**ORIGINAL ARTICLE**

# Temporal trends of epilepsy in multiple sclerosis

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**Objectives:** Epilepsy is associated with advanced multiple sclerosis (MS). We aimed to investigate whether the incidence of epilepsy in MS has been affected by the introduction of disease-modifying treatments (DMT) for MS.

**Materials and methods:** This retrospective study included 14,557 patients from the Swedish MS register with MS onset between 1991 and 2018. Incident diagnoses of epilepsy or any seizure were identified through cross-linkage with the National Patient Register. Next, yearly prevalence of epilepsy as well as 5- and 10 years incidence of epilepsy or any seizure for consecutive years of MS onset were estimated, the latter with Kaplan–Meier analysis. Cox regression was used to adjust the association between the year of MS onset and incidence of epilepsy for baseline variables.

**Results:** Prevalence of epilepsy in the MS cohort increased from 0.34% in 1991 to 2.54% in 2018 (yearly odds: 1.26 [1.22, 1.29]). The 5 years incidence rate of epilepsy, ranging from 0.4% (95% CI 0.008–0.79%) to 1.3% (95% CI 0.71–1.89%), and the 10 years incidence rate of epilepsy, ranging from 1.1% (95% CI 0.31–1.88%) to 2.6% (95% CI 1.22–3.97%) showed no significant trends ($p = .147$ and $p = .418$, respectively). Similarly, no significant trends were found for the incidences of any seizure. The incidence trends of epilepsy remained not significant after adjusting for sex, MS onset type (relapsing or progressive onset), or age at MS onset.

**Conclusions:** Our findings do not support the hypothesis that the introduction of novel DMT for MS has reduced the incidence of epilepsy among MS patients.

**KEYWORDS**
epilepsy, incidence, Multiple sclerosis, prevalence

## 1 | INTRODUCTION

In the past decades, prognosis of MS has improved substantially in part owing to the introduction of disease-modifying treatments (DMT) and improved treatment strategies.[1] In relapsing forms of MS, DMT can reduce the accumulation of demyelinating lesions in white as well as grey matter.[2–6] To some extent, DMT can also slow down the neurodegeneration characteristic of progressive forms.[7] Clinically, these findings translate into a reduced annualised relapse rate,[6] decrease in risk of sustained disability,[8,9] and delayed conversion to secondary progressive MS (SPMS).[10,11]

Epilepsy is a recognised complication of MS and is linked to an increased burden of cortical lesions and cortical atrophy.[12,13] Epilepsy affects approximately 3% of MS patients[14] and is strongly associated with increased morbidity and mortality.[15–17] Other risk factors for epilepsy include low age at MS onset, long disease duration, and severe disability.[14,18] Whether improved treatment strategies in MS can prevent the occurrence of epilepsy in MS is unknown. We examined changes in prevalence and incidence of epilepsy in MS in the Swedish MS population over the past two to three decades to identify any correlation between improved MS prognosis and epilepsy incidence.

## 2 | METHODS

### 2.1 | Study design, study population, and data sources

This was a retrospective register-based cohort study including all persons listed in the Swedish MS register (SMSreg) with MS onset from 1st January 1991 to 31st December 2018. The SMSreg is a national register established in 1998. As of 2018, it included 20,642 MS patients, of which living patients comprised approximately 80% of prevalent MS cases in Sweden.[19,20] SMSreg, which contains MS-related clinical data, was cross-referenced with the National Patient Register (NPR), a mandatory record of ICD-codes assigned for all hospital-based in- and outpatient visits, to retrieve information on the presence of and date of seizure-related diagnoses. The validity of epilepsy diagnosis in MS in the NPR has been estimated at 94%.[21] The NPR was established in 1987 and has full coverage for inpatient care since its inception. Outpatient codes were added in 2001 and full coverage achieved since 2005. To minimise the bias of detecting pre-existing epilepsy cases at register start, we allowed for a "run-in" period of 5 years, thus delaying study start to 1991. Additionally, date of death was extracted from the Cause of Death register (CODR). Linkage of register data was done by the National Board of Health and Welfare, which manages the NPR and CODR by matching data of individuals via their social security numbers. Data were anonymised before the start of the study.

### 2.2 | Definitions and outcomes

MS onset was defined as the date of symptom onset as entered into SMSreg. When missing, onset date was defined as the date of MS diagnosis. MS onset type was categorised as either primary progressive MS (PPMS) or relapsing onset MS (ROMS), defined as having relapsing–remitting MS (RRMS) or SPMS as entered disease course in SMSreg. Paediatric onset MS was defined as MS onset ≤18 years of age, and adult-onset MS was defined as MS onset >18 years of age.

The main outcome was epilepsy, which was defined as the presence of any of the following codes in the NPR: ICD-9345 except 345Q or ICD-10 G40. For a more comprehensive detection of epileptogenic cortical damage, we added "any seizure" as a secondary outcome. Any seizure was defined as a code for epilepsy or a code for seizure, the latter being defined as: ICD-9780D and 345Q or ICD-10 R56.8 and G41.

### 2.3 | Statistical analysis

#### 2.3.1 | Identification of incident epilepsy and any seizure

Incident epilepsy or any seizure were given by the first code for either at any time point in the lifetime of a patient. In estimating epilepsy prevalence, epilepsy diagnosed prior to MS onset was considered prevalent earliest the same year as MS onset. In estimating incidence, only patients with epilepsy or any seizure diagnosed after MS onset were included.

#### 2.3.2 | Estimation of prevalence

Point prevalence of epilepsy, given by the number of living MS patients with epilepsy divided by the total number of living MS patients, was estimated for 31st December of each year of study. The prevalence of epilepsy was estimated for the entire cohort as well as subgroups stratified by sex and MS onset type (ROMS or PPMS). Since the data were in the form of repeated measures, generalized estimating equations were used to describe prevalence trends and to compare prevalence in subgroups. Results are expressed as odds ratios (OR) and $p$-values.

#### 2.3.3 | Estimation of incidence

Five- and 10 years incidence rates of epilepsy were estimated using Kaplan–Meier survival analysis for different years or periods of MS onset. We limited the analysis to patients with MS onset 2001 or later so as to only analyse cohorts whose follow-up time included years with complete coverage in the NPR. Study subjects were followed from MS onset to date of incident epilepsy, death, or study end (31st December 2018), whichever came first. Incidence of epilepsy in the different temporal cohorts was compared using the log-rank test, and significance of trend tested with the log-rank test for trend. The above procedure was repeated for any seizure as a secondary outcome.

We also estimated the yearly change in the incidence of epilepsy using Cox regression analysis and adjusted it for sex, MS onset type, and paediatric vs adult onset of MS.

The significance level for all tests was set at $p \leq .05$. All analyses were conducted by the authors using SPSS version 26 (IBM Corp. 2019).

## 3 | RESULTS

### 3.1 | Cohort and demographics

A total of 14,557 patients with MS onset between 1991 and 2018 were included (Figure 1). The mean follow-up time was 12.8 (0–28) years. The majority were women (69.1%) and had RRMS (71.1%) (Table 1). The mean age at MS onset was 34.9 ± 11.3 years. We identified 422 (2.9%) cases of epilepsy and 705 (4.8%) cases of any seizure, of whom 212 (1.5%) had a diagnosis of any seizure at MS onset. Mean time from MS onset to epilepsy diagnosis was 5 ± 10.1 years. At the time of data export, 743 (5.1%) of cases were deceased.

## 3.2 | Prevalence of epilepsy

In the full MS cohort, prevalence of epilepsy increased during the study period from 0.34% in 1991 to 2.54% in 2018. Overall, the positive trend was significant with a yearly increase of OR 1.26 [1.22, 1.29] (Figure 2A). In 2001, outpatient codes were added to the NPR explaining the steep rise in epilepsy prevalence that year. The slopes just prior and subsequent to this were comparable; 1996–2000: OR 1.23 [1.19, 1.29] and 2003–2007: OR 1.27 [1.2, 1.33]). Prevalence did not differ significantly between subgroups stratified by sex ($p = .88$), or MS onset type ($p = .918$) (Figure 2B,C). Using an interaction term between sex or MS onset type and calendar year, there were no significant differences in prevalence trends between any of the subcategories; sex, $p = .992$, and MS onset type, $p = .797$.

## 3.3 | Incidence of epilepsy and any seizure

The 5 years incidence rate of epilepsy for cohorts with MS onset between 2001 and 2014 fluctuated between 0.4% (95% CI 0.008–0.79%) and 1.3% (95% CI 0.71–1.89%) (Figure 3A). However, there were no significant differences in incidence between the temporal cohorts ($p = .3$) and no significant trend ($p = .147$).

Comparatively, 5 years incidence of any seizure during the same time period fluctuated between 1.1% (95% CI 0.51–1.69%) and 2% (95% CI 1.21–2.78%) and here too differences between temporal cohorts as well as the trend were not significant ($p = .626$ and $p = .951$, respectively).

We also calculated 10 years incidence rates of epilepsy for cohorts with MS onset from 2001 to 2009. These ranged between 1.1% (95% CI 0.31–1.88%) and 2.6% (95% CI 1.22–3.97%) (Figure 3B). There were no significant differences in incidence between the temporal cohorts ($p = .854$) and no significant trend ($p = .418$).
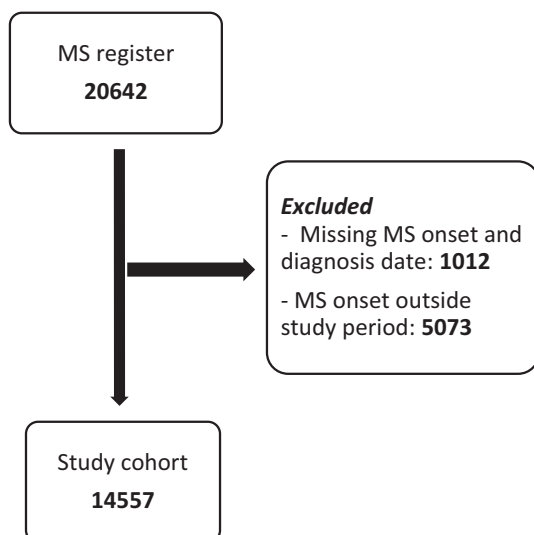


**FIGURE 1** Flow chart over inclusion into the study

The 10 years incidence of any seizure fluctuated between 1.6% (95% CI 1.2–1.99%) and 3.2% (95% CI 1.82–4.57%). Similarly, no significant differences in incidence between the temporal cohorts ($p = .784$) and no significant trend ($p = .228$) were found.

We estimated the crude yearly change in 5 years incidence rate to be hazard ratio (HR) 0.97 [0.91, 1.02], and the corresponding yearly change in 10 years incidence to be HR 1.03 [0.95, 1.12]. Adjusting these for sex, paediatric vs adult MS onset, or MS onset type did not significantly alter the results (Table 2).

## 4 | DISCUSSION

In the present study, incidence of epilepsy in MS was stable over the past two decades, suggesting that the improvements in MS prognosis related to novel DMT do not extend to the development of epilepsy in MS. Perhaps it is too early to detect any effects of improved MS treatment on epilepsy occurrence. Another interpretation is that DMT does not affect epileptogenesis, which must then reflect some pathophysiological process not directly related to inflammation in MS.

DMT has been available in Sweden since the mid 1990s (Figure 4, Table S1). As of 2018, 77% of RRMS patients aged 40 years and below were receiving DMT.[22] Major breakthroughs such as natalizumab and fingolimod were introduced relatively late, 2006 and 2011 respectively, and longer observation may be needed to detect the effects of these and other modern drugs on the occurrence of epilepsy. Additionally, longer individual observation may have been necessary since epilepsy is dependent on disease duration and disability accumulation.[14]

DMT reduce the accumulation of new cortical lesions and cortical atrophy.[3–5] It has been proposed that cortical lesions cause epilepsy,[12,13] but this cannot yet be considered as established.[23] Hence, a better understanding of the pathophysiology of epilepsy in MS is required to determine whether DMT has a role to play in the prevention of epilepsy. Unpromisingly, compared with epilepsy-free counterparts, patients with RRMS and epilepsy have a more rapid disability progression and cognitive decline despite DMT, indicating poorer response to DMT.[24–26] Furthermore, epilepsy correlates strongly with disability and is most prevalent among patients with progressive forms of MS who have little or no benefit of DMT.[7,14]

We found an increasing prevalence of epilepsy in patients enrolled in the SMSreg over the past three decades. This could be a consequence of following a relatively young cohort where increase in disease duration correlates with increased complications of MS such as seizures and comorbidities. Nevertheless, epidemiological trends such as increased female to male ratio implying increased life expectancy may have played a role.[27,28] Similar epilepsy prevalence,[29] and prevalence trend have been reported previously, an example of the latter being a population-based study conducted in a Norwegian county where prevalence increased from 2.9% to 7.4% between the years 1963 and 2003.[30] No details on epilepsy incidence trend were given. With the expected increase in life expectancy of persons with

MS,[28,31] prevalence of epilepsy is expected to rise. Considering the association between epilepsy and poorer prognosis,[15–17,32] this may translate into greater individual and clinical challenges.

There are some limitations to this study. Due to the dynamic nature of MS treatment and the retrospective study design, we were unable to stratify patients according to the specific drug or class of

**TABLE 1** Demographics and clinical characteristics at export

| Variable | n (%) or $\bar{x} \pm$ SD |
| --- | --- |
| *Sex* | *n = 14,557* |
| Female | 10,066 (69.1%) |
| Male | 4488 (30.8%) |
| Missing | 3 (0%) |
| *MS course* | |
| Primary progressive | 1360 (9.3%) |
| Relapsing–remitting | 10,347 (71.1%) |
| Secondary progressive | 2582 (17.7%) |
| Missing | 268 (1.8%) |
| Age at MS onset | 34.9 ± 11.3 |
| Paediatric onset of MS | 693 (4.8%) |
| Epilepsy | 422 (2.9%) |
| Any seizure | 705 (4.8%) |
| Years from MS onset to epilepsy diagnosis | 5 ± 10.1 |
| Deceased | 743 (5.1%) |

DMT. Nevertheless, we analysed temporal cohorts, which allow for some homogeneity of treatment strategy and can help answer the question whether improved therapeutic strategies, irrespective of DMT type or sequence used in, are associated with a reduced risk of epilepsy. Another limitation is that we lacked data on comorbidities that could increase the risk of epileptic seizures, such as cerebrovascular disease. It is also possible that some of the older MS patients in SMSreg were erroneously classified as MS, while in fact having other demyelinating diseases such as MOG-associated disease, which has been associated with epilepsy.[33,34] Last, coverage of the NPR as well as the SMSreg increased during the period of study. We tried to minimise the effect of the former on incidence estimates by including only individuals with follow-up extending into years when coverage was 100%. However, in the prevalence estimates, inclusion of outpatient codes gave a steep increase in prevalence in 2001, but the slope remained unaltered. As for the SMSreg, inclusion of patients with advanced disease is assumed to have increased for tertiary centres where coverage was originally higher, whereas smaller neurology units principally have included patients with ongoing treatment. As the incidence of epilepsy remained stable during the study period, the effect of this has presumably been minor.

To our knowledge, this is the first study investigating temporal trends of epilepsy in MS during years of improving MS treatment and prognosis. Strengths of this study include its nation-wide design and large cohort, use of comprehensive registers and long follow-up. Generalisability is further enhanced by the early introduction of
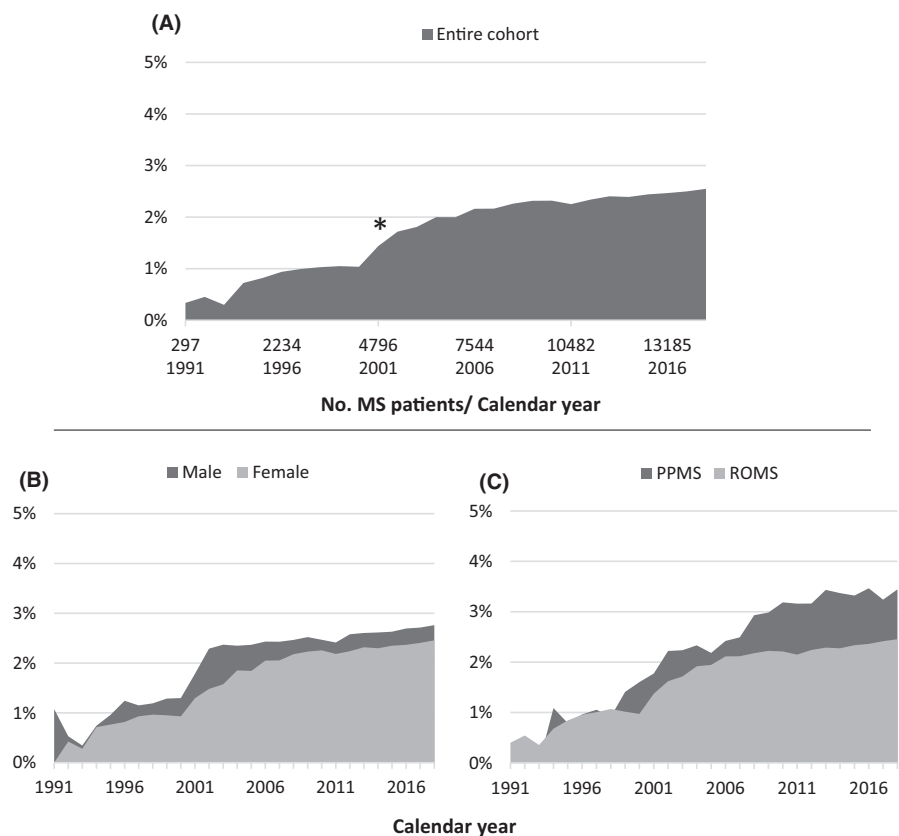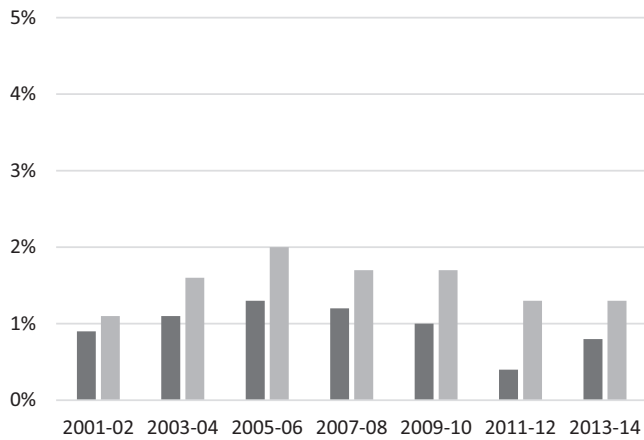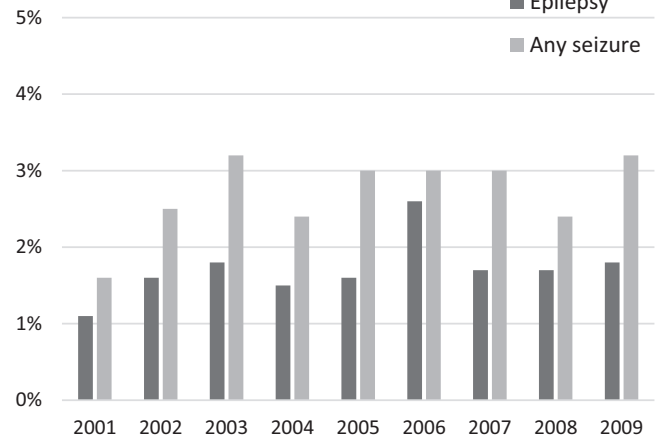


**FIGURE 2** Prevalence of epilepsy in MS between 1991 and 2018

* introduction of outpatient codes

**(A) Five-year incidence**

**(B) Ten-year incidence**

■ Epilepsy

■ Any seizure

**Year of MS onset**

**FIGURE 3** Incidence rate of epilepsy or any seizure after MS onset

**TABLE 2** Yearly change in incidence of epilepsy in MS during the study period

|  | HR [95% CI] | |
|---|---|---|
|  | 5-year risk[a] | 10-year risk[b] |
| Crude | 0.97 [0.91, 1.02] | 1.03 [0.95, 1.12] |
| *Adjusted for* | | |
| Sex | 0.97 [0.91, 1.02] | 1.04 [0.95, 1.12] |
| Paediatric or adult MS onset | 0.97 [0.91, 1] | 1.04 [0.95, 1.12] |
| MS onset type | 0.98 [0.92, 1.04] | 1.06 [0.96, 1.15] |

[a]Five-year risks estimated for MS onset between 2001 and 2014.
[b]Ten-year risks estimated for MS onset between 2001 and 2009.

approved MS drugs and high treatment rates in the Swedish cohort. Future studies on this topic could proposedly include patients over a longer time period, have longer individual follow-up, and correlate epilepsy occurrence with individual DMT. Another interesting avenue of research would be to correlate epilepsy incidence with radiological or serological response to treatment, since these can be important predictors of MS related complications in general.[35]

## 5 | CONCLUSION

Incidence of epilepsy in MS has remained stable over the past two decades despite the introduction of DMT and improved treatment
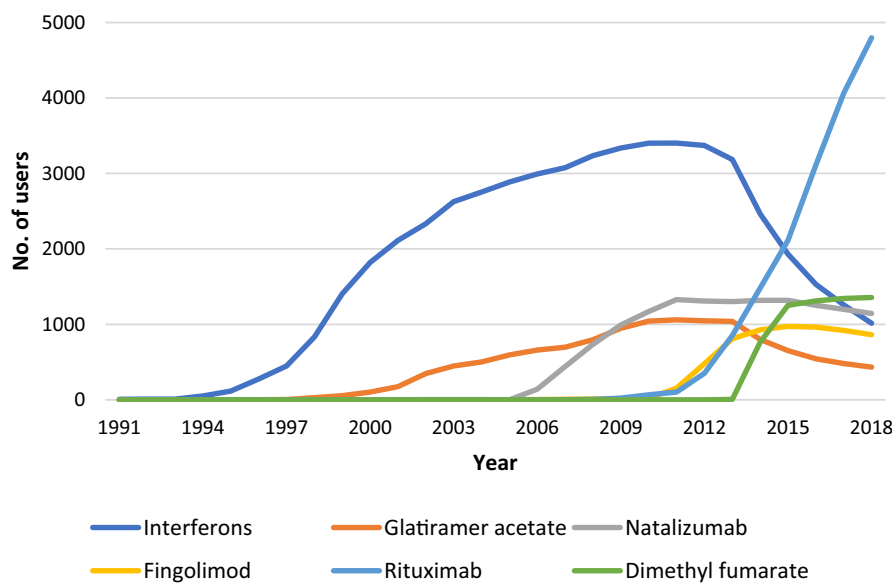


**FIGURE 4** Most common DMT by prescription in the Swedish MS register 1991 to 2018

strategies. Prevalence, however, is expected to increase as the MS population ages, suggesting that epilepsy in MS will be of growing clinical concern.

## CONFLICT OF INTEREST

J. Zelano is an associate aditor at Acta Neurologica Scandinavica. He also reports speaker honoraria from UCB and Eisai for non-branded educational events. As an employee of Sahlgrenska university hospital (no personal compensation), he is/has been an investigator in clinical trials sponsored by GW pharma, Bial, SK life science, and UCB. The other authors have no disclosures to report.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Swedish MS register. Restrictions apply to the availability of these data, which were used under license for this study. Data are thus not directly available from the author(s).

## PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ane.13671.

## ETHICAL APPROVAL AND PATIENT CONSENTS

This study was approved by regional ethics committee of Gothenburg (186–15). Upon enrolment into SMSreg, patients consent to their data being used for research.[20]

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.