SD)	41.2 (9.0)	F = 8	-	-	9.5 (7.7)	0.19 (0.19)	0.14 (0.10)
SPMS mean (SD)	53.3 (5.2)	F = 4	-	-	24.3 (5.9)	0.92 (0.07)	0.27 (0.09)

EDSS, Expanded disability status scale; RRMS, Relapsing-remitting multiple sclerosis; SPMS, Secondary progressive multiple sclerosis.

coefficient was used to investigate possible correlations between the FI and neurophysiological index. This analysis was adjusted for disease duration and sex. A case-wise diagnostic was used to detect outliers with standardized residual > ±2 standard deviations. The case-wise diagnostic detected 1 outlier (case 9 in Table 1) in the relation between FI and neurophysiological index.

3. Results

As expected, patients with SPMS were older than patients with RRMS ($p = 0.009$) and had higher EDSS values ($p < 0.001$). Consistent with previous studies, the neurophysiological index differed between RRMS (0.19 ± 0.19) and SPMS (0.92 ± 0.07) ($p < 0.001$). The FI was also significantly higher in patients with SPMS (0.27 ± 0.09) than in patients with RRMS (0.14 ± 0.10) ($p = 0.02$). Both FI ($\rho = 0.6$; $p = 0.008$) and neurophysiological index ($\rho = 0.7$; $p = 0.001$) correlated with EDSS.

A statistically significant, positive correlation between FI and neurophysiological index values was observed ($\rho = 0.5$; $p = 0.03$) (Figure 1).

4. Discussion

The positive correlation between the neurophysiological and frailty indices in patients with MS suggests that both reflect similar pathophysiological mechanisms involved in the progression to SPMS. Higher frailty levels and abnormalities in the considered neurophysiological measures may capture those neurodegenerative processes that underlie the progressive course of the disease. Abnormalities in both neurophysiological and frailty indices may depend on the involvement of gray matter (3, 6). This conclusion is also supported by MRI evidence of higher gray matter loss in patients with SPMS as compared to those with RRMS (12).

The correlation between FI and neurophysiological index also provides a more comprehensive understanding of the role of these candidate biomarkers in MS. For instance, the present observation that FI and neurophysiological index correlate in MS suggests that the age-related accumulation of health/biological deficits (as expressed by FI) is associated with neurophysiological changes that intervene at cortical level, thus reflecting neurodegenerative rather neuroinflammatory processes. This provides a neurobiological substrate to the previously documented role of frailty on MS clinical expression.

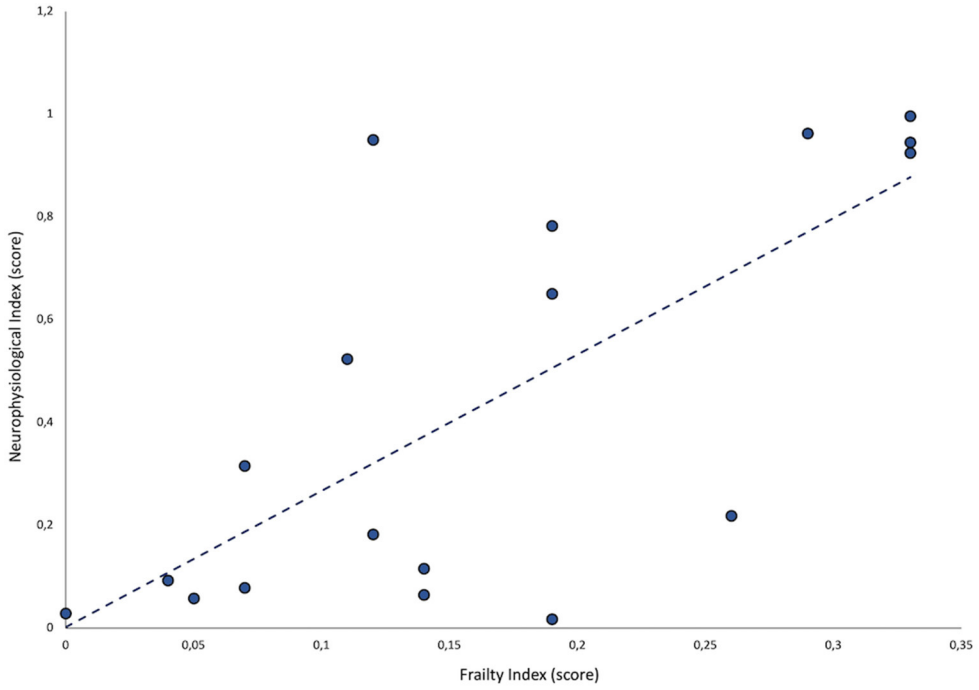

FIGURE 1
Correlation between neurophysiological index (NI) score and frailty index (FI) score.

The cross-sectional design constitutes the main limitation of the present study. The correlation that emerged between the neurophysiological index and FI should be interpreted with caution, and follow-up longitudinal investigations are needed to clarify their mutual relationship.

To conclude, we suggest the assessment of neurophysiological and frailty indices as objective markers in identifying patients at risk of disease progression. Future longitudinal investigations in naïve patients with MS are needed to demonstrate the predictive value of the frailty and neurophysiological indices in identifying RRMS-to-SPMS transition.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Sapienza University of Rome Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: AC, DB, and MC. Investigation: MT, LM, VB, GF, and GL. Writing—original draft: MT, MC, and DB. Writing—review and editing: MC, DB, AB, and AC. All authors approved the final version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Vilija Jokubaitis,
Monash University, Australia

REVIEWED BY
Timothy Coetzee,
National Multiple Sclerosis Society,
United States
Bianca Weinstock-Guttman,
University at Buffalo, United States

*CORRESPONDENCE
Roberta Lanzillo
✉ roberta.lanzillo@unina.it

†These authors have contributed equally to this work and share first authorship

‡These authors have contributed equally to this work and share last authorship

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Aging in multiple sclerosis: from childhood to old age, etiopathogenesis, and unmet needs: a narrative review

Nicola Capasso[1,2†], Eleonora Virgilio[3†], Antonio Covelli[4], Beatrice Giovannini[5], Matteo Foschi[6,7], Federico Montini[8], Martina Nasello[9], Annacarmen Nilo[10], Elio Prestipino[11], Giuseppe Schirò[12], Silvia Sperandei[13], Marinella Clerico[14‡] and Roberta Lanzillo[1,2*‡]

[1]Department of Neuroscience, Reproductive Sciences and Odontostomatology, Federico II University of Naples, Naples, Italy, [2]Multiple Sclerosis Unit, Policlinico Federico II University Hospital, Naples, Italy, [3]Neurology Unit, Department of Translational Medicine, AOU Maggiore della Carità Novara, University of Eastern Piedmont, Novara, Italy, [4]Department of Neurology, Santi Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy, [5]Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [6]Department of Neuroscience, MS Center, S. Maria delle Croci Hospital, AUSL Romagna, Ravenna, Italy, [7]Department of Biotechnological and Applied Clinical Sciences (DISCAB), University of L'Aquila, L'Aquila, Italy, [8]Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy, [9]Neurology Unit, Department of Neurosciences, Mental Health and Sensory organs (NESMOS), Sapienza University of Rome, Rome, Italy, [10]Clinical Neurology Unit, Department of Head, Neck and Neurosciences, Santa Maria della Misericordia University Hospital, Udine, Italy, [11]UOSC Neuro-Stroke Unit, AORN Antonio Cardarelli, Naples, Italy, [12]Section of Neurology, Department of Biomedicine, Neurosciences and Advanced Diagnostics (BiND), University of Palermo, Palermo, Italy, [13]Section of Neurology, Department of Medicine and Surgery, University of Perugia, Perugia, Italy, [14]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

Multiple sclerosis (MS) primarily affects adult females. However, in the last decades, rising incidence and prevalence have been observed for demographic extremes, such as pediatric-onset MS (POMS; occurring before 18years of age) and late-onset MS (corresponding to an onset above 50years). These categories show peculiar clinical-pathogenetic characteristics, aging processes and disease courses, therapeutic options, and unmet needs. Nonetheless, several open questions are still pending. POMS patients display an important contribution of multiple genetic and environmental factors such as EBV, while in LOMS, hormonal changes and pollution may represent disease triggers. In both categories, immunosenescence emerges as a pathogenic driver of the disease, particularly for LOMS. In both populations, patient and caregiver engagement are essential from the diagnosis communication to early treatment of disease-modifying therapy (DMTs), which in the elderly population appears more complex and less proven in terms of efficacy and safety. Digital technologies (e.g., exergames and e-training) have recently emerged with promising results, particularly in treating and following motor and cognitive deficits. However, this offer seems more feasible for POMS, being LOMS less familiar with digital technology. In this narrative review, we discuss how the aging process influences the pathogenesis, disease course, and therapeutic options of both POMS and LOMS. Finally, we evaluate the impact of new digital communication tools, which greatly interest the current and future management of POMS and LOMS patients.

KEYWORDS

multiple sclerosis, aging, pediatric-onset, late-onset, immunosenescence, risk factors, unmet need, engagement

1. Introduction

Multiple Sclerosis (MS) is a chronic, inflammatory, immune-mediated disease of the central nervous system disease (106). MS is one of the most relevant causes of neurological disability in young people, with an important social and economic impact (38). An early diagnosis is crucial for managing MS evolution and reducing morbidity and long-term effects (103). MS has a multifactorial etiology; young females are the most affected population (with a peak incidence between 20 and 40 years old). However, MS can emerge in all age groups, including pediatric patients (pediatric-onset MS, POMS), corresponding to children before 18 years of age (2–10% of total cases), and after 50 years of age (late-onset MS, LOMS; with a prevalence ranging from 1.1–21.3% of cases depending from cut-offs and diagnostic methods considered) (82). These demographic extremes present different clinical and pathogenetic characteristics (71).

The clinical phenotype of POMS differs from adult patients. POMS patients generally experience a more aggressive disease onset with disabling clinical symptoms, a polyfocal presentation at disease onset, and a higher relapse rate early in the disease course (60). In recent decades, evidence confirmed that early axonal damage in MS patients contributes to clinical disability and progression from early disease stages (113). In POMS, acute axonal injury following inflammatory demyelinating lesions is more pronounced than in the adult counterparts (89). In contrast, LOMS patients are more likely to convert in secondary progressive phases, suggesting that they may experience a more evident chronic axonal loss associated with physiological aging (1, 111). Children are less likely to develop primary or secondary progressive MS, and 98% of POMS present with a relapsing–remitting (RR) course, compared with 84% of adult patients and 50% of LOMS (3).

POMS and LOMS are also challenging during the diagnostic workup. For POMS, it is essential to rule out other disorders that may mimic MS and demyelinating syndromes that can occur more likely than MS in childhood, such as mog-associated disease (MOGAD) and acute disseminated encephalomyelitis (ADEM) (10). POMS must not only be differentiated from acute ADEM or MOGAD, but there is also an extensive list of other disorders that can mimic MS, which need to be excluded. Such diseases include neuromyelitis optica spectrum disorder (NMOSD), systemic lupus erythematosus (SLE), neurosarcoidosis, Sjögren syndrome, leukodystrophies, hereditary metabolic diseases, and encephalitic or meningoencephalitis infectious etiologies. Inflammation of the brain during critical developmental periods, including myelinogenesis in adolescence, may irreparably damage neural networks involved in cognition. This damage may also lead to the reduced brain and deep gray matter volumes in adulthood reported in POMS relative to sex- and age-matched patients with AOMS independent of disease duration (73). Several studies have demonstrated that individuals with POMS have slower disease progression than their adult-onset counterparts, particularly during the early stages of the disease. This discrepancy may suggest greater plasticity, less neurodegeneration, and potentially more repair and remyelination in the younger nervous system (4).

In the last decades, the average age of MS patients has progressively increased, as well as the number of patients with LOMS or very late onset MS (VLOMS, onset after 60 years of age) (13, 71, 102, 112). The yearly incidence of LOMS and VLOMS represents 3.4–4.8 and 0.5% of all new diagnoses (50, 91, 112). Moreover, an increasing number of young MS patients are getting older, along with the general population trend (71, 112). Better diagnostic accuracy, longer life expectancy, and the introduction of specific disease-modifying treatments (DMTs) are among the factors leading to the growing number of older MS patients (112).

The management of older MS patients represents a clinical and therapeutic challenge, and the risk of misdiagnosis is higher than in younger patients. This is mainly due to the higher prevalence of comorbidities and immunosenescence. Indeed, the clinical onset of older MS patients is generally characterized by motor symptoms (101) potentially sharing similar features with deficits from other neurological disorders (i.e., cerebrovascular diseases) prevalent in older age. In addition, LOMS patients are more frequently male and tend to have a progressive form of the disease (8, 68). Moreover, long disease duration is associated with a worse prognosis in old MS patients (85). Some radiological and laboratory biomarkers such as spine involvement (usually spared in vascular diseases), the presence of lesions in the septum callosum (typical of MS), and the presence of oligoclonal bands in cerebrospinal fluid could be helpful to support MS diagnosis in older patients (20).

Finally, demographic extremes, POMS and LOMS, have different clinical, pathogenic, and prognostic characteristics, with 16% of LOMS reaching a score of 6 in the Expanded Disability Status Scale (EDSS), compared to the 15% of POMS (82). Thus, the clinical management, therapeutic approach, and social engagement of these two groups of patients are completely different.

Here we present a narrative review discussing how the aging process influences the pathogenesis, disease course, and therapeutic options of both POMS and LOMS. Finally, we evaluate the impact of new digital communication tools, which greatly interest the current and future management of POMS and LOMS patients.

2. Pediatric-onset multiple sclerosis patients

2.1. Genetic background

Several pieces of evidence support the contribution of genetic factors in the onset of POMS (Figure 1). Moreover, some of the variants identified as possible genetic risk factors increase the susceptibility to the onset of the disease during the pediatric age and to the onset in adulthood, suggesting that the two forms of MS share similar and superimposable biological processes (42). Human leukocyte antigen (HLA) genetic variants and non-HLA variants extend the risk of developing MS in childhood (42). However, mainly the HLA molecules, among these, those of class II, confer a greater genetic susceptibility. Not surprisingly, the polymorphisms of the classic risk factor for adult MS HLA–DRB1*15:01 are also associated with an increased risk of developing the disease in childhood, although a greater association is described for adult-onset MS (7). The HLA-DRB1*03 allele was also identified - for the first time in a population of pediatric MS patients of Greek origin - as a genetic risk factor compared to healthy controls and adult MS patients. In particular, its presence identifies patients with greater inflammatory disease activity and more relapses, mainly with the involvement of the thoracic spinal cord (43). The HLA-DP alleles, although less studied

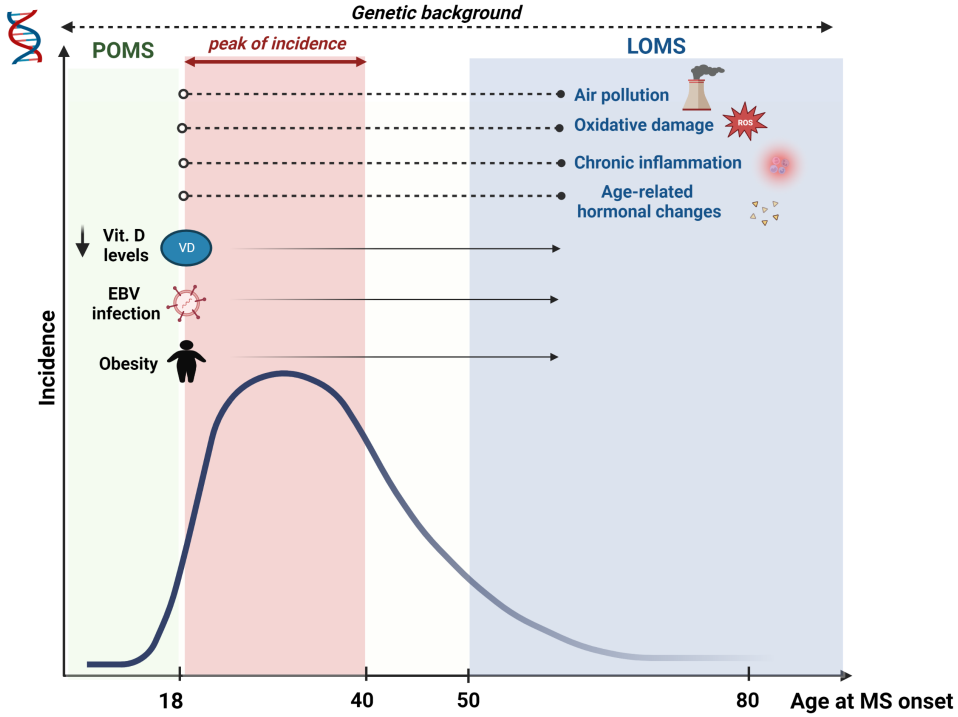

FIGURE 1
Multiple Sclerosis (MS) incidence and effects of risk factors according to the age of onset. MS incidence gradually increases from childhood, peaking between the second and the fourth decade. Subsequently, a gradual decrease is seen with aging. Several risk factors have been associated mainly with POMS (MS onset <18years), although their effect persists even in older ages (i.e., obesity, low blood vitamin D levels, viral infections, especially EBV). Other risk factors have been mainly associated with LOMS (MS onset >50 years), including air pollution, oxidative damage, chronic inflammation and hormonal changes. Although impacting on MS risk since childhood, the exposure to these factors may imply a longer time to increase the risk of developing MS. Lastly, genetic background influences MS risk throughout the lifetime.

than HLA-DR alleles, seem involved in the pathogenetic mechanisms of the disease. In particular, HLA-DPB1*03 allele, already known as allele risk for adult MS, plays a role also for pediatric MS, while the HLA-DPB1*04 allele has shown a protective role for the onset of the disease in both adults and children (6). Furthermore, it is unclear whether the known genetic susceptibility factors for disease onset may also influence the relapse rate. A genotyping analysis by Graves and collaborators on 181 patients from two pediatric MS centers in the United States found no association between the number of relapses and genetic risk score for non-HLA genes. Instead, HLA-DRB1*15 was found to modify the association of vitamin D status with relapse rate (44). It should be noted that many of the biological processes that play a decisive role in the onset of MS, including pediatric MS, result from complex gene–environment interactions. According to this view, the disease emerges from genetic susceptibility under the impulse of one or more environmental exposure factors. For example, the risk of pediatric MS associated with high levels of environmental pollutants in the air appears to be greater in patients carrying the GG genotypic variant of the single nucleotide polymorphism rs928264 (G/A) within CD86 or in patients with HLA polymorphisms DRB1*15:01 (119).

In conclusion, although several genetic variants have been identified as susceptibility factors for the onset of MS, each of these individually plays a marginal role in the development of the disease, and perhaps more genes participate together in increasing the risk of the disease. This would lead to considering both pediatric and adult-onset MS as a polygenic disease. Furthermore, the final expression of the disease is also the result of a complex interaction with environmental factors, whose phases and exact mechanisms are not yet fully known, and any future treatments should also consider this aspect.

2.2. Environmental factors

The environmental risk factors involved in the etiopathogenesis of pediatric MS are many, but for some of them, the data collected so far in the literature are few. Childhood obesity has often been proposed as an environmental risk factor in pediatric MS. A high BMI is associated with a higher risk of prepubertal and postpubertal pediatric MS in both boys and girls (26), and with a higher risk of MS onset in both females aged 7–13 years and in males between 8 and 10 years of age (80). A key role in the pathogenesis seems to be linked to increased leptin and pro-inflammatory cytokines (IL-2, IL-6, IFN-γ, and TNF-α) and reduced adiponectin levels in patients compared to controls (54, 84). Furthermore, obesity, through the dysregulation of Th17 and T-reg cell activity, could change the intestinal microbiome favoring the development of a pro-inflammatory environment (108). Furthermore, POMS may be less likely to consume sufficient iron compared to controls (87). Therefore, the promotion of a healthy diet and good weight control allows a modulation of the immune response in the pediatric age, potentially preventing chronic inflammatory diseases such as MS. Breastfeeding seems to constitute a protective factor for the development of pediatric MS in the perinatal period, data suggest a

potential reduction of autoimmune dysregulation and an increase in the activity of the immune system against pathogens. In this regard, proposing early breastfeeding, especially to women of gestational age with a family history of MS, would constitute a potential preventive therapy against the development of pediatric MS (46). In adults, low levels of vitamin D, due to a low sun exposure, which in its active form works by inhibiting the activity of inflammatory cells involving both vitamin D and non-vitamin D pathways, may increase susceptibility to MS, a finding not yet confirmed in children, although vitamin D levels are lower than the normal range in most pediatric MS patients (48, 79). Spending more time in the sun during summer may be strongly protective against developing POMS (100). In a previous meta-analysis, it was reported strong evidence for a casual and independent association between low serum concentrations of vitamin D and increased BMI and risk of POMS (41). Recent metagenomic analyses show an altered gut microbiome-related metabolic potential in POMS patients compared to controls, including higher breakdown of lipopolysaccharide molecules, higher prevalence of a methane producing pathway from *Archaea* and depletion of the lactate fermentation pathway, but lower resistant starch metabolism (76, 77). In a recent USA case–control study gut microbiota diversity was similar for POMS and controls, however at the gut-community-network level differences were observed, in particular POMS patients exhibited an overrepresentation of highly connected opportunistic pathogens, suggesting a possible contribute to MS pathogenesis (109).

Very recent works, using data from millions of US military recruits monitored over 20 years, proposes EBV as the leading cause of MS, showing that the risk increases approximately 32-fold after infection with EBV but does not appear to increase after infection with other viruses, even with a transmission mechanism similar to CMV (16). About that, EBV negative to positive seroconversion generally increases with age with a major incidence peak in early childhood and a second peak, especially for females, around puberty, coinciding with the approximate age of mononucleosis and with the highest female prevalence in MS (28, 34, 35, 63, 66, 81, 98). EBV infection is related to pediatric MS, and generally, all children with MS are EBV seropositive, whereas the positivity rate is considerably lower in healthy children (11, 15, 69, 86, 90). French authors in 2006 demonstrated an absence of correlation between an increased risk of the onset of MS after administration of the vaccine against the hepatitis B virus (HBV), nor between an increase in the relapse rate in a patient with a first episode of demyelinating disease of the CNS after HBV vaccination (74). The same authors then speculated on the risk of MS onset in childhood concerning exposure to secondhand smoke, which seems to be doubled compared to patients whose family members do not smoke and to be even higher in case of prolonged exposure aged 10 years or older (75). In the past, an increased susceptibility to MS has been described in patients with type I diabetes mellitus (DM). Data from American case–control studies show a 3- to 10-fold increased risk of developing MS in children of mothers with diabetes mellitus, particularly mothers who have had diabetes during pregnancy (44). Furthermore, a recent cohort study of newborns in Denmark from 1978 to 2008 observed a doubled risk of MS in children of mothers with pre-gestational diabetes compared with children of non-diabetic mothers (83). These data underline the importance of the anamnestic moment as an early opportunity to obtain such information even before conception so as to intercept the possibility of developing pediatric MS in this category of patients as soon as possible. However, it is still unclear today whether a common cause underlies both pathologies. However, there are no studies able to better define the intricate pathway involving OPN, Th17 cells and dendritic cells, which seems to link MS and type I DM.

2.3. Treatments for POMS

In POMS, relapse treatment is similar to the adult form of MS, consisting of high-dose steroids. Due to the high relapse rate and the improved recovery from relapses of POMS, early DMTs start is strongly recommended (23, 27). Low-efficacy DMTs available for POMS are interferon-β and glatiramer acetate. Although no randomized trials have been conducted, these drugs have shown adult-like efficacy and tolerance in various retrospective studies, and they have been at the base of treatment in pediatric patients for years (32). In case of failure or poor tolerability, high-efficacy DMTs should be considered. Several oral treatments are available in adult patients: Fingolimod, teriflunomide, and dimethyl fumarate. In US a multicenter study showed that initial treatment of POMS with this newer DMTs led to better disease activity control compared to injectables, supporting a greater effectiveness. However long-term safety data are still lacking (61). In POMS, the randomized trial PARADIGMS demonstrated an 81.9% efficacy of Fingolimod in reducing the annualized recurrence rate compared with IFNs and at least a 53% reduction in the annualized rate of new lesions on MRI (24). Furthermore, the greater efficacy of this drug has been highlighted in children than in adults, probably due to a greater inflammatory component of the juvenile form (29). Teriflunomide has been approved as a treatment in patients from 10 to 17 years old thanks to the data from the phase III, trial, TERIKIDS: the drug was well tolerated and had an excellent safety profile in this population (25). The two trials, FOCUS and CONNECTED, showed similar long-term safety and efficacy of dimethyl fumarate similar to the adult population, demonstrating that pediatric patients can benefit from this treatment (5). Natalizumab can be used in the case of very active diseases. Although not officially approved, various studies have shown excellent efficacy. Unfortunately, the risk of PML in children is not estimated due to the small samples that have been treated (40, 59). Clinical trials are currently underway on other highly effective drugs, including Ocrelizumab, Ofatumumab (anti-CD20) and Alemtuzumab (anti-CD52, LemKids trial) (52).

2.4. Engagement in POMS

In the management of POMS, it is essential an active involvement of the patient, the so-called "patient engagement," and his caregivers, usually represented by the parents. This main goal has to be pursued from the very first visits and at the communication of the diagnosis (2, 67). The days after MS diagnosis represents a time of great stress for families, and an overload of information could create confusion, misunderstandings, or false expectations. Therefore it is necessary to provide adequate personalized advice, easily understandable and exhaustive, for example, iconographic

stories. A better comprehension of the disease facilitates patient involvement (107). Due to the enormous impact of the disease, a multidisciplinary team composed of a neurologist, psychologist, and nurse who can meet the needs of patients and caregivers is essential. Adequate psychological support will be needed in dealing with the disruption of social life and family relationships. Therefore, it is important to encourage meetings between patients of the same age and between families of patients. Doctors must go beyond the simple medical care role by becoming a motivator. The young patient should feel part of a team that aims to fight the disease. The main weapons available are DMTs. In the past, injection therapy was the mainstay of treatment, with known and limited side effects. Otherwise, new, more effective, potentially dangerous oral drugs are now available. Therefore, the neurologist must debate the risk–benefit ratio with the patient and family members, encouraging their involvement in the decision-making process to choose the best treatment. Overcoming fear of therapy allows for avoiding harmful coping mechanisms in the future, encouraging better therapeutic adherence even in adulthood.

2.5. New communications tools: the digital

Our lifestyles and cognitive systems have changed throughout our evolutionary history, alongside human inventions, such as primitive tools, spoken language, writing, and arithmetics. Since the 1970s the Internet and the subsequent technological revolution have led to profound transformations of the human mind, thoughts and our way of life. In recent years the technological revolution has predictably reached the medical field as well, for example, in the field of cardiology, with FDA-approved devices to detect cardiac arrhythmias (95). Moreover, the current COVID-19 pandemic has further accelerated the technological transition in medicine and the role of telemedicine (78). Digital innovation is also emerging to monitor disease courses among patients with MS. A recent review (31) showed that digital technology has become part of clinical trials and was used to provide psychotherapy and motor rehabilitation with exergames, e-training, and robot-assisted exercises. Digital technology is particularly useful to standardize previously existing outcome measures, with automated acquisitions, reduced inconsistencies, and improved symptom detection (e.g., electronic recording of motor performance). Other clinical trials have used digital technology to monitor otherwise difficult-to-detect symptoms (e.g., fatigue, balance), to measure treatment adherence and side effects, and for self-assessment purposes. The collection of outcome measures is gradually shifting from on-site paper collection to Internet-based and, in the future, home-based Internet-based collection, with the detection of clinical and treatment characteristics that would otherwise have remained invisible. Similarly, remote interventions offer new possibilities for motor and cognitive rehabilitation. The role of technology in the therapeutic armamentarium to support MS patients appears to be of greater interest to pediatric patients, as they are more familiar than older patients with this latter. Examples included a recent trial that demonstrated the efficacy of an app in reducing stress and anxiety in POMS (22). Moreover, several studies explored the usefulness of digital technologies in POMS for motor exercise training program (114), physical activity and cognitive interventions (i.e., social-cognitive theory based) (70, 105).

2.6. Unmet needs: fears and confusions of POMS

POMS can be considered an "orphan" disease to all intents and purposes. Several studies have shown that there are still many unmet needs reported by children and adolescents affected by POMS, resulting not only from the physical and psychological effects of the disease in this specific age group but also from a lower availability of diagnostic and therapeutic information compared to the adult population (39). A recent meta-analysis analyzed 26 studies, including over 2,000 patients with POMS highlighting a profound negative impact on domains such as school performance, sociability and physical performance (39). Specifically, the lack of adequate knowledge of the disease has been reported as one of the main barriers experienced by patients with POMS in carrying out their daily activities, with important repercussions on the possibility of social integration. Several innovative ways have been proposed to improve communication between neurologists and caregivers to counter the sense of isolation that children and adolescents with MS often experience concerning the incorrect perception of being "different" from their peers due to illness. POMS patients, healthcare professionals and family members must adopt open communication, providing information in an age-appropriate and simple way. Taking the time to clearly explain the procedures, upcoming tests and treatments is essential to develop a comprehensive knowledge of MS, minimizing the risk of feeling confused and scared. From this point of view, modern technologies (i.e., telemedicine, online support groups) can represent a tool for sharing one's experiences and clarifying doubts and perplexities about symptoms, fears and personal expectations (65). Furthermore, constant psychological support, also aimed at family members, can reduce the negative impact of the pathology on the quality of life of patients with POMS and redefine a new balance in family relationships, especially in the months next to the diagnosis.

3. Late-onset multiple sclerosis patients

3.1. Genetic background and environmental factors

LOMS and VLOMS patients remain relatively under-investigated in the literature (92). The same risk factors for the adult MS population are probably responsible for the late forms. The duration and the onset of exposure to environmental factors could possibly influence the age at onset in MS patients (i.e., air pollution with exposure to PM10, PM2.5, and O3 or cigarette smoke later in life; Figure 1) (55, 57). However, these assumptions need further confirmation. MS is more frequent in adult females than males, but this gender difference appears less marked in LOMS patients (56), possibly related to hormonal variations. A study by Baroncini et al. highlighted a greater risk of disability progression after menopause (14), probably concerning age-related neurodegeneration phenomena (19). Since patients with LOMS have a greater chance of presenting a progressive phenotype and a lower relapse rate (30), it is possible to hypothesize that hormonal variation may influence the age at onset. However, specific literature in this regard is not currently available. Furthermore, a greater relapse risk for women in

the puerperium is known in the literature; a reduced birth rate could also be associated with a "delay" in time to the first clinical episode, thus postponing the clinical onset of the disease (57, 58). Some studies would then have indicated an increased risk of MS in men with low testosterone levels (117). Although age-related hormonal variations in men are not precocious and stereotyped, immunosenescence and hormonal factors may explain late onset in the male population. This area certainly deserves further investigation in the future. In contrast, the type of premorbid diet and the subsequent risk of developing LOMS was not shown to be associated in a large Danish registry study (92). Elderly patients also present numerous comorbidities more typical of the elderly subject, such as hypertension, dyslipidemia, and atherosclerotic processes with phenomena of chronic inflammation and oxidative stress, which could further influence the later onset of MS (64). The presence of such comorbidities might delay MS diagnosis in elderly patients; plus, evidence suggest that patients with vascular comorbidities will experience a faster progression. Finally, from a genetic point of view, while various studies have highlighted an earlier age of onset in association with several HLA alleles (for example, carriers of the HLA-DRB1*15 allele develop the disease earlier than non-carriers), few data are instead present for the patient LOMS and VLOMS (104). In an Australian study, the HLA-DRB1 *0801 allele was overrepresented in patients with LOMS, indicating a possible different genetic substrate even in late-onset patients (94).

3.2. Immunosenescence

Aging is a physiological process, typically occurring with the passing of the years, characterized by the progressive decline of bodily biological functions. This process is a major contributor to several comorbidities that frequently arise in the elderly (33). When this functional decline concerns the immune system, it is called immunosenescence. Modified proliferation and maturation of immune cells characterize immunosenescence and hempen the ability to develop an appropriate immune response. This leads to increased susceptibility to infection, improved autoimmune processes, and a worse response to vaccination (33). On the other hand, a compromised immune system causes a chronic inflammatory state, called "inflamm-aging," with an increased level of inflammatory cytokines, which increases the risk of morbidity in the elderly population (12, 96). Chronic infections, such as Epstein–Barr virus (EBV), and accumulated senescent cells are responsible for inflammation and increase inflammatory cytokines, growth factors, and autoreactive antibody levels.

The age-related changes in the immune system mainly involve the adaptive immune system compared to the innate immune system. Indeed, a lower number of T, NK, and B naïve cells and an altered balance between pro- and anti-inflammatory molecules are typical features of immune system aging (33). Moreover, telomerase activity is generally reduced, leading to cellular senescence, interrupted proliferation, and a higher level of cell death (96). On the other hand, less effective phagocytosis, degranulation, and production of reactive oxygen species (ROS) characterize the senescent innate immune system and are responsible for higher susceptibility to viral and bacterial infections.

3.2.1. Immunosenescence and MS

MS etiology is not fully known (80). Autoreactive CD4+ T lymphocytes, crossing the blood–brain barrier (BBB), infiltrating the CNS, and recognizing myelin antigens as not-self seems one of the pathogenetic determinants of MS. This process activates microglia and astrocytes, induces oligodendrocytes' apoptosis, and leads to demyelination and axonal loss (37). All MS patients, including POMS, are characterized by an early immunosenescence since disease onset, with shorter telomerase, thymic dysfunction, increased CD4+/CD28- T Lymphocytes and memory T cells levels, reduced number of naïve T cells, and less functional regulatory T cells (9). The immune system's premature senescence seems essential for the onset of MS and its progression (33). The evolution of the disease towards progressive forms and the progression independent of relapse activity (PIRA) is more tightly associated with immunosenescence and early neurodegeneration than with disease duration and patients' age (33). Moreover, sex has been reported to influence immunosenescence based on genetic, epigenetic, lifestyle, environmental, and social differences (19). For instance, the adaptive immune system tends to reduce its efficacy earlier in men (51). Hormonal changes are also important in MS progression (i.e., protective role in the third trimester of pregnancy and higher relapse risk in postpartum), as in immunosenescence. Estrogens, in fact, show neuroprotective effects in animal models of autoimmune encephalitis, binding beta receptors, activating oligodendrocytes, macrophages, and dendritic cells, and supporting remyelination and recovery from axonal loss (14). Thus, reduced estrogens level in menopause leads to reproductive, neurological, and immunological changes in MS women in the direction of a worsening of disease and disability (19).

3.2.2. Immunosenescence and elderly MS population

In the last decades, the number of LOMS and VLOMS has been growing, in line with the prevalence of elderly MS patients (17). Reduced cerebral plasticity and growth factor levels are typical of this population and lead to incomplete recovery from demyelination and diffuse axonal degeneration. Moreover, in the aging BBB, permeability increases, leading to a higher degree of inflammatory cells infiltrating CNS and facilitating astrocyte proliferation and glial scars development. This phenomenon contributes to incomplete recovery from demyelination and myelin debris clearance. The prevalence of progressive forms of MS is higher with increasing age (110). A higher number of B memory and plasma cells are typical of these forms and form lymphatic follicles. Increased numbers of memory B cells and plasma cells are characteristic of these forms and organize into meningeal ectopic follicles. In addition, with the transition to progressive MS, BBB permeability gradually decreases, leading to the compartmentalization of disease activity and significantly dampening therapeutic efficacy. Oxidative processes also increase and phagocytosis becomes much less efficient with aging. These mechanisms are responsible for progressive iron accumulation in the brain and in active chronic lesions called "smoldering lesions" (1, 62). These slowly expanding lesions are typical of elderly patients and are more frequent in long-term disease (1). Histologically, these are characterized by a central astrocyte scar and a peripheral rim of active macrophages full of iron and increased oxidative processes. Other radiological features of LOMS are global and regional cerebral atrophy (typical of grey matter), white matter lesion load atrophy (especially

of periventricular lesions, responsible for the accumulation of cerebrospinal fluid) and increased cortical lesions number (connected to higher cognitive disability) (20).

In summary, immunosenescence results in such biological and immune changes in LOMS that it can be considered a major determinant of increased disability in this population.

3.3. Treatments in LOMS and elderly patients: safety, discontinuation, and engagement

There is a lack of data on the safety and efficiency of DMTs in older people with MS (112). Patients over 55 are usually excluded from clinical trials (112). Therefore, it is very difficult to determine whether the treatments available for older people are safe and effective. Consequently, the decision to initiate DMTs in elderly patients should be carefully considered, considering the risks associated with the therapy and its limited efficacy. An Italian study on natalizumab-related Progressive Multifocal Leukoencephalopathy (PML) showed that older age at natalizumab (NTZ) start might be a risk factor for developing PML before 24 infusions (93). PML risk is probably related to a major susceptibility secondary to the immunosenescence process.

Regarding other DMTs, Fingolimod has recently been associated with cases of PML, and these also seem to have an age-dependent trend (45). Furthermore, PML in elderly patients appears to have a worse outcome in various studies: in fact, most fatal cases of PML are in elderly patients (99). Age-associated changes in humoral immunity reduce the ability to mount an effective antibody response, suggesting that age may represent an additional stratified risk for PML in patients treated with MS therapy (45). Higher age is also a risk factor for other types of infections: for example, a higher risk of VZV reactivation was seen in older patients receiving Fingolimod, Cladribine, Natalizumab, and Alemtuzumab (47). Cryptococcal meningitis also appears to have the same age-related trend in patients receiving Fingolimod (115).

Nevertheless, due to the wide clinical variation in this group of patients, it is essential to individualize the treatment. Schweitzer et al. (99) suggested that the benefits of high-efficacy DMTs could decrease with age. Weideman et al. (115, 116) also found that the efficacy of DMTs was negatively correlated with age. In another work, age over 53 predicted no efficacy of DMTs (88). Older patients present significant pharmacokinetic and pharmacodynamic differences compared to younger patients.

Moreover, in advanced ages, progressive forms are more prevalent than RRMS. Despite expanding the therapeutic arsenal in MS, only one drug is approved for treating the primary progressive forms (Ocrelizumab). This drug showed a 24% reduction in the risk of disability progression compared to the placebo (36). Mitoxantrone and Siponimod have shown positive results in secondary progressive forms (53, 72, 118), although evidence suggests that the benefit is most evident in patients with persistent inflammatory activity (72).

Another important factor to consider before starting a DMT is the risk of developing cancer in ancient people: actually, most of the studies on the current DMTs have not shown a real correlation between their use and a greater risk of developing tumors; however, due to the increased cancer risks in individuals of advancing age, the interactions of age, immunosenescence, and DMTs use needs further study (99).

An Italian study on naïve RR LOMS patients did not show statistical differences between injective and oral treatment regarding time to the first relapse, risk of disability, and treatment withdrawal (118). Another problem to discuss is the treatment discontinuation in light of the decreased efficiency and increased risk of DMT in elderly patients. Another important factor to consider in this type of patient is the treatment discontinuation problem. A recent study (53) highlighted how discontinuation of treatment in elderly and previously stable patients results in possible new worsening/progression of the disease. These findings are very interesting, considering the growing number of older patients with MS in recent years and the many uncertainties about how to treat them. As previously reported, it's generally accepted that older patients will benefit less from currently available DMTs. However, most studies involved ancient therapies; today, DMTs with better efficacy and safety profiles are available. The study, which involved adult patients of all ages, also found that disease worsening and progression resulting from therapy discontinuation were independent of patient age. The type of MS (RR versus progressive) also did not seem to influence disease progression. Notably, up to 40% of previously stable progressive patients showed worsening in disability after drug discontinuation. Recently, the ongoing DISCO-MS study evaluated discontinuation of DMT in participants aged 55 years or older, clinically stable (no relapses) for at least 5 years, and radiologically stable for three or more years. The study is probably the largest controlled study for DMTs conducted in MS patients older than 55. There is not a significant difference between treated and untreated patients regarding clinical activity and clinical worsening. Clinical relapses were particularly rare. An increase in the number of MRI lesions was highlighted in the group that stopped therapy: however, MRI changes involved a reduced number of new lesions (1 or 2 lesions), and numerous observational studies have shown that 1–2 new brain lesions on MRI scan after 1 year of therapy, are not associated with a significant risk of disability progression in the following 5–10 years. On the other hand, a higher number of lesions (3 or more new lesions), an active lesion or new relapses appear to correlate with significant disability progression. Thus, minimal evidence of new disease activity may be functionally acceptable in elderly patients after DMTs suspension. Therapy discontinuation is also a minor risk factor for elderly patients (over 55 years) with moderate disabilities. Interruption of therapy should be considered in patients with secondary progressive (SP) disease due to the poor therapeutic efficacy of most drugs in this disease stage. A retrospective study in patients with SPMS demonstrated that after discontinuation of INFβ or glatiramer acetate therapy, the rate of relapse and progression of disability remained similar to treated patients (18). In this context, it is now clear how it is essential to maintain a direct and one-to-one relationship between patient and neurologist in the therapeutic management of a chronic and complex pathology such as multiple sclerosis. It is known that older adults with MS are more likely to have a reduced health-related quality of life as a consequence of increased social isolation, the development of cognitive impairment, which, together with a physical disability, multiple comorbidities, and therefore to polytherapy, lead to a greater sense of dependence and "uselessness" (21).

Based on these considerations, an increasing number of Patient Health Engagement projects is emerging to guarantee shared treatment management (drug start and stop) and socioeconomic and

work aspects. One of the main challenges of the last years is increasing the patient's awareness of being a central point in the process of therapeutic decision. The active involvement of the MS patient should occur at any age through educational, listening, and empowerment programs. The purpose of these programs is to allow greater trust between doctor and patient and, consequently, greater autonomy and proactivity of the patient in the management of own lifestyle, health and care (97). The availability of new drugs, with their advantages and disadvantages, necessarily requires sharing the therapeutic choice, whether to start, continue or discontinue a drug, based on the single patient and needs. Several experts have reported how patients of MS appreciate direct and sincere communication, even when medical data are uncertain, resulting in better satisfaction of healthcare and so, greater adherence to the treatment (49).

Finally, in the elderly patient, it is essential to start a concomitant process of active involvement of caregivers (Caregiver Engagement), who play a fundamental and complementary role in the therapeutic, rehabilitative and social management of these patients.

4. Final remarks and conclusion

POMS and LOMS are two demographic extremes with different pathogenesis, clinical management, therapeutic approach, and social engagement. Both forms are the result of a complex gene–environment interaction, whereby the disease would emerge from a condition of genetic susceptibility under the impulse of one or more factors of environmental exposure. In this regard, both in POMS and above all in LOMS, immunosenescence could play an important role. There are many therapeutic challenges in these categories of patients and there is a lack of data on the safety and efficiency of DMTs especially in LOMS. However early DMTs start is strongly recommended and a multidisciplinary team that can meet the individual needs of the patient and caregivers is essential. A current challenge is the role of digital innovation in supporting the patient, especially POMS, not only in psychological and rehabilitation monitoring and support, but also in improving communication between the neurologist and the patient/family members, in a process of active involvement of patients and caregivers.

Author contributions

RL and MC contributed to conception, design of the study, and contributed in writing—review and editing the original draft. NC and EV organized the search literature. AC, BG, MF, EP, AN, FM, MN, GS, SS, NC, and EV wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Publisher's note

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EDITED BY
Alessandra Lugaresi,
University of Bologna, Italy

REVIEWED BY
Paolo Ragonese,
University of Palermo, Italy
Amin Zarghami,
University of Tasmania, Australia

*CORRESPONDENCE
Malthe Faurschou Wandall-Holm
✉ malthe.faurschou.wandall-holm@regionh.dk

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Socioeconomic status of the elderly MS population compared to the general population: a nationwide Danish matched cross-sectional study

Malthe Faurschou Wandall-Holm[1]*, Rolf Pringler Holm[1], Luigi Pontieri[1], Finn Sellebjerg[2] and Melinda Magyari[1,2]

[1]Danish Multiple Sclerosis Registry, Department of Neurology, Copenhagen University Hospital – Rigshospitalet, Glostrup, Denmark, [2]Department of Neurology, Danish Multiple Sclerosis Center, Copenhagen University Hospital – Rigshospitalet, Glostrup, Denmark

Introduction/objectives: Multiple sclerosis (MS) leads to physical and cognitive disability, which in turn impacts the socioeconomic status of the individual. The altered socioeconomic trajectory combined with the critical role of aging in MS progression could potentially lead to pronounced differences between MS patients and the general population. Few nations have the ability to connect long-term clinical and socioeconomic data at the individual level, and Denmark's robust population-based registries offer unique insights. This study aimed to examine the socioeconomic aspects of elderly Danish MS patients in comparison to matched controls from the general population.

Methods: A nationwide population-based study in Denmark was conducted, comprising all living MS patients aged 50 years or older as of 1 January 2021. Patients were matched 1:10 based on sex, age, ethnicity, and residence with a 25% sample of the total Danish population. Demographic and clinical information was sourced from the Danish Multiple Sclerosis Registry, while socioeconomic data were derived from national population-based registries containing details on education, employment, social services, and household characteristics. Univariate comparisons between MS patients and matched controls were then carried out.

Results: The study included 8,215 MS patients and 82,150 matched individuals, with a mean age of 63.4 years (SD: 8.9) and a 2:1 female-to-male ratio. For those aged 50–64 years, MS patients demonstrated lower educational attainment (high education: 28.3 vs. 34.4%, $P < 0.001$) and fewer received income from employment (46.0 vs. 78.9%, $P < 0.001$), and working individuals had a lower annual income (48,500 vs. 53,500€, $P < 0.001$) in comparison to the controls. Additionally, MS patients within this age group were more likely to receive publicly funded practical assistance (14.3 vs. 1.6%, $P < 0.001$) and personal care (10.5 vs. 0.8%, $P < 0.001$). Across the entire population, MS patients were more likely to live alone (38.7 vs. 33.8%, $P < 0.001$) and less likely to have one or more children (84.2 vs. 87.0%, $P < 0.001$).

Conclusion: MS presents significant socioeconomic challenges among the elderly population, such as unemployment, reduced income, and increased dependence

on social care. These findings underscore the pervasive impact of MS on an individual's life course, extending beyond the clinical symptoms of cognitive and physical impairment.

KEYWORDS

multiple sclerosis (MS), aging, income, education, socioeconomics, family, patient—centered care

1. Introduction

Over the last few decades, the mean age among patients with multiple sclerosis (MS) has increased (1, 2). This trend may be attributed to advances in diagnostics, the impact of disease-modifying therapies (DMT), improved supportive care enhancing prognosis, and a general increase in life expectancy in the general population. Another contributing factor is the rise in the incidence of late-onset MS, which includes individuals experiencing their first clinical symptom after the age of 50 (1, 2). This demographic shift is important as MS is primarily considered a disease of young adults. The approach to elderly patients is likely to be markedly different due to unique clinical characteristics, comorbidities, and daily life needs within this select patient group.

Traditional clinical parameters are limited in providing a comprehensive view of an MS population, as functional scores such as the Expanded Disability Status Scale (EDSS) have several shortcomings (3, 4). Consequently, socioeconomic factors become crucial in describing the state of patients with MS. These parameters directly impact patient's lives and are often more relatable for both patients and decision-makers, particularly when considering the long-term consequences of MS (5).

Universally, the general population's need for personal care and practical assistance increases with age (6). However, in a disease like MS, where disability accumulates over time, the interaction with age may further amplify this effect. It is thus essential to investigate the growing population of older patients with MS, especially given the high societal cost of caretaking for these patients (7, 8).

An MS diagnosis has also been shown to affect personal finances adversely. Patients with MS tend to experience reduced workability and the proportion of patients receiving disability pension or lacking labor-related income increases following an MS diagnosis (9–11). Our previous research has demonstrated that Danish patients with MS are at a higher risk of losing all income from earnings and face a much higher likelihood of receiving disability pension than healthy controls (12).

This study aims to describe multiple aspects of the aging population with MS, focusing on differences in employment, income, workability, and family-related outcomes in patients with MS over 50 years old by comparing them to matched individuals from the general population.

2. Methods

2.1. Study design and study population

We conducted a matched nationwide cross-sectional study in Denmark, with a reference date of 1 January 2021. From the Danish Multiple Sclerosis Registry (13) (DMSR), we identified all patients with a diagnosis of definite MS. To be included in the study, patients had to be above 50 years of age, alive, and living in Denmark at the reference date. We matched each patient to 10 controls from a 25% random sample of the entire Danish background population (excluding patients with MS) based on sex, exact age, ethnicity, and geographic region at the reference date. To investigate parental status, we constructed a population that included all children born to individuals from the MS population and the 25% random sample, selecting the children of all individuals enrolled in the study.

In addition, we performed a longitudinal sub-analysis on work-related measures that included all participants from the cross-sectional study aged between 50 and 64 years from 1980 to 2020. The cutoff at 64 years was due to the Danish state pension age of 65 years for people born before 1 July 1959. Since then, the state pension age has gradually increased to adjust for increased life expectancy and demographical changes, but the threshold at 64 years was set to reduce temporal selection bias. We collected their annual economic data for each integer age level within the specified age range. Subsequently, we created graphical representations, displaying the proportion of individuals receiving disability pension or having no income from employment and the annual income in euros for those with an income from work and were not receiving disability pension to analyze trends across age levels.

2.2. Data sources and variables

The unique personal identification code assigned to all Danish citizens or individuals with a permanent address residing in the country for more than 3 months enabled cross-linkage between registries on the individual level (14).

2.2.1. Clinical

The DMSR is a nationwide, population-based registry containing information on all patients with MS since 1948. Currently, data are obtained from each of the 13 MS clinics

distributed around the country and are entered directly into an online platform by clinicians. Since the introduction of DMTs on the Danish market in 1996, data entry on treated patients has been mandatory. The data are the basis for national clinical quality indicators ensuring a high degree of completeness and validity (15). The DMSR contains clinical data on demographic information, diagnostics, disease status, imaging, and more.

From the DMSR, we collected age, sex, age at clinical onset, current phenotype, latest EDSS score within 2 years, relapse activity, and time since the last clinical visit. We calculated disease duration as the difference in years between the onset and the reference date.

2.2.2. Socioeconomic

Socioeconomic and demographic information was collected from several national Danish population-based registries such as the Population Statistics Register (PSR), the Income Statistics Register (ISR), the Employment Classification Module (AKM), the Sickness Benefits Statistics Register (SBSR), the Danish Education Register (DER), the Elderly Documentation Register (EDR), the Immigrants and Descendants Register (IDR), the Danish Rational Economic Agents Model (DREAM), the Social Pensions Register (SOCP), the Cause of Death Register (CDR), the Historical Migration Register (VNDS), and the Register-based Labor Force Statistics (RAS). Through the Fertility Database (FER) we identified children of study participants from both the MS and general population. The nationwide registers have an expected coverage of 97% of the population and a high level of validity (16). For the cross-sectional study, all data were collected for 2020 except for work absence from SBSR, which was only available for 2019.

In Denmark, the municipality office functions as a local government authority. It provides a range of social services, including assistance with personal care (such as dressing, bathing, and toileting) and practical help (such as cleaning, grocery shopping, and laundry). The municipality conducts an individual assessment to determine the required level of support. Information about the services provided is reported to the EDR, from which we collected data on the weekly amount of personal and practical help.

From the AKM, we collected information about the occupational classification based on the International Standard Classification of Occupations (ISCO) to determine the primary source of income grouped as either "wage earner," "pensioner," "long-term unemployed," or "others." Long-term unemployed individuals are either unemployed for more than half a year or recipients of social security benefits, which is financial assistance provided to individuals who are unemployed or have a low income.

From the PSR, we collected cohabitation and marital status. Cohabitation was defined as living with another adult (18 years or older) or living alone.

We collected gross annual income from primary and secondary employment and benefits or allowances from the ISR. The income was subsequently adjusted using the net price index with 2015 as the reference year to account for inflation and allow for direct purchasing power comparisons.

From RAS, we collected information on working hours categorized as either "full-time" or "part-time." An individual was considered to be working full-time if they, on average, worked more than or equal to 32 h a week annually and part-time if they worked fewer than 32 h a week.

From SBSR, we collected information on the duration of long-term absence from work due to illness, with long-term defined as having 30 or more days of absence. In Denmark, an employer can receive public financial aid if an employee has 30 or more days of absence due to illness. As such, employers are highly incentivized to report long-term illness to the municipality office, but this registry does not ensure complete coverage.

From the DER, we collected the highest, completed education and converted it into three categories according to the International Standard Classification of Education (ISCED) classification (17): ISCED level 0–2, ISCED level 3–4, and ISCED level 5–8, corresponding to low, medium, and high educational levels. For an extended description of the ISCED classification and the translation from Danish to English terminology, see Supplementary Description 1.

From DREAM, we collected data on whether an individual had received a social transfer payment designated as "disability pension." In Denmark, disability pension is public support benefit provided to individuals whose work capacity is permanently and substantially reduced, rendering them unable to support themselves in the labor market. To apply for disability pension, a formal application must be submitted to the municipal office. The assessment process for eligibility involves an evaluation of the individual's work ability and potential for reskilling or receiving additional support for employment. A medical evaluation conducted by a healthcare professional is typically part of this process.

The structure of the disability pension system underwent a reform in 2003 to simplify and restrict access. Prior to 2003, the benefit was distributed across four levels, depending on the age of the individual and the degree of loss of working ability for individuals of working age (18–65 years). After 2003, the benefit was reduced to one level (adjusted for cohabitation) and was primarily granted to individuals between 40 and 65 years of age although exceptions for individuals under 40 years are permitted. In our study, we categorize the status of "receiving disability pension" binarily irrespective of whether it was granted before or after the 2003 reform.

2.3. Statistical analysis

Patient and control characteristics are displayed as frequencies with corresponding percentages, mean values, and standard deviation (SD) or median values with the 1st and 3rd quartiles. In the longitudinal analysis, we display the proportion of persons with disability pension and no taxable income (not mutually exclusive) and median annual income in euros with whiskers displaying the first and third quartile for those receiving a taxable income.

For the cross-sectional descriptive analysis, missing data are included as a missing category. For the longitudinal analysis, there was no missing data on disability pension. In the rare case of a patient missing a record for one or more income years in ISR

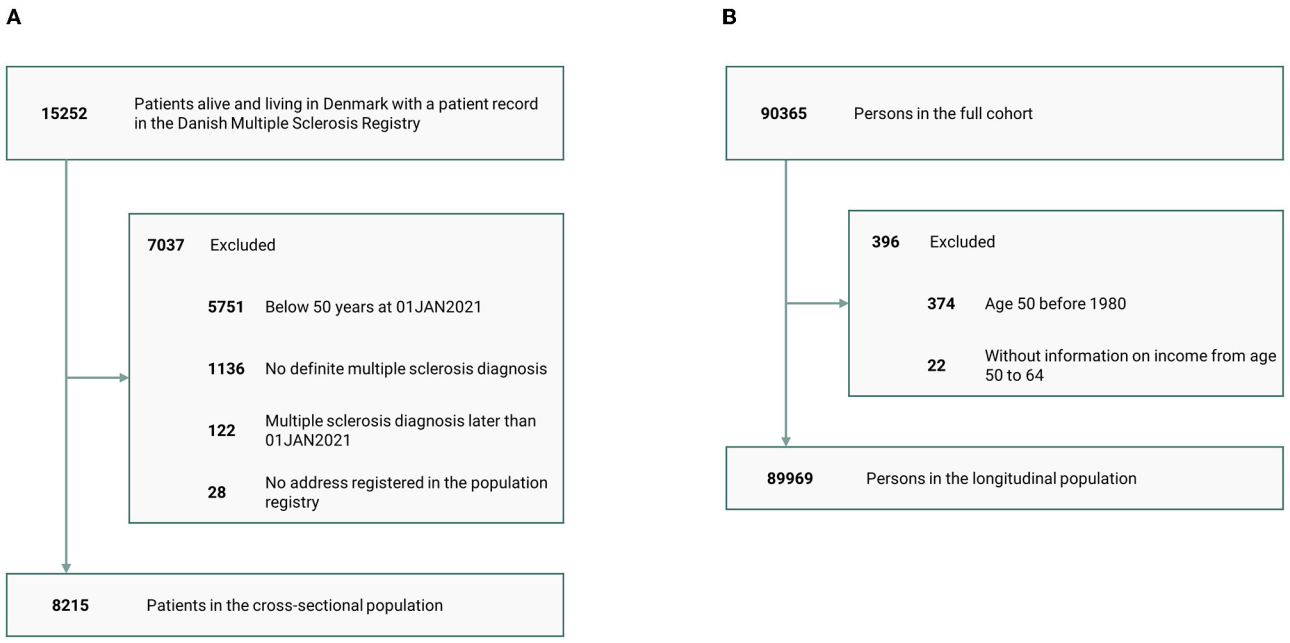

FIGURE 1
Patient disposition. **(A)** Cross-sectional study and **(B)** longitudinal study.

(present in 0.56% of patients), the years with missing information were disregarded.

For significance testing of differences between groups, multiple models were applied according to the outcome variable and accounting for the clustering of matches. For nominal outcomes, we used a Rao-Scott chi-square test. For all other outcomes, we used a generalized estimating equation: binary outcomes had a logit link function and ordinal outcomes had a multinomial distribution with a cumulative logit link, and for non-normally distributed continuous outcomes, we used a Wald-type rank test (18). *P*-values were adjusted for multiplicity by the Benjamini and Hochberg (FDR) procedure.

No sensitivity analyses were performed. Data management and table creation were carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and figures were created using R version 3.4.3.

2.4. Ethics, approvals, and data access

Informed consent or ethical approval is not a requirement for anonymized register-based studies in Denmark. The study is conducted under the Danish GDPR and registered at the Knowledge Center for Data Reviews, the data-responsible entity of the Capital Region of Denmark, approved by the Danish Data Protection Agency. Access to data is available upon qualified request.

All cells containing information from fewer than five subjects (or neighbors allowing cross-cell calculations) are censored to avoid personally identifiable data. Data preparation was performed on secure servers hosted by Statistics Denmark.

3. Results

A total of 15,252 patients in the DMSR were screened for eligibility, and 8,215 met the inclusion criteria and were enrolled in the study population (Figure 1A). Each patient was matched with 10 individuals, resulting in a control group of 82,150 individuals from the background population. The mean age of the entire population was 63.4 years (SD: 8.9) at the reference date with a female-to-male ratio of 2:1 (68.3% were female participants), and 99.2% were of Danish ethnicity. For patients who had an EDSS score recorded within the last 2 years, the median score was 3.5 (Q_1-Q_3 = 2.0–6.0); however, 44% (n = 3,585) did not have a recent EDSS assessment. See Table 1 for further characteristics of the MS population.

Table 2 presents the educational- and labor-related parameters. For individuals aged 65 years or older (mean age of 72.2 years), the difference in the educational level between people with MS and the controls was minor and not statistically significant. However, for patients younger than 65 years (mean age of 56.9 years), a greater proportion of individuals with MS had a low educational level (22.5 vs. 19.6%) and a medium educational level (48.8 vs. 44.9%), while a smaller proportion had a high educational level (28.3 vs. 34.4%). Overall, the education levels of both people with MS and the controls increased over time when comparing the two age groups.

Table 2 also highlights a significant difference in the proportion of people receiving income from work regardless of age. Among those under 65 years old, only 46.0% of people with MS received income from employment compared to 78.9% among controls. For individuals aged 65 years or older, the proportions were 5.9% for those with MS vs. 15.6% for controls. The primary source of income exhibited a similar pattern: among individuals under 65 years of

TABLE 1 Demographic and clinical characteristics of the MS population.

	MS population
Number of patients	8,215
Age, years, mean (SD)	63.4 (8.9)
Age at onset, years, mean (SD)	39.3 (11.2)
Disease duration, years, mean (SD)	24.1 (12.6)
Latest EDSS within 2 years, median (Q1–Q3), n_{miss}	3.5 (2.0–6.0), $n_{miss} = 3,585$
Time since last visit, years, median (Q1–Q3), n_{miss}	1.3 (0.4–11.5), $n_{miss} = 0$
Sex, *n* (%)	
Male	2,602 (31.7)
Female	5,613 (68.3)
Ethnicity, *n* (%)	
Danish	8,147 (99.2)
Other	68 (0.8)
Phenotype, *n* (%)	
RRMS	3,664 (44.6)
SPMS	2,043 (24.9)
PPMS	1,364 (16.6)
Unspecified	1,144 (13.9)
One or more relapses recorded in the last 2 years, *n* (%)	
Yes	449 (5.5)
No	7,766 (94.5)

EDSS, expanded disability status scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary-progressive multiple sclerosis.

age, only 39.7% of people with MS had "labor" as their primary source of income compared to 76.6% among controls. Conversely, 48.0% of the people with MS had "pension" as their primary source of income compared to 12.5% among controls. The overall trend persists among those aged 65 years or older though the differences were less pronounced.

Figure 2 presents results from the longitudinal analysis, allowing individuals to contribute data to each integer age (Patient disposition, Figure 1B). Figure 2A displays the prevalence of disability pension recipients among individuals aged 50–64 years with and without MS, illustrating a consistent relative difference throughout this senior working age. Figure 2B depicts the varying prevalence of individuals with no income from employment in the same age range for those with and without MS. This illustrates that among the control group, many individuals gradually stop receiving income from work without being granted disability pensions as they age. It is important to note that some individuals will be present in both figures, but not all.

Among individuals under 65 years of age who receive income from employment, we found a statistically significant difference in the median yearly income between those with MS and controls (48,500€ vs. 53,500€). Additionally, the proportion of people working part-time was more than double among people with MS (45.7 vs. 18.6%), and the percentage of people who had more than 30 sick days per year was also higher among the MS population (13.4 vs. 8.7%). Figure 2C illustrates the distinct median yearly incomes for individuals aged 50–64 years who have an income but are not on disability pension, displaying that the median income is slightly lower among people with MS across all age groups. However, if an individual with MS maintains income from employment, they follow a similar trajectory as the controls.

Table 3 presents information on municipal social services provided. Overall, the proportion of individuals receiving practical help or personal care increased with age when comparing those younger than 65 years to those older. In the under-65 age group, people with MS received practical help almost nine times more frequently than those without MS (14.3 vs. 1.6%). However, the amount of practical help received was similar (2.0 vs. 1.7 monthly hours). In the same age group, 10.5% of people with MS received personal care with a median of 18.3 monthly hours compared to just 0.8% of people without MS who received personal care with a median of 4.7 monthly hours. This trend persisted among individuals aged 65 years and older.

Table 4 presents family characteristics for the study population. People with MS tended to live alone more frequently (38.7 vs. 33.8%) and had a lower marriage rate (56.3 vs. 59.2%) compared to the control group at the reference date. Upon examining divorce prevalence, a difference between sexes emerged: male participants with MS had a higher proportion of divorce compared to male controls (18.9 vs. 15.8%), while this difference was not observed among female participants with MS (19.5 vs. 19.3%).

The proportion of people having children was lower in the MS population at 84.2% compared to 87.0% among controls. This difference was even more pronounced among female participants (85.7 vs. 89.1%) but less among male participants (80.7 vs. 82.6%). Among those with at least one child, the average number of children was nearly identical (2.1 vs. 2.2), and the parent's age at the birth of the first child was also similar (26.2 vs. 26.5 years), with male participants generally being older than female participants (27.9–28.5 vs. 25.4–25.6 years).

4. Discussion

In this Danish nationwide population-based study, we found significant socioeconomic differences between people with MS and the matched general population, such as reduced employment, lower earnings, and a higher reliance on social benefits. Various socioeconomic factors can serve as indicators of an individual's functional level, and we focused on education, employment, income, and family-related factors. Investigating socioeconomic outcomes is essential as MS typically has onset in early life, affecting individuals functionally and financially for the majority of their lives. Moreover, MS imposes considerable direct and indirect costs on society, especially evident in the growing proportion of elderly individuals in the MS population (19, 20).

In individuals younger than 65 years, the highest achieved educational level was lower in the MS population compared to the matched controls from the background population. However, for those aged 65 years or older, no difference in the educational level was observed between the two groups. Generally, both the MS and control population had lower education levels among those aged

TABLE 2 Socioeconomic parameters in the MS and the matched population.

	<65 years			≥65 years		
	Background	MS	*P*-value	Background	MS	*P*-value
Number of persons	50,040	5,004	–	32,110	3,211	–
Age, mean (SD)[a]	56.9 (4.2)	56.9 (4.2)	–	72.2 (5.7)	72.2 (5.7)	–
Educational level[b], *n* (%)						
ISCED 0–2 (low)	9,804 (19.6)	1,128 (22.5)	<0.001	10,074 (31.4)	1,048 (32.6)	0.08
ISCED 3–4 (medium)	22,473 (44.9)	2,443 (48.8)		13,285 (41.4)	1,345 (41.9)	
ISCED 5+ (high)	17,233 (34.4)	1,414 (28.3)		8,470 (26.4)	808 (25.2)	
Missing	530 (1.1)	19 (0.4)		281 (0.9)	10 (0.3)	
Primary source of income, *n* (%)						
Wage earner	38,311 (76.7)	1,987 (39.7)	<0.001	3,309 (10.3)	135 (4.2)	<0.001
Pensioner[c]	6,280 (12.5)	2,400 (48.0)		28,597 (89.1)	3,060 (95.3)	
Long-term unemployment	3,737 (7.5)	541 (10.8)		127 (0.4)	10 (0.3)	
Other	1,712 (3.4)	76 (1.5)		77 (0.2)	6 (0.2)	
Receiving income from work[d], *n* (%)	39,495 (78.9)	2,301 (46.0)	<0.001	5,008 (15.6)	189 (5.9)	<0.001
If receiving income from work[d]						
Number of persons	39,495	2,301		5,008	189	
Annual income in €, median (Q1–Q3)	53,500 (41,000–68,000)	48,500 (25,000–63,500)	<0.001	20,000 (3,000–49,500)	15,500 (2,000–45,500)	<0.001
Full time or part-time, *n* (%)						
Full time	28,286 (71.6)	1,032 (44.9)	<0.001	1,379 (27.5)	37 (19.6)	0.05
Part time	7,352 (18.6)	1,051 (45.7)		1,853 (37.0)	60 (31.7)	
Missing	3,856 (9.8)	218 (9.5)		1,776 (35.5)	92 (48.7)	
More than 30 days of absence	3,438 (8.7)	309 (13.4)	<0.001	219 (4.4)	8 (4.2)	0.93

[a]Matching variable.
[b]The highest completed education converted into three categories according to the International Standard Classification of Education (ISCED) classification: ISCED level 0–2, ISCED level 3–4, and ISCED level 5–8, corresponding to low, medium, and high educational levels.
[c]For the age group <65 years, this is mainly disability pensions (>95%), but also a few other minor early retirement pension schemes.
[d]Additionally not receiving disability pension.

65 years or older compared to those under 65 years. This finding implies that people with MS may have benefited less from the overall increase in educational levels observed in recent decades. A potential explanation for the observed divergence in educational levels between the populations above and below 65 years of age could be the increased cognitive demands associated with higher education levels. As a result, the cognitive impairment and fatigue commonly experienced by MS patients might hinder them from maintaining pace. Nevertheless, previous studies from other countries have reported mixed findings on this subject. Some found no differences in the educational level between the MS population and the background population (21), while other studies reported a higher educational level among people with MS (22, 23). The observed variations might result from important differences in data sources and study designs: discrepancies could arise from different data structures and classification of socioeconomic indicators (such as grouping of educational levels). Additionally, one of the studies only matched on age and sex and did not account for reported differences in ethnicity or geographical factors (22). The other two studies did not consider sex, age, ethnicity, or geographical differences when comparing the MS population, which had a highly specific composition of characteristics, to more general populations (21, 23). Furthermore, when conducting inter-country comparisons, it is crucial to consider differences in access and funding for education up to the university level. In Denmark, education is provided free of charge, and all residents are entitled to student grants. Moreover, if a person is disabled, the state offers additional financial and social support.

People with MS demonstrated a weaker connection to the labor market with a significantly lower proportion receiving income from employment and a lower proportion employed full-time. Additionally, a higher percentage of people with MS had over 30 days of absence or received disability pension. Among those receiving income from employment, people with MS had lower annual earnings in 2020. However, when examining temporal trends, the difference in earnings showed considerable year-to-year fluctuations (Supplementary Figure 1). Numerous studies have investigated employment-related outcomes, revealing a wide range of differences due to variations in data sources, study sizes, and social systems across countries. A study conducted in New

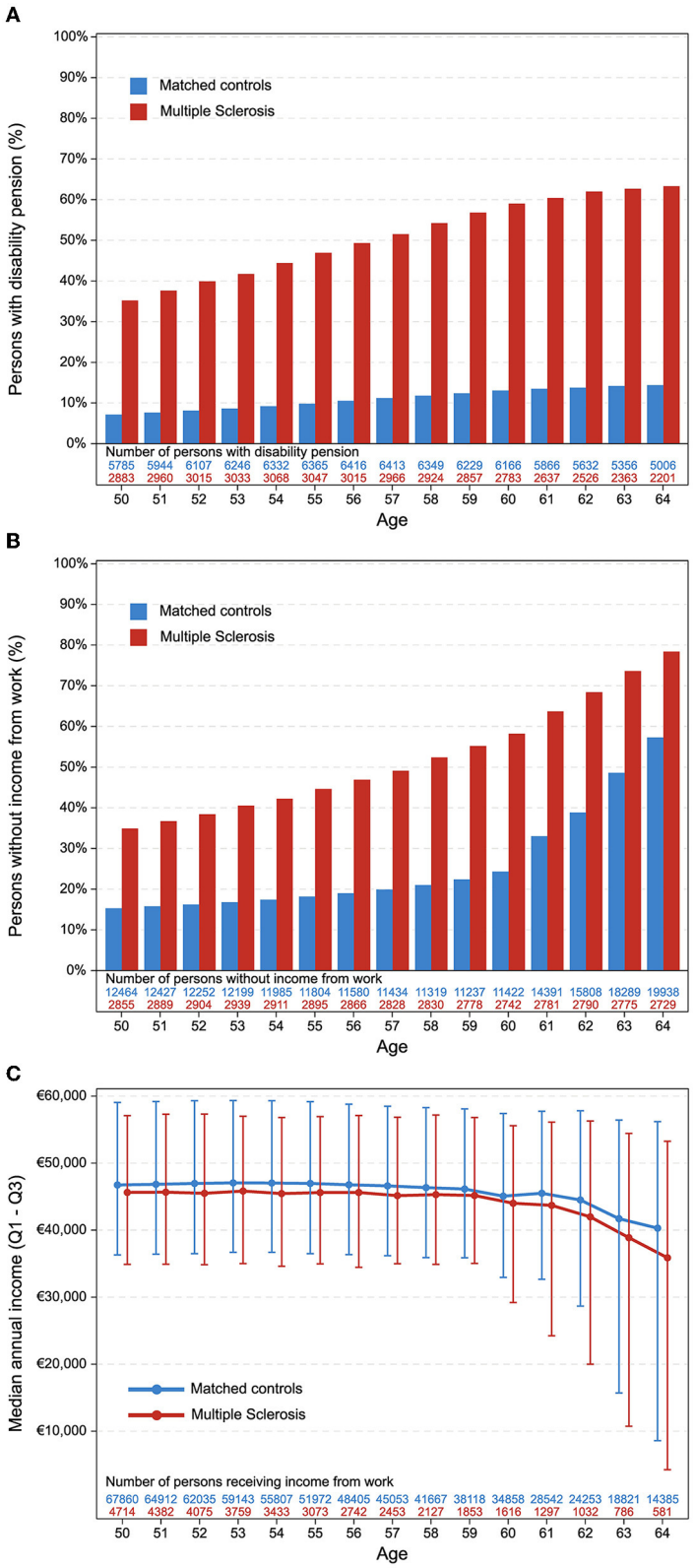

FIGURE 2
Longitudinal analysis. All panels display variable distributions according to age and group with "number of persons" at the bottom indicating the number of individuals in each data point. **(A)** Persons with disability pension. **(B)** Persons without income from work. Individuals can be present in both **(A, B)**. **(C)** Median annual income for persons with an income. Individuals can only contribute data to **(C)**, if not present in **(A)** or **(B)** (i.e., do not have disability pension and do have income from work).

TABLE 3 Municipal services provided.

Population	<65 years			65 years or more		
	Background	MS	*P*-value	Background	MS	*P*-value
Number of persons	50,040	5,004	–	32,100	3,210	–
Practical help, *n* (%)	777 (1.6)	715 (14.3)	<0.001	2,361 (7.4)	909 (28.3)	<0.001
If yes, hours, median (Q1–Q3)	1.7 (0.8–2.4)	2.0 (1.3–3.8)	<0.001	1.7 (0.9–2.6)	2.1 (1.3–4.2)	<0.001
Personal care, *n* (%)	376 (0.8)	524 (10.5)	<0.001	1,552 (4.8)	866 (27.0)	<0.001
If yes, hours, median (Q1–Q3)	4.7 (1.2–13.7)	18.3 (4.3–52.0)	<0.001	3.7 (1.0–11.6)	21.4 (5.2–61.8)	<0.001

Zealand demonstrated a significant disparity between the MS population and the general population (23), and a Danish study from 2010 found that among those receiving disability pension, the median time to obtain it was 10 years for MS patients and 24 years for controls (11). It is important to note that the eligibility criteria for disability pension are subject to temporal variations in accordance with contemporary implementations of social policies. All previous studies investigating income-related outcomes in MS patients showed pronounced differences when compared to the general population. A previous Swedish study indicated a 28% difference in the proportions of people with MS and those without, receiving income from employment (39 and 67%, respectively) (24). Income is strongly linked to disability and serves as an indicator of the clinical progression of MS. One study reported that individuals with higher levels of physical disability were more likely to receive social benefits and less likely to have earnings (25). However, the lower cognitive function has been reported to affect income independently from a physical disability level, revealing the shortcomings of the EDSS in capturing the comprehensive picture of the patient (26).

Assessing income and employment outcomes can offer valuable insights into the effectiveness of treatment strategies. Data from the DMSR have demonstrated that early treatment can lower the risk of disability pension among patients with RRMS (27). Another DMSR study showed that a clinically stable disease course was associated with a decreased risk of losing income from salaries and a reduced risk of disability pension, emphasizing the importance of adequate treatment (28).

People with MS received more practical help and personal care assigned by the municipality than the matched individuals from the background population. This not only underlines the difference in accumulated disability in the two populations but also exemplifies why MS caretaking is associated with high economic costs, as also shown in previous studies (7, 8, 19, 20). A person's need for practical help and personal care can also impact close relatives. We found differences in family-related parameters among people with MS compared to controls. They were more likely to live alone, and a lower proportion was married at the reference date. Our results also confirmed previous findings that male participants with MS were more likely to be divorced compared to the background (29, 30).

Parenthood was also affected as a smaller proportion of people with MS had children; however, the difference in the number of children between parents with MS and without MS was negligible. One possible explanation is that the average age at first childbirth is lower than the average age at MS onset resulting in many individuals having established a family before receiving the MS diagnosis. Furthermore, the recommendations on family planning have undergone significant changes over the past few decades. In the past, women were advised not to have children, while contemporary women with MS are encouraged to pursue parenthood due to increasing possibilities for treatment and strong evidence that pregnancy does not interact adversely with the course of MS (31, 32).

This study has several limitations primarily due to its cross-sectional design. The cross-sectional design does not allow for the establishment of causal relationships between variables, and the obtained results may differ if the study were conducted at a different time (reference date) as this design does not take temporal changes into account. Consequently, we cannot project the future trajectory of the observed differences between people with MS and controls from the background population. Furthermore, all comparisons between the two groups are univariate and unadjusted for potential confounders, apart from the matching covariates.

When investigating working ability, the study lacked specific data on the nature of the participants' employment, which limits the ability to provide a more nuanced understanding of what contributes to differences in working ability. A previous Danish study showed that the likelihood of early pension for patients with physical work was 26% higher than that of patients with non-physical jobs (11).

Another limitation of the study is the generalizability of socioeconomic differences among individuals with MS as these differences are largely dependent on the comparability of social systems and societal structures across different countries. However, socioeconomic characteristics have been shown to be robust outcome measures, indicating that MS can have broad adverse consequences on various areas of life. When investigating the development of socioeconomic measures over a longer period, changes in social legislation should be taken into consideration which further complicates comparing results from different countries. Therefore, while the study provides valuable insights into the socioeconomic differences among individuals with MS, it is essential to consider the unique contexts of each country when interpreting the findings and comparing them to other studies conducted in different countries.

The strength of this large study lies in the completeness of data and the possibility to link Danish nationwide registries at the individual level. By matching on age, sex, ethnicity, and geographical region, the study was able to remove possible biases associated with these covariates. Adjusting for ethnicity is

TABLE 4 Family characteristics.

	Full population			Female			Male		
	Background	MS	*P*-value	Background	MS	*P*-value	Background	MS	*P*-value
Number of persons	82,150	8,215	–	56,130	5,613	–	26,020	2,602	–
Cohabitation, *n* (%)									
With another	54,368 (66.2)	5,034 (61.3)	<0.001	35,966 (64.1)	3,385 (60.3)	<0.001	18,402 (70.7)	1,649 (63.4)	<0.001
Alone	27,782 (33.8)	3,181 (38.7)		20,164 (35.9)	2,228 (39.7)		7,618 (29.3)	953 (36.6)	
Marital status, *n* (%)									
Married (+ separated)	48,655 (59.2)	4,629 (56.3)	<0.001	32,282 (57.5)	3,080 (54.9)	<0.001	16,373 (62.9)	1,549 (59.5)	<0.001
Divorced	14,951 (18.2)	1,589 (19.3)		10,843 (19.3)	1,096 (19.5)		4,108 (15.8)	493 (18.9)	
Unmarried	11,494 (14.0)	1,259 (15.3)		7,009 (12.5)	816 (14.5)		4,485 (17.2)	443 (17.0)	
Widow(er)	7,050 (8.6)	738 (9.0)		5,996 (10.7)	621 (11.1)		1,054 (4.1)	117 (4.5)	
Has at least one child, *n* (%)	71,502 (87.0)	6,913 (84.2)	<0.001	50,020 (89.1)	4,813 (85.7)	<0.001	21,482 (82.6)	2,100 (80.7)	0.02
If yes, number of children, mean (SD)	2.2 (0.9)	2.1 (0.9)	<0.001	2.2 (0.9)	2.1 (0.8)	<0.001	2.2 (0.9)	2.2 (0.9)	0.01
If yes, parent age at first child, mean (SD)	26.5 (5.3)	26.2 (5.0)	<0.001	25.6 (5.0)	25.4 (4.7)	<0.001	28.5 (5.4)	27.9 (5.3)	<0.001

important as the background population in Denmark includes a significant proportion of 12% foreigners and descendants (compared to 0.8% in the Danish MS population), who may have different characteristics such as educational level, income, and family structure but also a different susceptibility for MS (33). Socioeconomic data, obtained from public registers, can capture other aspects of the disease such as fatigue and cognition, which physical disability measured by EDSS may not reflect. These data can serve as proxy parameters of disability or surrogate markers of the individual functional level.

In conclusion, MS can have a significant impact on the socioeconomical trajectory of an individual, which is particularly evident among elderly people with MS. This study highlights differences across multiple socio-economic domains such as education, employment, and family status. Therefore, when considering the comprehensive wellbeing of a patient, socioeconomic outcomes are important and robust measures of disability and individual function level. These measures reflect the broader consequences of MS on a person's life, extending beyond physical disability and providing a more holistic understanding of the challenges faced by individuals with MS.

Data availability statement

The datasets presented in this article are not readily available because access to data is only available upon qualified request and approval by the Knowledge Center for Data Reviews (data responsible entity of the Capital Region of Denmark, approved by the Danish Data Protection Agency) and the Danish Multiple Sclerosis group. Requests to access the datasets should be directed at: www.dmsr.dk.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MW-H and MM conceived and designed the study. MW-H and RH wrote the first draft of the manuscript. MW-H, RH, and LP were responsible for statistical analyses. RH, MM, and FS did the review of concurrent medical literature. All authors assisted in the study design, were involved in the interpretation and final review of the data, drafting, or revising the manuscript for intellectual content, and approved the final version.

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Conflict of interest

MW-H has served on scientific advisory board for Sanofi and has received honoraria for lecturing for Novartis and Sanofi. RH has served on scientific advisory board for Novartis and has received honoraria for lecturing for Novartis and Sanofi. FS has served on scientific advisory boards for, served as consultant for, received support for congress participation or received speaker honoraria from Alexion, Biogen, Bristol Myers Squibb, H. Lundbeck A/S, Merck, Novartis, Roche and Sanofi Genzyme. His laboratory has received research support from Merck, Novartis, Roche, and Sanofi Genzyme. MM has served in scientific advisory board for Sanofi, Novartis, Merck, and has received honoraria for lecturing from Biogen, Merck, Novartis, Roche, Sanofi Genzyme, and Bristol Myers Squibb.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1214897/full#supplementary-material

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EDITED BY
Kristen Marie Krysko,
St Michael's Hospital, Canada

REVIEWED BY
Omar Al-Louzi,
Cedars Sinai Medical Center, United States
Antje Bischof,
University Hospital Münster, Germany

*CORRESPONDENCE
Jodie R. Gawryluk
✉ gawryluk@uvic.ca

†These authors have contributed equally to this work

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How does the brain age in individuals with multiple sclerosis? A systematic review

Nataliya Tokarska[1†], Isabelle Tottenham[2†], Charbel Baaklini[3] and Jodie R. Gawryluk[4*]

[1]Department of Anatomy, Physiology and Pharmacology, University of Saskatchewan, Saskatoon, SK, Canada, [2]Department of Clinical Neurosciences, University of Calgary, Calgary, AB, Canada, [3]Department of Neuroscience, University of Alberta, Edmonton, AB, Canada, [4]Department of Psychology, University of Victoria, Victoria, BC, Canada

Multiple Sclerosis (MS) is a complex neurological disorder that involves demyelination, lesions and atrophy in both white and gray matter. Such changes in the central nervous system are diagnostic in MS and has a strong relationship with both physical and cognitive symptoms. As a result, magnetic resonance imaging (MRI) scans as a metric of brain atrophy have emerged as an important outcome measure in MS studies. Recently, research has begun to focus on the contribution of aging to the structural changes in the brain associated with MS; prompting questions about whether there is an amplifying effect of aging superimposed on MS-related brain atrophy. To examine current evidence of how the brain ages in individuals with MS, a systematic review of the literature was performed. Specific questions were focused on how aging affects gray and white matter structure, whether patterns of brain atrophy differ in younger and older cohorts and if there are structural differences in the brain as a function of sex in aging people with MS. This review considered studies that used MRI to examine the effects of aging in adults with MS. Twenty-one studies met eligibility criteria. Findings across these studies revealed that gray matter atrophy was more pronounced in older adults with MS, particularly in subcortical regions such as the thalamus; that the rates of atrophy were similar but varied by region for younger and older cohorts; and that males may experience more brain atrophy than females. Further studies that use multimodal MRI acquisition methods are needed to capture changes in both males and females over time, particularly in middle to older adulthood.

KEYWORDS

multiple sclerosis, aging, magnetic resonance imaging, systematic review, brain

Introduction

Globally, the population is aging at an unprecedented rate (1). Given the shifts in population demographics, it is essential to better understand the neurobiological aging process in both healthy conditions and in people with neurological disorders. Recent research has used magnetic resonance imaging (MRI), a non-invasive and easily repeatable technique, to depict normative trajectories of aging in gray and white matter. Specifically, Bethlehem et al. (2) used MRI data from more than 100,000 brain scans to create brain charts revealing patterns of gray and white matter atrophy in both males and females throughout middle and late adulthood (age 40 years onwards). These findings were largely in line with previous research indicating that after the age of 40 years, overall brain volume begins to decline by a rate of 5% per decade,

with increased rates of decline at 70 years onwards (3–6). These are expected changes in the brain with normative aging. Although a better understanding of the neurobiological underpinnings of aging is being developed, relatively less is known about how the brain changes with age in people with chronic neurological conditions, such as multiple sclerosis.

Multiple Sclerosis (MS) is an inflammatory demyelinating disorder which predominantly affects the central nervous system (CNS). Approximately 90% of MS cases initially present as relapsing–remitting (RRMS), with acute inflammation and demyelinating lesions associated with relapsing symptoms (7). Over time, the majority of people with MS (pwMS) develop secondary progressive symptoms (SPMS), and although less common, some individuals present with primary progressive symptoms from onset (PPMS). Notably, MS tends to affect women more than men at an approximate 3:1 ratio, although, men who develop MS tend to move toward progressive stages of the disease faster (8). Regardless of the subtype, MS is characterized by chronic and cumulative changes in the brain that are evident on magnetic resonance imaging (MRI) and represent a key diagnostic criterion. Specifically, diagnoses are based on MRI-detected lesions (which tend to occur in periventricular regions) disseminated in time and space, in conjunction with characteristic symptoms. From a research perspective, common MRI findings for pwMS include decreased whole brain volume, enlarged ventricles, and a measurable white matter lesion load, as well as a decreased white matter integrity on diffusion tensor imaging (DTI) (9). MRI metrics have emerged as important outcome measures in MS studies, given that brain atrophy and white matter lesions are strong predictors of motor impairment and cognitive dysfunction (10). Unlike many other neurological disorders, MS is typically diagnosed in young to middle adulthood. Yet, most pwMS live into older adulthood, with life expectancy at approximately 75 years (11). Along with the population as a whole, the proportion of older adults with MS is growing and many older adults with MS did not have access to disease modifying treatments at the time of their diagnosis (12).

Age is an important factor when considering the disease course of MS, especially given that pwMS over the age of 65 are more commonly in the progressive form of the disease (13). Reduced remyelinating capacity is observed independently in aging populations and in pwMS. It has been shown in animal models of MS that as age increases, oligodendrocyte precursor cells, the primary cells responsible for remyelination, have reduced capacity for differentiation into remyelinating oligodendrocytes (14). Further, iron accumulation and deposition are hallmarks of not only normal aging, but older pwMS tend to show exacerbated iron toxicity that can cause increased neurodegeneration (15). Additionally, it has been suggested that inflammation related to previous viral infections (e.g., Epstein–Barr virus) can result in decreased immune system function and reduced capacity for tissue repair (12, 16).

Essentially, emerging research has begun to focus on the contribution of normal aging to the structural changes in the brain associated with MS; prompting questions about whether there is an amplifying effect of aging superimposed on MS-related neurodegeneration. To examine current evidence, a systematic review of the literature that used MRI to examine aging in pwMS was performed. This is the first study to synthesize the literature on the effects of aging on brain structure in pwMS. The following questions were specifically examined and will be discussed in this review:

1. How does brain structure (e.g., volume, white matter microstructure) differ or change with age in pwMS?
2. Are there specific structural MRI findings in older pwMS compared to younger pwMS?
3. Are there structural differences in the brain as a function of sex in aging pwMS?

It was hypothesized that there would be differences in brain structure that were specific to pwMS beyond the changes associated with typical aging and that older pwMS would have greater whole brain atrophy than younger pwMS. Sex differences were examined because of the known differences in prevalence and progression of MS between females and males, although this question was purely exploratory.

Methods

Eligibility criteria

Specific eligibility criteria included studies that were peer-reviewed, in English, focused on adult (>18 years of age) human subjects and included an MS group (any subtype: RRMS, SPMS, PPMS) with full-text availability. Given the research questions of interest, studies must have also used MRI to examine brain structure. Any acquisition sequence was acceptable (e.g., T1-weighted, T2-weighted, diffusion weighted, FLAIR) because each provides different information about the brain. For example, T1-weighted scans can be used to examine gray matter volume, and diffusion-weighted scans can be used to examine white matter microstructure. Exclusion criteria included interventional studies and any studies focused on participants with other neurodegenerative conditions with comorbid MS. This review was registered on PROSPERO (CRD42021287667).

Search strategy

The literature search was conducted using two databases, PubMed and PsycINFO. Several preliminary search strategies were tested to determine the strategy that would be inclusive yet precisely able to identify papers of interest. The search strategy used a combination of terms relevant to the research questions and agreed upon by the authors (see Supplementary material for search terms in full). In summary, search terms included variables of interest including "aging," "multiple sclerosis," "white matter" "gray matter," and "MRI." Different variations of search terms were used to account for differing spellings and key words across articles. The reference sections of several articles were also screened to ensure that the search strategy was sufficient.

Screening strategy

Titles and abstracts of search results were extracted and uploaded into systematic review management software, Covidence. Duplicates were removed. An initial screening of the titles and abstracts was conducted based on the eligibility criteria stated previously to exclude

ineligible articles. The suitability of each article based on title and abstract was reviewed by two randomly selected authors (two of NT, IT, CB, JG) such that no more than one quarter of the articles were reviewed by the same two reviewers. Where disagreements occurred regarding eligibility of an article, a randomly selected third author would break the tie and determine the final eligibility of the article. Full-text articles were then uploaded and a second screening was conducted by two authors based on the entire research article using the same eligibility criteria. As per the initial screening, a randomly chosen third author resolved any conflicts.

Study quality ratings

To assess the quality of the articles included in this systematic review, the well-established critical appraisal tool for cross-sectional studies (AXIS) was used to rate each study. The AXIS tool uses a set of 20 questions that evaluate study design quality and quality of reporting. Studies were randomly assigned to authors, with each study assessed by a single author (one of NT, IT, CB, JG). Each study was assessed and interpreted for each of the 20 questions to evaluate its overall quality. To maintain consistency, both cross-sectional and longitudinal studies were assessed using the AXIS tool to rate the quality.

Data analysis and extraction

Studies were assigned to authors randomly (one of NT, IT, CB, JG) to extract relevant data. For each study, the information extracted included sample size, MS group subtypes at baseline, mean age at baseline, sex ratio, geography of study participants, study type (cross-sectional or longitudinal), acquisition/analysis measurement methods used in the study, and summarized results relevant to the research questions identified for this review.

Results

Systematic review

The search for studies was conducted on September 22, 2021. Initial search results yielded 318 studies. Covidence software automatically removed 133 duplicate studies based on titles. A total of 185 articles remained and their titles and abstracts were manually reviewed and screened further for inclusion and exclusion criteria, after which 144 irrelevant articles were excluded. Manual retrieval of full-text articles was conducted for the remaining 41 studies. These 41 full-text articles were then reviewed in-depth for inclusion. Each article was screened by two authors and any discrepancies for inclusion were resolved by a third author who was not involved in the initial voting for that article. Exclusions primarily resulted when studies did not have appropriate outcomes for this review (e.g., interventional studies, studies in which participants had concurrent neurodegenerative disorders, etc.). Supplementary Figure S1 details the papers that underwent full-text review but were ultimately excluded. The selection process is detailed in Figure 1 using a PRISMA flow diagram. A total of 21 studies published between 2003 and 2021 were included in the final review. Table 1 provides all the information extracted from the 21 full-text articles including sample size, MS groups, mean age, sex, geography, study type, acquisition/analysis, and summary of study results.

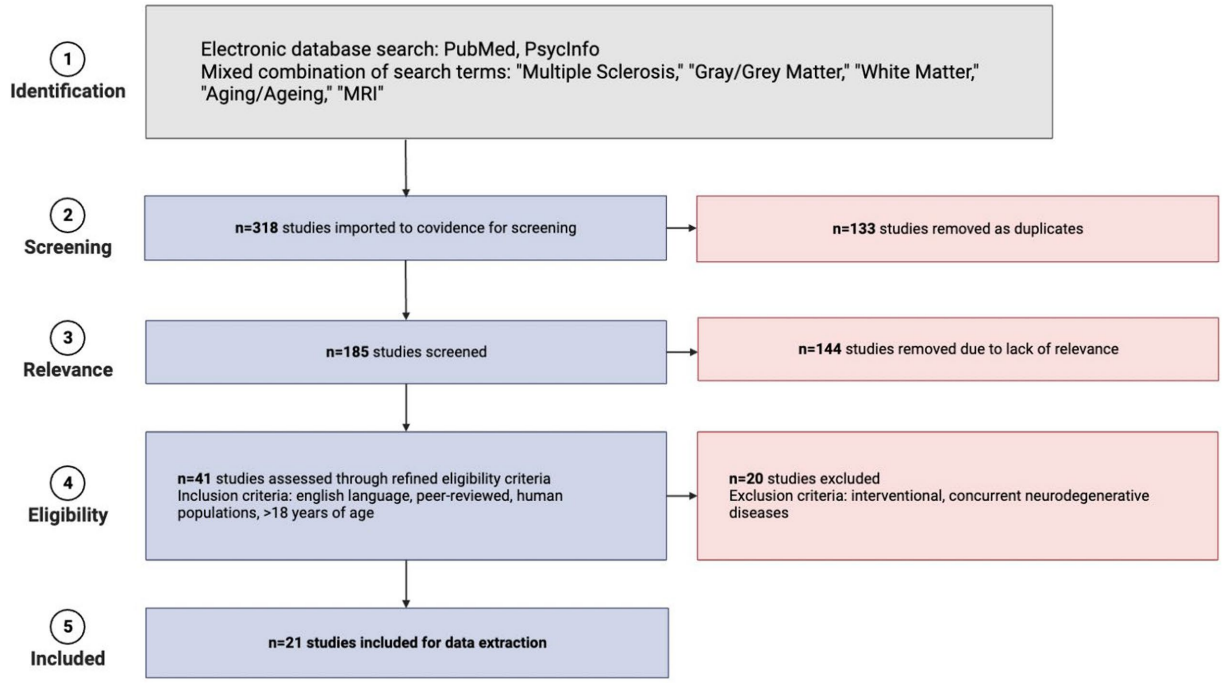

FIGURE 1
PRISMA flow diagram detailing the steps of literature collection for this systematic review (created in BioRender).

Study quality analysis

The AXIS tool (38) was used to assess study quality in both cross-sectional and longitudinal studies included in this review. Quality was assessed by 20 questions that allow for evaluation of any pitfalls that studies may have. Table 2 shows the breakdown of quality analysis across each of the 20 questions for the 21 included studies.

Main findings

Overall, 21 studies were included in the final analyses. A description of each study, including sample size, MS group breakdown, mean age and sex of participants, study geography, study type and duration, type of scans acquired/analyzed, and a summary of study results, are included in Table 1. The findings are discussed further in the context of the research questions guiding this review in the discussion section below.

Discussion

MS is a chronic neurological disorder that is characterized by lesions in the CNS and typically diagnosed in young to mid-adulthood. Relatively less research has focused on older adults with MS, although recent questions have emerged about whether there is an accelerated aging effect for pwMS. The current study involved a systematic review of the literature that used structural MRI methods to examine changes in the brain specific to aging with MS. This review considered cross sectional studies that examined differences between pwMS and healthy controls, as well as longitudinal studies tracking changes in the brain in pwMS over time with an aim to answer several specific questions. Herein, we pose each of the pre-determined questions along with conditional answers based on the extant literature.

How does the brain differ or change with age in pwMS?

With an aim to answer this overarching question, the search terms of the current review included both gray and white matter as well as specific imaging techniques, such as diffusion tensor imaging (DTI), which provides metrics of white matter microstructure. However, there were no studies that focused on white matter using DTI and although several studies examined total white matter volume, the vast majority of studies focused on gray matter volume using high resolution T1-weighted anatomical MRI scans.

Of the 21 identified studies, 13 compared pwMS and healthy controls and all of these revealed significant structural brain differences. Notably, some studies focused on broad metrics such as whole brain volume, while other studies extracted values representing gray and white matter volume or white matter lesion load. Several studies also extracted volumes for particular regions or carried out voxel-based morphometry analyses. Although there was variability in the regions examined across studies, 4 studies reported decreased whole brain volume in pwMS (27, 29–31, 39), 6 reported decreased gray matter volume (18, 24, 25, 29, 30, 36, 39), 6 reported decreased volume in subcortical gray matter structures (17, 18, 20, 24, 25, 29, 30) (particularly in the thalamus and basal ganglia) and 3 reported decreases in white matter based on volume or lesion load (19, 29, 30, 33). Notably, 6 of these studies examined how atrophy rates in healthy controls compared to pwMS. These studies suggested that pwMS showed accelerated rates of atrophy in the thalamus (17, 18) and other gray matter regions (24, 25, 39).

Three studies investigated predicted "brain age" using various algorithms and found that pwMS had significantly larger predicted brain age differences (higher biological age compared to chronological age) in comparison to healthy controls which also suggests accelerated aging in pwMS (22, 23, 28). Finally, a unique study from Krysko et al. (32) established that short leukocyte telomere length was associated with disability and brain atrophy (measured as total brain volume) in pwMS. The authors suggest that based on this finding, biological aging may contribute to disability worsening in MS (32).

Taken together, the studies included in this review provide evidence that supports acceleration of whole brain and gray matter atrophy as pwMS age when compared to normal aging in people without MS. Gray matter and subcortical regions including the thalamus appear particularly vulnerable to faster atrophy with age in pwMS as compared to healthy normal aging controls, although there were limited numbers of studies that focused on specific regions and on white matter which limits the conclusions that can be drawn from the literature.

Are there specific MRI findings in older pwMS compared to younger pwMS?

Of the 21 studies reviewed, 6 used MRI to examine brain structure differences in younger and older pwMS using a mix of cross-sectional and longitudinal approaches (18, 20, 21, 34, 35, 37). Using a cross-sectional approach, Newbould et al. (35) compared younger (30.4 years) and older (49.7 years) pwMS and found strong magnetization transfer ratio (MTR) differences between the two age groups within white matter lesions. This suggests decreased myelin integrity in the older age group. Bishop et al. (20) also took a cross-sectional approach and compared both younger (30.4 years) and older (48.7 years) pwMS to age-matched healthy controls. They found similar patterns of atrophy for each age group with MS in the putamen, thalamus and nucleus accumbens, but significantly more atrophy in the hippocampus and caudate in the younger group. A retrospective, cross-sectional approach was used by Tortorella et al. (37) to examine gadolinium-enhancing lesions in MS populations. They found that enhanced lesions were more frequently found in younger patients with lower disability. They also showed that the change in risk for gadolinium-enhancing lesions occurs at 35 years of age in pwMS. The authors proposed that these lesions may contribute to disease mechanisms in younger pwMS, whereas there are likely age-related neurodegenerative mechanisms occurring in older pwMS. Bove et al. (21) used a mixed design with a longitudinal component to examine changes in slopes of MRI extracted metrics including total brain volume and white matter lesion load over 2 years in pwMS who were under (younger group) or over (older group) 50 years of age (42 years and 58 years, respectively). The authors found no significant differences in slope of change as a function of age for either metric.

TABLE 1 Characteristics of papers included in this review.

Study	Sample size	MS groups (at baseline)	Mean age (years)	Sex (M:F)	Race/ Ethnicity	Expanded disability status scale	Disease modifying treatments	Geography	Study type (duration)	Acquisition (resolution of T1 scan provided)	Summary of results
Azevedo et al. (17)	520 MS/ CIS 81 HC	90 CIS 392 RRMS 38 SPMS	MS: 41.1 HC: 42.7	183:418	Not reported	Baseline: 1.8 (1.5)	22.3% no DMT; 77.7% up to 5 years of DMT	United States	LONG (4.1 years)	3T 3D T1-weighted 1 mm^3 resolution	Baseline thalamic volume reduced in pwMS compared to HCs. pwMS have significantly higher rates of thalamic atrophy compared to HC aging over time. Thalamic atrophy correlates with increase in disability. DMT use at baseline did not significantly impact the rate of thalamic decline.
Azevedo et al. (18)	520 MS/ CIS 130 HC	90 CIS 392 RRMS 38 SPMS	42.7	155:365	Not reported	Baseline: 1.8 (1.5)	22.3% no DMT; 77.7% up to 5 years of DMT	United States	XS LONG (5 years)	3T 3D T1-weighted 1 mm^3 resolution	GM structures are the top ranked regions of MS atrophy, including total GM volume, thalamus, putamen and caudate. Compared to HC aging, MS atrophy contribution seems to decrease from ages 30 to 60. In the thalamus, HC normal aging contribution to atrophy increases over time while MS contribution to atrophy decreases over time. In the putamen and caudate, HC aging and MS atrophy were more stable in their contributions to structural atrophy over time.
Baird et al. (19)	31 MS 22 HC	29 RRMS 2 PMS	MS: 63 HC: 63.7	11:42	83.9% Caucasian; 16.1% African American	4.0 (1.5)	22.6% no DMT; 77.4% yes DMT	United States	XS	3T 3D T1-weighted 1 mm^3 resolution	Mobility was significantly worse in older MS group compared to age-matched HC. There were no differences in GM volumes between MS and HC groups. Normal WM volume was significantly decreased and ventricular CSF was significantly increased in MS group, as compared to HC. In both groups, there was no correlation between brain atrophy or cognitive function with mobility.
Bishop et al. (20)	38 MS 52 HC	36 RRMS 2 SPMS	"Young" MS: 30.4 "Older" MS: 48.7 "Young" HC: 31.9 "Older" HC: 47.3	37:53	Not reported	"Young MS" 3.0 (1.2); "Older MS" 4.1 (1.3)	Not reported	United Kingdom	XS	3T 3D T1-weighted, FLAIR 1 mm^3 resolution	Brain volume loss in all MS groups compared to HCs was predominantly in the subcortical GM. Young and older MS groups showed similar, strong excess volume loss in the putamen, thalamus and nucleus accumbens, compared to HC aging. No excess volume loss was detected in the amygdala or pallidum. The young MS group also showed significant excess volume loss in the hippocampus and caudate compared to the young HC group.

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TABLE 1 (Continued)

Study	Sample size	MS groups (at baseline)	Mean age (years)	Sex (M:F)	Race/ Ethnicity	Expanded disability status scale	Disease modifying treatments	Geography	Study type (duration)	Acquisition (resolution of T1 scan provided)	Summary of results
Bove et al. (21)	551 MS/ CIS	481 RRMS/ CIS 26 PPMS 43 SPMS	"Young": 42 "Older": 58	140:411	Young 95.2% white; 3.6% Hispanic Older 95.4% white; 0.7% Hispanic	Young 1.42 (1.33) Older 2.39 (1.99)	Not reported	United States	XS LONG (2 years)	1.5T 3D T2-weighted 0.93 × 0.93 × 3 mm voxels	Whole brain atrophy increases with age in MS groups. Brain atrophy and disease severity was consistently higher in men compared to women in all MS groups. There were no significant differences between the young and older MS groups and no acceleration of decline with age. No interactions were found between age and sex.
Cole et al. (22)	1,204 MS/ CIS 150 HC	296 CIS 677 RRMS 111 SPMS 120 PPMS	MS: 39.41 HC: 37.29	501:853	Not reported	CIS 1.36 (1.02) RRMS 2.12 (1.40) SPMS 5.83 (1.20) PPMS 5.10 (1.32)	CIS 20% yes 79% no RRMS 53% yes 42% no SPMS 46% yes 47% no PPMS 7% yes 87% no	Netherlands, Catalonia, Switzerland, Austria, United Kingdom, Italy	LONG (HC: 1.97 years.; MS: 3.41 years) *retrospective*	1.5T and 3TT1-weighted Resolution not reported	MS group had significantly higher brain predicted age difference (brain-PAD) compared to HCs (10.3 years vs. 4.3 years). The highest brain-PADs were for people with SPMS (13.3 years). Higher brain-PAD reflect accelerated aging. Greater annual brain-PAD increases were also associated with higher disease severity.
Erramuzpe et al. (23)	10 MS 170 HC	Not stated	Not stated Age Range: 6–81 (10 HC children <18)	4:6	Not reported	Not reported	Not reported	United States	XS (HC) LONG (MS; 2 years)	3T 3D T1-weighted, FLAIR 0.93 × 0.93 × 3 mm voxels	Compared to HCs, MS group was predicted to have a higher biological age than their chronological age with the R1 (longitudinal relaxation based) age prediction method, even when only looking at normal appearing tissue. Differences between groups were revealed in parietal and occipital regions. The MS group also showed deficits in cortical thickness in midfrontal regions, compared to HC. The authors concluded that the MS group exhibited faster brain aging compared to HC aging.
Eshaghi et al. (24)	36 MS 19 HC	36 PPMS	MS: 42.8 HC: 37.6	34:21	Not reported	4 (min 1.5, max 7)	Not reported	United Kingdom	LONG (1,2,3,5 years)	1.5T 3D T1-weighted, T2-weighted 1.5 × 1.173 × 1.17 mm voxels	There was a marked progression of atrophy in several GM regions over time in the MS group compared to HC aging. Patients showed a greater decline of GM volume bilaterally in the cingulate cortex, thalamus, putamen, precentral gyrus, insula and cerebellum compared to HCs over five years. The progression of GM atrophy in the MS group occurs at different rates in different regions across the brain, with the fastest atrophy seen in the cingulate cortex and the slowest in the precentral gyrus. Some regions showed a significant volume loss at a later time point than other regions. There was a significant association between rate of volume loss in the cingulate cortex and worse clinical outcome at the five year time point.

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TABLE 1 (Continued)

Study	Sample size	MS groups (at baseline)	Mean age (years)	Sex (M:F)	Race/ Ethnicity	Expanded disability status scale	Disease modifying treatments	Geography	Study type (duration)	Acquisition (resolution of T1 scan provided)	Summary of results
Eshaghi et al. (25)	1,214 MS/ CIS 203 HC	253 CIS 708 RRMS 128 SPMS 125 PPMS	MS/CIS: 39.2 HC: 38.7	531:886	Not reported	CIS 1 (range 0–4.5) RRMS 2 (range 0–7) SPMS 6 (range 2.5–9) PPMS 5 (range 2–8)	CIS 20% yes RRMS 49% yes SPMS 41% yes PPMS 6% yes	Netherlands, Catalonia, Switzerland, Austria, United Kingdom, Italy	LONG (HC: 1.43 years.; MS/CIS: 2.41 years) *retrospective*	3T 3D T1-weighted, FLAIR 1 mm^3 resolution (varied slightly at different sites)	SPMS group had the lowest baseline volumes of cortical/deep GM (thalamus, putamen, globus pallidus, caudate, and amygdala) of all MS groups compared to HC. SPMS group showed a faster rate of temporal GM atrophy compared to RRMS, CIS and HC groups. SPMS group also showed faster parietal GM atrophy than the CIS group and HC. RRMS, SPMS and PPMS groups showed faster rates of deep GM atrophy and whole cortical GM compared to the CIS group and HC. However, deep GM rate of atrophy was higher than cortical/cerebellar GM and brain stem. Deep GM atrophy rate correlated with disability progression. SPMS and PPMS groups showed higher disability compared to RRMS and CIS groups.
Fisher et al. (26)	70 MS/CIS 17 HC	7 CIS 36 RRMS 26 SPMS	MS/CIS: 42.8 HC: 41.6	25:62	Not reported	CIS 0.86 (0.85) RRMS 2 (1.5) SPMS 5.39 (1.34)	Mean % time on DMT CIS 32.5% RRMS 77.6% SPMS 52.8%	United States	LONG (4 years)	1.5T T1-weighted, T2-weighted, FLAIR, PD 0.9 × 0.9 × 5 mm voxels	Whole brain atrophy and GM atrophy were accelerated in more advanced stages of MS. Increasing GM atrophy accounted for whole brain atrophy entirely as rates of WM atrophy were constant in all MS groups. There were no differences in atrophy rates between HC and the CIS group who did not convert to MS during the 4 years. Annual rate of change in volume of WM, GM and whole brain atrophy within all MS groups was not correlated with age but was positively correlated with disease severity. After adjusting for age, rate of GM atrophy in the RRMS and SPMS groups was significantly higher than HCs atrophy rate. This indicates that GM volume loss caused by MS accelerates over time.
Ghione et al. (27)	1982 MS 351 HC	1,530 RRMS 371 SPMS 81 PPMS	MS: 46.8 HC: 44.8	1718:615	90.3% Caucasian 8.9% African American 0.8% Other	Not reported	15.7% were not on DMTs at first MRI	Not stated	LONG (6 mons to 10 years) *retrospective*	1.5T and 3T 3D T1-weighted, FLAIR 1 mm^3 resolution	Development of brain atrophy manifests progressively in MS group, and occurs in a different pattern than that of HC aging. Percent lateral ventricular volume change (PLVVC) was increased across age in HCs as compared to MS group. Percent brain volume change (PBVC) decreased across age in both HC and MS groups.

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TABLE 1 (Continued)

Study	Sample size	MS groups (at baseline)	Mean age (years)	Sex (M:F)	Race/ Ethnicity	Expanded disability status scale	Disease modifying treatments	Geography	Study type (duration)	Acquisition (resolution of T1 scan provided)	Summary of results
Høgestøl et al. (28)	76 MS 3,443 HC (235 MRI data)	73 RRMS 1 SPMS 2 PPMS	MS: 34.8 HC: 47	1,028:2491	Not reported	Baseline median EDSS 2.0 (range 0–6)	22% were not on DMTs at first MRI	Norway	XS (HC) LONG (MS; 4.4 years)	1.5T 3D T1-weighted, T2-weighted, FLAIR; 3T 3D T1-weighted 1.2 × 1.25 × 1.25 mm voxels	On average, the MS group had a significantly higher brain age gap (biological brain age is older than chronological brain age) compared to HCs. In the MS group, compared to HCs, there was a high global brain age gap (4.4 years) and an even higher brain age gap (6.2 years) for subcortical/cerebellar brain regions. There was also an annual increase in brain age gap in the MS group. Progressive brain aging in the MS group was related with brain atrophy and WM lesion load (WMLL). Brain age gap and WMLL as well as brain age gap and global brain atrophy were shown to be positively correlated.
Jakimovski et al. (29)	2,199 MS/ CIS	192 CIS 1,554 RRMS 453 SPMS/ PPMS	46	548:1651	90.5% Caucasian 8.7% African American 0.8% Other	2.5 (IQR 1.5–4.5)	17.8% were not on DMTs	United States	XS	1.5T and 3T 3D T1-weighted, FLAIR 1 mm^3 resolution	Compared to age-matched females with MS, a greater proportion of males with MS were diagnosed with progressive MS and had lower whole brain volume, lower GM volume and increased lateral ventricular volume. These findings remained significant after correcting for head size, MS groups and treatment. The sex differences were not evident in individuals who were 60+ years old.
Jakimovski et al. (30)	112 MS 184 HC	59 RRMS 48 SPMS 5 PPMS	MS: 60.3 HC: 59.5	79:217	Not reported	3.5 (IQR 2.3–6)	Not reported	Not stated	XS	3T 3D T1-weighted, T2-weighted, FLAIR 1 × 1 × 3 mm voxels	The MS group had lower volumes compared to age-matched HCs in whole brain, WM, GM, deep GM, thalamus, caudate, putamen, globus pallidus and hippocampus, lateral ventricular regions.
Kassubek et al. (31)	33 MS 60 HC	33 RRMS	MS: 34.9 HC: 50.8	35:58	Not reported	Mean 2.4 (range 0–6.5)	Not reported	Germany	XS	1.5T T1-weighted, T2-weighted 1 mm^3 resolution	The MS group had significantly higher whole brain atrophy compared to age-matched HCs. Brain atrophy did also increase with age in HCs. In the MS group, whole brain atrophy was significantly increased in correlation with longer disease duration and higher disability.
Krysko et al. (32)	516 MS/ CIS	RRMS 367 CIS 80 SPMS 47 PPMS 17 PRMS 4 Unclear 1	42.6	160:356	Not reported	Median 1.5 (range 0–7)	29.3% were not on DMTs	United States	Observational LONG (5, 10 years)	3T 3D T1-weighted, T2-weighted, PD Resolution not reported	Shorter telomere length was shown to be associated with disability and brain atrophy (total brain volume) in the MS group, independent of chronological age and disease duration. The authors conclude that biological aging contributes to brain degeneration in pwMS and that individual variability in biological aging may contribute to heterogeneity in MS course.

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TABLE 1 (Continued)

Study	Sample size	MS groups (at baseline)	Mean age (years)	Sex (M:F)	Race/ Ethnicity	Expanded disability status scale	Disease modifying treatments	Geography	Study type (duration)	Acquisition (resolution of T1 scan provided)	Summary of results
Kuusisto et al. (33)	19 MS 19 HC	8 RRMS 8 SPMS 3 PPMS	51.6	12:26	Not reported	Monozygotic twins median 5.0 (range 2–7) Dizygotic twins median 2.5 (range 1–8)	2 monozygotic twins were on DMTs 5 dizygotic twins were on DMTs	Finland	XS *twin matched*	1.5T 3D T1-weighted, T2-weighted, FLAIR Resolution not reported	There were no significant differences found in brain and spinal cord volumes between twins in the MS group and their co-twins in the HC group. Results support that brain volume in twins is highly heritable. All twins in MS group had focal brain WM lesions and 3 had spinal cord lesions and 14 out of 19 fulfilled Barkhof MRI criteria. 9 out of 19 co-twins in the HC group had focal brain WM lesions but all lesions were significantly smaller than in the twins from the MS group and none fulfilled the Barkhof MRI criteria. There was no evaluation of associations between WM lesions and total brain atropy.
Martola et al. (34)	37 MS	16 RRMS 17 SPMS 4 PPMS	42	11:26	Not reported	Specific scores not reported, although EDSS was examined in relation to brain metrics	64.86% on Interferon treatment 35.14% Nontreatment	Sweden	LONG (7–10 years)	1.5T T1-weighted $0.9 \times 1.15 \times 5$ mm	There were evident linear annual decreases in brain volume, annual increases in left and right lateral ventricle volumes and linear annual increases in third ventricle volumes over the 4 decades of disease duration represented. There were no indications that differences between left and right ventricles would increase/decrease over disease duration. There was also no evidence of a specific timepoint altering brain atrophy or of acceleration or decline of atrophy over time. Corpus callosum atrophy and total brain atrophy were shown to be positively correlated with each other. There were no differences in atrophy patterns and no dependence on corpus callosum or ventricular size differences between MS courses. Disability increased with increases in atrophy rates of third and lateral ventricles. Older individuals showed larger ventricles at entry but rates of atrophy progression did not significantly differ from younger individuals.

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TABLE 1 (Continued)

Study	Sample size	MS groups (at baseline)	Mean age (years)	Sex (M:F)	Race/ Ethnicity	Expanded disability status scale	Disease modifying treatments	Geography	Study type (duration)	Acquisition (resolution of T1 scan provided)	Summary of results
Newbould et al. (35)	38 MS 11 HC	36 RRMS 2 SPMS	"Young" MS": 30.4 "Older" MS: 49.7 HC: 48.5	11:38	Not reported	Young 2.5 (range 2–6) Older 3.8 (range 2–6)	Not reported	United Kingdom	XS	3T 3D T1-weighted, FLAIR, MT 1 mm^3 resolution	Despite variable MS courses, brain atrophy seems to uniformly progress over longer periods of time. Normal aging of HCs from other studies in same age spans shows no signs of elevated age-related brain atrophy, but lack of HCs in this study limited the authors from determining how much MS disease added to annual brain atrophy rates caused by normal aging. Despite matching for disease duration and recording no significant WM lesion volume differences, there were strong magnetization transfer ratio (MTR) differences in WM lesions between the young and older MS groups. This implies that aging in MS exerts a direct negative effect on CNS myelin integrity in WM lesions that is reflected in MTR and also suggests that aging-related processes modify the tissue response to inflammatory injury and its clinical outcome correlates in MS.
Tiberio et al. (36)	21 MS 10 HC	21 RRMS	MS: 37.5 HC: 37.1	11:20	Not reported	Median 1 (Range 0–3)	7/21 participants started interferon B treatment in the first year	United Kingdom	LONG (2 years)	1.5T T1-weighted, T2-weighted, PD 1.2 × 1.2 × 1.5 mm voxels	A decrease in GM volume over 2 years was seen in the MS group, compared to HCs. There was no change observed in WM volume. However, WM volume change was seen with the MS group who had gadolinium-enhancing lesion loads. The authors concluded that GM atrophy but not WM atrophy was observed early in the clinical course of RRMS. Fluctuations in WM lesions are related to volume changes in WM over two years.
Tortorella et al. (37)	200 MS	172 RRMS 28 SPMS	35.3	81:119	Not reported	Median 2 (range 1–5.5)	No participants were on DMTs	Italy	XS *retrospective*	1.5T T1-weighted, T2-weighted 1.3 × 1 × 5 mm voxels	Frequency and number of gadolinium-enhancing lesions was higher in younger, less disabled individuals with MS with greater disease activity in the 2 years before MRI examination. Main changes in enhancement risk occurs after 35 years of age. In a previous study, they also had found a faster age-related rate of progression after a similar age. This supports that lesion burden and new inflammatory lesion formation in articulate parts of CNS are main pathogenetic mechanisms of disability in younger individuals with MS whereas neurodegenerative mechanisms might contribute to neuronal decline in older, higher disabled individuals with MS.

Includes, sample size, age, sex, geographic location, methods and results; XS, cross-sectional; LONG, longitudinal.
*Note that this study overlaps with Azevedo (17).

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Martola et al. (34) also used longitudinal observations to examine changes in brain volume at three time points over a decade in pwMS (ranging in age from 24–65 years) and found uniform progression of atrophy over time. Lastly, an interesting study by Azevedo et al. (18) examined annual MRI scans from 520 participants with RRMS over 5 years and found that the contributions of normal aging and MS-related atrophy differed by brain region. Findings revealed that the contributions of aging became greater with each decade from 30 to 60 years of age, while the contribution of MS-related atrophy lessened. In contrast, the contributions of aging and MS-related atrophy were relatively more stable over time in the putamen and caudate. These findings underscore the need for more comprehensive regional analyses to better understand patterns of brain atrophy in aging pwMS.

The various approaches to study design and analyses create challenges and limitations in synthesizing the results to date. Although there is some evidence that aging may have differential effects on brain atrophy in pwMS across the lifespan as compared to normal aging, more research is needed. In particular, the use of regional approaches in older age groups (e.g., 60+ years) that have not been well captured require further examination.

Are there structural differences in the brain as a function of sex in aging pwMS?

Typically, MS affects 3 times more females than males, although disability progression occurs quicker in males (40). Of the 21 studies included, 2 examined aging as a function of sex in pwMS (21, 29, 30). Although Bove et al. (21) did not find differences in rate of whole brain atrophy as a function of age, their findings did reveal significantly greater disease severity (based on EDSS scores) and whole brain atrophy in males compared to females. Further, Jakimovski et al. (29, 30) highlighted similar findings with males demonstrating lower whole brain and gray matter volumes as well as increased ventricular volume compared to females. However, this paper also showed that after the age of 60, there were no evident differences in brain structure between males and females with progressive MS (29, 30).

As evidenced by our literature search, there are a limited number of studies examining sex differences in aging pwMS. However, the evidence to date suggests that males have greater brain atrophy than females with age. One potential factor that may be attributed to the differences seen between sexes is menopause as it has been suggested to affect brain atrophy patterns in aging females with MS (41). Another factor may relate to the course of MS in males, as males have been shown to have more rapid disability accumulation and cognitive decline than females (42). More research including longitudinal studies that capture changes from age 40 to 60 in both females and males are essential to understanding the potential effects of sex on age-related atrophy over time and whether such differences are also stable over time.

Conclusion, limitations, and future directions

The current review represents the first synthesis of the literature examining brain aging in pwMS. It was hypothesized that there would be age-related differences in brain structure that were specific to pwMS and beyond the changes associated with typical aging, with older adults showing greater atrophy. Indeed, the literature revealed that cortical and subcortical gray matter are vulnerable to excess atrophy with age in pwMS. Predicted brain age was also consistently higher and atrophy rates were accelerated in pwMS compared to healthy controls. There were also indications that certain brain regions may become more prone to atrophy as pwMS age and that males may experience greater atrophy than females. However, more research is imperative to fully address each of the research questions posed in this review and there are several strengths and limitations within the current review, as well as within the literature that should be addressed.

With regards to the current review, strengths included the broad approach taken to search terms in combination with the focused questions on age related changes as measured by MRI in pwMS. The regional patterns and characteristics that influence brain atrophy for pwMS have important implications for clinical practice. In particular, understanding expected changes related to aging and whether there is accelerated neurodegeneration in MS can assist with interpretation of MRI findings for older adults with MS.

Conversely, a limitation was that studies examining correlations between structural brain changes with age and clinical variables were beyond the scope of the current review. Several studies that met the criteria for review happened to include comparisons of brain atrophy patterns and clinical outcomes (e.g., disease severity) with significant findings. Specifically examining such relationships between age related atrophy and symptoms of MS could form the topic of a separate focused systematic review.

Within the literature, the quality of the reviewed studies was consistently high. Assessment of study quality with the AXIS tool revealed that all of the studies in the current review clearly stated their objectives and designed their study appropriately, using proper outcome variables. The majority of studies were also clear on how significance was determined, and the conclusions made within each study were consistent with the presented results. The main limitations of the literature became apparent when synthesizing the findings. Specifically, there was heterogeneity in methods, including widely variable sample sizes (ranging from 19 to 2,199 pwMS), acquisition techniques (e.g., field strength, imaging sequences, parameters), analysis approaches (e.g., whole brain, gray matter volume, white matter lesion load, voxel-based morphometry, various brain age algorithms), and study designs (e.g., different age groups, study protocols) that yielded findings that are difficult to weigh and integrate across studies. As mentioned previously, there was a distinct lack of studies that examined aging pwMS using diffusion tensor imaging derived metrics of white matter microstructure. Given that changes in myelination and axonal integrity are characteristic of MS and that DTI is sensitive to both lesions and changes in normal appearing white matter, this technique could provide important information on the aging brain for pwMS. Additionally, in most of the included studies, the majority of participants had RRMS, although SPMS most commonly develops over the disease course of people with RRMS and should be better represented in studies on aging. Relatedly, people with different subtypes of MS may be more or less likely to be on disease modifying treatments (DMTs). Many, but not all, of the studies reviewed reported on DMTs, which was higher in people with RRMS than other subtypes. The differences

TABLE 2 AXIS tool responses to assess qualitative features of papers that were used in this review.

	Clear aims/ objectives?	Appropriate study design?	Sample size justified?	Target population defined?	Sample taken from appropriate population?	Appropriate sample selection process?	Addressed/ categorized non-responders?	Appropriate risk factor/ outcomes?	Appropriate risk factor/ outcome measures?	Appropriate statistical significance methods?	Methods sufficiently described?	Basic data adequately described?	Non-response bias?	Non-responder information described?	Results internally consistent?	Results described for all analyses?	Discussions/ conclusions justified by results?	Limitations discussed?	Funding sources/ conflicts of interest?	Ethical approval/ consent attained?
Azevedo et al. (17)	Y	Y	U	Y	U	U	N/A	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	U	Y
Azevedo et al. (18)	Y	Y	Y	Y	—	—	Y	Y	Y	Y	Y	Y	U	—	Y	Y	Y	Y	—	Y
Baird et al. (19)	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	U	Y	—	—	Y	Y	Y	Y	—	Y
Bishop et al. (20)	Y	Y	U	Y	—	U	U	Y	Y	Y	Y	Y	U	—	Y	Y	Y	Y	—	Y
Bove et al. (21)	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	—	—	Y	Y	Y	Y	—	Y
Cole et al. (22)	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y	Y	U	—	N/A	U	Y	Y	Y	—	Y
Erramuzpe et al. (23)	Y	Y	Y	Y	Y	U	U	Y	Y	U	U	Y	U	U	Y	Y	Y	Y	—	U
Eshaghi et al. (24)	Y	Y	Y	Y	—	U	N/A	Y	Y	Y	Y	Y	—	N/A	U	Y	Y	Y	—	Y
Eshaghi et al. (25)	Y	Y	U	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	U	Y
Fisher et al. (26)	Y	Y	—	Y	U	U	—	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	U	Y
Ghione et al. (27)	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	U	Y	—	U	Y	Y	Y	Y	—	Y
Høgestøl et al. (28)	Y	Y	Y	Y	Y	Y	—	Y	Y	Y	Y	Y	U	—	Y	Y	Y	Y	U	Y
Jakimovski et al. (29)	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	—	N/A	U	Y	Y	Y	—	Y
Jakimovski et al. (30)	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	U	N/A	Y	Y	Y	Y	—	Y
Kassubek et al. (31)	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	U	Y	Y	—	—	Y
Krysko et al. (32)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	—	—	U	Y	Y	Y	—	Y
Kuusisto et al. (33)	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	—	Y
Martola et al. (34)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	—	—	Y	Y	Y	Y	—	Y
Newbould et al. (35)	Y	Y	U	Y	U	U	U	Y	Y	Y	U	Y	U	—	Y	Y	Y	Y	U	Y
Tiberio et al. (36)	Y	Y	Y	Y	—	Y	N/A	Y	Y	—	Y	Y	—	—	U	Y	Y	Y	—	Y
Tortorella et al. (37)	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	—	U	Y

Y, yes; N, no; U, unclear; N/A, not applicable.

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and changes in brain volume detected in these studies were largely present in the context of DMT use. Although it is beyond the scope of the current review to determine whether DMT use has a modifying effect on neurodegeneration, ongoing research should report DMT use so that future reviews can examine whether any accelerated aging effects are muted by treatment (as current cohorts on these treatments age).

Importantly, previous research has shown that African Americans exhibit more rapid neurodegeneration than Caucasian Americans (43); however, most studies did not report on race or ethnicity and those that did report these characteristics had a majority of white participants. Moving forward, it will be important for research to be inclusive and involve transparent reporting.

In terms of other directions for future research, there is a clear need for large scale studies that use multimodal MRI acquisition methods to capture changes in both males and females over time, particularly in middle to older adulthood. Such studies would essentially aid the understanding of how the brain ages in pwMS, which will have implications for both the conceptualization of the disease course of MS and the interpretation of intervention related changes in the brain as pwMS age.

Author contributions

NT and IT drafted the initial manuscript. All authors were involved in conceptualizing the review, reviewing the literature, and critical revisions.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1207626/full#supplementary-material

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EDITED BY
Alessandra Lugaresi,
University of Bologna, Italy

REVIEWED BY
Maria Celica Ysrraelit,
Fundación Para la Lucha Contra las Enfermedades Neurológicas de la Infancia (FLENI), Argentina
Vincent Van Pesch,
Université Catholique de Louvain, Belgium

*CORRESPONDENCE
Gabrielle Macaron
✉ gabrielle.macaron@umontreal.ca
Pierre Duquette
✉ pierre.duquette.med@ssss.gouv.qc.ca

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Impact of aging on treatment considerations for multiple sclerosis patients

Gabrielle Macaron[1,2,3,4]*, Catherine Larochelle[1,2,3], Nathalie Arbour[1,2,3], Manon Galmard[1], Jean Marc Girard[1,2,3], Alexandre Prat[1,2,3] and Pierre Duquette[1,2,3]*

[1]Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada, [2]Department of Neurosciences, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada, [3]Neuroimmunology Research Laboratory, Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada, [4]Faculté de Médecine, Université Saint-Joseph de Beyrouth, Beirut, Lebanon

With a rapidly aging global population and improvement of outcomes with newer multiple sclerosis (MS)-specific disease-modifying therapies (DMTs), the epidemiology of MS has shifted to an older than previously described population, with a peak prevalence of the disease seen in the 55–65 years age group. Changes in the pathophysiology of MS appear to be age-dependent. Several studies have identified a consistent phase of disability worsening around the fifth decade of life. The latter appears to be independent of prior disease duration and inflammatory activity and concomitant to pathological changes from acute focal active demyelination to chronic smoldering plaques, slow-expanding lesions, and compartmentalized inflammation within the central nervous system (CNS). On the other hand, decreased CNS tissue reserve and poorer remyelinating capacity with aging lead to loss of relapse recovery potential. Aging with MS may imply longer exposure to DMTs, although treatment efficacy in patients >55 years has not been evaluated in pivotal randomized controlled trials and appears to decrease with age. Older individuals are more prone to adverse effects of DMTs, an important aspect of treatment individualization. Aging with MS also implies a higher global burden of comorbid illnesses that contribute to overall impairments and represent a crucial confounder in interpreting clinical worsening. Discontinuation of DMTs after age 55, when no evidence of clinical or radiological activity is detected, is currently under the spotlight. In this review, we will discuss the impact of aging on MS pathobiology, the effect of comorbidities and other confounders on clinical worsening, and focus on current therapeutic considerations in this age group.

KEYWORDS

multiple sclerosis (MS), aging, comorbidity, treatment efficacy and safety, treatment discontinuation

Introduction

The field of multiple sclerosis (MS) has grown considerably in the past 25 years, from the refinement of the diagnostic criteria to the expansion of the therapeutic arsenal. We now have a better understanding of the pathophysiological mechanisms driving clinical worsening and early factors impacting prognosis, such as baseline disease characteristics and treatment effect modifiers. Knowledge on the clinical potential of biomarkers of disease severity, prognosis, and treatment response has also significantly increased. Most of these advances are most useful for

the early phases of MS; however, advances in the field of late-stage and progressive MS remain modest. With a rapidly aging global population and improvement of outcomes with newer MS-specific disease-modifying therapies (DMTs), the epidemiology of MS has shifted to an older than previously described population. According to US-based health claims data, MS prevalence estimates demonstrate an overall aging of the MS population, with the highest prevalence of the disease seen in the 55–65 years age group (1). As an illustrative example, the peak age-specific prevalence in Manitoba, Canada, was seen in patients aged 35–39 years in 1984 vs. 55–59 years in 2004 (2).

Although the disease course is no longer dichotomized into a relapsing–remitting and a progressive course, as there is current consensus that progression independent from relapse activity (PIRA) starts at the earliest stages of the disease (3–5), natural history cohorts suggest that a consistent phase of overt clinical disability worsening is observed in most patients around the fifth decade of life (6–8). Moreover, patients with a primary progressive disease course tend to present at a later age than those with relapsing–remitting disease, and pediatric-onset MS almost exclusively presents with relapses. Importantly, while most DMTs are effective in reducing the acute inflammatory component of the disease – and are hence beneficial in younger patients with early relapsing–remitting MS, therapeutic options for patients with a predominantly progressive course are lacking. Treatment efficacy in patients older than 55 years has not been evaluated in pivotal randomized controlled trials. Nevertheless, an increasing number of large cohort studies have documented decreased DMT efficacy with age (9). In clinical practice, detecting a transition from a predominantly relapsing to a secondary progressive course is often difficult. Clinical disease activity can also be challenging to diagnose in older individuals, as aging is associated with a higher global burden of comorbid illnesses that contribute to overall impairments and represent a crucial confounder in the interpretation of clinical worsening (10, 11). Radiological disease activity may also be difficult to interpret in patients with cardiovascular risk factors who accumulate non-specific microangiopathic lesions on MRI over time. Patients often remain in this "transitional zone" for several years. Because of the lack of clear clinical practice guidelines in this setting (12), DMTs are often continued for decades after the diagnosis. Hence, aging with MS may imply longer exposure to DMTs and cumulative toxicity of sequential DMTs. On the other hand, older individuals are more prone to adverse effects of DMTs (13), an important aspect of treatment individualization. In this review, we discuss the impact of aging on MS pathology, the effect of comorbidities and other confounders on clinical worsening, and we focus on current therapeutic considerations in aging MS patients. We differentiate between late-onset MS (patients with an onset of the disease at an older age) and long-standing MS in aging patients, and will solely focus on the latter.

The effect of aging on MS pathophysiology

MS pathophysiology

MS is a sex-biased neuroinflammatory and neurodegenerative disease of the CNS. The hallmarks of MS neuropathology include multifocal areas of demyelination (lesions or plaques), neuroaxonal injury/loss, gliosis, inflammation, and infiltration of peripheral immune cells. Of note, diffuse neuroglial alterations in non-lesional areas, as well as slowly expanding lesions characterized by a rim of activated microglia with iron accumulation at the lesion edge, and subpial demyelination, are considered relatively unique to MS (14–18). These neuropathological characteristics, so far not reported in other CNS demyelinating disorders, are increasingly associated with the distinct course of MS progression occurring independently of relapses (18). Spontaneous remyelination is associated with improved function and reduced disability in MS, but is generally limited, especially in older individuals in the context of chronic inflammation, oxidative injury, and accumulation of debris/injury (5, 19–22).

Pathophysiological mechanisms underlying MS onset implicate the interaction between multiple predisposing genetic risk factors, such as the major histocompatibility complex class I and II (MHC I and II), polymorphisms, and environmental risk factors, such as exposure to EBV, low vitamin D levels, smoking, and obesity (23, 24). Major genetic and environmental risk factors for MS onset directly and indirectly influence the activation and trafficking of immune cells and consequently contribute to the greater risk of MS onset in susceptible individuals (25–27). In line with this, therapeutic approaches targeting peripheral T and B lymphocytes are highly effective, especially in younger people with MS, establishing the crucial contribution of peripheral immune cells to CNS neuroinflammatory processes in MS.

The biological mechanisms underlying the heterogeneous rate and severity of disability accumulation, e.g., the disease course, remain however poorly understood. Few genetic risks loci coding for genes highly expressed in neuroglial cells and linked to cognitive function were recently potentially associated with the severity of MS course, as were genetic polymorphisms associated with educational achievements, a proxy for cognitive reserve (28). In addition to older age being the greatest risk factor for onset of clinically overt progression in MS and for incomplete recovery from relapses (4, 29), this suggests a major contribution of the neurodegenerative aspects of MS to disease course and severity. Considering the increasingly recognized contribution of the immune system to other neurodegenerative disorders, as well as the modest but significant impact of a subset of DMTs on the progressive phase of the disease, neurodegeneration in MS is likely fueled by immune and CNS processes shaped by age-related alterations that tip the balance between immune-mediated injury and repair (5).

Biological aging

Biological aging is characterized by functional decline and loss of homeostasis over time. The combined accumulation of damage and exhaustion of repair/compensatory mechanisms partake in biological aging. Hallmarks of aging such as the accumulation of nuclear and mitochondrial DNA mutations, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, and gut dysbiosis, contribute to generate the state of chronic low-grade inflammation referred to as inflammaging (30).

Aging alters the innate and the adaptive immune systems

As put into light during the SARS-CoV-2 pandemic (31–34), biological aging of the immune system leads to a progressive deterioration of the capacity to mount an appropriate robust immune response, reduced immune surveillance, autoimmunity, and excessive levels of pro-inflammatory mediators. Immunosenescence affects the innate and adaptive immunity (35, 36), with a pronounced impact on lymphocytes and on CNS resident immune cells, the microglia (Figures 1A-C) (37–39). Aging

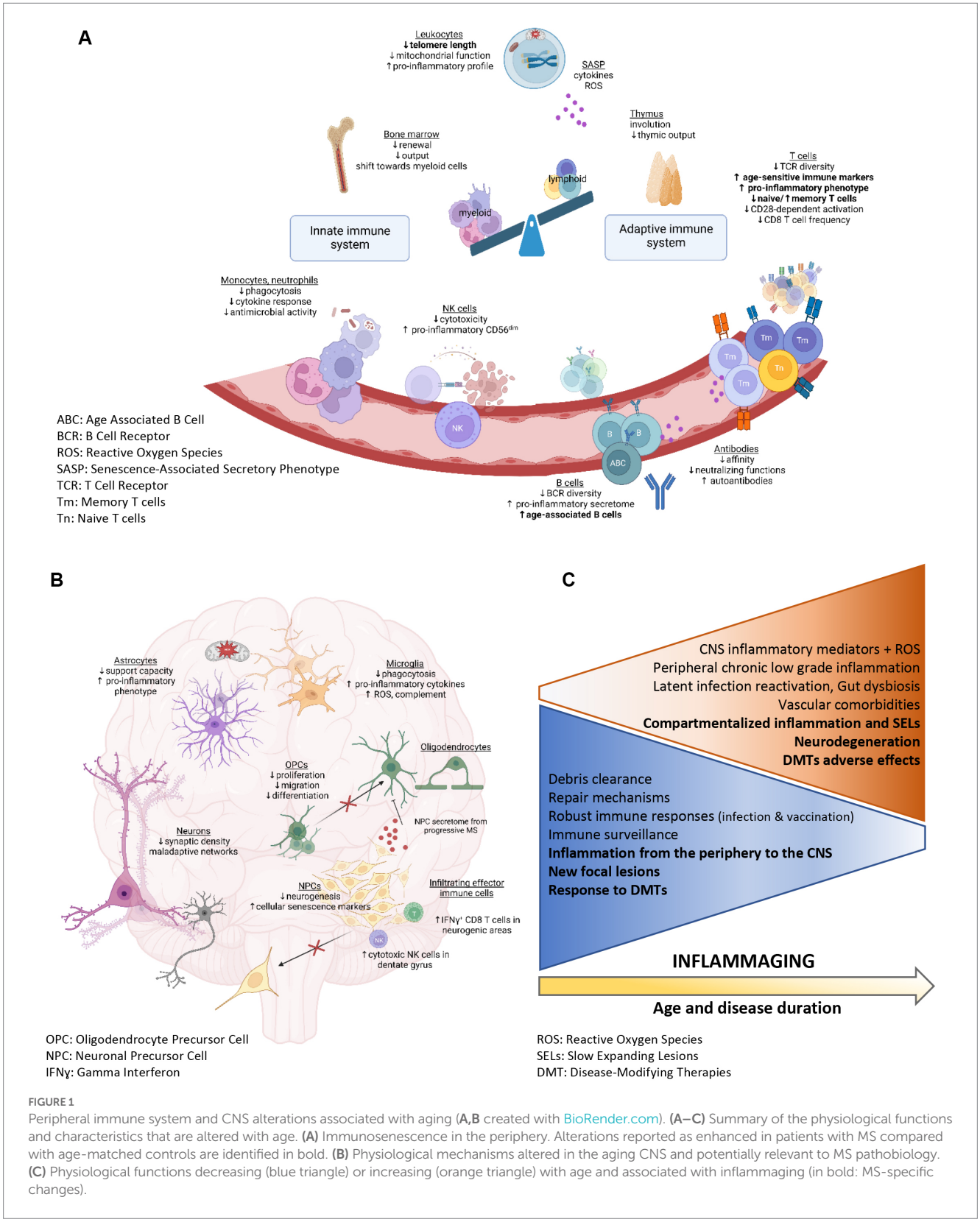

FIGURE 1
Peripheral immune system and CNS alterations associated with aging (**A,B** created with BioRender.com). **(A–C)** Summary of the physiological functions and characteristics that are altered with age. **(A)** Immunosenescence in the periphery. Alterations reported as enhanced in patients with MS compared with age-matched controls are identified in bold. **(B)** Physiological mechanisms altered in the aging CNS and potentially relevant to MS pathobiology. **(C)** Physiological functions decreasing (blue triangle) or increasing (orange triangle) with age and associated with inflammaging (in bold: MS-specific changes).

is associated with an altered immune cell output from the bone marrow. The volume of hematopoietic tissue within the bone marrow decreases as individuals age, and bone marrow hematopoietic stem cells exhibit a decreased capacity to self-renew and a shift toward myeloid cell differentiation (40, 41). The thymus involution starts as early as adolescence and data from animal models suggest that male sex hormones accelerate this process (42). Therefore, with aging, more neutrophils and monocytes but less T and B lymphocytes are generated (43). Despite the increased numbers of myeloid cells with aging, defective innate functions are observed. The antimicrobial functions, cytokine responses, and phagocytosis capacity of neutrophils and monocytes are diminished (44). NK cells are also more frequent in older individuals but show reduced cytotoxicity and proliferation and an enriched pro-inflammatory $CD56^{dim}$ phenotype (45). Similarly, aging dampens the capacity of microglia to clear debris and phagocyte proteins (46) but increases their production of pro-inflammatory cytokines, complement and reactive oxygen species (ROS) (47, 48).

The reduced renewal of T and B lymphocytes is partially compensated by homeostatic proliferation, leading to a decreased diversity of the T-cell and B-cell receptor (TCR and BCR) repertoires upon aging. A recent publication revealed a more severe TCR diversity loss in CD8 than CD4 T cells with aging (49). The reduced TCR repertoire diversity is associated with a diminished capacity to mount an efficient cellular immune response targeting encountered pathogens, such as JC virus (50), or tumorigenic cells (51). Increased proportions of dysfunctional regulatory lymphocytes and of terminally differentiated pro-inflammatory T cells are observed upon aging (29). CD4 T lymphocytes from older subjects show impaired autophagy and mitochondrial dysfunction leading to a Th17 profile (52). Moreover, highly differentiated T lymphocytes develop a pro-inflammatory phenotype reminiscent of the senescence associated secretory phenotype (SASP) (53). Aging is furthermore associated with numerous changes in the B cell compartment, including an enhanced proinflammatory B cell secretome or SASP (43). In the elderly, infection or immunization induces antibodies with lower affinity and neutralizing functions, whereas autoantibody levels increase. An age-associated specific subset coined Age-associated B cells (ABCs) has been shown to contribute to the autoantibody secretion (54), notably, ABCs are more prevalent in patients with autoimmune diseases, including MS (55).

Immunosenescence fuels neurodegenerative processes

An increasing number of studies suggest that short telomere length in peripheral leukocytes represents a surrogate marker of biological aging, associated with an elevated risk of developing diseases, including neurodegenerative diseases (56, 57). Senescent immune cells cause accelerated systemic aging and are associated with organ damage including in the CNS (48, 58–60). In particular, dysfunctional aged myeloid cells contribute to neurodegenerative processes and age-related cognitive decline in multiple diseases such Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and MS (61, 62). Exposure to rejuvenating interventions and to young bone marrow-derived immune cells can attenuate the age-related myeloid cell dysfunctions in animal models (63–65). Moreover, NK cells could accumulate in the dentate gyrus upon aging and show cytotoxicity towards neuroblasts, impairing synaptic plasticity and promoting cognitive decline (66). Interestingly, CD8 T lymphocytes showing clonal expansion are found in neurogenic regions of old animals, and their interferon-γ production could interfere with neural stem cell proliferation (Figure 1B) (67). Moreover, Th17 cells, which are increased upon aging, are implicated in a deleterious crosstalk with senescent cells such as fibroblasts (68). Notably, Th17 cells can form prolonged contact with oligodendrocytes in neuroinflammatory conditions and induce loss of distal myelinating processes followed by oligodendrocytic cell death (69).

Multiple age-related mechanisms can reduce the remyelination and neuroregeneration capacity observed in the elderly. Age-related sex hormone deficiencies, e.g., menopause and andropause, contribute to alterations in peripheral and central immune cell response and influence neurodegenerative processes (70). Increased oxidative stress, impaired phagocytosing capacity of myeloid cells (microglia and macrophages) (71), alterations in mitochondrial function and myelin biology, and reduced functionalities (migration, proliferation, differentiation) of oligodendrocyte precursor cells (72) have been identified as culprits in impaired remyelination (Figure 1B). Moreover, decreased neurogenesis, compromised support from astrocytes (73), reduced synaptic density, and maladaptive neuronal network alterations (48) participate in the age-related impaired neurodegeneration. Neural progenitor cells from subjects with progressive MS express markers of cellular senescence *in situ* and *in vitro*, and their secretome induces expression of senescence genes in OPCs and inhibits their differentiation (Figure 1B) (74). Recent studies suggest that aging of neuroglial cells shapes the clinical course and immune response in an animal model of MS (37). Therefore, concomitant age-sensitive processes in the peripheral immune and CNS compartment could contribute to the clinical and immunological shift seen over time in people with MS, from a relapsing to a progressive form. Such coexistent processes parallel a shift from aberrant peripheral immune cell activation and immune cell CNS infiltration to the subsequently intrathecal/diffuse CNS inflammation observed in later phases of MS.

Evidence of immunosenescence in MS

Telomere length shortening, a hallmark of biological aging of immune cells, is more pronounced in MS compared to age-matched controls (75). Shorter leukocyte telomere length is also associated with an increased risk of clinical progression over time (76). In line with this, the proportion of naïve T lymphocytes is reduced in MS compared to age-matched controls, and this alteration is observed even in pediatric MS cases (77). Antigen-experienced $CD28^{neg}$ T cells exhibiting cytotoxic properties are observed in MS peripheral blood and CNS lesions (29). Other studies reported premature senescent expression patterns of age-sensitive immune markers by CD8 T lymphocytes from young MS patients (78). Pender et al. observed a reduction in the proportion of CD8 T cells producing interferon-gamma in response to autologous EBV infected cells in older patients compared with healthy donors (79). One group recently documented that the percentage of naïve CD4 T lymphocytes was lower, while the proportion of effector memory counterparts was higher in MS patients compared with healthy donors across ages (77). They also reported that the proportion of T lymphocytes expressing activation and cytotoxicity markers linked to aging is increased in MS patients (77).

Finally, pro-inflammatory age-associated B cells are more frequent in MS patients before the age of 60 years than in age-matched controls (55).

Factors driving premature immunosenescence and neurodegeneration in MS

Numerous factors have been proposed as drivers of immunosenescence. Repeated antigen encounters, such as seen in autoimmune diseases and in chronic viral infections, accelerate immunosenescence (80, 81). Multiple MS risk or prognostic factors such as viral infections, smoking, obesity, and sedentary lifestyle can accelerate immunosenescence and CNS dysfunction.

Smoking and obesity are associated with increased markers of DNA damage and telomere shortening in peripheral blood cells (82). Obesity is associated with peripheral and CNS inflammation, lower synaptic plasticity, and accelerated brain atrophy (83). Obesity speeds up T cell immunosenescence, including thymic involution (84) and enhances the proportion of peripheral blood memory CD4 and CD8 T cells (85). In fact, the complications of obesity, e.g., the metabolic syndrome, are associated with a state of chronic inflammation (metaflammation) similar to inflammaging, suggesting overlapping mechanisms and causes between inflammaging and metaflammation (86).

Interestingly, exercise is one of the most effective anti-aging interventions; it has profound effects on the immune system and the CNS (87). Exercise increases thymic output, skew myeloid cells towards an anti-inflammatory phagocytosing phenotype, boosts immune responses to pathogens and limits clinical manifestations of latent viruses, autoimmunity and inflammation (36). In addition, exercise is associated with better brain microstructural integrity and lower retinal and hippocampal atrophy in patients with MS (88). Notably, exercise decreases CNS inflammation and promote remyelination in MS mouse models (89). In addition to exercise, effective anti-aging dietary/metabolic interventions, such as intermittent fasting (90), metformin (91), and methionine restriction (92), ameliorate inflammation, remyelination and disease course in MS and its animal models. Shared mechanisms between exercise and dietary interventions include a beneficial impact on gut microbiota composition. Gut dysbiosis is indeed observed upon aging and is considered to precede onset of multiple age-related comorbidities and contribute to immunosenescence (Figure 1C) (93). MS and other autoimmune diseases are associated with gut dysbiosis, which is considered to contribute to skew the immune system towards a pro-inflammatory response (94). The composition of the gut microbiota is further modulated by obesity, diet, exercise and DMTs (93). Interventions aimed at restoring a healthy gut microbiota environment are promising nonpharmacological avenues to improve age-related comorbidities, inflammation and subsequently MS outcomes.

Confounders of clinical worsening with aging

The total burden of illnesses increases with age, leading to the higher prevalence of several common diseases such as hypertension, coronary heart disease, osteoarthritis, cancers, Alzheimer's disease, among others. This increase also affects aging MS patients who suffer from an already lower than average health status. Comorbidities have an important functional impact independent of MS and may explain, at least in part, the heterogeneity in outcomes between individuals (11). The presence of comorbid disorders is particularly important in the interpretation of new symptoms in aging MS patients. Neurologists must ascertain whether a decline in function is attributable to worsening MS or comorbid illnesses, which has an impact on treatment strategies. Comorbidities also directly affect the MS course. In a 3-year longitudinal study, comorbidities significantly impacted clinical outcomes (specifically, patient-reported outcome measures and timed 25-foot walk scores) in a real-world MS cohort, and a cumulative effect with multiple comorbidities was observed (95). Cardiovascular comorbidities in particular may promote neurodegenerative processes, as observed in some studies showing accelerated brain atrophy among individuals with hypertension (96). In a retrospective US observational cohort, age-related comorbidities such as cardiovascular risk factors, osteoarthritis, osteoporosis, glaucoma, and cancer were highly prevalent in MS, particularly in patients older than 65 years (97). The presence of multiple comorbidities in an individual patient was also highly prevalent in this MS cohort (97).

Cardiovascular comorbidities

Multiple sclerosis patients are at a higher risk than the general population to develop cardiovascular comorbidities such as hypertension, diabetes, dyslipidemia, ischemic heart disease, and cerebrovascular events (98). In a recent population-based retrospective matched cohort study from England, the risk of acute coronary syndrome, and cerebrovascular disease was approximately 30% higher in patients with MS than in the general population (99). A 3.5-fold increased hazard of all-cause mortality and a 1.5-fold increased hazard in cardiovascular disease-related mortality was also observed in this cohort (99). Similar results were observed in other cohorts (100). In a large population-based study using administrative data from four Canadian provinces, the incidence of diabetes in the MS population appears to be increasing more than in the general population (101). Interestingly, MS-related disability was associated with an increased risk of acute myocardial infarction in a Canadian MS cohort, which probably reflects sedentarity, lower exercise levels, and associated risk of obesity (100). The increased risk of cardiovascular events in MS might not be explained by a higher risk of cardiovascular risk factors alone, as MS cohorts were matched to controls after adjusting for age, sex, race, socioeconomic status, traditional risk factors, and antihypertensive treatments, statin use, and antiplatelets use (99, 100). It is postulated that chronic inflammation in MS and several other inflammatory diseases such as rheumatoid arthritis contribute to increasing the cardiovascular risk in addition to traditional risk factors, although treatment-related effects cannot be excluded (100, 102).

The radiological correlate of the effect of cardiovascular comorbidities on the CNS is reflected by the accumulation of sub-cortical white matter abnormalities often referred to as microvascular changes. The pathogenesis of lesion formation in this case results from endothelial injury, decreased perfusion in distal arterioles, ischemia, and disruption of the blood–brain barrier (103). Features of microvascular lesions on brain MRI include acute

or sub-acute small subcortical infarcts seen on diffusion imaging, chronic lacunar infarcts mostly in the deep white and grey matter, sub-cortical white matter hyperintensities, enlarged perivascular spaces, microbleeds on susceptibility-weighted imaging, and global atrophy. Supratentorial MS lesions are typically ovoid periventricular, or juxtacortical. However, lesion formation in the sub-cortical regions is not uncommon with MS and the distinction can be difficult in practice (103). Differentiating microvascular lesions secondary to cerebral small vessel disease from new MS lesions is a key component in the evaluation of treatment response in older individuals with cardiovascular comorbidities. Although age-related whole brain and focal atrophy occur in all individuals with or without cardiovascular comorbidities, excess atrophy beyond what is expected from normal aging is seen in both MS and cerebrovascular disease. While MS-related atrophy is the main driver of global and focal brain volume loss in young individuals, the rate of normal aging increases and becomes the predominant contributor of atrophy after the age of 60 years (104). This has important implications when interpreting worsening atrophy in an older individual with long-standing MS.

Osteoarticular comorbidities

Reduced bone mineral density is more frequent in patients with MS since corticosteroid use and reduced mobility are known risk factors for osteoporosis (105). Combined with the fact that the risk of falls is increased in long-standing MS, aging patients are predisposed to fractures. Osteoarthritis and lower back pain are common in aging MS patients, affecting around 20–25% of those older than 65 years (97). Osteoarticular-related mobility impairment and pain is important to distinguish from MS-related worsening and can be the main disabling symptom in some patients. However, aging individuals in general are also at higher risk of gait imbalance, falls, and osteoarticular disorders, even without known neurological diseases, hence the influence of aging, polypharmacy, and comorbidities on disability measures could be significant. As an important illustrative point, aging individuals without MS or other neurological conditions also demonstrate high level of disability on the Expanded Disability System Score (EDSS), the most commonly used measure of disability in MS. Lynch et al. report an EDSS $\geq$4 in a third of individuals without MS who are 55 years or older, associated with impairment in all functional system scores of the EDSS, except the cerebellar and visual components (106).

Dementia

Both aging and long-standing MS independently impact cognitive functioning (107). Moreover, as patients age, several comorbid symptoms and disorders can contribute to patient-perceived cognitive impairment such as polypharmacy, poor sleep, depression, anxiety, and fatigue. With age, the risk of Alzheimer's disease (AD) and related dementias, as well as vascular dementia, increases in the general population (and in individuals with MS), which can be difficult to distinguish from MS-related cognitive impairment (108). AD is common in individuals >65 years old, and its prevalence is increasing with longer life expectancy in the Western world. In a large US retrospective cohort using private claims data, Mahmoudi et al. found that the incidence of early-onset AD and related dementias diagnosis was higher in individuals with MS aged 45–64 years and >65 years compared to non-MS individuals after adjusting for key confounders (109). This data suggests that MS patients may be at a greater risk of AD and related dementias, but is largely confounded by the high probability of misdiagnosis in this setting (i.e:, MS-related condition vs. AD) (109). Indeed, the major obstacle in identifying coexisting AD in an aging MS patient is the challenge of diagnosing AD in general, since a definitive diagnosis relies on post-mortem histopathological confirmation. Rare case reports and case series of probable or definite AD in MS patients have been published (110). As an example, cortical lesions containing amyloid plaques and neurofibrillary tangles suggestive of AD were found in 11 out of 67 patients with long-standing inactive MS in an autopsy case series (15). In practice, the differential diagnosis relies on the identification of different cognitive phenotypes and, when available, the use of paraclinical testing such as PET imaging and CSF biomarkers. AD often presents with deficits in episodic and semantic memory, executive functioning, apraxia, and agnosia (cortical dementia) and evolves in most cases to moderate to severe dementia, whereas MS-related cognitive dysfunction often involves processing speed, verbal memory, and visual memory impairments and dementia is rarely seen (111). Comparing cognitive phenotypes between patients with MS, patients with amnestic mild cognitive impairment, and healthy individuals all aged 60–80 years, a study showed that MS patients had poorer performance on measures of processing speed, but better performance on cued memory, language, and executive function tests compared to patients with amnestic mild cognitive impairment (112). Vascular cognitive impairment secondary to microvascular changes is highly variable but is generally associated with poor executive function and impaired processing speed and can evolve slowly into an insidious sub-cortical dementia (108). Due to the high inter-individual variability of cognitive phenotypes particularly in MS and vascular-related cognitive impairments, the diagnosis remains a challenge in clinical practice.

Frailty

Frailty is defined as a state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems which occurs with age. Fried et al. operationally defined that frailty is reached with three out of five phenotypic criteria: low grip strength, low energy, slowed walking speed, low physical activity, and unintentional weight loss (113). A pre-frail stage, in which one or two criteria are present, identifies a subset at high risk of progressing to frailty. Frailty, which often accompanies aging in the general population, has a negative impact on the invalidity level in MS (114). Frailty carries an increased risk for poor health outcomes, including falls, incident disability, hospitalization, and mortality. To date, it is unclear if frailty is a reliable marker of handicap and morbidity related to MS.

Treatment efficacy in aging MS patients

Pivotal randomized controlled trials leading to the approval and wide use of MS-specific DMTs have systematically excluded

individuals >55 years old. However, as already mentioned, these individuals represent the majority of MS patients in real-world settings (1). The age discrepancy between individuals with MS included in regulatory trials and real-world clinical practice is concerning when considering treatment efficacy in this age group (115).

There is increasing evidence to support an age-dependent decrease in the efficacy of DMTs, which is consistent with the pathophysiological changes associated with aging combined with the fact that approved DMTs exert their efficacy via their anti-inflammatory properties. The majority of trials evaluating the efficacy of DMTs in progressive MS, particularly without evidence of clinical or radiological activity, have shown negative results. In a meta-analysis of all randomized clinical trials (including more than 28,000 participants) evaluating the efficacy of DMTs and using a complex statistical approach, Weideman et al. reported a strong decrease in the efficacy of DMTs on MS-related disability progression with advancing age, with chronological age explaining a large proportion of the variance in inhibition of disability progression (9). The regression model predicted no efficacy beyond the age of 53 years. Moreover, higher efficacy DMTs were superior to platform therapies only in patients younger than 40.5 years (9). However, in another large real-word study, high-efficacy DMTs appeared to be superior until the age of 54.2 years (116). Age was a better predictor of lower benefit on disability progression than baseline EDSS (9). Despite several limitations related to the representativeness of subjects included in trials, this meta-analysis highlights the differential efficacy of DMTs based on age. Conversely, another meta-analysis using data from 26 trials of 14 different DMTs showed no significant associations between age and efficacy in reduction of inflammatory activity markers (annualized relapse rate (ARR), new T2 lesions, and gadolinium-enhanced lesions) between active and comparator groups. This can be explained by the inclusion of patients with baseline disease activity in these trials, therefore not representing real-world patients with RRMS above a certain age. In a Canadian population-based observational study using linked administrative health data and including more than 19,000 MS patients, a protective effect of DMTs on hospitalization rate was observed in subjects <55 years but the risk was not significantly lowered in those >55 years (117).

Subgroup analyses of the comparative DMT effectiveness based on age were conducted in most phase 3 pivotal trials (115) and are summarized in Table 1. Most DMTs show little to no effect on disability progression in patients older than 40 years compared to comparator arms. A positive effect on markers of disease activity such as the ARR is seen in patients >40 years in several but not most trials (ex: Natalizumab trials AFFIRM and SENTINEL, Dimethyl fumarate trial DEFINE - but not in CONFIRM, and in the Peginterferon Beta-1a ADVANCE trial). Again, this can be explained by the inclusion of patients with baseline disease activity in most trials.

Siponimod and ocrelizumab were evaluated in slightly older populations. The phase 3 Siponimod clinical trial (EXPAND) included patients up to 60 years of age with SPMS (122). The mean age in this cohort was 48 years whereas, in other trials, the mean age varied between 33 and 38 years old (130). The majority (64%) of patients had no clinical relapse in the past 2 years and around half needed assistance for walking, therefore including an underrepresented population in previous trials. Siponimod was superior to placebo in reducing the risk of disability progression as measured by the EDSS (but not the timed 25-foot walk test), radiological activity, and percent brain volume loss compared to placebo. The effect on confirmed disability progression was seen in patients younger and older than 50 years (Poster presentation by Hua L. et al. at the American Academy of Neurology meeting in 2022, P5.002). CONSONNANCE, an ongoing open-label single-arm study evaluating the efficacy of ocrelizumab in patients with SPMS and PPMS, is the first trial including patients up to 65 years old (131). Primary outcome measures include No Evidence of Progression (NEP) defined as the absence of 24-weeks confirmed clinical progression (measured by a clinically significant increase in the EDSS score, the timed 25-foot walk test, or the nine-hole peg test) and No Evidence of Progression or Active Disease (NEPAD) defined as NEP plus the absence of relapses or radiological activity. The mean age in this study was 48.5 years. In the year-1 interim analysis, ocrelizumab was effective in maintaining NEP in >70% and NEPAD in approximately 58% of patients with SPMS and PPMS. The relatively high proportion of patients not meeting NEPAD at year one is explained by the therapeutic lag expected with the drug, as new/enlarging MRI lesions in the first 6 months were the main driver of NEPAD. However, this suggests that subjects included had some degree of inflammatory activity, therefore not representing real-world cohorts of patients with long-standing progressive MS.

Treatment safety in aging MS patients

Risks associated with disease-modifying therapies

As discussed in the first section of this paper, biological aging-related qualitative and quantitative changes in the immune system are associated with decreased ability to counter infections and cancers. Added to treatment-specific immunomodulation and immunosuppression, older individuals are at higher risk of adverse events with prolonged DMT use (13). As patients age, they might also be exposed to a higher number of DMTs with different mechanisms of action and this cumulative effect is not without risks. In general, older individuals are more prone to serious adverse events, in particular severe adverse events (132–135). An important example is the risk of progressive multifocal leukoencephalopathy (PML), mostly associated to the use of natalizumab but with other DMTs as well. Older age is an independent risk factor for developing PML. Older individuals are more likely to develop PML after a lower number of natalizumab infusions and have higher mortality rates (50, 136, 137). *De novo* infections and reactivation of latent viruses also occur more frequently in older individuals both in the general population and in MS. Particularly, the risk of varicella zoster virus associated to shingosine-1-phosphate receptor modulators, cladribine, and alemtuzumab increases with age (13). The risk of grade 3 lymphopenia with dimethyl fumarate use increases with age, and dimethyl fumarate-associated PML risk is related to severe lymphopenia (98). B-cell depleting therapies are associated with a higher risk of infections than interferon-based preparation, glatiramer acetate, fingolimod, and natalizumab, particularly in older individuals with comorbidities (138). The risk of serious infection with these therapies is partially correlated to the degree of associated hypogammaglobulinemia (139). This risk can be mitigated by monitoring immunoglobulin levels while on

TABLE 1 Reported *post hoc* sub-group analysis from pivotal phase 3 trials of different DMTs based on age.

Treatment	Trial	Age-based effect on disease activity markers	Age-based effect on the risk of confirmed disability progression
Teriflunomide	TEMSO (118)	Significant reduction of the ARR in patients <38 and ≥38 years vs. placebo	Reduction of the risk of disability progression only in patients <38 years vs. placebo
Dimethyl fumarate	DEFINE (119) CONFIRM (120)	Significant reduction in the ARR in patients <40 and ≥ 40 years vs. placebo No significant reduction in the ARR in patients ≥40 years vs. glatiramer acetate	Reduction of the risk of disability progression only in patients <40 years vs. placebo No reduction in the risk of disability progression in both age groups (<40 and >40 years) vs. glatiramer acetate
Fingolimod	FREEDOMS (121)	No significant reduction in the ARR in patients ≥40 years vs. placebo	No reduction in the risk of disability progression in both age groups vs. placebo
Siponimod	EXPAND (122)	–	Significant reduction in the risk of disability progression in patients <50 and years ≥50 years vs. placebo
Ozanimod	SUNBEAM (123) and RADIANCE (124)	No significant reduction in the ARR in patients ≥40 years vs. IFN-b1a	No reduction in the risk of disability progression in both age groups vs. placebo vs. IFN-b1a
Cladribine	CLARITY (125)	Significant reduction in the odds of remaining free of disease activity in patients <40 and ≥40 years vs. placebo	Significant reduction in the risk of disability progression in patients <40 and years ≥40 years vs. placebo
Ocrelizumab	OPERA I and II (126) OROTARIO (127)	No significant reduction in the ARR in patients ≥40 years, but significant reduction in NEDA rates in both sub-groups vs. IFN-b1a Significant reduction in the ARR in patients <45 and ≥45 years vs. placebo	Significant reduction in the risk of disability progression in patients <40 and years ≥40 years vs. IFN-b1a Significant reduction in the risk of disability progression in patients <45 and ≥45 years vs. placebo with a notable trend to benefit younger subjects
Ofatumumab	ASCLEPIOS (128)	Significant reduction in the ARR in patients <40 and years ≥40 years vs. teriflunomide	Significant reduction in the risk of disability progression in patients <40 and years ≥40 years vs. teriflunomide
Natalizumab	AFFIRM and SENTINEL (129)	Significant reduction in the ARR in patients <40 and ≥40 years vs. placebo in AFFIRM and in combination with iINF-b1a vs. INF- b1a alone in SENTINEL	Reduction of the risk of disability progression only in patients <40 years vs. placebo in AFFIRM and in combination with INF-b1a vs. INF-b1a alone in SENTINEL

ARR, annualized relapse rate; INF, interferon; NEDA, no evidence of disease activity.

treatment. Reactivation of latent hepatitis B is a known risk of B-cell depleting therapies but does not seem to be affected by age. During the COVID-19 pandemic, MS patients on B-cell depleting therapies such as ocrelizumab and rituximab had worse outcomes than those on other DMTs, even after adjusting for age and other confounders (140, 141). Age, progressive MS phenotype, higher disability, and the presence of comorbidities were often associated with poorer Covid-19-related prognosis in MS cohorts (140–143). Importantly, vaccine responses are significantly blunted in patients on B-cell depleting therapies and fingolimod (144), added to an age-dependent decreased immune response even in healthy individuals (34).

Older individuals are also more susceptible to several non-infectious adverse events of DMTs. For example, hypertension is a potential adverse event of teriflunomide and fingolimod, and is also more frequent with aging. The negative chronotropic effects of fingolimod might also be age-dependent, at least in mice (145). Patients with type 2 diabetes, which becomes more frequent and more commonly associated with end-organ damage with aging, are more prone to fingolimod-related macular oedema. There are conflicting data regarding the risk of cancer in MS in general, with some studies (including a recent meta-analysis) reporting a lower risk of cancers in MS patients (146), and others a similar or slightly increased risk compared to the general population (147, 148). Cancer risk also increases with age and can be potentiated by the use of certain DMTs (148). For example, there is an increased risk of non-melanoma skin cancers with the use of fingolimod. B-cell depleting therapies, alemtuzumab, and natalizumab have also been associated with various cancers, but the evidence for causality is less robust. Despite the initial concern of increased carcinogenesis with cladribine, subsequent data showed no increase in risk of secondary malignancies (148). The overall cancer risk is probably not higher with exposure to IFN-b, glatiramer acetate, teriflunomide, and dimethyl fumarate (148–150).

Risk of polypharmacy

Polypharmacy, commonly defined as the concomitant use of at least 5 medications, is observed in up to 35 to 50% of adults >65 years of age in North America (151, 152). Polypharmacy is a major public health concern globally, and is associated with an increased risk of drug–drug interactions and adverse events, lower quality of life, worsening disability and cognitive function, and increased hospitalization rates (152). Older adults with multiple comorbidities might be more prone to slowed drug metabolism, side effects, adverse events and drug interactions. Adverse events are estimated to be the 14th leading cause of morbidity and mortality in the world as per the WHO (153). Moreover, the

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estimated prevalence of hospitalizations due to drug interactions-related morbidity is around 1% (154). Patients with chronic diseases such as MS are at higher risk of polypharmacy, mainly secondarily to the use of symptomatic therapies. In a large Canadian population-based study, using administrative and pharmacy data in the universal healthcare setting of British Columbia, 28% of MS patients met the criteria of polypharmacy, and more than 2/3 of these were exposed to polypharmacy for more than 180 days in 2017 (155). Patients in the polypharmacy group had a significantly higher odd of hospitalizations compared to the non-polypharmacy group. Additionally, one in 20 MS patients were treated with ≥10 medications. Within those exposed to polypharmacy, 82% were older than 50 years. Compared to those aged <50 years, the odds of being exposed to polypharmacy was 2 times higher in MS patients aged 50–64 years, and more than three times higher in those ≥65 years. MS patients with 1–2 or ≥3 comorbidities had 3- and 6-times higher odds, respectively, of being exposed to polypharmacy. Interestingly, women and people with lower socio-economic status were also at higher risk of polypharmacy in this cohort. Anti-depressants followed by antiepileptics with analgesic properties (pregabalin, gabapentin, clonazepam), proton-pump inhibitors, lipid-lowering agents, centrally-acting muscle relaxants, ACE inhibitors, opioids, and thyroid medication, were the most commonly prescribed drugs in this study; this is consistent with a larger scale Medicare study in the US (156).

Polypharmacy is associated with poorer outcomes in MS patients. For instance, the risk of falls seems to be higher. In a *post hoc* analysis of data from two observational cohorts from the US and Australia, the adjusted odds of falling increased by 13% with each additional medication used (157). This increase was even more pronounced with centrally-acting drugs, specifically anti-depressants. In this study, the use of MS-specific DMTs decreased the risk of falls. In another prospective study, in which 85 MS patients were evaluated for depression, fatigue, self-reported cognitive functioning, and objective cognitive tests, those exposed to polypharmacy had increased fatigue and poorer self-reported cognitive functioning and performances on objective memory tests (158). People with MS are also more prone to potential drug–drug interactions which are more frequent in older individuals with a longer disease duration and higher EDSS scores (159).

The consequences of polypharmacy remain underrecognized among patients with MS and should be taken into account when evaluating older patients who are experiencing new or worsening symptoms. As suggested by Bourdette et al., polypharmacy should be highlighted in the problem list, when appropriate, to incite routine evaluation of medication lists (160). Specifically, the efficacy of MS symptomatic therapies should be periodically revised and discontinuation of treatment with no or little benefit should be encouraged while promoting non-pharmacological interventions to address pain, spasticity, poor sleep, and fatigue.

Trends in DMT use in older MS patients

In practice, neurologists are often confronted with the decision to either maintain, escalate, de-escalate, or discontinue therapies in patients with long-standing disease who are 55 years or older. There are currently no evidence-based guidelines on treatment in this age group, and treatment decisions should remain individualized in a case-by-case approach. The European Academy of Neurology and American Academy of Neurology practice guidelines do not clearly address the indication of DMT de-escalation or discontinuation. Some patients with RRMS continue to have active disease despite their age and long disease duration, whereas a majority either have stable disease or evolve into a secondary progressive course as illustrated in the clinical vignettes (Figures 2,3).

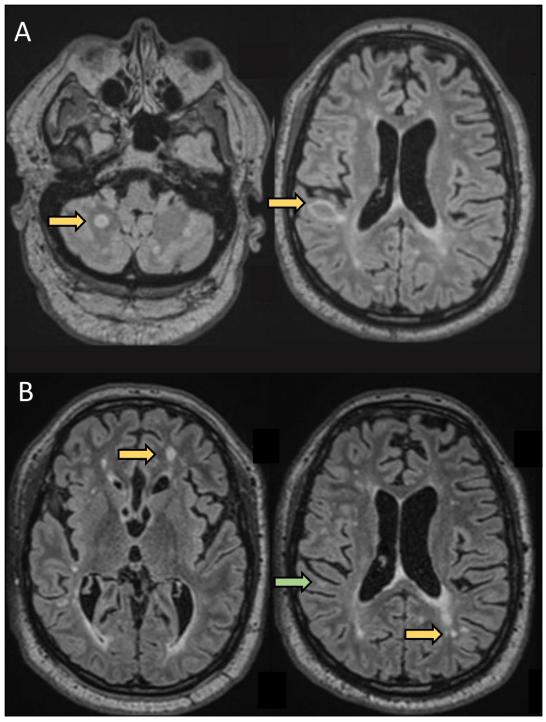

FIGURE 2
A 61-year-old man was evaluated for new neurological symptoms suggestive of a relapse. He was diagnosed with RRMS in 1998 after two episodes compatible with sub-acute sensory myelitis in 1994 and 1998. He did not receive any treatment for his MS between 1998 and 2019. Between 2000 and 2008, he had a couple of episodes suggestive of mild relapses. He had also noticed some progressively worsening gait instability and cognitive difficulties over the past few years, In April 2019 (at the age of 57), he experienced transient tingling followed by mild weakness and ataxia of the left upper extremity which resolved spontaneously over 5 weeks. Brain MRI showed 2 new lesions, one in the right juxtacortical posterior frontal lobe in the precentral gyrus explaining his symptoms. He was started on dimethyl fumarate 240 mg BID. He was doing well until August 2020 (at the age of 58 years), when he experienced tingling in the RUE associated with worsening cognitive difficulties. Repeat MRI showed 2 new lesions in the supratentorial regions. He was switched to oral cladribine without new clinical events or new radiological activity. *This case highlights that although rare, some patients have continued disease activity despite an older age and longer disease duration.*
(A) Axial FLAIR sequences of brain MRI in April 2019 showing 2 new lesions (arrows) compared to prior MRI in 2017, and concomitant with a relapse (weakness and proprioceptive ataxia of the left upper extremity). **(B)** Axial FLAIR sequences of brain MRI in August 2020, 13months after starting dimethyl fumarate, showing 2 new lesions (yellow arrows) compared to MRI in April 2019, with a decrease in size of the right posterior frontal lesion seen on prior MRI (green arrow) concomitant to a relapse: weakness of LUE and LLE.

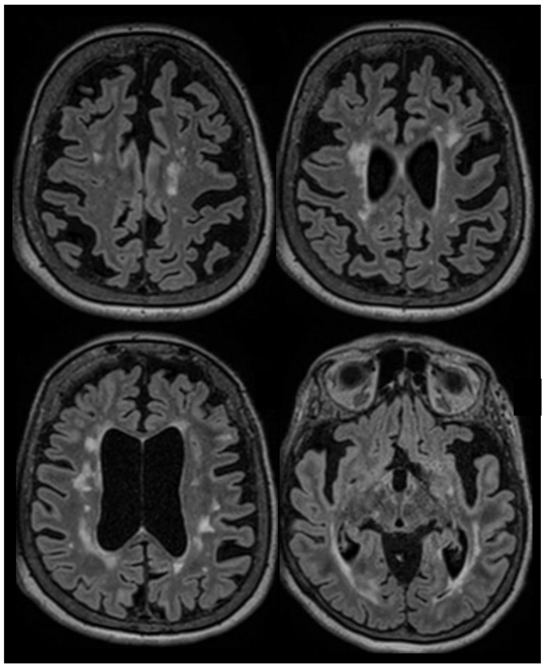

FIGURE 3
A 66-year-old woman was evaluated to establish care in our clinic. She was diagnosed with RRMS in 2002 after an episode compatible with sub-acute sensory myelitis. She was a participant in a Natalizumab trial, and was treated with this drug between 2003 and 2006. She experienced a relapse in 2007 after Natalizumab discontinuation, and was started on interferon beta1-a IM once a week between 2007 and 2015. She had a pseudo-relapse in 2014 in the context of acute illness. She did not report subacute symptoms since 2014, however she has noticed progressively worsening gait difficulties over the past few years, which she attributes to invalidating mechanical lower back pain related to severe spinal stenosis and degenerative disk disease. She continues to have flu-like symptoms after each interferon injection which last 12 to 24 hours. Her brain MRI in 2022 (at the age of 65) is stable compared to her MRIs between 2015 and 2019, except for a mild worsening of whole brain atrophy. After explaining the risks and benefits of treatment discontinuation, we decided to discontinue her interferon treatment. She has been clinically stable since. *This case highlights that treatment discontinuation is a reasonable option in older patients with long standing disease duration and no clinical/radiological activity.*
Axial FLAIR sequences of brain MRI in July 2022 showing extensive lesions in the supratentorial regions which were stable in number and size compared to prior MRI in 2017, associated with diffuse brain atrophy.

Treatment de-escalation

Little is known about de-escalation strategies in MS. The theoretical logic of de-escalation is based on the fact that the probability of disease activity is the highest in the first 5–10 years, and DMTs are mostly effective during this period (116). In a recent study, Vollmer et al. report a lower probability of disease activity in patients on higher-efficacy infusible DMTs vs. oral therapies until the age of 54.2 years, after which the difference in efficacy becomes non-significant (116). For this reason, de-escalation should be considered in older patients with stable disease, especially those at risk of serious adverse events (for ex: a patient with hypogammaglobulinemia on a B cell- depleting therapy). De-escalation can be done by switching to a lower efficacy DMT with more favorable safety profile before considering treatment discontinuation. However, whether the decrease in the risk of rebound disease activity is not counterbalanced by the safety and tolerability issues of cumulative exposure to DMTs is unclear. Another approach is de-escalation by interval extension for infusible DMTs (161, 162). The latter could offer the benefit of preserved efficacy with a reduced risk of adverse effects based on observations from the natalizumab and rituximab interval extension studies (161, 162). As proposed by Vollmer et al. de-escalation strategies developed to match the probability of disease activity across the lifespan need to be studied using randomized controlled trials (116).

Treatment discontinuation

The risk of treatment discontinuation should take into account the annualized relapse rate and the presence or absence of radiological activity on MRI in the recent years. Continued progressive worsening despite treatment is not an uncommon reason to discontinue DMTs in patients with secondary progressive MS. DMT-specific considerations should also be factored in, for example, a careful evaluation of the risk of long-lasting immunosuppression with B-cell depleting therapies, alemtuzumab, and cladribine in infection-prone patients with advanced MS. Discontinuing DMT in older patients appears to have no effect on quality of life measures based on a three-center study comparing those outcomes between stoppers and stayers in a cohort of 600 MS patients above the age of 60 (163). Importantly, patients' perspective on treatment discontinuation should be considered. Reluctance on treatment discontinuation is frequent in patients who have been stable for many years and are tolerating their therapies. A recent study evaluated patient-perspective on treatment discontinuation using a survey sent to patients from the North American Research Committee on Multiple Sclerosis (NARCOMS) registry who were ⩾45 years and on their most recent DMT for ⩾5 years (164). The mean age of respondents was approximately 56 years (164). In this study, 66.3% of respondents were unlikely or very unlikely to accept DMT discontinuation (164). In our experience, patients who are stable are usually more reluctant to treatment discontinuation compared to those with continued disability worsening.

Based on the observation of a lower benefit and potentially higher risk profile of DMT use in aging MS patients, recent research has focused on determining when and how to discontinue DMTs in older individuals. The DISCOMS (Discontinuation of Disease Modifying Therapies in MS) trial (NCT# 03073603) is the first randomized controlled trial evaluating the risk of disease activity after treatment discontinuation across 20 centers in the USA. The methodology of this trial was based on a non-inferiority analysis and the primary outcome was the combined measure of relapse and/or new T2 lesion on brain MRI. Other secondary and tertiary outcomes were also analyzed (6-months confirmed EDSS worsening, Symbol-Digit Modalities Test (SDMT) scores, and patient-reported outcome measures). Patients were randomized (1:1 by site) to either continue or discontinue their DMT. Clinical evaluation (relapse occurrence and EDSS scores), as well as MRI interpretation was performed by blinded raters. Mean

follow-up time was 22.4 months. Included individuals ($n = 259$) were 55 years or older of any MS phenotype, had no relapse in the past 5 years, no new MRI lesions in the past 3 years, and were continuously treated with an approved DMT for at least 5 years, with the most recently used DMT for at least 2 years. The mean age of this cohort was 63 years, with a majority of women and RRMS phenotype. Most patients had longstanding (mean disease duration of 22.2 years) and stable (mean time since last documented relapse of 14 years) disease. Around 75% of subjects were treated with low-efficacy injectable therapies (interferon beta1a or 1b or glatiramer acetate) or teriflunomide. The combined occurrence of disease events was 4.69% vs. 12.21% ($p = 0.521$) meaning that non-inferiority was not demonstrated for this combined outcome. Relapses occurred in 0.78% of subjects in the group of patients who continued their DMT and 2.29% in the group who discontinued their DMT ($p = 0.005$), which implies non-inferiority of treatment discontinuation for this outcome. New T2 lesions occurred in 3.9% of subjects in the group of patients who continued their DMT and 10.69% in the group who discontinued their DMT ($p = 0.422$), which implies that non-inferiority was not demonstrated for this outcome. Importantly, these primary outcome events were not associated with worsened disability. Moreover, relapses were very rare in both groups, and most participants with relapses did not have a new lesion on MRI to corroborate the clinical event, suggesting the possibility of pseudo-relapses. New MRI lesions were rare and most had one new lesion only. EDSS progression was seen in about 11% of patients who continued their DMT and 12% of patients who discontinued their DMT, a difference that was not statistically significant. There was also no difference in SDMT scores and patient-reported outcome measures. The authors conclude that although DMT discontinuation is not inferior to continuing DMT in this population, non-inferiority of discontinuing DMT was not demonstrated (in other words: stopping treatment is not non-inferior to continuing treatment).An extension study of the DISCOMS trial is expected (NCT# 04754542; Corboy J et al. ECTRIMS 2022; EP1089). Two other randomized trials are also ongoing: the STOP-I-SEP trial (Disease Modifying Therapies Withdrawal in Inactive Secondary Progressive Multiple Sclerosis Patients Older Than 50 Years, NCT# 03653273, estimated study completion date in January 2028) and the DOT-MS trial (Discontinuing Disease-modifying Therapies in Stable Relapsing-Onset Multiple Sclerosis, NCT# 04260711, estimated study completion date in January 2024).

Other observational studies have evaluated safety of treatment discontinuation in patients with MS, specifically platform therapies. In a large multicenter study using data from the MS base registry in patients with at least 5 years of disease stability treated with INF-b1a/b or glatiramer acetate, and using propensity score matching, patients who pursued and those who stopped their DMT were compared (165). Patients in both groups had a similar relapse rate, but those who discontinued their DMT had a 50% higher hazard for disability progression than those who stayed on treatment, and this higher risk was mostly driven by patients who were stable prior to DMT discontinuation (165). In a small retrospective cohort (n = 69) predominantly treated with glatiramer acetate and interferon with stable disease for >2 years, patients who were < 45 years had a significantly shorter time to first clinical or radiological activity event compared to older patients (166). In a cohort of 221 patients with RRMS treated with either glatiramer acetate or interferon beta 1a/b who discontinued their treatment, Bsteh et al. retrospectively identified an age of 45 years or older at the time of DMT discontinuation, the absence of relapses for more than 4 years, and the absence of active lesion on MRI as independent predictors of absence of clinical activity after stopping DMT (167). Patients who were both older than 45 years and had no relapses in the past 4 years had a very low risk of relapses after stopping their DMT (167). Importantly, higher EDSS scores, an age older than 45 years, and longer disease duration at treatment discontinuation were all associated with a higher risk of disability progression in this study after discontinuation (167). The same group evaluated the performance of a composite score taking into account age, radiological activity and the duration of disease stability prior to DMT discontinuation, and showed that patients with a high composite score had an 85% probability of recurrence of disease activity in the next 5 years after stopping their treatment (168). Similar results were observed in another observational study using propensity score matching to compare patients who stayed or stopped their injectable DMT (169). The mean age of this cohort was 54 years and all included patients were at least 50 years and did not have a relapse in the past 3 years (169). Stoppers did not have a higher likelihood of relapse or EDSS progression, but had a higher risk of reaching an EDSS of 6.0 (169). In another recent multi-center retrospective observational study from Jakimovsky et al. DMT discontinuation was associated with non-relapse disability progression, or PIRA, independently of prior stable disease and age, specifically in patients with an EDSS >6.0 (170). In this study, DMT discontinuation triggered *de novo* disability worsening in previously stable patients with both RRMS and SPMS (170). Taken altogether, the results of these studies corroborate the hypothesis that PIRA is the main driver of disability along the disease course and that DMTs do not halt or alter this neurodegenerative process once it is ongoing, but may play a role in controlling subclinical inflammation even at a later age, specifically in patients with no clear evidence of progressive disability worsening while on treatment and those in the so-called "transition phase."

Data on higher-efficacy DMT discontinuation after a certain age is scarce but yet less reassuring. A two-center study in France from Chappuis et al. retrospectively evaluated the risks of disease activity after platform (glatiramer acetate, interferon beta-1a/b, teriflunomide) and higher-efficacy (fingolimod, rituximab, natalizumab) DMT discontinuation in 232 patients who were older than 45 years (171). Median age in this cohort was around 53 years, median disease duration was 15.8 years, and mean EDSS was 3.8 at DMT discontinuation (171). Most patients did not have a relapse in the past year, but around 25% of those on higher-efficacy DMT and 16% of those on platform DMT did have clinical or radiological activity in the past 3 years (171). Nearly 40% of patients were classified as having SPMS. Importantly, 61.2% of patients who stopped their higher-efficacy DMT had progressive MS (171). A 6% relapse risk in the year after discontinuation was observed for the group on a platform DMTs, 9% for those on fingolimod and 43% for those on natalizumab was observed, peaking in the first 3 months after stopping fingolimod or natalizumab, while no patient had disease activity after stopping Rituximab (171). Hence, the well-established rebound effect after natalizumab discontinuation does not only occur in younger individuals with active relapsing–remitting disease, and remains a significant risk when considering stopping this treatment in older patients, even those with a secondary-progressive disease course. Results from a smaller

prospective observational study are also in line with this observation: in 15 patients with a mean age of 50 years and stable disease for the past 5 years who discontinued natalizumab, all experienced disease activity after a mean follow-up period of 19 months (172). Specifically, 10 patients had a recrudescence of clinical or radiological activity whereas 5 had rebound activity (4 out 5 where >50 years old). In conclusion, discontinuing natalizumab specifically is associated with a significant risk of disease activity at any age and should prompt early switching to another DMT. In regards to fingolimod, the risk of disease activity or rebound activity after discontinuation appears to be lower and more age-dependent compared to Natalizumab, yet present. For instance, a single-center retrospective study looking at all patients who discontinued fingolimod for more than 6 months found than an age > 50 years did not significantly decrease the risk of recurrence of disease activity even though it occurred less frequently in this age group compared to their younger counterparts. Specifically, 11/128 patients were older than 60 years and none of them had recurrence of disease activity after stopping fingolimod (173). In the previously mentioned French study, 2 patients who were older than 60 years experienced recurrence of disease activity after stopping fingolimod (171). Discontinuing fingolimod should therefore also be considered cautiously at any age. There is little evidence on the risk of disease activity reactivation or rebound activity after discontinuation of B-cell depleting therapies. Nevertheless, this category of DMT seems to exert a prolonged effect without a significant risk of rebound of clinical or radiological activity. In a large single-center Swedish cohort treated with rituximab, 808 patients were retrospectively identified, only 92 (11%) had discontinued treatment mostly due pregnancy, adverse events, stable disease, and other reasons (174). There was no difference in age, disease duration, number of previous DMT, and EDSS at rituximab start between those who stayed on and those who stopped rituximab (174). After rituximab discontinuation, 3/92 patients had a relapse and 4/92 had new T2 lesions (one of which had both) at least 3 months after treatment stop (174). Although some patients who discontinued rituximab were started on another DMT, disease activity was rare even in those who stayed off therapy (174). In the French cohort, 9 patients discontinued Rituximab after the age of 45 and none had a relapse after a mean follow-up time of 1.6 years (171). Based on these observations, disease activity appears to remain suppressed long after B-cell depleting therapies discontinuation. Whether this DMT category can be used as an induction therapy and later discontinued safely without an alternative DMT is not clear but would be an interesting treatment approach when considering long-term treatment planning.

In conclusion, there is growing evidence to suggest that treatment discontinuation is relatively safe after the age of 55–60 years in individuals with long-standing and stable disease on platform therapies. Recurrence of disease activity however remains a risk, specifically for patients on fingolimod and natalizumab, and relapse recovery declines with age (175). Clinicians need tools to stratify the risk of disease reactivation to guide clinical decisions, such as the Vienna Innsbruck DMT discontinuation score based on age, activity on MRI, and duration in stable course (VIAADISC score) developed by Bsteh et al. for patients on platform DMTs (168). Predictive scores should be developed for other DMTs, specially for higher-efficacy DMTs as well as for teriflunomide and dimethyl fumarate for which data on discontinuation risk is scarce. The difficulty in developing such tools resides in the high interindividual variability of MS phenotypes and in the lack of predictability and intraindividual variability of disease activity across the disease course. Moreover, we need more time to assess long-term effects of newer DMTs. There are inherent differences in the risk of disease reactivation and the risk of rebound activity with some DMTs after discontinuation and conversely a potential for induction properties of others such as B-cell depleting therapies and cladribine. Finally, it is essential to consider the patients' perspective when making such decisions; patient-reported outcome measures can guide clinicians understand how treatment decisions affect patients' quality of life (163). For now, the decision to discontinue or de-escalate DMTs should be taken in the context of each individual with a clear explanation of the risk–benefit balance to the patient, taking into account treatment-related morbidity and direct and indirect treatment-related costs.

Conclusion and recommendations

Caring for patients with long-standing MS is a quotidian and complex task for their health care providers. Several concerns must be integrated in treatment choices, including the disease process itself and its multiple sequelae, comorbidities, and measure of general health such as frailty. Development of clinical deterioration should be viewed as a potential complication from these several factors, and the management plan should be tailored accordingly. As patients age and transition to a predominantly progressive form, their needs increase as they accumulate symptoms such as weakness, ataxia, spasticity, cognitive impairment, pain, sphincteric and sexual dysfunctions, visual symptoms, sleep problems, and fatigue. Hence, management can become complex and requires frequent adjustments. To optimize health outcomes in this population, multidisciplinary care should be the cornerstone of management (176). Physical and occupational therapists, social workers, psychologists, speech therapists with an expertise in cognition, urologists, and physiatrists are all essential players in the treatment of long-standing MS, and can help patients to maintain their autonomy and quality of life (176). Involving patients in their own care can increase empowerment and coping abilities. In this regard, promoting physical activity, healthier life habits, weight control and good nutrition can delay disease progression and result in a higher sense of wellness. Unfortunately, MS care units remain a luxury in many regions, even in developed countries. As an example, using a survey targeting health care providers across Canada to assess models of MS care, Marrie et al. found that nearly half of MS clinics report an insufficient number of specialized neurologists, and nearly 70% report an insufficient number of non-physician providers (177). Sadly, a majority of clinics had wait times longer than 3 months for patients to be seen by the different providers of the multidisciplinary team (177). Another important aspect of MS management is recognizing polypharmacy and deprescribing when possible, as aging patients with MS often end up with several symptomatic therapies with additive side effects. Polypharmacy is an under-recognized problem and has an additive effect on MS symptoms particularly fatigue, cognitive impairment, and fall risk (160). As discussed throughout this review, the natural evolution of the disease, the shift of pathophysiological processes, the probable decreased efficacy of DMTs after the age of 55 years (supported by real-word data, clinical observations, and the DISCOMS trial), and the safety concerns in this age group, support

the rationale of considering DMT de-escalation and discontinuation in older patients with stable disease, particularly those on platform DMTs (178). Until we have more reassuring data, careful monitoring for recurrence of disease activity after discontinuation is prudent (178). However, the evidence to support this practice is still scarce and there are currently no guidelines on treatment discontinuation, although several consensus groups have published recommendations along these lines (179, 180).

In this regard, recommendations regarding treatment approaches in individuals after the age of 55 years may include the following, until more evidence-based data become available and practice guidelines are developed:

- The benefits and risks of DMTs should be reassessed and discussed with patients periodically taking into account their age, disease duration, clinical and radiological activity in the past few years, rate of disability accrual, comorbidities, and patient preferences. Treatment decisions should hence be individualized in a case-by-case approach.
- DMT discontinuation could be considered in individuals with long standing and stable disease on platform DMTs who are older than 55 years, especially in those older than 60 years.
- The benefit of platform therapies such as interferon beta-1a or b and teriflunomide in individuals with long standing disease after the age of 55 is questionable, and since there is no reported risk of rebound disease activity after discontinuation of these therapies, they could be safely discontinued with careful monitoring in most cases.
- In general, de-escalation could be considered after the age of 55 in patients who have been on high-efficacy DMTs for many years. Although the benefit of fingolimod and natalizumab in this population is questionable, the risk of breakthrough disease activity or rebound activity is non-negligible. De-escalation can be used as a strategy to mitigate this risk.
    - o Switching to lower efficacy DMTs such as teriflunomide, interferon-based preparation, or glatiramer acetate before considering treatment discontinuation could be an option.
    - o Another approach could be de-escalation by interval extension for therapies such as natalizumab and B cell-depleting therapies, although whether the risk of rebound activity is sufficiently mitigated with this approach is unclear.
    - o In patients with recent disease activity for whom natalizumab or fingolimod must be discontinued (e.g., lymphopenia, positive JCV serology), switching to other high-efficacy "induction" therapies such as cladribine or B-cell therapies can be useful in selected cases. These DMTs have more prolonged immunosuppressive effects and do not seem to be associated with rebound effects when stopped, although an additive effect on the risk of PML should be explained to patients.
- At each visit, symptomatic therapies should be reviewed and ineffective medications discontinued. Instead, non-pharmacological interventions, such as aerobic exercise and good sleep hygiene to improve fatigue or stretching to counter spasticity must be encouraged.
- General measures of wellness should be optimized by promoting physical activity and adequate nutrition, optimization of comorbidity management, and promotion of age-specific preventive measures
- Developing outcome measures that are adapted to aging individuals to detect MS-related handicap and appropriately identifying confounders is key to evaluating treatment response and optimally address drivers of disability progression, whether related to MS or not. The EDSS, the most commonly used scale of disability in MS, might not be the ideal tool in this population, as higher scores are associated with older age and polypharmacy, even when used on older individuals who do not have MS (106).

Author contributions

GM: conception and design of manuscript, data review and interpretation, drafting the manuscript, and reviewing the manuscript for intellectual content. CL and NA: drafting the manuscript and reviewing the manuscript for intellectual content. MG, JG, and AP: reviewing the manuscript for intellectual content. PD: conception and design of manuscript, data review and interpretation, and reviewing the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

GM has served on advisory boards for Genentech-Roche, Novartis, Mercks, and Biologix, received speaker fees from Biologix, Mercks, and Novartis, and participated in educational activities for Neurology Live and John Hopkin's e-Litterature Review. CL has served on scientific advisory boards and/or as speaker for EMD-Serono, Biogen, Bristol-Myers Squibb, Roche, Novartis, Actelion, FindTx and Sanofi-Genzyme and has received a Grant for Multiple Sclerosis Innovation from Merck/EMD-Serono.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Alessandra Lugaresi,
University of Bologna, Italy

REVIEWED BY
Eva Havrdova,
Charles University, Czechia
Annette Okai,
Texas Tech University Health Sciences Center, United States

*CORRESPONDENCE
Lorena Lorefice
lorena.lorefice@hotmail.it

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Menopausal transition in multiple sclerosis: relationship with disease activity and brain volume measurements

Lorena Lorefice[1]*, Giuseppe Fenu[2], Marzia Fronza[1], Federica Murgia[3], Jessica Frau[1], Giancarlo Coghe[1], Maria Antonietta Barracciu[4], Luigi Atzori[3], Stefano Angioni[5] and Eleonora Cocco[1]

[1]Department of Medical Sciences and Public Health, Multiple Sclerosis Center, Binaghi Hospital, ASL Cagliari, University of Cagliari, Cagliari, Italy, [2]Department of Neurosciences, ARNAS Brotzu, Cagliari, Italy, [3]Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy, [4]Radiology Unit, Binaghi Hospital, ASL Cagliari, Cagliari, Italy, [5]Division of Gynecology and Obstetrics, Department of Surgical Sciences, University of Cagliari, Cagliari, Italy

Background: Recent evidence has shown a significant association between menopause and multiple sclerosis (MS) progression. This study investigated the possible role of menopause in influencing MS from clinical and neuroradiological perspectives. Notably, the possible association between menopause and brain atrophy has been evaluated.

Materials and methods: This study included women with MS whose ages ranged from 45 to 55 years. Demographic and clinical characteristics were collected, and the reproductive phase was defined as non-menopausal or menopausal based on the final menstrual period. Thus, MS activity over the past year was reported as the annualised relapse rate (ARR), and MRI activity (defined as new T2 lesions and/or the presence of gadolinium-enhancing lesions at the last MRI assessment in comparison with the MRI performed within the previous 12 months) were compared between non-menopausal women (non-MW) and menopausal women (MW). Volume measurements of the whole brain (WB), white matter (WM), grey matter (GM), and cortical GM were estimated using the SIENAX software, and the possible relationship with menopausal status was assessed by regression analysis.

Results: The study included 147 women with MS. Eighty-four (57.1%) were MW, with a mean age of 48.5 $\pm$ 4.3 years at menopause onset and a mean duration of menopause of 4.1 $\pm$ 1.1 years. When compared for ARR, MW reported a lower rate than the non-MW (ARR of 0.29 $\pm$ 0.4 vs. 0.52 $\pm$ 0.5; $p < 0.01$). MRI activity was observed in 13.1% of MW and 20.6% of non-MW ($p = 0.03$). Lower cortical GM volumes (578.1 $\pm$ 40.4 mL in MW vs. 596.9 $\pm$ 35.8 mL in non-MW; $p < 0.01$) have also been reported. Finally, multivariate analysis showed a significant association of lower ARR ($p = 0.001$) and cortical GM volume ($p = 0.002$) with menopausal status after correction for chronological age and other variables.

Discussion: Menopause may be an adverse prognostic factor of MS. Our preliminary results suggest that menopause may facilitate cortical GM atrophy, probably due to a decline in the neuroprotective effects of estrogen, with negative effects on MS evolution.

KEYWORDS

aging, brain atrophy, menopause, multiple sclerosis, neurodegeneration, oestrogen deprivation

Introduction

One of the emerging topics in the field of gender medicine applied to multiple sclerosis (MS) is the issue of menopause (1), and its effects (often superimposed on those of aging) on various aspects of the disease (2). Menopause is a physiological event that marks the end of a woman's reproductive competence (3). Characterised by irreversible interruption of menstruation, it occurs in the general population at an average age of approximately 50 years (4). Several immunologic changes have been described in postmenopausal women. These modifications, mainly driven by oestrogen deprivation, overlap with age-related changes, resulting in decreased CD4 T lymphocytes, B lymphocytes, natural killer (NK) cells cytotoxic activity, and increased proinflammatory responses, with effects on the risk of infection and autoimmunity (5). Notably, MS is characterised by great pathogenetic, clinical, and neuroradiological heterogeneity, with different disease outcomes in relation to the inflammatory and neurodegenerative mechanisms underlying the disease (6), window for therapeutic intervention (7), and type of therapeutic intervention (8). Numerous studies have shown a predominance of the disease in females of all ages, and recent studies have shown a shift in MS onset to older age, with a higher frequency of late-onset forms among women (9). For these forms, the possible effect of menopause on susceptibility to the disease should be considered, attributable to the postmenopausal proinflammatory state and deprivation of the neuroprotective effects of oestrogens and progestins (10, 11), which would act to reduce the resilience of the central nervous system (CNS) thereby facilitating the onset of MS in the presence of other predisposing factors (12). Recently, a large study has shown that women with MS have greater inflammatory activity in terms of relapse than men, up to the age of 50 years. After that, the difference disappears, and the evolution of the disability worsens, becoming more similar in both the sexes (9, 13). Therefore, the possible effects of menopausal transition on the disease characteristics should be considered. Given the high number of women with MS among the aging population, it is crucial to understand the effects of menopause and its interaction with MS. Previously, in a longitudinal cohort of women with MS who were followed for approximately 10 years during the menopausal transition, Bove et al. showed that menopause represented an inflection point in their Expanded Disability Status Scale (EDSS) changes (14). In line with these findings, a multicentre study evaluating the effect of menopause on the clinical course of MS showed a significant decrease in annualised relapse rate (ARR) 2 years after menopause compared to the previous 2 years, while disability worsened (15). Conversely, Otero-Romero S et al. showed that menopause did not modify disability trajectories in a longitudinal cohort of women with MS who were followed from disease onset, after controlling for age and disease duration (16), thereby leaving controversial aspects to be investigated. Additionally, even less explored are the effects of menopause on neuroradiological activity and brain volume measurements in women with MS, which are significantly related to long-term disability (17). With regard to the latter point, a longitudinal study has recently shown that ovarian aging, as defined by anti-Müllerian hormone (AMH) levels, is associated with greater clinical disability and grey matter loss in women with MS (18) and is independent of the chronological age and disease duration, highlighting the crucial role of sex hormones in MS disease outcomes (19). In this framework, the present study aimed to evaluate, in a cohort of women with MS aged between 45 and 55 years, the possible impact of menopausal transition on clinical activity and MRI outcomes, and its effects on the whole brain (WB), white matter (WM), grey matter (GM), and cortical grey matter (cGM) volumes.

Methods

Participants

Women with relapsing–remitting MS (RRMS) (20) between the ages of 45 and 55 years were recruited from the Multiple Sclerosis Centre, Binaghi Hospital, University of Cagliari. Women were classified as as menopausal (MW) or non-menopausal (non-MW). Menopause onset was defined as the final menstrual period beyond which no menses occurred for 12 months (21) in association of neurovegetative menopausal symptoms (hot flushes). Women with surgical menopause were excluded, as were women exposed to oestrogen-progestin therapy (oral contraceptives) for up to 3 years before the final menstrual period or hormonal treatment during the menopausal transition. Demographic and clinical data [disease duration, disability level assessed by the EDSS (22), and disease-modifying therapy (DMT)], were recorded for each woman. MS clinical activity was defined as the presence of clinical relapse (new symptoms or the return of old symptoms for ≥24 h in the absence of an infection or fever). Thus, the annualized relapse rate (ARR), defined as the number of confirmed relapses in the last 12 months, was estimated after evaluation of medical records. MRI activity was defined as the presence of new or enlarged T2 lesions or gadolinium-enhancing T1 lesions at the last MRI assessment compared to the MRI performed within the previous 12 months (20). Quantitative MRI evaluations were performed for each patient, and brain volume measurements were estimated at the time of the last neurological assessment. Informed consent was obtained from all the participants after obtaining approval from the local ethics committee.

MRI acquisition

Brain volumes were measured using a 1.5 T scanner Siemens Magnetom Avanto (Siemens Medical Solutions, Erlangen, Germany). Three-dimensional magnetisation-prepared rapid gradient-echo

(MPRAGE) was used to obtain 174 contiguous sagittal 3D-T1WI images with the following parameters: slice thickness = 1.3 mm, repetition time/echo time = 2400/3.6 ms, inversion time = 1,000 ms, flip angle = 8°, field of view = 24 cm, number of excitations = 1, and pixel matrix = 192 × 192. Brain volumes were measured for each participant on T1 W gradient echo images using SIENAX, a previously described cross-sectional version of the Structural Image Evaluation using Normalisation of Atrophy (SIENA) software to estimate the global brain volume normalised for head size, as well as the selective measurement of normalised WM, GM, and cortical GM volumes (23). All brain volume measurements were performed in a single session using the same MRI protocol.

Statistical analyses

All statistical analyses were performed using SPSS for Mac version 20.0 (SPSS Inc., Chicago, IL, United States). First, a descriptive analysis was performed, reporting demographic, clinical, and MRI data as means (quantitative variables) or percentages (qualitative variables). A t-test was used to compare demographics (age), clinical data (MS duration, EDSS score, and ARR), and MRI measurements of the WB, WM, GM, and cortical GM in non-MW and MW. Similarly, analysis of variance (ANOVA) was used to compare qualitative variables (presence of MRI activity in the last year and use of high-efficacy DMTs).

Therefore, regression analyses were performed to investigate the relationship of ARR and MRI activity (entered into the models as dependent variables) with menopausal status, while controlling for other demographic and clinical variables. Similarly, the relationship between MRI measurements of WB, WM, GM, and cortical GM volumes and menopausal status was explored using regression analyses. Statistical significance (p) was set at <0.05 for all assays.

Results

The study included 147 relapsing remitting women with MS between the ages of 45 and 55, of whom 63 (42.9%) were non-MW and 84 (57.1%) were MW, with an average age of 48.5 ± 4.3 years at menopause onset. The mean age was 46.1 ± 3.1 years in non-MW and 52.6 ± 3.2 years in MW ($p < 0.01$), with disease duration of 15.5 ± 6.3 years and 18.2 ± 8 years, respectively ($p < 0.05$). Table 1 summarises the demographic and clinical characteristics of the patients included in this study, and also indicates the DMTs. In particular, high-efficacy DMTs were reported in 23.8% of non-MW compared to 17.8% of MW ($p < 0.05$). Table 2 shows the characteristics of non-MW and MW with clinical and neuroradiological activity in the last year of the disease and presents the comparison data of the brain MRI measurements obtained by an independent *t*-test. In particular, in the last year, an ARR of 0.52 ± 0.5 in non-MW vs. 0.29 ± 0.4 in MW ($p < 0.01$) was reported, with MRI activity observed in 20.6% of non-MW vs. 13.1% of MW ($p < 0.05$). Regression analysis was performed to evaluate the factors that influenced clinical activity, as indicated by the ARR: an inverse relationship was observed between chronological age ($p = 0.028$) and menopausal status ($p = 0.001$). Analogously, an inverse relationship that tends towards significance was observed between MRI activity and chronological age ($p = 0.064$), while no relationship was reported with menopausal status (Table 3). Multivariate analysis was then performed considering WB, WM, GM, and cortical GM as dependent variables while controlling for age, disease duration, EDSS score, and menopausal status, included in the model as independent variables. A significant association between lower cortical GM volume and menopausal status ($p = 0.002$) was reported, independent of other demographic (age) and clinical variables (MS duration and EDSS) (Table 4).

TABLE 1 Demographic and clinical features of MS women categorized in relation to menopausal status.

	MS women (147) (age range: 45–55 ys)	
	Non-menopausal MS women (63)	Menopausal MS women (84)
Age (mean ± sd) years	46.1 ± 3.1	52.6 ± 3.2**
MS duration (mean ± sd) years	15.5 ± 6.3	18.2 ± 8.7*
EDSS score	3.3 ± 1.8	3.4 ± 2.1
Age at Menopause onset (mean ± sd) years	NA	48.5 ± 4.3
Follow-up post menopause (mean ± sd) years	NA	4.2 ± 3.5
Use of II° line DMTs	15 (23.8%)	15 (17.8%)*

*p value: <0.05; ***p value: <0.005. Chi-square and independent-samples *t*-tests were used to compare demographic and clinical variables between the two groups.

Discussion

Several studies have shown that natural menopause may contribute to a more rapid decline in women with MS, resulting in a turning point in the worsening of MS (14–16). These studies evaluated the impact of menopausal transition on clinical activity and EDSS changes; however, its effects on MRI activity and neurodegenerative aspects remain poorly explored. In this context, our study aimed to evaluate the impact of menopause on the course of MS, and explore the effects on MRI inflammatory activity, which is defined as an increase in lesion burden and presence of gadolinium-enhancing lesions, and the impact on brain atrophy, a principal surrogate indicator of neurodegeneration and predictor of long-term MS outcomes. In line with the results of previous studies, a relationship between lower ARR with chronological age and menopausal status was observed. At the same time, lower MRI activity appears to be associated with increasing age but is independent of menopause. It is now known that aging affects many aspects of MS (2). On the one hand, the peripheral immune response decreases, resulting in immunosenescence and making inactive plaques predominant; on the other hand, inflammation becomes compartmentalised and thus more challenging to detect, while neurodegenerative processes become more evident (24). Therefore, it is difficult to distinguish the effects exclusively linked to aging from those of menopause, which have similar effects on many aspects of immunity, brain damage, and disease evolution. Previously, Graves et al. reported that ovarian aging,

as indicated by lower AMH levels, was associated with both clinical and radiographic metrics of MS severity, as shown by the relationship with lower grey matter volume after adjustments for chronological age and disease duration (18). Similarly, our study revealed an association between lower cortical grey volume and menopausal status, independent of chronological age and duration of MS, suggesting an increased level of neurodegenerative pathological processes after this reproductive biological transition. It is known that oestrogen levels decrease with menopause (3), and in line with this decrease, their neuroprotective effects decline (25). As shown in experimental autoimmune encephalomyelitis (EAE) models, oestrogen preserves synaptic transmission and has a role in sparing neurons and synapses in the brain and myelin and axons in the spinal cord (26, 27). Oestrogen exerts neuroprotective effects through various mechanisms. First, oestrogen has a suppressive effect on neuroinflammation and strongly inhibits microglial activation. In addition, a direct neuroprotective effect on the mitochondria, with increased aerobic glycolysis, respiratory efficiency, ATP generation, Ca2+ load tolerance, and antioxidant effects, has been reported (28, 29). EAE studies with various oestrogen treatments have led to clinical disease defence, as well as protection from CNS inflammation, axonal loss, demyelination, and promotion of remyelination processes (30). Thus, the reduction in the anti-inflammatory role of oestrogen after menopause could cause inflammatory damage to axons and myelin, contributing to brain damage and the accumulation of disability. Moreover, oestrogen depletion associated with menopausal transition facilitates the propensity for cardiovascular disease (4) thereby increasing the risk of aging-related comorbidities, and the impact of these comorbidities on brain damage should be considered (31). Beyond this, the effects of menopausal transition on frailty, conceived as a marker of the depletion of the organism's homeostatic reserves (32), and on brain resilience (33) to various types of brain chronic damages (MS related or not) remain unexplored.

The present study has several limitations. First, the effects of menopausal transition on MS evolution were evaluated by comparing groups of MW and non-MW in the same age range, but not longitudinally in the same cohort. Second, most women with MS were treated with DMTs, which may have improved the course of the disease, making it more difficult to detect the effects of the menopausal transition. However, we chose not to exclude treated patients to avoid selection bias (such as the inclusion of only benign or stable MS). Furthermore, MRI data were not available for healthy controls to determine whether the association between menopause and lower GM volume was specific to women with MS. Similarly, we did not collect data of male MS patients and controls, which would have helped distinguish the effects of menopause on clinical and MRI measurements from those of aging and andropause. Furthermore, normative values for brain volumes have never been established, but only specific cut-off values capable of distinguishing between 'physiological' and 'pathological' brain volume loss in MS patients assessed longitudinally (34). However, these values are not applicable to our study since we did not longitudinally evaluate the brain volumes.

Finally, it should be emphasised that the menopausal transition process is gradual and begins even before the final menstrual period; in addition, the duration of menopause was different in the group of WM examined, while hormonal changes, which can affect the disease's immunity, inflammation, and neurodegenerative aspects, were not evaluated in this study (5).

TABLE 2 Annualized Relapse Rate, MRI activity and brain volume measurements in menopausal and non-menopausal MS women.

	Non-menopausal MS women (63)	Menopausal MS women (84)
ARR in the last year	0.52 ± 0.5	0.29 ± 0.4**
MRI activity in the last years	13 (20.6%)	11 (13.1%)*
Whole brain Mean value (mL)	1453.1 ± 57.1	1438.6 ± 74.8
White matter Mean value (mL)	688.1 ± 36.9	684.4 ± 35.4
Grey matter Mean value (mL)	764.9 ± 43.2	754 ± 50.1
Cortical grey matter Mean value (mL)	596.9 ± 35.8	578.1 ± 40.4**

Chi-square and independent-samples *t*-tests were used to compare clinical and MRI variables between the two groups.

Conclusion

Menopause may represent an adverse prognostic factor for MS evolution, inducing a worsening of disability and neurodegenerative aspects of MS. Our preliminary results suggest that menopause could facilitate cortical GM atrophy, probably due to a decline in the neuroprotective effects of oestrogen. In this context, further studies are needed to evaluate the impact of menopause on disease evolution. In particular, it is crucial to define studies that consider homogeneous groups of MS women, also exposed to the same type of DMT, and studies with a longitudinal design, including healthy women in the same biological phase, to define better how menopause interacts with MS and

TABLE 3 Multiple regression analysis.

	Annualized Relapse Rate				MRI activity			
		95% C.I. for EXP (B)				95% C.I. for EXP (B)		
	B	Lower	Upper	*p*	*B*	Lower	Upper	*p*
Age	−0.028	−0.003	−0.052	0.026	−0.022	−0.045	0.001	0.064
MS duration	−0.009	0.001	−0.019	0.075	0.001	−0.009	0.010	0.889
Menopause	−0.443	−0.664	−0.223	0.001	0.105	−0.104	0.315	0.322

Relationship of ARR with demographic, MS features and menopausal status.

TABLE 4 Multiple regression analysis.

	Cortical Grey Matter			
		95% C.I. for EXP (B)		
	B	Lower	Upper	*p*
Age	1.265	−0.623	30.152	0.188
MS duration	0.220	−0.556	0.996	0.576
EDSS	−8.972	−12.098	−5.847	0.001
Menopause	−28.881	−45.906	−11.856	0.002

Relationship of cortical GM volume with demographic, MS features and menopausal status.

to discriminate the clinical, neuroradiological, and immunological effects induced by aging and aging-related comorbidities (35). Additionally, the effects of sex on immunosenescence and brain resilience should be further investigated with a view to facilitate an approach increasingly focused on gender medicine.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Multiple Sclerosis Centre, University of Cagliari. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LL conceptualized the study and wrote, reviewed, and edited the manuscript. GF, MF, JF, GC, FM, and MB were responsible for resources and data curation. LA, SA, and EC supervised the study. All authors contributed to the article and approved the submitted version.

Conflict of interest

LL, GF, JF, GC, and EC received honoraria for consultancy or speaking from Biogen, Novartis, Sanofi, Genzyme, Serono and Teva and Almirall.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Alessandra Lugaresi,
University of Bologna, Italy

REVIEWED BY
Shalom Haggiag,
San Camillo Forlanini Hospital, Italy
Abdorreza Naser Moghadasi,
Tehran University of Medical Sciences, Iran

*CORRESPONDENCE
Luigi Carbone
✉ drcarboneluigi@gmail.com

†These authors have contributed equally to this work and share first authorship

‡These authors have contributed equally to this work and share last authorship

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Optimizing the "Time to pregnancy" in women with multiple sclerosis: the OPTIMUS Delphi survey

Luigi Carbone[1*†], Doriana Landi[2†], Raffaella Di Girolamo[3], Paola Anserini[4], Diego Centonze[5,6], Girolama Alessandra Marfia[2‡], Carlo Alviggi[3‡] and the Interdisciplinary Group for Fertility in Multiple Sclerosis (IGFMS)

[1]Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy, [2]Multiple Sclerosis Clinical and Research Unit, University Hospital of Rome Tor Vergata, Rome, Italy, [3]Department of Public Health, School of Medicine, University of Naples Federico II, Naples, Italy, [4]UOS Physiopathology of Human Reproduction, IRCCS Ospedale Policlinico San Martino, Genova, Italy, [5]Department of Systems Medicine, Laboratory of Synaptic Immunopathology, "Tor Vergata" University, Rome, Italy, [6]Unit of Neurology, IRCCS Neuromed, Pozzilli, Isernia, Italy

Background: The debate on how to manage women affected by multiple sclerosis (MS) during reproductive age is still open, as is the issue of fertility in such patients. Main issue regard the identification of the optimal window for pregnancy and how to deal with medical therapy before and during conception. The aim of this Delphi consensus was to collect the opinions of a multidisciplinary group, involving reproductive medicine specialists and neurologists with experience in the management of multiple sclerosis women with reproductive desire.

Methods: Four experts plus scientific coordinators developed a questionnaire distributed online to 10 neurologists and later discussed the responses and amended a list of statements. The statements were then distributed *via* an online survey to 23 neurologists (comprising the first 10), who voted on their level of agreement/disagreement with each statement. Consensus was achieved if agreement or disagreement with a statement exceeded 66%.

Results: Twenty-one statements reached consensus after two rounds of voting, leading to the following main recommendations: (1) Fertility evaluation should be suggested to wMS, in case of the need to shorten time to pregnancy and before treatment switch in women on DMTs contraindicated in pregnancy, particularly in case of highly active disease and age > 35 years. (2) ART should not be discouraged in wMS, but the use of DMTs until pregnancy confirmation should be suggested; ART may be considered in order to reduce time to pregnancy in MS women with a reduced ovarian reserve and/or age > 35 years, but in case of an expected poor ART prognosis and the need for more than one ART cycle, a switch to a high-efficacy DMD before ART should be offered. (3) Oocyte cryopreservation may be considered in women with reduced ovarian reserve, with unpredictable time to complete diagnostic workup and achieve disease control; a risk/cost–benefit analysis must be performed in women >35 years, considering the diminished ovarian reserve.

Conclusion: This consensus will help MS neurologists to support family planning in wMS, respecting MS therapeutic needs while also taking into account the safety and impact of advancing age on fertility.

KEYWORDS

multiple sclerosis, infertility, time to pregnancy, Delphi, assisted reproductive technology

1. Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS) with a female-to-male sex ratio of 3:1 (1). It is more common among women of reproductive age (2). Previously, MS was considered an obstacle for motherhood, given the huge impact that the disease had on the quality of life of affected women, the social stigma, and the lack of data on fetal outcomes (3). Although the rate of childlessness is still higher in MS women compared to the general population, it is now ascertained that pregnancy in MS women is not associated with adverse obstetric outcomes (4). Likewise, MS course does not worsen during pregnancy (5). However, an increased risk of relapse after pregnancy is reported, especially in women with MS who relapse shortly before pregnancy and with higher pre-conceptional disability (6). Currently, the issue of fertility in women with MS is still debated. Roux et al. observed that the fecundity of MS women seems not different from the general population (7). However, some epidemiological studies have shown that women with MS may have fewer children than the general population (8). To date, the improvements in the clinical conditions of patients, obtained through the use of increasingly effective disease-modifying drugs (DMDs), have favored the openness to the maternity project by both patients and neurologists (9). It remains to be clarified, however, whether MS causes a reduction in fertility, as occasionally reported in the literature, and whether this condition should be ascribed to the therapies or to the disease itself (10–14). Potential underlying reasons for this could include the effects of the autoimmune disease on fertility (15). Furthermore, taking into account the ever-increasing age at which women are planning pregnancy nowadays, it happens more and more often that women with MS find themselves in the need to request assisted reproductive technology (ART) treatments to achieve pregnancy (16). In light of this scenario, it appears of striking importance to define strategies to manage women with MS who express a desire for conception, whether it can occur spontaneously or requires access to ART programs, with the aim of encouraging the realization of the maternity project in a context of safeguarding the neurological health of women with MS. As pregnancy planning is a fundamental driving factor in the treatment decision-making of women with MS, there is an emerging need to define how and when the fertility of the women with MS and more generally of the couple should be assessed to provide accurate and up-to-date counseling. The aims of this Delphi consensus were (1) to collect the expert opinion of neurologists involved in MS treatment and with expertise in pregnancy management, about the best practice in handling the reproductive desire in MS women and treatment plan in relation to pregnancy planning, and (2) to address the issue of couples' fertility evaluation and the feasibility of ART treatments and oocyte preservation, in collaboration with reproductive medicine experts, with the purpose to optimize the time to pregnancy while minimizing the risk of relapses and undertreatment in MS women.

2. Materials and methods

2.1. Participants

The Delphi consensus involved a scientific board, comprising the scientific coordinators (CA, DC, and GAM) and four additional experts (PA, DL, LC, and RDG). A panel of 10 experts and, successively, an extended panel of 23 experts (comprising the first 10) were suggested by the scientific board. The panel comprised neurology experts working in the field of MS (Table 1). Experts have been selected according to the following criteria: (1) clinical/research experience on the topic of pregnancy/fertility/women's health in MS and/or (2) consolidated experience in the management of wMS (i.e., working in large Italian MS centers). Geographical provenance has been considered in order to ensure that representatives from all the main Italian regions are included.

2.2. The consensus process

The scientific board generated a questionnaire (Step 1) with the aim of identifying the key topics and gaps in the treatment of fertility in women with MS. The questionnaire included open and multiple-choice questions and was distributed online to a restricted panel of 10 experts (Step 2). Based on the replies, the scientific coordinators developed the initial statements (Step 3). In Step 3, the scientific board discussed these statements during two web conferences, having the possibility to add, remove, or amend the proposed statements and references. The final selection of statements was decided by consensus and approved by the scientific coordinator and scientific board by email.

In Step 4, an online survey of the statements was circulated to the extended panel. Each participant anonymously rated his/her level of agreement with each statement using a 5-item Likert scale: 1 = totally disagree; 2 = disagree; 3 = neither agree nor disagree; 4 = agree; 5 = totally agree. Participants were also asked to provide the main reasons for their chosen level of agreement or disagreement (free text). Consensus was considered to have been achieved if the proportion of participants either disagreeing with a statement (responding 1 or 2) or agreeing with a statement (responding 4 or 5) exceeded 66%. If the proportion of participants either agreeing or disagreeing with a statement did not exceed 66%, that statement was discussed according to the feedback received and rephrased. In Step 5, the results of the online survey were discussed in a web conference by the scientific board. Another survey, including only the rephrased statement(s), was sent for a further round of voting (Step 6). The protocol required that this process be repeated, with the statements being revised, until consensus was reached for every statement (Figure 1).

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TABLE 1 Participants involved in the Delphi consensus process.

Name	Place	Step 1 Questionnaire development	Step 2 Questionnaire distribution	Step 3 Statements' development	Step 4 Statements' grading	Step 5 Statements' Rephrasing	Step 6 Statements' grading
Carlo Alviggi*	Naples	Y		Y		Y	
Diego Centonze*	Rome	Y		Y		Y	
Gerola Alessandra Marfia*	Rome	Y		Y		Y	
Paola Anserini*	Genova	Y		Y		Y	
Doriana Landi*	Rome	Y		Y		Y	
Luigi Carbone*	Naples	Y		Y		Y	
Raffaella Di Girolamo*	Naples			Y		Y	
Eleonora Cocco	Cagliari		Y		Y		Y
Emilio Portaccio	Florence		Y		Y		Y
Roberta Lanzillo	Naples		Y		Y		Y
Simona Bonavita	Naples		Y		Y		
Paola Perini	Padua		Y		Y		Y
Diana Ferraro	Modena		Y		Y		Y
Matilde Inglese	Genova		Y		Y		Y
Marinella Clerico	Turin		Y		Y		Y
Emanuele D'Amico	Catania		Y		Y		Y
Pietro Annovazzi	Gallarate		Y		Y		Y
Carla Tortorella	Rome				Y		Y
Giovanna Borriello	Rome				Y		Y
Massimiliano Di Filippo	Perugia				Y		Y
Paola Cavalla	Turin				Y		Y
Raffaella Cerqua	Ancona				Y		Y
Giovanna De Luca	Chieti				Y		
Roberta Fantozzi	Pozzilli				Y		Y
Paola Valentino	Catanzaro				Y		
Paolo Ragonese	Palermo				Y		Y
Pietro Iaffaldano	Bari				Y		
Cinzia Cordioli	Brescia				Y		Y
Valentina Torri Clerici	Milan				Y		Y
Cinzia Scandellari	Bologna				Y		Y

*Scientific board members.

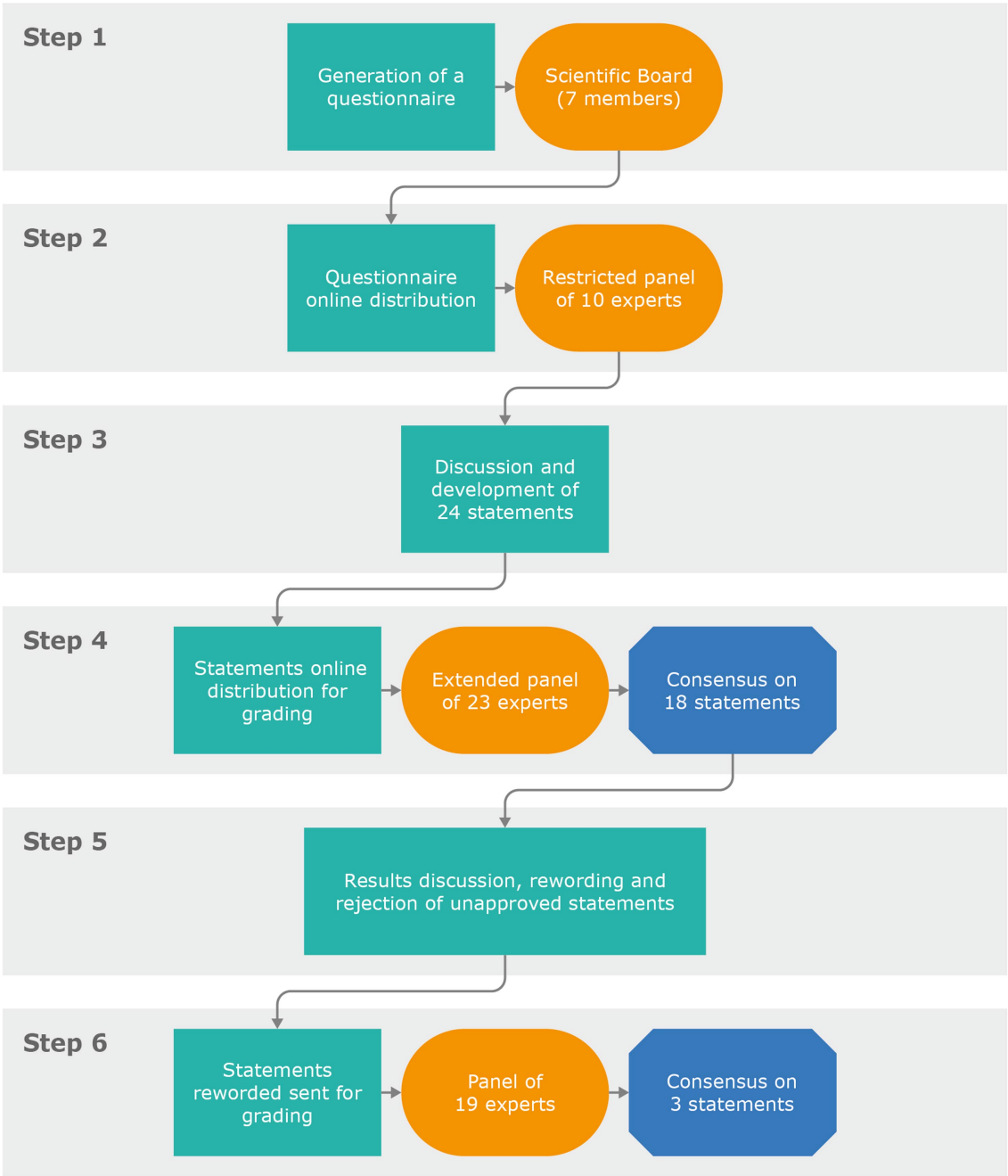

FIGURE 1
Steps of the Delphi consensus process.

3. Results

3.1. Results overview

The scientific board developed 24 statements (Table 2). Consensus on each statement was reached in a web conference and subsequent email discussion. All members of the scientific board approved the final wording. The 24 statements approved by the scientific board were related to the evaluation of fertility in women/couples with MS (7 statements); management of MS treatment strategies in relation to pregnancy planning (5 statements); and indications for and management of access to medically assisted reproduction in women with MS (12 statements), divided into three subsections: medically assisted reproduction treatments for women with MS, MS treatment during medically assisted reproduction, oocyte cryopreservation in women affected by MS. Overall, 23 members of the extended panel completed the entire survey. All statements were rated by all experts. Consensus was achieved for 18 of the 24 statements after the first round of voting. Statements that did not reach the consensus threshold were statements 1, 7, 12, 14, 17, and 18. For three statements (12, 14, and 18) for which consensus threshold was not achieved, the neutral option (neither agree nor disagree) was higher than the sum of the

TABLE 2 Statements approved by the scientific board.

	Evaluation of fertility in women or men with MS
1.	The fertility potential of women with multiple sclerosis (MS) should be evaluated before starting any treatment.
2.	The fertility evaluation of the couple should be suggested, if there is a need to shorten the time to pregnancy in a woman with MS.
3.	The fertility potential of women/couples should be always evaluated in women with highly active MS who wish to have children.
4.	Fertility potential evaluation should be considered in treatment decision-making in MS women of >35 years of age (advanced maternal age).
5.	Neurologists involved in MS care must be trained to interpret the couples' fertility potential accurately to optimize patients' counseling.
6.	Multidisciplinary fertility counseling should be offered to all women with MS and their partners.
7.	Fertility counseling should be proposed for all men with MS.
	Management of MS treatment strategies in relation to pregnancy planning
8.	First-line DMDs (interferons β and glatiramer acetate) should be continued until pregnancy confirmation and during pregnancy, if needed.
9.	In case of pregnancy desire, the couples' fertility potential should be evaluated before treatment switch in women on disease-modifying drugs (DMDs) that are contraindicated in pregnancy.
10.	In case of MS patients in treatment with DMDs not compatible with pregnancy, interferon β is a good bridging option.
11.	Contraception should be maintained during DMD washout if the treatment is not compatible with pregnancy.
12.	Considering that the elimination time of cladribine tablets is 1 week, in view of available scientific evidence, shortening the 6-month interval between cladribine treatment and conception is safe and may reduce the time to conception.
12 revote.	Considering that the elimination time of cladribine tablets is 1 week, in view of available scientific evidence, shortening the 6-month interval between cladribine treatment and conception could be safe and may reduce the time to conception. Further evidence is needed to confirm this statement.
	Indications for and management of access to medically assisted reproduction in women with MS
	Medically assisted reproduction treatments for women with MS
13.	Medically assisted reproduction is not contraindicated in women with MS.
14.	Assisted reproductive techniques (ARTs) should be considered in order to reduce time to pregnancy in MS women with a reduced ovarian reserve and/or age > 35 years.
14 revote.	In patients with stable disease, assisted reproductive techniques (ARTs) could be considered in order to reduce time to pregnancy in MS women with a reduced ovarian reserve and/or age > 35 years.
15.	The psychological wellness of a couple in which one member has MS should be evaluated before planning assisted reproduction cycles.
16.	Extensive counseling about the risk of MS worsening/relapse should be offered before starting ART.
17.	Time to pregnancy should be shortened in MS women who respond suboptimally to DMDs and require treatment switch.
	MS treatment during medically assisted reproduction
18.	Women with MS who have a poor ART prognosis, and may require more than one ART cycle to conceive, should be switched to a high-efficacy DMD before ART.
18 revote.	In women with MS who have a poor ART prognosis, and may require more than one ART cycle to conceive, a switch to a high-efficacy DMD before ART should be considered.
19.	First-line DMDs (interferons β and glatiramer acetate) should be continued until pregnancy confirmation after ART and during pregnancy, if needed.
20.	Second-line DMDs licensed for use during pregnancy should be continued during pregnancy after ART.
21.	Horizontal switch should be proposed for women with MS treated with DMDs not compatible with pregnancy before undergoing ART.
	Oocyte cryopreservation in women affected by MS
22.	Oocyte cryopreservation should be considered in women with reduced ovarian reserve, who require unpredictable time to complete diagnosis workup and achieve control of the disease.
23.	Oocyte cryopreservation should be proposed to women with MS who must postpone pregnancy due to poor disease control that requires highly effective treatments not compatible with conception.
24.	In women above 35 years of age, the option of oocyte cryopreservation should be evaluated in light of the ovarian reserve of the women and the risk-cost/benefit analysis.

"disagree" option. The comments provided are shown in the Supplementary material. The mean neutral opinion on the first round was 14% (max 34.78%; min 0%). Considering only the statements that reached the consensus in the first round, the mean agreement was 83% (max 100%; min 68%; Figure 2). Following a discussion concerning the statements that did not reach an agreement, the scientific board decided to reject three of them (1, 7, 17) for the following reasons: Statements 1 and 7 concerned fertility evaluation of all men and women with MS, regardless desires, conditions, etc. The board agreed that the evaluation of fertility potential, based on patients' conditions

and desires, was well-covered by the other statements under the fertility evaluation section. Statement 17 was considered redundant since the time to pregnancy and treatment switch are discussed in greater detail in other statements of the section. Three statements (12, 14, and 18) were rephrased and circulated to the panel for a second round of voting (Step 6). Nineteen out of 23 experts participated in the second round. All the statements rephrased reached consensus. Statements are discussed in detail below. To conclude, experts agreed on three main concepts that arose from this consensus (Table 3).

3.2. Multiple sclerosis statements approved (first and second rounds)

3.2.1. Topic 1. Evaluation of fertility in women or men with MS

S2. The fertility evaluation of the couple should be suggested, if there is a need to shorten time to pregnancy in a woman with MS.

S3. The fertility potential of women/couples should be always evaluated in women with highly disabling MS who wish to have children.

S4. Fertility potential evaluation should be considered in treatment decision-making in MS women of >35 years of age (advanced maternal age).

S5. Neurologists involved in MS care must be trained to interpret the couples' fertility potential accurately to optimize patients' counseling.

S6. Multidisciplinary fertility counseling should be offered to all women with MS and their partners.

The statements concerning fertility evaluation reached 86.96, 73.92, 82.61, 73.91, and 69.57% agreement, respectively. In women affected by MS, shortening the time to pregnancy could depend both on fertility and MS issues. Given that no biomarkers exist to discriminate fecundity, time to pregnancy is becoming a useful surrogate to describe it at the population level (17, 18). In fact, in relation to fertility issues, it is well acknowledged that fertility is a time-dependent condition that declines with aging (19). The decline in female fertility is constant after 30 years of age, but increases dramatically after 35 years (20). In this regard, both the quantity and the quality of oocytes decrease, with an increase in miscarriage rates and aneuploidy (20–22). Indeed, ovarian reserve markers reflect the pool of oocytes a woman might benefit for reproductive purposes and time to pregnancy shortens with increasing levels of them (23). Furthermore, advanced maternal age (i.e., over 35 years old) has been associated with an increase in adverse pregnancy outcomes (24, 25). Therefore, time to pregnancy acquires even more importance in relation to chronic and autoimmune diseases, whose incidence usually peaks during reproductive years and where various issues coexist, determining reproductive concerns. Specifically, fertility issues in MS have been a matter of debate for years (26). Despite reports of an increased prevalence of infertility among MS women (27, 28), the heterogeneity of the data and the presence of numerous confounding factors have not yet allowed for definitive conclusions (29). In particular, although pregnancy for MS women does not seem associated with severely adverse obstetric outcomes (30), the higher rate of childlessness among MS patients (31) could be explained by psychosocial factors, such as current disability or fear of future problems, fear of genetically transmitting MS, fear of not starting/discontinuing treatments (32), coexisting with biological factors, such as sexual dysfunction, reduced libido, altered sensitivity, abnormal endocrine patterns, and ovarian reserve (26). In addition, ovarian reserve has been studied in MS women with contrasting results (10–14, 33, 34). Interestingly, when the disease course is worse, the ovarian reserve has been found to be lower (12, 33), thereby complicating the eventual reproductive project. Moreover, considering different clinical phenotypes and the difficulty in predicting disease progression (35), fertility evaluation remains a remarkable practice to carry out in MS women who wish to have children whatsoever, even when there is a high activity of disease, the resolution of which could take years and thus be associated with a reduced ovarian reserve. Concomitantly, women with higher disease activity may require treatment with more powerful drugs; currently, there are very few data about the safety of the fetus for the majority of these treatments. For these reasons, women with worse prognostic factors desiring pregnancy may choose to be undertreated while trying to conceive or to waive the reproductive project. In this population, an objective assessment of fertility could be of utmost importance as it may dramatically impact patients' counseling in order to limit avoidable disability or to influence treatment choices. Considering the age-related decline of fertility, its evaluation should be explicitly proposed to women >35 years old, since later it may be too late. On the other side, it should not be taken for granted that women with MS aged >35 years should waive pregnancy desire. Bonavita et al. observed that childlessness was more common in the subgroup of patients aged 36–45 years (8), and in 78% of cases, the treatment was not selected considering family planning. In the general population, the average age of women at the birth of their first child has increased (36) for several social reasons that are also shared by women with MS. Additionally, these women start pregnancy planning after having spent years trying to achieve disease remission. Moreover, access to ART programs is becoming more common among healthy women as well as women with MS. Therefore, fertility evaluation should become ordinary practice at least in women >35 years before making treatment choices to individually tailor counseling and preserve both women's health and pregnancy plans. Thus, medical counseling acquires the utmost significance in driving women's and couple's choices regarding family planning. In 2014, Wundes et al. (37) evaluated what healthcare providers say to MS women about pregnancy, showing that almost all surveyed participants did not discourage pregnancy based solely on MS diagnosis, but few encouraged it, and a hypothesis could be that the lack of active encouragement might be perceived as a lack of support. Indeed, nowadays, such an attitude seems outdated. In addition, recommendations about DMD use vary considerably (37, 38). Recently, various attempts have been made to resume the main counseling issues and related management options for MS women with reproductive desires (39–43). Currently, the main topic of discussion is the therapeutic management of the window between pregnancy desire and conception as well as during gestation (44, 45). However, the issue of a couple's fertility evaluation before making such choices has never been addressed. Nevertheless, it should also be taken into consideration the partner's role in reproductive issues. As per definition, "infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse" (46). Therefore, although not mandatory, it seems advisable that both partners be evaluated whenever planning a pregnancy, in order to assess

whether infertility issues could complicate the road to conception. Initial screenings might include semen analysis and ovarian reserve markers' evaluation, as well as questions about menstrual cycle regularity, whose first interpretation could be done by a neurologist. Moreover, creating a multidisciplinary team of reproductive medicine experts would speed up the process. Then, this would help the MS treating physicians manage therapeutic options. These statements received 13.04, 26.08, 17.39, 26.09, and 30.43% disagreement or doubt (neither agree nor disagree), respectively. The motivations supporting disagreements are outlined in the Supplementary material. Of note, respondents argued to consider age, the severity of the disease, and true desire for motherhood as determinants in deciding fertility evaluation.

3.2.2. Topic 2. Management of MS treatment strategies in relation to pregnancy planning

S8. First-line DMDs (interferons β and glatiramer acetate) should be continued until pregnancy confirmation and during pregnancy, if needed.

S9. In case of pregnancy desire, the couples' fertility potential should be evaluated before treatment switch in women on disease-modifying drugs (DMDs) that are contraindicated in pregnancy.

S10. In case of MS patients in treatment with DMDs not compatible with pregnancy, interferon β is a good bridging option.

S11. Contraception should be maintained during DMDs wash-out if the treatment is not compatible with pregnancy.

S12 (rephrased). Considering that the elimination time of cladribine tablets is 1 week, in view of available scientific evidence, shortening the 6-month interval between cladribine treatment and conception could be safe and may reduce time to conception. Further evidence is needed to confirm this statement.

The statements concerning MS treatment decision-making reached 91.3, 78.26, 73.92, 91.3, and 70.0% agreement, respectively. It is now well-established that pregnancy reduces the risk of relapses in MS women (5, 30) with pregnancy advancement, due to the hormonal-driven downregulation of proinflammatory immune mechanisms. Despite robust evidence regarding the favorable course of the disease in pregnancy, there is still a longstanding debate about whether DMDs should be suspended before conception and for how long, considering that today the majority of women with MS of childbearing age are treated with these medications. Main concerns regard the safety of the exposure of the fetus to DMDs at the time of conception or during pregnancy; for this reason, in the past, DMDs were usually discontinued in women planning pregnancy before trying to conceive. Nevertheless, several lines of evidence identified, among other factors, the length of treatment washout before conception as a predictor of a higher risk of relapse (47–49). Therefore, the last ECTRIMS/EAN MS treatment guidelines (50) recommended considering continuing interferon (IFN) or glatiramer acetate until pregnancy is confirmed in women with a high risk of relapses, also keeping in mind that often it is not possible to predict the time to pregnancy. Injectables, in fact, are now considered safe for the fetus and are labeled for use during pregnancy and lactation (51–56). While the oldest studies showed that exposure to IFN-beta was associated with an increased risk of lower mean birth weight, shorter mean birth length, and preterm birth (57, 58), more recent works on large pregnancy registries disconfirmed these results and demonstrated that IFN-beta exposure before conception and/or during pregnancy does not adversely increase the rate of congenital anomalies or spontaneous abortions (59–61). Fewer studies have investigated the outcomes of infants exposed to glatiramer acetate showing that the exposure during the first trimester does not affect perinatal outcomes (62, 63). Limited data are available on the risk/benefit of continuing injectables DMD throughout pregnancy (64, 65), and new longitudinal studies are needed to address this issue. However, in agreement with ECTRIMS guidelines (50), such an option should be discussed with future parents, particularly in case of women with pre-conceptional adverse prognostic factors. A discussion is also open on the management of women seeking pregnancy that are treated with DMDs different from IFNs and glatiramer acetate. All of them are not licensed during pregnancy. Therefore, women who are on treatments not allowed during pregnancy should be ideally switched to other treatment options or discontinue therapies before conception. However, discontinuation of therapies may increase the risk of relapses and disability progression (66, 67). Several studies have shown that the odd of MS rebound after suspension, also motivated by pregnancy reasons, is particularly higher in women treated with sequestering drugs (i.e., natalizumab and fingolimod) (68–71), due to the rapid immune reconstitution occurring after treatment interruption. Hence, in this population, it would be advisable to assess women and couples' fertility before the treatment switch, also considering couples' age and the unknown toxic effect of chronic inflammation or DMDs (72) on ovarian reserve. Eventual detection of infertility before the treatment switch, which is not rare in older women, might help to optimize the timing of sequencing, in order to limit the risk of disability on one hand and to precociously manage treatable causes of infertility. Krysko et al. suggested (73) that, although not licensed for use during pregnancy, natalizumab could be continued at extended intervals dosing up until the third trimester, when it should be stopped to not incur in neonatal cytopenia (74). In addition, they proposed to target the last dose of anti-CD20 shortly before pregnancy, but ideally not during it. However, they have not stated the management during ART procedures, but underlined that women approaching fertility treatments should be on optimal disease control with a pregnancy-compatible DMD. Instead, in women with low-moderate disease activity treated with platform therapies not compatible with pregnancy and thus requiring lateral treatment switch, IFNs are considered a good bridging option due to the low risk of fetal abnormalities and the possibility of continuing treatments during pregnancy. In this case, it should be taken into account that the estimated therapeutic lag for relapses from treatment start ranges from 14 to 19 weeks (75); therefore, particularly for those women getting pregnant soon after treatment starts, it might be proposed to continue treatment during pregnancy to optimize treatment benefit. Conversely, contraception is recommended for all women on DMDs not compatible with pregnancy. Contraceptive methods are safe in MS; highly effective methods, including IUDs (intra-uterine devices) and implants, should be proposed to women taking DMDs with known teratogenicity (6, 76), and they should be maintained during treatment washout. Such an interval depends on the elimination half-life of each DMD; in fact, a drug is considered to have been fully eliminated after five half-lives. Currently, drug plasmatic concentration can be dosed only for teriflunomide, allowing personalizing of discontinuation of contraception when a plasma level of <0.02 mg/L is detected (77). For all the other DMDs, label

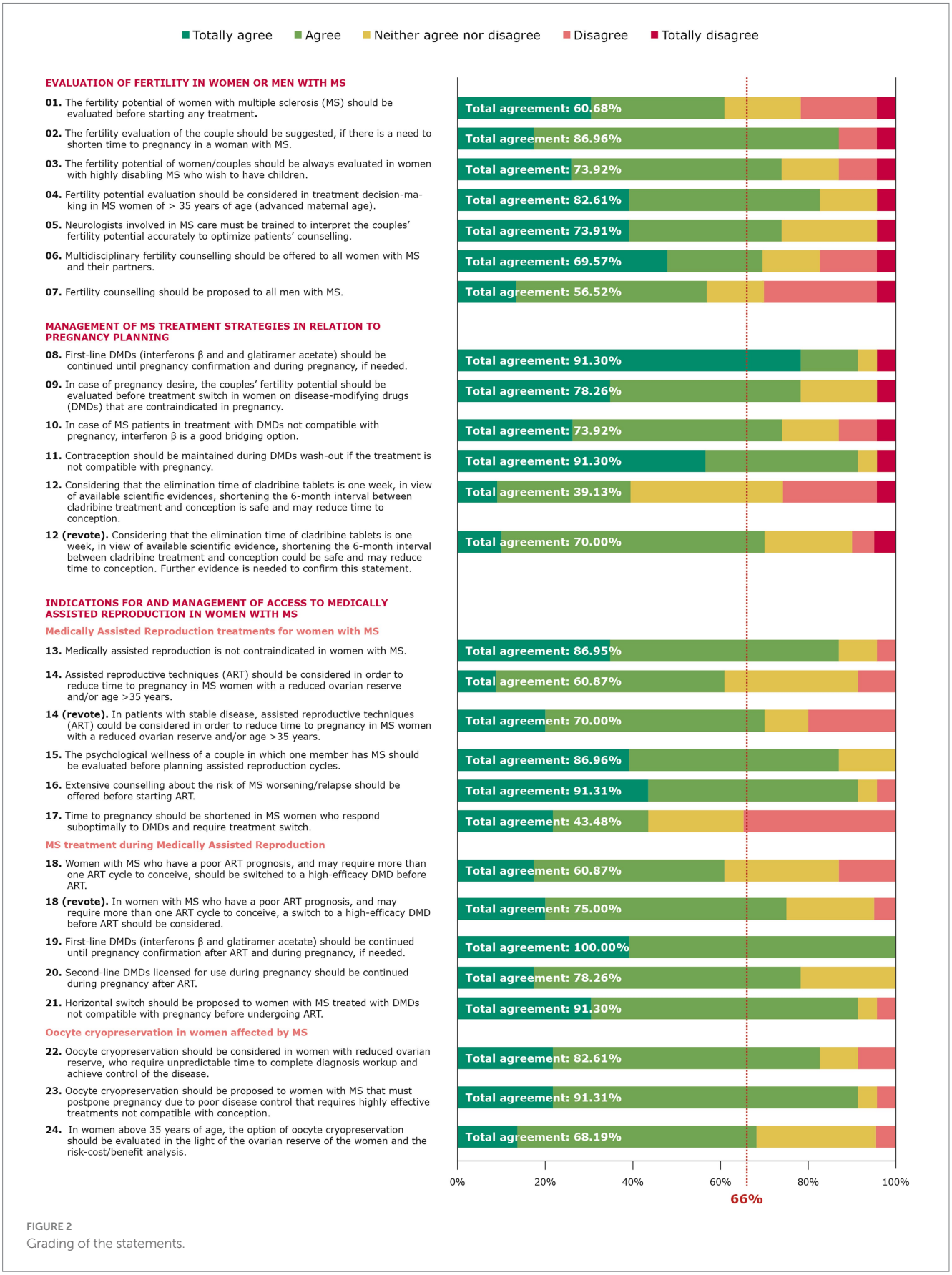

FIGURE 2
Grading of the statements.

indications should be followed. Nevertheless, for some of the most recently approved drugs, such as cladribine or anti-CD20 drugs (78), the recommended washout interval before trying to conceive exceeds the presumed drug half-life. For these treatments, regulatory authorities adopted a precautionary approach considering the lack of data on fetal safety and the prolonged immunological effects of these

TABLE 3 Three main concepts of the survey.

• Fertility evaluation should be suggested to wMS, in case of need to shorten time to pregnancy and before treatment switch in women on DMTs contraindicated in pregnancy, particularly in case of highly active disease and age > 35 years.
• ART should not be discouraged in wMS, but use of DMTs until pregnancy confirmation should be suggested; ART may be considered in order to reduce time to pregnancy in MS women with a reduced ovarian reserve and/or age > 35 years, but in case of expected poor ART prognosis and need of more than one ART cycle, a switch to a high-efficacy DMD before ART should be offered.
• Oocyte cryopreservation may be considered in women with reduced ovarian reserve, with unpredictable time to complete diagnostic workup and achieve disease control; a risk/cost–benefit analysis must be performed in women >35 years considering the diminished ovarian reserve.

treatments, despite their low frequency of administration. In the case of cladribine tablets, the complete drug elimination time is 1 week (79), while it is recommended that women prevent pregnancy during treatment and for at least 6 months after the last dose. Moreover, as it is not known if cladribine may reduce the efficacy of birth control pills, a barrier method of contraception should be added during treatment and for at least 4 weeks after the last dose. Considering its pharmacodynamic and pharmacokinetic, shortening the 6-month interval between cladribine treatment and conception seems safe and might represent a promising approach to reducing time to conception in women treated with this drug, in particular in those >35 years old. These statements received 8.7, 21.74, 26.08, 8.7, and 30% disagreement or doubt (neither agree nor disagree), respectively. The motivations supporting these disagreements are outlined in the Supplementary material. In detail, experts debated whether glatiramer acetate is a good bridging option; also, it would be better to gain more evidence before considering it safe to conceive prior to 6 months after cladribine treatment and to consider the effects on white blood cell count.

3.2.3. Topic 3. Medically assisted reproduction treatments for women with MS

S13. Medically assisted reproduction is not contraindicated in women with MS.

S14 (rephrased). In patients with stable disease, assisted reproductive techniques (ART) could be considered in order to reduce time to pregnancy in MS women with a reduced ovarian reserve and/or age > 35 years.

S15. The psychological wellness of a couple in which one member has MS should be evaluated before planning assisted reproduction cycles.

S16. Extensive counseling about the risk of MS worsening/relapse should be offered before starting ART.

The statements concerning ART in wMS reached 86.95, 70, 86.96, and 91.31% agreement, respectively. The safety of ART in MS women is still debated, as evidence reports an increased risk of disease reactivation after such procedures, which is mainly related to sex hormone manipulation and its proinflammatory effects (80–84). Not only clinical but also radiological evidence of relapse has been observed (85, 86). Currently, ART protocols for ovarian stimulation involve the use of GnRH agonists or antagonists to avoid the LH (luteinizing hormone) surge and the risk of spontaneous ovulation. While some studies showed increased relapse risk after GnRH agonist use (82–84), others did not find the same evidence (80, 81, 87); however, a recent meta-analysis demonstrated that no difference in risk of MS relapse was found between GnRH agonist and antagonist ART protocols (88). In addition, it has been observed that only wMS patients who suffered from relapses close to the start of the ART procedure were at risk of further relapses (89). Bove et al. (88) explored any confounding factors and found that age, parity, multiple IVF attempts, time without MS drugs, and disease duration had no effect on the association between ART and increased risk of relapse; interestingly, they also noticed that miscarriage after ART increased the risk of relapse 3 months after ART compared to 3 months before. The largest available study evaluating the relapse rate in 225 wMS undergoing ART compared 3-month exposed periods after IVF with unexposed periods before IVF and did not evidence an increase in the risk of relapse. Moreover, the results of this study do not support the hypothesis that patients stimulated with the GnRH agonist protocol have an increased risk of relapse (90). Finally, it was observed that there is no difference in live birth rates after ART between wMS and women without MS (16, 27). A very recent multicenter retrospective analysis observed that the relapse rate was not increased after ART and that being on therapeutic DMD was associated with a reduced relapse rate 3 months after ovarian stimulation: 10 out of the 13 patients relapsing after ART (over a 12-month period) were not on DMDs (91), enhancing the importance of continuing therapy when ART procedures are planned and performed.

Therefore, taking into account these data, it can be affirmed that MS is not a contraindication to ART treatments per sè, but a correct framework of the clinical conditions of the patients should be performed to allow its planning in the optimal window both for MS and pregnancy prognosis.

The diagnosis of infertility is associated with increased levels of emotional distress, anxiety, and depression (92). The importance of a couple's psychological evaluation and management was also recognized by the European Society of Human Reproduction and Embryology (ESHRE); in fact, Gameiro et al. (93) released a guideline on how to manage the main psychological aspects that could arise before, during, and after treatment for couples seeking fertility treatments. To overcome this issue, it was declared that psychological issues should be assessed and care should be tailored, especially in cases of ART failure. In this regard, specific tools could also be used (94). Actually, MS adds extra stress to the already acknowledged psychological burden with which couples are requested to deal when they need to refer to assisted reproduction in order to conceive. All the worries declared by people with MS, such as fear of disability, fear of transmitting the disease, fear of not being able to care for children, and fear of discontinuing MS treatments, would probably be the main reasons that could affect the decision not only to become pregnant but also to access ART programs in cases of infertility diagnosis (8, 31, 32). Actually, Houtchens et al. (27) observed that, despite the fact that a higher proportion of wMS have been found infertile compared to healthy controls, less wMS seek infertility treatments than women without MS. In contrast, Sadovnick et al. (38) observed that the proportion of MS women requesting ART treatments was not different from the general population. This data could be read in the way that infertile wMS are scared by the additional stressful path of assisted reproduction to be added to their chronic condition, thereby giving up on the idea of family planning. This is why multidisciplinary and extensive counseling is strongly needed for infertile wMS approaching

the possibility of ART treatments to conceive, to help them freely make reproductive choices after a thorough discussion on all the aspects, from the psychological to the pharmacological and clinical ones, covering the periods from before to after ART treatments and pregnancy. Indeed, wMS and their partners should be aware of the possibly increased risk of relapse after such treatments, which should be adequately discussed in place of pre-ART counseling by both the neurologist and the reproductive medicine specialist in relation to the abovementioned evidence and all the possible interfering factors. It has already been suggested that would be wiser to perform ART treatments during periods of disease stability (95, 96). Main indications remain related to infertility causes, but in order to not increase the likelihood of failure, it seems reasonable to consider wMS with reduced ovarian reserve and over 35 years old as the ones with time-dependent infertility conditions and therefore to get them soon into ART treatments. These statements received 13.05, 30, 13.04, and 8.69% disagreement or doubt (neither agree nor disagree), respectively. The motivations supporting these disagreements are outlined in the Supplementary material. Experts commented on the importance of the IVF protocol but also the need to inform patients about the risk of disease reactivation.

3.2.4. Topic 4. MS treatment during medically assisted reproduction

S18 (rephrased). In women with MS who have a poor ART prognosis, and may require more than one ART cycle to conceive, a switch to a high-efficacy DMD before ART should be considered.

S19. First-line DMDs (interferons β and glatiramer acetate) should be continued until pregnancy confirmation after ART and during pregnancy, if needed.

S20. Second-line DMDs licensed for use during pregnancy should be continued during pregnancy after ART.

S21. Horizontal switch should be proposed to women with MS treated with DMDs not compatible with pregnancy before undergoing ART.

The statements concerning MS treatments during ART procedures in wMS reached 75, 100, 78.26, and 91.3% agreement, respectively. Taking into account that it is still debated if MS or eventually some MS drugs could have an impact on fertility, whenever a wMS should ask for ART treatments to achieve a pregnancy, it seems appropriate to evaluate her (assisted) reproductive prognosis in advance, to tailor the optimal reproductive strategy. Indeed, the best parameters to define the prognosis of ART procedures include the combination of age, ovarian reserve markers such as antral follicle count (AFC) and Anti-Müllerian hormone (AMH), as well as the number of oocytes retrieved in previous IVF cycles. Embryo euploidy also has a fundamental role in the achievement of pregnancy, and its relationship with age should be taken into account, given that its probability decreases with increasing maternal age (97–100), for which pre-implantation tests can be performed (101, 102). Therefore, in women with poor ART prognosis, an accumulation strategy could be proposed in order to increase the number of mature oocytes that would reasonably allow for at least one euploid embryo (103–106). Actually, a recent large cohort study based on nationwide Danish health registries analyzing 2,267 embryo transfers in 815 women with MS has shown that the chance of a live birth was not decreased in these women compared with women without MS undergoing ART (16). Nevertheless, it should be considered that wMS could undergo biochemical pregnancy, miscarriage (107), repeated implantation failure, and therefore, several embryo transfer attempts. These unfavorable ART events might multiply the risk of disease reactivation, for the abovementioned reasons, much more than in case of ART success (92).

Therefore, in women with unfavorable prognostic factors regarding ART and/or MS, it is advisable to switch to higher efficacy DMDs before ART. Accumulating evidence suggests that natalizumab or anti-CD20 drugs can be viable options, as they have no impact on women's fertility (108) and no major obstetric or fetal complications emerged in exposed pregnancies (109–111). Patients switching to natalizumab for ART or already on treatment with this drug should continue the therapy during ART and pregnancy in order to minimize the risk of unwarranted relapses due to treatment suspension. The same approach should be proposed to women with MS treated with injectables compatible with pregnancy, given that IFNs or glatiramer acetate are not expected to have a detrimental impact on fertility or ART outcomes. Conversely, Bove et al. have shown that no treatment or treatment washout >3 months before ART increases the risk of relapses (88). So, in case of women treated with first-line orals not compatible with pregnancy, switching to injectables before starting ART procedures seems like a safer approach compared to treatment interruption.

These statements received 25, 0, 21.74, and 8.7% disagreement or doubt (neither agree nor disagree), respectively. The motivations supporting disagreements are outlined in the Supplementary material. One expert affirmed that it would be difficult to justify a therapeutical switch for a reason not intrinsically linked to the disease; in addition, many of them reinforced the importance of evaluating the disease course/activity.

3.2.5. Topic 5. Oocyte cryopreservation in women affected by MS

S22. Oocyte cryopreservation should be considered in women with reduced ovarian reserve, who require unpredictable time to complete diagnosis workup and achieve control of the disease.

S23. Oocyte cryopreservation should be proposed to women with MS that must postpone pregnancy due to poor disease control that requires highly effective treatments not compatible with conception.

S24. In women above 35 years of age, the option of oocyte cryopreservation should be evaluated in the light of the ovarian reserve of the women and the risk-cost/benefit analysis.

The statements concerning oocyte cryopreservation reached 82.61, 91.31, and 68.19% agreement, respectively. The first to suggest fertility preservation in MS patients was Cavalla et al. (26) in 2006. They proposed that, similarly to cancer patients, people with MS could take advantage of this technology to preserve their fertility potential before starting treatments. Recently, Massarotti et al. (96) reinforced this suggestion, stressing the concept that, in light of the many unanswered questions about fertility and assisted reproduction outcomes in patients with multiple sclerosis, multidisciplinary counseling and dedicated clinics should be put in place to manage these aspects over time. Oocyte or embryo cryopreservation is already a consolidated practice for fertile women diagnosed with cancer before starting anti-neoplastic treatments such as chemotherapy and/or radiotherapy (112, 113). This is because such treatments are gonadotoxic, and therefore, the ovarian reserve and follicular pool could be dramatically reduced after certain oncologic protocols (114). Likewise, some MS treatments could be cytotoxic (i.e., mitoxantrone

and cyclophosphamide), with effects also on gonads, although the impact of MS drugs on fertility is still a matter of debate for the majority of them (45, 115). For these reasons, MS could be considered a condition in which the preservation of gametes before therapy or during diagnostic workup could be considered, mainly in women showing signs of reduced fertility or in those patients who are candidates for gonadotoxic therapies such as bone marrow or stem cell transplantation. Data on fertility after autologous hematopoietic stem cell transplantation (aHSCT), which usually requires a conditioning regimen with alkylating agents, are still inconclusive. A study by Massarotti et al. (116) has shown that 70% of women recovered menses after treatment, especially if they were young, while Zafeiri et al. (117) observed a significant reduction of the AMH levels after the procedure. However, cryopreservation of ovarian tissue in eight women undergoing aHSCT resulted in good recovery of ovarian function in two women out of four with premature ovarian insufficiency after treatment (118). Despite the fact that ART treatments have been associated with an increased risk of post-procedure relapse, the evidence of reduced risk, whenever therapy is not discontinued (as the Boston cohort showed in the study from Bove et al. (88)), could open a new window in fertility preservation for women affected by MS, even if pregnancy is not advisable due to poor disease control. Gulekli et al. (119) were the first to report two cases of infertile women affected by MS who were treated with *in vitro* maturation (IVM) of oocytes to avoid the risk of ovarian stimulation and the related risk of disease reactivation, with successful pregnancy and live birth. The authors, therefore, suggested that MS would be considered an indication for this ART strategy. IVM could be a useful strategy for fertility preservation, in the centers that are familiar with this strategy, eventually in cases when disease control has not been achieved yet or when patients require highly effective treatments that are not compatible with conception. Finally, it is obvious that a risk/benefit analysis should be carried out by a multidisciplinary team in MS women of advanced reproductive age (e.g., over 35 years old), considering the markers of ovarian reserve. These statements received 17.39, 8.69, and 31.81% disagreement or doubt (neither agree nor disagree), respectively. The motivations supporting these disagreements are outlined in the Supplementary material. The main arguments commented on were that a long period for MS diagnosis is not acceptable or usually requested and that the decision on oocyte cryopreservation should always depend on the patient's age.

4. Discussion

This Delphi consensus, with 21 statements approved, provides a real-world clinical perspective on the specific approaches during key steps of fertility assessment and ART management from a diverse group of Italian experts. What emerges is that the evaluation of female and couple fertility is gaining more and more importance in light of the possibility of supporting pregnancy desire and motherhood with therapeutic regimens that are proving to be effective and safe, although further evidence is still urgently needed. The Delphi methodology represents the strength of this study, which also benefited from the knowledge of an Italian panel of highly respected experts in the field. The fertility experts participating in the consensus were from a diverse range of global regions of Italy, including different fertility centers from the northern, middle, and southern Italy, reflecting the quality of healthcare and different approaches to infertility treatment. The consensus allowed to include of a wider list of topics than what would be typically considered in a systematic review or in a guideline, which are usually based on strict methodology, limiting the scope of the investigation. However, there are a few limitations; first, the consensus does not represent an exhaustive list of statements, and the statements only represent the collective opinion of the experts included. The majority of the statements reached consensus (more than 66% agreement) at first voting, with only 3 statements rejected out of 24. Some statements reached consensus even though a few experts disagreed with them (motivations in Supplementary materials), while one was approved unanimously. Moreover, the statements have been conceived taking into account the evidence from the literature, which is quite heterogeneous and limited by the small sample size of the studies performed so far, especially in regard to ovarian reserve estimation and assisted reproduction outcomes in women with MS. At last, although these statements represent the point of view of the experts, individualized management with regards to treatment options should always be planned in relation to patients needs and clinical features. Dobson et al., in 2019, released the guidelines of the Association of British Neurologists regarding MS and pregnancy, developed through a Delphi consensus. They focused on the evidence about all the DMDs in relation to contraception, fertility, pregnancy, and lactation, but mainly on general management of pre-, during, and post-pregnancy times for MS women. Importantly, they stated that pre-pregnancy counseling should be organized at diagnosis or soon after it, and eventually repeated yearly in women of reproductive age. Moreover, they admitted that ART procedures are not contraindicated, although a multidisciplinary team should plan how to effectively manage the patient during those times (120). A recent consensus came also from Argentina, with 50 statements: they were of the same advice regarding the need for reproductive counseling before pregnancy and at regular (annual) intervals, as well as the possibility of asking for ART procedures to get pregnant. An interesting recommendation they released is to seek a fertility specialist if conception does not happen after 6 months of attempts when DMDs have been stopped, instead of the classical 12 months usually considered for infertility in the general population (121). Another consensus has been provided by the Portuguese Multiple Sclerosis Study Group, which has issued a list of statements similar to the others previously mentioned, analyzing the needs of MS women from the pre-conceptional period to the post-partum period. Similarly, they addressed the fertility issue, admitting that the evidence does not support a role for both the disease and related treatments in the determination of infertility. Furthermore, they confirmed the possibility of seeking ART treatments to get pregnant (122). Very recently, Oreja-Guevara et al. published some recommendations for ART in MS by a Spanish expert panel (123). The main arguments were the need to assess the partner's health and subfertility factors other than age, to consider less than 1 year of regular intercourse for infertility consultation after 35 years of age, single embryo transfer, and a maximum of three cycles of ovarian stimulation, and that a fertility preservation is a possible strategy. However, our consensus preferred to highlight the importance of proper fertility assessment and counseling, especially in relation to female age and the intrinsic reduction of fertility with aging, which prompts evaluation of fertility before it is too late. Although the reports on ovarian reserve suggested that highly active disease could cause impairment of AMH levels or AFC (12, 33), we suggest considering couple fertility

evaluation to help speed up the family planning process, independently from disease activity, so as to reduce the time to pregnancy. Nonetheless, we suggested the use of oocyte cryopreservation in selected cases. Further evidence is still urgently needed on the issue of fertility and ART treatments in women affected by MS, since the number of them with reproductive desire is increasing but the mean age at family planning request could be close to a window of reduced fertility, and therefore both neurologists involved in MS care and reproductive medicine experts should manage these aspects over time.

5. Conclusion

This Delphi consensus provides 21 statements by expert opinions on specific approaches during the neurological assessment of women diagnosed with multiple sclerosis, including fertility evaluation, assisted reproduction, and fertility preservation, especially when women are older than 35 years old, with the aim of reducing the time to pregnancy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants or participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Group member of Interdisciplinary Group for Fertility in Multiple Sclerosis

Carlo Alviggi and Raffaella Di Girolamo, Department of Public Health, School of Medicine, University of Naples Federico II, Naples, Italy; Luigi Carbone and Roberta Lanzillo, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy; Doriana Landi and Girolama Alessandra Marfia, Multiple Sclerosis Clinical and Research Unit, University Hospital of Rome Tor Vergata, Rome, Italy; Paola Anserini, UOS Physiopathology of Human Reproduction, IRCCS Ospedale Policlinico San Martino, Genova, Italy; Diego Centonze, Department of Systems Medicine, Laboratory of Synaptic Immunopathology, "Tor Vergata" University, Rome, Italy; Unit of Neurology–IRCCS Neuromed, Pozzilli, Isernia, Italy; Pietro Annovazzi, Multiple Sclerosis Center, Hospital of Gallarate–ASST della Valle Olona, Gallarate, Italy; Simona Bonavita, Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy; Giovanna Borriello, Multiple Sclerosis Center, 'S. Andrea' Hospital, Sapienza University of Rome, Rome, Italy; Paola Cavalla, Multiple Sclerosis Center, City of Health and Science University Hospital, Turin, Italy; Raffaella Cerqua, Neurological Clinic, Department of Experimental and Clinical Medicine, Ospedali Riuniti, Ancona, Italy; Marinella Clerico, Clinical and Biological Sciences Department, Neurology Unit, University of Torino, 'San Luigi Gonzaga' Hospital, Orbassano, Italy; Eleonora Cocco, Multiple Sclerosis Center, Department of Medical Science and Public Health, University of Cagliari, Cagliari, Italy; Cinzia Cordioli, Multiple Sclerosis Center, Spedali Civili of Brescia, Montichiari (BS), Italy; Emanuele D'Amico, Department of Medical and Surgical Sciences and Advanced Technologies 'G.F. Ingrassia', Section of Neurosciences, University of Catania, Catania, Italy; Giovanna De Luca, Multiple Sclerosis Center, 'SS Annunziata' Hospital, 'Gabriele d'Annunzio' University Chieti-Pescara, Chieti, Italy; Massimiliano Di Filippo, Section of Neurology, Department of Medicine and Surgery, University of Perugia, Perugia, Italy; Roberta Fantozzi, Unit of Neurology–IRCCS Neuromed, Pozzilli, Isernia, Italy; Diana Ferraro, Department of Neuroscience, UO of Neurology, AOU Policlinico OB, Modena, Italy; Pietro Iaffaldano, Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari Aldo Moro, Bari/Italy; Matilde Inglese, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genoa, Genova, Italy; Department of Neurology, Policlinico 'San Martino Hospital'-Sistema Sanitario Regione, Genoa, Italy; Paola Perini, Multiple Sclerosis Center, Neurological Clinic, University Hospital of Padua, Italy; Emilio Portaccio, Division Neurological Rehabilitation, Department of NEUROFARBA, University of Florence, Florence, Italy; Paolo Ragonese, Unit of Neurology, Department of Biomedicine, Neurosciences and Advanced Diagnostics, Palermo University, Palermo, Italy; Cinzia Scandellari, IRCCS Institute of Neurological Sciences, UOSI Multiple Sclerosis Rehabilitation, Bologna, Italy; Valentina Torri Clerici, Neuroimmunology and Neuromuscular Diseases Unit, Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta, Milan, Italy; Carla Tortorella, Department of Neurosciences, S. Camillo-Forlanini Hospital, Rome, Italy; Paola Valentino, Department of Medical and Surgical Sciences, Institute of Neurology, Magna Graecia University, Catanzaro, Italy.

Author contributions

LC: Visualization, Writing – review and editing. DL: Visualization, Writing – review and editing. RDG: Data curation, Writing – original draft. PA: Validation, Writing – review and editing. DC: Validation, Writing – review and editing. GM: Conceptualization, Supervision, Writing – review and editing. CA: Conceptualization, Methodology, Supervision, Visualization, Writing – review and editing.

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Supplementary material

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EDITED BY
Alessandra Lugaresi,
University of Bologna, Italy

REVIEWED BY
Nils Muhlert,
The University of Manchester,
United Kingdom
Giacomo Boffa,
University of Genoa, Italy

*CORRESPONDENCE
Fuqing Zhou
ndyfy02301@ncu.edu.cn
Yuxin Li
liyuxin@fudan.edu.cn

†These authors have contributed equally to this work

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Male and female are not the same: a multicenter study of static and dynamic functional connectivity in relapse-remitting multiple sclerosis in China

Yao Wang[1,2], Yunyun Duan[3], Yuling Wu[1,2], Zhizheng Zhuo[3], Ningnannan Zhang[4], Xuemei Han[5], Chun Zeng[6], Xiaoya Chen[6], Muhua Huang[1,2], Yanyan Zhu[1,2], Haiqing Li[7], Guanmei Cao[3], Jie Sun[4], Yongmei Li[6], Fuqing Zhou[1,2*†] and Yuxin Li[7*†]

[1]Department of Radiology, The First Affiliated Hospital, Nanchang University, Nanchang, Jiangxi, China, [2]Clinical Research Center For Medical Imaging In Jiangxi Province, Nanchang, Jiangxi, China, [3]Department of Radiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China, [4]Department of Radiology and Tianjin Key Laboratory of Functional Imaging, Tianjin Medical University General Hospital, Tianjin, China, [5]Department of Neurology, China-Japan Union Hospital of Jilin University, Changchun, Jilin, China, [6]Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [7]Department of Radiology, Huashan Hospital, Fudan University, Shanghai, China

Background: Sex-related effects have been observed in relapsing-remitting multiple sclerosis (RRMS), but their impact on functional networks remains unclear.

Objective: To investigate the sex-related differences in connectivity strength and time variability within large-scale networks in RRMS.

Methods: This is a multi-center retrospective study. A total of 208 RRMS patients (135 females; 37.55 ± 11.47 years old) and 228 healthy controls (123 females; 36.94 ± 12.17 years old) were included. All participants underwent clinical and MRI assessments. Independent component analysis was used to extract resting-state networks (RSNs). We assessed the connectivity strength using spatial maps (SMs) and static functional network connectivity (sFNC), evaluated temporal properties and dynamic functional network connectivity (dFNC) patterns of RSNs using dFNC, and investigated their associations with structural damage or clinical variables.

Results: For static connectivity, only male RRMS patients displayed decreased SMs in the attention network and reduced sFNC between the sensorimotor network and visual or frontoparietal networks compared with healthy controls [$P<0.05$, false discovery rate (FDR) corrected]. For dynamic connectivity, three recurring states were identified for all participants: State 1 (sparse connected state; 42%), State 2 (middle-high connected state; 36%), and State 3 (high connected state; 16%). dFNC analyses suggested that altered temporal properties and dFNC patterns only occurred in females: female patients showed a higher fractional time ($P<0.001$) and more dwell time in State 1 ($P<0.001$) with higher transitions ($P=0.004$) compared with healthy females.

Receiver operating characteristic curves revealed that the fraction time and mean dwell time of State 1 could significantly distinguish female patients from controls (area under the curve: 0.838-0.896). In addition, female patients with RRMS also mainly showed decreased dFNC in all states, particularly within cognitive networks such as the default mode, frontoparietal, and visual networks compared with healthy females ($P < 0.05$, FDR corrected).

Conclusion: Our results observed alterations in connectivity strength only in male patients and time variability in female patients, suggesting that sex-related effects may play an important role in the functional impairment and reorganization of RRMS.

KEYWORDS

relapsing-remitting multiple sclerosis, magnetic resonance imaging, sex, independent component analysis, static functional network connectivity, dynamic functional network connectivity

Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS) and is a leading non-traumatic cause of disability in young adults (1). Previous studies have reported that female MS patients have a higher incidence of recurrences (2–4), but male patients with MS seem to have more severe physical disability and to progress faster (5, 6). There is also strong evidence indicating that sex plays a crucial role in the recurrence and progression of MS. However, the underlying mechanisms of these sex-related effects within the CNS are complex and have not been fully studied in MS. Structural MRI studies found that male patients with MS seems to have a higher lesion load (7, 8), more severe microstructural damage, such as atrophy of gray matter and/or deep gray matter (9, 10), and demyelination of white matter (11), although these remain understudied.

In addition to structural damage, sex-related functional reorganization also appears to exist in relapsing-remitting MS (RRMS). Recently, static disconnectivity and network efficiency decreases of the default mode network were found in male RRMS patients and related to impaired visuospatial memory (12). However, only increased static functional connectivity was found in male RRMS patients from another study, but this sex-related difference of functional connectivity was no longer significant after regressing gray matter volume (13). These conflicting findings may result from sex-related differences in structural damage and functional reorganization of the CNS in RRMS patients with different sex.

Furthermore, recent research has shown that brain networks are not truly "static" but instead change over time during MRI scans (14). Dynamic functional network connectivity (dFNC) enables quantification of the connectivity strength and its temporal properties of dynamic changes on very short time scales (15). A growing number of studies have found that dFNC can identify recurring dynamic connectivity states in different subtypes and disease stages of MS and decreased dynamic functional connectivity was strong association with cognitive impairment (16, 17), fatigue (18), and disability (19). However, it remains unclear whether sex affects the dynamic connectivity of functional networks in RRMS patients.

As such, our study hypothesized that the connectivity strength and time variability of functional networks in RRMS patients are also affected by sex and related to brain structural damage or physical disability. To test this hypothesis, we retrospectively analyzed 208 patients with RRMS (135 females/73 males) and 228 healthy controls (123 females/105 males) from six centers in China, evaluating the spatial distribution strength, static functional connectivity strength, and dFNC pattern and its temporal properties of the resting-state networks (RSNs) in RRMS. Our study may reveal the pathophysiological mechanism of neurological damage in large-scale functional networks in RRMS patients by different sex.

Materials and methods

Standard protocol approvals and patient consents

All subjects signed written informed consent forms, and this study was approved by the local ethics review board at each center.

Subjects

This retrospective multicenter study recruited 593 subjects (including 263 MS and 331 healthy controls) from six centers in China (from 2009 to 2019). All subjects needed to be right-handed, 18 to 65 years old, undergo MRI scans, and have complete clinical information. All MS patients were diagnosed by the 2017 Revised

McDonald Criteria as being in the RRMS category. The Expanded Disability Status Scale (EDSS) was used to evaluate the patients' overall disability. Ultimately, 135 female patients with RRMS (RRMS females) and 73 male patients with RRMS (RRMS males), matched for age, disease duration (DD), and EDSS scores, and 123 healthy females and 105 healthy males were recruited as controls.

MRI acquisition

All participants underwent 3.0 T MRI scans; the required scan sequences included high-resolution 3D T1-weight, T2-weight, fluid-attenuated inversion recovery (FLAIR), and resting-state functional MRI (rs-fMRI). The specific scan parameters of each center are described in our previous study (20).

Structure measurement

White matter volume (WMV) and gray matter volume (GMV) were segmented and calculated automatically using the tissue probability maps method in the computational anatomy toolbox (CAT12). In addition, the ratio of brain parenchymal tissue (GMV plus WMV) to total intracranial cavity volume was defined as the brain parenchymal fraction (BPF).

As described in our previous study (20), lesion volume (LV) was manually delineated and checked by 5- and 11-year experienced radiologists based on the T2-weighted or FLAIR images, and lesion masks were created. The lesion masks were transformed into the Montreal Neurological Institute (MNI) space and the lesion volume calculated in the SPM12 platform.

Resting-state fMRI data preprocessing

fMRI data were preprocessed using the Resting-State fMRI Data Analysis Toolkit plus (REST plus v1.25) package based on SPM12 (Statistical Parametric Mapping) and MATLAB v8.40 (The Mathworks, Inc., U.S.). Since the scanning duration to acquire rs-fMRI data may be different in each center, fMRI data preprocessing was performed separately for each center (20). The processing pipeline included: 1) discarding the first 10 image volumes; 2) head movement realignment, the mean framewise displacement (FD) of each subject was evaluated to reflect mean head movement; 3) spatial normalization into the Montreal Neurological Institute (MNI) space and resampling with $3 \times 3 \times 3$ mm^3; and 4) spatial smoothing (full width at half maximum (FWHM)=6 mm).

Independent component analysis (ICA)

We used ICA to identify RSNs rather than using seed-based approaches because ICA is data-driven and does not require prior assumptions (e.g., selecting the seed regions). In this study, we implemented spatial ICA to extract temporally coherent and spatially independent sources within the fMRI time course using the Group ICA Of fMRI Toolbox (GIFT v3.0b). The pipeline included: 1) dimensionality reduction with principal component analysis; 2) evaluating components using the Infomax algorithm and ICASSO algorithm (100 iterations); and 3) back reconstruction using the GICA3 algorithm. According to the works of Allen et al. (21) and Yeo et al. (22), 20 independent components (ICs) and seven RSNs were then obtained for further analysis: the default mode network (DMN), the sensorimotor network (SMN), the visual network (VIS), the frontoparietal network (FPN), the dorsal attention network (DAN), the ventral attention network (VAN), and the basal ganglia network (BG). The composite maps and peak coordinates of the ICs and RSNs are shown in Figure 1 and Table S1.

Static functional network analysis

Multivariate analysis of covariance (MANCOVAN) was applied to assess the significant associations between the spatial map and static connectivity strength of the RSNs and group status (RRMS females, RRMS males, healthy females, and healthy males). We used univariate tests and regressed the age, mean FD, and multicenter variables as covariates to evaluate the effects of disease and sex.

Intra-network spatial maps

To assess the intra-network connectivity strength, SMs were thresholded based on the distribution of voxelwise T statistics (i.e., mean ± 4SD) to evaluate the consistent and highly activated voxels within each network. This procedure requires an individual t-test for each voxel within a spatial map with a false discovery rate (FDR) correction at $P<0.05$.

Inter-network static functional network connectivity

For inter-network sFNC, we selected the default options to perform postprocessing on subject-specific time courses, including detrending using 3dDespike and filtering using a fifth-order Butterworth low-pass filter with a high-frequency cutoff of 0.15 Hz. Pearson's correlations were computed for each pair of components and sFNC matrices were obtained for all subjects.

Dynamic functional network analysis

The dFNC was carried out in the Temporal dFNC toolbox in GIFT. A sliding window approach was used with a window width of 22 repetition times (TRs) (44s), a step of 1 TR (2s), and a Gaussian convolution of 3 TRs (6s). Furthermore, using L1 regularized inverse covariance matrix (repeated 10 times) was used to disperse the dFNC matrix, and Fisher's Z-transformation was applied. Then, K-means clustering with Manhattan distance (150 iterations and five repetitions) was performed to distinguish

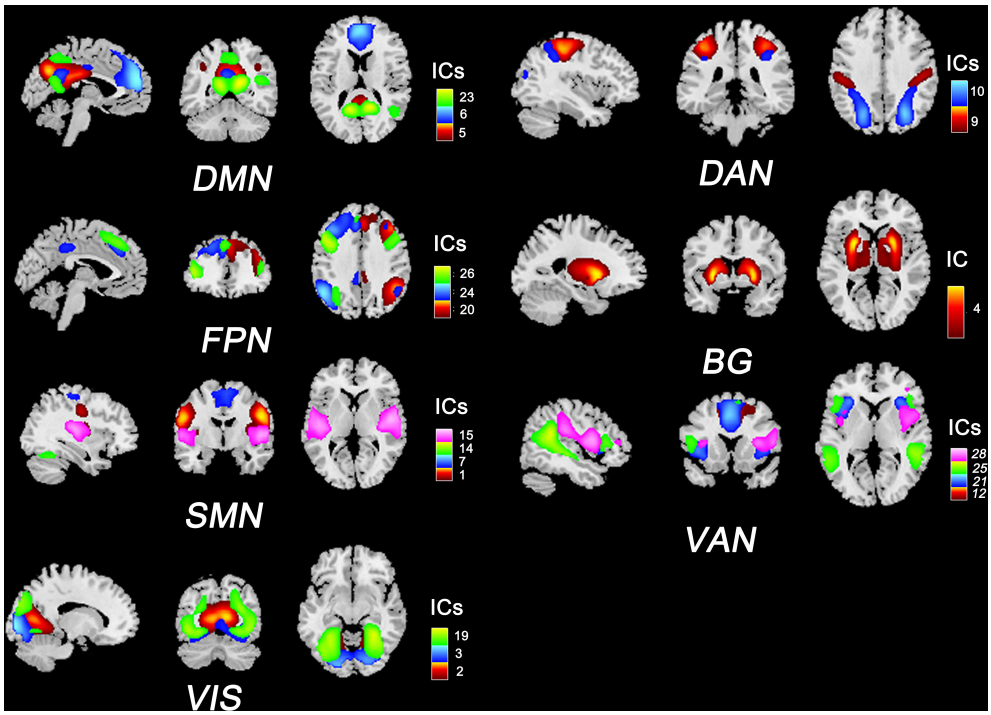

FIGURE 1
Composite maps of 20 independent components and seven RSNs. The number and color of each component correspond to the color bars. DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN: dorsal attention network; VAN, ventral attention network; BG, basal ganglia network.

recurring dFNC patterns within different windows for each subject. According to the elbow criterion, the optimal number of clusters was three or four (k= 3 or 4). The dFNC temporal properties included: 1) fraction time (the total time percentage of one subject staying in a state); 2) mean dwell time (the time each subject spent in a specific state); and 3) transition number (the total number of transitions from one state to another).

Control for head movement

The following approaches were to reduce the potential effects of head motion on sFNC and dFNC: 1) subjects with translation > 3 mm or rotation > 3° were excluded; 2) ICA was used to identify and remove motion-related components from the fMRI data (23); 3) rs-fMRI time courses were detrended using 3dDespike and filtered using a fifth-order Butterworth low-pass filter with a high-frequency cutoff of 0.15 Hz; 4) the mean FD was regressed in the ANOVA tests of sFNC and dFNC between groups; and 5) six motion-realignment parameters were regressed on the sFNC and dFNC matrix for each subject.

Statistical analysis

Figure 2 shows the flow chart of the Methods. The demographic data, lesion volume, and other clinical variables were analyzed in SPSS 23.0. We applied Kolmogorov–Smirnov tests to evaluate the normality of the clinical data and ANOVA or Mann–Whitney U tests for differences between groups. One-way ANOVA and *post hoc* tests ($P<0.05$) with FDR correction were performed to evaluate significant associations between the SM, sFNC, and dFNC of the RSNs and group status: 1) healthy female vs. healthy male; 2) RRMS female vs. healthy female; 3) RRMS male vs. healthy male; and 4) RRMS female vs. RRMS male. Moreover, we used the Mann–Whitney U test ($P<0.01$) to compare the temporal features of the dFNC between groups. Receiver operating characteristic (ROC) curves analysis assessed the performance of static and dynamic indicators in distinguishing RRMS from healthy controls. Spearman or partial correlation analysis was applied to explore the relationships between altered functional or structural measures and clinical variables. The ANOVA and correlation analysis were applied with age, mean FD, and multi-center variables as covariates or control variables. Moreover, to investigate the effect of gray matter volume on functional networks, we also supplemented the ANOVA analysis with gray matter volume as a confounding factor between groups.

Reproducibility

The choice of window width for a sliding window method is a matter of debate. Previous studies have suggested that a window width between 30 s and 60 s could extract physiological signals (24, 25) and was not affected by noise. Thus, we also added the results of a window width of 30 TRs and the number of clusters of three or four (k=3 or 4).

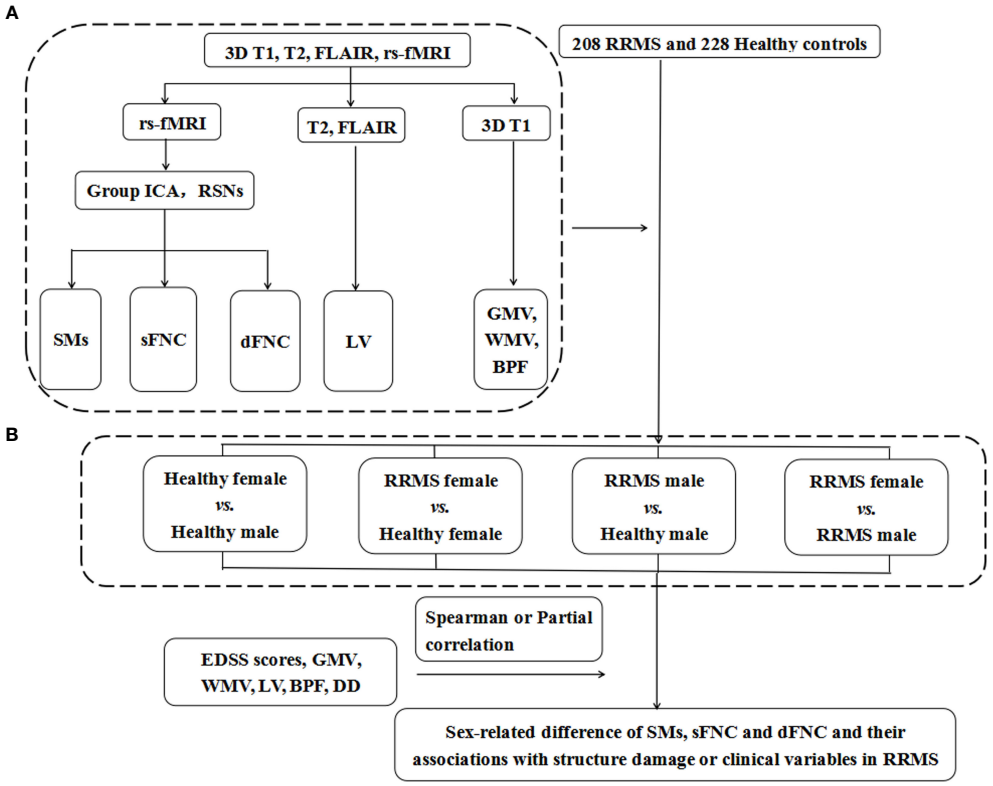

FIGURE 2
The flow chart of Materials and Methods. **(A)** The data of 3DT1, T2, rs-fMRI, and FLAIR images were preprocessed and postprocessed to calculate functional and structural indicators for each subject, including the SMs, sFNC, and dFNC and LV, GMV, WMV, and BPF. **(B)** A total of 208 RRMS patients and 228 healthy controls were recruited for this study, and they were divided into four groups according to sex. We compared the differences in SMs, sFNC, and dFNC between the above four groups to determine the sex effects in patients with RRMS. RRMS, relapsing-remitting multiple sclerosis; rs-fMRI, resting-state functional MRI; FLAIR, fluid-attenuated inversion recovery; Group ICA, group independent component analysis; RSNs, resting-state networks; SMs, spatial maps; sFNC, static functional network connectivity; dFNC, dynamic functional network connectivity; GMV, gray matter volume; WMV, white matter volume; BPF, brain parenchyma fraction; LV, lesion volume; DD, disease duration; EDSS score, Extended Disability Status Scale score.

Data availability

Correspondence and requests for the data can be addressed to our corresponding author, Fuqing Zhou.

Results

Table 1 shows all demographic data and group statistics. Lower GMV, WMV, and BPF were shown in RRMS patients compared with controls ($P \leq 0.002$). Male RRMS patients showed higher GMV and WMV than female patients ($P<0.001$), but there was no statistically significant difference in BPF between female and male RRMS patients ($P=0.423$). Among the patients with RRMS, male patients had a higher lesion load ($P=0.041$) than female patients, even though the recruited RRMS patients were matched between sexes for age, disease course, and clinical disability. There was no significant difference in age or mean FD between the RRMS groups and healthy controls (P: 0.101-0.730).

Static functional network analysis

Intra-network SMs and inter-network sFNC

In healthy controls, healthy males showed lower SMs within the DMN (bilateral precuneus) and lower sFNC within the SMN and SMN-VIS compared with healthy females ($P<0.05$, FDR corrected) (Figures 3A1, A2). However, this sex difference disappeared between female and male patients with RRMS. Compared with healthy controls, only RRMS males exhibited decreased SMs within DAN, increased sFNC within PFN, and reduced sFNC of SMN-PFN, SMN-VIS, and SMN-VAN ($P<0.05$, FDR corrected) (Figures 3B1, B2). There was no significance in RRMS females vs. healthy females and RRMS females vs. RRMS males.

Dynamic functional network analysis

dFNC clustering states

First, three recurrent dFNC states were identified after cluster analysis: State 1 (sparse connected state; 49%), State 2 (middle connected state; 36%), and State 3 (high connected state; 15%) (Figure 4A). State 1 was characterized by sparse connectivity both

TABLE 1 Demographic data and clinical characteristics.

	RRMS (n=208)		Healthy controls (n=228)		*P* value			
	Female (n=135)	Male (n=73)	Female (n=123)	Male (n=105)	*P1*	*P2*	*P3*	*P4*
Age (years)[a]	37.55 (11.47)	35.42 (10.98)	36.94 (12.17)	38.17 (10.87)	0.405	0.682	0.101	0.192
DD (months)[b]	17 (5–48)	24 (5–72)	–	–	–	–	–	0.492
Mean FD (mm)[a]	0.068 (0.107)	0.078 (0.117)	0.069 (0.105)	0.075 (0.119)	0.225	0.730	0.475	0.113
EDSS scores[b]	2 (1-3.5)	2.5 (1.5-3.5)	–	–	–	–	–	0.309
LV (ml)[b]	5.94 (1.43-16.70)	8.16 (3.36-19.70)	–	–	–	–	–	0.041
GMV (ml)[a]	604.20 (58.58)	656.31 (61.14)	653.84 (57.84)	687.42 (64.19)	<0.001	<0.001	0.002	<0.001
WMV (ml)[a]	453.51 (56.39)	512.96 (72.18)	498.03 (51.67)	549.67 (51.93)	<0.001	<0.001	<0.001	<0.001
BPF[a]	0.76 (0.05)	0.75 (0.04)	0.80 (0.03)	0.79 (0.03)	0.019	<0.001	<0.001	0.423

[a]indicates data are presented as the mean (standard deviation); [b]indicates data are presented as the median (interquartile range).
P1: Healthy females vs. healthy males.
P2: RRMS females vs. healthy females.
P3: RRMS males vs. healthy males.
P4: RRMS females vs. RRMS males.
RRMS, relapsing-remitting multiple sclerosis; FD, framewise displacement; DD, disease duration; EDSS, Extended Disability Status Scale; LV, lesion volume; GMV, gray matter volume; WMV, white matter volume; BPF, brain parenchyma fraction.

within and between networks, whereas State 3 showed a tightly connected matrix. State 2 was a transitional state between State 1 and State 3, which featured decreased dFNC between the SMN and DMN or FPN and increased dFNC within the DMN, FPN, SMN, and VIS. Figure 4B shows the percentage of specific states for each group: healthy females showed higher percentage in State 2 (99%), whereas healthy males and RRMS patients showed higher percentage in State 1 (98%, 99%,99%, respectively).

dFNC temporal properties

Next, the temporal properties of dFNC revealed significant differences in fraction time, mean dwell time, and transitions

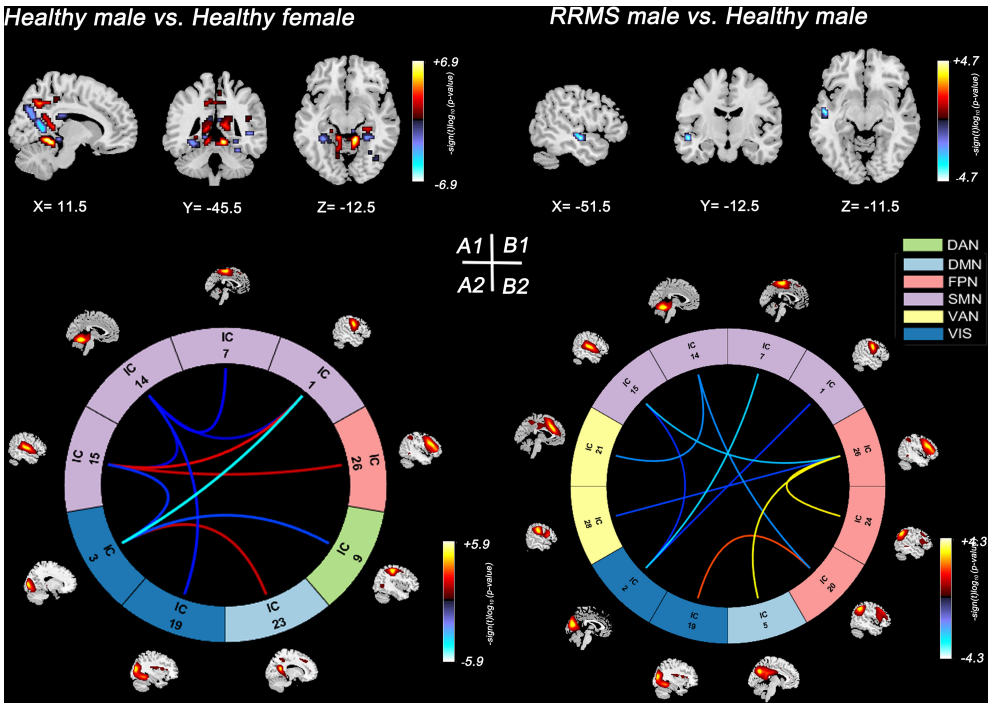

FIGURE 3
Significant results of the voxel-level comparison of RSN maps and sFNC between groups. Spatial maps of significant voxels **(A1)** and sFNC **(A2)** of RSNs in healthy groups, *P*<0.05, FDR corrected. Spatial maps of significant voxels **(B1)** and sFNC **(B2)** of RSNs between RRMS males and healthy males, *P*<0.05, FDR corrected. Significant cluster volume>10. RRMS, relapsing-remitting multiple sclerosis; DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN, dorsal attention network; VAN, ventral attention network.

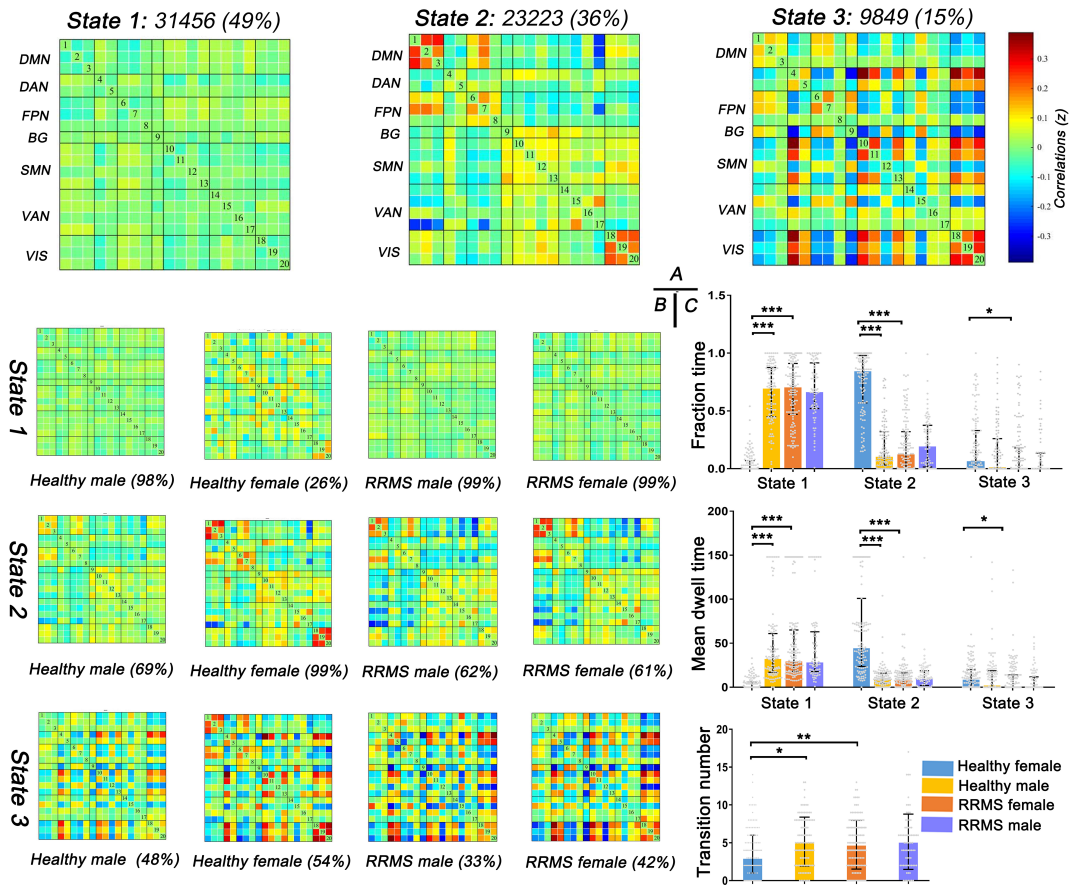

FIGURE 4
Results of clustering analysis and between-groups dynamic temporal properties. **(A)** Three dFNC states for all subjects with the total number of occurrences and percentage of total occurrences. **(B)** The specific connectivity state for each group. The percentage is calculated as the ratio of the number of subjects who entered one state to the total number of subjects in each group. **(C)** Significant differences in the temporal properties in healthy controls and RRMS groups: healthy females showed a higher fraction time and more dwell time in State 2 (P<0.001) with lower transitions (P=0.012) compared with healthy males, while female RRMS patients exhibited a higher fraction time and more dwell time in State 1 (P<0.001) and higher transitions (P=0.004) relative to healthy females. Fraction time: the total time percentage of one subject staying in a state. Mean dwell time: the time each subject spent in a specific state. Transition number: the total number of subject transitions from one state to another. *** indicates P<0.001, ** means P<0.01, * means P<0.05. RRMS, relapsing-remitting multiple sclerosis; DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN, dorsal attention network; VAN, ventral attention network; BG, basal ganglia network.

among the three states among the groups (Figure 4C). Compared with healthy males, healthy females showed a higher fraction time (healthy female vs. healthy male: 85% vs. 11%; P<0.001) and more dwell time in State 2 (healthy female vs. healthy male: 45.33s vs. 4.42s; P<0.001) with lower transitions (healthy female vs. healthy male: three times vs. five times; P=0.035). However, the tendency changed once RRMS was established; female RRMS patients exhibited a higher fraction time (RRMS female vs. healthy female: 71% vs. 0%; P<0.001) and more dwell time in State 1 (RRMS female vs. healthy female: 30.25s vs. 0.00s; P<0.001) and higher transitions (RRMS female vs. healthy female: four times vs. three times; P=0.004), relative to healthy females. No statistical difference was seen in RRMS males vs. healthy males and RRMS females vs. RRMS males. Furthermore, ROC curve analysis found that the fraction time and mean dwell time of State 1 could significantly distinguish female patients from controls [areas under the curve (AUC): 0.838, 0.896, respectively] (Data Sheet 1, Figure S1).

Between-group dFNC differences

Lastly, we also evaluated the dFNC differences between the healthy controls and RRMS groups. Similar to the results of the dFNC temporal properties, the dFNC pattern alterations were seen only in female groups: compared with healthy males, healthy females exhibited higher dFNC within DMN, FPN, and VIS in all states (P<0.05, FDR corrected) (Figure 5A). On the contrary, this trend disappeared among RRMS patients. Moreover, compared with healthy females, female patients mainly showed lower dFNC in all states, particularly within the DMN, FPN, and VIS (P<0.05, FDR corrected) (Figure 5B). There was no dynamic significance in RRMS males vs. healthy males and RRMS females vs. RRMS males.

We next analyzed the between-group differences in functional network with gray matter volume as a covariate, and we found that gray matter volume had no significant effect on the results of SMs, sFNC and dFNC between RRMS groups and healthy controls. For more detailed results (including the description), see Data Sheet 2, Figures S2–S4.

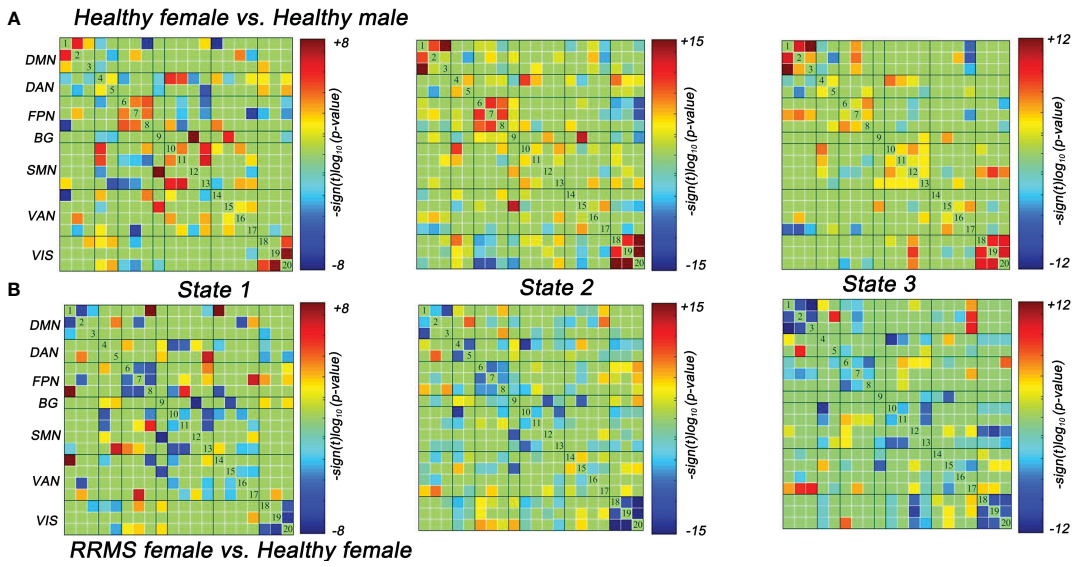

FIGURE 5
Significant differences in dFNC between groups. **(A)** Healthy females showed significantly higher dFNC within DMN, PFN, and VIS compared with healthy males (P<0.05, FDR corrected). **(B)** RRMS females showed significantly lower dFNC within DMN, PFN, and VIS compared with healthy females (P<0.05, FDR corrected). RRMS, relapsing-remitting multiple sclerosis; DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN, dorsal attention network; VAN, ventral attention network; BG, basal ganglia network.

Correlation analysis

In RRMS females, the lower fraction time (r = 0.224, P = 0.011) and mean dwell time (r = 0.305, P < 0.001) of State 1 related to lower GMV, and the higher numbers of transitions related to lower GMV (r=-0.314, P<0.001) and lower WMV (r=-0.225, P=0.011). For RRMS males, decreased sFNC of SMN-FPN was related to lower GMV (r=-0.311, P=0.012) and BPF (r=−0.284, P=0.022). The correlations with significant p values (P<0.05) are shown in Figure 6, Tables S2, S3.

Reproducibility

In these replication analyses, when the window width was 30 TRs or 22 TRs, and the clustering state was 3 or 4, we found that RRMS affected dFNC patterns and its temporal properties only in female patients with RRMS, indicating the dFNC results were very stable, reliable, and repeatable. The details are as follows:

The differences of temporal properties between groups suggested that RRMS females preferred State 1 (sparse connected state) and spent more time in State 1 compared with healthy females (P<0.001) (Figures S5–S7).

The dFNC differences between groups suggested that RRMS females showed decreased dFNC within DMN, FPN, and VIS in all states compared with healthy females (P<0.05, FDR corrected) (Figures S8–S10).

Discussion

Our study investigated the between-group differences in the strength and time-varying connectivity of brain networks between RRMS and healthy subjects by sex and the associations with structural damage and disability. sFNC alterations were only observed in male patients with increased sFNC within the FPN and decreased sFNC across the SMN-FPN and SMN-VIS networks, whereas dFNC abnormalities were observed only in female RRMS patients, manifested as a higher fraction time and more dwell time in State 1 (sparse connected state) with lower transitions compared with healthy females. A higher fraction time and more dwell time of State 1 could significantly distinguish female patients from controls. Altered sFNC and altered temporal properties were related to structural damage in RRMS patients.

Significant sFNC alterations in male patients with RRMS

Given the disease damage to the brain, it is easy to understand that RRMS patients have lower gray matter and white matter volumes compared with healthy controls, and atrophy of gray and white matter has been reported in MS (26). However, RRMS males still had a higher lesion burden compared with female patients, even though the recruited RRMS patients were matched for age, disease duration, and clinical disability between sexes. This is consistent with previous studies that male patients seem to have a higher level of brain structural damage (9, 13). Further analysis of sFNC revealed increased and reduced sFNC in only male patients with RRMS compared with controls, mainly decreased sFNC across the SMN-FPN and SMN-VIS networks; these results remained after regressing gray matter volume. Our findings could be understood by the “network collapse”, a widely accepted model for explaining sFNC changes in MS proposing that sFNC change is a dynamic process and network efficiency tends to deteriorate with subsequent declines in sFNC, due to progressive brain structural damage and the reduced compensatory capacity of functional networks in MS

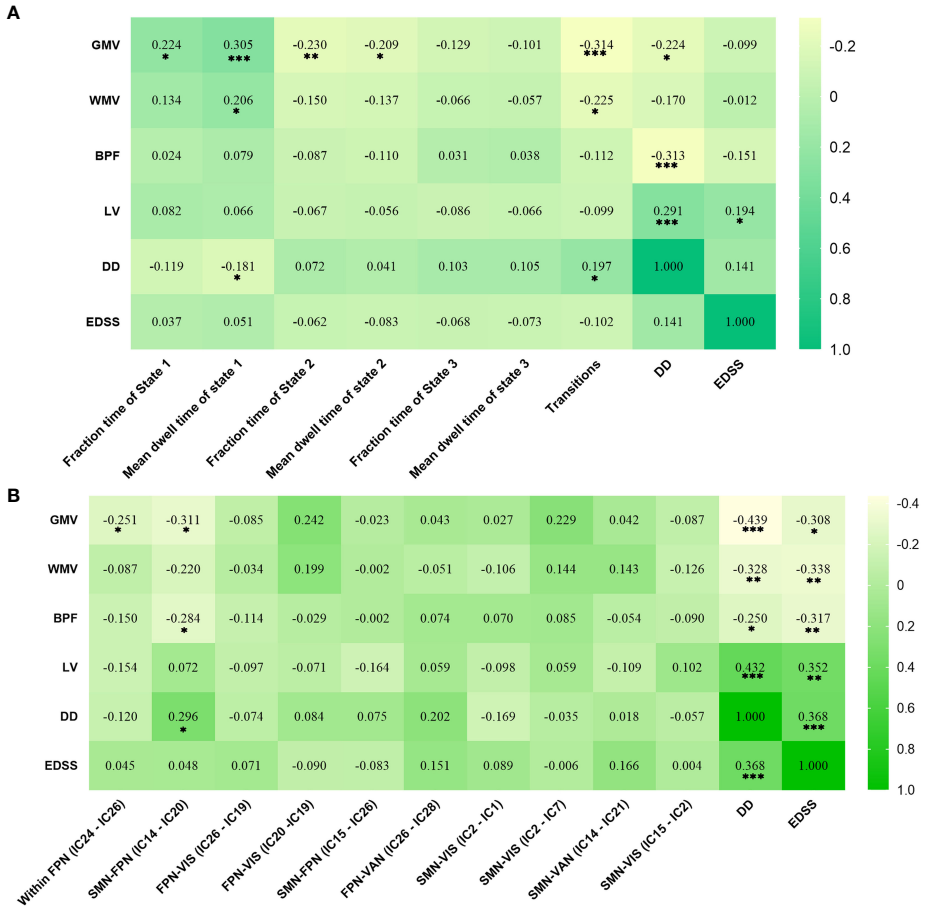

FIGURE 6
Significant correlation analysis results of RRMS patients. **(A)** Correlation results in female RRMS patients. **(B)** Correlation results in male RRMS patients. ***indicates P<0.001, **means P<0.01, *means P<0.05. Abbreviations: RRMS, relapsing-remitting multiple sclerosis; GMV, gray matter volume; WMV, white matter volume; BPF, brain parenchyma fraction; LV, Lesion volume, EDSS, extended disability status scale; DD, disease duration.

(27). Furthermore, these functional networks have been widely reported in MS, and functional reorganization of the SMN occurs in all stages of relapse, remission, and recovery in RRMS, and are closely related to clinical disability (28, 29). Furthermore, functional changes in the FPN and VIS are involved in cognitive dysfunctions in RRMS patients, including attention (30), working memory (31), and visual information processing (32).

We analyzed the correlation analysis between structural measures and connectivity changes and found that there was no correlation in statistics between lesion load and altered connectivity in both female and male patient cohorts. These results may indicate that the sFNC reorganization in MS patients may be caused by multiple factors, such as damage of gray matter and white matter (33, 34). Indeed, our study found that the decreased sFNC of FPN-SMN was associated with lower BPF and GMV in RRMS males. Our findings support the hypothesis that male RRMS patients may have a higher degree of static connectivity impairment based on functional network evidence, and these functional reorganizations may be associated with structural damage. Recently, a systematic review found no clear trend towards one FC direction change in MS, which may be associated with the large heterogeneity within and between different study cohorts (e.g., different fMRI indicators, MS phenotypes, disease status, duration, and age) (35). Hence, our results still need to be interpreted cautiously.

Altered dFNC temporal properties in female patients with RRMS

Three recurring states were identified for dFNC. State 1, a sparse connected state, is characterized by overall lower connectivity within and between networks; it possibly reflects the baseline state of minimal activity between brain neurons at rest. State 2 and State 3 are more tightly connected states within or between the DMN, FPN, SMN, and VIS, which may suggest the active states of cognitive and motor networks aroused by the brain. Results of the dFNC temporal properties showed that female RRMS patients exhibited a higher fraction time and more dwell time with lower transitions in State 1 rather than State 2 usually exhibited among healthy females, suggesting that RRMS could cause the transition from the active state of cognitive networks (State 2) to the baseline state (State 1) with sparse connectivity in female patients. These results are supported by a recent longitudinal study, which found decreased dFNC even in clinically isolated syndromes, and the

reduced dynamics were more significant over time. Importantly, the functional connectivity within a tightly connected state at baseline could predict cognitive performance after 5 years in MS (36).

Moreover, further ROC analysis indicted that the fraction time and mean dwell time of State 1 could discriminate female patients with RRMS from healthy females. The sparse connected state (State 1) is the most frequent dFNC state for RRMS patients, which is consistent with the findings of Hidalgo et al., which also observed that the decreased dFNC of State 1 was associated with poor motor and cognitive performance in MS patients (37). Our results indicated that the temporal properties of State 1 may be potential neuroimaging markers in female patients. Interestingly, the lower fraction and dwell time of State 1 related to lower GMV, and the higher numbers of transitions related to gray and white matter atrophy. These findings may suggest that female patients still trend toward dynamic functional compensation in response to structural damage in the early stages of disease, even if such functional compensation is unsuccessful.

Significant dFNC decreases in female patients with RRMS

Dynamic reorganization was only seen in female RRMS patients: reduced connectivity mainly within the DMN, FPN, and VIS in all states. These findings are consistent with a recent study into dynamic eigenvector centrality, which revealed that cognitively impaired MS patients had decreased dynamics in the DMN, FPN, and VIS compared with healthy controls (38). Our results further indicated that female patients not only show the transition of cognitive-related networks (from State 2 to State 1), but also decreased dFNC within the cognitive networks. As such, we speculate that altered dFNC temporal properties and decreased dFNC within the cognition networks may be maladaptive approaches to maintaining functioning in female patients.

However, the mechanism of how RRMS affects functional networks by sex is still unclear. It may be associated with the complex interactions of sex hormone levels, regulation of the immune system, and certain MS susceptibility genes (39–41). Studies have suggested that sex hormones may have beneficial effects on reducing inflammation and neurodegeneration in MS, which were confirmed in mouse models of MS/demyelination (42, 43). Although a previous study has reported gray matter loss associated with ovarian aging in MS (44), there is still a lack of research on how sex hormones affect functional network connectivity in MS patients. Moreover, recent studies have shown that sex is an important regulator of functional network reorganization in both healthy people and patients with Alzheimer's disease (45). Exploring sex-related differences in functional connectivity could provide important information to characterize the brain and cognitive changes of RRMS patients.

Our study is not without limitations. It is still preliminary work and may be affected by different disease durations, disabilities, and disease states. Thus, further research should be carried out based on these points to verify our results. Although our results revealed that female RRMS patients showed reduced dFNC on cognition-related networks, the lack of cognitive-related assessments limited our interpretation of cognitive-related networks (e.g., DMN) due to the retrospective design.

In conclusion, our study found that RRMS affected static connectivity in males and dynamic connectivity in females, suggesting that sex-related effects may be important factors for functional damage and reorganization of the CNS in RRMS patients. Exploring these sex-related differences might increase the possibility of sex-specific approaches to treating RRMS in the future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of The First Affiliated Hospital of Nanchang University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YW, FZ, YXL, and YD contributed to drafting/revising the manuscript. YLW contributed to data analysis. ZZ, NZ, XH, and CZ performed the statistical analysis. XC, MH, YZ, HL, and GC contributed to MRI data acquisition and analysis. JS and YML contributed to interpretation of the data. All authors approved and take public responsibility for the version to be published.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1216310/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Receiver operating characteristic curve of dFNC temporal properties. AUC, areas under the curve.

SUPPLEMENTARY FIGURE 2
Significant results of voxel-level comparison of RSN maps and sFNC between groups with gray matter volume as a covariate. Spatial maps of significant voxels **(A1)** and sFNC **(A2)** of RSNs in healthy groups, $P<0.05$, FDR corrected. Spatial maps of significant voxels **(B1)** and sFNC **(B2)** of RSNs between RRMS males and healthy males, $P<0.05$, FDR corrected. Significant cluster volume>10. RRMS, relapsing-remitting multiple sclerosis; DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN, dorsal attention network; VAN, ventral attention network.

SUPPLEMENTARY FIGURE 3
Results of clustering analysis and between-groups dynamic temporal properties with gray matter volume as a covariate. **(A)** Three dFNC states for all subjects with the total number of occurrences and percentage of total occurrences. **(B)** The specific connectivity state for each group. The percentage is calculated as the ratio of the number of subjects who entered one state to the total number of subjects in each group. **(C)** Significant differences in the temporal properties in healthy controls and RRMS groups: healthy females showed a higher fraction time ($P<0.001$) and more dwell time in State 2 ($P<0.001$) with lower transitions ($P<0.001$) compared with healthy males, while female RRMS patients exhibited a higher fraction time ($P<0.001$) and more dwell time in State 1 ($P<0.001$) and higher transitions ($P=0.005$) relative to healthy females. Fraction time: the total time percentage of one subject staying in a state. Mean dwell time: the time each subject spent in a specific state. Transition number: the total number of subject transitions from one state to another. *** indicates $P<0.001$, ** means $P<0.01$, * means $P<0.05$. RRMS, relapsing-remitting multiple sclerosis; DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN, dorsal attention network; VAN, ventral attention network; BG, basal ganglia network.

SUPPLEMENTARY FIGURE 4
Significant differences in dFNC between groups with gray matter volume as a covariate. **(A)** Healthy females showed significantly higher dFNC within DMN, PFN, and VIS compared with healthy males ($P<0.05$, FDR corrected). **(B)** RRMS females showed significantly lower dFNC within DMN, PFN, and VIS compared with healthy females ($P<0.05$, FDR corrected). RRMS, relapsing-remitting multiple sclerosis; DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN, dorsal attention network; VAN, ventral attention network; BG, basal ganglia network.

SUPPLEMENTARY FIGURE 5
Results of clustering analysis and between-groups dynamic temporal properties when the window width was 22 TRs, the step was 1 TR, and the number of clusters was four. **(A)** Four dFNC states for all subjects with the total number of occurrences and percentage of total occurrences. **(B)** The specific connectivity state for each group. The percentage is calculated as the ratio of the number of subjects who entered one state to the total number of subjects in each group. **(C)** Significant differences in the temporal properties in healthy controls and RRMS groups: healthy females showed a higher fraction time ($P<0.001$) and more dwell time in State 2 ($P<0.001$) with lower transitions ($P<0.05$) compared with healthy males, while female RRMS patients exhibited a higher fraction time ($P<0.001$) and more dwell time in State 1 ($P<0.001$) and higher transitions ($P=0.005$) relative to healthy females. Fraction time: the total time percentage of one subject staying in a state. Mean dwell time: the time each subject spent in a specific state. Transition number: the total number of subject transitions from one state to another. *** indicates $P<0.001$, ** means $P<0.01$, * indicates $P<0.05$. RRMS, relapsing-remitting multiple sclerosis; DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN: dorsal attention network; VAN, ventral attention network; BG, basal ganglia network.

SUPPLEMENTARY FIGURE 6
Results of clustering analysis and between-groups dynamic temporal properties when the window width was 30 TRs, the step was 1 TR, and the number of clusters was three. **(A)** Three dFNC states for all subjects with the total number of occurrences and percentage of total occurrences. **(B)** The specific connectivity state for each group. The percentage is calculated as the ratio of the number of subjects who entered one state to the total number of subjects in each group. **(C)** Significant differences in the temporal properties in healthy controls and RRMS groups: healthy females showed a higher fraction time ($P<0.001$) and more dwell time in State 2 ($P<0.001$) compared with healthy males, while female RRMS patients exhibited a higher fraction time ($P<0.001$) and more dwell time in State 1 ($P<0.001$) and higher transitions ($P=0.01$) relative to healthy females. Fraction time: the total time percentage of one subject staying in a state. Mean dwell time: the time each subject spent in a specific state. Transition number: the total number of subject transitions from one state to another. *** indicates $P<0.001$, ** means $P<0.01$. RRMS, relapsing-remitting multiple sclerosis; DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN: dorsal attention network; VAN, ventral attention network; BG, basal ganglia network.

SUPPLEMENTARY FIGURE 7
Results of clustering analysis and between-groups dynamic temporal properties when the window width was 30 TRs, the step was 1 TR, and the number of clusters was four. **(A)** Four dFNC states for all subjects with the total number of occurrences and percentage of total occurrences. **(B)** The specific connectivity state for each group. The percentage is calculated as the ratio of the number of subjects who entered one state to the total number of subjects in each group. **(C)** Significant differences in the temporal properties in healthy controls and RRMS groups: healthy females showed a higher fraction time ($P<0.001$) and more dwell time in State 2 ($P<0.001$) compared with healthy males, while female RRMS patients exhibited a higher fraction time ($P<0.001$) and more dwell time in State 1 ($P<0.001$) and higher transitions ($P=0.002$) relative to healthy females. Fraction time: the total time percentage of one subject staying in a state. Mean dwell time: the time each subject spent in a specific state. Transition number: the total number of subject transitions from one state to another. *** indicates $P<0.001$, ** means $P<0.01$, * indicates $P<0.05$. RRMS, relapsing-remitting multiple sclerosis; DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN: dorsal attention network; VAN, ventral attention network; BG, basal ganglia network.

SUPPLEMENTARY FIGURE 8
Significant differences in dFNC between groups when the window width was 22 TRs, the step was 1 TR, and the number of clusters was four. **(A)** Healthy females showed significantly higher dFNC within DMN, PFN, and VIS compared with healthy males ($P<0.05$, FDR corrected). **(B)** RRMS females showed significantly lower dFNC within DMN, PFN, and VIS compared with healthy females ($P<0.05$, FDR corrected). RRMS, relapsing-remitting multiple sclerosis; DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN: dorsal attention network; VAN, ventral attention network; BG, basal ganglia network.

SUPPLEMENTARY FIGURE 9
Significant differences in dFNC between groups when the window width was 30 TRs, the step was 1 TR, and the number of clusters was three. **(A)** Healthy females showed significantly higher dFNC within DMN, PFN, and VIS compared with healthy males ($P<0.05$, FDR corrected). **(B)** RRMS females showed significantly lower dFNC within DMN, PFN, and VIS compared with healthy females ($P<0.05$, FDR corrected). RRMS, relapsing-remitting multiple

sclerosis; DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN: dorsal attention network; VAN, ventral attention network; BG, basal ganglia network.

SUPPLEMENTARY FIGURE 10

Significant differences in dFNC between groups when the window width was 30 TRs, the step was 1 TR, and the number of clusters was four. **(A)** Healthy females showed significantly higher dFNC within DMN, PFN, and VIS compared with healthy males ($P<0.05$, FDR corrected). **(B)** RRMS females showed significantly lower dFNC within DMN, PFN, and VIS compared with healthy females ($P<0.05$, FDR corrected). RRMS, relapsing-remitting multiple sclerosis; DMN, default mode network; SMN, sensorimotor network; VIS, visual network; FPN, frontoparietal network; DAN, dorsal attention network; VAN, ventral attention network; BG, basal ganglia network.

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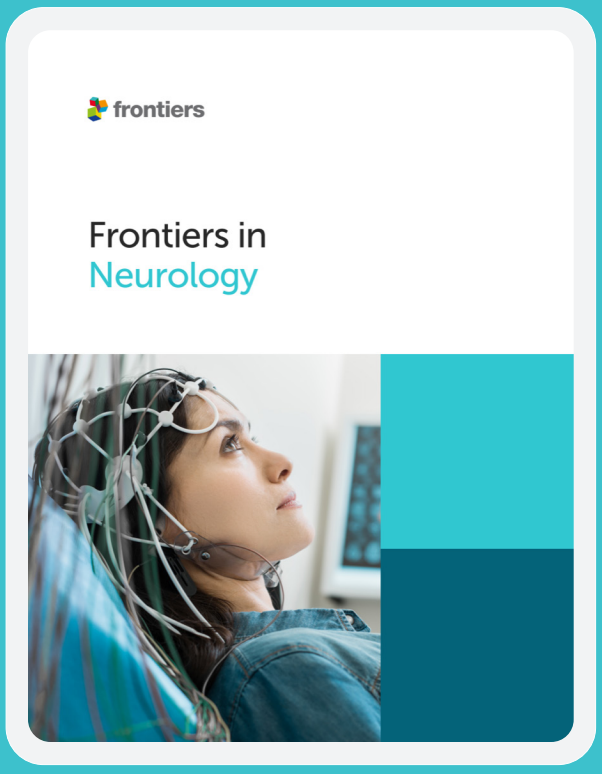

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