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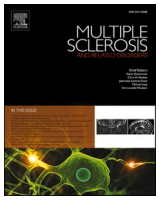

Impact of adherence to disease-modifying drugs in multiple sclerosis: A study on Italian real-world data

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ABSTRACT

Background: Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system requiring complex diagnostic and therapeutic management. Treatment with Disease Modifying Drugs (DMDs) is aimed at reducing relapse rate and disease disability. Few real-world, population-based data are available on the impact of adherence on relapse rate.
The objective of this study was to assess the impact of adherence to DMDs on relapses in a real-world Italian setting.
Methods: Population-based cohort study. People with MS (PwMS) older than 18 years and residing in the Emilia-Romagna region, Northern Italy, were identified through administrative databases using a validated algorithm. A Cox regression model with a time-varying exposure was performed to assess the association between level of adherence to DMDs and relapses over a 5-year period.
Results: A total of 2,528 PwMS receiving a first prescription of DMDs between 2015 and 2019 were included (average age of 42, two-thirds female). Highly adherent PwMS had a 25 % lower hazard of experiencing moderate or severe relapses than non-adherent PwMS (Hazard Ratio 0.75, 95 % CI 0.58 to 0.98), after adjusting for age and sex. Several sensitivity analyses supported the main result.
Conclusion: The results of our study support the hypothesis that a high level of DMD adherence in MS is associated with a lower risk of moderate or severe relapse. Therefore, choosing the DMD with which to start drug treatment and recommending adherence to treatment appear to be crucial aspects involving both physicians and patients.

1. Introduction

Multiple Sclerosis (MS) is the most common immune-mediated, chronic inflammatory demyelinating disease of the central nervous system affecting about 2.8 million people worldwide. In Italy MS affects almost 130,000 people, with a prevalence of 208 cases per 100,000 inhabitants (Walton et al., 2020) and more than 3,400 estimated new cases per year, corresponding to an incidence of 6 cases per 100,000 inhabitants.

Pharmacological treatments for MS can be symptomatic (i.e. targeting specific symptoms, such as muscular spasms, pain, urinary incontinence) or with disease-modifying drugs (DMDs), aimed at slowing the accumulation of disability and disease progression (Rae-Grant et al., 2018; Montalban et al., 2018), and at reducing the frequency of relapses. Relapse frequency is indeed one of the main MS-related outcomes and a widely used measure of treatment efficacy. The approved DMDs for treating MS include injectable, oral and infusion preparations. A crucial factor for the effectiveness of DMDs is their consistent administration, that is, patients' adherence to treatment. A recent systematic review including 24 studies reported overall adherence rates for DMDs in MS ranging from 52 % to 92.8 % (Washington and Langdon, 2022). Although several studies have investigated the determinants of treatment adherence to DMDs among People with MS (PwMS) (Kołtuniuk and Chojdak-Łukasiewicz, 2022), few real-world, population-based data

Abbreviations: MS, Multiple Sclerosis; DMDs, Disease-modifying drugs; PwMS, People with MS; E-RR, Emilia-Romagna region; DDD, Defined Daily Dose; PDC, Proportion of Days Covered; MCS, Multisource Comorbidity Score.

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are available on the impact of adherence on relapse rate. Moreover, some studies have considered adherence to treatment as a characteristic defined at baseline, and not as a measure that can evolve over time (Evans et al., 2017). However, it has been observed that in chronic conditions, as well as in PwMS (Evans et al., 2021), adherence is higher during the first year of treatment but tending to decrease in time. Consequently, ignoring the temporal issue and the dynamic nature of adherence may result in PwMS who relapse early in follow up, thus becoming "early cases", being more likely to be classified as adherent. This bias can produce an over-representation of adherent cases and an underestimation of beneficial effects of adherence (Di Martino et al., 2015).

The objective of our study was to assess the impact of adherence to DMDs on relapses in a real-world Italian setting, using a time-dependent approach to appropriately represent the dynamic nature of the exposure variable.

2. Materials and methods

The 'reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology' (RECORD-PE) guidelines (Langan et al., 2018) were followed.

2.1. Setting and data source

The data used for this study came from regional healthcare databases of the Emilia-Romagna region (E-RR) in Northern Italy with nearly 4.5 million people cared for by 8 Local Health Trusts.

Patient data were obtained by linking information about utilization of healthcare resources (in outpatient and inpatient settings) and drug prescription from regional administrative databases by means of a unique anonymized patient identifier. Namely, the following databases were accessed: the hospital discharge record database (SDO) (ICD-IX-CM codes for the International Classification of Diseases to identify diagnoses); the outpatient pharmaceutical supply (AFT) and the direct supply (FED) databases (international Anatomical Therapeutic Chemical (ATC) classification to identify dispensed drugs); the Emergency Information System (PS); the Mortality Registry (ReM); the co-payment Exemption Registry.

2.2. Study cohort

This historical population-based cohort included PwMS (with both relapsing and active progressive forms), living in E-RR, identified by means of a validated case-finding algorithm (Bargagli et al., 2016). Algorithm inclusion criteria are provided in the *supplementary material*. The cohort was then restricted to PwMS aged 18 or older who received a first-ever dispensation of a DMD (i.e., no other dispensation of a DMD in the preceding 3 years) between January 1, 2015 and December 31, 2019. The date of the first dispensation was defined as the index date.

2.3. Follow-up and outcome

Each patient was followed from the index date until either the date of the first relapse, the date of death, the date of emigration from E-RR or the end of the study period (December 31, 2019), whichever came first. Only PwMS with a minimum follow-up of 30 days were considered in the main analysis. Detection of the outcome of interest (first moderate or severe relapse) was carried out by implementing an Italian algorithm (Colais et al., 2017) validated via clinical and radiological diagnostic criteria by neurologists with expertise in MS management. It required the presence of at least one of the following: (a) hospitalization with primary diagnosis of MS – ICD-IX-CM 340; (b) access to the emergency department with primary diagnosis of MS – ICD-IX-CM 340; (c) use of systemic corticosteroids (ATC code H02AB) at a dosage of at least 0.5 g/day for 5 days.

2.4. Drug exposure

All prescriptions of DMDs dispensed during the follow-up were identified. The number of days during which each patient was treated was derived using the World Health Organization Defined Daily Dose (DDD) international metric, transforming the physical quantities of drugs (capsules, vials, inhalers, etc.) into a standard unit of measurement, allowing a comparative measure of drug exposure (Hollingworth and Kairuz, 2021; WHO 2022).

The adherence to DMDs was expressed as the Proportion of Days Covered (PDC): the ratio between the cumulative number of days in which the DMDs were available (starting from the index date) and the overall follow-up. For overlapping prescriptions, it was assumed that the start of the new prescription corresponded with the end of the previous one (Fig. A.1 in supplementary materials). Three categories of time-dependent exposure were considered: non-adherence (PDC<60 %), moderate adherence (60 %≤PDC<80 %) and high adherence (PDC≥80 %). The thresholds were defined considering that a cut-off point of 80 % or above is generally accepted as the optimal adherence level (Osterberg and Blaschke, 2005).

2.5. Covariates

Patients were characterized at baseline according to demographic and clinical factors: age, sex, Local Health Trust, index year (i.e., year of drug therapy initiation) and comorbidity. Multisource Comorbidity Score (MCS) was chosen as overall index of clinical complexity (Corrao et al., 2017). Individual total score was then aggregated into five categories corresponding to increasing severity: 0–4, 5–9, 10–14, 15–19, ≥20. DMD type (according to ATC code) and administration route (oral, injection and infusion) were also considered.

2.6. Statistical analysis

Exposure and outcome were both measured in the same time window. This means that unlike a classical (time-independent) framework in which exposure is defined at baseline, in our study adherence to therapy is defined over time as well as the outcome of interest (Fig. 1) (Spreafico and Ieva, 2021).

In a time-independent setting, PwMS on treatment experiencing outcomes early on are more likely to be classified as adherent to treatment than those with no or late outcomes during follow-up, since adherence levels usually decrease with increasing time from disease onset, treatment initiation or acute event. This systematic error – known as "change in adherence bias" (Di Martino et al., 2015) – was avoided in our study by using a time-dependent approach to manage exposure and implementing a Cox proportional hazards regression analysis with drug exposure as a time-dependent determinant. For each PwMS experiencing a relapse (case), the cumulative exposure status on the day of the first relapse was compared with the cumulative exposure status of all the other PwMS of the cohort who were still followed-up and event-free (risk set). Thus, there was as many strata as cases within the cohort: each stratum consisted of one case and the associated risk set (Stricker et al., 2010). The association between exposure (adherence to DMDs) and outcome (relapses) was assessed by Hazard Ratios (HR) with 95 % Confidence Intervals (95 % CI). Non-adherence (PDC<60 %) was defined as the reference group. All covariates (age, sex, Local Health Trust, index year, MCS score, DMD type and DMD administration route) were evaluated as potential confounding factors. In order to support the results of the main analysis, several sensitivity analyses were carried out by varying study design, minimum follow-up time, adherence thresholds, adherence indicator and outcome definition (details provided in the *supplementary material*). All analyses were performed using SAS Enterprise Guide version 8.3 (SAS Institute, Inc. Cary, NC, USA).

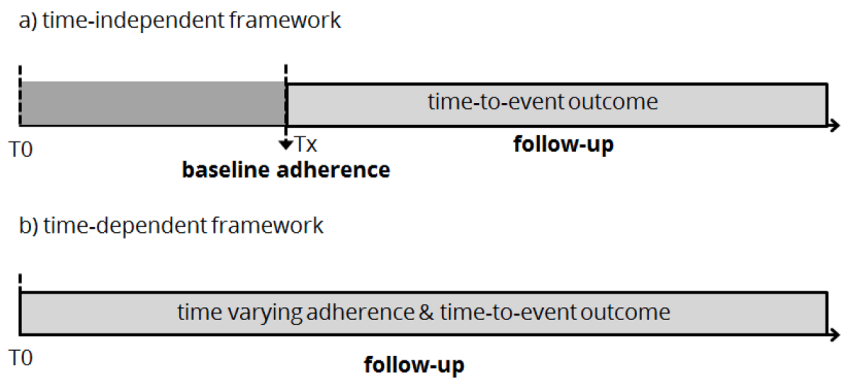

Fig. 1. Time-independent (a) and time-dependent (b) framework of exposure. In framework a) the observation period from T0 to Tx is used to compute a baseline adherence level, and the follow-up starts from Tx; in framework b) adherence is computed jointly with time-to-event outcome, so follow-up starts from T0.

3. Results

A flow diagram of the cohort identification is shown in Fig. 2.

A total of 2,528 of PwMS receiving a first-ever treatment with DMDs were included. The demographic and clinical characteristics of the cohort are shown in Table 1. PwMS receiving DMDs had a mean age of 42 years (standard deviation, 13 years; interquartile range, 32 - 51), two-thirds were female, and 73 % had a lower index of clinical complexity (MCS between 0 and 4).

Over the five years of follow up, there was an increase in the use of oral and infusion drugs as the first treatment option, at the expense of injectable drugs. Specifically, in 2019 there was an increase in the number of new DMDs users (+28 %), due almost entirely to the increased prescription of dimethyl fumarate and ocrelizumab (Tables A.1, A.2 and Fig. A.2 in supplementary materials). During the follow-up 341 patients (13 %) had at least one moderate or severe relapse. Fig. 3 shows the contribution of each information source in defining the outcome of interest.

Time-to-event data, analyzed by means of the Kaplan Meier method, showed that the probability of relapse-free survival dropped to 75 % (95 % CI 71–78) after 1,705 days, corresponding to 4.7 years.

3.1. Adherence with DMDs and risk of relapses

The association between the time-dependent drug exposure and the risk of moderate or severe relapses was explored in the main analysis. Each stratum, represented by each case and the corresponding risk set, consisted of, on average, 1,663 control periods, for a total of 567,352 exposure status. Compared with the non-adherent group, the relapse Hazard Ratio decreased progressively as the level of adherence increased from moderate (HR 0.79, 95 % CI 0.55 to 1.14) to high (HR 0.77, 95 % CI 0.60 to 0.998). After evaluating the effect of all possible confounding factors on the estimate of the exposure-outcome association, adjustment was performed only for age and sex. Multivariate analysis confirmed the univariate analysis findings. Specifically, the Hazard Ratio of moderate or severe relapses for moderately adherent

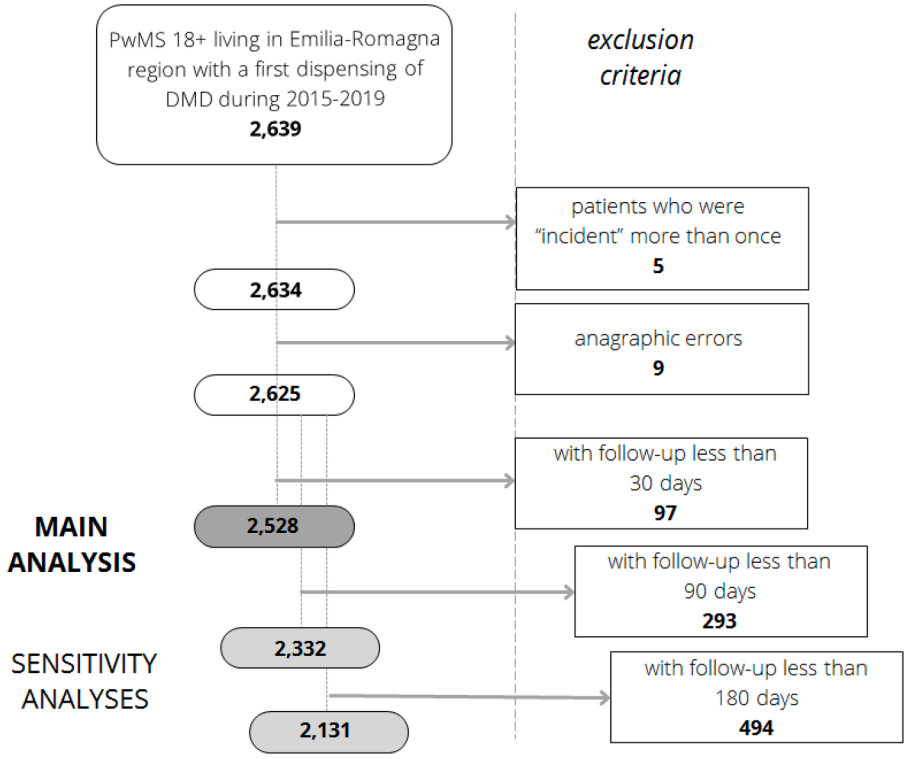

Fig. 2. Flow diagram of the cohort identification.

Table 1
Patient characteristics.

	N°	%
Sex		
Female	1682	66.53
Male	846	33.47
Age (mean ± std. dev.)	42.2 ± 13.1	
Index year		
2015	461	18.24
2016	472	18.67
2017	496	19.62
2018	482	19.07
2019	617	24.41
Local Health Trust		
Piacenza	149	5.89
Parma	279	11.04
Reggio Emilia	334	13.21
Modena	384	15.19
Bologna	490	19.38
Imola	65	2.57
Ferrara	223	8.82
Romagna	604	23.89
First DMD ATC code		
L03AB07 – INTERFERON BETA-1A	375	14.83
L03AB08 – INTERFERON BETA-1B	35	1.38
L03AB13 – PEGINTERFERON BETA-1A	77	3.05
L03AX13 – GLATIRAMER ACETATO	631	24.96
L04AA23 – NATALIZUMAB	203	8.03
L04AA27 – FINGOLIMOD	174	6.88
L04AA31 – TERIFLUNOMIDE	252	9.97
L04AA34 – ALEMTUZUMAB	15	0.59
L04AA36 – OCRELIZUMAB	81	3.20
L04AX07 – DIMETHYL FUMARATE	685	27.10
First DMD type		
Infusion	299	11.83
Injection	1118	44.22
Oral	1111	43.95
Multisource Comorbidity Score (mean ± std. dev.)	3.2 ± 3.5	
Multisource Comorbidity Score: class		
0 (MCS = 0)	737	29.15
1 (1 <= MCS <= 4)	1111	43.95
2 (5 <= MCS <= 9)	542	21.44
3 (10 <= MCS <= 14)	103	4.07
4 (15 <= MCS <= 19)	22	0.87
5 (MCS >= 20)	13	0.51

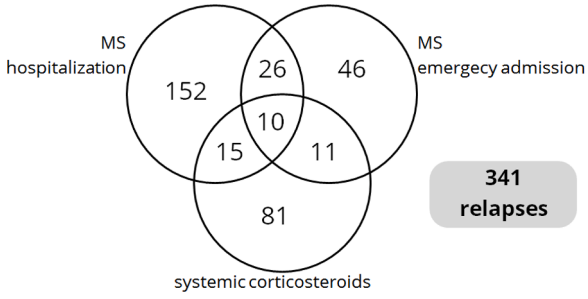

Fig. 3. Venn diagram showing the sources of events contributing to the identification of relapses.

PwMS decreased but did not reach statistical significance (HR 0.76, 95 % CI 0.53 to 1.10), while highly adherent PwMS had a 25 % lower hazard of experiencing a moderate or severe relapse than non-adherent PwMS (HR 0.75, 95 % CI 0.58 to 0.98) (p-value test for trend: 0.0452). All sensitivity analyses (Table 2) consistently showed that the Hazard Ratio of moderate or severe relapses was inversely proportional to the level of adherence.

4. Discussion

The present cohort study suggested an inverse relationship between adherence to drug therapy and the risk of moderate or severe relapses among PwMS starting their first-ever treatment with DMDs. The protective effect was particularly strong (25 % lower hazard) among highly adherent PwMS (PDC≥80 %), when compared to those non-adherent (PDC<60 %). By increasing the buffer period, i.e., excluding PwMS with minimum follow-up of less than 30, 90 and 180 days, respectively, the protective effect of high adherence seemed to be attenuated, suggesting that adherence to DMD therapy was particularly protective in the early stages of treatment. During the follow up of our study we observed an increasing number of PwMS initiating treatment with a DMD in 2019, mainly due to the local availability of dimethyl fumarate and ocrelizumab. Such patterns were in line with two recent Italian studies on dimethyl fumarate (Mantovani et al., 2019; Mirabella et al., 2018), and one on ocrelizumab (Moccia et al., 2022).

Healthcare utilization databases were used in this study as the data source. Through record-linkage procedures using unique identifiers, it was therefore possible to trace the entire medical history of each patient. Although a Randomized Controlled Trial (RCT) design is considered to be the ideal for assessing efficacy and safety of therapeutic agents, the contribution of real-world studies is becoming increasingly important to complement RCT evidence in terms of safety, efficacy, and cost of medical care in clinical practice (Corrao and Mancia, 2022). Observational studies, however, are prone to various types of bias, particularly selection bias, confounding by indication and misclassification, therefore the choice of the appropriate study design and statistical techniques are crucial aspects to safeguard their internal validity. In pharmacoepidemiologic research in particular, a precise definition of exposure is mandatory in order to reduce the risk of non-differential misclassification (BHCh and Stijnen, 2010). In our study, adherence to DMD treatment was defined as the exposure. Commonly, adherence measures are computed over a predefined observation period and included in a survival model as a baseline fixed covariate (usually dichotomous, i.e. adherent yes/no), taking the end of the predefined observation period as the start of the follow-up (Fig. 1, pattern a). Instead, by modeling medication adherence as a time-depending covariate that jointly evolves with the patient's outcome, we incorporated its dynamic nature into the analysis.

Previous research has shown that, compared to non-adherence, a high level of compliance and adherence to recommended treatments is associated with a decreased risk of relapses and lower frequency of hospital visits (Oleen-Burkey et al., 2011; Ivanova et al., 2012; Cohen et al., 2015; Burks et al., 2017). However, the directness and generalizability of such results is limited, since some studies included only a few categories of drugs (Oleen-Burkey et al., 2011; Ivanova et al., 2012), while others relied on claims data from health insurance plans, restricting the sample to commercially insured individuals only and/or employed, thereby potentially introducing selection bias (Cohen et al., 2015; Burks et al., 2017).

Performing a real-world observational study allowed us to overcome some limitations of pivotal trials, currently the main source of data concerning efficacy and safety of DMDs, thereby increasing the robustness and reliability of the observed association. Administrative data sources allow reliable estimates to be obtained in a relatively short time on population samples that are highly representative, both in terms of size and diagnostic variability, and with an adequate duration of follow up in relation to the natural course of MS (Cohen et al., 2020). Additionally, the possibility that the observed association between the exposure and the outcome was spurious is ruled out by a thorough evaluation and adjustment for of all the possible known confounders inferable from health administrative databases. Furthermore, by analyzing the exposure to drugs as a time-dependent variable in a Cox regression model, our study provided valid and precise risk estimates of drug-outcome associations, appropriately representing the dynamic nature of adherence. Lastly, several sensitivity analyses were performed, confirming the inverse relationship between exposure and outcome observed in the main analysis.

Table 2
Sensitivity analyses.

Sensitivity Analysis N°	What is changed from the main analysis	How it is changed	Results Adjusted HR (95 % CI)	
1	Design	**Nested case-control 1:5** (instead of cohort)	adherence < 60 %	reference
			60 %<=adherence<80 %	0.83 (0.55 – 1.25) [a]
			adherence >= 80 %	0.78 (0.59 – 1.04) [a]
2a	Buffer period	**90 days** (instead of 30 days)	adherence < 60 %	reference
			60 %<=adherence<80 %	0.78 (0.53 – 1.15)
			adherence >= 80 %	0.78 (0.59 – 1.02)
2b		**180 days** (instead of 30 days)	adherence < 60 %	reference
			60 %<=adherence<80 %	0.84 (0.56 – 1.27)
			adherence >= 80 %	0.80 (0.59 – 1.08)
3a	Adherence cut-off	**70 % & 90 %** (instead of 60 % & 80 %)	adherence < 70 %	reference
			70 %<=adherence<90 %	0.78 (0.59 – 1.03)
			adherence >= 90 %	0.75 (0.57 – 0.97)
3b		**60 % & 85 %** (instead of 60 % & 80 %)	adherence < 60 %	reference
			60 %<=adherence<85 %	0.76 (0.55 – 1.05)
			adherence >= 85 %	0.75 (0.57 – 0.98)
4	Adherence indicator	**MPR** (instead of PDC)	adherence < 60 %	reference
			60 %<=adherence<80 %	0.84 (0.56 – 1.25)
			adherence >= 80 %	0.78 (0.60 – 1.02)
5	Outcome definition	Excluded patients admitted for MS (principal diagnosis) with an **infection** among the secondary diagnoses	adherence < 60 %	1
			60 %<=adherence<80 %	0.73 (0.50 – 1.05)
			adherence >= 80 %	0.74 (0.57 – 0.96)

[a] Formally, they are Odds Ratios because come from a conditional logistic regression model; however, they should be interpreted as Hazard Ratios (Belleudi et al., 2011).

Some important limitations should be acknowledged. Firstly, administrative databases were not created for clinical research purposes, and therefore do not incorporate important clinical data such as date of onset, disease severity or disability. In addition, the validated algorithm used to identify the population (PwMS on treatment with DMDs) cannot distinguish among different MS phenotypes (relapsing-remitting rather than primary or secondary progressive MS). However, although relapse is an outcome generally associated with relapsing-remitting forms (which account for 80–85 % of cases), temporary and sudden clinical worsening warranting hospitalization, emergency room access, or steroid treatment are also observed in progressive forms. About 40 % of people with secondary progressive (Confavreux and Vukusic, 2006) and 11 % of the primary progressive (Montalban et al., 2017) phenotypes of MS present relapses, which can therefore be considered a fair overall proxy of MS, even in progressive forms.

Secondly, although the overall positive predictive value (PPV) and sensitivity of the algorithm we used to identify relapses were rather poor (58.9 %, 95 % CI 55.8–62.1 and 64.5 %, 95 % CI 61.3–67.7, respectively), among PwMS younger than 40 years of age they were higher (66.4 %, 95 % CI 62.3–70.5 and 65.6 %, 95 % CI 61.5–69.7, respectively), suggesting a higher sensitivity in identifying relapses occurring during the relapsing-remitting stage rather than in more advanced stages with fewer relapse episodes, such as secondary progressive MS (Colais et al., 2017). By selecting treatment naive PwMS, our study included mainly subjects in the early stages of the condition, where the algorithm may have been more accurate. Moreover, misclassification cannot be completely excluded in our setting since the algorithm was able to identify moderate or severe relapses, requiring pharmacological treatment or hospitalization, respectively. Therefore, mild episodes not requiring access to healthcare services might have been missed (low sensitivity). However, such a potential limitation of algorithm-based research on administrative databases is partially offset by greater generalizability of results, since they are population-based, involve large and highly representative samples and allow the detection of rare events due to long-term assessment (Corrao and Mancia, 2015). Thirdly, administrative databases do not provide the exact prescribed daily dose, which can only be inferred from the DDDs. When estimating medication adherence, we assumed that the proportion of days covered by a dispensation matches the proportion of days of actual medication use (i.e. we do not know if patients actually took what was prescribed). Therefore, we cannot rule out exposure misclassification. However, this is a widely used methodology and is thought to produce limited distortion in the estimates of exposure-outcome association (Belleudi et al., 2011).

5. Conclusion

Our study adds to the evidence base for recommending adherence to treatment with DMDs in clinical practice, a key aspect for reducing moderate or severe relapse rate. Expected adherence to treatment should be carefully addressed by clinicians and PwMS when making the important choice of which DMD to start treatment with, conveying the principle that it can have an important effect on the treatment's efficacy. In previously untreated PwMS, such as the ones included in our study, the choice of which DMD to start treatment with is therefore particularly important and needs a thorough discussion between the treating clinician and patient, considering not only the severity and stage of the disease, but also the patient's attitudes, preferences and expectations. Indeed, oral medications offer the advantage of self-administration but require high adherence to a daily administration schedule. Conversely, drugs delivered by infusion may be administered less often (once or twice a year) but require access to healthcare facilities, preparation and more complex management for both the patient and health care services.

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Ethical approval

This study is part of a more extensive project called CONERO (COvid-19 and chronic Neurological diseases in the Emilia-Romagna region) including also patients with epilepsy or Parkinson's disease. The protocol was reviewed and approved by the Institutional Review Board of the Local Health Trust of Bologna (Comitato Etico AVEC) on December 16, 2020 (protocol: 130145).

Author contributions

LMBB, MDM and FN conceptualized and designed the study and interpreted the results. LMBB performed data analysis and wrote the manuscript. CZ, LV, EB, BR and FB contributed to the critical interpretation and discussion of the results. All authors contributed to the article, revised the manuscript critically for intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.105094.

References

Bargagli, A.M., Colais, P., Agabiti, N., Mayer, F., Buttari, F., Centonze, D., et al., 2016 Apr. Prevalence of multiple sclerosis in the Lazio region, Italy: use of an algorithm based on health information systems. J. Neurol. 263 (4), 751–759.

Belleudi, V., Fusco, D., Kirchmayer, U., Agabiti, N., Di Martino, M., Narduzzi, S., et al., 2011. Definition of patients treated with evidence based drugs in absence of prescribed daily doses: the example of acute myocardial infarction: DIFFERENT MEDICATION USE MEASURES FOR EVIDENCE-BASED DRUG THERAPY. Pharmacoepidem. Drug. Safe 20 (2), 169–176.

BHCh, Stricker, Stijnen, T., 2010 Apr. Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies. Eur. J. Epidemiol. 25 (4), 245–251.

Burks, J., Marshall, T., Ye, X., 2017 Apr. Adherence to disease-modifying therapies and its impact on relapse, health resource utilization, and costs among patients with multiple sclerosis. CEOR 9, 251–260.

Cohen, B.A., Coyle, P.K., Leist, T., Oleen-Burkey, M.A., Schwartz, M., Zwibel, H., 2015 Jan. Therapy optimization in multiple sclerosis: a cohort study of therapy adherence and risk of relapse. Mult. Scler. Relat. Disord. 4 (1), 75–82.

Cohen, J.A., Trojano, M., Mowry, E.M., Uitdehaag, B.M., Reingold, S.C., Marrie, R.A., 2020 Jan. Leveraging real-world data to investigate multiple sclerosis disease behavior, prognosis, and treatment. Mult. Scler. 26 (1), 23–37.

Colais, P., Agabiti, N., Davoli, M., Buttari, F., Centonze, D., De Fino, C., et al., 2017. Identifying relapses in multiple sclerosis patients through administrative data: a validation study in the Lazio region, Italy. Neuroepidemiology. 48 (3–4), 171–178.

Confavreux, C., Vukusic, S., 2006 Mar 1. Age at disability milestones in multiple sclerosis. Brain 129 (3), 595–605.

Corrao, G., Mancia, G., 2015 Mar. Generating evidence from computerized healthcare utilization databases. Hypertension 65 (3), 490–498.

Corrao, G., Mancia, G., 2022 Sep 14. Research strategies in treatment of hypertension: value of retrospective real-life data. Eur. Heart J. 43 (35), 3312–3322.

Corrao, G., Rea, F., Di Martino, M., De Palma, R., Scondotto, S., Fusco, D., et al., 2017 Dec. Developing and validating a novel multisource comorbidity score from administrative data: a large population-based cohort study from Italy. BMJ Open 7 (12), e019503.

Di Martino, M., Kirchmayer, U., Agabiti, N., Bauleo, L., Fusco, D., Perucci, C.A., et al., 2015 Jun 10. The impact of time-window bias on the assessment of the long-term effect of medication adherence: the case of secondary prevention after myocardial infarction. BMJ Open 5 (6) e007866–e007866.

Evans, C., Marrie, R.A., Zhu, F., Leung, S., Lu, X., Kingwell, E., et al., 2017 Jun. Adherence to disease-modifying therapies for multiple sclerosis and subsequent hospitalizations. Pharmacoepidemiol. Drug Saf. 26 (6), 702–711.

Evans, C., Marrie, R.A., Yao, S., Zhu, F., Walld, R., Tremlett, H., et al., 2021 Feb. Medication adherence in multiple sclerosis as a potential model for other chronic diseases: a population-based cohort study. BMJ Open 11 (2), e043930.

Hollingworth, S., Kairuz, T., 2021 Mar 17. Measuring medicine use: applying ATC/DDD methodology to real-world data. Pharmacy 9 (1), 60.

Ivanova, J.I., Bergman, R.E., Birnbaum, H.G., Phillips, A.L., Stewart, M., Meletiche, D.M., 2012 Jan. Impact of medication adherence to disease-modifying drugs on severe relapse, and direct and indirect costs among employees with multiple sclerosis in the US. J. Med. Econ. 15 (3), 601–609.

Kołtuniuk, A., Chojdak-Łukasiewicz, J., 2022 Feb 15. Adherence to therapy in patients with multiple sclerosis—review. IJERPH 19 (4), 2203.

Langan, S.M., Schmidt, S.A., Wing, K., Ehrenstein, V., Nicholls, S.G., Filion, K.B., et al., 2018 Nov 14. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). BMJ k3532.

Mantovani, L.G., Furneri, G., Bitonti, R., Cortesi, P., Puma, E., Santoni, L., et al., 2019 Jul 30. Cost-effectiveness analysis of dimethyl fumarate in the treatment of relapsing remitting multiple sclerosis: an italian societal perspective. FE [Internet] 20 (1) [cited 2023 Mar 14]Available from: https://journals.seedmedicalpublishers.com/index.php/FE/article/view/1437.

Mirabella, M., Prosperini, L., Lucchini, M., Boffa, L., Borriello, G., Buscarinu, M.C., et al., 2018 Oct. Safety and efficacy of dimethyl fumarate in multiple sclerosis: an italian, multicenter, real-world study. CNS Drugs 32 (10), 963–970.

Moccia, M., Affinito, G., Berera, G., Marrazzo, G., Piscitelli, R., Carotenuto, A., et al., 2022 Dec. Persistence, adherence, healthcare resource utilization and costs for ocrelizumab in the real-world of the Campania Region of Italy. J. Neurol. 269 (12), 6504–6511.

Montalban, X., Belach, Shibeshih, Wolinsky, Jerry S, 2017 Apr 27. Ocrelizumab in primary progressive and relapsing multiple sclerosis. N. Engl. J. Med. 376 (17), 1692–1694.

Montalban, X., Gold, R., Thompson, A.J., Otero-Romero, S., Amato, M.P., Chandraratna, D., et al., 2018 Feb. ECTRIMS /EAN guideline on the pharmacological treatment of people with multiple sclerosis. Eur. J. Neurol. 25 (2), 215–237.

Oleen-Burkey, M.A., Dor, A., Castelli-Haley, J., Lage, M.J., 2011 Jan. The relationship between alternative medication possession ratio thresholds and outcomes: evidence from the use of glatiramer acetate. J. Med. Econ. 14 (6), 739–747.

Osterberg, L., Blaschke, T., 2005 Aug 4. Adherence to medication. N. Engl. J. Med. 353 (5), 487–497.

Rae-Grant, A., Day, G.S., Marrie, R.A., Rabinstein, A., Cree, B.A.C., Gronseth, G.S., et al., 2018 Apr 24. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 90 (17), 777–788.

Spreafico, M., Ieva, F., 2021 Feb. Dynamic monitoring of the effects of adherence to medication on survival in heart failure patients: a joint modeling approach exploiting time-varying covariates. Biom J. 63 (2), 305–322.

Walton, C., King, R., Rechtman, L., Kaye, W., Leray, E., Marrie, R.A., et al., 2020 Dec. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. Mult. Scler. 26 (14), 1816–1821.

Washington, F., Langdon, D., 2022 Apr. Factors affecting adherence to disease-modifying therapies in multiple sclerosis: systematic review. J. Neurol. 269 (4), 1861–1872.

WHO. 2022 [cited 2022 Feb 11]; Available from: https://www.who.int/tools/atc-ddd-toolkit/about-ddd.