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The impact of healthcare systems on the clinical diagnosis and disease-modifying treatment usage in relapse-onset multiple sclerosis: a real-world perspective in five registries across Europe

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Abstract

Introduction: Prescribing guidance for disease-modifying treatment (DMT) in multiple sclerosis (MS) is centred on a clinical diagnosis of relapsing–remitting MS (RRMS). DMT prescription guidelines and monitoring vary across countries. Standardising the approach to diagnosis of disease course, for example, assigning RRMS or secondary progressive MS (SPMS) diagnoses, allows examination of the impact of health system characteristics on the stated clinical diagnosis and treatment access.

Methods: We analysed registry data from six cohorts in five countries (Czech Republic, Denmark, Germany, Sweden and United Kingdom) on patients with an initial diagnosis of RRMS. We standardised our approach utilising a pre-existing algorithm (DecisionTree, DT) to determine patient diagnoses of RRMS or secondary progressive MS (SPMS). We identified five global drivers of DMT prescribing: Provision, Availability, Funding, Monitoring and Audit, data were analysed against these concepts using meta-analysis and univariate meta-regression.

Results: In 64,235 patients, we found variations in DMT use between countries, with higher usage in RRMS and lower usage in SPMS, with correspondingly lower usage in the UK compared to other registers. Factors such as female gender ($p = 0.041$), increasing disability via Expanded Disability Status Scale (EDSS) score ($p = 0.004$), and the presence of monitoring ($p = 0.029$) in SPMS influenced the likelihood of receiving DMTs. Standardising the diagnosis revealed differences in reclassification rates from clinical RRMS to DT-SPMS, with Sweden having the lowest rate Sweden (Sweden 0.009, range: Denmark 0.103 – UK portal 0.311). Those with higher EDSS at index ($p < 0.03$) and female gender ($p < 0.049$) were more likely to be reclassified from RRMS to DT-SPMS. The study also explored the impact of diagnosis on DMT usage in clinical SPMS, finding that the prescribing environment and auditing practices affected access to treatment.

Discussion: This highlights the importance of a healthcare system's approach to verifying the clinical label of MS course in facilitating appropriate prescribing, with some flexibility allowed in uncertain cases to ensure continued access to treatment.

Keywords: big data, clinical audit, decision tree, disease registers, international collaboration, multiple sclerosis

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Introduction

The last 20 years has seen the rapid development of a range of disease-modifying treatments (DMTs) that are licensed predominantly for relapsing forms of multiple sclerosis (MS). Guidance from key opinion leaders, regulators and national funders enforced to a variety of levels, encourages healthcare professionals (HCPs) to give DMTs only to those with the relapsing forms of the disease (RRMS). However, the interpretation of this guidance varies depending on whether the HCP feels DMTs are warranted, the difficulties in stopping DMTs that have been instituted in the relapsing phase and the extent of restriction of treatment availability based on disease classification. This can lead to people with (pw)MS being on a DMT licensed for RRMS whilst being in the progressive phase. Recently DMTs have emerged targeting the progressive phase of the disease, for example, primary progressive – ocrelizumab and secondary progressive – siponimod, that for some regions, have highlighted the importance of making a correct clinical diagnosis of the MS phenotype to enable access to these newer DMTs.

SPMS itself can be difficult to recognise clinically due to the fluctuating nature of the disease and the time required to confirm progression. The diagnosis of SPMS is also impacted by the perception that it is irrevocable which may result in HCPs delaying making a definitive decision. The problem pinpointing the onset of SPMS has been brought into focus recently with the emergence of algorithmic methods to define SPMS. These use objective measures such as age and/or disability scores at one,[1] two[2] or three timepoints[3] to determine the classification of an individual MS patient. There is a further issue in real-world data where 'data sparsity', for example, gaps in data collection, can bias outcome assessment. Problems can be identified with careful examination of the tabular variables or enhanced statistical techniques.[4] Utilising these techniques, a group of patients with clinically defined RRMS but who algorithmically have SPMS can be identified. By means of an algorithm, known as a decision tree classifier and its minimal data requirements, we were able to re-classify all subjects.[5]

A clinical diagnosis of SPMS effectively makes it clear to the patient and treating team that up until that point, the current DMTs may no longer be appropriate. Conversely, with an algorithmic diagnosis, neither the MS patient nor HCP have recorded a change in diagnosis; therefore, it is unknown if either is aware of the change in diagnosis. Here, we used the classifier in a counter-intuitive way, using it to standardise the diagnosis. Therefore, instead of evaluating the performance of the classifier on cohorts from countries it was not trained on, we assumed the classifier is right, aiming to identify diverging factors across countries impacting the attribution of a clinical SPMS diagnosis. In the case of a clinical diagnosis of SPMS, one would expect the use of DMTs to be less frequent and possibly focused on the more highly effective therapies. However, it is unknown how HCPs act when pwMS have the characteristics of SPMS, but the diagnosis has not been recorded. The multi-country/multi-registry European perspective of our study enables us to look at HCP behaviour under a range of DMT prescribing conditions. Here, we aim to look at treatment patterns across Europe to determine if HCPs are making treatment decisions consistent with the evidence and how they are responding to disease worsening.

Methods

Study population

Data on clinical and demographic characteristics were obtained from MS registries in the Czech Republic, Denmark, Germany, Sweden and United Kingdom (UK) in subjects with an initial diagnosis of RRMS. Two UK populations were used a clinical and an online portal population.[6] Information on date of birth, sex, Secondary Progressive (SP) conversion year (when applicable), visits with EDSS score (WebEDSS in UK portal), MS onset date, MS diagnosis date and DMT use were extracted. Treatments classified as highly active where Alemtuzumab, Cladribine, Daclizumab, Mitoxantrone, Natalizumab, Ocrelizumab, Ofatumumab, Rituximab and stem cell treatment. Visits without EDSS scores were excluded. Inclusion criteria were to have at least one visit during the index period from January 2017 to December 2019 and to have an age $\geqslant$18 years at the last visit. The last visit was considered as the 'index date' for each patient. Only patients with either a clinically assigned RRMS or SPMS were included. Due to the sensitive nature of the data and different information governance schemes

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among the participating registries, only non-identifiable summary data were collected. These were aggregated in their respective countries and securely sent for analysis at the lead centre in Swansea.

Objective classification of disease type

The decision tree algorithm was used to classify a patient as either Decision Tree (DT)-RRMS or DT-SPMS using an EDSS score and age at that time. The classifier rules have been described previously.[5] The classifier was developed using data from the Swedish registry and validated with an external and separate dataset from British Columbia.[1] Here, the algorithm parsed each patient's historical EDSS observations from the first EDSS and onwards, using each visit as a baseline and the following visits as follow-up. If a patient was first classified as RRMS and later as SPMS, the date of conversion was set to the first time point of SPMS classification. If a patient was not first classified as RRMS, date of conversion could not be established, but the patient would still be regarded as classifiable albeit without a conversion date.

Drivers of DMT utilisation

Through discussions with co-authors and a review of the literature, we developed five potential drivers of DMT prescribing and these were agreed to by the leads from each country. These drivers were then scored and tested for co-linearity. Each health system is summarised in Table 1 together with the coding given.

1. *Provision:* A measure of the availability of services based on the total number of pwMS in the country[7] divided by the number of centres where DMTs were made available.[8]
2. *Availability:* Based on the mechanism that DMTs are made available to pwMS in each country; a higher number indicates easier availability. Values: restricted availability –0, some restrictions –1, minimal restrictions – 2.
3. *Funding:* Based on the cost of DMTs to both the pwMS in each country but also to HCPs and their prescribing hospital. Countries have distinct discounts that were negotiated at different levels, and DMTs were available at a minimal direct cost to pwMS. Funding structure driving cost reduction that impacts HCPs directly was assessed; a higher number indicates a higher HCP incentive to use cheaper DMT. Values: national – 0; regional – 1, hospital – 2.
4. *Monitoring:* Based on whether centralised information was required for prescription. A higher number indicates lower barriers to prescribing. Values: centralised – 0; none – 1.
5. *Audit:* Based on any audit of the appropriateness of prescription compared to licence approved indications; a higher number indicates higher cost of inappropriate disease classification. Values: none – 0, yes, no clinical note review – 1, yes, with clinical note review – 2

Statistical analysis

Individual visit data of six large cohorts from five different European countries were summarised. Data governance standards from each registry required that individual data could not be shared for analysis, only summary statistics. A meta-analytic approach was formulated where each cohort was represented as a separate 'study'. Study numbers were six except for Figure 2 where study number was 12 subdivided into DT-RRMS and DT-SPMS then 6 by each subtype. Different summary statistics from each cohort could then be used as effect sizes in a meta-analysis or meta-regression. Random effects estimates were created using the function meta::metabin(), and regression analysis using the functions meta::metareg() and meta::metaprop(). Each country provided summary univariate statistics for their cohort in the form of frequencies, means and standard deviations. Effect sizes were derived from the proportions of patients on treatment in different populations at different times. All statistical analyses described here were done in the R statistical programming language (v4.1.2)[10] with the following significant packages Meta (v5.2-0) for the meta-analyses, tidyverse (v1.3.1) and ggplot2 (v3.3.5) for visualisations.[11]

Summary demographic variables (age at index, age at onset, EDSS at Index and percentage female in the population) were used for the starting and escalating populations in addition to the five drivers of DMT utilisation; the summary demographic variables were not available for the population stopping DMTs.

Table 1. Identified features of health systems impacting access to treatment in five European countries.[7–9].

Country	United Kingdom		Sweden		Germany		Denmark		Czech Republic	
DMT metric		**Score**		**Score**		**Score**		**Score**		**Score**
Provision	51 centres 130,000 pwMS	1	60 centres 22,200 pwMS	6.9	187 centres 130,000 pwMS	3.7	13 centres 12,800 pwMS	2.6	15 centres 16,000 pwMS	2.4
Availability	DMTs can only be used if approved by the National Institute for health and Care Excellence	0	DMTs are decided by the HCP in consultation with patient	2	DMT treatment options based on EMA licence initially, subsequent reimbursement dependent upon its inclusion by a national assessment organisation	1	Treatment options are driven by national guidance that restricts DMT options	1	Each DMT has its own reimbursement criteria. Only select DMTs can be started first-line with stricter criteria apply to escalation DMTs	0
Funding	Once approved DMTs are government funded with a national price agreed and are free	0	DMTs max annual cost of SEK2350. Hospital treatments provided free. Costs covered by the prescribing hospital clinical department funded by regions. Incentive to use the cheapest DMT	2	Statutory health insurance covers ~87% of German residents and reimburses the cost of all approved DMTs. Depending on the health insurance company, the patient pays a co-payment of a maximum of 10€ per prescription	0	Funding provided by five regions with some variation. All DMT's are fully covered. All prescribed symptomatic medications provided at a maximum total annual cost for the patients of DKK 3000 (~€200)	1	DMT treatment is fully covered by compulsory health insurance	0
Monitoring	Prescribing is centralised via NHS England that requires disease classification and EDSS scores to be updated yearly	0	No monitoring	1	No monitoring	1	No monitoring	1	If the patient meets criteria, neurologist does not have to apply specifically for authorisation when starting treatment	0
Audit	Regular audit ensures DMT use is appropriate to diagnosis and EDSS. If prescribed incorrectly, DMTs are not refunded to the prescriber	2	No audit of prescribing is undertaken	0	No audit of prescribing is undertaken	0	No regular audit of prescribing is undertaken	0	Health insurance audit. If not prescribed in accordance with criteria, they may refuse to cover the cost	1

Availability, funding, monitoring and audit were derived from expert consensus from all authors. Provision was scored based on total providers of DMTs provided by lead from each country/total pwMS in each country.
DKK, Danish krone; DMT, disease-modifying treatment; EMA, European Medical Agency; HCP, healthcare professional.

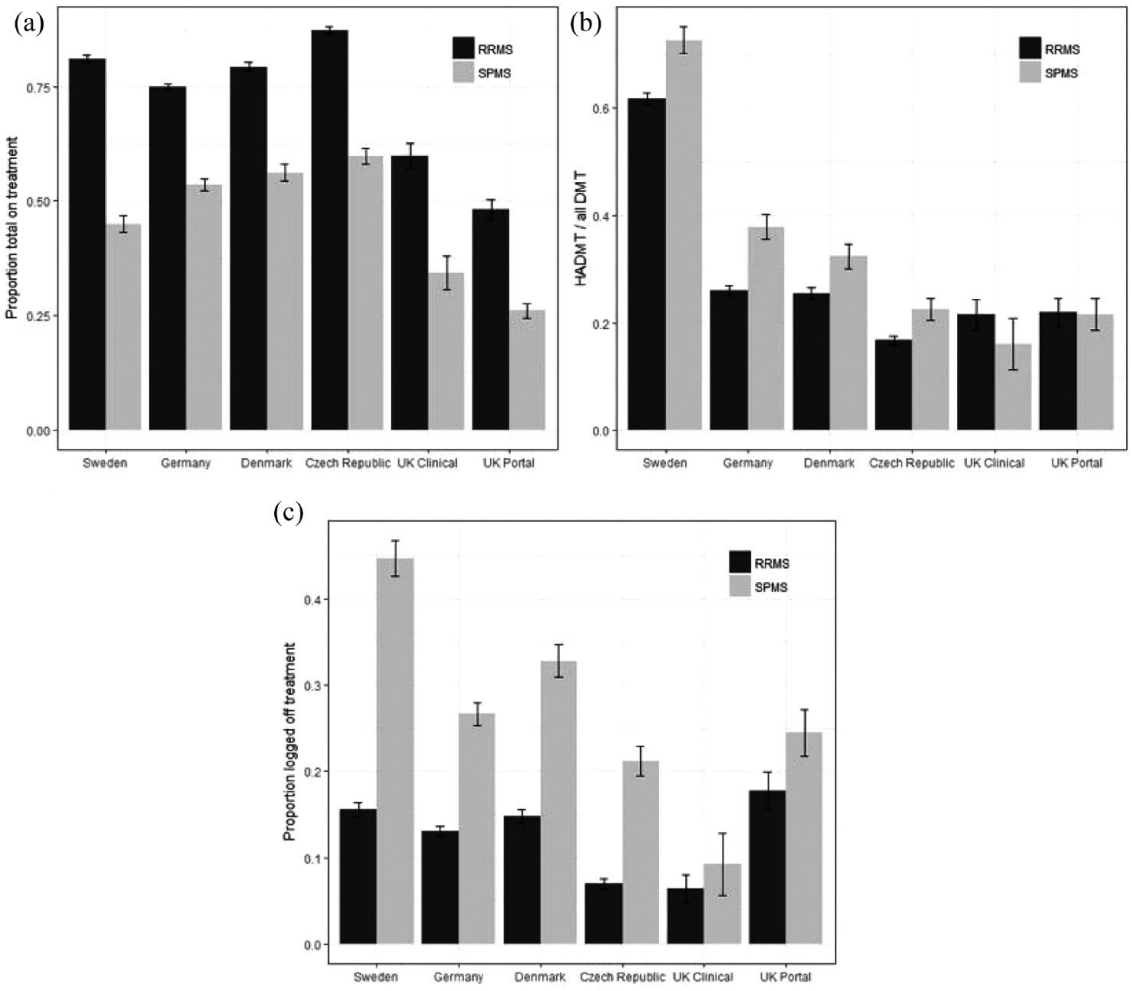

Figure 1. The proportion of clinical RRMS and SPMS subjects in each registry at index date in the total population who were still taking DMTs at index (a); the proportion of those on DMTs at index who were taking HADMTs (b) and those who have been on DMTs at some point in their illness and had stopped them at index (c). For absolute numbers see Supplemental Table. DMT, disease-modifying treatment; HADMT, highly active DMT; RRMS, relapsing–remitting MS; SPMS, secondary progressive MS.

Results

Standard and highly active DMT treatment in clinical RRMS and SPMS

In the total population [$n = 64{,}235$, Figure 1(a)], which includes pwMS who never had DMTs, the proportion on DMT at index date were higher in RRMS [0.767, 95% CI (0.763, 0.770)] than in SPMS [0.344 (0.335, 0.352)]. However, the treatment rates in the UK compared to the other countries in RRMS [UK: 0.524 (0.510, 0.538)]; other countries: 0.792 (0.788, 0.796)] and SPMS were lower [UK: 0.108 (0.095, 0.121)]; other countries: 0.397 (0.387, 0.407)]. Highly active DMT (HADMT) treatment was highest in Sweden in clinical RRMS [Sweden 0.617 (0.605, 0.628) *versus* all others 0.235 (0.23, 0.24)] and SPMS [Sweden 0.754 (0.728, 0.779) *versus* all others 0.296 (0.276, 0.315)] compared to all other registries [Figure 1(b)].

We next assessed a subset of the total population who had been on a DMT at some point ($n = 53{,}291$, Figure 1(c)) but who had stopped DMT by index date. A higher proportion had stopped DMTs in SPMS [0.296 (0.288, 0.304)] compared to RRMS [0.127 (0.123, 0.130)]. However, unlike in those starting DMTs, the stopping rates at index in the UK were the same as for the other countries in RRMS [UK: 0.131 (0.117, 0.146); other

countries: 0.126 (0.123, 0.130)] but lower in SPMS [UK: 0.215 (0.192, 0.237); other countries: 0.305 (0.296, 0.313)].

Demographic characteristics and health system features associated with DMT use in clinical RRMS and SPMS

We assessed the impact of demographic features and the health system characteristics on the rate of use of DMTs in clinical RRMS and clinical SPMS. Using meta-analysis with univariate meta-regression to assess the chance of being on DMTs, we found that the chance was lower in females with RRMS [Logit odds −0.182 (−0.35, 0.−01), $p=0.041$) and, in SPMS, with an increasing EDSS [−2.08 (−3.04, −1.12), $p=0.004$]. Of the drivers of DMT utilisation, the absence of Monitoring in SPMS [1.29 (0.21, 2.38), $p=0.029$] was associated with a higher chance of being on DMTs. There were no significant relationships associated with stopping treatments.

We can explain the implications of these models by taking an example. In the UK clinical RRMS data, the proportion of pwMS on DMT was 600 out of 1000 people. The percentage of females was 73.1% in this population. If the female population were increased to 74.1%, the proportion of pwMS on DMT would reduce to 560 out of 1000 people. In the UK clinical SPMS data, where 140 out of 1000 people were on DMT, the mean EDSS was 6.13. Increasing this by one point to 7.13 would reduce the proportion of pwMS on DMT by 120 people per 1000. In contrast, if the effect of monitoring was removed for the UK SPMS population, the proportion on DMT would increase by 240 people per 1000.

The impact of objective classification on the clinical populations' characteristics

In the cohort of 64,235 subjects, the sensitivity of identifying an DT-SPMS diagnosis in those with clinical SPMS diagnosis (number of SPMS diagnoses after applying the DT algorithm [DT-SPMS]/total initial clinical SPMS diagnoses) in Sweden was 0.991. For all other populations, there was a reduced sensitivity. The sensitivity was 0.897 for Denmark, 0.891 for Germany, reducing further to 0.839 for the UK clinical population and 0.806 for the Czech Republic and finally dropping to 0.689 for the UK portal population. Therefore, all registries compared to Sweden were more likely to categorise a person with likely SPMS using a standardised approach as having clinical RRMS. The populations subdivided by clinical diagnosis (RRMS/SPMS) and by classifier diagnosis (DT-RRMS/DT-SPMS) are described in Supplemental Table 1.

Demographic characteristics associated with reclassification of a clinical RRMS diagnosis to classified SPMS

Meta-analysis with a univariate meta-regression, excluding Sweden, was used to determine the characteristics of each population associated with those classified as SPMS but with a clinical diagnosis of RRMS. Both a higher percentage of females [Logit odds −0.19 (−0.37, −0.001), $p<0.049$] and a higher average EDSS at index [−0.65 (−1.18, −0.12), $p<0.03$] in an individual population were associated with a higher chance of being reclassified within that population. To explain the implications taking the example of Denmark where the proportion of those reclassified is 0.103, with a 1% increase in females in the population, the proportion reclassified from RRMS to DT-SPMS would increase to 0.12. Therefore, the proportion of those reclassified is 103 per 1000, with a 1% increase in females in the population, the proportion reclassified from RRMS to DT-SPMS would increase to 120 per 1000 an increase of 17 people per 1000. For the EDSS, where the average EDSS at index for Denmark is 2.9, and a one-point increase to 3.9 changes the sensitivity to 0.8198. Therefore, the proportion reclassified from RRMS to DT-SPMS would increase from (1–0.897) 0.103 to (1–0.819) 0.180.

Starting, escalating and stopping DMTs in a clinical SPMS population: The impact of reclassification

We next assessed whether changes in the clinical diagnosis, using the standardised approach, would impact a pwMS' chance of being on DMTs, for example, a clinical diagnosis of RRMS being classified DT-SPMS when using the objective classifier. We used this standardised approach to examine how DMT use was impacted in the clinical SPMS/RRMS population. To do this, we used meta-analysis to calculate the odds ratio (OR) of being on DMTs with a diagnosis of clinical SPMS compared to clinical RRMS in those classified as DT-SPMS or DT-RRMS (Figure 2).

We first studied whether there was any impact of reclassification on starting DMTs. There was no significant difference in the chance of starting on DMTs in clinical SPMS whether they were classified as DT-SPMS [OR 0.17 (0.11, 0.26), Figure 2(a)] or DT-RRMS [OR 0.23 (0.13, 0.39), meta-regression OR $n=12$: 1.0 (0.5, 1.99), $p=1$, Figure 2(d)].

Next, we determined whether there was any difference in those escalating treatment from being on DMT to a HADMT. We found no significant difference in the chance of being on a HADMT of those already on DMTs in those classified as DT-SPMS [OR 0.82 (0.39, 1.75), Figure 2(b)] or DT-RRMS [OR 1.57 (0.88, 2.79), meta-regression OR $n=12$: 0.53 (0.3, 1.21), $p=0.115$, Figure 2(e)].

Finally, we studied those who stopped DMTs. We found that the DT-SPMS subgroup of the clinical SPMS population was more likely to have stopped treatment [OR 4.13 (3.03, 5.63)] compared to the clinically RRMS patients reclassified to DT-SPMS subgroup [OR 2.43 (1.68, 3.52), both random effects model, Figure 2(c) and (f)]. From the meta-regression of this model [$n=12$, Figure 2(c) and (f)], the average change in the log-odds for stopping DMTs if the patient was classified DT-SPMS rather than DT-RRMS is 0.53 [0.113, 0.948], $p=0.018$. To illustrate this, we take Denmark as an example with an OR of 2.12 for stopping treatment if classified DT-RRMS. If we change the classification to DT-SPMS, then the model predicts an OR of 3.60 while the actual OR for DT-SPMS for Denmark is 3.34. Thus, the random effects model predicts those with a clinical SPMS diagnosis were almost twice as likely to stop DMTs across all studies when they were also classified as DT-SPMS.

DMT prescribing environments: Increasing treatment availability, monitoring and audit

We next examined the impact of the drivers of DMT utilisation (Table 1) using meta-regression and meta-analysis [Figure 2(a) and (d) ($n=12$)] where clinical RRMS was the control group. When looking at the log-odds, we found that having increasing Availability ['1' 0.94 (0.69, 1.19) $p<0.0001$, '2' 0.44 (0.15, 0.73) $p=0.0072$], no Monitoring [0.79 (0.42, 1.17) $p=0.0008$] and less rigorous Audit ['1' −0.57 (−1.01, −0.12)

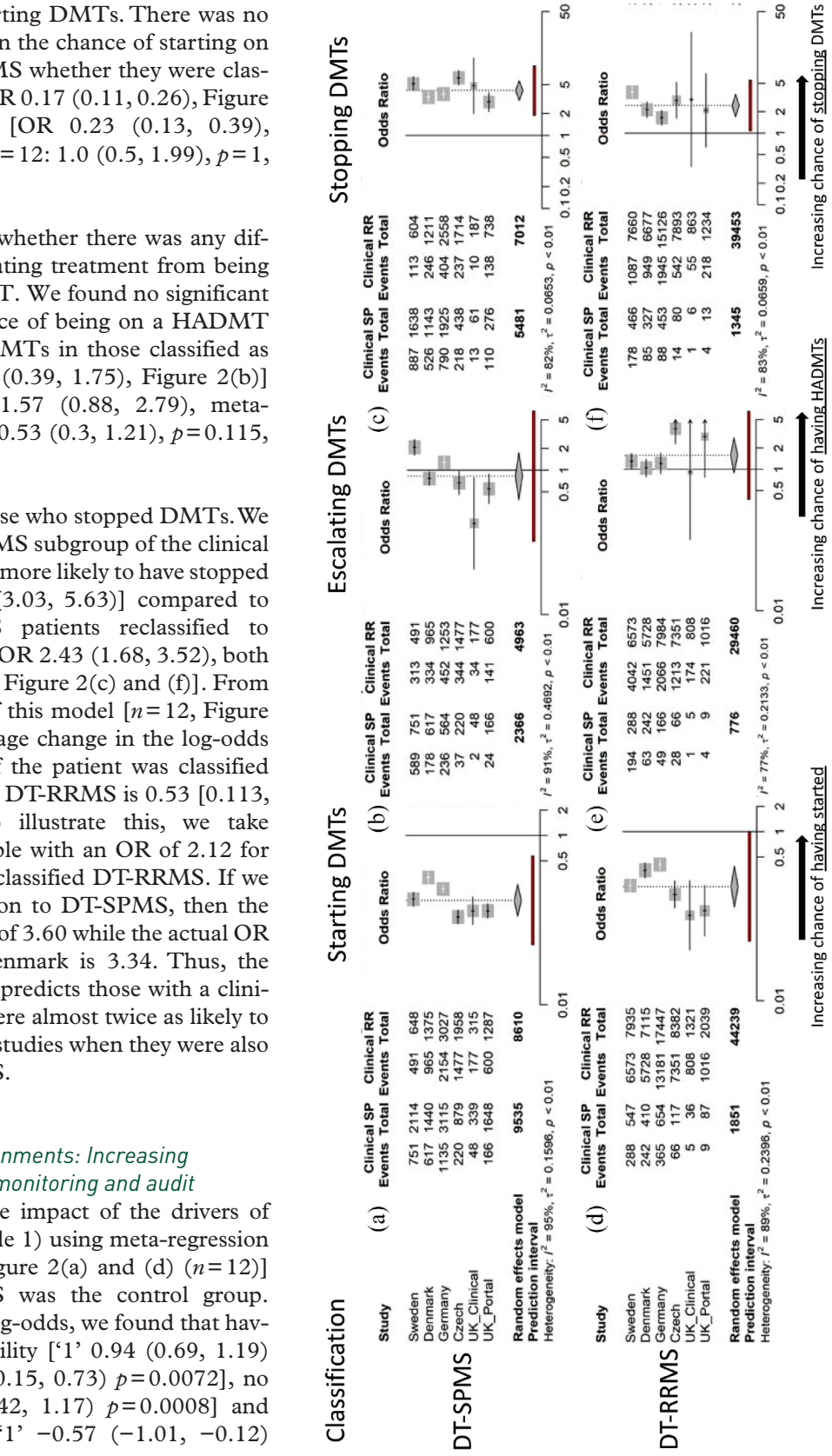

Figure 2. Forest plots of the meta-analyses of the six populations from the five registries with clinical SP as the experimental group and clinical RR as the control. These illustrate the chance (odds ratio) of starting DMTs (a and d), escalating to a HADMT (b and e) and stopping DMTs (c and f) based on an objectively classified (DT-)SPMS diagnosis (a–c) and (DT-)RRMS (d–f).
DMT, disease-modifying treatment; HADMT, highly active DMT; RR, Relapsing Remitting; RRMS, relapsing–remitting MS; SPMS, secondary progressive MS.

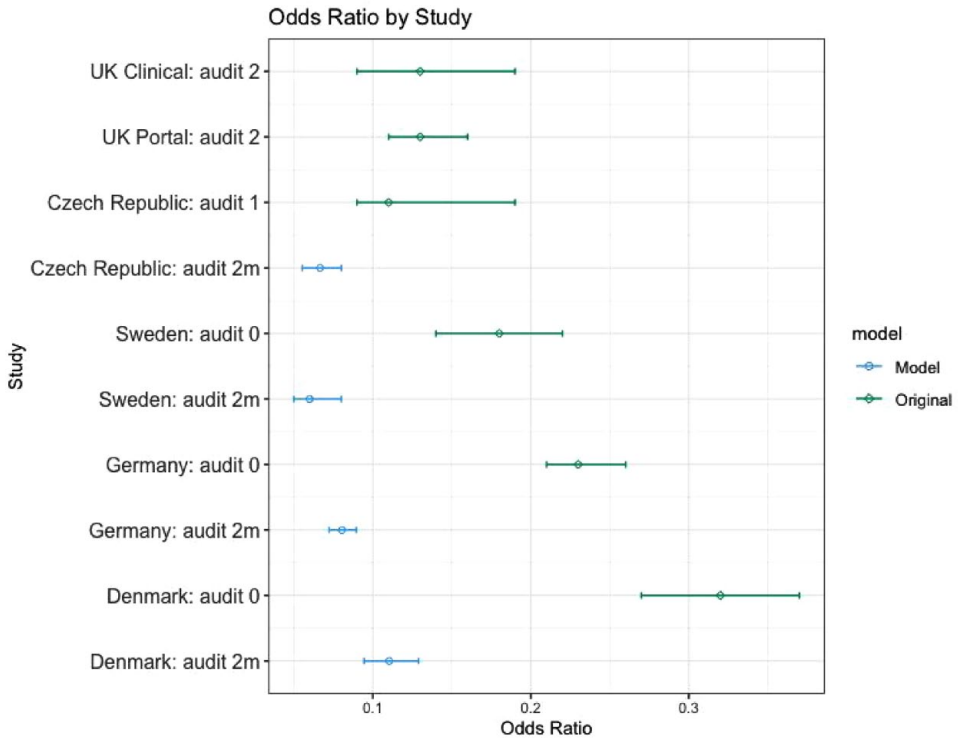

Figure 3. Odds ratio (±95% CI) of being on DMTs with a clinical diagnosis of SPMS when the classification is DT-SPMS for the UK clinical and portal populations (audit 2) and for the other populations with the actual result and the result from the model with the audit variable set at 2 (audit 2 m). There is a reduction in DMT use below that of the UK if the UK audit regimen is applied to the other populations.

$p = 0.017$, '2' −1.06 (−1.57, −0.56) $p = 0.0031$] was associated with a higher chance of being on treatment irrespective of the objective classification. None of the drivers had any impact on escalating to HADMTs in DT-SPMS nor on stopping DMTs in this analysis where DT-RRMS and DT-SPMS groups were considered together ($n = 12$).

Take, for example, Sweden's DT-SPMS classified population which has an OR of starting treatment as 0.18 (0.14, 0.22). If they had the same availability as the UK for both clinical [0.13 (0.09, 0.19)] and portal populations [0.13 (0.11, 0.16)], the model would give a new OR of 0.11 (0.09, 0.14). If they had the same monitoring as the UK, then the new OR would be 0.08 (0.07, 0.10). If Sweden (audit 0) had the same audit regime as the UK (audit 2), then the OR predicted by the model (audit 2 m) would be 0.06 (0.05, 0.08) significantly below levels of DMT use in the UK in the SPMS clinical population defined as DT-SPMS (Figure 3).

Discussion

This study has highlighted the importance of the clinical disease label in treatment initiation and escalation in MS. We show that there is no difference between the chance of starting or escalating DMTs in clinical SPMS regardless of the population's standardised diagnosis being SPMS or RRMS. In contrast, DMTs are stopped more often when both the standardised diagnosis, and the clinical diagnosis is SPMS. However, illustrating the key role of prescribing environment, increased Availability of DMTs, a lack of Monitoring or Audit, make it more likely that a pwMS will start a DMT, regardless of clinical label. Audit appears highly effective in limiting prescribing. Indeed, if the UK audit conditions were applied to Sweden, Swedish DMT use would be below that of the UK. Where Audit is present, such as in the UK, the change of a clinical RRMS label reclassified as SPMS is highest when compared to Sweden. This implies that the flexibility in the diagnostic label is the only modifiable condition that permits pwMS to start DMTs.

There are wide differences in the health, health provision and treatment of pwMS throughout Europe.[12,13] We are the first to integrate an analysis of disease and demographic factors with health system features to try to determine how they influence DMT prescribing. Prescribing of DMTs is a good example to dissect this problem as there is a global consensus on their use[14] but because of their high cost,[15] availability outside the private sector is subject to national rules that are enforced to a variable extent depending on the structure of the health system. Indeed, variations in prescribing practice driven by national strategies demonstrated differences in outcome in treatment escalation *versus* immediate initiation of HADMTs between the Swedish and Danish populations (Spelman *et al.*, 2021).[16] However, in general, the basis for DMT use is reliant on having a clinical label of RRMS. As there is a lack of clear diagnostic criteria for SPMS, this does introduce an element of flexibility in the timing of the diagnosis.[17]

Given the potential flexibility of the diagnosis to determine whether a clinical diagnosis of RRMS or SPMS is correct, we require a form of standardisation to allow us to make regional comparisons. Here, we utilised an objective classifier developed in Sweden to standardise the diagnosis; the classifier was chosen as its data requirements meant all pwMS could be categorised.[1] Classifier sensitivity was reduced in all groups compared to Sweden, with all other registries more likely to categorise a person with SPMS using a standardised approach as having clinical RRMS. This classifier is clearly most appropriate for the Swedish system where the prescribing approach is more driven by HCPs, but these findings imply non-random differences in the other populations. The EDSS, a key part of the objective classifier, is the main driver of differences in the different populations, and reclassification thus is more likely to occur where higher EDSSs have less influence in determining the clinical label. Gender also has a role though it was not part of the classifier. The implication is that women are more likely to have clinical RRMS when the classifier says they are SPMS (e.g. DT-SPMS) but from our DMT treatment data they have less chance of being on DMTs as previously seen.[18] Women are often treated less aggressively when it comes to a multitude of conditions such as acute coronary syndromes,[19] access to dialysis[20] and ICU,[21] but it does unmask a potential gendered, discriminatory decision-making process.

Access to DMTs is a known factor limiting DMT use,[22] but here all subjects were derived from registries and DMT provision was not a factor, as is borne out in the analysis. However, despite this, we have still found a wide range of rates of MS DMT prescribing within five countries in Europe. There was unsurprisingly higher DMT use in clinical RRMS versus clinical SPMS with lower DMT use in the UK compared to other countries. In Sweden, HADMT use was higher driven by the widespread use of rituximab.[12,23] Assessing the cessation of DMTs consistent with consensus guidance found more pwMS had stopped DMTs when assigned a clinical SPMS diagnosis *versus* RRMS. Again, in the UK, there was a lower rate of stopping DMTs in SPMS even though the actual numbers on DMTs were small. Complementary to classifier findings, this parallel evaluation of DMT use, found that treatment is less common in clinically diagnosed women with RRMS and in clinically diagnosed SPMS in those with a higher EDSS and where there is monitoring by the health system.

Changing a diagnosis of RRMS to SPMS is convoluted being both difficult from a clinical perspective but also in terms of how it is viewed by the patient and society.[16,24] A third less clear perspective is that a change in diagnostic classification affects how a health system views a pwMS. Importantly, depending on the structure of the health system, this can result in loss of access to DMTs. In the UK, where a structured approach to monitoring of DMT use is tightly controlled, the use of a SPMS clinical label will result DMT costs not being met centrally but falling to the local hospital to fund.[25] To understand how the clinical label impacted access to DMT, we studied the chance of being on DMT in SPMS versus RRMS. We found that the chance of being on DMTs in clinical SPMS was no different for starting or escalating DMTs irrespective of being classified as DT-RRMS or DT-SPMS. Thus, the clinical label is the most important feature enabling access to DMTs. Incorporating health system features, we found that clinically defined SPMS populations are more likely to be on treatment in a prescribing environment with increasing treatment availability, and a lack of monitoring

and audit. Thus, these measures do appear effective in health authority management of DMT prescribing.

Availability enables access to particular DMTs the rules for which can vary by country but overall DMTs offered cover similar aspects of RRMS in all countries. Monitoring and Audit enforce the clinical label. In the UK, access is formalised through guidance by the National Institute for Clinical Excellence (NICE) in England, Wales and Northern Ireland and by the Scotland intercollegiate Guidelines Network in Scotland, but monitoring and audit managed by national NHS organisations can result in hospitals bearing the direct cost of treatment as opposed to receiving central funding. Looking at the model in more detail. Comparing Sweden and the UK, we show that if such approaches were introduced in Sweden, they would reduce prescribing to a lower level compared to the UK. This implies that in the UK, there may be an element of adaptation by HCPs, given the importance of the clinical label in accessing DMTs and the fact that the UK and Czech Republic have the highest reclassification rate from RRMS to DT-SPMS. However, we see a different picture when DMTs are stopped. Here, we find if a pwMS had a clinical SPMS label who was also classified as DT-SPMS, they were more likely to stop DMTs and health systems have no impact. This is in agreement with general view that DMTs have less efficacy in SPMS.[14,25]

This study has several limitations. Firstly, is our use of an objective classifier as a way of standardising the clinical diagnosis. In SPMS, where there is no gold standard any standardisation, though consistent will be imperfect, especially when it appears to challenge a clinical diagnosis. We chose the DT classifier developed on Swedish data as it can classify based on a minimal dataset, and we did not explore other algorithms where evolution over time is incorporated.[1–3] The classifier uses a decision tree, trained on Swedish data, as a result, all populations were classified relative to Sweden reducing our ability to find issues with the Swedish system. Moreover, it was trained on a particular balance of RRMS/SPMS that biases the classifier, when in doubt, to favour the DT-RRMS label.[21] Despite the classifier bias naturally favouring a DT-RRMS classification, we observe the opposite, an increased DT-SPMS classification. This in itself is a further validation of our findings. A second limitation is that we only had access to summary data. This enabled access to large numbers across several registries whilst maintaining anonymisation but dictated our statistical approach and use of meta-analysis and meta-regression. A third limitation is that the drivers of DMT use apart from provision were based on a consensus approach focussing on features that may influence DMT use. These are likely not mutually exclusive but with the limited number of populations, we were not able to run a multivariate analysis to refine the analysis.

In summary, we have shown that differences in DMT prescribing persist beyond limitations in access and relate to healthcare environment. The clinical label is the primary factor enabling DMTs to be used, whereas the specific health systems' approach to verifying compliance with the label can be very effective in limiting prescribing. It appears the uncertainty surrounding that a change from a RR to a SPMS diagnosis is utilised in part to enable continuing access to treatment where the approach to verification has more consequences. The traditional approach to comparing disease outcomes is through the use of different interventions compared with unexposed control populations. Given the recent evidence of the impact of national strategies on outcome (Spelman *et al.*, 2021), our data suggest that it is of interest to determine in more detail how a health system's structures could impact MS outcomes.

Declarations

Ethics approval and consent to participate

The UK Multiple Sclerosis Register has research ethics approval from South West Central Bristol Research Ethics Committee with the approval coe 16/SW/0194. Consent to participate was not required for this anonymised retrospective study.

Consent for publication

Not applicable.

Author contributions

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James Witts: Formal analysis; Writing – review & editing.

Annalaura Lerede: Formal analysis; Writing – review & editing.

Tim Friede: Formal analysis; Writing – review & editing.

Jan Hillert: Investigation; Supervision; Validation; Writing – review & editing.

Lars Forsberg: Investigation; Supervision; Validation; Writing – review & editing.

Anna Glaser: Investigation; Writing – review & editing.

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Vladimir Bezlyak: Conceptualization; Funding acquisition; Writing – review & editing.

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Availability of data and materials

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Supplemental material

Supplemental material for this article is available online.

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