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Jonathan Roux, Elaine Kingwell, Feng Zhu, Helen Tremlett, Emmanuelle Leray

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Jonathan Roux[1,2], Elaine Kingwell[3,4], Feng Zhu[3], Helen Tremlett[3], Emmanuelle Leray[1,2] and the BeAMS Study group

[1] Univ Rennes, EHESP, REPERES (Pharmacoepidemiology and health services research) - EA 7449, 15 Avenue du Professeur Léon-Bernard, CS 74312, 35043 Rennes, France

[2] Inserm CIC-P 1414, CHU of Rennes, 2 Rue Henri Le Guilloux, 35000 Rennes, France

[3] Faculty of Medicine (Neurology),University of British Columbia and The Djavad Mowafaghian Centre for Brain Health, 2211 Wesbrook Mall, Vancouver, BC, V6T 1Z3, Canada

[4] Research Department of Primary Care & Population Health, University College London, Rowland Hill Street, London, NW3 2PF United Kingdom

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Corresponding author

Emmanuelle Leray

15, Avenue du Professeur Léon-Bernard - CS 74312

35043 RENNES Cedex FRANCE

Email: emmanuelle.leray@ehesp.fr / Tel: +33(0)2.99.02.25.13

Abstract

Background Persons with multiple sclerosis (PwMS) typically require complex multidisciplinary care, which is rarely formally assessed.

Objectives We applied multichannel sequence analysis (MCSA) to identify care consumption patterns by PwMS in British Columbia, Canada.

Methods We created two cohorts, comprising incident and prevalent MS cases, using linked clinical and administrative data. We applied MCSA to quantify and compare the care pathways of PwMS, based on all-cause hospitalisations and physician visits (divided into 5 specialities). Care consumption clusters were characterized using demographic and clinical features.

Results From 1,048 incident and 3,180 prevalent PwMS, the MCSA identified 12 and 6 distinct care consumption clusters over a median follow-up of 9.6 and 13.0 years, respectively. Large disparities between clusters were observed; the median number of annual consultations ranged from 5.6-21.3 for general practitioners, 1.2-4.6 for neurologists and 0-5.3 for psychiatrists in the incident cohort. Characteristics at MS symptom onset associated with the highest care consumption included high comorbidity burden and older age. There were similar disparities and associations for prevalent PwMS.

Conclusions The distinct patterns of care consumption, which were reminiscent of the heterogeneity of MS itself, may facilitate health service planning and evaluation, and provide a novel outcome measure in health research.

Introduction

Multiple sclerosis (MS) care management is complex, and a multidisciplinary approach is often required to manage MS effectively.[1–3] However, comprehensive, longitudinal data on care consumption in MS are lacking;[2,4,5] studies in this area have been cross-sectional.[6–8] Previous studies on differences in care consumption of persons with MS (PwMS) have compared groups defined, *a priori*, by initial MS course[7] or consultation with a neurologist,[2,8] or by comparison to the general population.[5,6] Thus patterns of an individual's care over time were not considered. Moreover, the physician specialty was either restricted to general practitioner (GP) and neurologist[7,8] or was not considered at all.[5,6] A recent study from our team accessed longitudinal administrative health data for PwMS in France, but MS-specific clinical data were not available and all health care providers (HCPs) were grouped together.[4] There remains a major unmet need to understand the combined 'care pathway' of PwMS, including the type, amount and chronology of care.

Using population-based linked clinical and administrative data, this study aimed to identify homogenous clusters demonstrating patterns of care consumption by PwMS without any *a priori* assumptions about subgroups and only based on care consumption first. Then, this study aimed to characterize these patterns of care consumption using clinical and demographical features to associate them to MS disease phenotypes.

Material and Methods

Design and settings

We accessed linked health administrative and clinical data in British Columbia (BC), Canada. These databases comprised physician visits (from the Medical Service Plan database,[9] with diagnoses identified by International Classification of Disease (ICD-9) codes), hospital admissions (from the Discharge Abstract Database,[10] with diagnoses identified by ICD9/10 codes), and prescriptions dispensed in outpatient and community pharmacies (from PharmaNet,[11] with medications coded by unique drug identification numbers). We accessed mortality data (from the BC Vital Statistics Agency database),[12] residency status in the province (from the BC Ministry of Health's Registration and Premium Billing Files),[13] and MS-specific clinical data (from the BC MS database [BCMS]),[14–16] for anyone in BC who was diagnosed with MS and had visited one of the 4 original MS clinics in the province The BCMS data provided the date of MS symptom onset, the initial disease course (relapsing or progressive),[17] the most recent (by the end of follow-up) disease course (including conversion to secondary progressive MS (SPMS), relapse date(s) (for the relapsing-onset PwMS), and disability scores as captured by the Expanded Disability Status Scale (EDSS)[18] at MS clinic visits. All data were available from January 1st, 1996, to December 31st, 2008 and were linked using unique personal health numbers. This study was approved by the University of British Columbia's Clinical Research Ethics Board (approval # H10-00984).

Study population

Two distinct cohorts were selected from the BCMS database.[14] The source cohort included all patients who were diagnosed with MS by a specialist neurologist and were first registered at one of the four original MS clinics in BC between 1980 and 2004. During this time period these four clinics were the only source of MS specialist care in the province. The incident cohort included PwMS with an MS onset date between January 1st, 1996, and December 31st, 2004. The prevalent cohort included PwMS who were alive and had a diagnosis of MS on January 1st, 1996. The start of follow-up (index date) was MS onset for the

incident cohort and January 1st, 1996 for the prevalent cohort. All PwMS were eligible for inclusion in one or the other cohort as long as they had at least one EDSS score (for the prevalent cases this score could have been recorded up to 3 years before the index date). In addition, the PwMS had to be resident in BC (i.e. registered in the BC health care plan) for at least 1 year before their index date until 4 years afterwards. PwMS in both cohorts were followed until the earlier of December 31st 2008, death, or emigration from BC.

Parameters of interest

The care consumption pathway

Data included in the care pathway were all-cause hospitalisations, and physician visits divided into 5 HCP specialities. GPs and neurologists were considered as they are the most involved in the daily management of MS. Psychiatrists and internal medicine specialists were included because they are frequently accessed by PwMS,[19,20] and to allow partial quantification of care related to comorbidities. Finally, for the fifth HCP category ('other') we included key specialists involved in the management of MS disability or symptoms, i.e. physical medicine and rehabilitation specialists, ophthalmologists, and urologists. For each PwMS, the number of each of the 6 types of health care interactions (all-cause hospitalisations plus the 5 HCPs) were calculated during every 6-month time window starting from the index date. The 6-month window was selected to allow sufficient time for specialist visits that might occur at a lower frequency, such as neurologists or internal medicine specialists For the last time window of follow-up, however, the number of health care interactions was calculated during the available time even if it was less than 6 months. The level of health care consumption was estimated based on the frequency of health care interactions within each time window for each of the 5 types of HCP visit and hospitalization (6 variables). The number of health care interactions were categorized into 2 to 4 levels of health care consumption (Supplementary

Table 1). Thus, an individual care pathway was defined as the successive values of care consumption, each value representing the categorized amount of care consumption with one HCP or hospitalisation during a 6-month window. The length of the care pathways ranged from 9 windows (4 years and 1 day of follow-up) to 26 windows (the full study period of 13 years). In addition, the number of consultations with all physicians regardless of the specialty was described (but not included in the construction of the care pathway).

Cohort characteristics

Demographic characteristics included age, sex, birth year, age and year of MS onset, follow-up duration and vital status by the end of follow-up. Clinical characteristics included the annualized relapse rate (ARR) over the follow-up, the initial and most recent MS disease course, the most recent available EDSS score, and, for the prevalent cohort only, the EDSS score closest (+/- 3 years) to the index date. The EDSS score at index was assumed to be 0 for the incident cohort. The EDSS scores were considered on a monthly basis and updated at each MS clinic visit, and categorised as low (0-2.5), medium (3-5.5), and high (≥6) disability. Disease-modifying therapy (DMT) use was defined as 'ever' (at least one prescription filled during the follow-up of beta interferon, glatiramer acetate or natalizumab).

Five of the most common comorbidities in MS (hypertension, hyperlipidemia, diabetes, chronic lung disease (CLD) and mood or anxiety disorders)[21] were identified, in the year before index and during follow-up, using algorithms based on the ICD diagnostic codes in the hospital and physician data (Supplementary Table 2).[22,23] Once a comorbidity was identified, a person was considered to be affected thereafter.

Statistical analysis

Care pathways were assessed using multichannel sequence analysis (MCSA). The MCSA is an extension of the conventional state sequence analysis (SSA); conventional SSA allows a sequence with only one dimension for each individual,[4] while the MCSA permits individual trajectories on several dimensions simultaneously.[24–26] Such methods have mainly been used in social sciences,[24–26] but are gaining interest in the field of public health.[4,27–30] With the MCSA, each individual is associated with multiple distinct but synchronized sequences (aligned to the time-windows), called 'channels'. Each channel taps a distinct aspect of the whole trajectory.[24–26] The dissimilarity matrix is estimated by the optimal matching method, as with classic SSA, using the different channels and their derived costs.[24,31] Here, the care pathways were formed of 6 different channels (one per HCP plus hospitalisation). The choice of the costs (insertion/deletion and substitution costs) used to compute the dissimilarity measure between the care pathways was based on our previous work.[4] The insertion/deletion costs were fixed to 1, and the substitution costs were based on observed state transition rates. The distances were normalized using Yujian and Bo normalization to take into account the different lengths of follow-up.[32] An agglomerative hierarchical clustering with Ward's criterion was then applied to the resulting distance matrix. The optimal number of clusters was set by both maximizing the weighted average silhouette width and minimizing Hubert's C.[4,33]

The clusters were characterized by interpretation of the channel trajectories and the cohort characteristics. Chronograms were used to summarize the EDSS trajectories of each cluster, whereby the y-axis shows the cumulative proportion of PwMS at each disability level and the x-axis depicts the time window. Computational and statistical analyses were performed using R statistical software (v.3.4.1)[34] with TraMineR[31] and WeightedCluster[33] packages.

Results

Population characteristics

Overall, 1,048 incident and 3,180 prevalent MS cases were included (Figure 1 & Table 1). The incident cases had a median age of 36.6 years at the index date (MS symptom onset) and were followed for a median of 9.6 years. The prevalent cases had a median age of 45.0 years and a median MS duration of 11 years at the index date (1st January 1996), and were followed for a median of 13.0 years. The use of DMTs was higher in the incident (66.7%) than the prevalent (31.8%) cohort. Accordingly, the incident cases visited neurologists more frequently than the prevalent cases (1.6 versus 0.8 visits per person-year).

Figure 1 here

Table 1 here

Application of the MCSA

MCSA led to the identification of 12 distinct clusters of PwMS (labelled as Clusters 1 to 12) in the incident cohort. The characteristics of these clusters are presented in Table 2 with their key features summarized in the final row; the evolution of their EDSS is shown in Figure 2.

Table 2 here

Figure 2 here

Compared to the other clusters, PwMS from Clusters 4 (n=200) and 5 (n=105) had low overall care consumption (14.7 and 13.9 visits with any physician per person-year), which included fewer visits to neurologists (1.4 visits per person-year). Cluster 7 (n=88) also comprised PwMS with low care

consumption (14.4 consultations with any physician per person-year) and few with at least one comorbidity by study end. The PwMS in Cluster 11 (n=81) also had low care consumption (13.4 consultations with any physician per person-year), but a lower EDSS score and lower proportion with comorbidity by study end.

In contrast, PwMS from Cluster 2 (n=63) had a high number of consultations with other key specialists (1.5 consultations per person-year), which is consistent with their faster disability progression (Figure 2) and relatively high ARR (median of 0.20) compared to the other clusters. Also characterized by a rapid increase in disability, Cluster 9 (n=83) included more PwMS who had converted to SPMS by study end. Cluster 1 (n=221) corresponded to older PwMS with a somewhat lower exposure to DMT (59.7%) and the lowest frequency of consultations with a neurologist (1.2 per person-year) relative to other clusters. This cluster also had the largest proportion of PwMS who had converted to SPMS (19.0%). Cluster 10 (n=32) had similar characteristics to Cluster 1, except for more comorbidity (59.4% with at least one comorbidity on the index date) and greater care consumption overall and particularly frequent interactions with psychiatrists (6.8 consultations per person-year).

Cluster 3 (n=59) included PwMS with a high burden of comorbidity at the index date (44.1%), with a high frequency of GP consultations (15.0 per person-year). Similarly, Cluster 6 (n=58) included PwMS with frequent GP visits (18.7 per person-year) and a high burden of comorbidity by study end (86.2% of PwMS with at least one comorbidity). In addition, this cluster was older at disease onset (median age of 38.4 years), and demonstrated a large increase in EDSS score over time (29.3% of PwMS with a high score by end of follow-up). The PwMS in Cluster 12 (n=14) had significant overall care consumption with a high frequency of visits across all physician specialties, including psychiatrists (5.3 per person-year), and a rapid increase in their EDSS scores after only 5.2 years of follow-up, despite a low ARR (virtually zero). Finally,

the PwMS in Cluster 8 (n=44) were the youngest with the most recent year of MS onset (2004). They had a high frequency of consultations with neurologists (2.7 per person-year) with virtually no disease activity (ARR of 0.0).

For the prevalent cohort, the MCSA identified 6 distinct clusters (labelled as Clusters A to F). Their characteristics are presented in Table 3 and the corresponding evolution of their EDSS scores is shown in Figure 3. Compared to other clusters, the 1,622 PwMS from Cluster B had fewer GP visits (6.0 per person-year) and fewer cases had at least one comorbidity, at index and study end. On the other hand, the majority of the 121 PwMS from Cluster A had at least one comorbidity at index (65.3%), and almost all (>95.9%) had one by study end; these PwMS had especially high care consumption with psychiatrists and neurologists. Cluster E (n=629) included a higher proportion of PwMS with at least one comorbidity by study end (84.4%), the highest proportion of DMT-treated PwMS (39.9%), and PwMS with particularly high GP care consumption (16.0 visits per person-year). The PwMS from Cluster D (n=352) had a high number of interactions with other key specialists compared to the other clusters (1.6 per person-year). Compared to the other clusters, Clusters C (n=251) and F (n=205) included higher proportions of men, larger proportions (64.1% and 64.0%) of PwMS with high EDSS scores by study end, and PwMS with virtually no disease activity during follow-up. Moreover, the majority of these PwMS had reached SPMS by study end and few PwMS (17.1% and 12.7%) were treated with a DMT during follow-up). These clusters included significantly less PwMS who survived to the study end; consequently, the follow-up duration (9.7 and 5.7 years) was shorter.

Table 3 here

Figure 3 here

Discussion

This study aimed to gain a better understanding of MS care through a detailed description of care pathways. The MSCA provided 12 clusters for the incident cohort, and 6 for the prevalent cohort, that revealed distinct profiles of care consumption among PwMS in relation to clinical phenotypes.

In comparison to previous studies,[1,4–6,23] we assessed care consumption of PwMS at a finer level. Rather than grouping all physician visits together, we have considered the main HCPs that are involved in MS management as separate specialty groups, which allowed for generation of more precise profiles of care consumption. Moreover, the creation of clusters was based only on the care consumption of PwMS and not on clinical or demographic features, in contrast to previous studies.[2,5–8] The overall care consumption of PwMS in our study was somewhat higher than in other studies that have also used longitudinal data. We found that PwMS had 18 to 19 visits per person-year whereas 12 visits per person-year were observed during the first 5 years after MS diagnosis in Manitoba, Canada,[5] and 16 visits were counted per person-year in a French MS cohort.[2] However, the annual numbers of visits with GPs and neurologists in our study were similar to those in another French cohort.[4] These variations may be explained by differences in case ascertainment (clinical versus administrative data, incident and/or prevalent cases) and baseline characteristics, such as the MS phenotype (relapsing versus progressive MS), disease duration, available DMTs, health care systems (funding, care reimbursement, healthcare access), and practices in MS care. Moreover, the study authors from Manitoba, Canada noted that their care consumption may have been underestimated.[5] Due to the time period, more DMTs were available in the French cohorts (natalizumab and oral DMTs), which may have had an impact on care consumption.[2,4]

In the incident cohort, over one third (Clusters 1 and 9 combined) of PwMS had reached SPMS by the study end. Clusters 2 and 10 could be assimilated to active MS with symptoms requiring frequent physician visits and hospitalisations. The high burden of MS disease activity and comorbidity could explain the more frequent use of psychiatrists in Cluster 10. Clusters 3, 6 and 12 correspond to PwMS with comorbidities that require a major role for the GP. Cluster 8 may represent PwMS with well-controlled MS or naturally low disease activity. Finally, the remaining clusters (4, 5, 7 and 11) may represent the classic relapsing-remitting trajectory, where PwMS with few comorbidities are using DMTs, and thus require a relatively low level of care.

PwMS in Clusters C and F in the prevalent cohort had a high disability level; most had SPMS, and most did not survive to the study end; the high care consumption for these clusters, is consistent with literature describing increased care consumption during the last year of life.[35] Cluster D may represent PwMS with advanced MS and active disease. Clusters A and E correspond to PwMS with comorbidity which is likely to explain their frequent use of GPs and all physicians.[1] Finally, Cluster B, which is by far the largest cluster, reflects expected care consumption of the majority of PwMS.

Such profiles could potentially be used in policy planning to anticipate the demand on specialists according to disease evolution or regions (for example, with cross-reference or residence data). They could also be used to study the potential impact of the amount of care consumption on important clinical outcomes, such as disability progression.

SSA provides a useful and innovative means to study care pathways.[4,29,30] These are holistic methods, with the whole care pathway as the statistical unit of interest. However, a limitation of conventional SSA is that the different interactions with HCPs must be grouped together into a single variable,[4] which can only

provide a macroscopic overview of the variations of care consumption. In contrast, MCSA offers simultaneous comparison of the different dimensions of a sequence of healthcare interactions between individuals.[24–26] It therefore provides a more nuanced view of the care consumption by different HCPs, and enables identification of the clinically relevant phenotypes that are linked to each care consumption profile.

From a methodological point of view, to avoid the creation of a cluster that only included PwMS with a short follow-up duration due to death, we selected only individuals with at least 4 consecutive years of follow-up and normalized the dissimilarity measure. However, we cannot rule out the possibility that the length of the care pathways influenced the formation of clusters C and F.

The linked administrative and clinical datasets offered the opportunity to access extensive population-based longitudinal data with up to 13 years of follow-up. The information captured in administrative health databases are comprehensively, objectively, and systematically collected which essentially removes the risk of recall bias and provides a true representation of care consumption of PwMS. On the other hand, we were not able to consider encounters with paramedical specialists (physiotherapists and nurses), which are important in the care of PwMS.[2] Moreover, we did not have access to data on lifestyle and environmental factors that could be directly associated with care consumption, such as obesity, smoking, diet, physical activity, or educational level. However, we identified comorbidities (hypertension, hyperlipidemia, diabetes, chronic lung disease) for which these lifestyle and environmental characteristics can be risk factors. To include relevant MS-specific clinical data, we considered only PwMS whose data were captured in the BCMS database (i.e. clinic users); MS clinic users are not necessarily representative of the general MS population though; they may have a lower care consumption and fewer comorbidities than non-clinic users, for example.[23] Thus, it is possible that these care consumption profiles may not be

generalizable beyond clinic-based populations of PwMS, or to other geographical regions or time periods. As the study follow-up period ended in December 2008, the more recent marked changes in diagnosis and treatment (particularly newer DMTs) are not considered in the care pathways.

To conclude, this is one of the first studies to use MCSA in the study of care pathways. The identification of several different profiles of care consumption that are associated with distinct MS phenotypes reflect the heterogeneity of MS. From a public health point of view, these profiles and methods could help health services planning, and may provide a novel outcome in health research or economic evaluation.

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Declaration of Conflicting Interests

Jonathan Roux has nothing to disclose.

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Table 1 Demographic and clinical characteristics of the incident and prevalent multiple sclerosis cohorts

	Incident MS cohort (N=1,048)	Prevalent MS cohort (N=3,180)
Women, n (%)	796 (76.0%)	2,334 (73.4%)
Median birth year (q1-q3)	1962 (1955-1970)	1951 (1944-1958)
Median year of MS onset (q1-q3)	1999 (1997-2001)	1985 (1977-1990)
Median age at MS onset (q1-q3) (years)	36.6 (29.3-43.7)	30.5 (24.3-37.9)
Median follow-up (q1-q3) (years)	9.6 (7.4-11.4)	13.0 (13.0-13.0)
Deaths, n (%)	25 (2.4%)	400 (12.6%)
Disability level (EDSS score) at index (%)		
Low (0-2.5)	-	998 (31.4%)
Medium (3-5.5)	-	656 (20.6%)
High (≥6)	-	676 (21.3%)
Missing	-	850 (26.7%)
Most recent disability level (EDSS score) (%)		
Low (0-2.5)	611 (58.3%)	977 (30.7%)
Medium (3-5.5)	261 (24.9%)	821 (25.8%)
High (≥6)	176 (16.8%)	1,382 (43.5%)
Median ARR during follow-up[a] (q1-q3)	0.16 (0.00-0.30)	0.00 (0.00-0.15)
Initial RRMS course, n (%)	989 (94.4%)	260 (8.2%)
SPMS course by end of follow-up, n (%)	105 (10.0%)	1,380 (43.4%)
At least one comorbidity on index date[b], n (%)	210 (20.0%)	713 (22.4%)
At least one comorbidity by end of follow-up[b], n (%)	612 (58.4%)	2,075 (65.3%)
At least one DMT prescription filled during follow-up[c], n (%)	699 (66.7%)	1,010 (31.8%)
Use of healthcare services - Median (q1-q3)		
Visits with a GP[d]	8.4 (5.5-12.8)	8.5 (5.5-12.7)
Visits with a neurologist[d]	1.6 (1.2-2.1)	0.8 (0.5-1.3)
Visits with an internal medicine specialist[d]	0.2 (0.0-0.5)	0.3 (0.1-0.8)
Visits with a psychiatrist[d]	0.0 (0.0-0.1)	0.0 (0.0-0.1)
Visits with other key specialists[d, e]	0.6 (0.2-1.2)	0.5 (0.2-1.2)
At least one hospitalisation, n (%)	717 (68.4%)	2,559 (80.5%)
Hospitalisations[d, f]	0.2 (0.1-0.4)	0.3 (0.2-0.6)
Visits with all physicians[e, g]	18.5 (12.7-26.3)	18.8 (12.1-28.0)

ARR: annualized relapses rate. DMT: disease-modifying therapy. EDSS: expanded disability scale status. GP: general practitioner. MS: multiple sclerosis. RRMS: relapsing-remitting multiple sclerosis. SPMS: secondary progressive multiple sclerosis. q1-q3: quartiles 1 and 3.

[a] Excluding the onset attack (relapse date of first relapse = MS onset date) and only for people having a relapsing-remitting initial disease course. [b] Included comorbidities: hypertension, hyperlipidemia,

diabetes, chronic lung disease (CLD) and mood or anxiety disorders. [c] Included DMTs: beta-interferon, glatiramer acetate and natalizumab. [d] Number per person-year. [e] Other specialists: physical medicine and rehabilitation specialist, ophthalmologist, urologist. [f] Denominator = persons with MS with at least one hospital admission during follow-up. [g] All physicians, regardless of specialty (including physicians with specialties other than those in the 5 identified categories).

Table 2 Characteristics of the incident multiple sclerosis cohort according to the 12 clusters identified by multichannel sequence analysis (n=1,048)

	1 (n=221)	**2 (n=63)**	**3 (n=59)**	**4 (n=200)**	**5 (n=105)**	**6 (n=58)**	**7 (n=88)**
Women[†], n (%)	173 (78.3%)	49 (77.8%)	45 (76.3%)	151 (75.5%)	72 (68.6%)	49 (84.5%)	61 (69.3%)
Median birth year (q1-q3)	1959 (1953-1965)	1962 (1953-1972)	1969 (1955-1975)	1961 (1954-1968)	1966 (1958-1971)	1959 (1952-1964)	1966 (1960-1971)
Median year of MS onset (q1-q3)	1997 (1996-1997)	1999 (1999-1999)	2002 (2002-2003)	1998 (1998-1999)	2000 (2000-2000)	1997 (1996-1668)	2002 (2002-2003)
Median age at MS onset (q1-q3) (years)	37.2 (31.4-43.2)	36.6 (26.0-45.2)	33.7 (27.5-44.3)	37.0 (30.2-43.3)	33.7 (29.0-41.9)	38.4 (32.1-45.1)	35.1 (30.4-41.5)
Median follow-up (q1-q3) (years)	12.0 (11.9-12.7)	9.8 (9.1-10.0)	6.2 (5.9-6.4)	10.6 (10.0-11.0)	8.8 (8.6-9.0)	11.7 (11.0-12.3)	6.4 (6.0-6.8)
Deaths[†], n (%)	≤5 (≤2.3%)	≤5 (≤7.9%)	≤5 (≤8.5%)	0 (0.0%)	≤5 (≤4.8%)	≤5 (≤8.6%)	≤5 (≤5.7%)
Most recent disability level (EDSS score) [†] (%)							
Low (0-2.5)	114 (51.6%)	30 (47.6%)	35 (59.3%)	130 (65.0%)	71 (67.6%)	23 (39.7%)	63 (71.6%)
Medium (3-5.5)	58 (26.2%)	19 (30.2%)	13 (22.0%)	45 (22.5%)	24 (22.9%)	18 (31.8%)	17 (19.3%)
High (≥6)	49 (22.2%)	14 (22.2%)	11 (18.6%)	25 (12.5%)	10 (9.5%)	17 (29.3%)	8 (9.1%)
Median ARR during follow-up[b] (q1-q3)	0.17 (0.08-0.25)	0.20 (0.10-0.27)	0.16 (0.00-0.36)	0.18 (0.09-0.29)	0.22 (0.11-0.34)	0.13 (0.00-0.33)	0.15 (0.00-0.29)
Initial RRMS course[†], n (%)	207 (93.7%)	57 (90.5%)	≥54 (≥91.5%)	191 (95.5%)	99 (94.3%)	≥53 (≥91.4%)	≥83 (≥94.3%)

SPMS course by end of follow-up, n (%)	42 (19.0%)	6 (9.5%)	<5 (<8.5%)	14 (7.0%)	9 (8.6%)	8 (13.8%)	0 (0.0%)
At least one comorbidity on index date[c], n (%)	32 (14.5%)	12 (19.0%)	26 (44.1%)	21 (10.5%)	15 (14.3%)	27 (46.6%)	8 (9.1%)
At least one comorbidity by end of follow-up[†, c], n (%)	135 (61.1%)	47 (74.6%)	46 (78.0%)	96 (48.0%)	41 (39.0%)	50 (86.2%)	31 (35.2%)
At least one DMT prescription filled during follow-up[†, d], n (%)	132 (59.7%)	43 (68.3%)	44 (74.6%)	128 (64.0%)	71 (67.6%)	39 (67.2%)	67 (76.1%)
Use of healthcare services - Median (q1-q3) [ranked from #1 – highest use to #12 – lowest use]							
Visits with a GP[e]	7.9 (5.5-10.7)	11.9 (9.2-15.7)	15.0 (11.9-19.7)	6.6 (4.7-9.4)	6.3 (4.4-9.7)	18.7 (16.4-26.5)	6.1 (4.7-8.0)
Rank	*#8*	*#5*	*#3*	*#9*	*#10*	*#2*	*#11*
Visits with a neurologist[e]	1.2 (0.9-1.6)	2.0 (1.3-2.6)	2.1 (1.4-2.8)	1.4 (1.1-1.7)	1.4 (1.1-1.8)	1.8 (1.4-2.4)	1.7 (1.3-2.2)
Rank	*#12*	*#4*	*#3*	*#10*	*#10*	*#7*	*#8*
Visits with an internal medicine specialist[e]	0.2 (0.0-0.4)	0.4 (0.1-0.8)	0.3 (0.0-0.7)	0.1 (0.0-0.4)	0.1 (0.0-0.2)	0.8 (0.2-1.7)	0.0 (0.0-0.4)
Rank	*#7*	*#4*	*#5*	*#9*	*#9*	*#2*	*#12*
Visits with a psychiatrist[e]	0.0 (0.0-0.0)	0.0 (0.0-0.1)	0.0 (1.0-0.4)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.6)	0.0 (0.0-0.0)

Rank	*#3*	*#3*	*#3*	*#3*	*#3*	*#3*	*#3*
Visits with other key specialists[e, f]	0.5 (0.2-1.0)	1.5 (0.6-2.3)	0.8 (0.4-1.9)	0.4 (0.1-0.7)	0.4 (0.1-0.9)	1.2 (0.4-2.5)	0.5 (0.2-1.0)
Rank	*#8*	*#2*	*#6*	*#10*	*#10*	*#3*	*#8*
At least one hospitalisation[†], n (%)	169 (76.5%)	57 (90.5%)	41 (69.5%)	129 (64.5%)	57 (54.3%)	53 (91.4%)	42 (47.7%)
Hospitalisations[e, g]	0.2 (0.1-0.3)	0.3 (0.2-0.5)	0.5 (0.3-0.8)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.4 (0.2-0.8)	0.3 (0.2-0.5)
Rank	*#9*	*#7*	*#2*	*#9*	*#9*	*#3*	*#7*
Visits with all physicians[e, h]	16.8 (12.3-22.3)	24.0 (20.3-29.9)	29.5 (23.7-35.9)	14.7 (10.8-20.2)	13.9 (10.1-19.3)	38.8 (32.8-50.1)	14.4 (11.2-16.9)
Key features (relative to the other clusters)	• Older • Lower DMT exposure • Higher proportion reached SPMS by study end • Fewer neurologist visits	• Higher ARR • More visits with other key specialists	• Higher proportion of cases with a comorbidity on the index date • More visits with GPs	• Lower care consumption • Fewer neurologist visits	• Lower care consumption • Fewer neurologist visits	• Older at MS onset • Higher EDSS score by study end • Higher proportion of cases with a comorbidity by study end • More visits with GPs	• Lower care consumption • Lower proportion of cases with a comorbidity by study end

Table 2 contd. Characteristics of the incident multiple sclerosis cohort according to the 12 clusters identified by multichannel sequence analysis (n=1,048) (continued)

	8 (n=44)	**9 (n=83)**	**10 (n=32)**	**11 (n=81)**	**12 (n=14)**	**p-value[a]**
Women[†], n (%)	32 (72.7%)	71 (85.5%)	27 (84.4%)	53 (65.4%)	≥9 (≥64.3%)	**0.035**
Median birth year (q1-q3)	1970 (1961-1975)	1964 (1955-1971)	1959 (1953-1966)	1965 (1955-1972)	1965 (1958-1970)	**<0.001**
Median year of MS onset (q1-q3)	2004 (2003-2004)	2001 (2000-2001)	1998 (1997-2000)	2001 (2001-2001)	2003 (1999-2003)	**<0.001**
Median age at MS onset (q1-q3) (years)	31.2 (28.3-40.7)	36.7 (29.4-45.3)	39.6 (32.4-43.1)	36.7 (26.8-45.7)	37.2 (30.5-44.6)	0.595
Median follow-up (q1-q3) (years)	4.9 (4.3-5.2)	7.8 (7.4-8.0)	10.7 (8.8-12.0)	7.4 (7.1-8.0)	5.2 (4.9-5.6)	**<0.001**
Deaths[†], n (%)	≤5 (≤11.4%)	6 (7.2%)	≤5 (≤15.6%)	≤5 (≤6.2%)	≤5 (≤35.7%)	**<0.001**
Most recent disability level (EDSS score) [†] (%)						**<0.001**
Low (0-2.5)	≥31 (≥70.5%)	37 (44.6%)	16 (50.0%)	57 (70.4%)	≤5 (≤35.7%)	
Medium (3-5.5)	8 (18.2%)	29 (34.9%)	9 (28.1%)	13 (16.0%)	≥5 (≥35.7%)	
High (≥6)	≤5 (≤11.4%)	17 (20.5%)	7 (21.9%)	11 (13.6%)	≤5 (≤35.7%)	
Median ARR during follow-up[b] (q1-q3)	0.00 (0.00-0.40)	0.15 (0.11-0.38)	0.16 (0.08-0.30)	0.15 (0.00-0.28)	0.00 (0.00-0.21)	0.102
Initial RRMS course[†], n (%)	≥39 (≥88.6%)	74 (89.2%)	32 (100.0%)	76 (93.8%)	14 (100.0%)	0.409
SPMS course by end of follow-up, n (%)	≤5 (≤11.4%)	13 (15.7%)	≤5 (≤15.6%)	≤5 (≤6.2%)	≤5 (≤35.7%)	**<0.001**
At least one comorbidity o index date[c], n (%)	10 (22.7%)	21 (25.3%)	19 (59.4%)	11 (13.6%)	8 (57.1%)	**<0.001**

At least one comorbidity by end of follow-up[†, c], n (%)	26 (59.1%)	63 (75.9%)	≥27 (≥84.4%)	32 (39.5%)	14 (100.0%)	**<0.001**
At least one DMT prescription filled during follow-up[†, d], n (%)	30 (68.2%)	62 (74.7%)	19 (59.4%)	54 (66.7%)	≥9 (≥64.3%)	0.229
Use of healthcare services - Median (q1-q3) [ranked from #1 – highest use to #12 – lowest use]						
Visits with a GP[e]	9.0 (6.9-13.1)	13.7 (10.7-17.0)	10.2 (6.4-15.0)	5.6 (4.0-7.2)	21.3 (18.8-37.7)	**<0.001**
Rank	*#7*	*#4*	*#6*	*#12*	*#1*	
Visits with a neurologist[e]	2.7 (1.8-3.4)	2.0 (1.5-2.6)	1.9 (1.4-2.7)	1.6 (1.3-2.1)	4.6 (2.4-5.4)	**<0.001**
Rank	*#2*	*#4*	*#6*	*#9*	*#1*	
Visits with an internal medicine specialist[e]	0.2 (0.0-0.4)	0.3 (0.1-1.4)	0.6 (0.3-1.2)	0.1 (0.0-0.3)	0.9 (0.6-2.2)	**<0.001**
Rank	*#7*	*#5*	*#3*	*#9*	*#1*	
Visits with a psychiatrist[e]	0.0 (0.0-0.0)	0.0 (0.0-0.7)	6.8 (3.1-11.7)	0.0 (0.0-0.0)	5.3 (1.8-18.8)	**<0.001**
Rank	*#3*	*#3*	*#1*	*#3*	*#2*	
Visits with other key specialists[e, f]	0.9 (0.2-1.5)	0.8 (0.3-1.3)	1.2 (0.6-1.7)	0.4 (0.1-1.5)	1.8 (1.2-3.5)	**<0.001**
Rank	*#5*	*#6*	*#3*	*#10*	*#1*	
At least one hospitalisation[†], n (%)	23 (52.3%)	63 (75.9%)	≥27 (≥84.4%)	40 (49.4%)	≥9 (≥64.3%)	**<0.001**
Hospitalisations[e, g]	0.4 (0.2-0.7)	0.4 (0.1-0.9)	0.4 (0.2-1.0)	0.1 (0.1-0.3)	0.8 (0.5-2.5)	**<0.001**

	Rank	*#3*	*#3*	*#3*	*#12*	*#1*	
Visits with all physicians[e, h]		20.3 (14.0-25.6)	28.1 (22.2-35.0)	34.3 (22.9-43.1)	13.4 (9.9-17.4)	55.5 (40.0-77.1)	**<0.001**
Key features (relative to the other clusters)		• Younger • More recent MS onset • Lower ARR • More neurologist visits	• Higher proportion reached SPMS by study end • Increase of EDSS score during follow-up	• Higher care consumption • Older • Higher proportion of cases with a comorbidity on the index date • Lower DMT exposure	• Lower care consumption • Lower EDSS score by study end • Lower proportion of cases with a comorbidity by study end	• Higher care consumption • Lower ARR • Increase of EDSS score during follow-up • More psychiatrist visits • Higher proportion of cases with a comorbidity on index date and by study end	-

ARR: annualized relapses rate. DMT: disease-modifying therapy. EDSS: expanded disability scale status. GP: general practitioner. MS: multiple sclerosis. RRMS: relapsing-remitting multiple sclerosis. SPMS: secondary progressive multiple sclerosis. q1-q3: quartiles 1 and 3.
[†] The presented data are restricted to prevent direct or residual disclosure of identifiable data.

[a] p-value comparing the different clusters using the Kruskal-Wallis, Pearson's chi-square, or Fisher's exact test as appropriate. [b] Excluding the onset attack (relapse date of first relapse = MS onset date) and only for people having a relapsing-remitting initial disease course. [c] Included comorbidities: hypertension, hyperlipidemia, diabetes, chronic lung disease (CLD) and mood or anxiety disorders. [d] Included DMTs: beta-interferon, glatiramer acetate and natalizumab. [e] Number per person-year. [f] Other specialists: physical medicine and rehabilitation specialist, ophthalmologist, urologist. [g] Denominator = persons with MS with at least one hospital admission during follow-up. [h] All physicians, regardless of specialty (including physicians with specialties other than those in the 5 identified categories).

Table 3 Characteristics of the prevalent multiple sclerosis cohort according to the 6 clusters identified by multichannel sequence analysis (n=3,180)

	A (n=121)	**B (n=1,622)**	**C (n=251)**	**D (n=352)**	**E (n=629)**	**F (n=205)**	**p-value[a]**
Women, n (%)	103 (85.1%)	1,163 (71.7%)	171 (68.1%)	255 (72.4%)	512 (81.4%)	130 (63.4%)	**<0.001**
Median birth year (q1-q3)	1953 (1950-1959)	1953 (1946-1959)	1948 (1937-1955)	1948 (1941-1955)	1951 (1944-1958)	1947 (1936-1955)	**<0.001**
Median year of MS onset (q1-q3)	1984 (1978-1991)	1986 (1979-1991)	1983 (1974-1988)	1983 (1975-1990)	1984 (1976-1990)	1980 (1972-1988)	**<0.001**
Median age at MS onset (q1-q3) (years)	28.1 (22.6-35.2)	30.0 (24.5-37.0)	30.6 (24.4-39.7)	32.6 (24.8-40.7)	30.4 (23.5-37.9)	31.4 (24.5-39.7)	**0.003**
Median follow-up (q1-q3) (years)	13.0 (13.0-13.0)	13.0 (13.0-13.0)	9.7 (8.4-10.4)	13.0 (13.0-13.0)	13.0 (13.0-13.0)	5.7 (4.9-6.6)	**<0.001**
Deaths[†], n (%)	≤5 (≤4.1%)	36 (2.2%)	177 (70.5%)	15 (4.3%)	33 (5.2%)	136 (66.3%)	**<0.001**
Disability level (EDSS score) at index (%)							**<0.001**
Low (0-2.5)	37 (30.6%)	562 (34.6%)	48 (19.1%)	95 (27.0%)	208 (33.1%)	48 (23.4%)	
Medium (3-5.5)	28 (23.1%)	313 (19.3%)	40 (15.9%)	71 (20.2%)	155 (24.6%)	49 (23.9%)	
High (≥6)	17 (14.0%)	254 (15.7%)	110 (43.8%)	87 (24.7%)	120 (19.1%)	88 (42.9%)	
Missing	39 (32.2%)	493 (30.4%)	53 (21.1%)	99 (28.1%)	146 (23.2%)	20 (9.8%)	
Most recent disability level (EDSS score) (%)							**<0.001**
Low (0-2.5)	44 (36.4%)	580 (35.8%)	52 (20.7%)	78 (22.2%)	186 (29.6%)	37 (18.0%)	
Medium (3-5.5)	38 (31.4%)	427 (26.3%)	38 (15.1%)	91 (25.9%)	190 (30.2%)	37 (18.0%)	
High (≥6)	39 (32.2%)	615 (37.9%)	161 (64.1%)	183 (52.0%)	253 (40.2%)	131 (64.0%)	
Median ARR during follow-up[b] (q1-q3)	0.08 (0.00-0.15)	0.04 (0.00-0.15)	0.00 (0.00-0.11)	0.08 (0.00-0.15)	0.08 (0.00-0.15)	0.00 (0.00-0.15)	**<0.001**
Initial RRMS course[†], n (%)	≥116 (≥95.9%)	1,496 (92.2%)	223 (88.8%)	321 (91.2%)	585 (93.0%)	177 (86.3%)	**0.003**

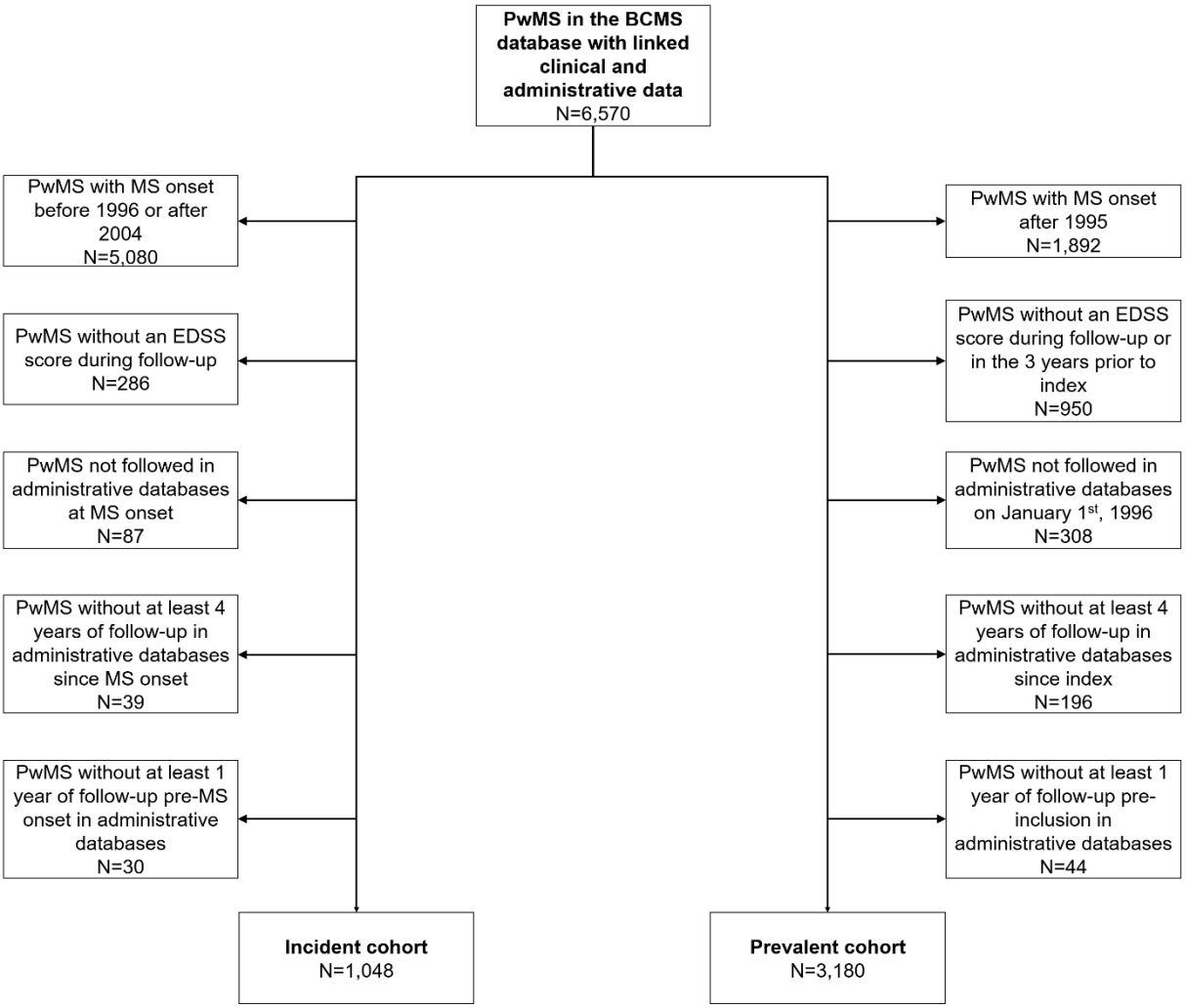
SPMS course by end of follow-up, n (%)	46 (38.0%)	629 (38.8%)	140 (55.8%)	180 (51.1%)	262 (41.7%)	123 (60.0%)	**<0.001**
At least one comorbidity on index date[c], n (%)	79 (65.3%)	216 (13.3%)	56 (22.3%)	77 (21.9%)	223 (35.5%)	62 (30.2%)	**<0.001**
At least one comorbidity by end of follow-up[†, c], n (%)	≥116 (≥95.9%)	883 (54.4%)	161 (64.1%)	259 (73.6%)	531 (84.4%)	124 (60.5%)	**<0.001**
At least one DMT prescription filled during follow-up[d], n (%)	48 (39.7%)	521 (32.1%)	43 (17.1%)	121 (34.4%)	251 (39.9%)	26 (12.7%)	**<0.001**
Use of healthcare services - Median (q1-q3) [ranked from #1 – highest use to #6 – lowest use]							
Visits with a GP[e]	12.8 (9.1-18.2)	6.0 (4.2-8.1)	9.4 (6.1-14.1)	9.8 (8.1-11.8)	16.0 (13.0-20.4)	10.6 (7.0-15.5)	**<0.001**
Rank	*#2*	*#6*	*#5*	*#4*	*#1*	*#3*	
Visits with a neurologist[e]	1.2 (0.9-1.9)	0.8(0.5-1.2)	0.7 (0.4-1.1)	1.1 (0.7-1.5)	1.0 (0.6-1.5)	0.8 (0.4-1.5)	**<0.001**
Rank	*#1*	*#4*	*#6*	*#2*	*#3*	*#4*	
Visits with an internal medicine specialist[e]	0.5 (0.2-1.1)	0.2 (0.0-0.5)	0.5 (0.1-1.3)	0.5 (0.2-1.0)	0.5 (0.2-1.2)	0.5 (0.0-1.6)	**<0.001**
Rank	*#1*	*#6*	*#1*	*#1*	*#1*	*#1*	
Visits with a psychiatrist[e]	4.2 (2.6-8.0)	0.0 (0.0-0.0)	0.0 (0.0-0.1)	0.0 (0.0-0.1)	0.0 (0.0-0.2)	0.0 (0.0-0.1)	**<0.001**
Rank	*#1*	*#2*	*#2*	*#2*	*#2*	*#2*	
Visits with other key specialists[e, f]	0.9 (0.5-1.8)	0.3 (0.2-0.7)	0.5 (0.1-1.1)	1.6 (1.0-2.5)	0.8 (0.4-1.8)	0.8 (0.2-1.6)	**<0.001**
Rank	*#2*	*#6*	*#5*	*#1*	*#3*	*#3*	
At least one hospitalisation, n (%)	106 (87.6%)	1,158 (71.4%)	215 (85.7%)	325 (92.3%)	586 (93.2%)	169 (82.4%)	**<0.001**

Hospitalisations[e, g]		0.4 (0.2-0.8)	0.2 (0.1-0.3)	0.6 (0.3-1.2)	0.4 (0.2-0.7)	0.4 (0.2-0.8)	1.0 (0.5-2.0)	**<0.001**
	Rank	*#3*	*#6*	*#2*	*#3*	*#3*	*#1*	
Visits with all physicians[e, h]		33.9 (24.3-44.1)	13.2 (9.5-17.9)	20.7 (13.8-29.3)	23.4 (18.9-28.3)	31.3 (24.7-41.3)	25.9 (16.1-36.9)	**<0.001**
Key features (relative to the other clusters)		• Higher care consumption • Higher proportion of cases with a comorbidity on index date and by study end • More psychiatrists and neurologist visits	• Lower care consumption • Lower proportion of cases with a comorbidity on index date and by study end	• Higher death rate • Higher proportion reached SPMS by study end • Lower DMT exposure • Lower ARR • Higher EDSS score by study end	• Older at MS onset • Higher proportion reached SPMS by study end • More visits with key specialists	• Higher care consumption • Higher proportion of cases with a comorbidity by study end • Higher DMT exposure	• Older at onset • Higher death rate • Higher proportion reached SPMS by study end • Lower DMT exposure • Lower ARR • Higher EDSS score by study end	-

ARR: annualized relapses rate. DMT: disease-modifying therapy. EDSS: expanded disability scale status. GP: general practitioner. MS: multiple sclerosis. RRMS: relapsing-remitting multiple sclerosis. SPMS: secondary progressive multiple sclerosis. q1-q3: quartiles 1 and 3.
[†] The presented data are restricted to prevent direct or residual disclosure of identifiable data.

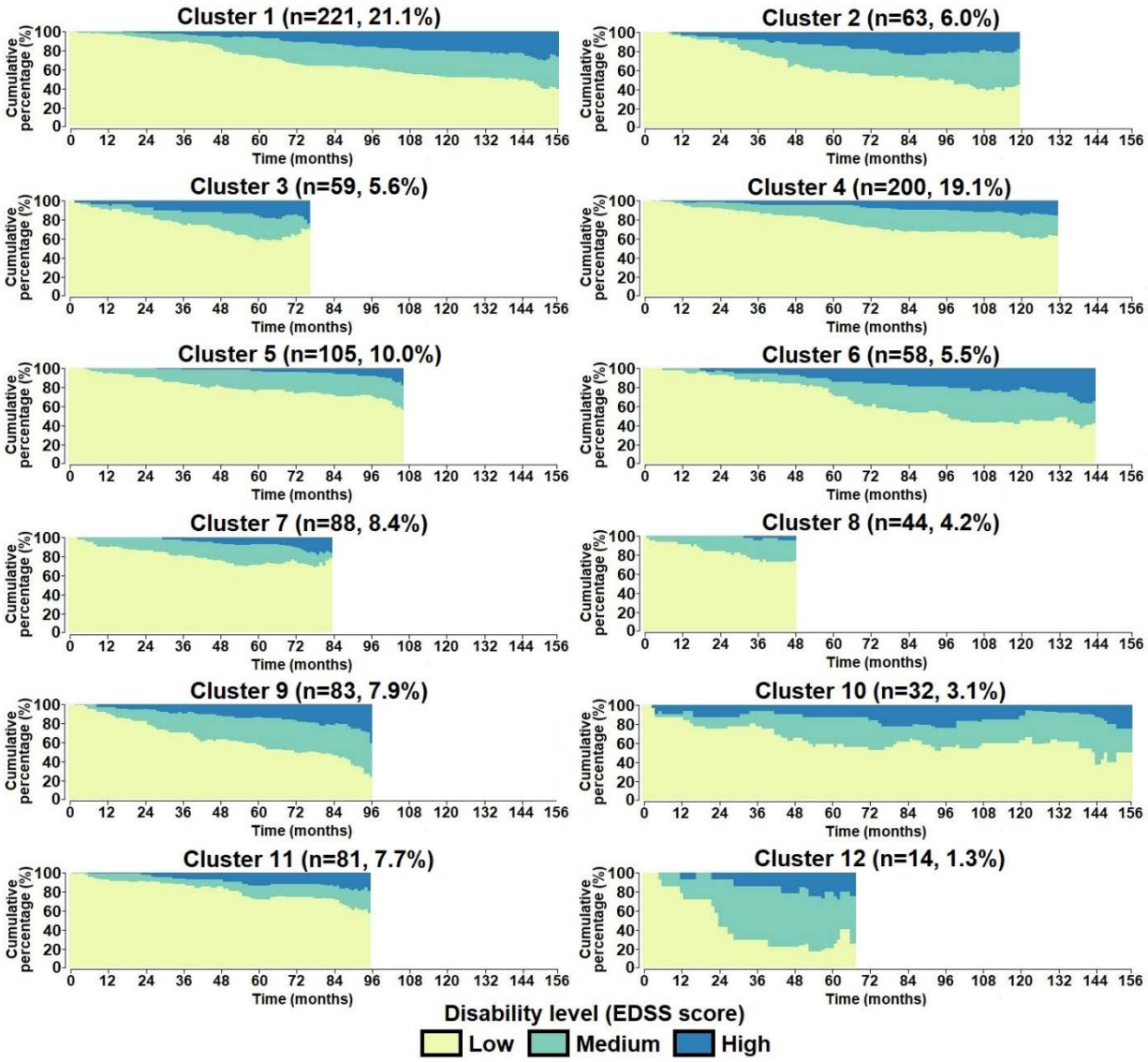
[a] p-value comparing the different clusters using the Kruskal-Wallis, Pearson's chi-square, or Fisher's exact test as appropriate. [b] Excluding the onset attack (relapse date of first relapse = MS onset date) and only for people having a relapsing-remitting initial disease course. [c] Included comorbidities: hypertension, hyperlipidemia, diabetes, chronic lung disease (CLD) and mood or anxiety disorders. [d] Included DMTs: beta-interferon, glatiramer acetate and natalizumab. [e] Number per person-year. [f] Other specialists: physical medicine and rehabilitation specialist, ophthalmologist, urologist. [g] Denominator = persons with MS with at least one hospital admission during follow-up. [h] All physicians, regardless of specialty (including physicians with specialties other than those in the 5 identified categories).

Figure 1 Flow chart for selection of the incident and prevalent multiple sclerosis cohorts



PwMS: Persons with Multiple Sclerosis. BCMS: British Columbia MS database. EDSS: Expanded Disability Status Scale. MS: Multiple Sclerosis.

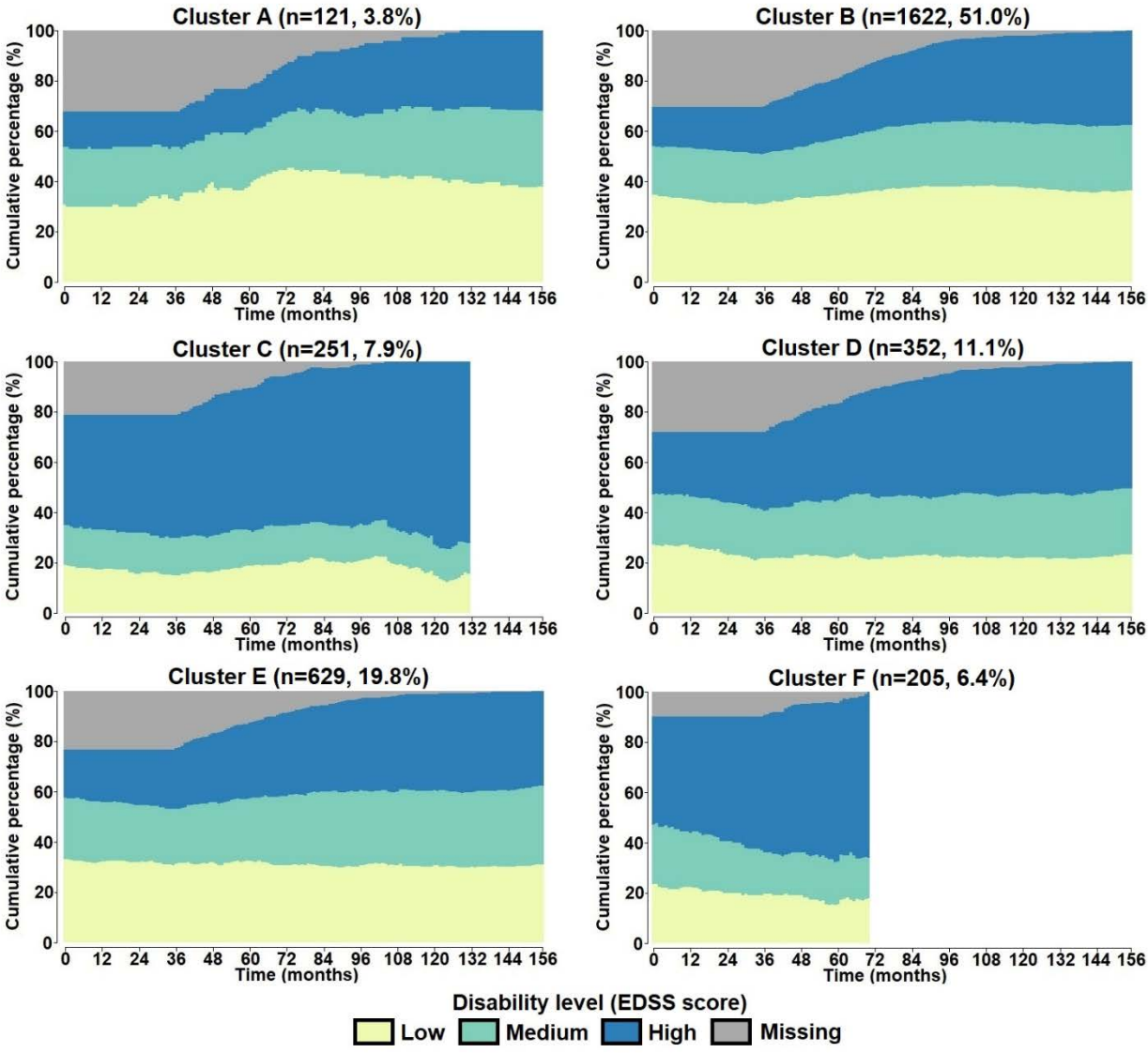
Figure 2 Chronograms of the evolution of the EDSS scores of PwMS within the 12 clusters resulting from the application of the MCSA for the incident MS cohort



PwMS: Persons with Multiple Sclerosis. EDSS: Expanded Disability Status Scale. MCSA: Multichannel Sequence Analysis. MS: Multiple Sclerosis.

Interpretation: For each time unit on the x-axis, the cumulative proportion of PwMS at each disability level (based on the EDSS score) is presented on the y-axis.

Figure 3 Chronograms of the evolution of the EDSS score of PwMS within the 6 clusters resulting from application of the MCSA for the prevalent MS cohort



PwMS: Persons with Multiple Sclerosis. EDSS: Expanded Disability Status Scale. MCSA: Multichannel Sequence Analysis. MS: Multiple Sclerosis.

Interpretation: For each time unit on the x-axis, the cumulative proportion of PwMS at each disability level (based on EDSS score) is presented on the y-axis. Grey represents missing values of EDSS scores, for the time period before the first available EDSS score.

Supplementary material

Supplementary Table 1 Boundaries used to categorize health care consumption, according to the number of health care interactions, within each time window

Health care interaction	Categorization
Visits with a GP	0; [1-3]; [4-6]; ≥7
Visits with a neurologist	0; 1; ≥2
Visits with an internal medicine physician	0; ≥1
Visits with a psychiatrist	0; ≥1
Visits with other key specialists	0; 1; ≥2
All-cause hospitalisation	0; 1; ≥2

GP: General practitioner.

Supplementary Table 2 The comorbidities and the algorithms used to identify them in the administrative health data

Comorbidity	ICD-9 codes	ICD-10 codes	Algorithm[a]	Source
Hypertension	401-405	I10-I13, I15	≥1H or ≥2P in 2 years	[22]
Hyperlipidemia	272	E780, E782, E784, E785	≥1H or ≥2P in 5 years	[22]
Diabetes	250	E10-E14	≥1H or ≥2P in 5 years	[22]
Chronic lung disease (CLD)	491-493, 496	J40, J42-J46	≥1H or ≥2P in 5 years	[22]
Mood or Anxiety disorder	296, 298, 300, 311, 50B	F40, F41, F31-F34 F25	≥1H or ≥5P in 5 years	[23]

[a] H: Hospitalisation; P: Physician visit.