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Multiple Sclerosis Relapses: Epidemiology, Outcomes and Management. A Systematic Review

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Key Words
Multiple sclerosis · Relapse · Therapy · Phenotype · Recurrence · Disease outcomes · Steroids · MRI · Registry · Geography

Abstract
Relapses (episodic exacerbations of neurological signs or symptoms) are a defining feature of relapsing-remitting multiple sclerosis (MS), the most prevalent MS phenotype. While their diagnostic value relates predominantly to the definition of clinically definite MS, their prognostic value is determined by their relatively high associated risk of incomplete remission resulting in residual disability. The mechanisms governing a relapse incidence are unknown, but numerous modifiers of relapse risk have been described, including demographic and clinical characteristics, many of which represent opportunities for improved disease management. Also relapse phenotypes have been associated with patient and disease characteristics and an individual predisposition to certain phenotypic presentations may imply individual neuroanatomical disease patterns. While immunomodulatory therapies and corticosteroids represent the mainstay of relapse prevention and acute management, respectively, their effect has only been partial and further search for more efficient relapse therapies is warranted. Other areas of research include pathophysiology and determinants of relapse incidence, recurrence and phenotypes, including the characteristics of the relapsing and non-relapsing multiple sclerosis variants and their responsiveness to therapies.

Background

Episodes of transient exacerbations of neurological disability – known as relapses – are a defining feature of relapsing-remitting multiple sclerosis (MS). From the clinical perspective, relapses represent an essential element in the diagnostics of relapse-onset MS [1]. From the societal perspective, they result in increased consumption of healthcare resources and incur significant costs [2–5].

Relapses represent clinical correlates of impaired axonal conductivity triggered by flair-ups of localised autoimmune process within the CNS (for detailed reviews of immunology and pathology of MS relapses see [6, 7]). Loss of myelin, which is the target of MS autoimmune attack, results in increased electrical capacitance of axons, and is considered to be the primary pathophysiological mechanism of the conduction block [8]. In addition, several substances involved in the MS autoimmune cascade were shown to interfere directly with axonal conductivity. These comprise pro-inflammatory cytokines (such as

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interferon γ, tumour necrosis factor α) [9], nitric oxide [10] or 'neuroelectric blocking factors' contained within the IgG fraction of serum [11]. In addition to their possible direct interaction with ion channels [12], they may potentially interfere with the mitochondrial function [13] or synaptic transmission [14].

It is of interest that only a proportion of inflammatory CNS events present clinically as MS relapses. In a serial analysis of 3-monthly brain and spinal cord magnetic resonance imaging (MRI), new or contrast-enhancing lesions were observed on 26 of 28 scans coinciding with relapses (sensitivity 93%) but also on 19 of 51 scans with no coincident relapses (63% specificity) [15]. Interestingly, the load of the enhancing lesions was markedly larger among the patients presenting with relapses than those with only subclinical MRI activity [16]. It can be speculated that several factors, including lesion topography, size, time since demyelination and magnitude of the myelin loss determine the clinical phenotype and severity of relapses [8, 17].

Changes in relapse-related outcomes have been used as the primary endpoint in the majority of pivotal randomised phase III trials of MS disease-modifying therapies [18]. While relapse activity has been proposed as a marker of treatment response, its relationship to long-term disability outcomes has been a subject of ongoing debate [19]. The purpose of this systematic review is to summarise the published literature concerning relapses – their epidemiology, determinants, diagnostic and prognostic value, clinical outcomes and management – with the emphasis on the increasing volume of literature published over the recent four years.

Review Criteria

References for this review were identified using an electronic database of peer-reviewed literature (PubMed), following a pre-specified review protocol. The search included the terms 'multiple sclerosis' in combination with 'relapse', 'exacerbation', 'attack' or 'bout' within the article title or abstract, published between 1970 and 2014 (the latter two terms were added to the search protocol in response to suggestions from the reviewers). After removing duplicate records, the reference list was hand-searched to identify potentially relevant studies. The abstracts were read and evaluated with respect to the predefined inclusion criteria: studies done in patients with MS or clinically isolated syndrome (CIS), reporting original data, meta-analysis or systematic review of literature, with the primary focus on the epidemiology, prognostics or management of MS relapses, containing sufficient information to evaluate the quality of presented evidence, and published in English. Case reports were not reviewed. The quality assessment evaluated population description and representativeness, control of bias (at the outcome level) and generalizability of the results. The articles selected based on their abstracts were reviewed in full, and relevant information was extracted to be used in the synthesis. Figure 1 represents the PRISMA flow diagram of the reviewed literature.

Epidemiology of MS Relapses

In their review of relapse incidence in placebo arms from 32 randomised clinical trials published between 1980 and 2008, Inusah and colleagues summarised the reported annualised relapse rates, which ranged from 0.27 to 1.66 relapses per year. The review indicated that the annualised relapse rate has been showing a sustained decline, with the magnitude of this change being 0.36 relapses per 10 years [20]. While this may reflect a long-term decreasing trend in the incidence of relapses among the treatment-naïve patient population, it is more likely that the observed decline is determined by changing criteria of patient inclusion in randomised clinical trials. Due to ethical restraints, an increasingly greater proportion of patients with active disease have been likely to be treated with high-efficacy medication, thus biasing randomised trials to preferentially include patients with relatively less active disease. Additional contributing factors are the increasing baseline patient age and MS duration, and the Will Rogers phenomenon [21, 22]. The decreasing baseline relapse activity and the increasing homogeneity of the trial cohorts may lead to an inflation of relative treatment effects. Attrition bias is an additional source of confounding, introduced by selective withdrawal of patients with on-study MS activity from clinical trials [21]. It can be eliminated by modelling the time to first on-trial relapse [23]. All the above long-term trends need to be considered and accounted for in the design of meta-analyses, which compare outcomes of trials conducted at various points in time.

Seasonal variation in the incidence of MS relapses, with the incidence peak in spring and trough in winter, was demonstrated in a meta-analysis of nine reports of relapse incidence in the northern hemisphere [24]. This observation was confirmed and extended by a large multicentric observational study from the MSBase cohort,

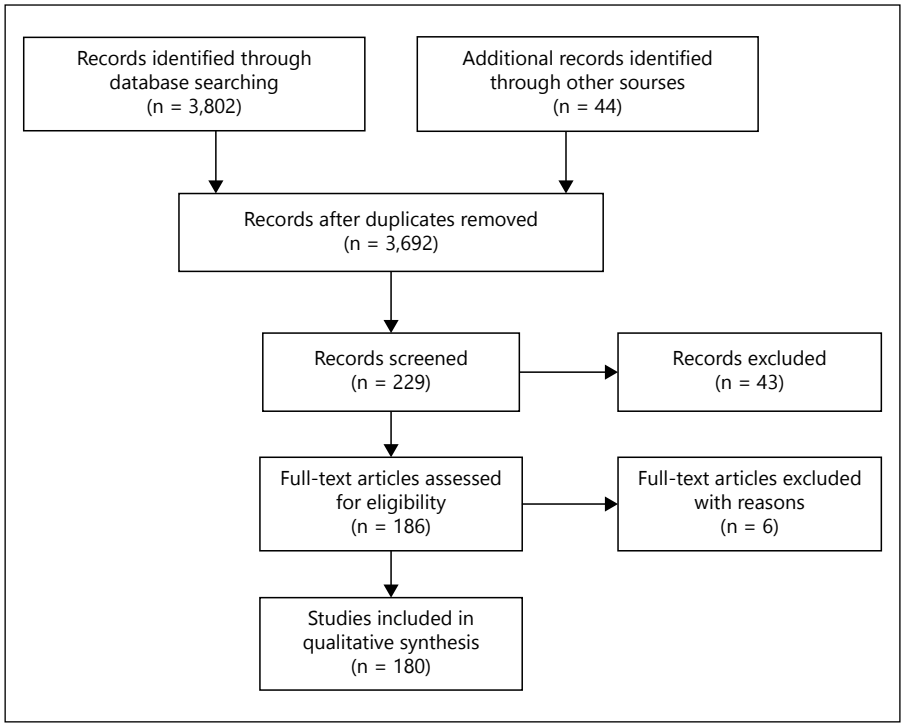


Fig. 1. PRISMA flow diagram of the reviewed literature.

which showed consistent trends in both northern and southern hemispheres [25]. Interestingly, the lag between seasonal ultraviolet radiation trough levels in midwinter and subsequent peak in relapse probability was inversely associated with the latitude (mean of 28.5 days per 10° of latitude). The observed mean lag was approximately 5 months in Melbourne (37.8° of latitude) and 3 months in Montreal (45.5° of latitude). Studies from several smaller patient cohorts showed variable results, some reporting a spring [26] and other earlier works reporting a summer peak [27, 28] of relapse incidence (table 1). A hypothesis was proposed that the seasonality of the peak relapse incidence may show a long-term trend towards phase-shift [29], but this view requires further validation.

Individual Risk Factors and Predictors

A popular hypothesis, which may partially explain the seasonal variation of relapses (see above), indicates an association between the seasonality of relapse incidence and serum levels of 25-hydroxyvitamin D [30–33]. An increment in vitamin D concentration by 10 nmol/l was associated with reduced hazard of relapses by 9% in adults [34], and 34% in paediatric-onset MS [35]. Similarly, reduction in the hazard of new T2 brain lesions by 15% and of contrast-enhancing brain lesions by 32% per each 10 nmol/l of vitamin D concentration was reported [36]. In addition, serum levels below 50 nmol/l were associated with a decreased hazard of progression of neurological disability [37]. It is therefore not surprising that vitamin D supplementation has been suggested as an intervention aimed at decreasing the risk of relapses [38, 39], a hypothesis that is currently being evaluated in four randomised interventional trials in patients with MS or CIS (PrevANZ, VIDAMS, SOLAR, D-Lay-MS) [40, 41], with the additional aim of defining optimal serum vitamin D levels for reducing clinical MS activity.

A number of previous studies, including large cohort studies and a meta-analysis of 33 observational studies of patients with CIS consistently showed that females are more likely to experience relapses throughout the course of the disease [42–44] (table 1). Relapse incidence is known to decrease with time, represented either by patient age or by MS duration [20, 42, 44–48]. In a direct comparison of the effects of these largely collinear determinants of relapse frequency, we showed that older age is relatively more closely associated with decline in relapse activity than MS duration [42]. Interestingly, our study suggested that an interaction between sex- and time-dependent changes in relapse frequency may exist, with the attenuation of relapse activity delayed in females com-

Table 1. Factors predisposing to MS relapses

	Diagnosis	Cohort	Effect size	Reference
Female sex				
	CIS, CDMS	11,570	HR 1.08 (CI 1.06–1.11)	Kalincik et al. [42]
	CIS*	4,732 (from 33 studies)	RR 1.20 (CI 0.98–1.50)	Dobson et al. [43]
	CDMS	2,477	RR 1.14 (CI 1.06–1.23)	Tremtlett et al. [44]
Young age				
	CDMS	11,570	HR 1.22 (CI 1.16–1.20) per 10 years	Kalincik et al. [42]
	CIS	1,047	HR 1.22 (CI 1.10–1.22) per 10 years	Kuhle et al. [59]
	CIS	330	HR 1.5 (CI 1.3–1.8) per 10 years	Mowry et al. [45]
	CIS	186	HR 1.76 (CI 1.07–2.89) for age <30 years	West et al. [48]
	CIS	131	RR 2.81 (CI 2.07–3.81) pediatric versus adult MS	Gorman et al. [46]
Short MS duration				
	CDMS	2,477	RR 1.20 per 5 years	Tremtlett et al. [44]
	CDMS	921 (from 22 trials)	RR 1.02 per year	Held et al. [47]
Ethnicity				
Non-white	CIS	330	HR 2.4 (CI 1.6–3.6)	Mowry et al. [45]
Non-white	CIS	186	HR 2.54 (CI 1.48–4.36)	West et al. [48]
Hispanic	CIS, CDMS	469	HR 1.2 (CI 0.7–2.1)	Mowry et al. [36]
Season				
	CDMS	9,811	spring peak, RR 1.08	Spelman et al. [25]
	CDMS	199	mid-late summer peak, RR 2.2	Tremlett et al. [73]
	CDMS	96	spring peak, RR 1.12	Salvi et al. [26]
	CDMS	336	summer peak, RR 1.61	Goodkin et al. [28]
	CDMS	178	spring-summer peak, RR 1.11	Bamford et al. [27]
	CDMS*	(from 10 studies)	spring peak, RR 1.1	Jin et al. [24]
Low serum vitamin D levels				
	CIS	465	RR 2.3 (CI 1.1–5) per 50 nmol/l decrement	Ascherio et al. [37]
	CDMS	267	RR 1.96 per 10 nmol/l decrement	Smolders et al. [30]
	CDMS	73	RR 1.36 (CI 1.08–1.72) per halving serum concentration	Runia et al. [31]
	CDMS	145	HR 1.10 (CI 1.03–1.18) per 10 nmol/l decrement	Simpson et al. [34]
	pediatric onset CIS/CDMS	110	RR 1.52 (CI 1.05–2.17) per 10 nmol/l decrement	Mowry et al. [35]
Smoking				
	CIS	1,047	HR 0.95 (CI 0.79–1.14) – serum cotinine levels	Kuhle et al. [59]
	CIS, CDMS	469	HR 1.43 (CI 1.01–2.03)	Mowry et al. [36]
	CIS	129	HR 1.8 (CI 1.2–2.8)	Di Pauli et al. [183]
	CDMS	183	HR 0.94 (CI 0.41–1.58)	Pittas et al. [58]
Stress				
	CDMS*	1,082 (from 14 studies)	Cohen's d +0.53 (CI 0.40–0.65)	Mohr et al. [60]
	CDMS	101	OR 1.52 (CI 1.01–2.29)	Brown et al. [184]
	CDMS	73	HR 2.2 (CI 1.2–4.0)	Buljevac et al. [185]
	CDMS	156	increased relapse activity during war	Golan et al. [62]
	CDMS	32	decreased relapse activity during war	Nisipeanu and Korczyn [61]
Vaccination				
Multiple vaccines	CDMS	643	HR 0.7 (CI 0.4–1.3)	Confavreux et al. [65]
Hepatitis B, tetanus	pediatric CIS	356	hepatitis B: HR 0.8 (CI 0.3–1.9), tetanus: HR 1.0 (CI 0.6–1.7)	Mikaeloff et al. [66]

Table 1. (continued)

	Diagnosis	Cohort	Effect size	Reference
Influenza, H1N1	CDMS (RCT)	61	incidence: vaccination 12% vs. placebo 14%	Bamford et al. [67]
Influenza, H1N1	CDMS (RCT)	88	incidence: vaccination 3% vs. placebo 6.5%	Myers et al. [68]
Yellow fever	CDMS	7	RR 12.8 (CI 4.3–38)	Farez et al. [69]
Infections				
Influenza A, EBV	CDMS	407	influenza A: OR 6.5 (CI 1.8–24), EBV: OR 4.4 (CI 1.3–15)	Oikonen et al. [186]
	CDMS	73	RR 2.1 (CI 1.4–3.0)	Buljevac et al. [70]
Chlamydia	CDMS	73	RR 3.1 (CI 1.3–6.7)	Buljevac et al. [71]
URTI	CDMS	41	RR 2.0 (CI 1.3–3.2)	Edwards et al. [72]
URTI	CDMS	199	r (Pearson) 0.39	Tremlett et al. [73]
	CDMS	170	RR 2.8	Sibley et al. [74]
	CDMS	60	RR 1.3	Andersen et al. [75]
Pregnancy				
	CDMS	365 (269 pregnancies)	3rd trimester RR 0.4; postpartum RR 2.4	Confavreux et al. [77]
	CDMS	227	3rd trimester RR 0.3; postpartum RR 1.7	Vukusic et al. [78]
	CDMS	674 (893 pregnancies)	3rd trimester RR 0.4; postpartum RR 1.9	Hughes et al. [81]
	CDMS	33 (49 pregnancies)	postpartum RR 1.6	Roullet et al. [187]
	CDMS	111 (191 pregnancies)	postpartum versus pregnancy RR 3.4	Nelson et al. [79]
	CDMS	70 (98 pregnancies)	pregnancy RR 0.6; postpartum RR not significant	Salemi et al. [80]
Assisted reproduction				
	CDMS	32 (70 IVF cycles)	RR 2.0	Michel et al. [90]
	CDMS	16 (26 IVF cycles)	RR 6.9 (CI 3.4–14)	Correale et al. [93]
	CDMS	10	RR 4.8	Laplaud et al. [91]
	CDMS	23 (78 IVF cycles)	RR 1.5	Hellwig et al. [92]

* Meta-analysis. CI = Confidence interval; CIS = clinically isolated syndrome; CDMS = clinically definite multiple sclerosis; EBV = Epstein-Barr virus; HR = hazard ratio; MS = multiple sclerosis; OR = odds ratio; RCT = randomised clinical trial; RR = rate ratio; URTI = upper respiratory tract infection.

pared to males. In addition to sex and age, non-white ethnicity was associated with a relatively increased risk of relapse in patients with CIS [45, 48].

Pooled data from the placebo arms of 22 randomised trials demonstrated that pre-trial relapse activity was strongly associated with on-trial relapse incidence [47]. This suggests that the level of relapse activity is in part individually determined. However, the existence of genetic determinants of relapse frequency has not been proven as yet. It was previously reported that the major histocompatibility locus that has the strongest association with susceptibility to MS, HLA-DRB1*1501, may also be associated with the probability of conversion to definite MS in patients with a CIS [49]. In another study, three susceptibility loci were associated with relapse severity: MPHOSPH9 positively, and RGS1 and TNFRSF1A negatively [50]. In contrast, other studies did not find any associations between the relapse hazard and the known loci of MS susceptibility [51–53]. Moreover, the HLA-DRB1 polymorphism was not found to be associated with the relapsing- vs. progressive-onset MS course [54–57].

In addition to the above non-modifiable risk factors, many modifiable relapse risk factors are known. A large cohort study demonstrated positive association between smoking and the increased relapse risk in patients with definite relapsing-remitting MS as well as clinically isolated syndrome, an observation that was also supported by the greater risk of developing new hyperintense

T2 lesions [36]. Moreover, smokers with CIS are at greater risk of conversion to clinically definite MS through experiencing further relapses [48]. In contrast, two other studies did not find any association between smoking status [58] and serum cotinine concentration [59] and the relapse hazard but the former study showed a quantitative association of smoking with disability accrual. It is generally believed by patients and physicians that stress may potentiate disease reactivation presenting with a clinical relapse. A meta-analysis of 14 studies showed that a positive association between non-traumatic stressful life events and the incidence of relapses is consistently supported by literature [60]. The magnitude of this pooled effect even exceeded the observed effect of treatment with interferon β (Cohen's d = 0.56 vs. 0.36, respectively). A question was raised whether the quality of the stressor may modulate this relationship. Two studies that examined relapse rates in patients exposed to the threat of missile attacks in war arrived at contrasting conclusions [61, 62]. Interestingly, there was no indication of an association between relapses and physical trauma [63]. A more detailed discussion of the impact of stress on MS activity is provided in a review by Artemiadis and colleagues [64]. The majority of studies investigating relapse incidence in patients undergoing vaccinations against influenza (including the H1N1 subtype), hepatitis B and tetanus did not demonstrate any associations [65–68]. The relationship between attenuated vaccines (such as the vaccine against yellow fever) and relapse risk warrants further investigation [69]. Episodes of infectious diseases were invariably associated with higher risk of relapses [70–75]. An association of pregnancy with relapse frequency was noted by Millar and colleagues already in 1959 [76]. Later, a number of studies demonstrated decreased risk of relapses during pregnancy, in particular during its third trimester [77–85]. However, the relatively lower risk of relapses is outweighed by the markedly increased relapse activity during the first post-partum trimester, observed in most of these studies. These observations have led to an ongoing discussion concerning optimal post-partum management, with some authors advocating early post-partum resumption of immunomodulatory therapy [86]. Some studies suggested that the effect of breastfeeding was protective; however, these studies were vulnerable to confounding with the provided evidence being inconclusive and warranting further confirmation [79, 85, 87–89]. Women undergoing an assisted reproductive technique are exposed to additional risks of experiencing increased disease activity, presumably in association with the hormonal stimulation procedures [90–93]. The quantitative changes in the immune system associated with hormonal stimulation were in keeping with the changes induced by the gonadotropin releasing hormone [93], and some studies proposed that higher relapse risk may be triggered selectively by gonadotropin-releasing hormone agonists but not antagonists [90, 91].

A number of other factors were proposed as potential modifiers of the risk of MS episodic activity, including poor ambient air quality [94, 95], however, most of these are based on anecdotal evidence and therefore warrant further investigation.

Discontinuation of highly effective therapy, in particular natalizumab, was reported to lead to clinical reactivation of MS [96–99], with 27% of patients experiencing relapses during the time between discontinuing natalizumab and initiating subsequent immunomodulatory therapy (i.e. the 'wash-out' period) [98, 100]. The control of disease activity was improved by switching to another highly active therapy, namely fingolimod, and further amelioration of the post-switch relapse activity was achieved by minimising the duration of the wash-out period [98, 101].

Relapse Phenotype

The initial presentation suggestive of MS is most commonly associated with visual, motor or sensory features. Cossburn and colleagues reported a study in a population-based cohort of 1,424 patients with the following proportions of the initial events: visual 18%, long tract-related 47%, cerebellar 10%, brainstem 10%, cerebral 1% and polyregional 11% [102]. An analysis from 14,969 patients from the MSBase cohort showed a similar distribution of the initial presenting clinical features: visual 27%, pyramidal 22%, sensory 46%, cerebellar 7%, brainstem 20%, sphincteric 3% and cognitive 1.4% [103]. In a study of 105 patients with pediatric MS, the initial clinical attacks involved visual system in 25%, spinal cord in 36%, brainstem or cerebellum in 51%, and cerebrum in 9% of the reported events [104]. It is noteworthy that the proportions of relapse phenotypes change with time, either expressed as patient age or the time from the first MS clinical presentation. While the relative incidence of visual, sensory and brainstem relapses declines with time, pyramidal (in particular concerning the lower limbs), sphincteric and cerebellar relapses become more frequent later in the disease course or in older patients [102, 103]. Moreover, severe relapses are more commonly observed among young patients [105, 106]. These data confirm the

experience of many clinicians and patients that MS-related symptomatology tends to follow time-dependent patterns. The mechanisms underlying this shift in functional (and, presumably, topographic) susceptibility to relapses remain to be explained.

In addition to the effect of time, sex may contribute to the phenotypic patterns of MS relapses. We showed that women tend to present with visual and sensory relapses more frequently than men, who are relatively more likely to present with pyramidal, brainstem and cerebellar relapses [103].

It is of interest that patients tend to experience relapses, which are phenotypically similar to their preceding clinical episodes [103, 107, 108]. This 'phenotypic relapse recurrence' could potentially be attributed to individual patterns of structural CNS damage. In fact, studies showed that areas of demyelination are commonly localised within previously remyelinated regions [109, 110]. This inherent predisposition is likely to be determined by numerous polygenic factors, including genetic factors, such as some of the MS susceptibility factors [111], several genes involved in the regulation of immune cell function, myelin and neural growth [112], and genetically correlated CD4 T-cell immunoreactivity [113].

Prognostic Value of Relapses

While a debate may exist about the significance of MS relapses [19, 114, 115], a positive relationship between relapses and the accumulation of permanent neurological disability was demonstrated. It was shown that incomplete recovery follows a marked proportion of relapses, with 42–49% of relapses resulting in a residual increase in Expanded Disability Status Scale (EDSS) by at least 0.5 steps and 28–33% of relapses leading to a 1-step EDSS accrual [116, 117]. In particular, the accumulation of disability is correlated with the level of relapse activity within the initial 2–5 years after the first clinical presentation of MS [118–121] and it was suggested that the impact of relapses on long-term disease outcomes decreases thereafter [122].

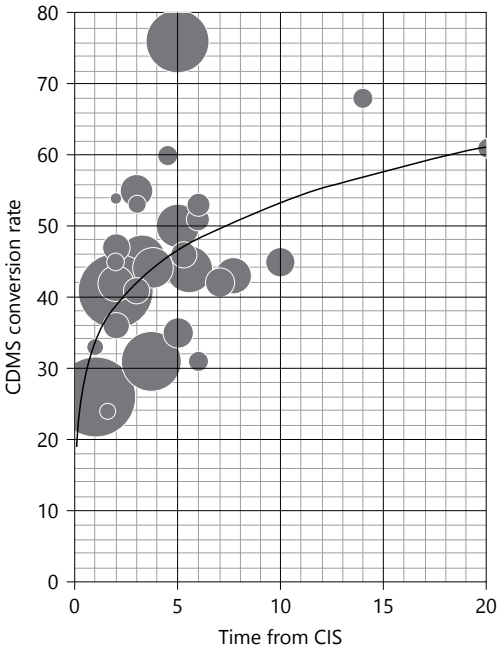
Besides relapse frequency, the long-term disability accrual is also associated with relapse phenotype. Several studies identified attacks (i.e. relapses or the initial clinical events) with the impact on sphincteric [123–127] or pyramidal function [124, 126, 128] as being predictive of poorer long-term disability outcomes, while the cerebellar and brainstem attacks showed mixed results (for review, see [129]). In contrast, attacks with the features of optic neuritis were associated with relatively more favourable disability outcomes [127, 128, 130]. This is in keeping with our study in which sensory, visual and brainstem relapses were relatively more likely to result in complete recovery compared to pyramidal, sphincteric, cognitive and cerebellar relapses [103].

It is of interest that while women tend to present with more frequent relapses (see above), males are predisposed to poorer long-term disability outcomes [120, 121, 123, 125]. This seemingly paradoxical phenomenon could be explained by the differential effect of various relapse phenotypes on the long-term disability accrual. While men are more likely to develop pyramidal, cerebellar and brainstem relapses, of which pyramidal and cerebellar relapses pose a relatively higher risk of incomplete remission, women are more prone to visual and sensory relapses, which are relatively more likely to recover completely [103]. In fact, relapse recovery was shown to be negatively associated with the male gender. A similar association was reported for older age, progressive MS course and relapse severity [48, 102, 103, 105, 127]. These associations could be mediated through a number of mechanisms related to sex, age or lesion location, such as variations in susceptibility to inflammatory damage, structural changes underlying relapses and synaptic plasticity [131, 132].

Persistent impairment of a certain neurological function is commonly preceded by relapses of similar phenotype, with the visual and sensory pathways being relatively more susceptible to recurrent damage than the pyramidal and cerebellar pathways [133]. In addition, relapse severity and the subsequent recovery tend be individually specific [106]. These observations are reminiscent of the phenotypic relapse recurrence discussed earlier and suggest that the phenotypic presentations of relapses as well as the subsequent accumulation of permanent neurological disability, including its phenotype and trajectory, constitute disease features with a high degree of individual specificity.

Relapses and the Diagnosis of MS

Besides their importance as a marker of disease activity and their association with irreversible neurological impairment, MS relapses are a defining feature of relapsing MS and are therefore an important diagnostic marker. Clinical dissemination in time (i.e. incidence of at least two MS-related attacks) has been a crucial element of the MS diagnostic criteria [1] and in numerous jurisdictions



Reference	Follow-up (years)	Conversion rate, %	n
Giorgio et al. [188]	1	26	1,165
Kuhle et al. [59]	2	41	1,047
Kuhle et al. [59]	5	76	761
Ruet et al. [189]	3.7	31	652
Ruet et al. [189]	5.5	44	401
Mitjana et al. [190]	3.2	45	520
Hartung et al. [191]	5	50	358
Comi et al. [192]	3.8	44	289
Tintore et al. [141]	7.7	43	246
Kalincik et al. [119]	2	42	220
Ferraro et al. [144]	3	55	205
Tintore et al. [136]	5	35	175
Tintore et al. [136]	7	42	156
Kinkel et al. [193]	10	45	155
Miller et al. [194]	2	36	141
Filippi et al. [195]	2	47	132
Runia et al. [196]	3	41	127
Sombekke et al. [140]	5.3	46	121
Chard et al. [197]	6	51	105
Chard et al. [197]	20	61	70
DiFilippo et al. [142]	6	53	99
Patrucco et al. [198]	6	31	75
Rovaris et al. [199]	4.5	60	73
Brex et al. [200]	14	68	71
Dalton et al. [201]	3	53	58
Dalton et al. [202]	1	33	55
Villar et al. [203]	2	45	55
Liu et al. [204]	1.6	24	42
Magraner et al. [205]	2	54	24

Fig. 2. Probability of conversion to clinically definite MS. The rate of conversion from CIS to clinically definite multiple sclerosis (CDMS) as reported in previously published studies. A marked variance in the clinical and radiologic inclusion criteria and therapy exists among the studies.

has been a requisite of disease-modifying therapy. Therefore, the occurrence of a second attack, marking the conversion from CIS to clinically definite MS, has received considerable attention in the literature (fig. 2). The average estimated cumulative probability of experiencing a second, diagnostic clinical attack is about 40% at 2 years from the onset of the initial presenting symptom. Thereafter, the increment in the cumulative probability of a relapse slows, with the estimated risk at 5 years from CIS being 47%. It should be noted that these estimates were derived from multiple studies with a great variability in the definition of CIS. The clinical and paraclinical phenotype at the time of the first clinical presentation may markedly influence the probability of a second attack.

Phenotype of the first clinical presentation suggestive of MS has long been used by clinicians as an empirical estimator of the risk of conversion to clinically definite MS (for review see [134]). This risk is further modified by surrogate (paraclinical) markers. Patients with abnormal MRI appearance at the time of CIS are at a significantly higher risk of conversion to clinically definite MS [135–139]. In a multicentric study of 1,047 patients, the conversion rates for those with 0–1, 2–9 and more than 9 hyperintense T2 lesions were 15%, 40% and 52% at 2 years and 55%, 75% and 83% at 5 years, respectively [59]. In another study among 175 patients, the conversion rates over the median of 7 years were 9% for those with normal MRI, 44% for those fulfilling 1–2 Barkhof criteria (hazard ratio 6.1) and 61% for those fulfilling 3–4 Barkhof criteria (hazard ratio 17) at the time of the first clinical event [136]. The location of the hyperintense T2 lesions further increases the predictive value of MRI, with brainstem and spinal cord lesions heralding a relatively higher risk of further demyelinating activity [140, 141]. Moreover, quantitative changes, presenting as accelerated global or regional brain atrophy contribute to the prediction of the

second attack [119, 137, 142, 143]. Laboratory analysis of cerebrospinal fluid is another commonly used paraclinical tool. The presence of cerebrospinal fluid-specific oligoclonal bands at the time of the CIS is associated with increased odds of the second attack (the reported odds ratios range between 1.7 and 4.7) [59, 144–146].

Management and Prevention of Relapses

Treatment with high-dose corticosteroids has been the mainstay of acute therapy of MS relapses. A meta-analysis of 3 studies reported a significant effect of high-dose methylprednisolone on the recovery of relapse-associated disability (difference of EDSS scores 0.76, 95% confidence interval 0.50–1.02, over 5–7 days compared to placebo) [147]. In addition, a study of acute optic neuritis showed an effect of intravenous methylprednisolone but not of oral prednisone on the recovery of visual function [148]. This phenomenon appears to be determined by the dose rather than the route of administration, as another three studies showed that the effect of high-dose oral methylprednisolone on relapse recovery was comparable to that of methylprednisolone administered intravenously [149–152] and that the effect of methylprednisolone was dose-dependent [153]. A substantially more expensive treatment option is adrenocorticotropic hormone. Its immunomodulatory effect is mediated through the stimulation of endogenous steroid production, but a contribution of direct modulation of the NF-κB signalling pathway by the melanocortin system was also implied [154] (for review see [155]). Two early studies comparing intravenous methylprednisolone and adrenocorticotropic hormone reported similar efficacies of both therapeutic regimens, but implied a relatively more prompt effect of high-dose corticosteroids [156, 157]. Two randomised, double-blind trials showed non-inferiority of either of the two therapies [158, 159]. A meta-analysis of six studies confirmed the effect of both therapies on relapse recovery (odds ratio 0.37, 95% confidence interval 0.24–0.57), with a statistically non-significant trend towards a more pronounced recovery after treatment with methylprednisolone [160]. In addition, plasma exchange and intravenous immunoglobulins have occasionally been used to facilitate post-relapse remission; however, consistent evidence of their effect has been lacking [161, 162]. For a more detailed overview of acute therapy of MS relapses see [163].

A large body of evidence obtained from randomised clinical trials showed the effect of the currently used immunomodulatory therapies on decreasing the hazard of relapses (by 36–85%, depending on the agent) in patients with relapsing-remitting MS [18]. In fact, the majority of the pivotal trials used the effect on relapse incidence as their primary outcome and the evaluated therapies have been approved mostly for the prevention of relapses. However, some evidence from the clinical trials [164–166] as well as from observational studies is strongly suggestive of the positive effect of these medications also on disability outcomes [167–170]. A meta-analysis of 40 randomised clinical trials of disease-modifying therapies in MS suggested that treatment-related attenuation of relapse activity is positively associated with improved disability outcomes [171].

Relapse activity also carries important prognostic information about the predicted effect of disease modifying therapy. Patients with a high relapse rate prior to or shortly after initiating disease modifying therapy are more likely to suffer from ongoing relapses despite continued treatment compared with those with low pre-treatment relapse activity or good early response to therapy [47, 101, 172–174]. This may seem to be in contrast with the fact that while the effect of the available immunomodulatory therapies has been demonstrated in relapsing-remitting MS, compelling evidence for its effect in progressive-onset MS has been lacking. Therefore, a certain minimum relapse activity, sufficient to define the disease as relapsing-remitting, is instrumental in determining the treatment-responsive MS phenotype. An excellent example is provided by chemotherapy followed by salvage haematopoetic stem cell transplantation, which was suggested to ameliorate disease activity only in patients with relapsing-remitting but not progressive MS course [175–177].

Patient Perspective

It is the experience of many patients and their physicians that comprehensive evaluation of symptoms within the limited scope of routine clinical appointments is challenging. Therefore, on many occasions relapse-related symptoms may remain unnoticed or unaddressed [178]. While validated scales are commonly used to evaluate the various aspects of MS-related disability (e.g. EDSS, MS Functional Composite, Minimal Assessment of Cognitive Function in MS), specialised screening tools aiming at evaluation of relapses are scarce. In this context, screening questionnaires aimed at the identification of patient-reported symptoms (such as the Assessing Relapse in Multiple Sclerosis questionnaire) hold the potential to improve recognition of relapses in routine clinical care [179].

In addition to screening for the symptoms of potential relapses, such questionnaires enable better evaluation of MS burden from the patient perspective. A web-based self-report study showed that MS relapses are associated with significant decline in the quality of life, functional ability and increased costs to the patients [180]. Another study assessing patient-reported outcomes, including several physical and mental health scales, indicated that patients experienced decreased quality of life over one year following relapses [181]. The effect of acute therapy on the subjective recovery from relapses was also studied. In a study of patient-reported data from the North American Research Committee on Multiple Sclerosis (NARCOMS) registry, patients indicated a relatively better recovery from relapses when treated with intravenous or oral corticosteroids in comparison to no treatment [182]. However, a sizeable proportion of patients felt that the steroid therapy did not result in complete resolution of the relapse-related symptoms (32 and 34%, respectively). This is in keeping with the conclusions of the randomised clinical trials of relapse therapies (see above) and provides additional evidence supporting the role of the disease-modifying therapy in the management of MS.

Summary

Relapses of MS activity represent a significant physical, emotional and economic burden to both patients and society. Their incidence is influenced by numerous factors, including patient sex, age, disease duration, ethnicity, season, latitude, serum vitamin D levels, smoking, stress, infectious diseases, pregnancy, and assisted reproduction. Importantly, many of these risk factors are modifiable and as such deserve appropriate attention in the process of maximising favourable MS outcomes. Neither the mechanisms governing the relapse patterns associated with patient sex, age or disease duration, nor individual predisposition to relapse frequency, phenotype, severity, and recovery have so far been deciphered. These represent questions with the potential to cast light onto the pathophysiology of relapsing-remitting MS. Despite the proven effect of acute relapse therapy, a large proportion of relapses leads to the accumulation of residual disability. Therefore, the prevention of relapses represents an important goal of disease-modifying therapy, with the potential for a marked impact on the accumulation of permanent neurological disability.

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Conflict of Interests Statement

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