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Highlights

- The risk of serious infections in MS patients varies according to MS phenotype
- Higher rates of infection were observed in older, male, and progressive individuals
- Progressive MS patients had 4-times as many serious infections as those with RRMS
- Most SIs were of bacterial origin or impacted respiratory and genitourinary tracts

Serious infections in patients with relapsing and progressive forms of multiple sclerosis: a German claims data study

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DECLARATION OF INTEREST STATEMENT
R.K., F.H. and J.K. are employees of Cytel Inc. T.W. is an employee of IPAM e.V. and has received honoraria from several pharmaceutical/consultancy companies (Novo Nordisk, Abbvie, Merck, GSK, BMS, LEO Pharma, Astra Zeneca, Bayer, Boehringer Ingelheim, Pfizer). U.M. works for a statutory insurance fund (AOK PLUS), which provided the data used in this study. E.M.L.R. is an employee of F. Hoffmann-La Roche Ltd. C.C. and L.C. are employees and shareholders of F. Hoffmann-La Roche Ltd.

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ABSTRACT

Background: People with multiple sclerosis (pwMS) have a higher risk of serious infection (i.e., infection-related hospitalizations) than people without MS. Few studies have explored the risk of serious infections by MS phenotype in a real-world setting. This retrospective study compared the incidence of serious infections among people with relapse remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).

Methods: Adult pwMS were selected from a German claims database, based on one inpatient or two outpatient diagnoses of MS (ICD-10 G35) by a neurologist from 01/01/2016 to 12/31/2018. Three cohorts (RRMS, PPMS, SPMS) were identified based on codes for MS subtypes included in the German Modification of the ICD-10 system. A fourth cohort of unspecified MS patients combined those with conflicting MS subtype diagnoses and multiple unspecified codes for MS. Serious infections were defined as hospitalizations for which infections were selected as the primary inpatient diagnosis. Infections were identified from a basket of ICD-10 codes distributed across 11 main categories, according to possible pathogen (e.g., other bacterial diseases [A30-A49]) or anatomical location (e.g., urinary tract infection [N39.0]). Multiple infections were counted if an interval of at least 60 days was recorded between episodes. Serious infections were counted from index (i.e., first recorded MS code) until the end of the study period or death. Incidence rates (IRs) were reported per 100 patient years (PY).

Results: A total of 4,250 pwMS (RRMS: 2,307, PPMS: 282, SPMS: 558, unspecified MS: 1,135) were included; 32 patients progressed from RRMS to SPMS during the follow-up period. Mean (SD) age at baseline was 46.6 (13.6), 61.9 (12.4) and 62.5 (11.8) years in patients with RRMS, PPMS and SPMS respectively. Most pwMS were female (RRMS 74.8%, PPMS 62.1%, SPMS 67.4%). Progressive pwMS were more likely to have at least 1 comorbidity (PPMS 87.2%, SPMS 87.5%) compared to those with relapsing MS (61.9%). Most RRMS patients received disease modifying therapy during follow-up (82.1%), while less than half of progressive MS patients did (PPMS 23.8%, SPMS 31.4%). Over a mean (SD) follow-up period of 3.5 (0.8) years, the IR of serious infections per 100 PY was higher in progressive MS cohorts [PPMS 13.5 (11.3-16.1), SPMS 13.6 (12.0-15.3)] than in the RRMS group [3.4 (3.0-3.7)]. Yearly IRs remained stable over time in each cohort. Where anatomical location was specified, respiratory (2.0 per 100 PY) and genitourinary (1.9 per 100 PY) infections were most common. Across all subtypes, higher rates of serious infections were observed in men and older patients.

Conclusions: Progressive MS, older age and male sex are associated with an increased risk of serious infections. Overall, respiratory and genitourinary infections were the most commonly reported serious infections.

Keywords: claims data, Germany, multiple sclerosis, incidence, infections, hospitalizations
1. INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and neurodegenerative disease of the central nervous system (CNS), and a common cause of neurological disability in young adults.\(^1\) Compared with the general population, people with MS (pwMS) have an increased comorbidity burden including a greater risk of respiratory, cardiovascular, autoimmune, and mood disorders.\(^2,3\) Importantly, multiple studies have shown that comorbidities may negatively impact health outcomes in pwMS, corresponding with an increased risk of disability worsening.\(^4,5\)

Infections constitute a common cause of comorbidity in pwMS. Real-world studies have demonstrated an increased risk of serious infections (i.e., infection-related hospitalizations) in pwMS compared with those without MS.\(^6\)\(^-\)\(^9\) often in association with respiratory and urinary tract infections (UTIs).\(^7,9,10\) The risk of intensive care unit admission is also higher in pwMS in association with infections.\(^2\) Evidence suggests that infections, in particular those of respiratory and urinary origin, are a common cause of mortality in MS.\(^11,12\)

While use of disease-modifying therapies (DMTs) has been associated with an increased risk of infection,\(^13\)\(^-\)\(^15\) susceptibility to infections is also likely modulated by other factors such as age, sex, and MS phenotype.\(^6,10\) Few real-world studies have explored the risk of serious infections (SIs) associated with these factors. Moreover, the low representativeness of datasets used to explore the risk of SIs in MS represents one key limitation of existing research, which has primarily taken place in the United States (US), United Kingdom (UK), Sweden, and Canada, while the availability of data on certain DMTs was limited. Consequently, this study sought to evaluate the incidence of SIs in a recent cohort of pwMS in Germany (for whom there were complete DMT data), and to compare findings among sub-cohorts of patients with relapse-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS), as well as age- and sex-related subgroups.

2. MATERIAL & METHODS

2.1 Study design and data source

This was a retrospective analysis of administrative claims data covering 3.4 million patients from 01/01/2015 to 31/12/2019. An anonymized patient-level dataset was provided by AOK PLUS, a statutory health insurance fund, which covers around half of the population in Saxony and Thuringia. The dataset contains relevant information on primary care, including all inpatient and outpatient diagnostic codes recorded using the German Modification of the International Classification of Diseases, 10\(^{th}\) revision (ICD-10-GM), outpatient prescriptions according to Anatomical Therapeutic Chemical (ATC) codes, and sociodemographic characteristics.

2.2 Patient population
The study included individuals with ≥1 inpatient or ≥2 outpatient MS diagnoses (ICD-10-GM G35) from a neurologist (recorded in separate quarters within one year) from 01/01/2016 to 31/12/2018. Patients were continuously insured throughout the entire study period (01/01/2015 to 31/12/2018) and ≥18 years at index (i.e., date of the first observed MS code). Baseline characteristics were assessed during the one-year period preceding the index MS code and pwMS were followed from index until the end of the study period or death, whichever came first. A minimum follow-up period of one year (with the only exception as death) was required to ensure sufficient time for observation of SIs.

Three sub-cohorts of RRMS, PPMS, and SPMS patients were delineated based on index MS diagnoses recorded in the form of G35.1, G35.2, and G35.3 ICD-10-GM codes, respectively. Patients with illogical code combinations or only “Unspecified” codes (G35.0 and G35.9) were allocated to a fourth sub-cohort of patients with “Unspecified MS”. A logical change in MS subtype from RRMS to SPMS was permitted, in which case individuals were censored as patients with RRMS after the first SPMS code without a subsequent RRMS code. Patients with fewer than two codes for one MS subtype were excluded from the base cohort of pwMS. Figure 1 provides an overview of the study period. Supplementary Table 1 summarizes criteria used to delineate MS cohorts.

2.3 Patient characteristics

Age and sex were evaluated at index. Baseline comorbidities were assessed according to inpatient and confirmed outpatient diagnoses, based on an adapted version of the Charlson Comorbidity Index (CCI), and grouped into 13 categories. A list of ICD-10-GM codes included in each comorbidity category is outlined in Supplementary Table 2. DMTs were tracked during the 12-month baseline period and patient-individual follow-up period, using inpatient Operational and Procedure Key (OPS) and outpatient ATC codes. A list of therapies used to treat MS is outlined in Supplementary Table 3.

2.4 Identification of SIs

Identification of infections was based on a basket of ICD-10 codes distributed across 11 categories (Supplementary Table 4), organized according to either etiology (e.g., Category 1: Certain infectious and parasitic diseases) or anatomical location (e.g., Category 10: Diseases of the genitourinary system). Infection codes were selected based on methodologies used in previous studies. Codes within each category were grouped into sub-categories describing similar concepts (e.g., ICD-10-GM N10 [aggregation of acute tubulo-interstitial nephritis], N11 [chronic tubulo-interstitial nephritis], and N12 [tubulo-interstitial nephritis not specified as acute or chronic] were grouped into a single subcategory representing Nephritis [10A]). These subcategories were used to distinguish between the onset of “new” infections and the re-occurrence of previously recorded infections (Supplementary Table 4).

Next, a determination of the seriousness of infections was made. Within the German context, two types of inpatient ICD-10-GM diagnoses are recorded: one main code (defined as the most important diagnosis considered by the statutory health insurer for billing purposes), and multiple primary codes.
(consisting of auxiliary diagnoses associated with all inpatient treatment received by the patient). In this study, SIs were defined as infection-related hospitalizations, i.e., hospitalizations during which infections (recorded at any point between admission and discharge) were selected as the main diagnosis.

2.5 Statistical analyses

The primary outcome of this study was the incidence rate (IR) of SIs. SIs were counted from index until the end of the study period or death. A new infection was counted if >60 days had elapsed since the last infection code from the same designated sub-category (e.g., 10A, 10B, 10C). This strategy was selected to minimize the potential impact of repeated hospital encounters for the same infection on incidence outcomes. To understand the impact of SI detection strategies on IRs, a sensitivity analysis of various detection strategies was performed. Identification strategies varied based on code type (main vs. primary) and the time window (0, 60, and 180 days) used for reporting new infections. IRs of SIs per 100 patient years (PY) were calculated for all pwMS and each MS sub-cohort separately (RRMS, PPMS, SPMS, and Unspecified MS) at 12-, 24-, and 36-month intervals after the index date, and cumulatively over the entire follow-up period. IRs were also reported according to age strata (18–50, 51–65, and >65 years) and sex subgroups (male, female). IR ratios (IRRs) and two-tailed tests were used to evaluate differences in IRs between RRMS, PPMS, and SPMS cohorts. An IRR<1.0 indicates a lower risk among those in the first comparison group (e.g., IRR RRMS/PPMS = 0.5 indicates a 50% lower incidence rate in patients with RRMS).

Eligibility criteria were applied, and patient-level data were queried using Microsoft SQL Server 2019 (Microsoft Corporation, Redmond WA). Categorical variables were analyzed using absolute and relative frequencies, while continuous variables were reported using sample statistics, including mean, standard deviation (SD), minimum, median, and maximum values. All incidence measures including cumulative incidence, IRs, IRRs, p-values, and 95% confidence intervals (CIs) based on the Poisson distribution were computed in STATA (StataCorp. 2019. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) and Microsoft Excel 2019 (Microsoft Corporation, Redmond WA).

No ethical approval was required for this study, given the anonymization of patient-level data provided by AOK PLUS. Data that support the findings of this study are not publicly available due to privacy and ethical restrictions related to the use of patient-individual data.

3. RESULTS

3.1 Patient cohorts and length of follow-up

A total of 4250 individuals satisfied the criteria for inclusion as pwMS (RRMS: 2307, PPMS: 282, SPMS: 558, Unspecified: 1135). A total of 32 patients first included in the RRMS cohort were later censored and re-included in the SPMS cohort (Table 1).
The overall median (range) length of follow-up was 3.87 (0.01–4.00) years with no differences observed across sub-cohorts. Around 6.92% of all pwMS died during the follow-up period, with a disproportionate share of deaths occurring in patients with progressive MS (PPMS: 16.67%, SPMS: 14.52%, RRMS: 2.77%).

3.2 Patient characteristics

Demographic and clinical characteristics are shown in Table 2. Mean (SD) age at baseline was 46.56 (13.55), 61.94 (12.27), and 62.48 (11.81) years in patients with RRMS, PPMS, and SPMS, respectively, and most patients were female. Progressive MS patients were more likely to have ≥1 comorbidity at baseline (PPMS: 87.23%, SPMS: 87.46%) compared with those with RRMS (61.86%). Urinary tract disorders (34.64%), depression (31.39%), malignancies (15.22%), and cardiovascular disorders (14.49%) were the most common baseline comorbidities. Overall, 2617 pwMS received DMTs during the follow-up period; higher rates of DMT use were observed among RRMS patients than among patients with progressive MS (RRMS: 82.10%, PPMS: 23.76%, SPMS: 31.36%) (Figure 2). The most widely prescribed agents were interferon beta-1a and 1b (34.47%), glatiramer acetate (12.85%), dimethyl-fumarate (16.47%), fingolimod (13.57%), teriflunomide (11.35%), natalizumab (7.64%), ocrelizumab (6.04%), peginterferon beta-1a (5.58%), and azathioprine (5.31%).

3.3 Incidence of SIs

Cumulative incidence, including the number and percentage of patients with an SI after 12 months, is reported in Table 4. Overall, the incidence of SIs was found to be highest among patients with progressive MS (PPMS: 14.54%; SPMS: 10.39%), as compared to those with RRMS (2.82%). The overall IR of SIs throughout the entire study period was 6.98 per 100 PY (95% CI: 6.56–7.41). The IR per 100 PY in progressive patients was nearly four-fold higher (PPMS: 13.52; SPMS: 13.58) than in patients with RRMS (3.36). The overall IR was almost twice as high in men (10.40 per 100 PY) than in women (5.69 per 100 PY), and a similar distribution was observed across the different MS cohorts (see Table 5). The IR of SIs was highest among patients >65 years of age (16.47) and lowest for patients aged 18–50 years (2.74). A detailed overview of IRs for each MS cohort according to sex and multiple age strata can be found in Supplementary Table 5.

Within sensitivity analyses (outlined in Supplementary Table 6), IRs of SIs per 100 PY were found to be substantially higher when considering all primary diagnostic codes (23.63) recorded during a hospitalization, compared with the main diagnostic code only (6.98). Use of different time windows (0 and 180 days) for detecting new episodes of SIs had a minor impact on assessed rates. When observation was censored on the date of the first SI, IRs were substantially lower for all pwMS (3.39 vs. 6.98 per 100 PY). Generally, rates of SIs remained stable over time (Figure 3).

3.4 Types of SIs
Respiratory (1.99 per 100 PY) and genitourinary (1.90 per 100 PY) tract infections were the most common types of SIs, where anatomical location was reported (Table 5). Patients with progressive MS had a significantly higher rate of respiratory tract infections relative to patients with RRMS (IRR RRMS/PPMS: 0.24, p < 0.001; IRR RRMS/SPMS: 0.28, p < 0.001), while no differences were observed among progressive MS patients (IRR PPMS/SPMS: 1.19, p = 0.38). Genitourinary tract infection rates were also significantly higher in patients with progressive MS (IRR RRMS/PPMS: 0.27, p < 0.001; IRR RRMS/SPMS: 0.13, p < 0.001) and SPMS patients were at greatest risk (IRR PPMS/SPMS: 0.49, p < 0.001) (Supplementary Table 7).

3.5 Anti-infective treatment and length of hospitalization

Use of anti-infective drugs was reported in 66.71% (n = 2835) of pwMS during the follow-up period, with some differences observed across sub-cohorts (RRMS: 66.67%, PPMS: 58.51%, SPMS: 72.76%, Unspecified: 65.55%). Most patients were prescribed anti-infectives for systemic use (n = 2830, 66.59%), administered either orally (65.34%) and/or intravenously (9.76%). Antibacterials were the most prescribed anti-infectives (95.79%, n = 2711/2830), followed by antivirals (12.37%, n = 350/2830). The mean (SD) length of hospitalizations related to SIs across the entire base cohort of pwMS was 9.58 (7.46) days.

4. DISCUSSION

This study used a large German claims database to investigate IRs of SIs in more than 4000 pwMS, according to age, sex, and MS phenotype. We found that patients with a progressive MS course experienced four times as many SIs per 100 PY compared with patients with relapsing MS. A higher risk of SIs was also observed in males and patients >50 years. IRs were stable over time, and most SIs were of bacterial origin or located in the respiratory and genitourinary tracts.

Rates of SIs in this study were approximately 2.5–4.5 times higher than those reported in previous analyses using administrative data, which may be explained by differences in study methodology and population characteristics. Five studies examined the rates of infection-related hospitalizations with censorship at the first infection, resulting in IRs of around 1.25–1.92 per 100 PY. Conversely, in our study, IRs included all SIs reported over time. In a sensitivity analysis with censorship at first infection (Supplementary Table 6), more comparable IRs (3.39 per 100 PY) were observed, although these were still 1.5–1.7 times higher than respective rates reported in studies from the US and Sweden. While a similar sex distribution (~70% female) was observed across these studies, patients in the US and Swedish cohorts were younger, with an average age of 41 years, compared with 51.8 years in this study. Additionally, patients in Sweden were newly diagnosed at the time of inclusion, thus restricting disease duration and treatment history to the follow-up period (of up to 9 years).

Another study, featuring almost 7000 pwMS in Canada, applied a similar methodology, in which multiple medical encounters were factored into IR calculations over time (without censorship at the
first infection-related hospitalization). Nevertheless, reported IRs were lower (1.88 per 100 PY), which may be explained by the younger age of Canadian pwMS (age: 45.4 vs. 51.8 years), a lower comorbidity burden (no comorbidities: 81.2% vs. 30.1%), and a low DMT exposure rate (25.3%). Furthermore, the study period covered almost 2 decades (1996–2013) and therefore infections were identified using a combination of ICD-9 and ICD-10 codes, which may have lowered the sensitivity of the detection strategy used in the Canadian context. Our cohort is more contemporaneous (2015–2019) and was identified based on more granular codes from the ICD-10-GM codebook, which are of particular relevance to the German Diagnosis Related Groups (G-DRG) system, used in medical billing. Consequently, this warrants a higher level of data completeness. Furthermore, disparities in observed infection rates across countries may reflect differences in inpatient and outpatient care utilization related to the structure of each health system. Additionally, we selected a more comprehensive list of ICD-10-GM codes to detect infections than the Canadian study, which did not account for some organ-specific codes (e.g., related to the respiratory and genitourinary tracts) and broader categories of infection (e.g., infections of the cardiovascular system).

Consistent with previous studies, infections of the respiratory, urinary, and gastrointestinal tracts prompted the highest rates of SIs in our study. UTIs are common in pwMS due to MS-related bladder dysfunction, which can present as urinary frequency, urgency, and incontinence, as well as hesitancy, incomplete emptying, and urinary retention. Respiratory infections are also common in MS due to respiratory disorders that impair respiratory muscle strength, resulting in the inability to cough and clear the lungs. Accordingly, in our study, patients with progressive MS were more likely to have genitourinary tract infections, and overall respiratory disorders were a common comorbidity.

Importantly, the current study also enabled the characterization of the risk of infection-related hospitalizations according to MS phenotype. Three studies (one in the US and two in Sweden) have previously assessed this association, but IRs were only reported in two of the studies. One of the studies using data from the US Veterans Health Administration included predominantly male veterans with a diagnosis of MS from 01/01/1999 to 31/12/2010. IRs per 100 PY across different phenotypes in this study were much lower than those in our study (RRMS: 1.16, PPMS/PRMS: 2.46–3.36, SPMS: 3.73, Unspecified MS: 1.97). In one Swedish study, IRs of SIs per 100 PY were reported to be 3.26 for progressive patients, and 0.98 in patients with relapsing MS. Some important methodological considerations should be noted. Patients in both studies were censored at first infection leading to a hospitalization stay >24 hours and infections were identified using the ICD-9-CM coding system. More importantly, in the US study, MS subtypes were extracted from patients’ clinical notes using natural language processing, using keywords from clinical experts. This resulted in 64.9% of patients being classified as having "Unspecified MS", compared with only 26.7% in our study. Both the US and Swedish studies have ultimately shown that patients with progressive MS exhibit a greater risk of hospital admission due to infections. These results are consistent with our findings, reflecting the fact that progressive MS patients were older, more disabled, had a longer DMT history, and a greater comorbidity burden.
Finally, our study demonstrated that age and sex are important factors that may impact the risk of SIs in pwMS. Many previous administrative claims studies have reported higher IRs of SIs among males,⁶ ⁷ ⁹ ¹⁰ and our results are concordant with these findings. The study in Canada¹⁰ suggested that these sex-related differences could be explained in part by the higher risk of urinary system infections in men with MS. Men also accumulate disability faster than women, particularly in those with a relapse onset, which may in turn increase the risk of infections. ²⁵ Nevertheless, in a recent multi-database study from the US and UK,⁸ IRs of hospitalized infections were similar between sexes. It should be noted that data from two distinctive databases were used in the aforementioned analysis. One of these databases, UK-CPRD GOLD, is based on electronic medical records, featuring data from general practitioners and some hospital records. Consequently, the authors from the multi-database study were not able to confirm whether patients with infections, recorded within 1 week of a hospitalization code, were truly hospitalized—a factor that could have affected men and women differently. Other population characteristics such as age distribution may help to further explain the results. While in most studies older patients show higher IRs of SIs,⁷ ⁹ ¹⁰ the age threshold at which risk significantly increases is likely influenced by other factors such as sex, MS phenotype, disability level, and presence of comorbidities. Our findings are also suggestive of these thresholds (Supplementary Table 5).

To our knowledge, this is the first study to examine the IR of SIs across different MS phenotypes stratified by age and sex within a recent time window (2015-2019), allowing for the analysis of a modern cohort of pwMS treated with multiple DMTs. Study strengths include the use of a large population dataset with information on different MS subtypes, in addition to a robust methodological approach in which all hospitalizations were included in IR calculations. Moreover, a validated algorithm was used to identify people with MS and different MS phenotypes, although we cannot rule out the possibility that the MS subtypes are not accurately characterized by the codes included in patient records. Also, changes in MS phenotype (e.g. progression from RRMS to SPMS) may not have been accurately timely recorded, as our data suggest a conversion rate to SPMS lower than the expected 2–3% per year. ⁲⁰ As the study ended in December 2019, it remains unclear and to be determined whether the COVID-19 pandemic may have had an impact on detected rates of SIs.

There are some limitations in this study. SIs were detected only in association with main inpatient diagnoses, to account for only the most severe infection-related hospitalizations, which may have resulted in an underestimation of SIs. Results from sensitivity analyses that used different detection windows and coding strategies suggest that the SI identification methodology does indeed have an impact on the reported infection rates. Consequently, this research may not capture less severe infections experienced by younger and less comorbid patients who receive treatment in outpatient care. Furthermore, our study is geographically restricted to two administrative regions in Germany. Generalizability of the results to other federal states is expected, although the average age of our pwMS cohort is higher than the national average in Germany. ²⁷ ²⁸ Moreover, observed differences in IRs between countries may reflect deviations in billing/coding and care delivery.
While this study reported use of anti-infective drugs during the follow-up period, it was not possible to link anti-infective prescription codes with corresponding infections for which they were prescribed. Our analysis did not explore infection rates by disability status, comorbidity burden, DMT exposure, and other modulating factors, which may influence the risk of SIs. It is possible that the differences observed across MS phenotypes may be simply due to distinct disability and comorbidity patterns. We recommend that future studies address these gaps.

5. CONCLUSIONS

This study provides new evidence to understand factors modulating clinical susceptibility to infections in pwMS. We found that progressive MS, older age, and male sex are associated with an increased risk of infection-related hospitalizations; respiratory and genitourinary infections were the most common SIs.

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CONFLICT OF INTERESTS
R.K., F.H. and J.K. are employees of Cytel Inc. T.W. is an employee of IPAM e.V. and has received honoraria from several pharmaceutical/consultancy companies (Novo Nordisk, Abbvie, Merck, GSK, BMS, LEO Pharma, Astra Zeneca, Bayer, Boehringer Ingelheim, Pharmerit). U.M. works for a statutory insurance fund (AOK PLUS), which provided the data used in this study. E.M.L.R. is an employee of F. Hoffmann-La Roche Ltd. C.C. and L.C. are employees and shareholders of F. Hoffmann-La Roche Ltd.

AUTHORS’ CONTRIBUTIONS
All authors contributed to the conceptualization and methodology of the study and developed the study protocol and analysis plan. R.K., F.H., and J.K. conducted the formal analysis based upon the methodology described in a research protocol. All authors interpreted the findings, provided critical feedback, and gave the submitted manuscript version final approval. All authors agree to be accountable for the accuracy and integrity of the work.

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ETHICS APPROVAL
This study used one anonymized health insurance claims dataset, which was provided free of charge by AOK PLUS. The dataset was used under the formal agreement and legal basis of §75, Tenth Book of the Social Code (SGB X). Since all patient data provided by the sickness funds were fully anonymized, no ethical approval from an institutional review board was required to implement this project.

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FIGURE LEGENDS

FIGURE 1. Overview of the study period and patient examples.

MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Note: Patients were followed from their index MS code until the end of the study period or death.

FIGURE 2. DMT use among all patients with MS (N = 4250) during the follow-up period.
DMT, disease-modifying therapy; MS, multiple sclerosis.

FIGURE 3. Incidence rate of serious infections (per 100 PY) over time, according to type of MS. From left to right: All patients with MS (light blue), RRMS (orange), PPMS (green), SPMS (dark blue), Unspecified MS (yellow)

MS, multiple sclerosis; PY, patient years; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; SIs, serious infections.

TABLE 1. Patient-individual follow-up by MS cohort.

<table>
<thead>
<tr>
<th>Patient observation</th>
<th>All MS (N = 4250)</th>
<th>RRMS (N = 2307)</th>
<th>PPMS (N = 282)</th>
<th>SPMS (N = 558)</th>
<th>Unspecified MS (N = 1135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up period, years</td>
<td>3.49 (0.80)</td>
<td>3.56 (0.72)</td>
<td>3.36 (1.02)</td>
<td>3.44 (0.90)</td>
<td>3.30 (0.90)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.87 (0.01-4.00)</td>
<td>3.89 (0.14-4.00)</td>
<td>3.84 (0.05-3.99)</td>
<td>3.86 (0.01-4.00)</td>
<td>3.79 (0.15-4.00)</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Censored, n (%)</td>
<td>3956 (93.08%)</td>
<td>2211 (95.84%)</td>
<td>235 (83.33%)</td>
<td>477 (85.48%)</td>
<td>1036 (91.28%)</td>
</tr>
<tr>
<td>End of the study period</td>
<td>294 (6.92%)</td>
<td>64 (2.77%)</td>
<td>47 (16.67%)</td>
<td>81 (14.52%)</td>
<td>99 (8.72%)</td>
</tr>
<tr>
<td>Death</td>
<td>32 (1.39%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.
### TABLE 2. Baseline characteristics of patients by MS cohort.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All MS (N = 4250)</th>
<th>RRMS (N = 2307)</th>
<th>PPMS (N = 282)</th>
<th>SPMS (N = 558)</th>
<th>Unspecified MS (N = 1135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3072 (72.28%)</td>
<td>1725 (74.77%)</td>
<td>175 (62.06%)</td>
<td>376 (67.38%)</td>
<td>820 (72.25%)</td>
</tr>
<tr>
<td>Male</td>
<td>1178 (27.72%)</td>
<td>582 (25.23%)</td>
<td>107 (37.94%)</td>
<td>182 (32.62%)</td>
<td>315 (27.75%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>51.82 (15.22)</td>
<td>46.56 (13.55)</td>
<td>61.94 (12.27)</td>
<td>62.48 (11.81)</td>
<td>54.91 (15.69)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>52 (18-96)</td>
<td>47 (18-96)</td>
<td>63 (28-92)</td>
<td>63 (29-92)</td>
<td>56 (18-95)</td>
</tr>
<tr>
<td>18-50, n (%)</td>
<td>1959 (46.09%)</td>
<td>1402 (60.77%)</td>
<td>50 (17.73%)</td>
<td>101 (18.10%)</td>
<td></td>
</tr>
<tr>
<td>51-65, n (%)</td>
<td>1494 (35.15%)</td>
<td>726 (31.47%)</td>
<td>118 (41.84%)</td>
<td>228 (40.86%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 65, n (%)</td>
<td>797 (18.75%)</td>
<td>179 (7.76%)</td>
<td>114 (40.43%)</td>
<td>229 (41.04%)</td>
<td></td>
</tr>
<tr>
<td>DMTs in the baseline year, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No DMTs</td>
<td>2119 (49.86%)</td>
<td>754 (32.68%)</td>
<td>234 (82.98%)</td>
<td>387 (69.35%)</td>
<td>765 (67.40%)</td>
</tr>
<tr>
<td>1 DMT</td>
<td>1992 (46.87%)</td>
<td>1442 (62.51%)</td>
<td>45 (15.96%)</td>
<td>168 (30.11%)</td>
<td>348 (30.66%)</td>
</tr>
<tr>
<td>≥ 2 DMT(s)</td>
<td>139 (3.27%)</td>
<td>111 (4.81%)</td>
<td>3 (1.06%)</td>
<td>3 (0.54%)</td>
<td>22 (1.94%)</td>
</tr>
<tr>
<td>Comorbidities in the baseline year, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No comorbidities</td>
<td>1281 (30.14%)</td>
<td>880 (38.14%)</td>
<td>36 (12.77%)</td>
<td>70 (12.54%)</td>
<td>304 (26.78%)</td>
</tr>
<tr>
<td>1 comorbidity</td>
<td>1135 (26.71%)</td>
<td>678 (29.39%)</td>
<td>60 (21.28%)</td>
<td>111 (19.89%)</td>
<td>291 (25.64%)</td>
</tr>
<tr>
<td>≥ 2 comorbidities</td>
<td>1834 (43.15%)</td>
<td>749 (32.47%)</td>
<td>186 (65.96%)</td>
<td>377 (67.56%)</td>
<td>540 (47.58%)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>1472 (34.64%)</td>
<td>543 (23.54%)</td>
<td>162 (57.45%)</td>
<td>365 (65.41%)</td>
<td>402 (35.42%)</td>
</tr>
<tr>
<td>Depression</td>
<td>1334 (31.39%)</td>
<td>667 (28.91%)</td>
<td>101 (35.82%)</td>
<td>205 (36.74%)</td>
<td>361 (31.81%)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>647 (15.22%)</td>
<td>300 (13.00%)</td>
<td>57 (20.21%)</td>
<td>104 (18.64%)</td>
<td>186 (16.39%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>616 (14.49%)</td>
<td>229 (9.93%)</td>
<td>67 (23.76%)</td>
<td>108 (19.35%)</td>
<td>212 (18.68%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>538 (12.66%)</td>
<td>186 (8.06%)</td>
<td>53 (18.79%)</td>
<td>111 (19.89%)</td>
<td>188 (16.56%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>505 (11.88%)</td>
<td>256 (11.10%)</td>
<td>35 (12.41%)</td>
<td>64 (11.46%)</td>
<td>150 (13.22%)</td>
</tr>
<tr>
<td>Chronic pulmonary</td>
<td>380 (8.94%)</td>
<td>198 (8.58%)</td>
<td>34 (12.06%)</td>
<td>38 (6.81%)</td>
<td>110 (9.69%)</td>
</tr>
<tr>
<td>Rheumatological &amp; autoimmune</td>
<td>361 (8.49%)</td>
<td>173 (7.50%)</td>
<td>27 (9.57%)</td>
<td>47 (8.42%)</td>
<td>114 (10.04%)</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>304 (7.15%)</td>
<td>101 (4.38%)</td>
<td>40 (14.18%)</td>
<td>67 (12.00%)</td>
<td>96 (8.46%)</td>
</tr>
<tr>
<td>Gastrointestinal and liver</td>
<td>271 (6.38%)</td>
<td>120 (5.20%)</td>
<td>27 (9.57%)</td>
<td>43 (7.70%)</td>
<td>81 (7.14%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>233 (5.48%)</td>
<td>44 (1.91%)</td>
<td>31 (10.99%)</td>
<td>70 (12.54%)</td>
<td>88 (7.75%)</td>
</tr>
<tr>
<td>Renal</td>
<td>206 (4.85%)</td>
<td>58 (2.51%)</td>
<td>17 (6.03%)</td>
<td>54 (9.67%)</td>
<td>77 (6.78%)</td>
</tr>
<tr>
<td>HIV</td>
<td>4 (0.10%)</td>
<td>4 (0.17%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
</tbody>
</table>

DMT, disease-modifying therapy; HIV, human immunodeficiency virus; MS, multiple sclerosis; n.r., not reported; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.
TABLE 3. IR of serious infections per 100 PY during the entire follow-up period.

<table>
<thead>
<tr>
<th>Rate of serious infections per 100 PY (95% CI)</th>
<th>All MS (N = 4250)</th>
<th>RRMS (N = 2307)</th>
<th>PPMS (N = 282)</th>
<th>SPMS (N = 558)</th>
<th>Unspecified MS (N = 1135)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5.69 (5.25-6.16)</td>
<td>2.98 (2.57-3.45)</td>
<td>10.05 (7.65-12.97)</td>
<td>11.54 (9.77-13.55)</td>
<td>n.r.</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-50</td>
<td>2.74 (2.36-3.16)</td>
<td>2.25 (1.85-2.70)</td>
<td>6.29 (3.14-11.25)</td>
<td>5.82 (3.60-8.89)</td>
<td>n.r.</td>
</tr>
<tr>
<td>51-65</td>
<td>7.76 (7.03-8.54)</td>
<td>3.94 (3.22-4.78)</td>
<td>11.91 (8.78-15.79)</td>
<td>14.34 (11.83-17.23)</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

CI, confidence interval; IR, incidence rate; MS, multiple sclerosis; n.r., not reported; PPMS, primary progressive multiple sclerosis; PY, patient years; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

TABLE 4. Cumulative incidence of serious infections at 1-year post-index, according to pathogen or anatomical location

<table>
<thead>
<tr>
<th>Cumulative incidence of serious infections measured at 12 months after index</th>
<th>All MS Patients (N=4,250)</th>
<th>RRMS (N=2,307)</th>
<th>PPMS (N=282)</th>
<th>SPMS (N=558)</th>
<th>Unspecified MS (N=1,135)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any serious infection</strong></td>
<td>263 6.19%</td>
<td>65 2.82%</td>
<td>41 14.54%</td>
<td>58 10.39%</td>
<td>104 9.16%</td>
</tr>
<tr>
<td>Certain infectious and parasitic diseases</td>
<td>103 2.42%</td>
<td>26 1.13%</td>
<td>16 5.67%</td>
<td>3 20 3.58%</td>
<td>43 3.79%</td>
</tr>
<tr>
<td>Inflammatory diseases of the CNS</td>
<td>4 0.09%</td>
<td>3 0.13%</td>
<td>1 0.00%</td>
<td>0 0.00%</td>
<td>0 0.00%</td>
</tr>
<tr>
<td>Diseases of the eye and adnexa</td>
<td>1 0.02%</td>
<td>1 0.04%</td>
<td>0 0.00%</td>
<td>0 0.00%</td>
<td>1 0.09%</td>
</tr>
<tr>
<td>Diseases of the ear and mastoid process</td>
<td>1 0.02%</td>
<td>0 0.00%</td>
<td>0 0.00%</td>
<td>0 0.00%</td>
<td>1 0.09%</td>
</tr>
<tr>
<td>Diseases of the circulatory system</td>
<td>3 0.07%</td>
<td>0 0.00%</td>
<td>1 0.35%</td>
<td>1 0.18%</td>
<td>1 0.09%</td>
</tr>
<tr>
<td>Diseases of the respiratory system</td>
<td>79 1.86%</td>
<td>12 0.52%</td>
<td>17 6.03%</td>
<td>3 18 3.23%</td>
<td>33 2.91%</td>
</tr>
<tr>
<td>Diseases of the digestive system</td>
<td>13 0.31%</td>
<td>8 0.35%</td>
<td>1 0.35%</td>
<td>1 0.18%</td>
<td>3 0.26%</td>
</tr>
<tr>
<td>Diseases of the skin and subcutaneous tissue</td>
<td>15 0.35%</td>
<td>5 0.22%</td>
<td>3 1.06%</td>
<td>0 0.00%</td>
<td>7 0.62%</td>
</tr>
<tr>
<td>Diseases of the musculoskeletal system and connective tissue</td>
<td>5 0.12%</td>
<td>3 0.13%</td>
<td>0 0.00%</td>
<td>0 0.00%</td>
<td>2 0.18%</td>
</tr>
<tr>
<td>Diseases of the genitourinary system</td>
<td>68 1.60%</td>
<td>8 0.39%</td>
<td>8 2.84%</td>
<td>25 4.48%</td>
<td>28 2.47%</td>
</tr>
<tr>
<td>Pregnancy, childbirth, and the puerperium</td>
<td>1 0.02%</td>
<td>0 0.00%</td>
<td>0 0.00%</td>
<td>0 0.00%</td>
<td>1 0.09%</td>
</tr>
</tbody>
</table>

*Includes infections for which the main ICD-10 code does not specify anatomical location.

CNS, central nervous system; ICD, International Classification of Disease; MS, multiple sclerosis; PY, patient years; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.
TABLE 5. IR of serious infections per 100 PY (95% CI), according to pathogen or anatomical location during the entire follow-up period.

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>All MS (N = 4250)</th>
<th>RRMS (N = 2307)</th>
<th>PPMS (N = 282)</th>
<th>SPMS (N = 558)</th>
<th>Unspecified MS (N = 1135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial, viral, fungal, and parasitic infections†</td>
<td>2.30 (2.06-2.56)</td>
<td>1.13 (0.91-1.39)</td>
<td>5.15 (3.80-6.83)</td>
<td>3.54 (2.75-4.49)</td>
<td>3.52 (2.95-4.18)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>1.99 (1.78-2.24)</td>
<td>0.99 (0.79-1.24)</td>
<td>4.51 (3.25-6.09)</td>
<td>3.80 (2.98-4.78)</td>
<td>2.64 (2.15-3.22)</td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>1.90 (1.68-2.13)</td>
<td>0.64 (0.48-0.84)</td>
<td>2.68 (1.74-3.96)</td>
<td>5.31 (4.33-6.45)</td>
<td>2.72 (2.22-3.31)</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>0.28 (0.20-0.38)</td>
<td>0.27 (0.17-0.41)</td>
<td>0.32 (0.07-0.94)</td>
<td>0.36 (0.15-0.75)</td>
<td>0.24 (0.11-0.46)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>0.27 (0.19-0.37)</td>
<td>0.17 (0.09-0.29)</td>
<td>0.43 (0.12-1.10)</td>
<td>0.31 (0.11-0.68)</td>
<td>0.43 (0.24-0.69)</td>
</tr>
<tr>
<td>Musculoskeletal system and connective tissue</td>
<td>0.10 (0.06-0.17)</td>
<td>0.07 (0.03-0.16)</td>
<td>0.11 (0.00-0.60)</td>
<td>0.05 (0.00-0.29)</td>
<td>0.19 (0.08-0.38)</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>0.07 (0.03-0.12)</td>
<td>0.01 (0.00-0.07)</td>
<td>0.32 (0.07-0.94)</td>
<td>0.21 (0.06-0.53)</td>
<td>0.05 (0.01-0.19)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>0.04 (0.01-0.09)</td>
<td>0.05 (0.01-0.13)</td>
<td>&lt;0.01 (0.00-0.40)</td>
<td>&lt;0.01 (0.00-0.19)</td>
<td>0.05 (0.01-0.19)</td>
</tr>
<tr>
<td>Eye and adnexa</td>
<td>0.01 (0.00-0.04)</td>
<td>0.01 (0.00-0.07)</td>
<td>&lt;0.01 (0.00-0.40)</td>
<td>&lt;0.01 (0.00-0.19)</td>
<td>&lt;0.01 (0.00-0.10)</td>
</tr>
<tr>
<td>Ear and mastoid process</td>
<td>0.01 (0.00-0.04)</td>
<td>&lt;0.01 (0.00-0.05)</td>
<td>&lt;0.01 (0.00-0.40)</td>
<td>&lt;0.01 (0.00-0.19)</td>
<td>0.03 (0.00-0.15)</td>
</tr>
<tr>
<td>Infections during pregnancy and childbirth</td>
<td>0.02 (0.00-0.05)</td>
<td>0.01 (0.00-0.07)</td>
<td>&lt;0.01 (0.00-0.40)</td>
<td>&lt;0.01 (0.00-0.19)</td>
<td>0.03 (0.00-0.15)</td>
</tr>
</tbody>
</table>

†Includes infections for which the main ICD-10 code does not specify anatomical location.

CI, confidence interval; CNS, central nervous system; ICD, International Classification of Disease; IR, incidence rate; MS, multiple sclerosis; PY, patient years; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.
Figure 2

Patients with RRMS (N = 2067): DMT use during the follow-up period

- Dimethyl fumarate: 253
- Fingolimod: 288
- Teriflunomide: 171
- Natalizumab: 146
- Peginterferon beta-1a: 116
- Copaxone: 86
- Cladribine: 55
- Azathioprine: 50
- Methotrexate: 38
- Cyclophosphamide: 30
- Rituximab: 19
- Mitoxantrone: 17
- Tacroimun: 12
- Mycophenolate mofetil: 9
- Ozanimod: 8
- Siponimod: 1

Patients with PPMS (N = 252): DMT use during the follow-up period (by agent)

- Azathioprine: 16
- Copaxone: 13
- Glairain acetate: 20
- Dimethyl fumarate: 12
- Fingolimod: 11
- Cyclophosphamide: 3
- Peginterferon beta-1a: 1
- Copaxone: 1
- Cladribine: 1
- Rituximab: 1

Patients with SPMS (N = 568): DMT use during the follow-up period (by agent)

- Interferon beta-1a and -1b: 31
- Glairain acetate: 13
- Copaxone: 9
- Azathioprine: 7
- Methotrexate: 6
- Peginterferon beta-1a: 4
- Cladribine: 4
- Methotrexate: 3
- Mitoxantrone: 3
- Siponimod: 2
- Cladribine: 1
- Ozanimod: 1
- Fingolimod: 1
- Alemtuzumab: 1