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TESI DI DOTTORATO IN SANITA' PUBBLICA E MEDICINA PREVENTIVA

Use of Routinely Collected Healthcare Data to support Decision Making in Public Health: The Case Study of Multiple Sclerosis

RELATORE **CANDIDATO**

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To my Family

Contents

Abstract

Routinely collected healthcare data plays a pivotal role in modern healthcare systems and public health research. These datasets encompass a wide array of information gathered as part of routine healthcare operations.

Data sets of routinely collected healthcare are invaluable in offering a comprehensive description of disease epidemiology, comorbidities, and treatment pathways, particularly when linked to clinical registries. Additionally, big data can be interconnected longitudinally and across diverse data sources to create comprehensive individual records and multi-tiered data structures. This approach allows for a multifaceted understanding and management of diseases in various aspects, including identifying incident cases, treatment and medication management, resource utilization, and cost analysis.

Multiple sclerosis (MS) is a complex neurological condition characterized by inflammation, demyelination, and degeneration of the central nervous system. This multifaceted disease presents one of the most formidable challenges in modern medicine, primarily due to its high social impact and associated costs.

Routinely collected data is an indispensable resource for addressing the challenges posed by MS. It empowers healthcare providers, researchers, and patients to understand better, manage, and potentially find a cure for this complex neurological condition. By utilizing data effectively, we can improve patient outcomes, enhance quality of life, and optimize healthcare resource utilization, ultimately reducing the social and economic burden of MS.

In the first part of the study, we validated an algorithm based on routinely collected healthcare data to detect incidence of multiple sclerosis (MS) in the Campania Region (South Italy) and to explore

its spatial and temporal variations. We included individual's resident in the Campania Region who had at least one MS record in administrative datasets (drug prescriptions, hospital discharge, outpatients), from 2015 to 2020. We merged administrative to the clinical datasets to ascertain the actual date of diagnosis and validated the minimum interval from our study baseline (Jan 1, 2015) to first MS records in administrative datasets to detect incident cases.

We used Bayesian approach to explore geographical distribution, also including deprivation index as a covariate in the estimation model. We used the capture-recapture method to estimate the proportion of undetected cases.

The best performance was achieved by the 12-month interval algorithm, detecting 2,150 incident MS cases, with 74.4% sensitivity (95%CI =64.1%, 85.9%) and 95.3% specificity (95%CI =90.7%, 99.8%). The cumulative incidence was 36.68 (95%CI =35.15, 38.26) per 100,000 from 2016 to 2020. The mean annual incidence was 7.34 (95%CI =7.03, 7.65) per 100,000 people-year. The geographical distribution of MS relative risk shows a decreasing east-west incidence gradient. The number of expected MS cases was 11% higher than the detected cases.

In the second part of the study, we provide real-world evidence on the use of DMTs for treating multiple sclerosis (MS), with specific regard to prescription pattern, adherence, persistence, healthcare resource utilization and related costs, also in relation to other disease-modifying treatments (DMTs). We collected hospital discharge records, drug prescriptions, and related costs, and calculated persistence (time from first prescription to discontinuation or switch to other DMT), adherence (proportion of days covered (PDC)), annualized hospitalization rate (AHR) for MS-related hospital admissions, and DMT costs.

Ocrelizumab stands out as one of the most commonly prescribed disease-modifying therapies (DMTs), accounting for 26% of prescriptions to treatment-naïve patients. This suggests its pivotal role in addressing unmet clinical needs, particularly as the first approved treatment for primary progressive multiple sclerosis (MS). Notably, Ocrelizumab demonstrates the highest treatment persistence, underscoring its favourable benefit-risk profile. Moreover, the costs associated with Ocrelizumab are lower compared to similarly effective DMTs, all while not resulting in increased healthcare resource utilization.

Moreover, we evaluated the impact on healthcare resources and costs of adopting Extended-Interval Dosing (EID) for Natalizumab. Findings indicate that Natalizumab EID is associated with reduced direct treatment costs, apparently without additional healthcare burden.

Finally, we evaluated the impact on healthcare delivery to people with MS and the recovery of the system have never been explored. In this population-based study in the Campania Region (Italy), we included MS people across pre-COVID-19, lockdown, pre-vaccination, and vaccination periods. Differences in continuous outcomes between periods were explored using linear mixed models (annualized hospitalization rate (AHR) and adherence measured as medication possession ratio (MPR)). Differences in new disease-modifying treatment (DMT), prescription rates (first DMT prescription, any DMT switch, switch from platform to highly effective DMT, and combination of first DMT prescription and any DMT switch) were assessed employing an interrupted time series design. In this population-based study in the Campania Region (Italy), we included MS people across pre-COVID-19, lockdown, pre-vaccination, and vaccination periods. Differences in continuous outcomes between periods were explored using linear mixed models (annualized hospitalization rate (AHR) and adherence measured as medication possession ratio (MPR)). Differences in new disease-modifying treatment (DMT), prescription rates (first DMT prescription, any DMT switch, switch from platform to highly effective DMT, and combination of first DMT prescription and any DMT switch) were assessed employing an interrupted time series design. In conclusion DMT usage returning to pre-pandemic levels reflects good health system recovery. However, adherence has remained lower than in the past, as from suboptimal care. Assessing long-term COVID-19 impact on MS healthcare needed.

1 Introduction

1.1 Routinely Collected Data in Healthcare

Data have become an omnipresent concept in our daily lives with the routine collection, storage, processing and analysis of immense amount of data. This characteristic is cross-sectorial, ranging from the domain of machine learning and engineering, to economics and medicin[1,2].

The complexity of Big Data analysis arises from combining different types of information, which are electronically captured. The last years have seen an explosion of new platforms, tools and methodologies in storing, and structuring such data, followed by a growth of publications on Big Data and Healthcare (Figure 1). To date, we can collect data from electronic healthcare records, social media, patient summaries, genomic and pharmaceutical data, clinical trials, telemedicine, mobile apps, sensors and information on well-being, behaviour and socio-economic indicators[3].

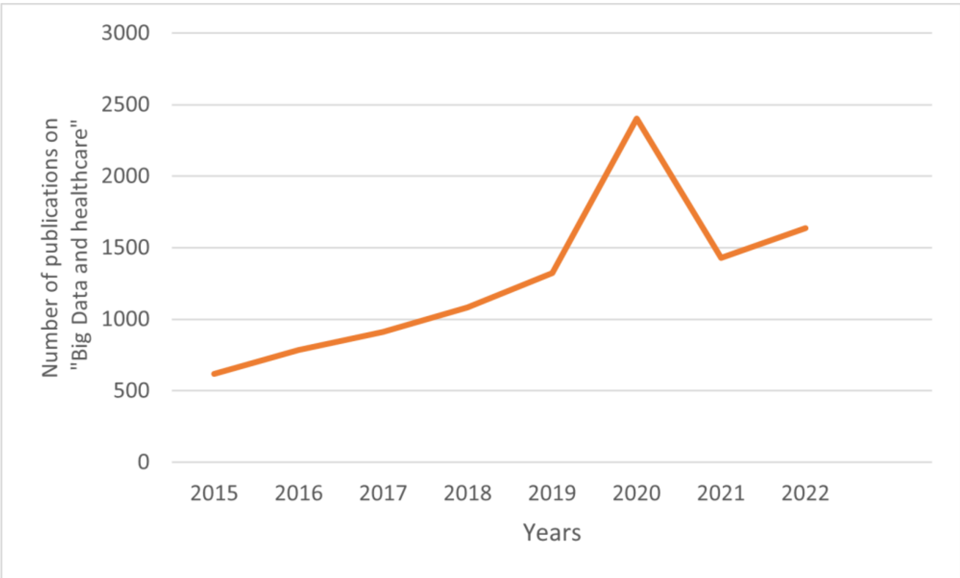

Figure 1: Number of publications on 'Big Data and healthcare' reported by year (from 2015 to 2022). The publications are identified through a search of MEDLINE with the following terms for the literature search: ('Big Data') AND ('Healthcare')

Big Data can be linked over time, and across data sources, to create longitudinal records for individuals and multilevel data structures (e.g., patients within practices within geographic areas). This, in turn, facilitates the creation of an observational evidence base for clinical questions that would otherwise not be possible.

Moreover, Big Data and predictive analytics can contribute to precision public health by improving public health surveillance and assessment, therefore, in a public health perspective, the gathering of a very large amount of data, constitute an inestimable resource to be used in epidemiological research, analysis of the health needs of the population, evaluation of population-based intervention and informed policy making.

1.1.1 Routinely collected healthcare data and multiple sclerosis

Diagnosis of neurological diseases is a growing concern and one of the most difficult challenges for modern medicine due to high social impact and costs.

To study MS epidemiology, it is preferable to use population-based studies. These studies are useful also to describe comorbidities, care pathways, the burden of this disease and to plan the management strategies and resource allocation necessary to cope with it (Lix et al. 2008; Di Domenica Antonio et al. 2014).

The presence of comorbid disease is a critical issue for clinicians given the breadth of adverse impacts with which it is associated. Especially in MS, comorbidity is associated with a longer delay between MS symptom onset and diagnosis, more severe disability at diagnosis even after accounting for diagnostic delays, greater disability progression, increased health-care utilization, and higher mortality[4].

Therefore, using routinely collected data to evaluate the comorbidity is a key importance to manage MS. An example is a study conducted by Palladino et al.27 that showed an association between multiple sclerosis and increased risk of macrovascular disease by using a population-based cohort of 84,823 people with or without multiple sclerosis.

Factors affecting the distribution of MS, which may help determine what causes the disease include age, sex, race, genetics, and geographical location. Also in this setting, big data have been used, in fact, a retrospective cohort of more than 9 million person-years has been used to calculate the Incidence of multiple sclerosis in multiple racial and ethnic group[5].

Regarding the geographical location factor, a population-based cohort study about 6,6 million has been conducted to assess the association between residential proximity to major roadways and the incidence of MS in Ontario, Canada[6]

The above demonstrates the usefulness of routinely collected data to investigate MS in order to improve patient health and quality of life and to optimize health resource use.

1.2 Model approaches to analyze data and support public decision making.

As we progress further into the digital age, the sheer amount and speed at which environmental, population, and public health data are growing have become increasingly evident. Over the past few decades, the field of big data analytics has witnessed remarkable advancements, including statistical analysis, Bayesian statistic, data mining, machine learning, and deep learning, which have piqued the interest of researchers and scientists across various domains[7]. The importance of making decisions grounded in concrete evidence cannot be overstated, as it holds a profound impact on public health and the effective implementation of programs. Furthermore, in handling data related to human health and medicine, we must also grapple with scientific integrity concerns, encompassing issues like privacy, data sharing, bias, and statistical inference. It is with these considerations in mind that this Special Issue centres on the utilization of big data analytics and various decision-making models in the realm of public health, bridging the gap from theoretical foundations to practical applications.

The analysis of longitudinal data is essential to understand the evolution of disease and the effect of interventions over time. A source of longitudinally recorded data that is being used increasingly often in medical research is health care consumption data; that is, data sources that have been constructed by extracting and linking electronic health records from primary, specialist, and hospital care with other data sources such as nationwide registries for epidemiological surveillance.

Data cohorts constructed by extracting medical records have thousands—if not millions—of individuals with hundreds of measurements each: The availability to researchers of such vast amount of data allows answering more relevant and detailed clinical questions but poses new challenges.

In the past years, several methods have been developed to deal with longitudinal data. However, all too often methodological approaches that overstate how much variability is present misdirect policy and practice. In the extreme case where no real differences exist between organisations or geographies, insufficient methods may suggest that variation does exist when in fact the data simply reflect chance.

1.2.1 Mixed-effects regression

Mixed-effects regression models are a powerful tool for linear regression models when your data contains global and group-level trends.

Mixed-effect models are common in scientific experiments where a given effect is assumed to be present among all study individuals which needs to be teased out from a specific effect on a treatment group. In a similar vein, this framework can be helpful in pre/post studies of interventions.

Mixed-effects regression models are a well-established tool which can be employed to partition observed variance into that which is due to chance and that which can be attributed to underlying differences between organisations. Mixed-effects regression models (also known as multi-level models) have become a standard tool in medical research over recent decades and are used to model situations where observations are not independent, for example when clustered by hospital or medical practice. Mixed-effects models also can be used to facilitate the investigation of cluster-level effects while still making use of the patient-level data (e.g., examining whether certain subtypes of organisation perform better or worse, on average, than others). As we argue below, taking a simpler approach can lead to an overestimate of between organisation variance, especially when the within-organisation sample size is small[8].

1.2.2 Bayesian Approach

Bayesian decision making is the process in which a decision is made based on the probability of a successful outcome, where this probability is informed by both prior information and new evidence that the decision maker obtains. Bayesian analysis is the statistical analysis that underlies the calculation of these probabilities.

In its more general form, Bayes' Theorem gives the full posterior distribution of a given parameter rather than just a single probability (and the probability can be calculated from the full distribution). This posterior distribution is equal to the prior distribution modified by the new information (the likelihood). The two approaches to analysis usually lead to differences in statistical inference—that is, what sorts of statements are made to summarize the results of the analysis and contribute to decision making based on the analysis. Frequentist analysis results in point estimates of parameter values, standard errors and CIs for these point estimates, and P values arising from hypothesis tests.

Decision making and analysis using a Bayesian framework can be contrasted with the more traditional framework for statistical analysis, often referred to as the frequentist approach. Frequentist statistical analysis does not use prior information about the parameter being estimated, but instead relies entirely on new evidence from data collected specifically for the purpose of estimating that parameter. More fundamentally, the frequentist approach operates under the assumption that the parameter being estimated has a single true value, about which we have no prior information. The Bayesian approach, by contrast, assumes that unknown parameters have distributions of values, and we do know something about these distributions based on prior information. So rather than disregard prior knowledge, it is considered together with new knowledge. Under a Bayesian framework, the researcher starts with prior beliefs about or estimates of the effects of the weight loss program, then collects data in the study to provide new evidence. The Bayesian analysis combines the new data with prior beliefs to estimate the posterior distribution of the effect of the weight loss program. Statistical inference in the framework is then based on this estimated posterior distribution. Based on this distribution, a researcher can calculate the mean value of the distribution, which can be interpreted as a single estimate of the parameter, similar to the point estimate in frequentist analysis.

1.3 Objective

The study aims to use routinely collected health data to support decision making in public health with a specific focus on multiple sclerosis. It is a case study of:

1. **Epidemiology of multiple sclerosis:** Validate an algorithm based on routinely collected healthcare data to detect incidence of multiple sclerosis (MS) in the Campania Region (South Italy) and to explore its spatial and temporal variations.

2. **Real-world pharmacological effectiveness**: Provide real-world evidence on the use of DMTs for treating multiple sclerosis (MS), with specific regard to prescription pattern, adherence, persistence, healthcare resource utilization and related costs.

3. **Impact of COVID-19 and system recovery in delivering healthcare:** Explore the impact of COVID-19 on healthcare delivery to people with MS and the subsequent recovery of the system.

2 Epidemiology of multiple sclerosis in the Campania region (Italy): derivation and validation of an algorithm to calculate the 2015-2020 incidence.

2.1 Introduction

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system[9], whose onset is usually in young adults [10]. More than 2.8 million people live with MS around the globe, with a median prevalence rate of 36 per 100,000 and a median incidence rate of 2.1 per 10,000 [11]. However, spatial and temporal variations in MS incidence and prevalence are expected as a consequence of different factors [12–14]. First, specific genetic background can affect the risk of developing MS [15]. Environmental exposures (e.g., infections, sunlight, vitamin D) can further affect the risk of MS [16]. Not least, changes in healthcare organization (e.g., COVID19 restrictions) could have affected the likelihood of being diagnosed with MS. As such, up-to-date and reliable estimates of MS incidence and prevalence are needed for healthcare planning and resource allocation, to ultimately reduce the overall burden of this chronic disease [17],[18].

So far, most estimates in epidemiological studies rely on clinical registries, which might be influenced by selection bias (i.e. only including patients from participating centres whose clinical and socio-economic characteristics might differ from the general population[19]), and do not allow for continuous monitoring of the MS epidemiology. Therefore, the use of routinely-collected healthcare data to identify people with MS in a population is deemed highly useful [20]. Still, these algorithms would need formal validation (i.e., sensitivity and specificity), which is not always feasible [21–23] Further challenges arise from the study of a relatively low-prevalence disease (i.e., MS), which would require Bayesian methodology, rather than frequentist approach, to explore spatial and temporal variations[24,25]. Not least, socioeconomic determinants of MS risk have not been always accounted for when estimating MS incidence [26].

In the present study, we aim to 1) validate an algorithm to estimate incidence of MS using routinely collected healthcare data in the Campania Region (South Italy); 2) estimate spatial and temporal trends in MS relative risks using a Bayesian-based methodology; and 3) estimate the proportion of undetected cases.

2.2 Materials and Methods

2.2.1 Study Design

This is a population-based study, obtained from the retrospective analysis of routinely collected healthcare data of individuals with MS resident in the Campania Region (South Italy) from 2015 to 2020 (population on 1 January 2021 5,712,143 with 2,84,616 males and 2,927,527 females) [27].

The Italian healthcare system is based on regional healthcare services operating under the principles of universal coverage. The regions are responsible to organize and deliver healthcare services through Local Health Authorities (Azienda Sanitaria Locale) [28].

Under the Italian Law, each region is divided into a number of provinces. The Campania Region is divided into five provinces: Naples, Benevento, Avellino, Caserta and Salerno. Over half of the population is resident in the province of Naples[29].

Healthcare services delivered to residents in the Campania Region by healthcare providers located outside of the Region are then reported to the Campania Region Healthcare Regulatory Society (So.Re.Sa.) for billing purposes, and thus included in our datasets.

The study was approved by the Federico II Ethics Committee (332/21). All patients signed informed consent authorizing the use of anonymized, routinely collected healthcare data, in line with data protection regulation (GDPR EU2016/679). The study was performed in accordance with good clinical practice and the Declaration of Helsinki.

2.2.2 Study Population

The dataset was created by merging different regional data sources. Following validation study[30], the cohort comprised all residents in the Campania Region who had at least one MS-specific record, from 2015 to 2020, in any of the routinely-collected healthcare databases, including:

1. Regional Drug Prescription database, which includes all MS-specific DMTs pre- scribed in the study period (e.g., alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1b, natalizumab, ocrelizumab, peg- interferon beta-1a, teriflunomide).
2. Hospital Discharge Record database, which includes all admissions in the study period with an ICD-9 CM code of MS as one of the discharge diagnoses.
3. Outpatient database, which includes all outpatient consultations with exemption code for MS.

The case-identification algorithm was validated towards a clinical registry, and showed 99.0% sensitivity, with only 2.7% of cases remaining undetected[30].

All three datasets included demographics (age, sex) with province of residence. Data was fully anonymized using the same algorithm, so that data linkage was possible, by the Campania Region Healthcare Regulatory Society (So.Re.Sa.) before releasing the datasets.

From the datasets, individuals with a diagnosis of MS not resident in the Campania Region were excluded.

2.2.3 Clinical Dataset

About 30% of the MS population resident in the Campania Region is currently registered with the MS Unit at the Policlinico “Federico II” University Hospital of Naples (Italy)[30]. Therefore, for hospital discharge records, outpatients, and prescriptions of the MS population followed-up at this MS Unit, linkage with clinical data was available. Anonymization was performed using the same algorithm adopted for the administrative dataset. Hence, we used the date of formal diagnosis in the clinical dataset to ascertain identified and unidentified incident MS cases in the administrative datasets[30].

2.2.4 Statistical Analysis

The extraction included individuals living in the Campania Region who had at least one MS record from the administrative datasets (drug prescriptions, hospital discharge records, outpatients), from 2015 to 2020. The first record in the administrative databases was considered as the index date.

First, to identify incident cases (aim 1), we assessed the minimum time interval between our study baseline (Jan 1, 2015) and the index date [31,32], hypothesizing the index date was the date of MS diagnosis (as per routinely collected healthcare data), using the clinical dataset to ascertain the actual date of diagnosis and to validate the algorithm. Therefore, we tested four variants of the algorithm, which differed for the length of the time interval between study baseline and index date: 1) at least 12 months, from Jan 1, 2015; 2) at least 18 months, from Jan 1, 2015; 3) at least 24 months, from Jan 1, 2015; and 4) at least 36 months, from Jan 1, 2015. We assessed the discrimination power of the candidate algorithms (using a time frame of 12, 18, 24 and 36 months from Jan 1, 2015) to identify incident cases by calculating sensitivity, specificity, positive and negative predictive values, as well as area under the curve (AUC).

Using the most accurate algorithm, we calculated cumulative MS incidence rate for the years 2016–2020, annual MS incidence rate, and 95% confidence intervals (CI). MS incidence rate was expressed as the number of new cases per 100,000 inhabitants. 95%CI were calculated using Byar's approximation of the Poisson test [33].

To explore the geographical distribution of MS relative risk in the Campania region (aim 2), we adopted both frequentist (Standardized Morbidity Ratio (SMR)) and Bayesian approaches (i.e., Besag, York, and Mollie (BYM))[34]. The Bayesian approach is considered the gold standard when assessing the geographical distribution of disease frequency in small geographical areas when the condition is not rare[32,35].

In the frequentist approach, SMR was estimated for each province (Naples, Benevento, Avellino, Caserta and Salerno). The SMR is the ratio between the number of observed cases and the number of expected cases in a province if the population has the same specific rates as the standard population.

The number of expected cases was calculated using indirect internal standardization [32]. In the Bayesian approach, the relative risk of local area estimate can be seen as 'borrowing strength' from the general mean and from neighboring areas (prior distribution)[34,36,37]. In particular, we used the convolution prior[38]. Moreover, to explore and quantify associations between the MS incidence and relative deprivation for each province of the Campania region, we also considered the deprivation index as a covariate in the estimation model[39]. The deprivation index is a measure intended to provide a summary of the socioeconomic conditions and living disadvantages of the inhabitants of a given area. The higher the value of the deprivation index is in a given area, the more that area is at risk of socioeconomic hardship and material deprivation[40].

We conducted a comparative analysis of both the frequentist and Bayesian approach to provide a more accurate estimate of the relative risk.

Finally, to estimate the proportion of undetected cases (aim 3), we used the capture-recapture method. Keeping the boundary conditions of sampling unchanged is essential for the accuracy of the capture-recapture method. Because of the impact of SARS-CoV-2 on healthcare service (e.g., COVID19 restrictions), the 2020 year did not satisfy this assumption and was therefore not considered in the capture and recapture analysis.

Model selection was based on Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and good-ness-of-fit based confidence intervals following the method published by Regal and Hook[41,42] .

Statistical analyses were performed using Stata (17.0, StataCorp LLC, College Station, TX) and WinBUGS.

2.3 Results

The study included 7,431 people with MS resident in the Campania region between 2015 and 2020 (age, 46.11 ±13.55 years; females, 64.10%). Linkage to the clinical dataset was available for 25.48% of the regional MS population.

2.3.1 MS Incidence

The developed algorithms were compared by looking at their sensitivity and specificity. We favored the algorithm identifying individuals with at least 12 months of lack of data, from Jan 1, 2015. This algorithm included 2,150 incident MS cases, with 74.4% sensitivity (95%CI =64.1%, 85.9%), 95.3% specificity (95%CI =90.7%, 99.8%), 0.85 ROC area (95%CI = 82.3%, 87.8%), 75.3% positive predictive value (95%CI =64.9%, 86.9%) and 95.5% negative predictive value (95%CI =90.5% ,99.1%). Other tested algorithms using longer intervals between Jan 1, 2015, and the index date, did not show significant improvements in sensitivity, specificity and AUC (**Appendix A**).

The cumulative incidence obtained was 36.68 (95%CI =35.15, 38.26) per 100,000 from 2016 to 2020. The annual incidence of MS for Campania Region was 7.34 (95%CI =7.03, 7.65) per 100,000 people-year [42]. The female/male ratios ranged from 1.16 to 1.67 (**Table 1**).

Table 1. MS Incidence and prevalence per year. The MS incidence rate per years was calculated by dividing the total number of cases by the total number of persons in the population, and was expressed as the number of new cases per 100,000 inhabitants. 95% CI was calculated according to Byar's approximation of the Poisson test.
Note: [a]patients: Number of newly diagnosed patients in a year; [b] Prevalent patients: total number of patients in the dataset; 95%CI, 95% confidence interval.

Year	2016	2017	2018	2019	2020
Incident Patients [a]	569	407	431	325	418
Prevalent Patients [b]	5,850	6,257	6,659	6,948	7,338
Incidence Rate per 100,000 (95% CI)	9.37 (8.94-10.56)	6.97 (6.31-7.68)	7.40 (6.37-8.13)	5.66 (5.06-6.31)	7.32 (6.63-8.05)
Prevalence Rate per 100,000 (95% CI)	99,99 (97.4-102.5)	107.16 (104.52-109.85)	114.28 (111.55-117.06)	121.04 (118.21-123.92)	128.46 (125.54-131.44)
Male Prevalent Patients	2,020	2,203	2365	2,467	2,629
Female Prevalent Patients	3,830	4,054	4,294	4,481	4,709
Male Incident Patients	228	183	175	118	172
Female Incident Patients	341	224	256	207	246
Male Incidence Rate per 100,000 (95% CI)	8.31 (7.00-9.12)	6.44 (5.54-7.44)	6.16 (5.28-7.14)	4.21 (3.49-5.05)	6.18 (5.29-7.17)
Female Incidence Rate per 100,000 (95%CI)	11.35 (10.18-12.62)	7.48 (6.53-8.52)	8.57 (7.56-9.69)	7.04 (6.11-8.07)	8.40 (7.39-9.52)
Female/Male ratio	1.37	1.16	1.39	1.67	1.36

Figure 2 shows age-specific MS incidence cases. Most people were diagnosed between the ages of 20 and 50. In particular, the distribution has two peaks that correspond to the 25-34 and 45-54 age groups, respectively.

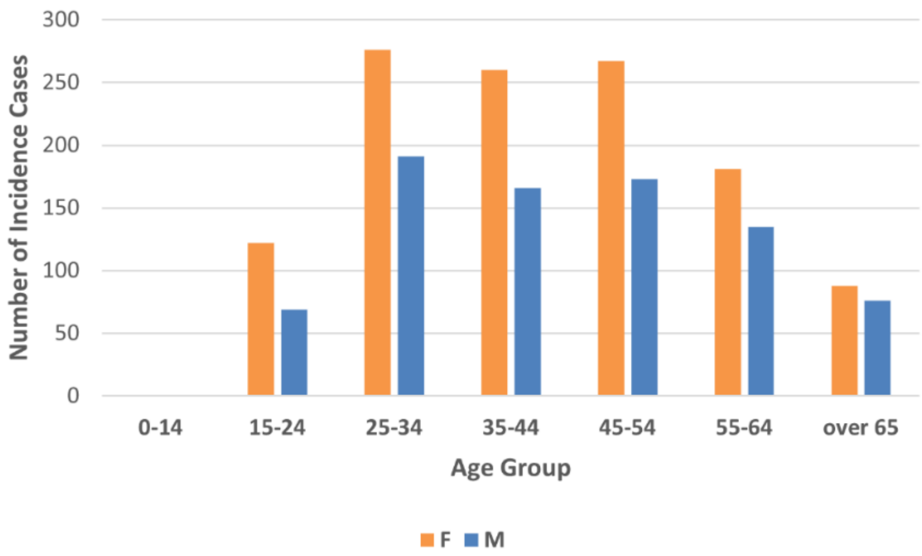

Figure 2. MS incidence by age group

2.3.2 Temporal and spatial trends in MS incidence

Looking at temporal trends, no significant differences in MS incidence were observed between years (**Figure 3a**). On the contrary, the prevalence rate of MS steadily increased each year (**Figure 3b**).

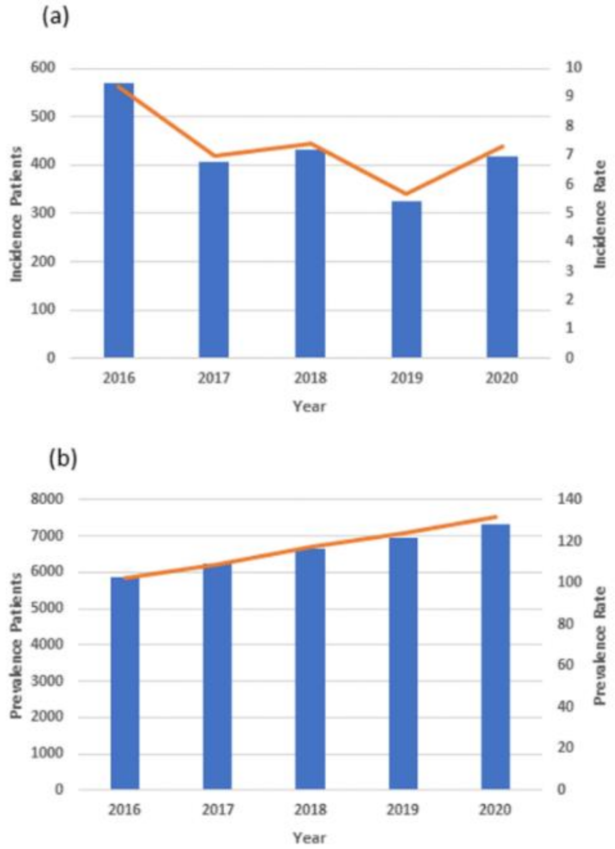

Figure 3. Incidence rate and prevalence rates per year. (a) MS incidence rate for the years 2016–2020 was calculated by dividing the total number of incident cases in a year by the total population. It was expressed as the number of new cases per 100,000 inhabitants. (b) The MS prevalence rate for the years 2016–2020 was calculated by dividing the total number of patients in the dataset in a year by the total population per 100,000 inhabitants.

Looking at spatial trends, the relative risk for each province of the Campania Region is presented in **Table 2**. In particular, the range values of the Bayesian models (BYM) were always smaller than those of SMR, indicating that Bayesian models were smooth-er than the frequentist model [37].

Table 2. Relative risks for all provinces of the Campania Region. The SMR is the ratio between the number of cases observed and the number of expected cases in a province if the population has the same specific rates as the standard population. In the Bayesian approach, the BMY model was used to estimate the relative risk of the local area using the convolution prior and the deprivation index as a covariate in the estimation model.
Note: SMR, Standardized Morbidity Ratio; BYM, Besag York Mollié Model.

Province	**SMR**	**95% CI**	**BYM**	**95% CI**
Naples	1.003	0.941-1.068	1.002	0.944-1.067
Caserta	1.126	1.007-1.256	1.125	1.009-1.256
Benevento	1.262	1.039-1.521	1.261	1.054-1.496
Salerno	1.478	1.353-1.612	1.472	1.342-1.601
Avellino	1.734	1.518-1.974	1.701	1.488-1.931

We drew a map of the geographical variation of MS incidence across the five provinces using Bayesian hierarchical models (**Figure 4a**). The figure shows a decreasing gradient of MS risk from the eastern mountainous part of the region to the western sea-side part; in particular, the MS risk was the lowest in Caserta and Naples, and the highest in Avellino.

The relative risk maps (**Figure 4a**), adjusted for deprivation index, showed a similar distribution to incidence maps (**Figure 4b**). This result suggests a relation of direct proportionality between social-economic condition and incidence.

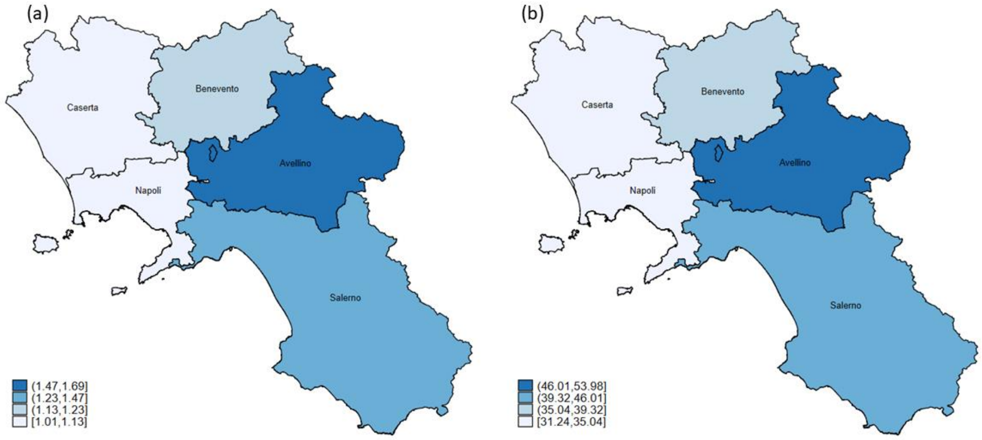

Figure 4. Map of the geographical variations of MS relative risks across the 5 provinces of the Campania Region. (a) The BMY model was used to estimate the relative risk of the province adjusted for deprivation index; different scales of blue are proportional to the magnitude of values: the lighter the shade of blue, the lower the risk of MS (Caserta and Naples); the darker the shade, the higher the risk of MS (Avellino). Then (b), the MS incidence rate for the years 2016–2020 was calculated by dividing the total number of cases by the total population and was expressed as the number of new cases per 100,000 inhabitants; different scales of blue are proportional to the magnitude of values: the lighter the shade of blue, the lower the incidence rate of MS (Caserta and Naples); the darker the shade, the higher the incidence rate of MS (Avellino). The two maps showed a similar distribution of MS cases**.**

2.3.3 Undetected cases

In the capture-recapture analysis, the model with the best fit showed that the number of expected MS cases was equal to 1930 (95%CI = 1839, 2097), with a 11% increase, when compared with the number of detected cases (**Appendix B**)

2.4 Discussion

We validated a case-finding algorithm to identify MS incident cases using routinely collected healthcare data and estimated the temporal and spatial trends in MS incidence in the Campania Region (South Italy). We proposed an approach to measure the change of MS incidence, potentially, in relation to risk factors, which could be used to inform policy and support prevention strategies.

The algorithm showed a sensitivity of 74.4% and a specificity of 95.3%. This algorithm used a 12-month interval between baseline (Jan 1, 2015) and index date (first detected MS record in routinely collected healthcare data), as discrimination period to detect incident over prevalent cases. This time interval is significantly shorter than previous algorithms[31], and possibly reflects the universal healthcare coverage in Italy which leads to more frequent access to services, when compared to insurance-based systems[43]. The cumulative incidence obtained was 36.68 (95%CI =35.15, 38.26) per 100,000 from 2016 to 2020 and the mean annual incidence of MS was 7.34 (95%CI =7.03, 7.65) per 100,000 people-year. Moreover, we performed a Bayesian estimation of MS relative risk in the Campania region, which proved superior to conventional frequentist approach. Thus, we have validated a robust approach to measure MS incidence and its variations in a well-defined geographical area, with availability of both clinical and administrative data.

Previous algorithms for MS incidence were based on either clinical registers[32,44,45],or administrative data[46], but did not perform cross-validation between datasets. Estimating incidence by using only disease registries and clinical records might be influenced by selection bias (i.e., only including patients consenting to the study from participating centers, whose clinical and socio-economic characteristics might differ from the general population), and do not allow for continuous monitoring of the MS epidemiology. Our algorithm was developed considering recommendations for case identification in the setting of Italian routinely collected healthcare data [33]. In particular, we equally weighed the use of DMTs and other healthcare resources (e.g., hospital admissions, outpatients), thus including both treated and untreated MS patients (when compared with clinical registers usually focusing on treated MS). Also, in this study, a Bayesian analysis was used to study MS geographical distribution in the region, while conventional statistical approaches did not appear to be reliable enough. Several works relied on administrative data to estimate incidence rate[45,47]Nevertheless, to the best of our knowledge, this is the first study to adopt high granularity datasets to estimate the geographic distribution of MS relative risk using the Bayesian method. Therefore, we believe our algorithm might be applied to other fields of medicine and neurology in the Campania Region, which could represent a proof-of-concept laboratory for epidemiological studies. Similarly, the algorithm might be easily employed in similar settings to provide epidemiological estimates supporting public health policy decision making.

Our estimate of annual incidence rate (7.34 per 100,000 people; 95%CI:7.03, 7.65) is in line with estimates for other Italian regions and European countries[45–48] and remained stable across the study period (2016-2020). On the contrary, we observed progressively increasing MS prevalence, suggesting longer survival with MS. Looking at the sex-incidence rate, the results were similar with previous studies. Indeed, the incidence in women was approximately two times higher when compared with males [35,46,49–51].

Our study also shows a gradient in incidence decreasing while moving from the eastern mountainous part of the region, to the western areas closer to the sea, thus pointing towards the association between sun exposure and MS risk [22,52]. In the future, our algorithm could be used for epidemiological studies evaluating the changes in MS incidence in relation to potential medical (infection, vaccination) and environmental (pollution) risk factors.

We have to acknowledge that the most reliable data sources for timing of MS onset and diagnosis are registry data and clinical records. However, we specifically aimed to develop an algorithm to detect formal diagnosis of MS using different healthcare data (prescriptions, hospital discharge records, exemption codes), and to validate clinical registry data. Indeed, we found 74.4% sensitivity and 95.3% specificity, towards clinical registry which was used as diagnostic reference. This work builds on previous evidence aiming to use routinely collected healthcare data to identify MS[53,54]. This algorithm will allow the study of the spectrum of MS, including risk factors, biological onset and prodromal MS[55]. Another limitation of the study is the implementation of the analysis in a small geographical area, though the Campania Region counts about 6 million inhabitants, and is the second most populated region in Italy [22] Socioeconomic factors such as education level, access to healthcare, and life course socioeconomic position, may be linked to MS incidence and its subsequent progression [56], and will definitely be considered in the future; still, in this work, we used the deprivation index as a surrogate of socioeconomic status. Furthermore, we observed double peak curves for MS incidence over years that could suggest a lack of sensitivity in specific periods; however, since the study period covers a relatively long-time span, we may assume this bias is mitigated.

2.5 Conclusions

We have validated a case-finding algorithm based on administrative data to estimate up-to-date incidence of MS, and its spatial and temporal variations in the Campania Region. This algorithm will be used in future studies to evaluate changes in MS incidence in relation to different risk factors to inform policy and to support prevention strategies in the MS field.

2.6 APPENDIX A

The algorithms developed in the study have been compared in terms of sensitivity and specificity. We favored the algorithm identifying individuals with at least 12 months of lack of data, from Jan 1, 2015. This algorithm included 2,150 incident MS cases, with 74.4% sensitivity (95%CI =64.1%, 85.9%), 95.3% specificity (95%CI =90.7%, 99.8%), 0.85 ROC area (95%CI = 82.3%, 87.8%), 75.3% positive predictive value (95%CI=64.9%, 86.9%) and 95.5% negative predictive value (95%CI =90.5% ,99.1%). Other tested algorithms did not show significant improvements in sensitivity, specificity and AUC (**Table 3**).

Table 3: Validation Criteria for Model Selection. Note: AUC, Area Under the Curve; PPV, Positive predictive value; DoF, Degree of freedom. NPV, Negative predictive value. We tested four variants of the algorithm, which varied according to the length of this time span of: at least 12 months, from Jan 1, 2015; at least 18 months, from Jan 1, 2015; at least 24 months, from Jan 1, 2015; and at least 36 months, from Jan 1, 2015.

Algorithm	Sensitivity	Specificity	AUC	PPV	NPV
≥ 12 months (95% CI)	74.4% (64.1%-85.9%)	95.3% (90.7%-99.8%)	85.1% (82.3%-87.8%)	75.3% (64.9%-86.9%)	95.5% (90.5%-99.1%)
≥ 18 months (95% CI)	69.4% (58,5%-81.5%)	96.1% (91.5%-101.6%)	82.1% (79.5%-86.1%)	73.5% (62.1%-86.5%)	90.5% (90.8%-101.8%)
≥ 24 months (95% CI)	69.5% (58.1%-82.5%)	97.4% (92.4%-102.5%)	83.4% (80.1%-86.7%)	76.9% (64.3%-91.3%)	96.2% (91.4%-101.3%)
≥ 36 months (95% CI)	58.7% (45.2%-75.0%)	98.3% (93.5%-103.4%)	78.1% (74.5%-83.1%)	71.1% (54.8%-90.8%)	98.3% (93.5%-103.4%)

2.7 Appendix B

In the capture-recapture analysis, the model with the best fit showed that the number of expected MS cases was equal to 1930 (95%CI = 1839, 2097), with an 11% increase, when compared with the number of detected cases (**Table 4**).

Table 4. Goodness of Fit Criteria for Model Selection in Capture-Recapture Analysis. Note: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; Gp2, Goodness of fit; DoF, Degree of freedom. X, the estimated number of undetected cases that were not recorded in any of three sources: N, The estimated total number of detected cases in Italy from 2015 to 2019. A, SDO source; B, Drug Prescription source; C, Outpatient source. C/A/B, A model where all available resources are independent; CA/B, A model where sources C and A are dependent and independent of the source B; CB/A, A model where sources C and B are dependent and independent of the source A; AB/C, A model where sources A and B are dependent and independent of the source C; CA/CB, A model where two sources C and A and also two sources C and B are mutually interdependent and two sources A and B are independent; CA/AB, A model where two sources C and A and also two sources A and B are mutually interdependent and two sources C and B are independent; CB/AB, A model where two sources C and B and also two sources A and B are mutually interdependent and two sources C and A are independent; CA/CB/AB, A model where all two-way interaction between resources existed.

Model	DoF	Gp2	AIC	BIC	X	N	95% CI
C/A/B	3	343.15	337.15	337.31	22	1754	(1745 -1766)
CA/B	4	243.23	239.23	239.34	7	1739	(1734 -1747)
CB/A	4	316.54	312.54	312.65	35	1767	(1754 -1784)
AB/C	4	171.14	167.14	167.25	63	1795	(1777 -1818)
CA/CB	5	229.14	227.14	227.2	11	1743	(1736 -1753)
CA/AB	5	109.85	107.85	107.9	22	1754	(1743 -1769)
CB/AB	5	40.14	38.14	38.19	558	2290	(2079 -2653)
CA/CB/AB	6	0	0	0	198	1930	(1839 -2097)

3 Real-World pharmacological effectiveness

3.1 Interferon beta for the treatment of multiple sclerosis in the Campania Region of Italy: Merging the real-life to routinely collected healthcare data.

3.1.1 Introduction

In the past decades, several injectable, oral and monoclonal antibody disease modifying treatments (DMTs) have become available for multiple sclerosis (MS)[57]. However, DMTs have been rarely compared directly in relation to clinical and healthcare outcomes. On the one hand, MS registries include clinical and treatment data, but are at risk of patient selection (e.g., inclusion of patients and clinical variables only from participating centers), and follow-up (e.g., variable follow-up duration, with patients doing poorly being most likely to be lost to follow-up)[58,59]. On the contrary, datasets based on routinely-collected healthcare data provide detailed healthcare resource utilization with high external validity, in the long-term and on fully representative populations, but lack of clinical data[60]. In our previous studies, we have differentiated interferon beta formulations for the treatment of MS using our clinical registry [60,61], and, separately, using routinely-collected healthcare data of the Campania Region of Italy , and showed that Rebif1 might be characterized by better efficacy and healthcare utilization profile, when compared with other formulations. Hereby, we aim to overcome limitations of our previous studies by merging real-world clinical data to routinely collected healthcare data, to describe differences in clinical outcomes, healthcare resource utilization and costs between interferon beta formulations.

3.1.2 Methods

3.1.2.1 Study design and population

The present observational cohort study is a retrospective analysis of prospectively collected data on people living with MS attending the MS Clinical Care and Research Centre at the Federico II University of Naples, which were linked to routinely collected healthcare data (prescription data, hospital admissions, outpatient services). Study population was defined considering the following inclusion criteria: 1) diagnosis of MS and clinical follow-up at the MS Clinical Care and Research Centre (Federico II University of Naples); 2) 2015–2019-year range; 3) interferon beta prescription and utilization for at least 3 months. The MS population of the MS Clinical Care and Research Centre at the Federico II University of Naples is thought to be representative of the MS population of the Campania Region [62,63]. Exclusion criteria were: 1) age < 18 years; 2) incomplete clinical records.

Anonymization was performed using the same algorithm on clinical registry and routinely collected healthcare data to allow data linkage. Data extraction and linkage was approved by the Federico II Ethics Committee (355/19). All patients signed informed consent authorizing the use of anonymized and aggregated data collected routinely as part of the clinical practice, in line with data protection regulation (GDPR EU2016/679). The study was performed in accordance with good clinical practice and the Declaration of Helsinki.

3.1.2.2 Clinical outcomes

Clinical outcomes were extracted from the clinical registry and were referred to each individual treatment period. During follow-up, patients were evaluated every 3 months, or on the occurrence of a clinical relapse, by an Expanded Disability Status Scale (EDSS) qualified neurologist. The following major clinical outcomes were extracted: occurrence of clinical relapse, time from baseline to the first relapse (time to first relapse), annualized relapse rate (ARR), EDSS progression, and time to EDSS progression (confirmed after 6 months, using a roving EDSS as reference) [64]. Disease duration was estimated as the time between reported clinical onset and baseline.

3.1.2.3 Persistence and adherence

DMT supply was obtained from electronic records of pharmacy services. Persistence was measured as the time spent on a specific DMT (related to each individual treatment period)[65]. Medication possession ratio (MPR) was calculated as an indirect measure of adherence (MPR = (medication supply obtained during follow-up period/medication supply expected during follow-up period)*100)[66]. Healthcare resource utilization and costs As from our previous paper [30], healthcare resource utilization was extracted from Campania Region datasets (i.e., hospital discharge records, regional prescribing database, and outpatient services). Based on the number of inpatient hospital admissions, we computed the annualized hospitalization rate (AHR). Healthcare costs were derived from the Regional registry for corresponding healthcare resource utilization [60], and were inflated to the most recent values (2019), in order to avoid variations in price per unit of service through different years, and were reported on a monthly basis. For patients with hospital discharge records, we computed the Charlson Comorbidity Index [67].

3.1.2.4 Statistics

Descriptive statistics were performed as appropriate considering each variable distribution. To evaluate differences in study variables between interferon beta formulations, we used mixed effect linear regression models (for adherence and costs), Poisson regression models (for ARR and AHR), and Cox-regression models (for time varying variables, such as time to DMT discontinuation, first relapse, EDSS progression). Rebif® was used as reference in the statistical models. Covariates were age, sex, treatment duration, baseline EDSS and adherence (MPR). Results were presented as coefficients (Coeff), incidence rate ratio (IRR), hazard ratios (HR), 95% confidence interval (95%CI), and p-values, as appropriate. Results were considered statistically significant if $p<0.05$ 5. Stata 15.0 was used for data processing and analysis.

3.1.2.5 Results

We included 850 patients with MS treated with interferon beta formulations, for overall 887 individual treatment periods (with some patients being treated with different interferon beta formulations during the study period). Patient disposition flow diagram is presented in **Figure 5**. Demographics, clinical features, persistence, adherence, healthcare resource utilization and costs are reported in **Table 5**. ARR was lower for Avonex® (IRR = 0.61; 95%CI = 0.40, 0.93; p = 0.02), while there was no significant difference between Rebif®, Betaferon®/Extavia® (IRR = 0.71; 95%CI = 0.46, 1.10; p = 0.12), and Plegridy® (IRR = 0.26; 95%CI = 0.06, 0.93; p = 0.06). There was no significant difference in relapse risk (time to first relapse) between Rebif®, Avonex® (HR = 0.40; 95%CI = 0.15, 1.06; p = 0.06), Betaferon®/Extavia® (HR = 0.67; 95%CI = 0.28, 1.62; p = 0.38), and Plegridy® (HR = 0.57; 95%CI = 0.13, 2.38; p = 0.44). Risk of roving EDSS progression was lower for Avonex® (HR = 0.29; 95%CI = 0.11, 0.77; p = 0.01), while there was no significant difference between Rebif®, Betaferon®/Extavia® (HR = 0.90; 95%CI = 0.41, 1.96; p = 0.79), and Plegridy® (HR = 0.72; 95%CI = 0.31, 1.69; p = 0.45). Risk of discontinuation was 3.3-fold greater for Betaferon®/Extavia® (HR = 3.28; 95% CI = 2.11, 5.12; p<0.01), while there was no significant difference between Rebif®, Avonex® (HR = 0.92; 95%CI = 0.66, 1.29; p = 0.63) and Plegridy® (HR = 1.24; 95%CI = 0.88, 1.75; p = 0.21). Adherence was 5% lower for Betaferon®/Extavia® (Coeff = -0.05; 95%CI = -0.10, -0.01; p = 0.02), 6% lower for Avonex® (Coeff = -0.06; 95%CI = -0.11, -0.02; p<0.01), and 8% higher for Plegridy® (Coeff = 0.08; 95%CI = 0.01, 0.16; p = 0.02), as compared with patients taking Rebif®. There were 35 hospital admissions during the study period. AHR was greater for Betaferon®/Extavia® (IRR = 2.38; 95%CI = 1.01, 5.55; p = 0.04), while there was no significant difference between Rebif®, Avonex®(IRR = 1.54; 95%CI = 0.56, 4.19; p = 0.39), and Plegridy® (IRR = 1.61; 95%CI = 0.19, 13.20; p = 0.65). Costs for hospital admissions were higher for Plegridy®(Coeff = 22.98; 95%CI = 9.65, 36.32; p<0.01), while there was no significant difference between Rebif®, Avonex® (Coeff = 3.41; 95%CI = -7.57, 14.41; p = 0.54), and Betaferon®/Extavia® (Coeff = 0.83; 95%CI = -11.64, 13.31; p = 0.89). Costs for MS hospital admissions were higher for Betaferon®/Extavia® (Coeff = 14.95; 95%CI = 1.39, 28.51; p = 0.03), while there was no significant difference between Rebif®, Plegridy® (Coeff = 2.88; 95%CI = -6.70, 12.46; p = 0.55), and Avonex® (Coeff = -3.37; 95%CI = -12.07, 5.32; p = 0.44). Costs for DMTs were lower for Avonex® (Coeff = -157.29; 95%CI = -182.28, -132.29; p<0.01), Plegridy® (Coeff = -131.28; 95%CI = -173.60, -88.96; p<0.01), and Betaferon®/ Extavia® (Coeff = -452.80; 95%CI = -480.15, -425.46; p<0.01) , as compared with patients taking Rebif®.

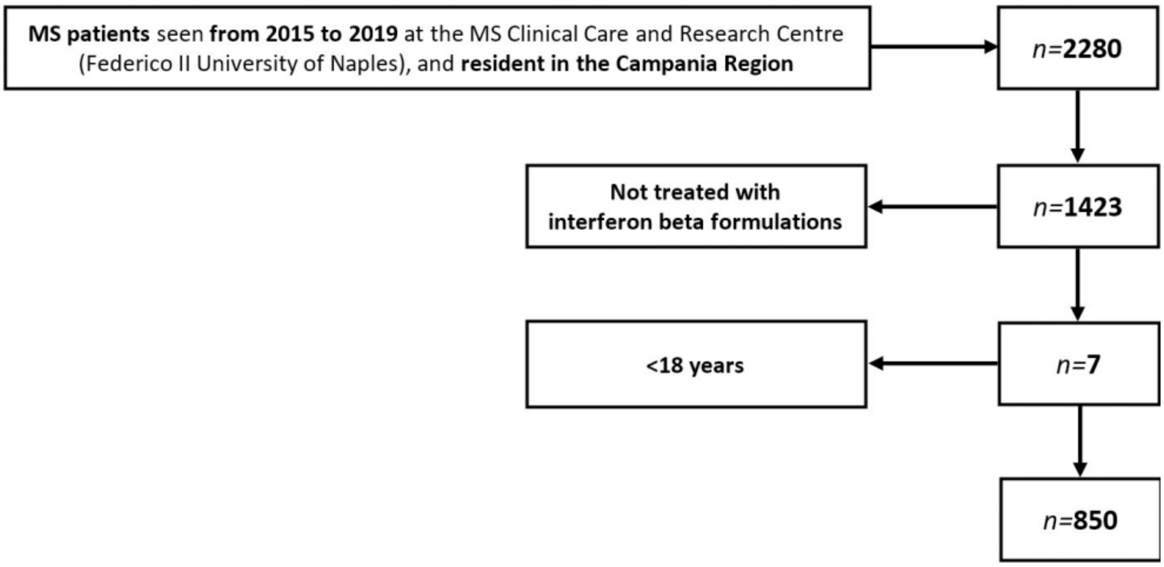

Figure 5. Patients disposition flow diagram.

Table 5. Demographics, clinical features, persistence, adherence, healthcare resource utilization and costs. Note: For patients with hospital discharge records.

		Rebif®	Avonex®	Plegridy®	Betaferon®/Extavia®
Patients, *n*		361	231	60	198
Individual treatment periods, *n*		382	238	60	207
Females, *n (%)*		250 (69.2%)	173 (74.9%)	47 (78.3%)	132 (66.7%)
Age, *years*		35.7±10.4	39.4±10.5	39.4±9.6	42.3±11.9
Charlson comorbidity index*	*0*	368	227	60	194
	1–2	2	6	0	8
	≥*3*	0	0	0	0
Disease duration, *years*		2.8±1.8	3.5±1.9	1.9±1.2	2.9±1.7
EDSS at baseline		3.01±1.21	2.95±0.99	2.51±1.11	4.22±1.54
Relapse occurrence, *n*		81	37	3	30
ARR		0.16±0.54	0.11±0.41	0.06±0.31	0.09±0.37
Roving EDSS progression, n		149	93	0	112
Adherence (MPR)		0.84±0.29	0.81±0.31	0.92±0.32	0.80±0.27
Treatment discontinuation, *n*		91 (23.8%)	67 (28.1%)	30 (50.0%)	65 (31.4%)
Time to discontinuation, *years*		2.87±1.86	3.52±1.90	1.95±1.21	2.90±1.72
AHR		0.01±0.07	0.02±0.21	0.01±0.07	0.05±0.27
Hospital admission costs, *EUR*		36.98±41.00	40.12±70.98	45.59±32.32	47.82±97.90
MS hospital admission costs, *EUR*		34.08±30.70	32.67±40.89	45.59±32.32	41.26±86.87
DMT costs, *EUR*		886.74±275.26	701.26±218.72	796.78±258.01	423.29±134.33

3.1.3 Discussion

In the present study, we have confirmed our previous clinical and population-based results on the use of interferon beta formulations[60,61,65,68], and have showed the feasibility of merging routinely-collected healthcare data and clinical registry for future MS research. One third of MS patients have received at least one prescription of interferon beta from 2015 to 2019, with Rebif1 being the preferred interferon beta formulation, especially in young patients [60]. We have confirmed that adherence is kept at optimal levels in our center (overall above 80%) [60,68], with higher rates in Rebif1 and Plegridy®, when compared with Betaferon®/Extavia® and Avonex®. Also, MS patients remained on interferon beta treatment for 2–3 years, with higher discontinuation rates for Betaferon®/Extavia®, when compared with Rebif®, Avonex®, and Plegridy®. Costs were mainly driven by the use of DMTs, though some interferon beta formulations (e.g., Rebif®, Avonex®) are associated with reduced rates of hospital admissions and related costs. Looking at clinical outcomes, rates of relapses and disability progression (estimated using a roving EDSS as reference) were lower than studies run on previous cohorts [61], possibly also as a consequence of new diagnostic criteria [69], with difficulties in finding and interpreting statistical differences. For instance, we found no differences in time to the first relapse, but in overall ARR, suggesting these differences are a consequence of switching timeliness, with some patients not being switched to more effective DMTs after the first relapse and, thus, accumulating additional relapses. Similarly, differences in rates of disability progression might be biased by the available follow-up to establish sustained progression, which is possibly further increased by the use of a roving EDSS as reference [64]. Our study suffers from different limitations, mostly arising from the single center design and differences in baseline characteristics, that we tried to mitigate by using covariates in the statistical models. However, we have showed the feasibility of combining routinely collected healthcare data to clinical register, for future MS research. We confirmed that interferon beta formulations play a significant role in the management of MS and are overall associated with positive clinical outcomes in the mid-term. Differences between interferon beta formulations are mostly driven by adherence and healthcare resource utilization.

3.1.4 Acknowledgments

Marcello Moccia has received research grants from ECTRIMS-MAGNIMS, the UK MS Society, and Merck; honoraria from Merck, Roche, and Sanofi-Genzyme; and consultant fees from Veterans' Evaluation Services. Roberta Lanzillo has received honoraria from Biogen, Merck, Novartis, Roche, and Teva. Vincenzo Brescia Morra has received research grants from the Italian MS Society, and Roche, and honoraria from Bayer, Biogen, Merck, Mylan, Novartis, Roche, Sanofi-Genzyme, and Teva. Antonio Capacchione is an employee of Merck Serono S.p. A., Rome, Italy, an affiliate of Merck KGaA, Darmstadt, Germany. Other authors have nothing to disclose.

3.2 Persistence, adherence, healthcare resource utilization and costs for ocrelizumab in the real-world of the Campania Region of Italy

3.2.1 Introduction

Ocrelizumab is approved for the use in both relapsing–remitting and primary progressive multiple sclerosis (MS)[70,71]. Ocrelizumab efficacy and safety have been preliminarily explored in clinical trials and their long-term extensions[71,72]. More recently, insights on ocrelizumab real-world use and related clinical efficacy have been gained through clinical registries[73,74]. However, clinical registries do not include healthcare resource utilization and, more in general, do not cover the complexity of MS management[75,76]. Also, few studies have directly compared different DMTs in terms of efficacy measures[77]. Datasets based on routinely collected healthcare data can overcome these limitations and provide detailed information on healthcare resource utilization in the long term and on fully representative populations[78]. In the Campania Region of Italy, we have developed an algorithm, specific for individuals with a diagnosis of MS, to merge healthcare data (e.g. planned and unplanned hospital admissions with related diagnoses and costs) and prescription data[79], and to derive measures of DMT utilization (e.g., adherence, persistence) and economic viability.

Hereby, we aim to provide real-world evidence on the use of ocrelizumab, with specific regard to prescription pattern, persistence, adherence, healthcare resource utilization and related costs, and also to compare ocrelizumab to other DMTs, based on administration (e.g., injectable, oral, and infusion) and activity (e.g., low/medium efficacy and highly active DMTs).

3.2.2 Methods

3.2.2.1 *Study design*

This is a population-based study, based on the retrospective analysis of routinely collected healthcare data, prospectively recorded from 2018 to 2020, on individuals with a diagnosis of MS living in the Campania Region of Italy. The original dataset has been fully described elsewhere[79]. For the purposes of the present study, we have selected this time frame to include ocrelizumab-treated patients, from the beginning of its use in the real-world (first prescription is recorded on Nov 6, 2018). The study was approved by the Federico II Ethics Committee (355/19). All patients signed informed consent authorizing the use of anonymized data collected routinely as part of the clinical practice, in line with data protection regulation (GDPR EU2016/679). The study was performed in accordance with good clinical practice and the Declaration of Helsinki.

3.2.2.2 Population

The dataset was created by merging different data sources of the Campania Region[79]. We specifically included all individual's resident in the Campania Region who had at least one MS record, from 2018 to 2020, in the Hospital Discharge Record database, the Regional Drug Prescription database, or the outpatient database with payment exemptions for MS. The case-finding algorithm has 99.0% sensitivity, with very low risk of missing individuals (2.7%)[79]. We have referred to both individual patients and individual treatment periods (ITPs), since the same patient could have been using different DMTs during the study period. Inclusion criteria were: (1) new DMT prescriptions from Jan 1, 2018, to Dec 31, 2020 (switch from a previous DMT or DMT start in absence of previous treatment records, using data from 2015 to 2017 as characterization period); (2) DMT prescription maintained for at least 6 months (e.g., corresponding to two full infusions for ocrelizumab). Exclusion criteria were: (1) individual treatment periods already including a DMT at baseline (Jan 1, 2018); (2) incomplete records; (3) lack of written consent to participate in the study; (4) residence outside of the Campania Region.

3.2.2.3 Treatment variables

DMT prescriptions were collected, and following DMT groups were defined based on

• DMT administration route: infusion (alemtuzumab, natalizumab), oral (cladribine, fingolimod, teriflunomide, dimethyl fumarate), and injection (glatiramer acetate, interferon beta-1a, interferon beta-1b, and peg-interferon beta-1a), using ocrelizumab as reference for comparison[80];

• DMT treatment line: low/medium efficacy (teriflunomide, dimethyl fumarate, glatiramer acetate, interferon beta-1a, interferon beta-1b, and peg-interferon beta-1a) and highly active treatments (alemtuzumab, natalizumab, cladribine, fingolimod), using ocrelizumab as reference for comparison[60,81].

Based on DMT prescriptions in the previous 12 months, ITPs were classified into treatment naïve (no treatment records in the previous 12 months) and switcher patients (presence of previous treatment records).

3.2.2.4 Persistence, adherence, healthcare resource utilization and costs

DMT discontinuation was defined as a switch to another DMT or complete discontinuation (i.e., no further record of medication initiation) [76,82].

Adherence was calculated as the proportion of days covered (PDC) over 1-year time (total days covered during 1 year divided by 365 days of follow-up, using the expected refill/retreatment timing from current regulatory indications); PDC≥0.8 was considered adherent[80]. Considering that some DMTs have low frequency administration that would have caused too much variability in estimating adherence in 6 months (e.g., alemtuzumab, cladribine, ocrelizumab), we have included in adherence analyses only patients with at least 12 months' follow-up.

Healthcare resource utilization included MS-related and non-MS-related hospital admissions, which were classified based on the main discharge diagnosis. The number of hospital admissions was then reported on annual basis (annualized hospitalization rates (AHR)) [60,83].

Direct healthcare costs were derived from regional datasets, referred to corresponding healthcare resource utilization, and inflated to the most recent values (2020), to avoid variations in price per unit of service through different years [60,83].

We further collected age, sex, and, for patients with Hospital Discharge Records, Charlson Comorbidity Index [84,85].

3.2.2.5 Statistics

Study variables are presented as mean (±standard deviation), number (percent) or median (range), as appropriate. Differences between DMT groups (using ocrelizumab as reference in the statistical models) were explored using Cox regression models (i.e., persistence), and linear regression models (i.e., adherence, AHR, costs), as appropriate. Covariates were age, sex, year of treatment start (2018, 2019, or 2020), treatment duration, and adherence; statistical models were then run for the subgroup of patients with hospital discharge records, also including Charlson comorbidity index among covariates. Results were reported as adjusted coefficient (Coeff), adjusted hazard ratio (HR), 95% confidence intervals (95%CI), and p values, as appropriate. Statistical analyses were performed using Stata 15.0. Results were considered statistically significant for $p<0.05$.

3.2.3 Results

From the population of people with MS in the Campania Region from 2015 to 2020 (n=7080), we included 2495 individuals who were commenced on a DMT from 2018 to 2020, corresponding to 2918 ITPs (the same individual being treated with different DMTs within the study period). Reasons for exclusion are reported in **Figure 6**.

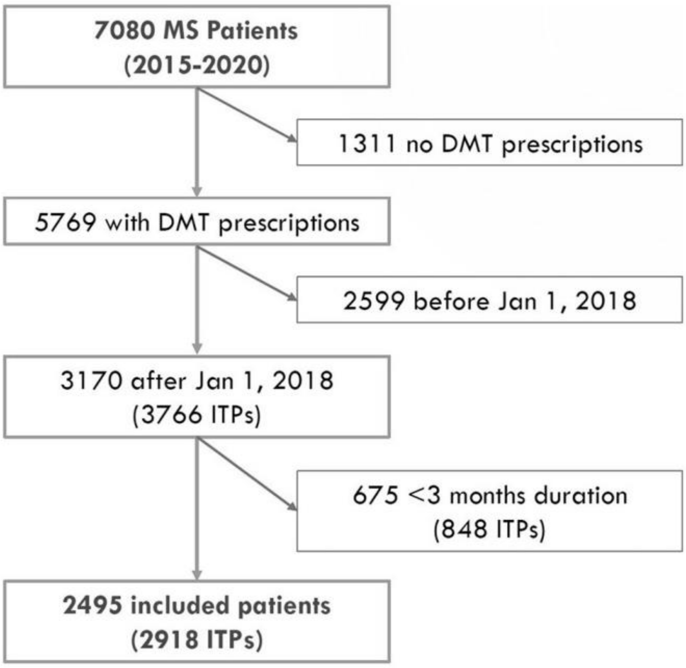

Figure 6. Study flow diagram. Figure shows the number of included and excluded patients, along with reasons for exclusion.

Demographics, comorbidities and treatment features of included patients (and respective ITPs) are reported in **Table 6.**

Table 6. Demographics, comorbidities and treatment features

DMT	Patients (*n*)	ITPs			Age (years)	Females (*n*)	Charlson Comorbidity Index			
		2018	2019	2020			0	1–2	3–4	≥5
Ocrelizumab	398	27	281	91	45.74 ± 10.98	224	395	5	–	–
Alemtuzumab	31	18	13	0	35.39 ± 8.31	21	31	–	–	–
Natalizumab	261	82	72	108	34.05 ± 10.99	183	360	2	–	–
Cladribine	30	0	26	4	43.13 ± 11.97	22	30	–	–	–
Fingolimod	399	197	139	65	39.17 ± 11.42	259	398	3	–	–
Teriflunomide	305	176	71	59	48.51 ± 11.18	202	302	4	–	–
Dimethyl fumarate	587	269	196	123	38.98 ± 12.10	408	583	3	1	–
Interferon beta1a im	87	63	14	10	48.84 ± 12.73	59	87	–	–	–
Interferon beta1b	67	52	14	7	52.12 ± .10.10	40	67	–	–	–
Glatiramer acetate	239	175	182	41	46.73 ± 11.66	164	236	3	–	–
Peg-interferon beta1a	80	39	28	13	39.86 ± 13.62	60	80	–	–	–
Interferon beta1a sc	262	179	48	36	40.88 ± 12.54	199	262	1	–	–

Overall, we included 398 patients treated with ocrelizumab, corresponding to 399 ITPs. Looking at administration route, we included 293 ITPs with other infusion DMTs (alemtuzumab, natalizumab), 1325 with oral DMTs (cladribine, fingolimod, teriflunomide, dimethyl fumarate), and 901 with injectable DMTs (glatiramer acetate, interferon beta-1a, interferon beta-1b, and peg-interferon beta-1a). Looking at efficacy line, we included 724 ITPs with other highly active DMTs (alemtuzumab, natalizumab, cladribine, fingolimod), and 1795 with low/medium efficacy DMTs (teriflunomide, dimethyl fumarate, interferon beta-1a, interferon beta-1b, and peg-interferon beta-1a). Most frequently prescribed DMTs were dimethyl fumarate (n=588, 20.1%), fingolimod (n=401, 13.7%) and ocrelizumab (n=399, 13.6%), with ocrelizumab being the most frequently prescribed DMT in 2019. Also, we observed an overall drop in new DMT prescriptions in 2020 (**Table 6**). Most patients treated with ocrelizumab were newly diagnosed and drug naïve (n=104), followed by patients previously treated with fingolimod (n=76), dimethyl fumarate (n=54), teriflunomide (n=51), glatiramer-acetate (n=37), natalizumab (n=34), interferon beta1a (n=16), interferon beta1b (n=13), alemtuzumab (n=12), and peg-interferon beta1a (n=2). ITP durations and number of patients switching to other DMT or completely discontinuing DMTs are reported in **Table 7**. A minority of ocrelizumab ITPs was discontinued (4 over 399), after 13.71±5.42 months; in particular, 1 patient was switched to natalizumab, 2 patients to dimethyl fumarate, and 1 patient to interferon beta1a. When compared with ocrelizumab, the risk of discontinuation was higher for other infusion (HR=3.64; 95%CI=1.18, 11.18; p=0.02), oral (HR=9.19; 95%CI=3.29, 25.65; p< 0.01), and injectable DMTs (HR = 5.54; 95%CI = 1.96, 15.08; p<0.01) (**Figure 7a**). Similarly, when compared with ocrelizumab, the risk of discontinuation was higher for other highly active (HR=3.78; 95%CI=1.33, 10.76; p=0.01), and low/medium efficacy DMTs (HR=7.59; 95%CI=2.75, 20.95; p<0.01) (**Figure 7b**). Results were confirmed also after adjusting by Charlson Comorbidity index.

Table 7. Treatment duration. Table shows mean (±standard deviation (SD)) and median (and interquartile range (IQR)) of duration of IPTs, and number of patients that were switched to other DMT or were completely discontinued from DMT.

DMT	ITP duration (months)		Switch to other DMT	Complete DMT discontinuation
	Mean ± SD	Median (IQR)		
Ocrelizumab	13.71 ± 5.42	13 (8–19)	4	0
Alemtuzumab	13.77 ± 2.62	13 (12–15)	0	17
Natalizumab	15.53 ± 9.65	12 (7–24)	73	17
Cladribine	11.80 ± 3.21	13 (12–14)	0	0
Fingolimod	19.41 ± 9.97	19 (11–29)	135	62
Teriflunomide	19.79 ± 10.74	19 (10–30)	116	39
Dimethyl fumarate	19.10 ± 10.55	19 (10–29)	64	64
Interferon beta1a im	23.73 ± 12.03	30 (10–35)	130	17
Interferon beta1b	24.32 ± 12.32	30 (10–35)	93	24
Glatiramer acetate	23.41 ± 11.24	21 (9–34)	140	45
Peg-interferon beta1a	16.49 ± 10.38	15 (7–24)	85	16
Interferon beta1a sc	21.61 ± 11.50	23 (11–34)	248	56

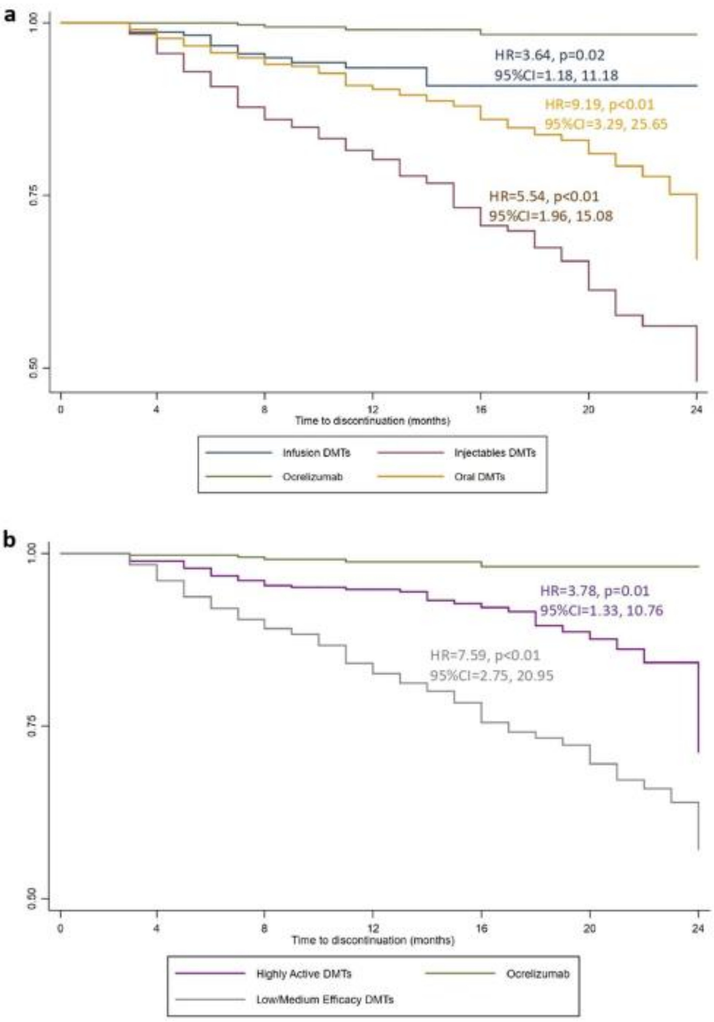

Figure 7. Kaplan–Meier estimates treatment persistence. Adjusted hazard ratio (HR), coefficients (Coeff) and p-values are shown from Cox regression models evaluating administration route (a) and clinical efficacy (b), and including age, sex, year of treatment start (2018, 2019, or 2020), treatment duration, and adherence as covariates.

Adherence to treatment is reported in Table 3. When compared with ocrelizumab, adherence (PDC) was lower for oral DMTs (Coeff=− 0.18; 95%CI=− 0.26, − 0.12; p<0.01), but similar to other infusion (Coeff = − 0.08; 95%CI = − 0.19, 0.02; p = 0.14), and injectable DMTs (Coeff=− 0.01; 95%CI=− 1.11, 0.11; p=0.90). When compared with ocrelizumab, adherence was lower for other highly active DMTs (Coeff = − 0.11; 95%CI = − 0.19, − 0.02; p < 0.01), and low/medium efficacy DMTs (Coeff=− 0.18; 95%CI=− 0.26, − 0.10; p<0.01). Results were confirmed also after adjusting by Charlson Comorbidity index.

Healthcare resource utilization and costs are reported in Table 4. When compared with ocrelizumab, AHR was higher for other infusion DMTs (Coeff=0.05; 95%CI=0.01, 0.09; p = 0.03), and similar to oral (Coeff = − 0.01; 95%CI = − 0.03, 0.03; p = 0.97) and injectable DMTs (Coeff = 0.01; 95%CI = − 0.02, 0.05; p = 0.45). When compared with ocrelizumab, AHR was similar to other highly active (Coeff = 0.01; 95%CI = − 0.02, 0.04; p=0.51), and low/medium efficacy DMTs (Coeff=0.01; 95%CI=− 0.02, 0.04; p=0.55). Results were confirmed also after adjusting by Charlson Comorbidity index.

When compared with ocrelizumab, monthly costs for MS hospital admissions were similar to other infusion DMTs (Coeff=7.83; 95%CI=− 12.94, 28.61; p=0.46), but lower for oral (Coeff=− 18.95; 95%CI=− 35.27, − 2.64; p< 0.01). Results were confirmed also after adjusting by Charlson Comorbidity index.

When compared with ocrelizumab, monthly costs were similar to other infusion DMTs (Coeff=7.83; 95%CI=− 12.94, 28.61; p=0.46), but lower for oral (Coeff=− 18.95; 95%CI=− 35.27, − 2.64; p<0.01) and injectable DMTs (Coeff=− 28.25; 95%CI=− 46.44, − 2.64; p = 0.02). When compared with ocrelizumab, monthly costs for MS hospital admissions were similar to other highly active (Coeff=− 0.77; 95%CI=− 18.12, 16.57; p=0.93), but lower for low/medium efficacy DMTs (Coeff = − 26.02; 95%CI = − 42.45, − 9.58; p < 0.01). Results were confirmed also after adjusting by Charlson Comorbidity index.

When compared with ocrelizumab, monthly costs were similar to other infusion DMTs (Coeff = − 57.28; 95%CI = − 119.15, 4.59; p = 0.07), but lower for oral (Coeff=− 675.83; 95%CI=− 723.16, − 628.50; p<0.01) and injectable DMTs (Coeff=− 675.83; 95%CI=− 1205.92, − 1100.75; p<0.01). When compared with ocrelizumab, monthly costs were higher for other highly active DMTs (Coeff = 92.30; 95%CI = 53.01, 131.60; p<0.01), but lower for low/medium efficacy DMTs (Coeff=− 1043.61; 95%CI=− 1080.02, − 1007.20; p<0.01). Results were confirmed also after adjusting by Charlson Comorbidity index.

3.2.4 Discussion

In this population-based study, we specifically aimed to describe the use of ocrelizumab in the real-world of the Campania Region of Italy, with regards to prescription pattern, persistence, adherence, healthcare resource utilization and related costs. Ocrelizumab was the most frequently prescribed DMT for MS in 2019, with 26% prescriptions being made to treatment-naïve MS patients, suggesting it was addressing unmet needs in the MS treatment scenario. This is the first real-world study on ocrelizumab describing both utilization pattern (i.e., persistence, adherence), and related healthcare resource utilization and costs. When compared with other high-efficacy DMTs, ocrelizumab was used on much more complex populations (i.e., older age, higher comorbidity burden), as already described by some previous studies[86,87]. Notwithstanding this, in our cohort, only 1% of patients were discontinued from.
ocrelizumab, suggesting optimal efficacy and safety[88,89], with higher persistence rates compared with other oral, infusion and injectable DMTs. This could be at least in part due to the use of ocrelizumab on newly diagnosed and treatment-naïve patients in our cohort, which is a known factor of optimal treatment response[73]. Ocrelizumab has already proved high persistence rates in previous studies[80,90,91] ,with efficacy and safety issues being the most common causes of discontinuation[91]. Of note, relapses, disability progression and MRI activity are expected to occur in a minority of patients treated with ocrelizumab[86,87,92] .Taken together, our data suggest that ocrelizumab high persistence rates might be a consequence of optimal efficacy and safety. We also found high rates of adherence to

ocrelizumab compared with lower and similar efficacy class. While we have to acknowledge that adherence analyses were run on the subset of patients with at least 12 months of follow-up, our rate of adherence is in line with previous similar studies[80], and overall suggests optimal safety profile (e.g., no need to delay infusions). Looking at previous real-world studies, side effects were reported by 10% of patients, mostly consisting of mild infusion-related reactions and infections [18], independently from age[86] .The main novelty of our study is the inclusion of healthcare resource utilization and costs. In particular, ocrelizumab was associated with lower direct treatment costs, but was associated with similar probability of MS-related hospital admissions and costs, when compared with other DMTs similar in administration route (e.g., natalizumab, alemtuzumab) and efficacy class (e.g., natalizumab, alemtuzumab, cladribine, fingolimod). Similarly, in a previous US claims' study including 189 patients treated with ocrelizumab, alemtuzumab or natalizumab for 1 year, authors showed reduced costs for ocrelizumab treatment and related procedures[93]. Overall, these findings suggest that ocrelizumab is less expensive but similarly effective to other high-efficacy DMTs. Limitations of our study include the generalizability of our results, since we only included patients from a specific Italian region. However, our cohort had similar distribution (e.g., age, DMT use), when compared to other international studies[86,87,94], and, hence, may reflect the general MS population treated with ocrelizumab. Also, rates of disability progression, relapses and related healthcare resource utilization are expected to increase over the follow-up[95] . Therefore, longer follow-up is warranted to confirm our findings. In addition, we have also included 2020 year in the analysis, with the bias of COVID19 pandemic that could have caused extended interval dosing for ocrelizumab[96] ;however, based on adherence results, this was not the case for most infusions and the drop of new prescriptions in 2020 is in line with a previous English study[97]. Our study also holds limitations derived from the use of routinely collected healthcare data, including the definition of MS-related hospital admission based on the primary diagnosis that could be biased by the physician perspective. We compared ocrelizumab to other approved DMTs specifically approved for MS, while did not extend the analysis to other treatments (e.g., rituximab) due to sample size constraints and possible selection bias, deriving from their use in highly selected populations (e.g., non-responders to approved DMTs). In conclusion, we confirmed previous results on high persistence and adherence rates of ocrelizumab, when compared with DMTs of similar efficacy and mode of administration. We also showed that ocrelizumab is less expensive than other high-efficacy DMTs, while possibly equally effective based on indirect measures on routinely collected healthcare data (i.e., AHR and related costs).

3.2.4.1 Declarations

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3.3 Healthcare resource utilization and costs for extended interval dosing of natalizumab in multiple sclerosis

3.3.1 Introduction

Natalizumab is a monoclonal antibody approved for the treatment of relapsing-remitting multiple sclerosis (MS)[98]. Natalizumab is approved for infusions every 4 weeks (standard-interval dosing [SID]), which provides >80% saturation of its molecular target (i.e., the mononuclear cell α4β1-integrin receptor) for 1 month after administration[99,100]. The safety and tolerability profile of natalizumab is well defined and supported by extensive real-world evidence. In a real-world study with a follow-up of 10 years, over the course of natalizumab treatment >85% of patients had no serious adverse events (SAEs)[101]. In those patients who did experience a SAE, infection was the most commonly reported, occurring in 4.1% of patients [4]. Among serious opportunistic infections associated with use of natalizumab, the risk of progressive multifocal leukoencephalopathy (PML) has to be considered in patients independently exposed to John Cunningham virus (JCV) [101]. Established risk factors for PML in patients positive for anti-JCV antibodies are level of anti-JCV antibodies in serum, previous use of immunosuppressant and duration of natalizumab treatment, especially beyond 2 years; these factors allow evaluation of the individual risk, with subsequent clinical decisions of treatment start, reinfusion or discontinuation [102]. Real-world studies have investigated the use of extended-interval dosing (EID) to reduce the risk of PML [99,103]. In a large observational study, based on the dataset from the Tysabri Outreach Unified Commitment to Health (TOUCH) program and including a retrospective cohort study of 35.521 anti-JCV antibody-positive patients, natalizumab EID significantly reduced the risk of PML[104]. More recently, a prospective, interventional, randomized controlled study showed that patients who were stable on natalizumab dosing every 4 weeks could switch to dosing every 6 weeks without meaningful loss of efficacy, maintaining a similar safety profile between the two arms [100,105]. As such, the use of EID natalizumab could affect healthcare resource use and costs directly, through reduced use of natalizumab and indirectly through reduced administration costs and changes in side effects. However, the extent to which EID can have an impact on healthcare resources and costs remains unknown. In the present population-based study, we aimed to describe the effect of natalizumab SID and EID in clinical practice on healthcare resource utilization and costs using Regional Administrative Databases of the Campania region in Italy.

3.3.2 Methods

3.3.2.1 Study design

This is a population-based study, obtained from the retrospective analysis of routinely collected healthcare data of individuals with MS resident in the Campania region (southern Italy) from 2015 to 2017.

The study was approved by the Federico II Ethics Committee (355/19). All patients signed informed consent authorizing the use of anonymized, routinely collected healthcare data, in line with data protection regulation (GDPR EU2016/679). The study was performed in accordance with good clinical practice and the Declaration of Helsinki.

3.3.2.2 Population

The dataset was created by merging different data sources of the Campania region, comprising ten qualified MS treatment centers, as fully described elsewhere[62] .Briefly, the cohort comprised all individuals living in the Campania region who had at least one MS-related record from 2015 to 2017 in the hospital discharge record database, regional drug prescription database and outpatient database (which includes all outpatient consultations with an MS-specific exemption). From the MS population identified using this algorithm, we further extracted non-MS-related records from hospital discharge record database, regional drug prescription database and outpatient database. For the purposes of the present study, from the MS cohort, we identified all patients receiving natalizumab (ATC code: L04AA23) for at least 18 months during the study period (January 2015–December 2017).

Demographic information retained from each dataset were year of birth and sex. For patients with Hospital Discharge Records, Charlson Comorbidity Index (CCI) was computed[85], as in previous population-based studies in MS [106]. The CCI assigns different weights to comorbidities reported with ICD codes in Hospital Discharge Records. Myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease and diabetes correspond to one weight. Hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor, leukemia and lymphoma correspond to two weights. Moderate or severe liver disease corresponds to three weights. Metastatic solid tumor and acquired immunodeficiency syndrome correspond to six weights. The overall score (from 0 to 29) is obtained from the sum of different weights and provides the risk of death from comorbidities [85].

3.3.2.3 Treatment exposure

From the group of patients in treatment with natalizumab, we identified two subgroups: the SID and EID cohorts. Following the classification applied in previous real-world studies [105,107], SID was defined as having received >15 infusions of natalizumab in the previous 18 months of treatment, and EID was defined as ≤15 infusions of natalizumab in the previous 18 months of treatment. Patients with 'dosing gaps' (infusions >12 weeks apart) or 'overdoses' (infusions <3 weeks apart) between two consecutive infusions were excluded. The overall treatment duration was calculated as the time each patient of SID and EID cohorts was on natalizumab treatment; for both EID and SID patients, only the last 18 months of treatment were considered for the statistics of the study.

3.3.2.4 Healthcare resource utilization and costs

Healthcare resource utilization for each individual was obtained from the combination of hospital discharge records (including all hospital admissions and diagnoses), drug prescriptions (including the frequency of natalizumab infusion) and outpatient visits (including MS and non-MS related outpatient visits). In the Campania region, natalizumab infusions and related MS outpatient visits are registered either as day hospital (e.g., classified within hospital discharge records, with one day hospital aggregating all yearly needs of natalizumab infusions and neurological consultations) or as outpatient (e.g., with one outpatient corresponding to one natalizumab infusion or neurological consultation) [108]. Thus, we grouped MS outpatients and day hospital admissions to depict healthcare resource utilization related to natalizumab infusions and MS management (i.e., infusion-related costs, neurology consultations). We further classified hospital admissions into regular and emergency admissions. In addition, on the basis of each main discharge diagnosis (i.e., the condition that occasioned the need for that hospitalization), we classified hospital admissions and outpatients into MS-related and non-MS-related [109]. We also decided to include hospital admissions without MS as the main discharge diagnosis (non-MS-related hospital admissions); in chronic conditions (i.e., MS), these admissions might refer to long-term complications and/or treatment side effects[26,109]. Healthcare costs were derived from the regional registry for corresponding healthcare resource utilization.

Healthcare costs were inflated to the most recent values (2017) and were reported on an annual basis.

3.3.2.5 Clinical variables

For a large subgroup of patients, it was possible to perform a record linkage to the clinical registry of the MS Clinical Care and Research Centre at the Federico II University of Naples, Italy (the largest MS center of the Campania region): extraction of data regarding expanded disability status scale (EDSS) at baseline and the most recent JCV status was done.

3.3.2.6 Power calculation

The sample was selected from the MS population of the Campania region of Italy, based on the previously described inclusion criteria[30] .Considering a normal distribution of variables to be analyzed in regression models, given a 5% minimum detectable effect size, a two-sided tail and a 5% α error, a sample of 208 patients would be able to achieve 94% power[110].

3.3.2.7 Statistics

Distribution of variables between natalizumab SID and EID was assessed using chi-square test, t-test or Mann– Whitney U test, as appropriate. Differences between SID (reference in the statistical models) and EID in healthcare resource utilization and costs were explored using logistic and Poisson regression models to evaluate the individual probability for each MS patient of using each healthcare resource and the individual rate of utilization, respectively. Differences between SID (reference in the statistical models) and EID in costs were explored using linear regression models to evaluate the individual cost reduction for each section. In the absence of clinical data, the covariates were age, sex and year of treatment start (before 2015, in 2015 or in 2016, accounting for different treatment scenarios and knowledge on natalizumab EID). Statistical models were then rerun on patients with Hospital Discharge Records, including the CCI as an additional covariate in the statistical models.

Results were reported as odds ratio (OR), incidence rate ratio (IRR) coefficient (Coeff.), 95% CI and p-values, as appropriate. Results were considered statistically significant for $p < 0.05$. Statistical analyses were performed using Stata 15.0.

3.3.3 Results

The case-finding algorithm identified 5362 MS cases, with 99.0% sensitivity [62]. From this cohort, we identified 426 patients that received natalizumab during the study period (7.9% of the overall MS population in the Campania region from 2015 to 2017). The overall population that received any natalizumab dosing had mean ± standard deviation (SD) of 4.3 ± 1.0-week infusion interval (from 2.5 to 12.2 weeks; on average, 11.4 infusions of natalizumab/year). We included 208 patients treated with natalizumab for at least 18 months; details of included and excluded patients are reported in **Figure 8**.

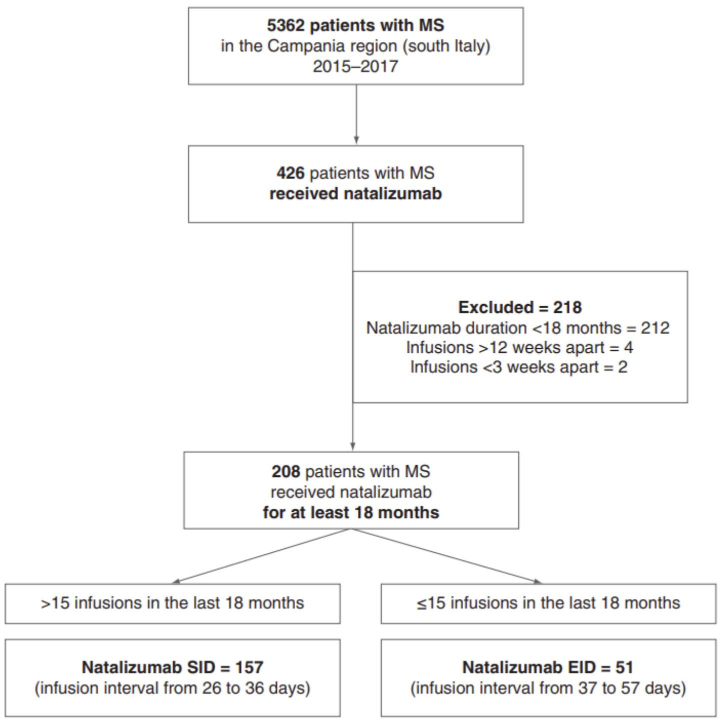

Figure 8.. Study flow diagram. Figure shows number of included and excluded patients with reasons for exclusion. EID: Extended-interval dosing; MS: Multiple sclerosis; SID: Standard-interval dosing**.**

In particular, 157 patients had SID (75.5%) with mean ± SD of 4.4 ± 0.3- week infusion interval (from 3.7 to 5.2 weeks; on average, 11.5 infusions of natalizumab/year), and 51 had EID (24.5%) with mean ± SD of 6.1 ± 0.6-week infusion interval (from 5.2 to 8.1 weeks; on average 8.3 infusions of natalizumab/year). Among included patients, natalizumab treatment was in place at baseline (1 January 2015) for 49 patients; 85 patients commenced natalizumab in 2015, and 74 in 2016. We did not include any patients commencing on treatment in 2017 due to the lack of sufficient follow-up (set at 18 months for the present study). Overall, EID patients had been on treatment with natalizumab for a longer time compared with SID (33.5 ± 3.2 months vs 29.9 ± 6.2 months; p < 0.01; **Table 8**).

Table 8. Demographics, treatment features and comorbidities. The table shows the demographic characteristics, treatment features, and comorbidities (for patients with hospital discharge records), in patients receiving natalizumab SID and EID. p-values are reported from chi-square test, t-test, or Mann–Whitney U test, as appropriate. EID: Extended-interval dosing; SID: Standard-interval dosing.

Parameter	SID (n = 157)	EID (n = 51)	p-values
Age, years	36.5 ± 10.8	33.7 ± 11.1	0.11
Sex, female (%)	107 (68.1%)	37 (72.5%)	0.67
Treatment duration, months	29.9 ± 6.2	33.5 ± 3.2	<0.01
Infusion interval, weeks	4.4 ± 0.3	6.1 ± 0.6	<0.01
Charlson Comorbidity Index	(n = 135)	(n = 21)	0.27
– 0	125 (92.6%)	18 (89.5%)	
– 1–2	9 (6.7%)	2 (9.5%)	
– >2	1 (0.7%)	1 (4.8%)	

For both EID and SID patients, only the last 18 months of treatment were considered for the purposes of the following statistics. Demographics, treatment features and comorbidities are reported in Table 1. Comorbidities from the CCI were cerebrovascular disease (n = 8), hemiplegia (n = 8), metastatic solid tumor (n = 2), chronic pulmonary disease (n = 1), connective tissue disease (n = 1), mild liver disease (n = 1) and diabetes with end-organ damage (n = 1) and were equally distributed between SID and EID (p = 0.27). No cases of PML were detected in the included population. Demographics and clinical features of the subset of patients with linkage to the clinical registry (n = 105, 50.5%) are reported in Supplementary Table 1. Healthcare resource utilization and costs are reported in **Table 9**. Compared with SID, in EID, the individual rate of MS outpatients and day hospitals was 72% lower (IRR: 0.28; 95% CI: 0.10, 0.73; p = 0.01), costs for MS outpatients and day hospitals were 63% lower (Coeff.: -390.51; 95% CI: -784.62, -35.99; p = 0.03) and costs for natalizumab treatment were also lower (Coeff.: -4328.43 €/patient/year; 95% CI: -5169.74, -3687.12; p < 0.01).

Table 9. Healthcare resource utilization and costs: outpatients and day hospital admissions. Table shows the overall number and percentage of patients with MS, and costs for MS-related and non-MS-related outpatients and day hospitals admissions. Costs are reported on an annual basis. IRR, OR, Coeff., 95% CI and p-values are reported from Poisson regression (for the individual rate of healthcare resource utilization), logistic (for the individual probability of healthcare resource utilization), and linear regression models (for individual cost reduction per year), as appropriate; covariates were age, sex and year of treatment start. EID: Extended-interval dosing; IRR: Incidence rate ratio; MS: Multiple sclerosis; NA: Not assessed due to collinearity or small number of observations; OR: Odds ratio; SID: Standard interval dosing.

Parameter	SID (n = 157)	EID (n = 51)	IRR/OR/coeff.	95% CI		p-values
				Lower	Upper	
MS outpatients and day hospitals						
Overall admission (n)	329	93	IRR = 0.28	0.10	0.73	0.01
Patients, n (%)	157 (100%)	51 (100%)	NA			
Average cost per patient, per year	€616.59 ± 1521.58	€110.23 ± 245.21	coeff. = -390.51	-784.62	-35.99	0.03
Non-MS related outpatients and day hospitals						
Overall admission (n)	64	43	IRR = 1.62	0.18	14.67	0.66
Patients, n (%)	10 (6.4%)	6 (11.8%)	OR = 1.80	0.21	15.45	0.58
Average cost per patient, per year	€296.41 ± 889.93	€276.89 ± 950.37	coeff. = -178.57	-787.30	430.14	0.56

No differences were found in other healthcare resource utilization and costs (**Table 10**). After adjusting by CCI, we confirmed a 64% decrease between SID and EID in the individual rate of MS outpatients and day hospitals (IRR: 0.36; 95% CI: 0.14, 0.93; p = 0.03), a 65% decrease in the individual costs for MS outpatients and day hospitals (Coeff.: -403.27 €/patient/year; 95% CI: -1052.99, -153.56; p < 0.01), and also a decrease in the individual costs for natalizumab treatment (Coeff.: -4345.78 €/patient/year; 95% CI: -5067.82, -3623.75; p < 0.01), in absence of differences in other healthcare resource utilization and costs.

Table 10. Healthcare resource utilization and costs: hospital admissions and emergency hospital admissions. Table shows the overall number and percentage of patients with MS and costs for MS-related and non-MS-related hospital admissions and emergency hospital admissions. Costs are reported on an annual basis. EID: Extended-interval dosing; MS: Multiple sclerosis; SID: Standard-interval dosing.

Parameter	SID (n = 157)	EID (n = 51)
MS hospital admissions		
Overall admission (n)	6	1
Patients, n (%)	3 (1.9%)	1 (2.0%)
Average cost per patient, per year	€88.73 ± 558.59	€25.61 ± 114.63
Non-MS related hospital admissions		
Overall admission (n)	1	1
Patients, n (%)	1 (0.6%)	1 (2.0%)
Average cost per patient, per year	€39.76 ± 450.26	€121.38 ± 777.21
MS emergency hospital admissions		
Overall admission (n)	2	1
Patients, n (%)	2 (1.3%)	1 (2.0%)
Average cost per patient, per year	€23.70 ± 145.30	€25.61 ± 114.63
Non-MS related emergency hospital admissions		
Overall admission (n)	1	0
Patients, n (%)	1 (0.6%)	0 (0.0%)
Average cost per patient, per year	€6.15 ± 81.21	€0.00

3.3.4 Discussion

In the Campania region of Italy from 2015 to 2017, EID was used in 25% of natalizumab-treated MS patients. The adoption of EID posology could have been due to a number of factors, such as evidence indicating that EID reduces the risk of PML compared with [104], and budget restraints could have contributed to a preference for extended over conventional dosing [111]. Thus, EID natalizumab use in the 2015–17 period was a frequent practice in this region. We also observed that in this cohort, patients on EID were on treatment for longer periods compared with SID patients, which could potentially be linked to a perception of lower risk of PML in EID patients compared with patients on SID. Of note, our EID group had an average of 8.3 infusions of natalizumab per year, which is slightly lower than what is believed to provide therapeutic molecular target saturation (nine infusions/year)[100,107]. Looking at healthcare resource utilization and costs, EID was associated with a 72% lower rate and 63% lower costs for MS outpatient visits and day hospital admissions, as well as lower costs for natalizumab treatment, compared with SID, apparently in the absence of changes in other healthcare resource utilization and costs. As expected, we observed lower costs for natalizumab in EID compared with SID as a consequence of the reduced number of infusions (8.3 vs 11.5 infusions of natalizumab/year). It is important to note that the SID cohort also has a lower number of infusions per year compared with administration every 4 weeks (11.5 vs 13 infusions per year), with a consequent reduction in patient cost per year. All patients had at least one MS outpatient or day hospital, but the individual rate of MS outpatients and day hospitals was 72% lower in EID natalizumab compared with SID, and related costs were 390.51 €/year lower. This result was not necessarily granted, because EID could have been responsible for increased MS management needs and/or complexity (e.g., relapses) [18,112]. We did not observe any difference between EID and SID in hospital admissions at the descriptive level, although we were not able to run statistical models due to the small number of observations, and thus longer follow-up should be considered. We have also adjusted for the impact of comorbidities on our results by using the CCI. Overall, EID natalizumab seems to reduce direct costs due to natalizumab infusions and MS management, in absence of further burden on the Italian national health system. These savings may be further increased by a potential reduction of societal and indirect costs as a consequence of fewer MS outpatient and day hospital admissions, which may require patient sick leave or result in caregiver burden [113]. To our knowledge, this is the first study that seeks to quantify the consumption of health resources in SID and EID cohorts. Of note, in our study, the difference in dosing intervals between the SID and EID groups (4.4 vs 6.1 weeks) was substantially in line with previous real-world studies (4.2–4.3 vs 6.0–6.2 weeks)[104,111] suggesting that extending dosing intervals by 1–2 weeks may produce a significant reduction of healthcare resource utilization and costs. Of note, EID and SID patients also had similar EDSS at baseline in the subgroup of patients for which linkage to clinical registry was available. As such, natalizumab EID corresponds to different costs, and its pharmacoeconomic should be revised accordingly. Limitations of the present study are mainly related to the use of routinely collected healthcare data within a limited time frame (2015–17), which does not allow for the collection of clinical data (e.g., disability level, JCV status), and long-term treatment features (e.g., periods of SID before switching to EID and prior immunosuppressant). Because routinely collected healthcare data does not include information about therapeutic efficacy, we could not assess the benefit–risk profile of EID compared with SID. Also, there might be a bias arising from the clinical decision of EID or SID (e.g., comorbidities, disease severity); thus, we have included different variables accounting for disease features (e.g., age, sex)[113,114] ,treatment decision-making (e.g., year of treatment start) [115], comorbidities (e.g., CCI) [116] and clinical variables (e.g., EDSS) even if only for one subgroup of patients with limited numbers, especially for the EID group. Unfortunately, linkage to clinical registry was available only at baseline for a subset of patients, and further clinical characterization of EID and SID patients should be considered in the future. Furthermore, this dataset could be further implemented with a longer follow-up and a larger sample size, especially for EID cohort.

3.3.5 Conclusion

In this cohort, natalizumab EID was used in 25% of natalizumab-treatment patients and appears to be associated with reduction of healthcare resource utilization and costs without additional burden to the Italian national health system. Even with the limitations described, the information provided in this study is highly relevant to policy makers, healthcare providers and MS patients considering initiating or continuing natalizumab therapy. In the future, and as a follow-up to the NOVA clinical trial, comparing the efficacy and safety of every-6-week and every-4-week dosing regiments [9], this dataset could be further expanded over a longer follow-up period and with improved patient profiling.

3.3.6 Financial & competing interests' disclosure.

This study was funded by Biogen Italia. M Moccia has received research grants from ECTRIMS-MAGNIMS, UK MS Society and Merck; honoraria from Merck, Novartis and Roche; and consultant fees from Veterans Evaluation Services. Carotenuto has received research grants from Almirall and honoraria from Almirall and Novartis. R Lanzillo has received honoraria from Merck, Novartis, Roche, Sanofi-Genzyme and Teva. V Brescia Morra has received research grants from the Italian MS Society and Roche and honoraria from Bayer, Biogen, Merck, Mylan, Novartis, Roche, Sanofi-Genzyme and Teva. S Masera was an employee of Biogen Italia at the time of this study and manuscript. L Santoni is an employee of and may hold stock/stock options in Biogen. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

4 Impact of covid-19 and system recovery in delivering healthcare

4.1 Introduction

Coronavirus disease 2019 (COVID-19) was first identified in December 2019 in the city of Wuhan, China, and rapidly became a pandemic, with 6,636,278 deaths out of 646,266,987 confirmed cases worldwide, as of December 2022[117]. Italy was the first European country affected by COVID-19 with 24,709,404 confirmed total cases and 182,419 deaths to date[118]. In the initial phase of the pandemic (e.g., emergency phase, the great lockdown), massive disruptions involved healthcare systems all over the world, leading to a fast reorganization of people, structures, and devices. All the non-urgent clinical activities, such as follow-ups, treatments, and tests for chronic diseases, were suspended[119]. Moreover, the outbreak of COVID-19 has led to increased workload, psychological distress, and infection risks among medical staff causing a drastic decrease in its recovery[120–122]. COVID-19 pandemic has had multiple waves of contagion (e.g., autumn 2020 and spring 2021), and has only improved across 2021 thanks to mass vaccination campaign, which has proven effective at reducing both risk and severity of infection, with some caveats in immunocompromised patients.

As such, the COVID-19 pandemic has brought challenges to the healthcare management of people with multiple sclerosis (PwMS). Indeed, PwMS require multidisciplinary management and access to a broad range of services, including regular specialty examinations, diagnostic tests, rehabilitation, psychological support, social care and inclusion services[123–126]. In addition, PwMS needs long-term treatment with immunomodulatory and immunosuppressive disease-modifying therapies (DMT), to decrease the relapse rate and potentially prevent disability accumulation. Still, very few studies have quantified the impact of COVID-19 on healthcare delivery to people with MS[127,128], and none has evaluated whether and to what extent activities have resumed to pre-pandemic levels.

Therefore, in our population-based study conducted in the Campania Region (South Italy), we aimed to evaluate the impact of the COVID-19 pandemic (i.e., across its distinct phases and after vaccination campaign) and the recovery of the healthcare system in delivering services to PwMS.

4.2 Methods

4.2.1 Study Design

This is a population-based study, obtained from the retrospective analysis of routinely collected healthcare data of individuals with MS resident in the Campania Region (South Italy), from 2015 to 2021 (5,624,420 inhabitants).

The study was approved by the Federico II Ethics Committee (332/21). All patients signed informed consent authorizing the use of anonymized, routinely collected healthcare data, in line with data protection regulation (GDPR EU2016/679). The study was performed in accordance with good clinical practice and Declaration of Helsinki.

4.2.2 Study Population

The dataset was created by merging different data sources of the Campania Region[30]. Following validation study,[62] the cohort comprised all residents in the Campania Region who had at least one MS-specific record, from 2015 to 2021, in any of the routinely-collected healthcare databases, including:

1) Hospital Discharge Record database, which included all admissions in the study period with ICD-9 CM codes of MS in discharge diagnoses.
2) Regional Drug Prescription database, which included all MS-specific DMTs prescribed in the study period (e.g., alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferon Beta-1a, interferon Beta-1b, natalizumab, ocrelizumab, peg-Interferon Beta-1a, teriflunomide).
3) Outpatient database with exemption code for MS.

The case-identification algorithm was validated towards a clinical registry, and showed 99.0% sensitivity, with only 2.7% of cases remaining undetected[62]. From the datasets, individuals with a diagnosis of MS not resident in the Campania Region were excluded. Data was fully anonymized by the Campania Region Healthcare Regulatory Society (So.Re.Sa.) before releasing the datasets.

4.2.3 COVID-19 timeline

The first recorded case of COVID-19 in the Campania Region dates to 26 February 2020. Starting in early-March 2020, activities within hospitals underwent a rapid re-organization suspending all non-urgent clinical activities. From mid-May 2020, elective and specialty outpatient activities were resumed. Finally, in January 2021 the vaccination campaign began, with priority to healthcare workers and at-risk groups, including PwMS. As of December 2021, there have been 2,368,439 confirmed total COVID-19 cases and 11,423 COVID-19 related deaths.

Thus, in the study, we identified four-time periods:

- Pre-COVID-19 Period (as reference): from 1st January 2015 to 29th February 2020
- Lockdown Period: from 1st March 2020 to 31st May 2020

- Pre-Vaccination Period: from 1st Jun 2020 to 31st December 2020
- Vaccination Period: from 1st January 2021 to 31st December 2021

4.2.4 Demographic, clinical and treatment variables

Demographic information were year of birth and sex.

The Charlson Comorbidity Index was computed in patients with hospital discharge records, by assigning different weights to comorbidities reported in primary and secondary discharge diagnoses; the Charlson Comorbidity Index provides the risk of death from comorbidities[67] and has already been applied to MS studies[43].

DMT prescriptions were collected and based on regulatory approval. DMTs were further classified into platform (teriflunomide, interferon beta, glatiramer acetate, dimethyl fumarate) and highly effective (fingolimod, alemtuzumab, cladribine, ocrelizumab, natalizumab). Also, based on our previously validated algorithm, we identified newly diagnosed patients and respective first DMT[129].

Considering that the same individual might have been treated with different DMTs over time, or with the same DMT over different COVID-19 phases, we used individual treatment periods (ITPs) as units for the analyses clustered at the individual level.

We also evaluated the following outcomes related to prescriptions: any DMT switch; switch from platform to highly effective DMT; and combination of first DMT prescription and any DMT switch. For each modality of new DMT prescription (first DMT prescription, any DMT switch, switch from platform to highly effective DMT, and combination of first DMT prescription and any DMT switch), we calculated the rate of prescription as the number of patients with new DMT prescription per month, divided by the total number of patients.

Adherence was estimated using the medication possession ratio (MPR) (MPR=(medication supply obtained during follow-up period/medication supply expected during the follow-up period))[130].

4.2.5 Healthcare resource utilization and costs

Healthcare resource utilization was extracted from Campania Region datasets (i.e., hospital discharge records, regional prescribing database, and outpatient services). Healthcare resource utilization included MS-related and non-MS-related hospital admissions, which were classified based on the main discharge diagnosis. The number of hospital admissions was then reported on an annual basis (annualized hospitalization rates (general AHR and MS AHR)).

Direct healthcare costs were derived from regional datasets, referred to corresponding healthcare resource utilization, and inflated to the most recent values (2021) (https://www.soresa.it/), to avoid variations in price per unit of service through different years.

4.2.6 Statistical Analysis

Study variables were described as mean (standard deviation), median (range), or number (percent), as appropriate. Differences in continuous outcomes between periods (Pre-lockdown (as reference), Lockdown, Pre-Vaccination and Vaccination) were explored using linear mixed models (for AHR, costs, and MPR). Covariates were age, sex, and treatment duration. Statistical models were then run including adherence and Charlson comorbidity index (for the subgroup of patients with hospital discharge records) among covariates.

Differences in new DMT prescription rates were assessed employing an interrupted time series design using a Poisson distribution with robust standard errors accounting for heteroskedasticity across patients (partly adjusted models)[131]. Specifically, for these analyses, we divided the study period as pre-lockdown and post lockdown, considering lockdown as the intervention period. Pre- and post-vaccination periods were merged in a single post-lockdown period to allow sufficient time to switch from one treatment to another (i.e., pre-vaccination period lasted only six months which might be not sufficient for a clinical evaluation before switching to another treatment). These models provided the step change after the lockdown and the slope change over the following months, as compared with pre-lockdown period (January 2019 to March 2020). In particular, we restricted the pre-lockdown period to account for the most recent DMT prescription trend before COVID-19, and also in light of new DMTs being approved from 2019 (e.g., ocrelizumab, cladribine)[132]. Analyses were then adjusted for sex and age (fully adjusted models).

Results were reported as adjusted coefficient (Coeff), incidence rate ratio (IRR), 95% confidence intervals (95%CI), and p values, as appropriate. Results were considered statistically significant for $p<0.05$. Statistical analyses were performed using Stata 15.0.

4.3 Results

Out of 7,431 prevalent MS patients in the Campania Region from 2015 to[129], we included 6,097 patients(age 41.47$\pm$12.42; females 64%), corresponding to 8,760 ITPs (the same individual being treated with different DMTs within the study period). We excluded 1,334 patients due to missing data in relation to demographics or other study variables. Demographics, comorbidities, treatment features of included patients are reported in **Table 5**.

Table 11. Demographic, treatment, and clinical variables. Note: MPR medication possession ratio

	Pre-Covid	***Lockdown***	***Pre-Vaccination***	***Vaccination***
***Age, years**, mean (SD)*	41.91 (12.19)	45.66 (12.27)	44.92 (12.39)	45.37 (12.63)
***Sex**, female (%)*	*65%*	*66%*	*66%*	*65%*
***Individual Treatment Period** (N)*				
Interferon beta 1	*2,646*	*1,004*	*1,139*	*1,135*
Glatiramer acetate	773	301	366	356
Fingolimod	1,219	346	741	804
Alemtuzumab	75	*0*	1	0
Cladribine	9	1	11	20
Ocrelizumab	209	11	63	418
Dimethyl fumarate	1,206	682	848	989
Natalizumab	580	362	445	565
***Months of treatment duration, mean** (SD)*	42.22 (17.92)	2.03 (0.43)	5.53 (1.11)	9.81 (2.14)
***MPR**, mean (SD)*	0.98 (0.20)	1.11 (0.27)	0.99 (0.22)	0.94 (0.26)
***MPR>80%,** number (%)*	*84%*	*93%*	*85%*	*82%*
Charlson comorbidity index				
0	2,597	27	458	1,033
1-2	60	0	5	23
>=3	2	0	0	0

4.3.1 New DMT prescriptions

New DMT prescription rates, along with partly and fully adjusted results, are reported in **Table 6.**

After the lockdown, there was a two-fold increase in any DMT switch (step change IRR 2.05 95%CI 1.38, 3.05; p<0.01), as compared with before COVID-19, which however was not sustained over time (slope change IRR 0.95; 95%CI 0.93, 0.98; p<0.01) (**Table 6**; **Figure 5a**). After the lockdown, there was a four-fold increase in switch from platform to highly effective DMTs (step change IRR 4.45; 95%CI 2.48, 8.26; p<0.01), as compared with before COVID-19, which however was not sustained over time (slope change IRR 0.92; 95%CI 0.88, 0.95; p<0.01) (**Table 6**; **Figure 5b**). After the lockdown, there was a two-fold increase in first DMT prescription (step change IRR 2.48; 95%CI 1.64 , 3.74; p<0.01), as compared with before COVID-19, which however was not sustained over time (slope change IRR 0.94 ; 95%CI 0.91, 0.97; p<0.01) (**Table 6**; **Figure 5c**). After the lockdown, there was a two-fold increase in combination of first DMT prescription and any DMT prescription (IRR 2.01; 95%CI 1.53 , 2.66; p<0.01), as compared with before COVID-19, which however was not sustained over time (slope change 0.96 ; 95%CI 0.94, 0.97; p<0.01) (**Table 6**; **Figure 5d**).

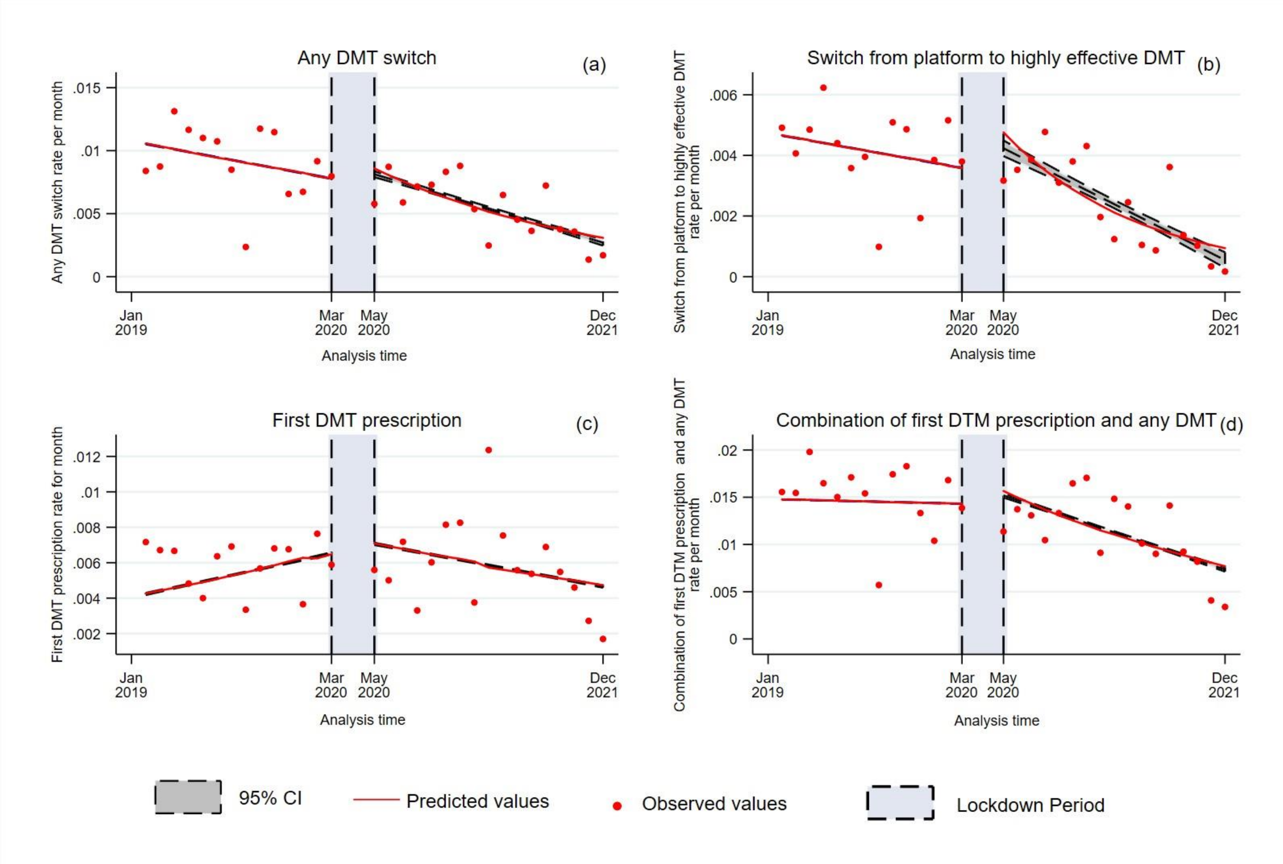

Figure 9. New DMT prescription rates as a function of analysis time (2019-2021). Figure shows differences in the rates of new DMT prescription (a, any DMT switch; b, switch from platform to highly effective DMT; c, first DMT prescription; d, combination of first DTM prescription and any DMT), which were assessed employing an interrupted time series design using a Poisson distribution with robust standard errors. Specifically for these analyses, we divided the study period as pre-lockdown and post lockdown, considering lockdown as the intervention period (blue shades). Monthly new DMT prescription rates (red dots) were measured as the number of patients with new DMT prescription per month, divided by the total number of patients (over 1000). Red lines show slope changes (along with 95%CI as grey shades)

Table 12. New DMT prescriptions. The table shows the monthly rate of new DMT prescriptions, including first DMT prescription, any DMT switch, switch from platform to highly effective DMT, and combination of first DTM prescription and any DMT. The monthly rates were calculated as the number of patients with new DMT prescription per month, divided by the total number of patients (over 1000). Differences in the DMT prescription rates were assessed employing an interrupted time series design using Poisson distribution with robust standard errors accounting for heteroskedasticity across patients. For this analysis, we restricted the pre-lockdown period from Jan 2019 to March 2020. The adjusted analyses were adjusted for sex and age. Note: * Incidence rate ratio

Outcome	Monthly rate		Partly Adjusted Results			Fully Adjusted Results		
	Pre-Lockdown (Over 1000)	Post-Lockdown (Over 1000)	IRR*	p-value	95%CI	IRR*	p-value	95%CI
Any DMT switch	9.12	5.42						
Step change			2.06	p<0.01	(1.39; 3.06)	2.05	p<0.01	(1.30; 3.05)
Slope change			0.96	p<0.01	(0.93; 0.98)	0.95	p<0.01	(0.93; 0.98)
Switch from platform to highly effective DMT effective DMT	4.12	2.31						
Step change			4.54	p<0.01	(2.49; 8.29)	4.45	p<0.01	(2.48; 8.26)
Slope change			0.92	p<0.01	(0.88; 0.96)	0.92	p<0.01	(0.88; 0.95)
First DMT prescription	6.02	5.54						
Step change			2.52	p<0.01	(1.67; 3.79)	2.48	p<0.01	(1.64; 3.74)
Slope change			0.94	p<0.01	(0.91; 0.96)	0.94	p<0.01	(0.91; 0.97)
Combination of first DMT prescription and any DMT switch	15.01	11.02						
Step change			2.03	p<0.01	(1.54; 2.68)	2.01	p<0.01	(1.53; 2.66)
Slope change			0.95	p<0.01	(0.94; 0.97)	0.96	p<0.01	(0.94; 0.97)

4.3.2 Adherence

Adherence to treatment is reported in **Table 5**. When compared with pre-COVID-19 period, adherence (MPR) remained similar during lockdown (Coeff =0.06; 95%CI = 0.05,0.07; p<0.01) but decreased during pre-vaccination (Coeff = -0.04; 95%CI = -0.05, -0.03; p<0.01) and vaccination periods (Coeff = -0.07; 95%CI =-0.08, -0.07; p<0.01).

4.3.3 Healthcare resource utilization and costs

Healthcare resource utilization and costs are reported in **Table 7.**

When compared with pre-COVID-19 period, AHR decreased during lockdown (Coeff=-0.64; 95%CI = -0.69, -0.59; p<0.01), and remained significantly lower during pre-vaccination (Coeff=-0.37; 95%CI = -0.41, -0.33; p<0.01), and vaccination periods (Coeff = -0.35; 95%CI = -0.39, -0.32; p<0.01). Results were confirmed also after adjusting by adherence. After adjusting by Charlson Comorbidity index, when compared with pre-COVID-19 period, AHR was higher during lockdown (Coeff=4.44; 95%CI = 3.98, 4.90; p<0.01), pre-vaccination period (Coeff=1.42; 95%CI = 1.30, 1.55; p<0.01), and during vaccination period (Coeff = 0.31; 95%CI = 0.21, 0.39; p<0.01), thus suggesting that comorbidities have increased the probability of hospitalization across all COVID-19 phases.

Table 13. Healthcare resource utilization and costs. Table shows the annualized hospitalization rate and monthly costs described as mean (standard deviation). Differences in outcomes between periods (Pre-lockdown (as reference), Lockdown, Pre-Vaccination and Vaccination) were explored using linear mixed models. *The analyses were adjusted for age, sex, and treatment duration.

	Pre-Covid (ref)	*Lockdown*				*Pre-Vaccination*				*Vaccination*			
			*Adjusted Results**				*Adjusted Results**				*Adjusted Results**		
	Mean (SD)	*Mean (SD)*	*Coeff*	*p-value*	*95%CI*	*Mean (SD)*	*Coeff*	*p-value*	*95%CI*	*Mean (SD)*	*Coeff*	*p-value*	*95%CI*
Annualized hospitalization rates	0.86 (0.97)	0.06 (0.55)	*-0.64*	*p<0.01*	*(-0.69; -0.59)*	0.33 (14.08)	*-0.37*	*p<0.01*	*(-0.41; -0.33)*	0.38 (1.01)	*-0.35*	*p<0.01*	*(-0.39; -0.32)*
MS Annualized hospitalization rates	0.79 (0.93)	0.03 (0.47)	*-0.57*	*p<0.01*	*(-0.62; -0.53)*	0.29 (0.99)	*-0.31*	*p<0.01*	*(-0.36; -0.23)*	0.34 (0.95)	*-0.29*	*p<0.01*	*(-0.32; -0.26)*
Monthly Hospital admission Costs (EUR)	40.70 (137.86)	7.71 (150.53)	*-40.19*	*p<0.01*	*(-48.83; -31.56)*	26.18 (179.74)	*-22.34*	*p<0.01*	*(-30.08; -14.59)*	29.30 (200.24)	*-22.25*	*p<0.01*	*(-29.35; -15.16)*
Monthly MS hospital admission costs (EUR)	30.65 (103.81)	1.08 (18.37)	*-35.26*	*p<0.01*	*(-40.93; -29.61)*	18.26 (130.08)	*-18.99*	*p<0.01*	*(-24.07; -13.91)*	19.89 (132.30)	*-19.56*	*p<0.01*	*(-24.22; -14.91)*
Monthly DMT costs (EUR)	902.68 (406.47)	804.11 (418.64)	*-56.06*	*p<0.01*	*(-68.58; -43.80)*	854.19 (436.78)	*-58.06*	*p<0.01*	*(-69.18; -46.94)*	939.32 (470.68)	*-31.72*	*p<0.01*	*(-41.91; -21.53)*

When compared with pre-COVID-19 period, MS AHR decreased during the lockdown (Coeff=-0.57; 95%CI = -0.62, -0.53; p<0.01), and remained significantly lower during pre-vaccination (Coeff=-0.31; 95%CI = -0.36, -0.23; p<0.01), and vaccination periods (Coeff = -0.29; 95%CI = -0.32, -0.26; p<0.01). Results were confirmed also after adjusting by adherence. After adjusting by Charlson Comorbidity index, when compared with pre-COVID-19 period, MS AHR was higher during lockdown (Coeff=2.91; 95%CI = 2.45, 3.37; p<0.01) and pre-vaccination period (Coeff=1.37; 95%CI = 1.25, 1.50; p<0.01), but returned to pre-pandemic values during vaccination period (Coeff = 0.35; 95%CI = 0.26, 0.44; p<0.01), thus confirming the effect of comorbidities on MS hospitalizations.

When compared with pre-COVID-19 period, costs for hospital admissions were lower during lockdown (Coeff = -40.19; 95%CI = -48.83, -31.56; p<0.01), pre vaccination period (Coeff = -22.34; 95%CI = -30.08, -14.59; p<0.01), and vaccination periods (Coeff = -22.25; 95%CI =-29.35, -15.16; p<0.01). Results were confirmed also after adjusting by adherence.

When compared with pre-COVID-19 period, costs for MS hospital admissions were lower during lockdown (Coeff = -35.26; 95%CI = -40.93, -29.61; p<0.01), pre vaccination (Coeff = -18.99; 95%CI = -24.07, -13.91; p<0.01), and vaccination periods (Coeff = -19.56; 95%CI =-24.22, -14.91; p<0.01). Results were confirmed also after adjusting by adherence.

When compared with pre-COVID-19 period, costs for DMTs were lower during lockdown (Coeff =-56.19; 95%CI = -68.58, -43.80; p<0.01), pre vaccination (Coeff = -58.06; 95%CI = -69.18, -46.94; p<0.01), and vaccination periods (Coeff = -31.72; 95%CI =-41.91, -21.53; p<0.01). Results were confirmed also after adjusting by adherence. After adjusting by Charlson Comorbidity index, when compared with pre-COVID-19 period, costs for DMTs remained similar during lockdown (Coeff=-81.14; 95%CI = -167.77, 5.48; p=0.06), but decreased during pre-vaccination (Coeff=-75.56; 95%CI = -99.04, -52.07; p<0.01) and vaccination periods (Coeff=-22.06; 95%CI = -39.15, -4.96; p<0.01).

4.4 Discussion

Our population-based study showed changes in MS management during and following COVID-19 pandemic. We observed a decrease in all-cause and MS hospital admissions (and related costs) from lockdown and until recent time, thus suggesting a re-organization with de-centralized healthcare delivery. When including comorbidities in the statistical models, we found higher probability of hospitalization, when compared with pre-COVID-19, possibly reflecting increased awareness of comorbidities and related risks. This de-centralized model of care, however, might have resulted in reduced quality of care, with lower rates of adherence and lower DMT costs (e.g., as from the use of low/medium-efficacy DMTs). In keeping with this, we observed a drop in new DMT prescriptions during the lockdown, which however quickly surged to pre-COVID-19 levels. Overall, our results suggest a significant impact of COVID-19 on MS management, but satisfactory recovery of the healthcare system in resuming activities after the great lockdown.

Healthcare utilization is high in the MS population, with up to 25.8% of the MS population being hospitalized annually, well above the rate of hospitalizations in the general popolation[76,133] Hospitalizations are generally related to MS (e.g., new or worsening symptoms), its treatments (e.g., side effects), and chronic consequences of disability, such as urinary tract infections, which are the most common reason for hospitalization[43,126,134,135]. The observed declines in hospitalizations during and after COVID-19 may reflect changes in healthcare delivery, including the administration of therapy for relapses in outpatients or at home, rather than inpatient setting. However, a decentralized model of care might have been responsible for reduced rates of adherence, resulting from both limited access to usual medical services due to unavailability, and fear of SARS-CoV-2 infection[136,137]. An assessment of the impact on long-term outcomes is needed[138].

Our study findings support that comorbidity is associated with a greater burden on healthcare systems. In fact, people with MS have higher rates of hospitalizations due to comorbidities (e.g., hypertension, diabetes, ischemic heart disease, chronic lung disease, depression, and bipolar disorder), compared with the general population[133]. This has further increased during and after COVID-19, thus suggesting PwMS have been further exposed to their frailty over the recent years.

Furthermore, consistent with other studies, we confirmed that comorbidities and their severity (i.e., Charlson comorbidity index) are strong predictors of hospitalization[133]. In particular, severe kidney disease, diabetes, ongoing chemotherapy, severe immunodeficiency, heart failure, and Down syndrome stand out as having a higher associated risk of hospitalization due to COVID-19[139,140].

Due to the possible effect of some DMTs on the frequency and severity of SARS-Cov-2 infection, the decision of whether to start, discontinue or continue on medications has been a critical issue for both patients and physicians. Most national neurological/MS societies and international working groups have advised against the use of highly effective DMTs amid the peak of COVID-19 pandemic and lockdown[141,142]. This is fully reflected in our results. However, this is the first study to explore the recovery of the healthcare system after the pandemic, and we showed that delays in DMT use (including both new and switch prescriptions) quickly recovered to pre-COVID-19 levels.

Limitations of this study include the conduction in a single Italian Region, from which data is available at population level. However, COVID-19 has affected healthcare systems worldwide, and described impact and recovery are expected. Also, we did not assess the direct impact of COVID-19 infections that could have affected some outcomes (e.g., reduced adherence due to suspended or delayed treatment during active infection), which will grant further investigations. We have decided to focus on healthcare resource utilization only and did not include clinical data that would be available only for a subgroup of patients.

Moreover, there might be patterns of healthcare resource utilization that are associated with treatment decisions (e.g., patients less in contact with MS centers being less likely to use highly effective DMTs); this was not fully accounted in our study and warrants further investigations.

In conclusion, we have described profound changes of MS management following COVID-19 pandemic. While reduced hospitalization rates (and related costs) could be read as a proxy of improved care, there is the possibility of missed clinical events due to COVID-19 re-organization of healthcare delivery, as also suggested by reduced adherence. Similarly, the use of DMTs plunged during the lockdown, but quickly came back to pre-COVID-19 levels, thus suggesting good recovery of the healthcare system and minimal effect on PwMS.

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5 Conclusions and future perspectives

The present thesis aimed to use routinely collected health data to support decision making in public health with a specific focus on multiple sclerosis. Our findings have provided insights into the comprehensive management of MS, encompassing the identification of MS cases, treatment and medication management, resource utilization, and cost analysis.

In the first part of the study, we validated an algorithm based on routinely collected healthcare data to detect incidence of multiple sclerosis (MS) in the Campania Region (South Italy) and to explore its spatial and temporal variations. The cumulative incidence was 36.68 per 100,000 from 2016 to 2020 and the mean annual incidence was 7.34 per 100,000 people-year. The geographical distribution of MS relative risk shows a decreasing east-west incidence gradient. The number of expected MS cases was 11% higher than the detected cases. In the second part, we provided real-world evidence on the use of DMTs for treating multiple sclerosis (MS), with specific regard to prescription pattern, adherence, persistence, healthcare resource utilization and related costs. The results highlighted Ocrelizumab as a prevalent choice, offering cost-effectiveness. We also evaluated the impact of Extended-Interval Dosing for Natalizumab, which reduced direct treatment costs. Finally, we assessed the impact on healthcare delivery to people with MS during various periods in Campania, finding that while DMT usage returned to pre-pandemic levels, adherence remained suboptimal.

In the future, knowledge acquired from our study can be leveraged to improve outcomes and efficiently allocate resources for the care of individuals facing complex chronic conditions. Moreover, the methodology employed in this study can be adapted for diverse geographic regions and various medical conditions, contributing to enhanced planning in public health domains.

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