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RESEARCH ARTICLE

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Clinical and economic impact on people with relapsing-remitting multiple sclerosis in the United States: a matched-cohort study

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ABSTRACT

Objectives: To understand the real-world clinical and economic impact of relapsing-remitting multiple sclerosis (RRMS) in the United States (US).

Methods: This retrospective, matched-cohort study used a large, integrated US administrative health database from 01 January 2012 to 31 December 2021. People with RRMS (PwRRMS) were identified using a validated algorithm or through electronic health records and matched 1:1 to MS-free controls based on age, gender, race, region, and insurance. Demographics, comorbidities, healthcare resource utilization (HCRU), and healthcare costs (HCCs) were compared between the RRMS cohort and MS-free controls during 1-year follow-up. All costs were reported in 2021 US dollars.

Results: The final cohort comprised 9,290 people (RRMS, $n = 4,645$; MS-free controls, $n = 4,645$) with a mean ± SD age of 52.9 ± 14.4 years; 79.1% were female. During the follow-up period, compared with the controls, the RRMS cohort had significantly higher prevalence of infections (60.9% vs. 51.5%; $p < 0.001$) and MS-related comorbidities, including malaise/fatigue (34.3% vs. 15.7%), major depressive disorders (27.6% vs. 17.7%), anxiety (21.4% vs. 15.1%), burning/numbness (19.4% vs. 5.8%), and abnormal gait (16.1% vs. 5.2%) (all $p < 0.001$). RRMS was associated with significantly higher mortality (5.0% vs. 1.2%), hospitalizations (18.2% vs. 11.5%), emergency department visits (40.3% vs. 28.1%), and physician visits (13.7 vs. 10.0) (all $p < 0.001$) versus controls. Mean total HCCs were significantly higher for RRMS versus controls ($54,244 vs. $19,671; $p < 0.001$), driven primarily by medical claims ($31,154 vs. $15,944; $p < 0.001$).

Conclusions: PwRRMS experienced a greater impact of comorbidities and significantly increased HCRU and HCCs, highlighting the need to integrate these impacts into everyday clinical decision-making.

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Introduction

Multiple sclerosis (MS) is a neuroinflammatory disorder of the central nervous system, characterized by demyelination and neuronal damage[1]. It is among the leading causes of non-traumatic disability in young adults[1]. The global prevalence of MS was estimated to be 36 cases per 100,000 people, with the United States (US) among the countries with a high prevalence (288 cases per 100,000 people)[2]. MS presents with variable symptoms, including fatigue, difficulty in walking, pain, numbness, sexual dysfunction, and bowel and bladder issues[3]. Relapsing-remitting multiple sclerosis (RRMS) is the most common phenotype of MS that affects up to 85.0% of people with MS at initial diagnosis[4].

RRMS is characterized by periods of neurological symptom exacerbation followed by partial or complete recovery and represents the most common MS phenotype[4]. Although many people with RRMS initially experience a relapsing disease course, disability may accumulate over time, resulting in substantial physical, cognitive, and psychosocial impacts[3,4].

Disease-modifying therapies (DMTs) are the mainstay of treatment for RRMS and have been associated with a reduction in disease impact and disability[5,6]. Several DMTs with differing mechanisms of action, efficacy profiles, and safety considerations are currently available for the management of RRMS, allowing treatment to be tailored according to disease characteristics and patient needs[5,6]. Despite the availability of

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several DMTs for RRMS in the US, a majority of people with RRMS continue to accumulate disability and experience persistent symptoms that affect daily functioning. A retrospective, cross-sectional survey conducted in the US showed that people with RRMS experienced higher work-related and activity impairment and healthcare resource utilization (HCRU) than people without MS, but this survey included only employed people[7].

The existing US real-world evidence (RWE) on RRMS impact is limited by narrow study populations, lack of appropriate comparators, or insufficient clinical characterization. To address these gaps, this study used a large, integrated electronic health record (EHR)-claims database to describe the clinical comorbidities, HCRU, and economic impact associated with RRMS relative to matched MS-free controls. This updated, real-world assessment provides clinically relevant insights into the ongoing challenges faced in RRMS management and the resource implications for routine care.

The preliminary findings from this work were presented as a poster at ACTRIMS 2024[8]. This manuscript provides a complete methodological description, full statistical results, and an expanded clinical and economic interpretation that were not included in the poster.

Methods

Study design and data source

This was a retrospective, matched-cohort study of people with RRMS identified in the Optum Market Clarity database, which is a large, integrated US-based administrative database. This database integrates EHR data with medical and pharmacy claims, allowing the analysis of demographics, disease phenotypes, diagnosis codes, signs and symptoms, biomarkers, laboratory tests and results, HCRU, and healthcare costs (HCCs) of >63 million people in the US. This study utilized data collected during a 10-year period from 01 January 2012 to 31 December 2021. People with RRMS were matched 1:1 to unique MS-free controls based on age, gender, race, region, and insurance.

Study population

The RRMS cohort comprised unique people with MS who either met a previously published and validated claims-based RRMS identification algorithm developed by Van Le et al.[9] or had a diagnosis of RRMS in the EHR data during the identification period. The algorithm demonstrated a positive predictive value of approximately 84% for identifying RRMS in US healthcare data[9]. The index date was the date of a randomly picked medical claim with MS diagnosis or an EHR with RRMS during the identification period. Patients were identified using the validated claims-based algorithm or RRMS phenotype information recorded directly in the EHR. In cases where both sources identified the same individual ($n = 563$), EHR-based RRMS classification was prioritized because it provided direct clinical phenotype information. This hierarchical approach was used to maximize phenotype specificity while leveraging the strengths of both data sources. As a part of the RRMS claims-based algorithm, people were considered to have RRMS if they had ≥1 medical claim for a primary diagnosis of MS (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 340 and ICD-10-CM codes G35.xxx) or continuous enrollment in medical and pharmacy plans during the follow-up period (1-year after the index date or until death) and were aged ≥18 years. During the identification period, people were also required to have ≥1 medication claim for DMT; ≥1 claim for brain or spinal magnetic resonance imaging; ≥1 claim for a diagnosis of internuclear ophthalmoplegia ≥30 days apart from an MS diagnosis; ≥1 claim for MS-related symptom therapy medication; or ≥1 claim for a diagnosis of any MS-related symptom ≥30 days apart from an MS diagnosis.

People were excluded if they used medications commonly prescribed for a progressive disease (mitoxantrone, cyclophosphamide, or methotrexate) anytime during the study period. The disease progression was indicated by worsening of a claims-based Expanded Disability Status Scale (EDSS) proxy derived from Kurtzke Functional Systems Score (KFSS)-mapped ICD-9/10-CM codes. The proxy methodology was based on a previously described real-world adaptation of the EDSS for administrative healthcare data[10,11]. People with evidence of exacerbation within 1-year of the index date were also excluded to limit the influence of acute relapse-related HCRU and HCCs and to support characterization of the clinical and economic profile of a relatively stable RRMS population rather than outcomes occurring during an acute relapse period. This approach was also intended to improve comparability between the RRMS and MS-free control cohorts at baseline.

A separate MS-free control cohort was also generated and matched to people with MS based on age, gender, region, race, and insurance (commercial, Medicare, Medicaid, or unknown). People without an MS diagnosis during the study period were considered

MS-free. The index date for the MS-free controls was the same as that for the matched people with RRMS. All MS-free controls had the same enrollment requirements. Individuals were not required to remain in the database indefinitely; all study participants were required to have continuous medical and pharmacy enrollment during the 1-year follow-up period (or until death, if it occurred within the follow-up period).

Study measures

Demographics and comorbidities

Age, gender, race, ethnicity, insurance, and geographic regions have been reported. The Charlson Comorbidity Index (CCI) and specific comorbidities of interest of people with RRMS were measured and compared with those of the MS-free controls during the 1-year follow-up period. The CCI was used as a measure of overall comorbidity burden and was calculated according to the method described by Charlson et al.[12].

Clinical characteristics

Clinical characteristics including infections, leukopenia, and mortality were measured during the 1-year follow-up period. Infections were defined as having a medical claim for a diagnosis of relevant infection in any field. The list of infections was derived from the clinical trials of ocrelizumab, ofatumumab, and fingolimod[13–15]. Infections were evaluated as an overall composite outcome and were not stratified according to infection severity. Leukopenia was defined as having a claim for the ICD-9-CM diagnosis code of 288.50 or the ICD-10-CM diagnosis code of D72.819 in any healthcare setting. National Death Index linkage was not available for this study; therefore, all-cause mortality was defined as the proportion of individuals who died during the follow-up period, based on death information recorded in the integrated EHR–claims database. As with most real-world data sources, mortality capture may be incomplete and should be interpreted accordingly.

Healthcare resource utilization and healthcare costs

The HCRU and HCCs (adjusted to the year 2021 US dollars) included all-cause and MS-specific utilization and costs reported during the 1-year follow-up period and were compared between people with RRMS and MS-free controls. MS-specific utilization was defined as having an MS primary diagnosis code in the relevant claim. All-cause costs included inpatient admissions, emergency department (ED) visits, non-ED outpatient service visits (office visits), medical costs, and pharmacy costs. MS-specific costs included inpatient admissions, ED visits, non-ED outpatient service visits, medical costs, pharmacy costs, the use of specific services such as physical therapy (PT), occupational therapy (OT), speech therapy (ST), and durable medical equipment (DME) for MS-related disability (for example, a cane, walker, or wheelchair), and the cost of infections (costs of medical claims with a diagnosis of infections in any field and costs of antibiotics or antivirals pharmacy claims with a supply of $<$21 days filled within 7 days of an infection).

Operational definitions

MS-specific utilization and costs were defined as claims with a primary MS diagnosis and included inpatient stays, ED visits, non-ED outpatient services (office visits), and MS-related services such as PT, OT, ST, and DME. All-cause measures included all visits and costs regardless of diagnosis. Infection-related costs combined medical claims with infection diagnoses and short-course antibiotic or antiviral prescriptions ($\leq$21 days' supply) filled within 7 days of the infection claim. A claims-based EDSS proxy was derived from KFSS-mapped ICD-9/10-CM codes using a previously described real-world, claims-based adaptation of the EDSS methodology developed for administrative healthcare data. The EDSS proxy was used solely as an operational criterion during cohort selection to identify evidence of disease progression and support the inclusion of a relatively stable RRMS population; it was not evaluated as a study endpoint and no disability outcomes based on the EDSS proxy were included in the reported analyses. The clinician-assessed EDSS and the claims-based EDSS proxy should be considered distinct measures, and the proxy was applied only for patient identification purposes in the current study.

Statistical analysis

Descriptive statistics were reported for the RRMS cohort and MS-free controls. Descriptive statistics, including means and standard deviations (SDs), were reported for continuous data, whereas relative frequencies and percentages were reported for categorical data. Based on distributional assumptions, *t*-tests, Chi-square tests (or the exact Chi-square test when a cell count was $<$5), or Wilcoxon rank-sum and signed-rank tests were also performed as appropriate. The statistical tests used for between-group comparisons are indicated in the corresponding tables and figure legends. HCCs were

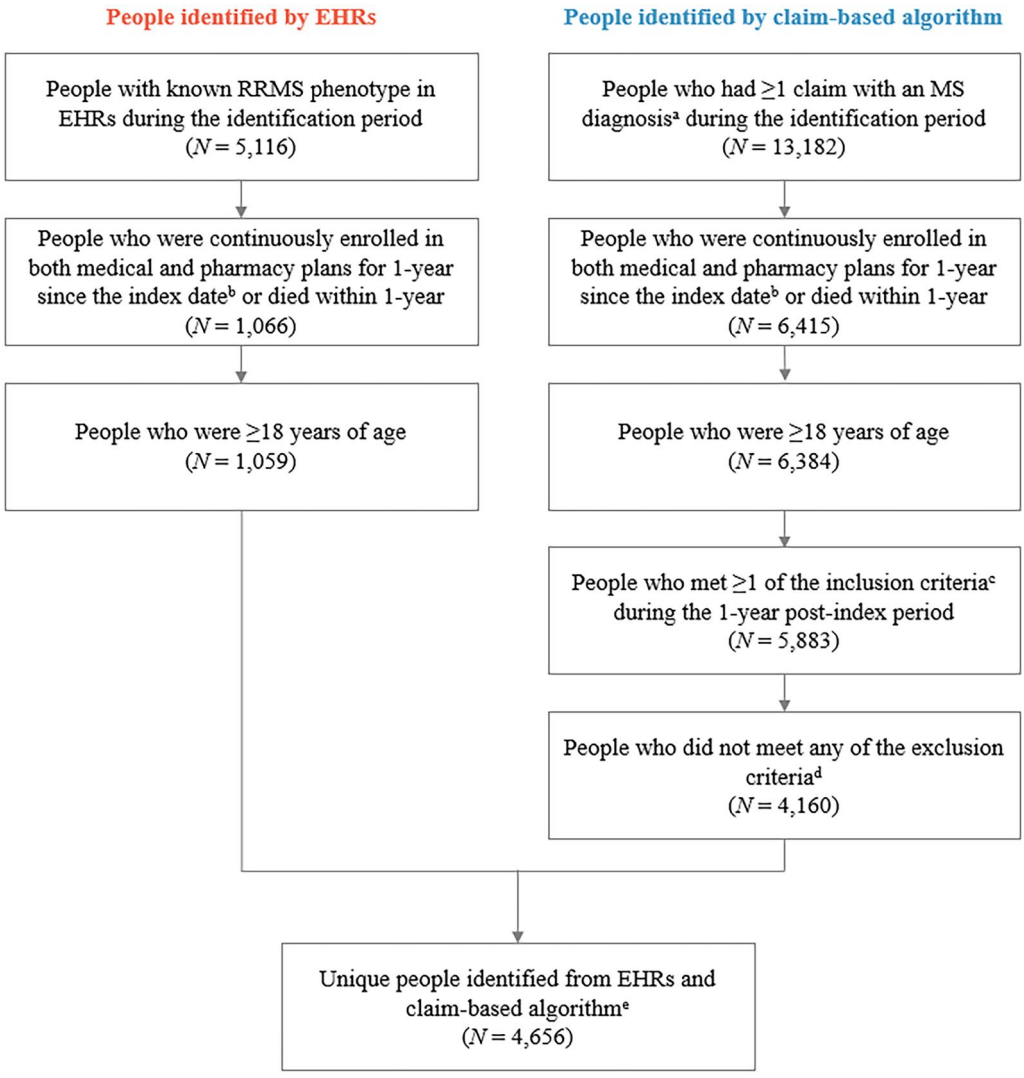

Figure 1. Attrition chart for the RRMS cohort. [a]ICD-9-CM code 340 and ICD-10-CM codes G35.xxx. [b]Index date: the date of a randomly picked MS claim during the identification period. [c]Inclusion criteria: ≥1 DMT medication claim; ≥1 brain or spinal MRI claim; ≥1 internuclear ophthalmoplegia claim ≥30 days apart from an MS diagnosis; ≥1 MS-related symptom therapy medication claim; ≥1 MS-related symptom claim ≥30 days apart from an MS diagnosis. [d]Exclusion criteria: use of medications commonly prescribed for a progressive disease (mitoxantrone, cyclophosphamide, or methotrexate) at any time during the study period; disease progression based on the worsening of EDSS scores within the 1-year follow-up period; evidence of exacerbations within the 1-year follow-up period. [e]EHR-based identification was used for people identified from both sources ($n = 563$). Abbreviations. DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; EHR, electronic health record; ICD-9-CM, International Classification of Disease, 9th Revision, Clinical Modification; ICD-10-CM, International Classification of Disease, 10th Revision, Clinical Modification; MRI, magnetic resonance imaging; MS, multiple sclerosis; *N*, total number of patients; RRMS, relapsing-remitting multiple sclerosis.

reported on the original dollar scale to facilitate interpretation of the economic impact of RRMS. Given the descriptive objectives of the study, cost variables were not log-transformed, and statistical comparisons were performed using methods selected based on the underlying data distribution. The costs were reported in US dollars and adjusted to the year 2021. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Data transformations and statistical analyses were performed using SAS© version 9.4.

Results

A total of 9,290 people were included in the final cohort (4,645 people with RRMS and 4,645 MS-free controls; Figure 1). Eleven people with RRMS were excluded from the final cohort, as MS-free controls could not be found for them.

Patient demographics

The mean ± SD age of people in the RRMS cohort was 52.9 ± 14.4 years, and the largest proportion of people

Table 1. Demographics of people in the RRMS cohort versus MS-free matched-controls.

Variable	RRMS cohort ($N = 4,645$)	MS-free matched-controls ($N = 4,645$)
Age (years), mean ± SD	52.9 ± 14.4	52.9 ± 14.4
18–34	495 (10.7)	495 (10.7)
35–54	2,007 (43.2)	2,007 (43.2)
55–64	1,120 (24.1)	1,120 (24.1)
65+	1,023 (22.0)	1,023 (22.0)
Gender		
Female	3,672 (79.1)	3,672 (79.1)
Male	972 (20.9)	971 (20.9)
Unknown	1 (0.0)	2 (0.0)
Race		
Caucasian	3,901 (84.0)	3,901 (84.0)
African American	426 (9.2)	426 (9.2)
Other/Unknown	318 (6.8)	318 (6.8)
Region		
Midwest	2,078 (44.7)	2,078 (44.7)
Northeast	946 (20.4)	946 (20.4)
South	727 (15.7)	727 (15.7)
West	691 (14.9)	691 (14.9)
Other/Unknown	203 (4.4)	203 (4.4)
Plan type		
Commercial	2,435 (52.4)	2,435 (52.4)
Medicaid	210 (4.5)	210 (4.5)
Medicare	1,654 (35.6)	1,654 (35.6)
Unknown	346 (7.4)	346 (7.4)
Year of index date		
2012	351 (7.6)	351 (7.6)
2013	305 (6.6)	305 (6.6)
2014	317 (6.8)	317 (6.8)
2015	464 (10.0)	464 (10.0)
2016	559 (12.0)	559 (12.0)
2017	586 (12.6)	586 (12.6)
2018	591 (12.7)	591 (12.7)
2019	695 (15.0)	695 (15.0)
2020	777 (16.7)	777 (16.7)

Note. Statistical comparisons were performed using Student's t-test for continuous variables and Chi-square tests for categorical variables. Data are presented as *n* (%) unless otherwise specified. Abbreviations. *N*, total number of patients; *n*, number of patients; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

were aged 35–54 years (43.2%). People in the RRMS cohort were primarily female (79.1%), Caucasian (84.0%), from the Midwest (44.7%), and covered by commercial insurance (52.4%; Table 1).

Clinical characteristics

During the 1-year follow-up period, the mean CCI score of people in the RRMS cohort was significantly higher than that of the MS-free controls (1.6 vs. 1.2; $p < 0.001$). A significantly higher proportion of people in the RRMS cohort reported infections and leukopenia than that of the MS-free controls ($p < 0.001$; Figure 2). DMT utilization was also evaluated in the RRMS cohort. Overall, 1,212 (26.1%) patients received a DMT at index and 1,720 (37.0%) received a DMT during follow-up. Among those who received a DMT during follow-up, the most frequently used therapies were glatiramer acetate (21.7%), dimethyl fumarate (17.7%), beta-interferon (13.2%), ocrelizumab (10.9%), teriflunomide (7.9%), natalizumab (7.3%), and fingolimod (7.0%).

Specific comorbidities of interest

The top five most frequent MS-related comorbidities in people with RRMS versus MS-free controls were malaise/fatigue (34.3% vs. 15.7%; $p < 0.001$), major depressive disorders (27.6% vs. 17.7%; $p < 0.001$), anxiety (21.4% vs. 15.1%; $p < 0.001$), burning/numbness, (19.4% vs. 5.8%; $p < 0.001$), and abnormal gait (16.1% vs. 5.2%; $p < 0.001$; Figure 3).

Other MS-related comorbidities that were significantly higher in people with RRMS than in the MS-free controls included abnormal involuntary movements (7.9% vs. 2.0%; $p < 0.001$), ataxia (4.1% vs. 1.2%; $p < 0.001$), cognitive impairment (3.0% vs. 0.7%; $p < 0.001$), diplopia (2.0% vs. 0.3%; $p < 0.001$), dizziness (12.9% vs. 6.7%; $p < 0.001$), fibromyalgia/myalgia (12.6% vs. 7.9%; $p < 0.001$), lack of coordination (3.2% vs. 0.9%; $p < 0.001$), muscle weakness (11.5% vs. 3.4%; $p < 0.001$), neuropathic pain (5.3% vs. 1.2%; $p < 0.001$), optic neuritis (5.3% vs. 0.04%; $p < 0.001$), paraplegia (2.4% vs. 0.2%; $p < 0.001$), peripheral neuropathy (10.1% vs. 5.4%; $p < 0.001$), spasticity (9.1% vs. 4.0%; $p < 0.001$), spasms (7.9% vs.

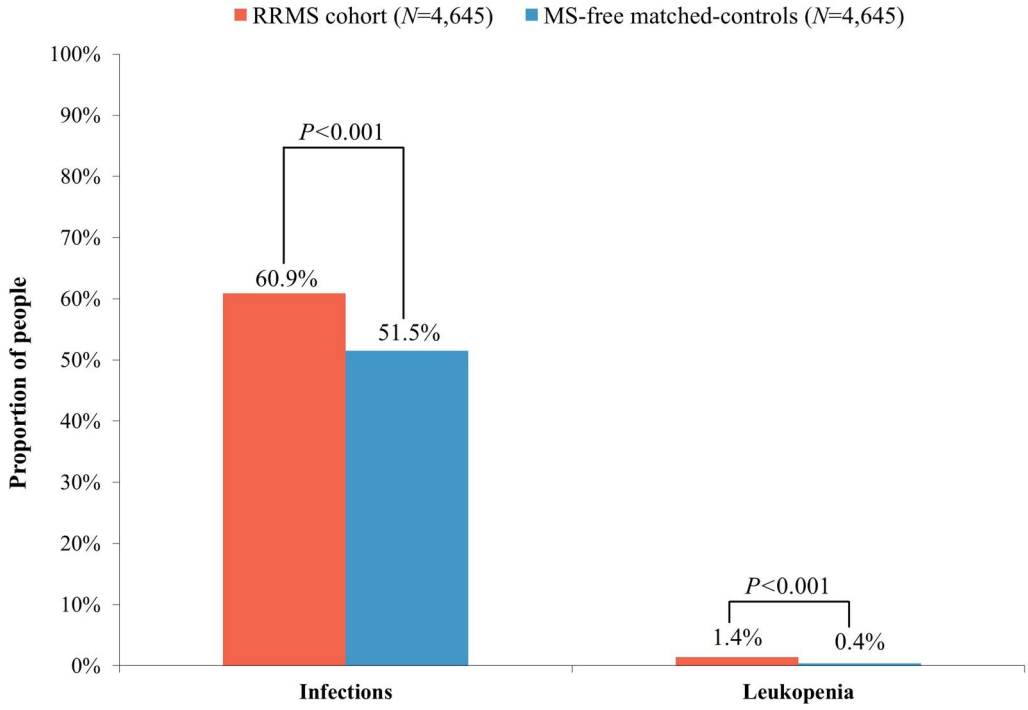

Figure 2. Proportion of people with infections and leukopenia in the RRMS cohort versus MS-free matched-controls. *Note.* Between-group comparisons for infections and leukopenia were performed using Chi-square tests. All comparisons were statistically significant ($p < 0.001$). Abbreviations. *N*, total number of patients; RRMS, relapsing-remitting multiple sclerosis.

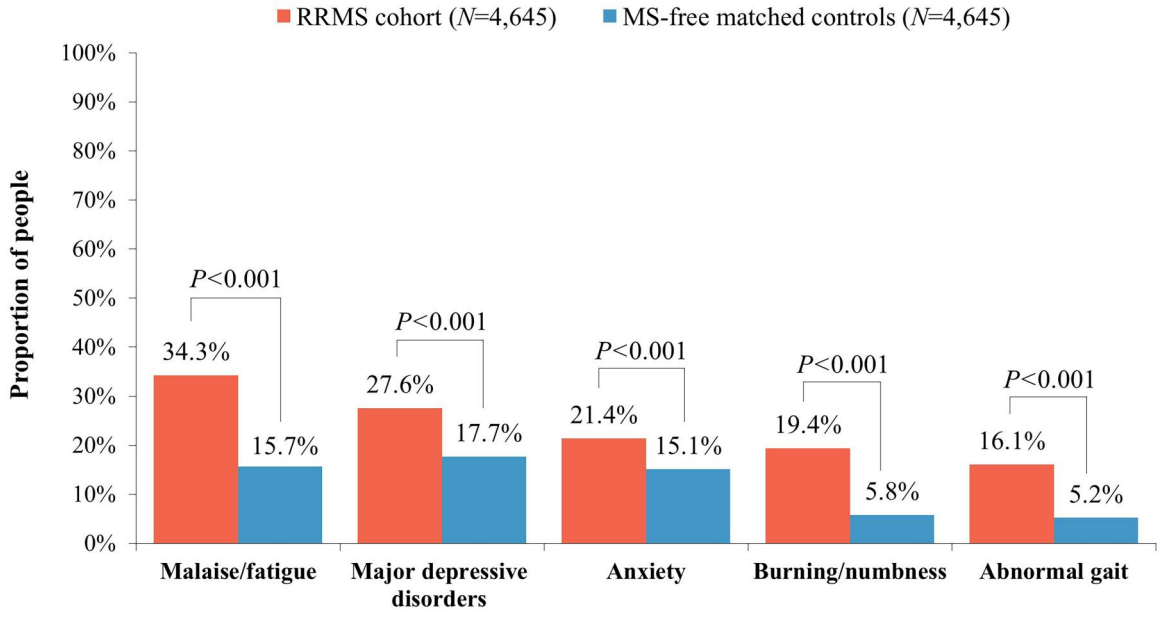

Figure 3. Most frequent MS-related comorbidities in the RRMS cohort versus MS-free matched-controls. *Note.* Between-group comparisons for MS-related comorbidities were performed using Chi-square tests. All comparisons were statistically significant ($p < 0.001$). Abbreviations. *N*, total number of patients; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

2.0%; $p < 0.001$), tremor (1.4% vs. 0.7%; $p = 0.003$), trigeminal neuralgia (2.3% vs. 0.3%; $p < 0.001$), urinary incontinence (8.3% vs. 3.7%; $p < 0.001$), and voice disturbances (4.1% vs. 2.1%; $p < 0.001$; Table 2). A significantly higher proportion of people in the RRMS cohort reported other comorbidities (71.9% vs. 60.1%; $p < 0.001$) and autoimmune comorbidities (23.1% vs. 18.1%; $p < 0.001$) than those of the MS-free controls. All other comorbidities are listed in Table 2.

Table 2. Other specific comorbidities of interest in the RRMS cohort versus MS-free matched-controls.

	RRMS cohort ($N = 4,645$)	MS-free matched-controls ($N = 4,645$)	p-Value
Any specific comorbidities of interest	4,235 (91.2)	3,402 (73.2)	<0.001
Multiple sclerosis comorbidity	3,629 (78.1)	2,225 (47.9)	<0.001
Abnormal involuntary movements	365 (7.9)	93 (2.0)	<0.001
Ataxia	191 (4.1)	55 (1.2)	<0.001
Cognitive impairment	138 (3.0)	34 (0.7)	<0.001
Diplopia	91 (2.0)	15 (0.3)	<0.001
Dizziness	598 (12.9)	313 (6.7)	<0.001
Erectile dysfunction and psychosexual dysfunction with inhibited sexual excitement	75 (1.6)	56 (1.2)	0.095
Fibromyalgia/myalgia and myositis	584 (12.6)	366 (7.9)	<0.001
Lack of coordination	150 (3.2)	44 (0.9)	<0.001
Muscle weakness	533 (11.5)	157 (3.4)	<0.001
Neuropathic pain	244 (5.3)	54 (1.2)	<0.001
Optic neuritis	244 (5.3)	2 (0.04)	<0.001
Paraplegia	110 (2.4)	8 (0.2)	<0.001
Peripheral neuropathy	467 (10.1)	250 (5.4)	<0.001
Spasms	365 (7.9)	93 (2.0)	<0.001
Spasticity	424 (9.1)	184 (4.0)	<0.001
Transient paralysis of limb	3 (0.1)	0 (0)	0.083
Tremor	63 (1.4)	34 (0.7)	0.003
Trigeminal neuralgia	108 (2.3)	16 (0.3)	<0.001
Urinary incontinence	384 (8.3)	172 (3.7)	<0.001
Voice disturbances	190 (4.1)	98 (2.1)	<0.001
Other comorbidity	3,340 (71.9)	2,790 (60.1)	<0.001
Alopecia	154 (3.3)	140 (3.0)	0.407
Alzheimer's disease	35 (0.8)	21 (0.5)	0.061
Arthritis (rheumatoid and osteoarthritis)	918 (19.8)	929 (20.0)	0.775
Atrial fibrillation and flutter	199 (4.3)	143 (3.1)	0.002
Autonomic dysreflexia	1 (0.02)	1 (0.02)	1.000
Bipolar disorder	167 (3.6)	156 (3.4)	0.533
Chronic kidney disease	347 (7.5)	281 (6.0)	0.006
Chronic liver disease	263 (5.7)	199 (4.3)	0.002
Complications of infusion and injection	48 (1.0)	21 (0.5)	0.001
Convulsions	201 (4.3)	67 (1.4)	<0.001
Diabetes	721 (15.5)	770 (16.6)	0.166
Drug-induced hepatitis	13 (0.3)	10 (0.2)	0.531
Epilepsy	226 (4.9)	87 (1.9)	<0.001
Headache	1,267 (27.3)	640 (13.8)	<0.001
High blood pressure	1,913 (41.2)	1,805 (38.9)	0.022
High cholesterol	442 (9.5)	464 (10.0)	0.442
Neutropenia	55 (1.2)	22 (0.5)	<0.001
Parkinson's disease	61 (1.3)	15 (0.3)	<0.001
Pressure ulcers	118 (2.5)	27 (0.6)	<0.001
Stroke	371 (8.0)	194 (4.2)	<0.001
Unspecified adverse drug effects	60 (1.3)	34 (0.7)	0.007
Unspecified neuralgia, neuritis, and radiculitis	244 (5.3)	54 (1.2)	<0.001
Autoimmune comorbidity	1073 (23.1)	841 (18.1)	<0.001
Anemia	311 (6.7)	233 (5.0)	<0.001
Nephropathy	54 (1.2)	60 (1.3)	0.572
Thrombocytopenia	87 (1.9)	58 (1.2)	0.015
Unspecified acquired hypothyroidism	750 (16.1)	588 (12.7)	<0.001
Encephalitis, myelitis, and encephalomyelitis	74 (1.6)	13 (0.3)	<0.001
Urinary tract infections	729 (15.7)	368 (7.9)	<0.001

Note. Statistical comparisons were performed using Chi-square or exact Chi-square tests, as appropriate. Data presented as *n* (%) unless otherwise specified. Abbreviations. *N*, total number of patients; *n*, number of patients; RRMS, relapsing-remitting multiple sclerosis.

Healthcare resource utilization and healthcare costs

During the 1-year follow-up period, the RRMS cohort had a significantly higher proportion of people with mortality, hospitalizations, and ED visits and a significantly higher mean number of physician visits than those reported for the MS-free controls (Figure 4; all $p < 0.001$). Specifically, 18.2% of people with RRMS experienced at least one hospitalization compared with 11.5% of MS-free controls, while 40.3% versus 28.1% had at least one ED visit, respectively. People with RRMS also had a higher mean number of physician visits (13.7 vs. 10.0) than MS-free controls.

The mean total HCCs were significantly higher for the RRMS cohort than for the MS-free controls ($54,244 vs. $19,671; $p < 0.001$; Figure 5A), primarily driven by higher medical claim costs ($31,154 vs. $15,944; $p < 0.001$; Figure 5B) and outpatient pharmacy claim costs ($23,090 vs. $3,727; $p < 0.001$; Figure 5A). Infection-related costs were also significantly higher among people with RRMS than MS-free controls ($4,801 vs. $2,514; $p < 0.001$; Figure 5C).

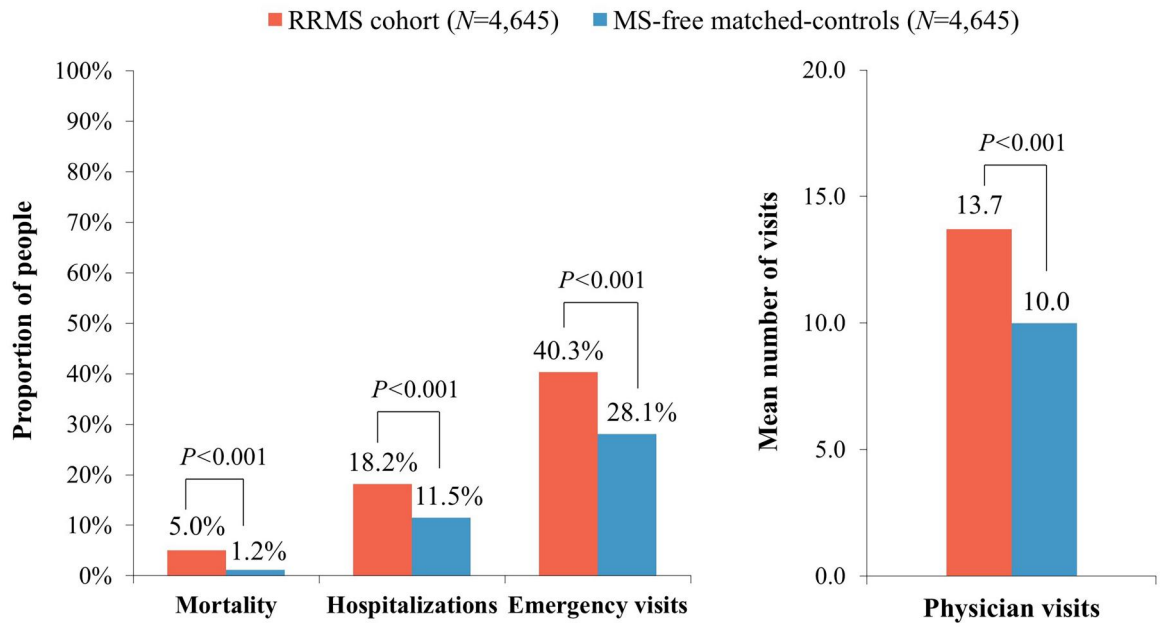

Figure 4. All-cause HCRU in the RRMS cohort versus MS-free matched-controls. *Note.* Between-group comparisons for mortality, hospitalizations, and emergency department visits were performed using Chi-square tests. Mean physician visits were compared using Student's t-test. All comparisons were statistically significant ($p < 0.001$). Abbreviations. *N*, total number of patients; HCRU, healthcare resource utilization; RRMS, relapsing-remitting multiple sclerosis.

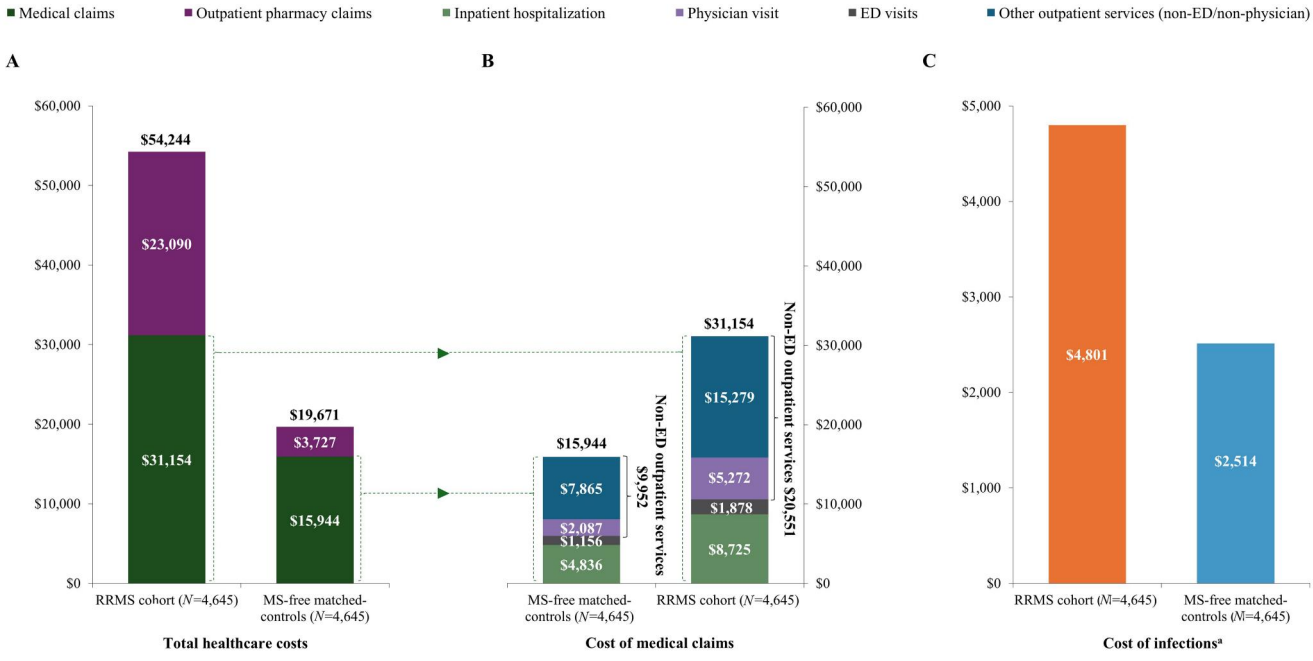

Figure 5. Total healthcare costs (A), cost of medical claims (B), and cost of infections (C) in the RRMS cohort versus MS-free matched-controls. The healthcare costs were significantly higher in the RRMS cohort than for the MS-free matched-controls (all $p < 0.001$). Medical claims included the costs of inpatient hospitalizations, ED visits, and non-ED outpatient services. [a]Cost of infections: the costs of medical claims for a diagnosis of infections in any field plus the costs of antibiotics or antivirals pharmacy claims, with days of supply <21, filled within 7 days of an infection medical claim. *Note.* Between-group comparisons for total healthcare costs, medical claim costs, and infection-related costs were performed using Student's t-test. All comparisons were statistically significant ($p < 0.001$). Abbreviations. *N*, total number of patients; ED, emergency department; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

These results highlight the importance of having a well-coordinated multidisciplinary follow-up in routine RRMS care.

Discussion

This matched-cohort analysis demonstrates consistent and clinically meaningful differences across comorbidity impact, HCRU, and HCCs between people with RRMS and MS-free controls. It further characterizes the demographic and clinical profile of this population and quantifies the associated healthcare impact in routine US clinical practice.

In this study, the CCI score was significantly higher in the RRMS cohort versus the MS-free controls, indicating a higher disease impact on this population. Infections and leukopenia were observed in a higher proportion of people with RRMS versus MS-free controls. Among infection-related conditions evaluated, urinary tract infections were observed approximately twice as frequently in people with RRMS as in matched controls (15.7% vs. 7.9%; $p < 0.001$), highlighting the increased susceptibility to infection in this population. A higher proportion of people in the RRMS cohort reported MS-related comorbidities, other comorbidities, and autoimmune-related comorbidities versus MS-free controls, indicating a substantial clinical impact in people with RRMS. In this study, the most frequent MS-related comorbidities in people with RRMS versus MS-free controls were malaise/fatigue, major depressive disorders, anxiety, burning/numbness, and abnormal gait. Fatigue is one of the most common debilitating symptoms in people with RRMS and interferes with patients' daily activities and negatively impacts their quality of life (QoL)[16]. A prospective cohort study conducted among 230 people with RRMS reported anxiety and depression as the most prevalent comorbidities[17]. The US National Health and Wellness Survey conducted among people with RRMS identified fatigue, difficulty balancing or walking, and numbness as the most frequently reported symptoms; all symptoms were experienced by more than half of the respondents[18]. MS involves impairment in a wide range of neurologic functions, including muscle strength and tone, coordination, cognition, vision, and sensation, which can lead to abnormal gait and reduced mobility[19].

The higher prevalence of fatigue, depression, anxiety, pain-related symptoms, and gait impairment observed in the RRMS cohort may be particularly important because these manifestations are known to contribute substantially to reduced QoL, impaired daily functioning, and increased healthcare needs. Together, these findings suggest that the overall impact of RRMS extends beyond traditional measures of relapse activity and disability progression and may be influenced by a broad spectrum of clinical comorbidities.

These observations also have important clinical implications. The higher rates of infections, fatigue, depression, anxiety, and gait impairment in people with RRMS highlight the need for regular symptom screening in routine visits. Thus, providing timely access to supportive services, including PT, OT, ST, and DME, can help address functional limitations, support day-to-day management and support overall patient outcomes.

Our study depicted the economic impact on people with RRMS in the US. During 1-year follow-up period, the RRMS cohort had a significantly higher proportion of people with mortality, hospitalizations, ED visits, and a higher mean number of physician visits versus MS-free controls, indicating substantially greater healthcare resource requirements in routine clinical practice. These findings suggest that the impact of RRMS extends beyond disease-specific management and may require coordinated multidisciplinary care. Total HCCs were also significantly higher in the RRMS cohort, driven primarily by medical claims and outpatient pharmacy costs. Previously, a retrospective cross-sectional survey of employed adults with RRMS in the US reported decreased work productivity and health-related quality of life (HRQoL) along with increased HCRU versus people without MS[7]. Another retrospective, cross-sectional, observational study utilizing pooled data from the US National Health and Wellness Survey (2017 and 2019) reported a higher economic impact on people with RRMS, and this impact was associated with higher fatigue[20]. Furthermore, the post-2021 real-world studies continue to demonstrate that fatigue and functional limitations remain the key drivers of economic impact in RRMS, reinforcing the persistence of these impacts despite ongoing therapeutic advances[21]. Together, these findings are broadly consistent with previous RWE demonstrating substantial clinical and economic impacts associated with RRMS. To provide additional context, selected findings from prior studies are compared with those of the current analysis in Table 3. Overall, the current study extends previous evidence by using a large integrated EHR–claims database and matched-control design, enabling simultaneous assessment of comorbidities, HCRU, and HCCs in a geographically diverse US RRMS population.

Table 3. Comparison of selected findings from the current study with previous real-world studies of RRMS.

Study	Data source/population	Study design	Key findings	Comparison with current study
Nicholas et al., 2019 [7]	Employed US adults with RRMS	Cross-sectional survey	Higher work impairment and HCRU	Current study confirms increased HCRU in a broader population
Le et al., 2022 [20]	US NHWS RRMS population	Cross-sectional analysis	Fatigue associated with greater economic impact	Current study identified fatigue as the most common comorbidity
Wasem et al., 2024 [21]	MS population	Economic/QoL analysis	Disability progression associated with costs and reduced QoL	Current study similarly found substantial comorbidity and resource impacts
Current study	RRMS vs. matched-controls	Matched cohort EHR–claims analysis	Higher comorbidity burden, HCRU, infections, and costs	Broader real-world assessment with matched comparators

Abbreviations. EHR, electronic health record; HCRU, healthcare resource utilization; MS, multiple sclerosis; NHWS, National Health and Wellness Survey; QoL, quality of life; RRMS, relapsing-remitting multiple sclerosis; US, United States.

Higher inpatient costs in our analysis likely reflect acute complications commonly encountered in RRMS, such as severe infections, relapses, or other events requiring hospitalization. Higher outpatient pharmacy costs, on the other hand, are consistent with the increasing use of high-efficacy DMTs, which offer clinical benefits but carry substantial acquisition costs. Recent post-2021 literature describes a shift in RRMS care toward earlier initiation and sustained use of high-efficacy DMTs along with the evolving treatment-sequencing strategies, with clear implications for both clinical outcomes and pharmacy-driven HCCs[22–24]. Thus, accounting for these cost components separately will help to elucidate the events/steps where healthcare resource demands are the most concentrated in routine RRMS care and how different clinical events contribute to overall healthcare utilization. These findings are particularly relevant for outpatient medical services and pharmacy settings, where the demand is the highest. Improved understanding of these cost drivers can support more informed planning of care pathways, staffing, and budgeting, helping healthcare systems better align services with the real-world needs of people living with RRMS.

These patterns should also be viewed in the context of an evolving treatment landscape. With increased availability of high-efficacy DMTs in recent years, clinical practice and healthcare use are continuously changing. Treatment patterns observed in this study should be interpreted in the context of the 2012–2021 study period, during which the availability and use of higher-efficacy DMTs evolved substantially. Although this study was not designed to evaluate treatment effects, keeping these shifts in mind can help interpret the current utilization patterns and anticipate future care needs. DMTs have been shown to improve clinical outcomes in RRMS; however, the current study was not designed to evaluate treatment effectiveness or compare outcomes according to specific therapies. Therefore, the observed differences in clinical and economic outcomes should not be interpreted as evidence regarding the effect of DMT treatment.

Although therapeutic practice has continued to evolve in recent years, many contributors to clinical and economic impact, such as infection risk, functional limitations, depression, anxiety, and relapse-related care, tend to change gradually over time. These patterns help support the relevance of the findings despite the dataset ending in 2021.

Compared with previous US studies that relied primarily on self-reported survey data or employed populations, this analysis uses a large, clinically rich EHR-claims dataset and a matched-cohort design, enabling more granular characterization of comorbidities and healthcare use across a broader RRMS population. This approach improves generalizability and enhances the understanding of real-world clinical presentation and cost drivers.

Nevertheless, it is important to consider the limitations of this study when interpreting these results. The identification and follow-up periods reflect the most recent data cut available from the licensed real-world EHR-claims data source at the time the analysis was conducted. Obtaining an updated extract would have required a full dataset refresh involving relicensing, data governance review, and vendor processing, which was not feasible within the scope and timelines of this project. While the data do not capture the most recent calendar years, this trade-off enabled a clinically rich, longitudinally stable EHR-claims cohort with detailed characterization of comorbidities, healthcare utilization, and costs across a large, representative RRMS population.

Possible miscoding is a limitation of claims data research, which could have impacted patient

identification and the reported rates of comorbidities. Exclusion of individuals with recent exacerbations may limit the generalizability of the findings to all people with RRMS, particularly those experiencing active relapse-related disease. This study was designed to characterize the clinical and economic profile of a relatively stable RRMS population rather than outcomes associated with acute relapse events. Future studies should evaluate clinical and economic outcomes among individuals with and without recent exacerbations. Disease progression was identified using a claims-based EDSS proxy rather than clinician-assessed EDSS scores. As with other claims-based disability measures, this approach may not fully capture disability status or short-term changes in disability and should be interpreted accordingly[11,25]. Infection outcomes were evaluated as a composite measure and were not stratified by severity; therefore, differences between serious and non-serious infections could not be assessed.

Although we used 1:1 matching, residual confounding is still possible. Given the large sample size, some statistically significant differences may reflect small absolute differences between groups. Therefore, the findings should be interpreted in the context of both statistical significance and their potential clinical relevance. Moreover, the study results may not be fully generalizable to uninsured populations or care settings outside integrated EHR-claims systems. Another limitation of this study is the relatively short follow-up duration of 1-year. A 1-year observation period was selected to balance several important considerations, including maintaining an adequate sample size under continuous enrollment requirements, providing a standardized observation window across all participants, and capturing meaningful clinical and economic outcomes while minimizing loss of follow-up. However, longer follow-up periods may provide additional insight into the long-term clinical and economic impact of RRMS and better characterize the evolution of disease burden over time. Therefore, longer-term studies are warranted to further evaluate these outcomes in real-world clinical practice.

Conclusions

During the 1-year follow-up period, people with RRMS experienced a greater clinical and economic impact, including a higher prevalence of comorbidities and significantly increased HCRU and HCCs, than matched MS-free controls. These findings highlight the persistent challenges in everyday RRMS management and support routine symptom surveillance, proactive infection-risk mitigation, and timely rehabilitation/assistive supports (e.g. PT/OT/ST/DME) as a part of coordinated multidisciplinary care. Future studies should examine the drivers of these patterns over longer follow-up periods and across diverse care settings. Studies of incident RRMS populations and temporal trends in outcomes may provide additional insights into the evolving impact of the disease.

Transparency

Declaration of funding

This study was sponsored by Sanofi.

Declaration of financial/other relationships

Nupur Greene, Ines Hemim, and Keiko Higuchi are employees of Sanofi and may hold stocks or stock options in the company. Ashis K. Das, Eunice Chang, and Marian H. Tarbox were employees of PHAR (now a part of ADVI Health) at the time of this study. PHAR was paid by Sanofi to conduct the research described in this manuscript. PHAR also discloses financial relationships with the following commercial entities outside of the submitted work: Akcea, Amgen, Celgene, Delfi Diagnostics, Dompe, Exact Sciences Corporation, Genentech, Gilead, GRAIL, Greenwich Biosciences, Ionis, Nobelpharma, Novartis, Pardes, Prothena, Pfizer, Recordati, Regeneron, Sanofi US Services, and Sunovion. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Authors contributions

Nupur Greene: Conceptualization; Supervision; Data curation; Validation; Writing – review and editing; Ashis K. Das: Methodology; Investigation; Writing – review and editing, Supervision; Ines Hemim: Conceptualization; Project administration; Resources; Supervision; Writing – review and editing; Eunice Chang: Conceptualization, Methodology, Formal analysis, Data curation, Visualization; Marian H. Tarbox: Writing – review and editing, Visualization, Project administration; Keiko Higuchi: Funding acquisition; Supervision; Writing – review and editing.

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Ethics statement

This study used de identified data from a licensed US electronic health record–claims database. In accordance with applicable US regulations for research involving de-identified data, institutional review board approval and informed consent were not required.

Data availability statement

The data that support the findings of this study were obtained from the Optum Market Clarity database under license for the current study and are not publicly available. Access to these data may be obtained directly from Optum, subject to applicable licensing agreements, data use restrictions, and approval requirements.

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