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Costs of illness progression for different multiple sclerosis phenotypes: a population-based study in Sweden

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Abstract

Background: Little is known of how the cost of illness and health-related quality of life changes over time after a diagnosis of multiple sclerosis.

Objectives: The aim was thus to explore the progression of annual direct and indirect costs and health-related quality of life among people with multiple sclerosis of working ages, following diagnosis with relapsing–remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis (PPMS) or conversion to secondary progressive multiple sclerosis (SPMS) after RRMS.

Methods: Swedish nationwide registers were linked to estimate the annual cost of illness in 2006–2013 among people with a registered new multiple sclerosis phenotype, including: direct costs, indirect costs, and health-related quality of life.

Results: Drugs and indirect costs for sick leave were the main cost drivers after diagnosis with RRMS. After conversion to SPMS, the RRMS cost drivers were replaced by indirect costs for disability pension. The main cost driver in newly diagnosed PPMS was indirect costs for sick leave, later replaced by disability pension. Health-related quality of life scores were similar after RRMS and SPMS.

Conclusions: After initial high indirect costs for sick leave, people with RRMS had higher drug costs compared to people with PPMS. Cost drivers during SPMS initially followed the pattern in the RRMS population, but were replaced by indirect costs for disability pension.

Keywords: Multiple sclerosis, cost of illness, healthcare costs, registries, sick leave, health-related quality of life, disease progression

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Introduction

Multiple sclerosis (MS), a chronic progressing neurological disease, is the most common degenerative neurological condition among people of working ages,[1] with onset in the ages 20–40 years for most people.[2]

In terms of societal impact, MS leads to healthcare costs, indirect costs (i.e. productivity losses)[3] during sick leave and disability pension, as well as intangible costs related to pain and suffering, and health loss in terms of health-related quality of life (HRQoL).[4,5] The total costs of illness (COI), for MS in Europe were in 2010 estimated at €14,500 million, of which almost €5000 million were indirect costs.[6] The annual COI of MS in Sweden were estimated at €600 million in 2005[7] and at €414 million in 2010 excluding non-medical direct costs.[8] Moreover, costs among people with MS have been found to increase with disease severity,[9] and to be associated with disease state and phenotype.[10–12] Phenotypes in MS range from relapsing to progressive disease, or combinations.[13,14]

In Sweden, sick leave and disability pension before and after MS diagnosis has been found to be associated with sex, age, educational level and country of birth.[15]

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However, a knowledge gap remains regarding how other costs develop over time following MS diagnosis, and whether such progressions are related to MS phenotype or other patient characteristics.

The aim of the study was to describe the progression of annual direct and indirect costs and of HRQoL, among people with MS of working ages, after diagnosis with relapsing–remitting multiple sclerosis (RRMS) or primary progressive multiple sclerosis (PPMS), and conversion to secondary progressive multiple sclerosis (SPMS) after RRMS, respectively. A further aim was to describe heterogeneities in the trajectories of such costs.

Materials and methods

People in Sweden with MS were identified through the Swedish nationwide clinical register for MS (SMSreg) held by the Karolinska University Hospital, which started in 2001.[16] The study population included people with newly registered RRMS, PPMS, or SPMS during 2006–2013, and aged 21–64 years during each year, as 65 years is the official age of retirement in Sweden and disability pension is not possible after that. People with progressive relapsing MS were excluded.

Linkage, using the personal identification numbers assigned to all residents of Sweden, was conducted to include sociodemographic characteristics and data on resource use from four other nationwide registers. Sociodemographic characteristics of identified people with MS were obtained from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) kept by Statistics Sweden. Resource use was obtained from the Swedish Prescribed Drug Register (SPDR)[17] and the National Patient Register (PAR),[18,19] kept by the National Board of Health and Welfare, and from the Micro Data for the Analysis of Social Insurance register (MiDAS) kept by the Social Insurance Agency.

Cost estimates

The cost estimates were prevalence-based, i.e. the costs which arose during each year (i.e. after being assigned a phenotype), including costs for drugs, healthcare and sick leave. Societal costs were estimated, including costs to all payer categories; i.e. patient out-of-pocket costs, healthcare costs and costs resulting from lost productivity.

Information on out-of-pocket costs and reimbursement costs for dispensed prescribed drugs were obtained from SPDR, including all prescribed drugs purchased in pharmacies in Sweden. Information about indented injection and infusion drug use to treat MS (i.e. natalizumab and rituximab) were obtained from SMSreg, as such drugs are generally administered through healthcare clinics. Costs for indented drugs were calculated based on prices reported by the Swedish Dental and Pharmaceutical Benefits Agency (approximated on the available generic products), and the treatment intervals reported in the Swedish National Drug Formulary (FASS), or intervals suggested by clinical expertise.

Information on healthcare use for all causes, and with MS as the main condition, was obtained from PAR. PAR includes information on inpatient and specialised outpatient care in Sweden. Healthcare with MS as the main diagnosis was identified by the International Classification of Disease (ICD) code for MS (ICD-10: G35). Healthcare costs were calculated from diagnosis-related group (DRG) codes in PAR; the DRG code of each contact was translated to costs by multiplying the assigned DRG weight for that code (for each year)[20] by the national average cost per 1.0 DRG in 2013 (SEK 50,229).[21] Hospitalisation costs were applied to the date/year of discharge. Patient co-payments represent a small proportion of the overall costs of healthcare in Sweden,[22] and were not included. No discounting of costs was conducted, because costs were analysed for each separate year and not summarised.

Information about sick leave and disability pension (for all causes, and with MS as the main diagnosis, respectively) were obtained from MiDAS. Indirect costs included the productivity losses calculated from the number of net days on sick leave and/or disability pension compensated by the Social Insurance Agency. The indirect costs were calculated by the human capital approach,[3] multiplying the identified time each patient was absent from work by the age-adjusted mean wage and the social security contribution. Thus, sick leave paid by the employer was not included. In Sweden, sick leave of 14 days or less is usually paid by the employer.

Health outcomes

SMSreg includes HRQoL measured by the EuroQol Group's health state questionnaire (EQ-5D), thus EQ-5D scores reported in the year of being assigned a new phenotype and during subsequent years were obtained for 854, 15 and 105 people with RRMS, PPMS and SPMS, respectively. All registrations of EQ-5D scores were conducted in the years

2010–2013. The EQ-5D is a generic HRQoL instrument with five dimensions and three levels of severity. The responses for each dimension create a health profile for each respondent, which were translated to the respondents' EQ-5D index value using both the Swedish experience-based value set[23,24] and, as a sensitivity analysis, the UK society-based value set.[25]

Analyses

Analyses were conducted to explore costs during eight consecutive years after diagnosis with either PPMS or RRMS, and after registered conversion to SPMS. Pairwise comparisons, between phenotypes or identified trajectory groups, of the distribution of patients by characteristics were made using the *z*-test ($P < 0.05$ indicating statistically significant differences). Mean costs were calculated, by cost components, with bootstrapped bias-corrected 95% confidence intervals (CIs) (1000 iterations, seed 74593). HRQoL was described for each phenotype as both median and quartiles for each dimension of EQ-5D and as mean utility with bootstrapped bias-corrected 95% Cls.

Semi-parametric group-based multi-trajectory modelling[26] was used to explore heterogeneity in trajectories of costs among people with MS, during 5 years after diagnosis with either PPMS or RRMS, and after registered conversion to SPMS. The analysis used a zero-inflated Poisson model to identify groups with similar progression in direct and indirect costs (each categorised into quintiles) over time. This model was chosen based on a combination of high average posterior probabilities (>0.87, should be at least 0.7,[26] thus indicating little ambiguity in group assignment of individuals), high odds of correct classification (>13, should be at least 5),[26] and higher Bayesian information criterion[26] than other model specifications. Model fit statistics were calculated (AP Wheeler, University of Dallas). (For codes, see https://andrewpwheeler.wordpress.com/2016/10/06/group-based-trajectory-models-in-stata-some-graphs-and-fit-statistics/.)

A sensitivity analysis was conducted based on the relationship between years of diagnosis with RRMS and conversion to SPMS, as there was sometimes contradictory data registered in SMSreg (e.g. conversion to SPMS before diagnosis with MS).

The project was approved by the regional ethical review board of Stockholm, Sweden (approvals 2007/762-31-2014/236-32). No informed consent was sought from included participants.

Results

From the SMSreg, 15,449 people were identified (Figure 1), of which 13,900 had a registered phenotype of RRMS, PPMS or SPMS. Exclusion was made of: (a) 8961 people without a new phenotype registered during the study period; (b) 41 people registered to convert to SPMS before their initial diagnosis with MS (as this may indicate an uncertain year of diagnosis); and (c) 421 people not in our intended study population due to age, or living outside Sweden. In total, 3528 people with RRMS and 252 with PPMS were included in the study population. In addition, 847 people were included who converted to SPMS, of which 109 were initially assigned with RRMS during the study period (at least one year before progressing to SPMS) and were, thus, included in both study groups. For the trajectory analysis, an additional exclusion was conducted to ensure that all individuals had at least 5 years of data in the register (i.e. assigned a phenotype in 2006–2009 and surviving at least 5 years),

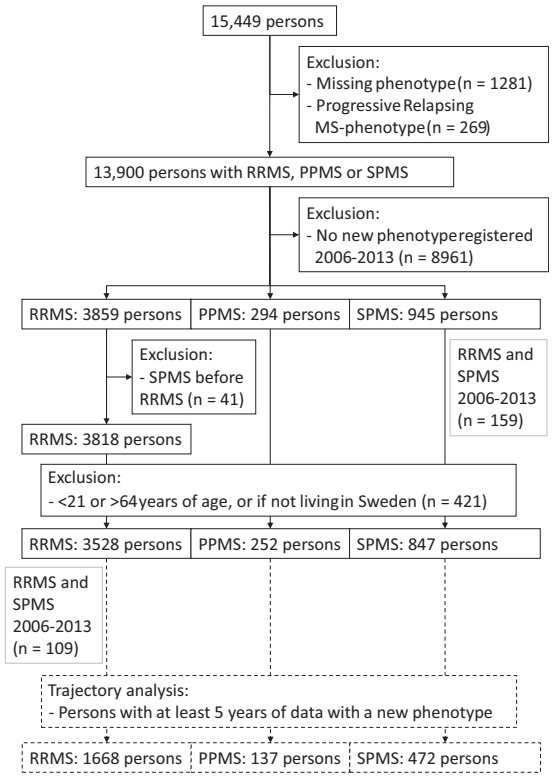

Figure 1. Study flow diagram. *n*: number of people; RRMS: relapsing–remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

resulting in a study population for that analysis of 1668 people with RRMS, 137 people with PPMS and 472 people with SPMS.

The proportion of men was higher among patients with PPMS, while a higher proportion of RRMS patients were found in the younger age categories compared to other phenotypes (Table 1). In addition, statistically significant differences were found in the distribution of patients with different phenotypes, based on educational level, country of birth, type of living area and geographical region. Among patients with RRMS, almost all patients (94%) were in the lowest disability category at diagnosis, while a larger proportion of patients was in the higher Expanded Disability Status Scale (EDSS) categories at diagnosis with PPMS or conversion to SPMS.

In the year of diagnosis, mean direct costs were SEK 96,644 (95% CI SEK 93,951–99,281) for individuals with RRMS, SEK 49,928 (42,363–58,472) for individuals with with PPMS and SEK 109,537 (102,843–116,870) for individuals with with SPMS (Table 2). The corresponding mean indirect costs were SEK 68,761 (64,881–72,732), SEK 108,710 (89,532–130,694) and SEK 88,345 (77,009–99,327). Using the 2013 exchange rate (€1 = SEK 8.6494), the mean estimates correspond to €11,174 direct costs and €7950 indirect costs with RRMS, €5772 direct and €12,568 indirect with PPMS and €12,664 direct and €10,214 indirect with SPMS, respectively.

Among people with RRMS, drugs and sick leave were the main cost drivers over the 8 years after diagnosis (Figure 2), decreasing slowly with time. This pattern remained after conversion to SPMS; costs for drugs and sick leave being the most important cost drivers initially, thereafter replaced by disability pension. During the first 2–3 years with PPMS, the main cost driver was sick leave, thereafter replaced by disability pension. Among people with RRMS, disease modifying therapies (DMTs) represented approximately 95% of all drug costs throughout the 8 years, while costs for DMTs varied between 40% and 70% of drug costs among people with PPMS. At conversion to SPMS, DMTs represented on average 90% of all drug costs, but this decreased over time to 70% of all drug costs in the last year of follow-up (Figure 3).

For all phenotypes, 38–63% of all specialised outpatient visits during each analysed year had MS as the main condition. For inpatient care, the corresponding interval was 19–55%. For people with RRMS, there was a slight peak in the proportion of inpatient care with MS as the main condition one year after diagnosis, while the patterns for PPMS and SPMS were less clear.

Indirect costs for sick leave and disability pension decreased over time, for all phenotypes; however, they remained stable for sick leave and disability pension due to MS. Thus, indirect costs with MS as the main diagnosis corresponded to an increasing proportion of all sick leave and disability pension over time in RRMS; from 35% in year 1 to 72% of all indirect costs for sick leave in year 8, and from 13% to 91% of all disability pension. For PPMS; the proportion of all sick leave due to MS increased from 24% in year 1 to more than 80% from year 4 (thereafter, decreasing, but with large CIs), and of all disability pension from 44% in year 1 to more than 70% from year 4. For SPMS, MS was the main diagnosis of 63–79% of all costs for sick leave and 78–86% for all disability pension throughout that period.

Patients with SPMS reported on average lower HRQoL than patients with RRMS, with non-overlapping CIs (Table 3). Although based on single/few EQ-5D reports per patient, it appears that HRQoL remained stable and slightly increasing over time after diagnosis with RRMS or conversion to SPMS (Figure 4).

Three distinct groups were identified (hereafter called trajectory groups), each trajectory group included people with similar trajectories of direct and indirect costs over time. Compared to the other trajectory groups, a larger proportion of people in trajectory group 1 (i.e. named, decreasing direct and indirect costs, Figure 5) had either PPMS or SPMS, were in the older age categories, in the lowest education category, and had intermediate MS according to EDSS scores 5 years after MS diagnosis (Table 4). Both trajectory group 2 (increasing direct and decreasing indirect costs) and trajectory group 3 (increasing direct and high indirect costs) consisted of a large proportion of people with RRMS (Table 4), compared to trajectory group 1. Sex distribution in group 2 was equal to that of group 1, while the proportion of women was higher in group 3. Group 2 included a higher proportion of people in the two youngest age categories, and people in the highest education category. In addition, a larger proportion of individuals in group 2 had mild MS according to EDSS scores both at diagnosis and 5 years later. Distributional differences in country

Table 1. Background characteristics of people with MS by phenotype (RRMS, PPMS and SPMS).

Background characteristics	RRMS *N* = 3528 *n* (%)	PPMS *N* = 252 *n* (%)	SPMS *N* = 847 *n* (%)
Sex[a]			
Men	1015 (29)*	112 (44)**	264 (31)*
Women	2513 (71)*	140 (56)**	583 (69)*
Age group[a] (years)			
21–24	312 (9)**	<15 (0)*	<15 (0)*
25–29	549 (16)**	<15 (3)*	<15 (1)*
30–34	573 (16)**	<15 (3)*	30 (4)*
35–39	567 (16)**	<15 (4)**	74 (9)**
40–44	558 (16)	34 (13)	132 (16)
45–49	411 (12)**	47 (19)*	146 (17)*
50–54	294 (8)**	54 (21)*	165 (19)*
55–59	174 (5)**	48 (19)*	166 (20)*
60–64	90 (3)**	46 (18)*	118 (14)*
Educational level[a]			
Elementary school (≤9 years)	347 (10)**	58 (23)**	131 (15)**
High school (10–12 years)	1653 (47)	123 (49)	422 (50)
University (≥13 years)	1528 (43)**	71 (28)*	294 (35)*
Country of birth[a]			
Sweden	3118 (88)*	233 (92)*	748 (88)
Other than Sweden	410 (12)*	19 (8)*	99 (12)
Type of living area[a,b]			
Larger cities	1435 (41)*	78 (31)**	358 (42)*
Medium-sized municipalities	1150 (33)	93 (37)*	254 (30)*
Smaller municipalities	943 (27)	81 (32)	235 (28)
Geographical region[a,c]			
East Sweden	1427 (40)*	99 (39)	390 (46)*
South Sweden	1374 (39)**	82 (33)*	288 (34)*
North Sweden	727 (21)*	71 (28)**	169 (20)*
Disease information			
MS diagnosis/conversion in 2006	414 (12)*	27 (11)	129 (15)*
MS diagnosis/conversion in 2007	430 (12)	31 (12)	108 (13)
MS diagnosis/conversion in 2008	419 (12)*	45 (18)*	116 (14)
MS diagnosis/conversion in 2009	405 (11)*	34 (13)	119 (14)*
MS diagnosis/conversion in 2010	424 (12)**	45 (18)*	124 (15)*
MS diagnosis/conversion in 2011	484 (14)**	16 (6)*	86 (10)*
MS diagnosis/conversion in 2012	503 (14)	33 (13)	101 (12)
MS diagnosis/conversion in 2013	449 (13)**	21 (8)*	64 (8)*
Years from onset to MS diagnosis, median (interquartile range)	1 (0–4)	4 (2–6)	NA
Years from onset to SPMS conversion, median (interquartile range)	NA	NA	14 (8–21)
EDSS at MS diagnosis/conversion			
0–3.5	1738 (94[d])**	86 (66[d])*	289 (45[d])*
4–6.5	109 (6[d])**	39 (30[d])**	305 (48[d])**
7–9.5	<15 (0[d])**	<15 (4[d])**	46 (7[d])**

Statistically significant differences between groups (pairwise comparisons between phenotypes using *z*-test, $P<0.05$) are indicated by asterisk, two asterisks indicate statistically significant difference to both the other groups. NA for comparing years from onset to diagnosis/conversion between groups.

[a]Identified the year of diagnosis with each phenotype.

[b]Based on population density according to the H-region classification scheme: larger cities (H1–H2), medium-sized municipalities (H3–H4), or smaller municipalities (H5–H6)).[33]

[c]Based on Eurostat's Nomenclature of Territorial Units for Statistics classification (NUTS1): East Sweden (SE1), South Sweden (SE2) or North Sweden (SE3).[34]

[d]Percentages based on EDSS scores registered 3 years before diagnosis up to the year of diagnosis.

EDSS: Expanded Disability Status Scale; NA: not applicable; *n*: number of people; RRMS: relapsing–remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

Table 2. Mean costs by cost components among people with MS, during the year of diagnosis with RRMS or PPMS, or conversion to SPMS.

	RRMS	PPMS	SPMS
Cost components	*N* = 3528 SEK (95% CI)	*N* = 252 SEK (95% CI)	*N* = 847 SEK (95% CI)
Prescription drug use	52,628 (50,921–54,346)	10,885 (8251–13,897)	72,450 (67,845–77,018)
Outpatient specialised healthcare use	20,194 (19,732–20,785)	19,442 (17,771–21,195)	14,732 (13,156–17,341)
– with MS as the main condition	9492 (9205–9811)	8670 (7787–9796)	8263 (7559–9042)
Inpatient healthcare use	23,822 (22,067–25,598)	19,600 (13,938–27,425)	22,355 (18,274–27,085)
– with MS as the main condition	9987 (8967–11,236)	7424 (3973–12,703)	10,627 (8128–13,650)
Direct costs	96,644 (93,951–99,281)	49,928 (42,363–58,472)	109,537 (102,843–116,870)
Sick leave[b]	64,120 (60,276–67,750)	96,303 (78,974–118,193)	44,156 (37,935–51,406)
– with MS as the main diagnosis	22,332 (20,095–24,429)	22,692 (14,529–32,435)	27,893 (22,976–33,697)
Disability pension	4641 (3330–6174)	12,407 (4572–22,576)	44,189 (35,757–52,651)
– with MS as the main diagnosis	604 (203–1209)	5501 (494–12,365)	35,716 (28,371–43,835)
Indirect costs	68,761 (64,881–72,732)	108,710 (89,532–130,694)	88,345 (77,009–99,327)
Costs of illness	165,405 (159,907–170,583)	158,637 (136,802–182,351)	197,881 (185,459–211,985)

The exchange rate is approximately SEK 10 to €1 (€1 = SEK 8.6494 in 2013).
SEK: Swedish Krona; RRMS: relapsing–remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; 95% CI: 95% confidence interval.

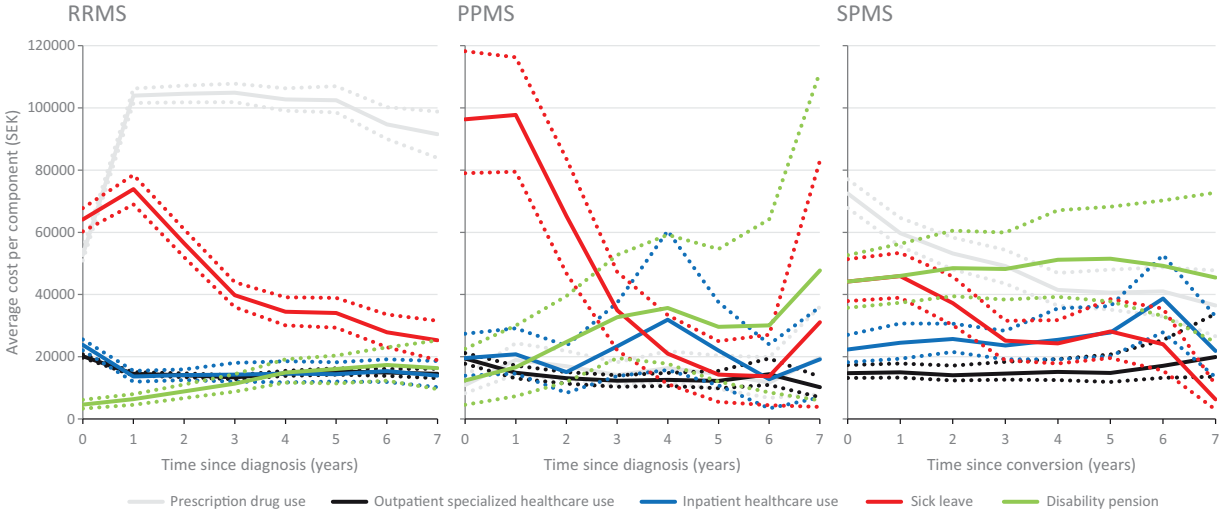

Figure 2. Progression in costs by cost components among individuals with MS, during the years after diagnosis with RRMS or PPMS, or conversion to SPMS. Dotted lines indicate 95% confidence intervals. Time since diagnosis = 0 indicates year of MS diagnosis/conversion to SMPS. RRMS: relapsing–remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; SEK: Swedish Krona; SPMS: secondary progressive multiple sclerosis.

of birth, geographical region and type of living area and marital status are presented in Table 4.

Limiting the analysis of costs among individuals with SPMS to only those with a prior diagnosis with RRMS (Table 5) resulted in slightly higher mean costs, but with overlapping CIs.

Discussion

We identified the main cost drivers to be drugs and sick leave among people with RRMS throughout the 8 years after diagnosis. Costs for sick leave were high among people with PPMS during the first few years and thereafter decreased rapidly, while intermediate costs for drugs and indirect costs were found among people converting to SPMS. Although few had registered HRQoL scores, these scores when available were similar between years after diagnosis with RRMS and conversion to SPMS, when using the Swedish experience-based value set. Moreover, we found three groups of people with MS with different trajectories of direct and indirect costs, for which it was possible to identify background characteristics.

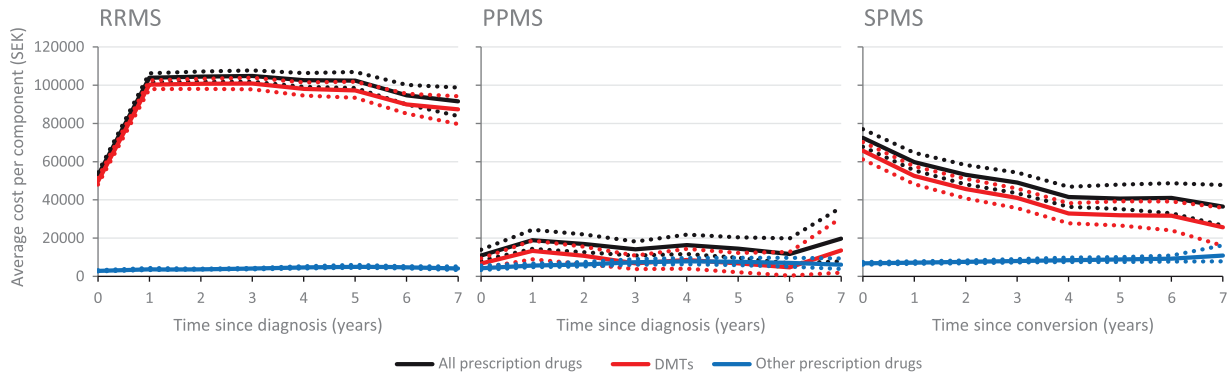

Figure 3. Progression in costs for DMTs and other prescription drugs among individuals with MS, during the years after diagnosis with RRMS or PPMS, or conversion to SPMS. Dotted lines indicate 95% confidence intervals. Time since diagnosis = 0 indicates year of MS diagnosis/conversion to SMPS. DMT: disease modifying therapy; RRMS: relapsing–remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; SEK: Swedish Krona; SPMS: secondary progressive multiple sclerosis.

Table 3. HRQoL among people with MS by phenotype,a during the first 8 years after diagnosis with RRMS or conversion to SPMS.

	RRMS	SPMS
Health dimensions	*N* = 147 median (Q1–Q3)	*N* = 17 median (Q1–Q3)
Mobility	1 (1–2)	2 (1,5–2)
Self-care	1 (1–1)	1 (1–1)
Usual activities	2 (1–2)	2 (1,5–2)
Pain/discomfort	1 (1–2)	2 (2–2)
Anxiety/depression	2 (1–2)	2 (2–2)
	Mean (95% CI)	Mean (95% CI)
Swedish experience-based index values	0.82 (0.79–0.84)	0.70 (0.64–0.76)
UK society-based index values	0.67 (0.61–0.71)	0.46 (0.29–0.59)
EQ-5D VAS scale	*N*=135 67 (64–71)	*N*=16 48 (39–58)

[a]PPMS not included due to few registered responses (<10 per year after diagnosis).
EQ-5D-3L: EuroQol Group's five-dimension health state questionnaire with three levels of severity; HRQoL: health-related quality of life; RRMS: relapsing–remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; VAS: visual analogue scale (part of the EQ-5D tool); Q1–Q3: interquartile range, 1st to 3rd quartile.

According to previous reports, the SMSreg covers more than 80% of all people with MS in Sweden.[16] Although it is possible that, for example, severity of disease could affect the probability of being registered in the SMSreg, the registration appears largely to be related to regional differences in reporting.[27] Moreover, it was possible to link microdata at an individual level from nationwide registers with complete coverage and high quality.[17–19] Thus, the findings are expected to be based on a large proportion of all people with MS in Sweden.

However, register-based studies have limitations, e.g. data availability. DRG-based cost calculations are available only from 2006 onwards and the Prescribed Drug Register from July 2005 onwards, thus limiting the possible number of years of follow-up (and only individuals being assigned a new phenotype in 2006 being possible to follow during all 8 years). There may thus be a stronger cohort effect in later follow-up years, given that treatment patterns were changing over the follow-up period. This has, however, not been explored in the above analyses. There are also known limitations in the use of DRGs to calculate costs (it is used to compare resource use between settings, but is not an exact account of costs for a specific healthcare encounter), and using the human capital approach to estimate indirect costs is

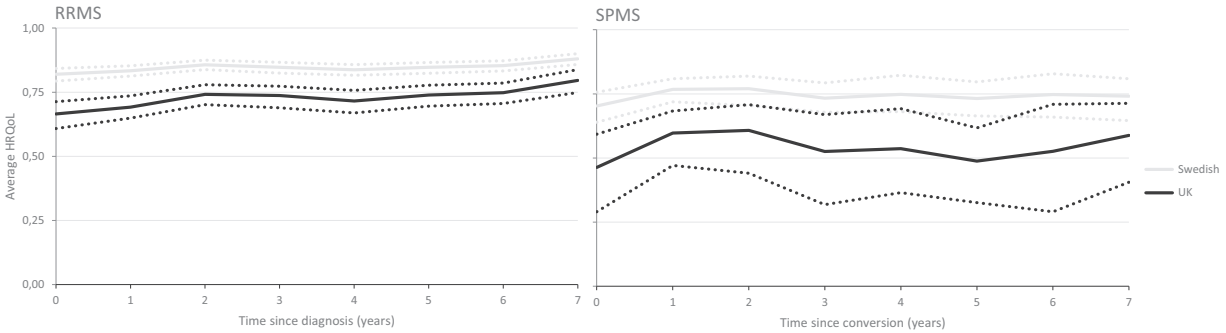

Figure 4. Progression in HRQoL among individuals with MS, during the years after diagnosis with RRMS or conversion to SPMS.* Dotted lines indicate 95% confidence intervals. Time since diagnosis = 0 indicates year of MS diagnosis/conversion to SPMS. *PPMS not included due to few registered responses (<10 per year after diagnosis). HRQoL: health-related quality of life; RRMS: relapsing–remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

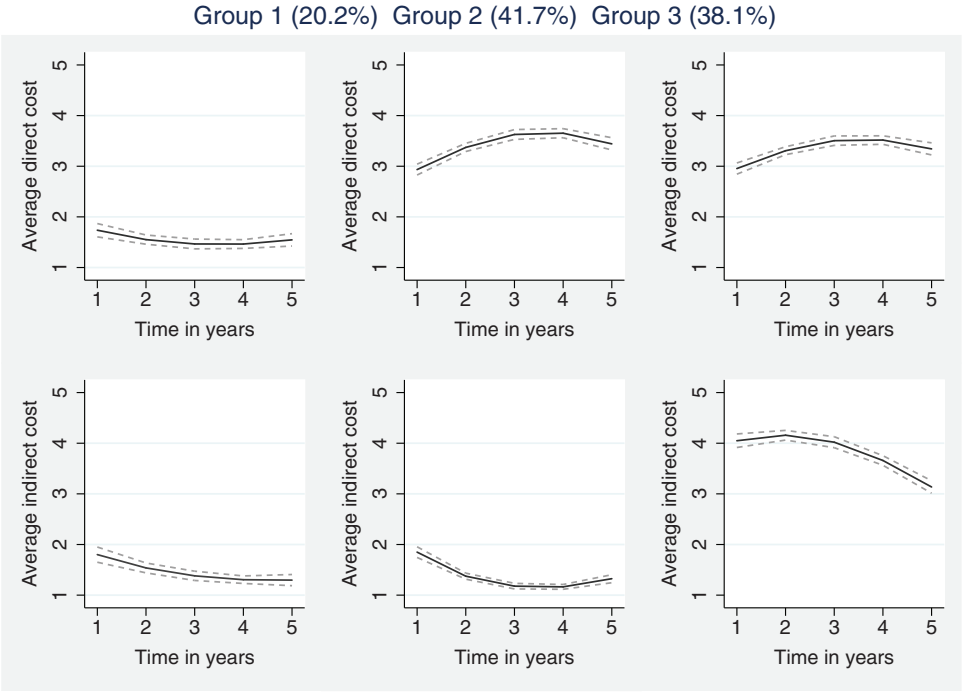

Figure 5. Trajectories of direct and indirect costs among individuals with MS, during 5 years after diagnosis. The trajectory groups are groups of patients with similar trajectories of direct and indirect costs over time, identified using a group-based trajectory modelling approach. MS: multiple sclerosis.

disputed but it is the recommended method in Sweden. Although the SMSreg was useful for identifying indented drugs, the associated cost estimation had to be based on current use on 1 July each year, thus excluding costs among people with paused treatment in July, and overestimating treatment costs among those with a very brief treatment period during only July. Our data sources did not cover all costs for non-medical direct costs (personal assistance, etc.), informal care and intangibles.[5] Personal assistance and other community services represented a large proportion of the COI among people with MS in Sweden,[28] but probably less so in our sample of newly diagnosed people with MS and relatively low EDSS scores. Such services probably contribute more to the COI among people converting to SPMS. Moreover, longitudinal data on EDSS and EQ-5D were often missing. Despite missing EDSS information, the trajectory groups with high direct costs had the largest proportion of people with RRMS (groups 2 and 3). Comparing these two groups, the group with the largest majority of people with mild MS (group 2)

Table 4. Characteristics of people with MS by trajectory group.

Background characteristics	Group 1 *N* = 467 *n* (%)	Group 2 *N* = 958 *n* (%)	Group 3 *N* = 852 *n* (%)
Phenotype			
RRMS	217 (46)**	791 (83)**	660 (77)**
PPMS	76 (16)**	17 (2)**	44 (5)**
SPMS	174 (37)**	150 (16)*	148 (17)*
Sex[a]			
Men	162 (35)*	331 (35)*	174 (20)**
Women	305 (65)*	627 (65)*	678 (80)**
Age group[a] (years)			
20–24	10 (2)*	93 (10)**	25 (3)*
25–29	25 (5)**	151 (16)**	96 (11)**
30–34	37 (8)**	159 (17)*	114 (13)*
35–39	38 (8)**	164 (17)*	126 (15)*
40–44	63 (13)**	148 (15)	161 (19)*
45–49	67 (14)*	100 (10)**	118 (14)*
50–54	69 (15)*	82 (9)**	110 (13)*
55–59	84 (18)**	43 (4)**	70 (8)**
60–64	74 (16)**	18 (2)**	32 (4)**
Educational level[a]			
Elementary school (≤9 years)	80 (17)**	103 (11)*	85 (10)*
High school (10–12 years)	211 (45)*	433 (45)*	465 (55)**
University (≥13 years)	176 (38)*	422 (44)**	302 (35)*
Country of birth[a]			
Sweden	408 (87)*	832 (87)*	782 (92)**
Other than Sweden	59 (13)*	126 (13)*	70 (8)**
Type of living area[a,b]			
Larger cities	217 (46)*	430 (45)*	311 (37)**
Medium-sized municipalities	128 (27)*	298 (31)	285 (33)*
Smaller municipalities	122 (26)	230 (24)*	256 (30)*
Geographical region[a,c]			
East Sweden	226 (48)**	401 (39)*	335 (39)*
South Sweden	146 (31)**	389 (37)*	315 (37)*
North Sweden	95 (20)	168 (24)*	202 (24)*
Disease information			
MS diagnosis/conversion in 2006	137 (29)*	200 (21)**	233 (27)*
MS diagnosis/conversion in 2007	113 (24)	232 (24)	224 (26)
MS diagnosis/conversion in 2008	105 (22)*	273 (29)**	202 (24)*
MS diagnosis/conversion in 2009	112 (24)	253 (26)	193 (23)
EDSS at MS diagnosis/conversion	*N* = 261	*N* = 523	*N* = 446
0–3.5	185 (71[d])*	444 (85[d])**	342 (77[d])*
4–6.5	65 (25[d])*	73 (14[d])**	92 (21[d])*
7–9.5	<15 (4[d])*	<15 (1[d])*	<15 (3[d])
EDSS 5 years after MS diagnosis/conversion	*N* = 345	*N* = 798	*N* = 713
0–3.5	195 (57[e])**	654 (82[e])**	480 (67[e])**
4–6.5	129 (37[e])**	114 (14[e])**	197 (28[e])**
7–9.5	21 (6[e])	30 (4[e])	36 (5[e])

The trajectory groups are groups of patients with similar trajectories of direct and indirect costs over time, identified using a group-based trajectory modelling approach.
Statistically significant differences between groups (pairwise comparisons between trajectory groups using *z*-test, $P<0.05$) are indicated by asterisk, two asterisks indicate statistically significant difference to both the other groups.
[a]Identified the year of MS diagnosis with each phenotype.
[b]Based on population density according to the H-region classification scheme: larger cities (H1–H2), medium-sized municipalities (H3–H4), or smaller municipalities (H5–H6)).[33]
[c]Based on Eurostat's Nomenclature of Territorial Units for Statistics classification (NUTS1): East Sweden (SE1), South Sweden (SE2), or North Sweden (SE3).[34]
[d]Percentages based on EDSS scores registered 3 years before diagnosis up to the year of diagnosis.
[e]Percentages based on EDSS scores registered in years 2 to 5 after diagnosis.
EDSS: Expanded Disability Status Scale; NA: not applicable; *n*: number of people; RRMS: relapsing–remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

Table 5. Sensitivity analysis of the mean costs by cost components among people with MS, during the year of conversion to SPMS.

Description	Study population	Direct costs	Indirect costs	Costs of illness
		SEK (95% CI)	SEK (95% CI)	SEK (95% CI)
All converting to SPMS during 2006–2013	847	109,537 (102,843–116,870)	88,345 (77,009–99,327)	197,881 (185,459–211,985)
Converting to SPMS the same year or later than diagnosed with RRMS	690	116,134 (108,069–124,978)	98,786 (85,851–110,744)	214,920 (198,459–229,112)
Converting to SPMS after RRMS	651	117,823 (109,085–126,490)	97,605 (85,763–110,575)	215,430 (200,457–231,872)

The exchange rate is approximately SEK 10 to €1 (€1 = SEK 8.6494 in 2013).
SEK: Swedish Krona; SPMS: secondary progressive multiple sclerosis; RRMS: relapsing–remitting multiple sclerosis; 95% CI: 95% confidence interval.

5 years after diagnosis was also, expectedly, the group with comparably lower indirect costs. There were few responses to EQ-5D overall, which was expected because this variable mainly was included for patients in the Immunomodulation and MS Epidemiology Study (study acronym IMSE), a post-marketing study of patients on novel disease-modifying drugs.[16] However, the pattern of responses indicated a slowly increasing HRQoL over time when using the UK society-based values (while little difference was seen when using the Swedish experience-based values), which could be in line with the decreasing sick leave patterns during the same period. Moreover, the responses to EQ-5D were fairly evenly divided over the years after diagnosis, thus not centred solely on the year of diagnosis.

Furthermore, there was a group of people not diagnosed with MS before their SPMS conversion, or with a very short time span between MS diagnosis and SPMS conversion. It can be speculated that unless there is a severe relapse, a person may not be diagnosed with MS before the progressive state of SPMS. However, the sensitivity analysis did not indicate large differences in COI between people initially assigned with SPMS compared to those with previous RRMS. It needs to be acknowledged, however, that this finding has consequences for when people were included in the study population.

It has previously been found that relapses are associated with younger age, and consequently more often occur earlier in the disease course, and that conversion to SPMS is associated with fewer relapses.[29] That would be in line with the identified patterns of sick leave. Also, PPMS appears to be associated with a period of high disease activity and much sick leave, as reflected in the high indirect costs. It is noteworthy that all trajectory groups initially included high indirect costs that with time decreased, indicating a pattern of high initial indirect costs among the majority of people. There are previous studies on the increased costs during relapses,[30] but to our knowledge these costs have not been explored in relation to the time since diagnosis. While an MS diagnosis is often set or phenotype assigned during a period of worsening symptoms, such as a relapse, the high proportion of other diagnoses causing sick leave identified during the first years after MS diagnosis may indicate that a MS diagnosis is also made during the worsening of other symptoms, not necessarily associated with MS.

The average time from MS diagnosis to conversion to SPMS was approximately 14 years in our study population, but with large variation, and there was a clear continuing pattern in the development of costs from RRMS to SPMS. A previous study found a lower average cost 10 years after diagnosis if patients had converted to SPMS.[31] This can be compared to our identified high treatment cost 8 years after being assigned with RRMS, because people included throughout the 8 years would be those who had not yet converted to SPMS. Our results appear to be consistent with findings that those individuals with higher direct costs were to a lesser extent converting to SPMS,[32] thus indicating either that the patient group associated with high healthcare costs is less likely to develop SPMS or that people converting to SPMS are being taken off

costly (DMT) treatments. It was interesting to see that direct costs, i.e. for DMTs, remained high in the early years after conversion to SPMS but then dropped rapidly to levels similar to PPMS, reflecting the notion that DMTs may be useful in the early years of SPMS, as reflected in the national guidelines for Swedish MS care.[33]

Our results are in line with previous findings that drug costs are the main cost driver among people with MS with low EDSS and indirect costs among those with high EDSS.[10] However, in this study, drug costs (in particular DMT costs) were high among people with RRMS, of which a large majority (>90%) started out in the lowest EDSS category, while indirect costs were more pronounced among people with SPMS after the initial years of high indirect costs related to sick leave in both RRMS and PPMS. As our results indicate DMTs were causing a large proportion of all costs for drugs, in particular among RRMS patients. It is thus possible that the recent approvals of biosimilars to some of these drugs may have an impact on the future costs among people with MS. Biosimilars include the so-called follow-on glatiramer acetate, or FoGA, that was approved in 2016 (Glatimyl® is the registered product in Sweden, but is currently not available) and several biosimilars to MabThera® (rituximab); Ritemvia® and Rixathon® are currently available in Sweden. However, none of the products currently have a registered price and they are dispensed through the healthcare units thus making deductions about the cost effects unfeasible.

Conclusions

After an initial period of high indirect costs for sick leave, people with RRMS on average had much higher costs for prescription drugs compared to people with PPMS. The pattern of costs for people converting to SPMS initially followed the pattern in the RRMS population, but was thereafter replaced by indirect costs from disability pension.

Data availability

The data used in this study are administered by the Division of Insurance Medicine, Karolinska Institutet, and cannot be made public. According to the General Data Protection Regulation, the Swedish law SFS 2018:218, the Swedish Data Protection Act, the Swedish Ethical Review Act and the Public Access to Information and Secrecy Act, these types of sensitive data can only be made available, after legal review, for researchers who meet the criteria for access to these types of sensitive and confidential data. Readers may contact Professor Kristina Alexanderson (kristina.alexanderson@ki.se) regarding the data.

Conflicts of Interest

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