Patient characteristics in observational studies of the relative risk of infection in people using diseases-modifying treatments for multiple sclerosis: a literature review.

Writing Assignment

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Layman summary

Multiple sclerosis (MS) is a chronic medical condition that affects the brain and spinal cord. It occurs when the protective covering of nerve fibres, called "myelin," gets damaged. Disease-modifying treatments (DMTs) are considered promising treatments for this condition, with strong evidence supporting their benefits in MS. However, most of the information we have about MS and these drugs comes from controlled studies called clinical trials, where volunteers are assigned to a treatment and or no treatment. We don't have much information about the patient characteristics in the real-world settings, where people have different characteristics and experiences. To address this gap, we conducted a literature review to describe the patient characteristics reported in real-world studies of individuals using DMTs for MS. We searched biomedical databases like "PubMed" and "Embase" for studies published in English language that focused on MS patients using DMTs and experiencing infections as a primary outcome. Studies published until 05 Apr 2023 were included based on our search criteria. From this search, we removed irrelevant publications and duplications. Finally, in our analysis we ended up with 30 studies. Our findings revealed that the average age of patients with MS using DMTs in these real-world studies ranged from 24.5 to 54.4 years with the majority being women. The MS duration was between 2 to 17.7 years. There are mainly four different types of MS and the most common type of MS observed in these studies was relapsing-remitting MS (RRMS). RRMS is defined by a certain duration with symptom worsening, known as relapses phase, followed by periods of recovery, known as remission. Important patient characteristics like ethnicity and socio-economic status were frequently not reported in these studies. These findings highlight the need for further research to better understand the patient characteristics of the MS population receiving DMT treatment with risk of infection in real-world settings. It is crucial to look at demographics like age, sex, race, and social factors such as education, job, and

income. Through a more rigorous examination of these factors, we can gain a deeper understanding of their impact on the risk of infection, the selection of treatment options, and the progression of the disease. This will also help healthcare professionals to provide better and personalised care to people who are using DMTs for MS.

Abstract

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease. Infection is one of the commonly reported outcomes in patients who are under disease-modifying treatments (DMTs). The Influence of patient characteristics on risk of infection was well documented in clinical trials. However, the understanding of patient characteristics and their impact on treatment outcomes in real-world settings, particularly in observational studies, remains limited.

Objective

To examine patient characteristics like demographics, geographical factors, and socioeconomic factors in observational studies investigating the relative risk of infection among individuals on DMTs for MS.

Methods

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. We included observational studies that examined the impact of DMTs use on the occurrence of infection in the MS population. A search was performed in PubMed and Embase and key patient characteristics were extracted from the included studies.

Results

A total of 30 studies were included in the final analysis. The sample size ranged from 56 to 15,375 participants. The mean age of the study participants ranged from 24.5 to 54.4 years. The proportion of women ranged from 60% to 100%. The geographic representation of the included studies are Americas, Europe, the Middle East, and Oceania. The disease duration ranged from 2 to 17.7 years. Ethnicity, Expanded Disability Status Score (EDSS), Socio-Economic Status (SES), and treatment history were missing in many studies.

Conclusion

Within this sub-group, our findings indicate that people who are under DMTs for MS consists of younger adults and a higher proportion of women. The reporting of patient characteristics such as ethnicity, SES, EDSS score, and previous use of DMTs were inconsistently reported in the observational studies. This highlights the need for a standardised reporting structure to gain a better understanding of the specific patient characteristics that are associated with infectious risk.

Key words: Multiple sclerosis, Diseases modifying treatments, Real world studies, Infections, Patient characteristics

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease characterised by inflammation and damage to the central nervous system, specifically the myelin sheath and nerves [1]. The aetiology of MS remains unknown [2]. As of 2020, the global prevalence rate was reported to be 35.9 per 100,000 individuals [3]. The prevalence rate in Europe was estimated at 83 per 100,000 individuals for the past three decades [4]. MS primarily

affects individuals between the ages of 20 and 40 and is recognised as a leading cause of nontraumatic disability in adults [3], [5]. The most common type of MS is relapsing-remitting MS (RRMS) [5]. While there is currently no cure for MS, pharmacological interventions, particularly disease-modifying treatments (DMTs), are considered the gold standard for the management of MS [6].

DMTs play a pivotal role in the management of MS and other autoimmune diseases. The European Medicines Agency (EMA) has approved sixteen DMTs specifically for RRMS [7]. When making treatment decisions for MS, factors such as prognostication, response to treatment initiation, and patient preferences are taken into consideration, along with careful evaluation of the risk-benefit ratio [8]. Recent findings indicate that individuals with MS have a higher risk of serious infections compared to the general population [9], particularly in those with progressive disease and higher disability score [10].

The use of DMTs in MS has been extensively studied in both clinical trials and real-world studies. However, the available data on patient characteristics and the risk of infection associated with DMT are limited. Previous studies have generated data based on various sources, including clinical trials [1], [11], or a combination of clinical trials and real-world evidence studies (RWS) [12], but there is a lack of specific focus on observational studies. Consequently, there is a significant knowledge gap regarding the patient characteristics associated with the risk of infection in individuals using these treatments. While previous studies have examined the overall risk of infection in MS patients [13], [14], there is a limited understanding of how specific patient characteristics such as demographics, geographical, and socioeconomic factors contribute to infection risk in the context of DMT use in MS patients. Addressing this research gap is crucial for optimising treatment decisions, improving patient care, and minimising potential adverse outcomes.

Hence, the objective of this literature review was to examine patient characteristics like demographics, geographical factors, and socioeconomic factors in observational studies investigating the relative risk of infection among individuals on DMTs for MS.

Research question

What are the patient characteristics in observational studies of the relative risk of infection in people using disease-modifying treatments for multiple sclerosis?

Methods

Search strategy

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to perform this literature review. Two electronic databases, PubMed and Embase, were systematically searched on 5 April 2023. Our search strategy included the key terms for the population, intervention, and outcome of interest: People with MS, All EMA-approved disease-modifying therapies for the treatment of MS, and infections. For the full search strategy, please refer Appendix 1. Additionally, we restricted our search to include only research published in the English language.

Selection process

A systematic filtering process was implemented, starting with the selection of studies published abstract and full text. The initial screening involved evaluating titles and abstracts, followed by reading the full text. Duplicate search results were eliminated using the Rayyan ai tool [15]. Then, one reviewer applied manually screened all titles and abstracts of the search results from PubMed using these inclusion criteria: observational study reporting the occurrence of infection as an adverse event of DMT use for MS, with at least one comparison between different DMTs or DMT and no DMT, study population

aged 18 years or over, and published on or before 5 April 2023. The same inclusion criteria as above stated were used for Embase. By labelling the data based on PubMed criteria, papers were screened in ASReview [16]. Studies that examined COVID-19 infection as the only infection outcome were excluded. In the screening process, if the main text referenced the reporting of infections in an appendix, we included the appendix in the full data extraction process. Additionally, two independent reviewers screened a random sample of 200 papers in the Rayyan ai tool.

Data collection and extraction

Data extraction was carried out by a single reviewer. Variables extracted from the final set of papers include data source, sample size, age, sex, ethnicity, location, socio-economic status (SES), MS type, disease duration, Expanded Disability Status Score (EDSS), and treatment history of DMTs.

Results

Search results

Among the 5,373 papers identified from PubMed and Embase, a screening process was conducted, resulting in the selection of 3,892 for further scrutiny. Eventually, a final set of 30 studies was included in the final analysis (Fig. 1). These studies were published between year 2008 and 2022 and encompassed various study designs such as prospective cohort studies, retrospective cohort studies, observational studies, nested case-control studies, and nested cohort studies. Many studies (47%, n=14) reported data obtained from patient medical records, indicating a significant proportion. Additionally, some studies utilised MS registries 23% (n= 7), while others relied on data from insurance and claim databases 17% (n= 5). Approximately 40% of the included

studies (N = 30) reported using claims databases or electronic medical records as primary data sources.

Patient Characteristics

The sample sizes in the studies ranged from 56 to 15,375 participants. The mean age of the study participants ranged from 24.5 to 54.4 years. Much of the study population consisted of women, with percentages ranging from 60% to 100%, except for one study that specifically focused on male populations. The included studies were conducted in various geographic regions, representing the Americas, Europe, the Middle East, and Oceania (Fig.2).

The duration of MS was reported in 80% (n = 24) of included studies and ranged from 2 to 17.7 years. Regarding the reporting of MS types, there was variability among the included studies. 27% (n = 8) of the included studies did not provide information on the specific MS types examined. Among the studies that did report MS types, some included all four types of MS (RRMS, SPMS, PPMS, PRMS), while others focused on three types. However, the most frequently reported MS type across the studies was relapsing-remitting multiple sclerosis (RRMS) reported in 70% (n =21) of studies. The severity of MS was evaluated using the EDSS score, with a median score ranging from 1.5 to 6 points. The treatment history revealed a wide range of DMT usage across the studies, with the percentage of study participants having a history of DMT usage varying from 17% to 99%. We observed a positive trend between age and EDSS score, indicating that as age increases, the EDSS score tends to rise. The patient characteristics of included studies were reported in Table 1.

Unreported

In this literature review, we found significant gaps in the reporting of patient characteristics relevant to the risk of infection in MS patients receiving DMTs. Notably, SES was unreported in 80% (n=24) of the studies, and ethnicity was absent in 77%

(n=23) of the studies. Treatment history with DMTs and MS duration were also frequently unreported, with 43% (n=13) and 23% (n=7) of the studies lacking this information, respectively. The reporting of the Expanded Disability Status Scale (EDSS) score, a crucial measure of disability, was absent in 43% (n=13) of the studies. Additionally, one study did not report age (Fig.3).
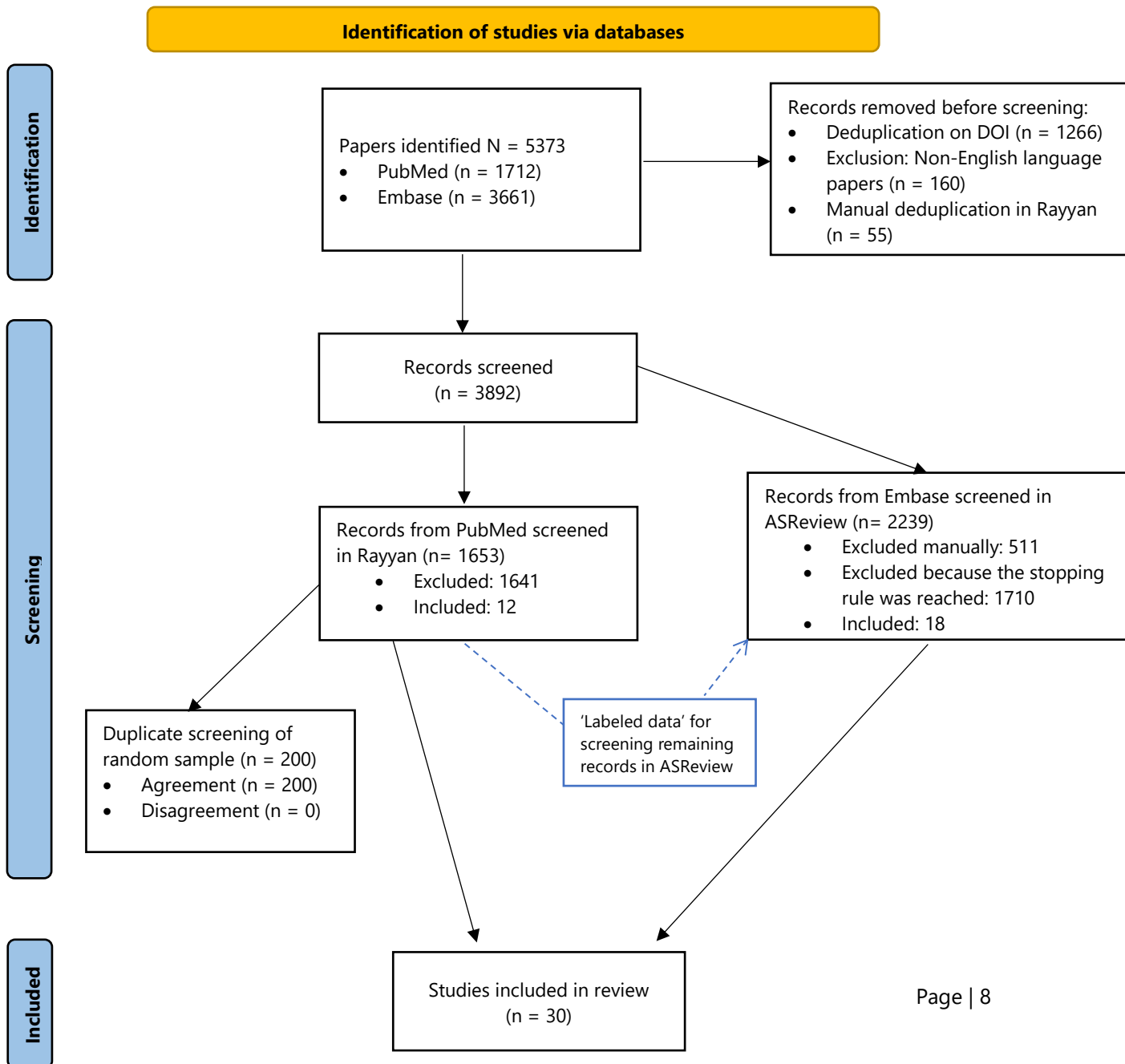
Figure 1: Flow chart for selection of studies.

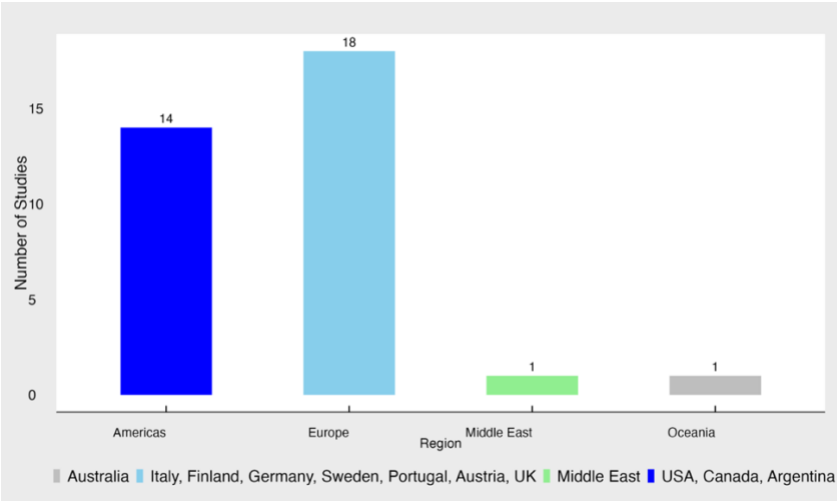## Figure 2: Distribution of included studies by geographic region.

Figure 3: Summary of not reported data for patient characteristics in the included studies.
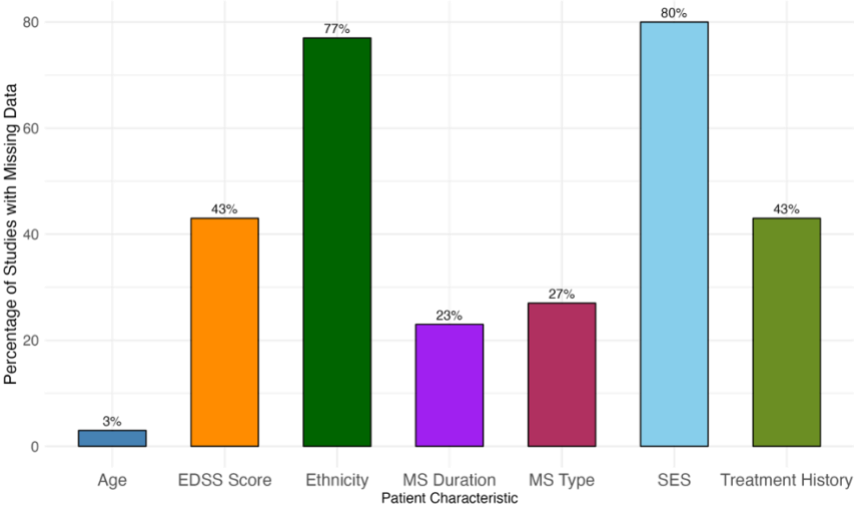
Table 1: Patient Characteristics of selected studies

Reference	Data source	Sample size, N	Age in years Mean (SD)	Women (%)	Ethnicity	Country	SES	MS duration (years) Mean (SD)	Type of MS	Severity of MS EDSS score Median [IQR]	Prior treatment with DMT N (%)
Wijnands et al 2018 [17]	Population-based health administrative data; Insurance data	6,793	45.4 (13.3)	4,999 (73.6)	NR	Canada	Yes	8.5 (4.6-12.7) [a]	NR	NR	1,716 (25.3)
MacDonald et al 2019 [18]	Truven Health Marketscan® Commercial Claims and Encounters Database	984,058*	NR	984,058 (100)	NR	USA	NR	NR	NR	NR	1,649 (17)
Simbrich et al 2019 [19]	German Pharmacoepidemiological Research Database	15,377	39.6 (10.5)	10,518 (68.4)	NR	Germany	NR	NR	NR	NR	8,903 (51.9)
Luna et al 2019 [20]	Swedish MS register	6,421	30 (10.7)	6,186 (71.9)	Yes	Sweden	Yes	NR	RRMS	NR	NR
Zappulo et al 2019 [21]	Paper charts and electronic medical records @ Centre of Neurodegenerative Diseases	163	44.5 (11.4)	100 (61)	NR	Italy	NR	9.8 (4.4-15.8) [a]	RRMS, SPMS, PPMS, NMO	5.5 (4-6.5)	146 (89.6)
Pirttisalo et al 2020 [22]	Hospital registries, patient charts and the Finnish MS register	898	47.3 (14.1)	642 (71.5)	NR	Finland	NR	NR	RRMS, SPMS, PPMS, UNS	NR	NR
Alping et al 2021 [23]	Swedish MS register + National health care register	11,113	39 (10.6)	7,691 (69)	Yes	Sweden	Yes	7.6 (3.7)	RRMS, PPMS SPMS	2.3 (1.7) [c]	NR

Study	Source	N	Age	Female n (%)		Country		Disease duration	MS type	EDSS	
Zanghì et al 2021 [24]	Tertiary Italian MS centres	120	24.5 (9.7)	81 (67.5)	NR	Italy	NR	NR	RRMS	2.5 (1.0-4.5)	NR
Epstein et al 2021 [25]	Chart review	56	64 (56-77) [a]	40 (71)	Yes	USA	NR	17.7 (10.8-25.3) [a]	PPMS, SPMS	6.0 (4.9-6.5)	30 (54)
Ferro et al 2021 [26]	MS clinic and IIROC	149	37 (29-46) [a]	107 (72)	NR	Portugal	NR	8 (4-12) [a]	NR	NR	NR
Nicholas et al 2022 [27]	Optum US claims database	4,599	50 (12.5)	3,275 (71)	NR	USA	NR	NR	NR	NR	NR
Achiron et al 2017 [28]	Routine medical care	247	36.5 (11.5)	159 (64.4)	Yes	Middle East	NR	6.5 (6.4) 4.2 (0.0–32.0) [a]	RRMS	NR	177 (71.6)
M. Baharnoori et al 2018 [29]	CLIMB Study	705	43.3 (10.8)	516 (73.1)	NR	USA	NR	11.7 (7.3)	RRMS	2.0 (1.7) [c]	480 (68.3)
Boffa et al 2020 [30]	Medical records from MS center of the University of Genoa	212	41 (10.6)	135 (63.6)	NR	Italy	NR	12.1 (8.6)	RRMS	FTY group 2.5 (0-8) DMF group 1.5 (0-8)	NR
Boremalm et al 2019 [31]	Swedish MS register + medical records	241	NTZ group 34.9 (28.9-42.0) [a] RTX group 39.1 (31.7-46.7) [a] FGL group 37.1 (30.9-44.7)[a]	172 (71.3)	NR	Sweden	NR	NTZ group 5.6 (2.1-10.6) [a] RTX group 6.7 (3.6-13.0) [a] FGL group 6.6 (2.9-13.5) [a]	RRMS	NTZ group 2.5 (1.5-3.1) RTX group 2.0 (1.0-3.0) FGL group 2.0 (1.0-3.0)	NTZ group 1.4 (0.8-5.0) [a] RTX group 2.4 (1.0-4.9) [a] FGL group 2.9 (1.3-6.1) [a]
Bose et al 2021 [32]	MS clinic	111	Alemtuzumab	84 (75.6)	NR	Canada	NR	Alemtuzumab 5.3 (2.5-10.0) [a]	RRMS	Alemtuzumab 3.0 (2.0-4.0)	Alemtuzumab

			36.1 (31-42) [a] Cladribine 43.8 (37-50) [a]					Cladribine 10.6 (4.4-17.1) [a]		Cladribine 4.0 (2.5-6.0)	1.5 (1-2.75) [a] Cladribine 1 (1-2) [a]
D'Amico et al 2018 [33]	Medical records	903	41.2 (10.7)	615 (68.1)	NR	Italy	NR	8.8 (7.0)	RRMS	DMF group 1.5 (1-3) TRF group 2.0 (1.5-3.5)	894 (99)
De Jong et al 2017 [34]	MS registry	2485	41.3 (10.0)	1,936 (77.9)	NR	Canada	Yes	9.5 (8.7) 7.0 (2.3–14.5) [a]	RRMS	2.0 (1.5-3.0)	NR
Frisell et al 2015 [35]	Drug monitoring registry (IMSE)	1516	37.1 (10)	1084 (71.5)	Yes	Sweden	Yes	8.6 (6.6)	RRMS SPMS PPMS PRMS	2.4 (1.7) [c]	2.1 (1.6) [c]
Gajofatto et al 2014 [36]	Clinical and MRI	87	38.4 (8.8)	64 (73.6)	NR	Italy	NR	9.4 (0.5–35.1) [b]	RRMS	2.5 (0-8)	81 (93)
Harding et al 2019 [37]	Clinical records	592	30.1 (10.1)	425 (71.7)	NR	UK	NR	NR	NR	Early Intensive group 3.5 (2.0-5.0) Escalation group 3.5 (2.0-5.0)	NR
Minagar and Murray et al 2008 [38]	Chart review	136	37.5 (8.5)	110 (80.8)	NR	Austria, Australia, Canada, USA	NR	IM IFNβ-1a group 3.7 (0–150) [b] SC IFNβ-1a group 4.9 (0–109) [b]	RRMS	1.9 (1.4) [c]	NR

Study	Data source	N	Age mean (SD)	Female n (%)		Country		Disease duration	MS type	EDSS	n (%)
Montanari et al 2016 [39]	Medical records + CRF	250	36.41 (9.43)	186 (74.4)	NR	Italy	NR	2.6 NR	NR	1.50 (0.00–5.50)	NR
Moreira Ferreira et al 2021 [40]	PartnersOracle Database	88	54.4 (9.6)	58 (65.9)	NR	USA	NR	12 (8.4)	SPMS PPMS PRMS	6[c] NR	75 (85.2)
Pecori et al 2014 [41]	Italian Pregnancy Database	78	34.8 (4.8)	0 (0.0)	NR	Italy	Yes	8.4 (5.9)	NR	NR	45 (57.7)
Prosperini et al 2020 [42]	MS clinics	813	32.5 (8.4)	577 (71)	NR	Italy	NR	2 (1.4)	RRMS	Escalated group 1.5 (0-4.0) Induction group 2.5 (1.0-4.0)	NR
Rojas et al 2022 [43]	CRF	431	38.6 (9.9) (18-55) range	259 (60)	NR	Argentina	NR	7.4 (2.4) (5–10) range	RRMS	2.5 (1.6) [c] (0–8) range	NR
Vollmer et al 2017 [44]	Clinician-reported data	613	44.3 (11.8)	433 (70.6)	Yes	USA	NR	11.2 (7.4)	All forms of MS	NR	463 (75.5)
Vollmer et al 2019 [45]	Electronic medical record	1064	42.4 (11.9)	779 (73.2)	NR	USA	NR	11.3 (7.5)	RRMS SPMS PPMS	NR	744 (70)
Vollmer et al 2019 [46]	Medical records	1272	45 (11.1)	898 (70.5)	Yes	USA	NR	13.3 (9)	RRMS SPMS PPMS	NR	831 (65.3)

NR: Not Reported, SD: Standard Deviation, IQR: Interquartile Range, SES: Socio-economic Status, MS: Multiple sclerosis, EDSS: Expanded Disability Status Score, RRMS: Relapsing-Remitting Multiple Sclerosis, SPMS: Secondary Progressive Multiple Sclerosis, PPMS: Primary Progressive Multiple Sclerosis, PRMS: Progressive-Relapsing Multiple Sclerosis, UNS: course of disease unspecified, NMS: neuromyelitis optica, IIROC: Immunomodulation and Infectious Risk Out- patient Clinic, *Number of pregnancies identified in the database, CRF: Case reported forms, CLIMB Study :Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women's Hospital, IMSE: Immunomodulation and MS Epidemiology Study, [a] Median (interquartile range), [b] Median (range), [c] Mean (SD)

Discussion:

In this review, we observed that the population in the observational studies tends to be relatively younger adults, ranging from 24.5 to 54.4 years. The majority of participants were female, indicating a higher representation of women in the MS population. Ethnicity and SES were not reported in more than 70% (N = 30) of the studies. The frequently studied type of MS in the included observational studies was RRMS. The reporting structure of patient characteristics such as ethnicity, SES, EDSS score and treatment history were inconsistently reported across the studies. This indicates a lack of standardised methodology and documentation in real-world observational studies.

Sex was consistently reported in 30 studies, which provides us with a better understanding of the prevalence of MS among individuals using DMTs. In all included studies, the proportion of female participants was greater than 60%, except for one study where the study population exclusively consisted of males [41]. Our analysis observed, approximately 70% of the participants in the studies were observed to be female. To ensure balanced gender representation, we excluded two studies focusing exclusively on either male [41] or female participants [18]. In one systematic review [47], the gender distribution in clinical trials and real-world observational studies evaluating the DMTs in MS patients were compared. They found no significant difference in gender distribution between the two study types with females comprising 71% in real-world studies and 66% in clinical studies. These findings suggest that the gender distribution observed in our study aligns with the trends observed in previous research and the importance of reconsidering gender-specific factors in the treatment of MS.

Furthermore, age was reported in 97% of the papers indicating a high level of data availability. The reported mean age ranged from 24.5 to 54.4 years, indicating a wide

age range that encompasses a relatively young adult population. Only one study did not report data on age [18]. In this systematic review [47], comparing observational studies and randomized controlled trials (RCT) it was found that the average age in observational studies was 38.4 years, slightly younger than the average age of 39.2 years reported in RCTs. This finding suggests a trend of relatively younger participants in observational studies compared to RCTs in the subset of multiple sclerosis population who are under DMTs.

Our analysis revealed a positive trend between age, MS duration, and the EDSS score, indicating that disease severity tends to increase with advancing age. This finding was consistent with previous research [48] in a large hospital-based cohort study where they studied the relationship between disability and aging in MS patients. They recruited 1,463 MS patients into the study and followed for a median of 8.24 years, where they observed correlation between age and EDSS score. The alignment of our findings with their results supports the observed association between age and disease severity in multiple sclerosis with DMT use. However, due to the inconsistent reporting we were not able to consider all the included papers in this conclusion, and importantly this correlation was not statistically tested in our study but assessed based on the aggerated data.

We also observed that most of the studies were conducted in Europe (n = 18) and the USA (n = 9), within European countries a higher frequency was observed in Italy (n = 8). Interesting, a previous study [43] reported a similar result, where they saw a high frequency of both observational and RCT studies conducted in Italy (n=13). This information may contribute to our understanding of the diversity and representation of patients across the different geographical distributions of DMTs used in the MS

population in research. However, we are not certain about the reasons behind this high frequency of studies conducted in Italy.

In this review, we observed that approximately 40% of the included studies (N = 30) reported using claims databases or electronic medical records as a primary data source, which raises potential concerns regarding information bias [49]. These databases are primarily intended for administrative or clinical use and may not have been specifically targeted for research [50]. Consequently, the accuracy and reliability of such databases for research purposes remain unknown. The utilisation of such databases introduces the possibility of incomplete or inconsistent information [43]. Future studies should consider incorporating data validation methods to limit this bias [51].

Our research has three limitations. Firstly, we found heterogeneity in study designs within the literature review, ranging from nested case control to retrospective cohort study designs. The utilisation of different data sources, collection techniques, and reporting structures across these studies poses challenges in directly comparing and synthesising the findings. This heterogeneity in study design restricts our ability to identify consistent patterns across the literature leading to the limited generalisability of findings. Secondly, the quality and reliability of this evidence may be influenced by variations in sample sizes and comparison groups among the studies. It is worth noting that we observed a wide range of sample sizes among the included studies, which adds to the overall variability and may potentially impact the interpretation of our results. Finally, there is a chance of publication bias [52], as we searched two databases where studies with positive or significant findings are more likely to get published, while negative or non-significant findings might get rejected for publication or inaccessible. We acknowledge that these limitations may have influenced the strength of the evidence and the conclusions drawn from our study.

In conclusion, our analysis of observational studies on the risk of infection in patients using DMTs for MS reveals that the study population tends to consist of younger adults and a high proportion of women. Our review has highlighted the inconsistencies and limitations in the reporting of patient characteristics such as ethnicity, SES, EDSS score, and treatment history which are known to influence the risk of infection. To address this drawback, a thorough and standardised reporting structure is needed to gain a better understanding of the specific patient characteristics that are associated with a risk of infection. This ultimately directs towards the development of individualised treatment approaches which could enhance patient care.

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