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Trends and characteristics of infection-related hospital admissions in multiple sclerosis patients in Southwest Finland in 2009–2018

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ABSTRACT

Background: Multiple sclerosis (MS) patients are at increased risk for infections. The aim of this study was to investigate the trends in hospital admissions of patients with MS and to identify the factors predisposing to infection-related admissions.

Methods: Hospital admissions with MS as a primary or an auxiliary diagnosis in the hospital district of Southwest Finland in 2009–2018 were searched and MS patients with infection admissions compared with other MS patients in the hospital district. Data were derived from hospital registries, patient charts and the Finnish MS register. Group comparisons were performed using Pearson´s chi-squared test, Fisher´s exact test or Wilcoxon rank sum test. Overdispersion-adjusted Poisson regression was used to analyze the annual admission numbers and multivariable logistic regression to examine the predictors of infection-related admissions.

Results: 1380 hospital admissions for 532 patients were identified. The annual number of admissions decreased by 8.9% annually ($p<0.001$). Proportion of infection-related admissions declined from 26.5% to 19.5% ($p = 0.049$). The patients with infection admissions were on average 8.2 years older ($p<0.001$), more often male ($p<0.001$), had on average 5.3 years longer disease duration ($p<0.001$), more disability (median EDSS 5.0 vs. 2.0; $p<0.001$), more often progressive disease ($p<0.001$) and more comorbidities ($p = 0.006$) than other MS patients. Disease modifying therapies (DMTs) were used less often by patients with infection admissions ($p<0.001$). Infection admissions were not associated with the number of recent relapses. In-hospital mortality was higher in the infection-related admissions (3.57% vs 0.29%; $p<0.001$). Only 14.3% of patients with over two infection admissions had a DMT during the study period.

Conclusion: Hospital admissions, with or without an infection, have become more infrequent in MS patients of Southwest Finland over the decade from 2009 to 2018. Infection-related admissions were associated with lesser use of DMTs, older age, male gender and disability.

1. Introduction

Patients with multiple sclerosis (MS) use health services more than the general population (Pohar et al., 2007). The need of these services is associated, among other factors, with comorbidity burden and higher age in MS (McKay et al., 2018). Overall need for hospital treatment of MS patients would therefore be expected to rise considering that the incidence and prevalence of the disease, the average age at diagnosis and life-expectancy with MS have all increased (Kingwell et al., 2013 ; Krökki et al., 2011 ; Pirttisalo et al., 2019 ; Grytten et al., 2015 ; Sumelahti et al., 2014 ; O'Connell et al., 2017 ; Magyari and Sorensen, 2019). However, hospitalization due to MS has become more infrequent (Marrie et al., 2014).

Disease modifying therapies (DMTs) of MS modulate or suppress the immune system. The risk of hospital admission due to infection as well as infection-related mortality have been found to be increased in MS patients and new high-efficacy DMTs carry an increased risk of infections compared to traditional injectable therapies (Winkelmann et al., 2016 ; Wijnands et al., 2018 ; Luna et al., 2019 ; Montgomery et al., 2013). Indeed, although the hospital admission rate of MS patients and costs related to their hospital care markedly declined from 2004 to 2014 in Finland, the proportion of admissions caused by infection

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increased. Admissions with an infection as the primary diagnosis were longer than admissions with MS as the primary diagnosis, and associated with an increased in-hospital mortality (Pirttisalo et al., 2018).

In this study we further investigated the trends in MS hospital admissions in Finland using new 2009–2018 data from the hospital district of Southwest Finland. The main objective of the study was to identify the factors predisposing to infection-related MS admissions.

2. Materials and methods

2.1. Data collection

The hospital district of Southwest Finland provides health services to over 470 000 residents. Treatment of MS patients in the region is centralized to Turku University Hospital. All hospital admissions in all wards with MS (ICD-10 code G35) as a primary or an auxiliary diagnosis in Turku University Hospital in 2009–2018 were searched from the hospital administrative data. Admissions during the study period (1 January 2009 to 31 December 2018) were divided into those that were associated with an infection (infection diagnosis as a primary or the first auxiliary diagnosis for a primary MS diagnosis) and those that were not. Patients from other hospital districts without regular contact to Turku University Hospital were excluded (47 patients and 74 hospital admissions). Some patients may have immigrated/emigrated during the study period, but all the admissions of patients living in the hospital district at the time of the admission were included.

To study the risk factors for infection–related hospitalizations, we compared the baseline demographics of the MS patients with infection admissions (infection cohort) with other MS patients in Southwest Finland (reference cohort) in the end of 2008. Only patients diagnosed before this baseline date were included into this analysis. Validity of the MS diagnoses of the study population was scrutinized by neurologists. Demographics of all the study patients were obtained from the StellarQ MS register (www.neurorekisteri.fi), which is an MS treatment register and decision making tool integrated into the electronic patient documentation system (Laakso et al., 2019). We searched for patients' gender, age, smoking status, BMI (Body Mass Index), time since MS diagnosis, disease course (relapsing remitting MS, RRMS; secondary progressive MS, SPMS; primary progressive MS, PPMS), latest Expanded Disability Status Scale (EDSS; within two years from the baseline date), ongoing DMT, number of relapses in past year and number of diagnosed comorbidities at the study baseline. Comorbidities of interest (hypertension, diabetes, chronic obstructive pulmonary disease, asthma, ischemic heart attack, stroke and transient ischemic attack, ulcerative colitis, Crohn´s disease, rheumatoid arthritis, cancer, depression and bipolar disorder) were chosen based on their relevance to MS and previous studies regarding the impact of comorbidities (RA Marrie et al., 2015 ; Krökki et al., 2017 ; Murtonen et al., 2018). MS patients with more than two infection admissions during the study period were analysed separately.

The study was approved by the Turku University Hospital Clinical Research Services (permission number T98/2019). The data processing practices followed the EU Data Protection Directive rules.

2.2. Statistical methods

P-values for categorical variables were calculated using Pearson's chi-squared test except for number of relapses in past year and comorbidities where Fisher´s exact test was used. P-values for continuous variables were calculated using independent samples *t*-test or Wilcoxon rank sum test as appropriate. P-values of Pearson's chi-squared test and Wilcoxon rank sum test were adjusted using Benjamini & Hochberg method (1995) where false discovery rate (FDR) is controlled penalizing smaller p-values more than higher p-values. Poisson regression was used to analyze the annual admission numbers, adjusted for overdispersion.

Table 1
Frequencies of the most common infection diagnoses among the 336 infection-related admissions.

ICD-10	Disease	Frequency (n)	%
J15.9/J18.9	Bacterial pneumonia / Pneumonia, unspecified organism	100	29.8
N10	Acute pyelonephritis	50	14.9
N39.0	Urinary tract infection	32	9.5
A49.9	Bacterial infection, unspecified	25	7.4
A46	Erysipelas	19	5.7
N30.0/N30.9	Acute cystitis	15	4.5
A41.9	Sepsis, unspecified organism	7	2.1
J06.9	Acute upper respiratory infection	6	1.8
A41.5	Sepsis due to other Gram-negative organisms	6	1.8

Multivariable logistic regression was used to examine the predictors of infection-related admissions. The proposed adjusted variables included gender, age, disease course (RRMS vs. SPMS/PPMS), categorized diagnosis year, latest EDSS and ongoing DMT. The data was modelled with the whole study population where disease course and latest EDSS were assessed (357 patients). Best model was selected using manual forward selection where simple model was the starting point and terms were added based on deviance analysis until model did not significantly improve.

3. Results

We identified 1380 hospital admissions for 532 individuals (median frequency of admissions per patient: 1; interquartile range (IQR) 1–3; range 1–47) associated with MS. In almost two thirds of the admissions (62.2%) the patient was female. An infection was associated with 24.3% (336) of the admissions, the most common infections being pneumonia non specificata (27.3%) and pyelonephritis (14.9%, table 1). Over the study period, the number of all admissions decreased by 8.9% (95% confidence intervals 13.0% − 4.6%; $p < 0.001$) annually and there was no difference between genders in the rate of decline ($p = 0.736$, Fig. 2). The number of infection-related admissions declined from 26.5% (standard deviation (SD) 3.1) in 2009–2013 to 19.5% (SD 5.6) in 2014–2018 ($p = 0.049$; Fig. 1). Median length of stay was 4 days (IQR 2–7). Admission for an infectious cause lasted longer than non-infectious admission (median 6, IQR 4–9 vs. median 3, IQR 2–5; $p < 0.001$).

The 336 infection-related admissions were recorded for 181 individual MS patients with 137 of them (with 82% of the infection-related admissions) diagnosed before the beginning of the study period and with full disease history documentation in the MS register (table 2). MS patients with at least one infection admission were older (mean age 54.3 years vs. 46.1 years; $p < 0.001$) and more often male (44.5% vs. 25.6%; $p < 0.001$) than the MS patients in the hospital district of Southwest Finland without infection-related admissions during the study period (reference population, $N = 761$). Patients in the infection admission cohort had longer disease duration (mean 15.4 years vs. 10.1 years; $p < 0.001$) and more often progressive disease (SPMS or PPMS) compared to reference population ($p < 0.001$). The proportion of patients diagnosed before any DMTs were available for MS in Finland (year 1995) was higher in the infection cohort (50.4% vs. 24.8%; $p < 0.001$; Fig. 3). Patients in the reference cohort had a DMT at the beginning of the study period more often than patients in the infection cohort (50.9% vs. 21.2%; $p < 0.001$, supplementary Table 1). Treatment change was also less frequent in the infection admission cohort (supplementary figure 1). The patients with an infection admission were more disabled than the reference patients (median EDSS 5.0 vs. 2.0; $p < 0.001$). They were also more likely to have comorbidities ($p = 0.006$). The number of recent relapses was not associated with infection admissions. BMI or smoking were not either associated with

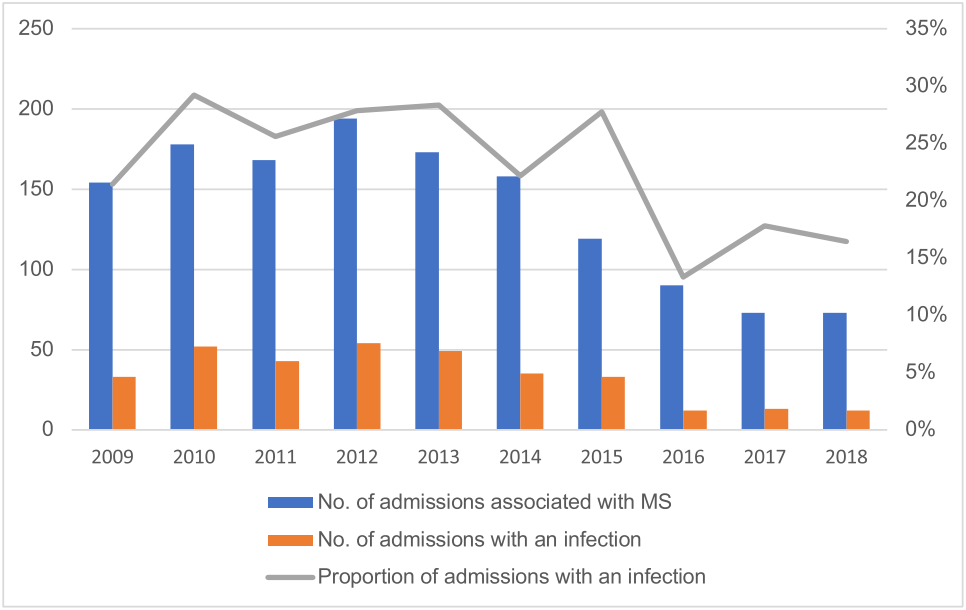

Fig. 1. Hospital admissions associated with MS and proportion of admissions with an infection in Southwest Finland in 2009–2018.

infection admissions, but data was available only for minority of patients. Mean age at death was 67.9 years (SD 12.3) for the 19.7% of patients in the infection admission cohort who died during the study period. Infection-related admissions were associated with an increased in-hospital mortality compared to the non-infectious admissions (3.57% vs 0.29%; $p < 0.001$).

A total of 35 patients (57.1% male) had more than two admissions with infection during the study period. Median frequency of admissions in this subgroup was 3 (IQR 3–5). At the time of the first admission, these patients were severely disabled (median EDSS 8, IQR 7–8) with a mean age of 57.5 years (SD 10.0). Most of them had never used a DMT (71.4%) and only 14.3% of these patients had a DMT during the study period. At the time of first infection admission, three of these patients used natalizumab and one patient used azathioprine while the rest did not have an ongoing DMT.

Gender, age and latest EDSS score were predictors of infection-related admissions in the logistic regression analysis (table 3). The probability for females to fall into infection group was 45% lower compared to males. Keeping gender and latest EDSS score at a fixed value, every unit increase in age increased odds to fall into infection group by 6%. Every unit increase in latest EDSS score increased odds to fall into infection group by 48%, when gender and age were kept at a fixed value.

4. Discussion

This study showed that MS-associated hospital admissions became more infrequent in Southwest Finland over a decade from 2009 to 2018. Moreover, the annual number and proportion of infection-related MS admissions also decreased. Infections requiring hospitalization were associated with older age, male gender and advanced disability. The patients with infection-related admissions had used DMTs less often than those without such admissions.

Our previous report showed that between 2004 and 2014 the annual number of hospital admissions related to MS declined in Finland while the proportion associated with infections increased (Pirttisalo et al., 2018). The current study regarding hospital district of Southwest Finland, showed that the annual number of MS-related admissions continued to decrease and the number and proportion of MS admissions due to an infection also began to decrease. Our results are consistent

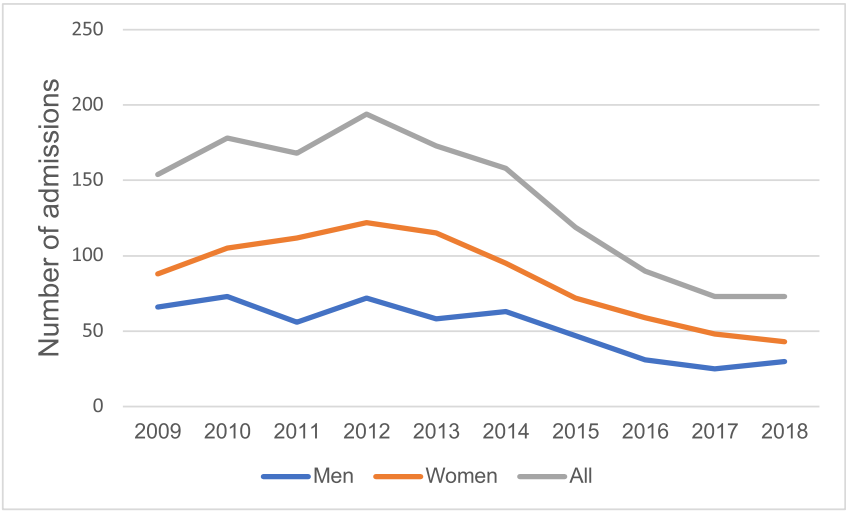

Fig. 2. The annual number of hospital admissions associated with MS in Southwest Finland in 2009–2018 by gender.

Table 2
Demographic baseline characteristics of MS patients hospitalized for infection during 2009–2018 and other MS patients.

	Infection (*N* = 137)	Other (*N* = 761)	Raw p-value	Adjusted p-value
Sex - N (%)			<0.001	<0.001
Female	76 (55.5)	566 (74.4)		
Male	61 (44.5)	195 (25.6)		
Age (years) - N; Mean (SD)	137; 54.3 (11.02)	761; 46.1 (12.67)	<0.001	<0.001
Disease course - N (%)			<0.001	<0.001
RRMS	40 (29.2)	540 (71.0)		
SPMS	67 (48.9)	135 (17.7)		
PPMS	23 (16.8)	54 (7.1)		
UNS	7 (5.1)	32 (4.2)		
Time since MS diagnosis (years) - N; Mean (SD)	137; 15.4 (9.63)	761; 10.1 (9.18)	<0.001	<0.001
Diagnosis year - N (%)			<0.001	<0.001
<1995	69 (50.4)	189 (24.8)		
≥1995	68 (49.6)	572 (75.2)		
BMI - N; Mean (SD)	31; 25.3 (5.79)	148; 26.2 (5.64)	0.553	0.553
Smoking - N (%)			0.178	0.196
Have smoked	35 (25.5)	143 (18.8)		
Have not smoked	22 (16.1)	124 (16.3)		
Unknown	80 (58.4)	494 (64.9)		
Latest EDSS score - N; Median (min, max)	33; 5.0 (0.0, 7.5)	324; 2.0 (0.0, 8.0)	<0.001	<0.001
Time difference to 31.12.2008 (years) - Mean (SD)*	0.1 (0.65)	0.2 (0.67)		
Ongoing DMT – N (%)			<0.001	<0.001
Yes	29 (21.2)	387 (50.9)		
No	108 (78.8)	374 (49.1)		
Number of relapses in past year – N (%)**			0.047	0.057
0	90 (65.7)	530 (69.6)		
1	17 (12.4)	103 (13.5)		
2	0	31 (4.1)		
≥3	0	11 (1.4)		
Comorbidities – N (%)			0.005	0.006
0	104 (75.9)	661 (86.9)		
1	28 (20.4)	83 (10.9)		
2	4 (2.9)	16 (2.1)		
≥3	1 (0.7)	1 (0.1)		
Mean (SD)	0.3 (0.56)	0.2 (0.44)		

SD, standard deviation; RRMS, relapsive remitting multiple sclerosis; SPMS,.
secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; UNS,.
course of the disease unspecified; BMI, body mass index; EDSS, expanded disability status scale;.
DMT, disease modifying therapy;.
* , positive time difference denotes that EDSS assessment is after 31.12.2008;.
** , only patients with RRMS and SPMS included.

with earlier studies from Canada, which also reported decreased hospital admission rates for MS patients over the last decades (Marrie et al., 2014 ; Evans et al., 2012 ; Al-Sakran et al., 2020). Altered treatment practices may affect the number of admissions. However, annual reports of somatic health care in Finland show only slight decrease in nationwide hospital admissions in specialized health care during the past decade. Furthermore, admissions to neurology wards have generally increased during the study period (Fredriksson et al., 2013 ; Vainio et al., 2017 ; Järvelin and Martikainen, 2019). Neither are the decreased hospital admissions explained by changes in MS prevalence since the number of MS patients in Southwest Finland has increased during our study period (Pirttisalo et al., 2019 ; Äivo et al., 2017).

Increased DMT use has been associated with a reduction in hospital admissions (Al-Sakran et al., 2019 ; Sanchirico et al., 2019). Considering that the use of more effective DMTs has increased in Finland since 2004 (Pirttisalo et al., 2018), it was expected that the need for hospitalization due to a severe relapse had probably decreased. However, an increase in the number of infection-related hospital admissions related to more potent immunosuppressive therapies was hypothesized. Therefore, the decrease in the annual number and proportion of infection-related MS admissions was unexpected. However, considering that there is therapeutic lag of up to several years for benefits to be observed from disease modifying therapy (Giovannoni, 2017), it appears that their effect on infections necessitating hospitalization also manifests very slowly through halting or delaying disease progression (Dekker et al., 2019 ; Claflin et al., 2019). This suggestion was supported by the findings that patients with infection-related hospital admissions during the study period were older and more often male compared to the control patients, had longer disease duration, more often a progressive disease (primary or secondary), and more disability. Furthermore, they used DMTs far less often than patients with no infection admissions. The fact that they also had more comorbidities compared to other MS patients, does not appear associated with this but the number of comorbidities is known to be associated with an increased risk of all-cause hospitalizations in MS population (Marrie et al., 2015) and is quite logical in itself.

Demographic characteristics of the MS patients with over two infection admissions over the study period were similar to the characteristics of the whole infection cohort, but they had even more disability and lower current and prior use of DMTs. However, it should be noted that there were three patients (9%) using natalizumab at the time of first infection admission in the cohort with over two infections. The proportion of patients using natalizumab was slightly higher in the total infection cohort compared to the reference cohort and these three patients amount to 12.5% of the patients that were using the drug in the hospital district at the beginning of the study period. Of note, in one of these patients the infection leading to the first hospital admission, progressive multifocal encephalopathy (PML) was clearly related to the natalizumab therapy. In general, PML has been reported to be quite rare in Finland (Sipilä et al., 2019). Similar to epidemiological MS studies, one quarter of the reference patients were male, but the proportion of male patients was markedly higher among the patients with infections and more than half of the patients with repeated infection admissions were male. It has been shown that progression of MS from onset is more rapid in men, and patients with aggressive MS are more likely to be male (Tremlett et al., 2006 ; Menon et al., 2013). Functional limitations related to more advanced disease may increase the risk of infections, which may explain the larger proportion of men in the infection cohort.

MS treatment has developed significantly during the study period and several new drugs have become available since 2009. Recent Swedish register-based study supported earlier reports showing that MS patients have an increased risk of infections generally and newer high-efficacy DMTs and especially off-label use of rituximab were associated with higher risk of serious infections (Luna et al., 2019). However, in our study most patients with an infection admission had no DMT at the beginning of the study period. This was even more evident in the patients with over two infections, of which up to 71% had never had a DMT for MS. There were only few medication changes during the study period in the infection cohort, whereas the use of DMTs and treatment change/escalation was clearly more common in the reference cohort. It is of note that in Finland the off-label use of rituximab is much less

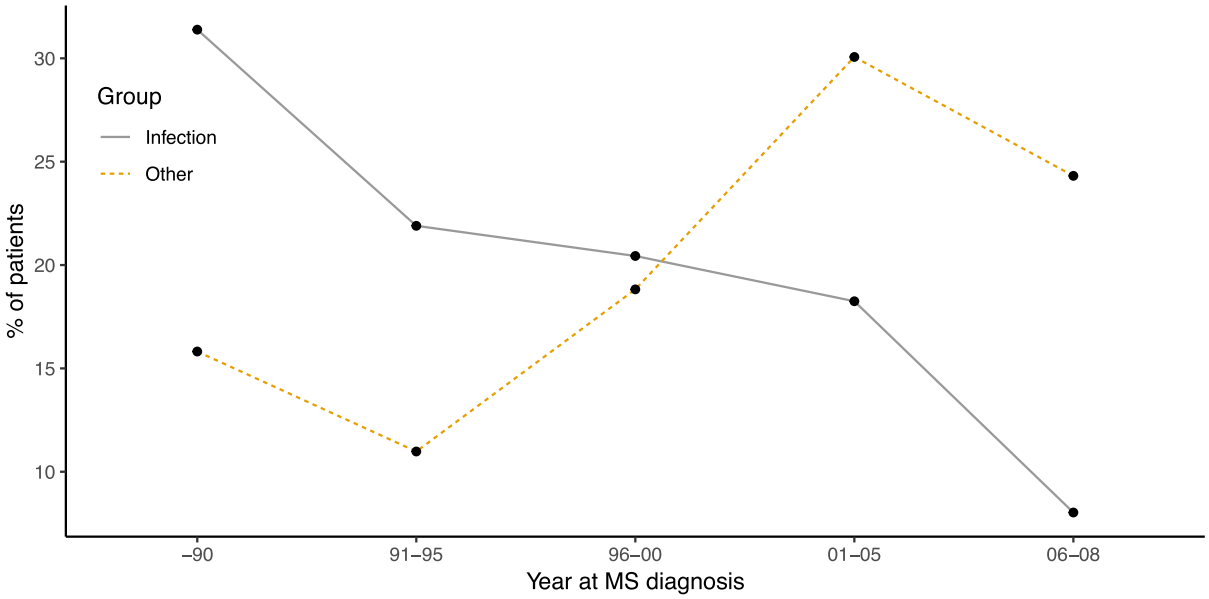

Fig. 3. Calendar year of MS diagnosis in the infection cohort and in the reference cohort of MS patients without infection admissions.

frequent than in Sweden (neurorekisteri.fi) (Berntsson et al., 2018). Indeed, our results may not be directly applicable to healthcare systems where the use of the most aggressive treatments is common, since the proportion of patients receiving these drugs was modest in our study.

Limitations of this study include its retrospective nature and reliance on MS register data. Since the MS register was launched in January 2014, and only patients who were alive then were included, we do not have the data of MS patients deceased before the start of the register. MS register does not cover primary health care. Therefore, we may miss some data on patients followed up in later stages of the disease in municipal health centres. Thus, minor infections treated in primary health care may still have increased during the study period. This would not, however, have had any impact on the distribution and characteristics of the hospitalized patients. It is possible that some patients with advanced disease and no neurological follow-up may have been taken to primary care wards with infections. However, these patients do not have ongoing DMTs and including these cases would only have strengthened our conclusions. Moreover, the MS register data in the hospital district of Southwest Finland is updated regularly during control visits in the MS outpatient policlinic and MS diagnoses have been ensured by staff neurologists of Turku University Hospital. In Finland, MS is diagnosed and treated almost exclusively by neurologists working in public healthcare, which makes the coverage and validity of the register high. However, earliest register data which has been collected retrospectively is partly lacking information on BMI and smoking. The limited number of patients with the most potent new DMTs in our data does not allow us to make firm conclusions on their risk of infections in this setting.

In conclusion, hospital admission rate of MS patients in Southwest Finland steadily declined over the decade from 2009 to 2018. The number and proportion of admissions related to infections also decreased. Infection-related admissions were driven by older age, male gender and severe disability. Importantly, MS patients with admissions due to an infection had received less DMTs compared to the reference group.

Funding

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Ethical standards

According to Finnish law, ethical committee approval was not required since the study was based on administrative register data and included no contact with patients.

CRediT authorship contribution statement

Anna-Leena Pirttisalo: Conceptualization, Methodology, Investigation, Writing - original draft. **Jussi O.T. Sipilä:** Conceptualization, Methodology, Writing - review & editing. **Matias Viitala:** Software, Formal analysis. **Merja Soilu-Hänninen:** Conceptualization, Methodology, Writing - review & editing.

Table 3
Factors associated with infection-related hospital admissions in MS patients.

Variable	Univariate model	Full model	Selected model
	OR (95% CI); p-value	OR (95% CI); p-value	OR (95% CI); p-value
Gender - Female	0.54 (0.32, 0.92); 0.020	0.55 (0.31, 0.99); 0.042	0.55 (0.31, 0.99); 0.042
Age	1.08 (1.05, 1.12); <0.001	1.06 (1.02, 1.10); 0.006	1.06 (1.02, 1.10); 0.003
Latest EDSS score	1.65 (1.37, 2.01); <0.001	1.48 (1.14, 1.95); 0.003	1.48 (1.20, 1.84); <0.001
Disease course - SP/PP	3.26 (1.92, 5.54); <0.001	0.89 (0.41, 1.92); 0.768	
Diagnosis year - ≥1995	0.48 (0.27, 0.87); 0.011	1.13 (0.58, 2.31); 0.729	
Ongoing DMT - Yes	0.46 (0.27, 0.77); 0.003	0.69 (0.38, 1.29); 0.239	

OR, odds ratio; CI, confidence interval; EDSS, expanded disability status scale; SP, secondary progressive; PP, primary progressive; DMT, disease modifying therapy.

Declaration of Competing Interest

A-LP has received congress fee covering by Biogen and Sanofi Genzyme. JS has received honoraria, travel grants and congress fee covering (Orion Corporation, Merck, Pfizer, Abbvie, Sanofi Genzyme) and holds shares (Orion Corporation). MV reports no disclosures. MS-H has received congress fee covering and lecture and consultation fees by Biogen, Cellgene, Merck, Novartis, Roche, Sanofi and Teva.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2020.102328.

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