Multiple Sclerosis and Related Disorders 36 (2019) 101396

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Economic burden of multiple sclerosis in France estimated from a regional medical registry and national sick fund claims

Detournay Bruno[a,*], Debouverie Marc[b], Pereira Ouarda[c], Seyer Dominique[c], Soudant Marc[d], Courouve Laurène[a], Jomaa Khalil[e], Epstein Jonathan[d], Guillemin Francis[d]

[a] Cemka, 43 boulevard du Maréchal Joffre, 92340 Bourg-la-Reine, France
[b] CHRU-Nancy, INSERM, Université de Lorraine, CIC, Epidémiologie Clinique, F-54000 Nancy, France
[c] DRSM du Nord-Est 85 rue de Metz CS 70237, 54004 Nancy Cedex, France
[d] CHRU de Nancy, Inserm, Université de Lorraine, CIC 1433 Epidémiologie clinique -Hôpitaux de Brabois, 9 allée du Morvan, 54505 Vandoeuvre-les-Nancy, France
[e] BIOGEN, 1 passerelle des reflets, tour CBX, 92913 Paris La Défense Cedex, France

ARTICLE INFO

Keywords:
Multiple sclerosis
Cost of illness
Budget impact
High cost risk factors

ABSTRACT

Background: Estimating direct healthcare costs of patients with multiple sclerosis (MS) and identifying risk factors of high costs including relapse are important drivers of public health decision making in France.
Methods: This is a longitudinal retrospective study based on patient charts (qualified registry of MS in Lorraine (ReLSEP)) and claims data (from the main compulsory health insurance and national hospital database estimated monthly. All patients with MS not deceased or lost to follow-up reported in the registry in 2013–2014 were included. Outpatient costs were those paid to the healthcare provider and inpatient costs were those related to national cost estimates. Mean total costs per patient by disease severity were estimated monthly, accounting for MS evolution over the study period. Costs of MS relapse were estimated using a general linear model.
Results: A total of 4373 patients were identified in the ReLSEP registry, and 2166 of these patients were included in the study. Among those, outpatient claims were available for 1366 and 627 were hospitalized at least once. The average annual direct costs for patients with MS were estimated to be €12,296 in 2014. Furthermore, ambulatory costs represented 87.8% out of those costs and were mainly driven by medications (60.6%) and paramedic visits (11.2%). Monthly direct costs were higher in patients with severe disease (€1249 for EDSS 7–9) compared to those with mild or moderate disease (€992 for EDSS 0–3; €953 for EDSS 4–6) ($p < 0,006$). Interestingly, drug costs were higher in patients with mild disease, whereas costs related to paramedical care, medical devices, and transportation were higher in those with severe MS. The unit cost of relapse was estimated between €1681 and €2193.
Conclusions: Costs were mainly driven by medications and highly related to disease severity. Relapse cost was the main contributor to total cost.

1. Introduction

According to the French National Authority for Health, the prevalence of multiple sclerosis (MS) was estimated to 70–90,000 patients in France with an annual incidence rate of 4–6 per 100,000 inhabitants (Haute Autorité de la Santé - HAS, 2006). However, El Adssi et al. found a higher incidence and prevalence of MS using a capture–recapture method with log-linear models (8.5 and 188.2 cases per 100,000 inhabitants, respectively) (El Adssi et al., 2012). A total of 99,123 patients with MS were identified based on hospital (PMSI – Programme de Médicalisation des Systèmes d'Information) and outpatient claims (SNIIRAM - Système national d'information inter-régimes de l'Assurance maladie), leading to a prevalence rate of 151.2 per 100,000 inhabitants (female 210.0 and male 88.7) (Foulon et al., 2017).

The prevalence rate of MS was higher in the north-east compared to the south-west of France. This finding was confirmed by Fromont et al. who reported a higher prevalence rate in north-eastern France compared to the Atlantic coast, the Alps, and both sides of the Rhône River (Fromont et al., 2013). No true North South gradient but rather a geographical heterogeneity was reported (Fromont et al., 2010; Pivot et al., 2016). Infection with Epstein-Barr virus (EBV) is the most pertinent environmental factor of MS, especially if it is symptomatic and arises after childhood. The role of smoking in MS has been confirmed, but it is modest (Leray et al., 2016) compared to long-term exposure to

* Corresponding author.
E-mail address: bruno.detournay@cemka.fr (D. Bruno).

https://doi.org/10.1016/j.msard.2019.101396
Received 14 February 2019; Received in revised form 22 August 2019; Accepted 8 September 2019

the sun.

Association between mortality risk and MS is quite controversial as reported by French data. Leray et al. found that less disabled MS patients had a better survival and highly disabled a worse survival (eight-fold increase of mortality) as opposed to the French population (Leray et al., 2007). Despite that France is a high-risk country, life expectancy is only slightly reduced by MS (Leray et al., 2016).

As a chronic disease with multiple clinical symptoms affecting several organs (Fromont et al., 2013; Jasse et al., 2013; Moisset et al., 2013; Kobelt and Giovannoni, 2017) along with short and long-term adverse drug reactions (Lebrun et al., 2011), MS patients are usually experiencing an irreversible progression of disability. Severe socio-economic consequences could result from this incapacity such as impact on health related quality of life, high level of disutility, loss of productivity and high cost to the national sick funds. Moreover, it has been established that MS is the major cause of nontraumatic disability in young adults (Pugliattia et al., 2006). Interestingly, social costs associated with MS are high due to its long duration, early loss of productivity, need for assistance in activities of daily living, use of immunomodulatory and immunosuppressive treatments, and multidisciplinary healthcare.

Multiple sclerosis is one of the chronic conditions specifically listed by the French healthcare system as a long-term disease for which the main Health Insurance Fund provides full coverage of healthcare costs (Guide affection longue durée, 2006).

According to a retrospective survey conducted by a patient association (Ligue Française contre la Sclérose en Plaques), 74.3% of MS patients had declared an impact on employment and 27.2% had discontinued their occupational activities (Fantoni-Quinton et al., 2016). Furthermore, 16.3% of MS patients had a disability pension according to claims data (Foulon et al., 2017). In addition, an annual disability pension (€8918) was perceived by 19.1% of patients, and 20% had received an annual daily allowance (€3317) (Fromont et al., 2014).

According to Gold et al. the burden of MS relates to three dimensions: clinical, humanistic, and economic (Gold et al., 2016). Cost-effectiveness analysis is the gold standard in France for economic evaluation and could be requested with the pricing negotiation by the Economic Committee of Health Care Products. As such, more and more publications report efficiency results especially on MS (Chevalier et al., 2016; Le Pen et al., 2003). Therefore, feeding model with accurate and unbiased estimates becomes crucial to support public health authorities for making the right decision.

According to a survey conducted by Flachenecker et al. twenty MS registries were identified in Europe (Flachenecker et al., 2014). Although these registries differed widely for objectives (epidemiology, long-term therapy outcome, healthcare research, support for clinical trials), the economic aspect and patients' perspectives were rarely mentioned.

Therefore, it appears that there is a need to collect both medical and economic information, ideally retrospectively to avoid observational bias, and also at a patient level. However, there is currently no database for collecting this information in France. Combining patient charts from a MS registry with claims data could be one of the most appropriate method. Thus, it was important to carry out a new study based on an exhaustive population of MS patients using the best source of information for care consumption and validated medical information in France.

The objective of this study was to estimate the direct healthcare costs of MS in France and to identify risk factors of high costs from a regional registry and claims database.

2. Patients and method

This is a French observational, retrospective study, involving clinical and longitudinal data from a regional MS registry (ReLSEP - Registre Lorrain des Scléroses En Plaques) combined with outpatient claims from the regional health insurance database and inpatient claims from the national hospital discharge database.

This study was conducted according to the French law and was approved by the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (approval number: 14-276) and by the Commission Nationale de l'Informatique et des Libertés (authorization number: DR-2014-501).

2.1. The ReLSEP registry

Created in 1996 and covering the north-east of France, the ReLSEP registry received its certification by the French authorities in 2009. Data were collected with EDMUS (European Database of Multiple Sclerosis) software (Confavreux et al., 1992), and patients were identified from hospitals, neurologists, and sick funds with a quasi-exhaustive representation. MS diagnosis were medically confirmed based on Poser et al. (1983) or McDonald et al. (2001) criteria and modified by Polman et al. (2005, 2010), whereas disability was evaluated with Expanded Disability Status Scale (EDSS) score (Kurtze, 1983). On average, patients were documented every 6 months during routine visits, and quality was controlled by the Centre d'Investigation Clinique of Nancy Hospital. The ReLSEP registry has been authorized by the Commission Nationale de l'Informatique et des Libertés.

Data extracted from the ReLSEP registry included socio-demographics, MS onset date, comorbidities, EDSS score, MS relapse, MS type (clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), MS treatments, and all types of hospitalization.

Patients' characteristics retrieved from the ReLSEP registry included age $>$ 18, MS diagnosis prior to 01/01/2013 and patient still present in the registry on 01/01/2015, mandatoryhealth insurance fund coverage for salaried workers and living in the area during the study period (2013–2014). Patients deceased and lost to follow-up during the study period, switching to another sickness fund, and patients diagnosed with Devic's disease or neuromyelitis optica were excluded.

2.2. Claims data sources

Outpatient claims were extracted from the claim sickness fund database managed by the Direction Régionale du Service Médical DRSM) in Alsace-Moselle area from 01/01/2013 to 31/12/2014. Extracted data were represented by variables such as long term condition coverage, low income coverage, practitioner visits, medical acts, drugs, nurses, physiotherapists and other paramedical acts, biology, imagery, medical devices, transportation, daily and disability allowances, and hospital resources excluded from DRG financing (Diagnosis Related Group). Variables were expressed as number of units, cost paid, socialized tariff and reimbursed amount.

Inpatient claims were extracted from the National hospital database, and acute and long-term stays defined as home hospitalization were covered. The main data of interest were DRG and hospitalization duration. In addition, stays of interest were identified from the ReLSEP and DRSM and then documented in the National hospital database.

2.3. Data management and costs

The economic analysis was conducted following the HAS recommendations (HAS, 2011). Data management and the statistical analysis were conducted with SAS© software Version 9.3 (Cary, USA).

Drugs were clustered according to the ATC classification (WHO, 2017). Costs were aggregated in patient-month units which became the statistical unit of the analyses. EDSS score, relapse, and type of MS were estimated monthly on a patient basis and aligned with economic data.

The economic analysis was conducted from the societal perspective as defined by the HAS, and all direct costs were analysed independently

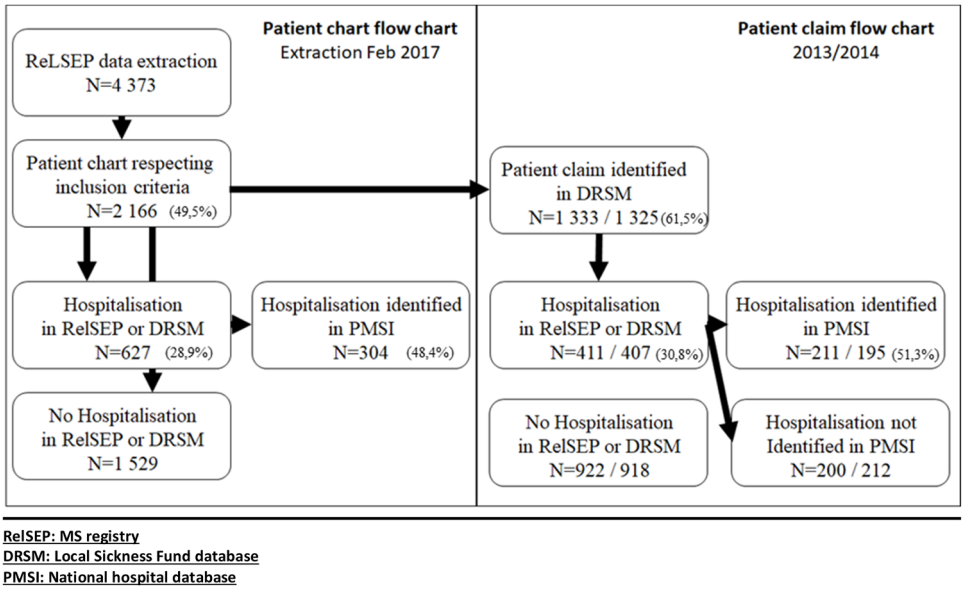

Fig. 1. Study population flow chart.

of the payer. Outpatient care costs were those paid to the care provider. Only MS related resources were reported, representing about 90% of the healthcare expenses. Specialist visits except neurologist were excluded and as some cash benefits. However, hospital activities that do not generate DRGs (e.g., external visits) were not captured in this survey.

Inpatient care was evaluated using the National Hospital Cost studies (ATIH, 2019). Annual population average hospitalisation cost was imputed to all patients who were not identified in the National hospital database. Total annual cost was represented by the sum of all collected resource costs. Costs Breakdown were limited to the cluster of interest (as reported above). Results are expressed in €2013 and €2014 for each respective year.

2.4. Statistical analysis

Quantitative variables were described by sample size, Q1, median, Q3, min, max, average, and standard deviation. Qualitative variables were documented by sample size of each modality.

Pre-defined sub-groups of interest were year of MS exposure (2013/2014), EDSS (0–3; 4–6; 7–9) and type of MS (CIS, RR, SP and PP). Differences between groups were compared using *T*-tests or Wilcoxon ranks sum tests for continuous variables, and Chi-squared or Fisher's exact tests for categorical data. All p-values were interpreted at a 5% threshold, two-sided, without adjustment for test multiplicity in the context of a descriptive approach.

Cost of relapse was estimated with a multivariate general linear model, for year 2014. Total annual cost was the explained variable. Covariables included patient age, gender, disease duration, EDSS score, type of MS, number of relapses during the year of interest (qualitative 0,1,2), number of relapses the 3 prior years, and all variables known to be associated with overall costs. A stepwise approach was chosen with p-entry and p-exit criteria fixed at a 0.05 threshold. Relapse was forced into the model as being the parameter of interest. Least square means were the reported estimates.

National extrapolation was based on relative population size of our sample to the data published by Foulon et al. (2017) without standardisation in the absence of rational explanation of the regional heterogeneity in France.

3. Results

Data of 4373 patients were retrieved from the ReLSEP registry in February 2017, and 2166 (49.5%) were included in this study. Among patients who were excluded, 2 were less than 18 years old, 12 had Devic's disease, 20 died before 31/12/2014, 1804 were not documented during the study period, and 369 were lost to follow-up. Of note, baseline data were comparable between excluded and included patients (data not presented).

Medical characteristics are presented in the hereunder table.

The average age was 47.5 ± 12.1 years, and 72.9% were female. A relapsing-remitting multiple sclerosis was reported in 51.2% of patients with a secondary progressive form (with or without relapse) in 27.6% of cases, aprimary progressive form in 13.2% of cases and a clinically isolated syndrome in 8%. The mean MS duration was 14.6 ± 9.2 years and degree of disability at study entry was mild in 57.3% of patients (EDSS 0–3), moderate in 34.9% of patients (EDSS 4–6) and severe in 7.8% of patients (EDSS 7–9). Furthermore, a disease modifying treatment (DMT) at study entry was observed in 61% of patients who had been prescribed an immunomodulator in 85.5% of cases. Most patients (95.9%) had no change in EDSS during the 2 years of follow-up, however, a relapse was reported in 20.2% of patients. Patients had 1.3 (0.6) different DMT, on average: 30.1% of patients had no treatment during the study period, 44.4% maintained the same treatment, and 25.5% had one or several changes (switch, add-on, or stop). Lastly, important heterogeneity exists between types of MS.

Flow of patient and claim charts are reported in Fig. 1.

Claims data were available for 61.5% (1333/2166) of patients. Availability of claims data was not related to gender, relapse during the study period, visit to the practitioners, MS treatment, and treatment line. However, patients documented for reimbursement were older (46.4 versus 49.2 years; $p < 0{,}0001$) notably at MS onset (32.3 versus 33.9 years; $p = 0{,}0004$).

Among the reimbursed claims data, about 50% (406/818) of the hospitalizations were identified in the National hospital database. Being documented in this database was found to be associated with more visit to the practitioners (4.0 versus 3.2) but not related to age, gender, age at MS onset, relapses, MS treatment, and treatment line, Table 1 present the main characteristic of MS patients according to type of MS.

Table 2 describes total annual MS costs, year 2013 and 2014.

Average total annual costs increased by 16.2% from 2013 (€10,580) to 2014 (€12,296). More than 75% of total cost were attributed to drug

Table 1
Socio-demographics and multiple sclerosis characteristics at baseline.

	Clinically isolated syndrome $N = 171$	Relapsing Remitting MS $N = 1110$	Secondary progressive MS without relapses $N = 226$	Secondary progressive MS with relapses $N = 373$	Primary progressive MS $N = 289$	Total $N = 2\,166$	P-value
Gender Male	41 (24.0%)	238 (21.4%)	75 (33.2%)	102 (27.3%)	130 (45.5%)	586 (27.1%)	< 0.0001
Female	130 (76.0%)	872 (78.6%)	151 (66.8%)	271 (72.7%)	156 (54.5%)	1 580 (72.9%)	
Age at MS onset (years)	34.4 (10.3)	30.4 (9.1)	32.0 (9.4)	31.9 (9.7)	43.8 (10.5)	32.9 (10.5)	< 0.0001
Age at study entry (years)	39.0 (11.2)	43.2 (10.7)	52.0 (9.9)	54.0 (9.4)	57.2 (10.6)	47.5 (12.1)	< 0.0001
Study follow-up (years)	7.4 (3.8)	15.5 (7.7)	22.6 (9.4)	24.7 (8.7)	15.4 (7.4)	17.2 (9.1)	< 0.0001
MS duration (years)	4.6 (3.7)	12.8 (7.7)	20.0 (9.5)	22.1 (8.7)	13.5 (7.4)	14.6 (9.2)	< 0.0001
Number of visits with EDSS scoring 2013–2014	3.6 (1.8)	3.7 (2.1)	3.3 (2.0)	3.6 (2.1)	3.0 (2.2)	3.6 (2.1)	< 0.0001
EDSS at study entry							< 0.0001
03.5	166 (97.1%)	997 (89.8%)	31 (13.7%)	15 (4.0%)	32 (11.2%)	1 241 (57.3%)	
4–6.5	5 (2.9%)	113 (10.2%)	171 (75.7%)	274 (73.5%)	194 (67.8%)	757 (34.9%)	
7–9	–	–	24 (10.6%)	84 (22.5%)	60 (21.0%)	168 (7.8%)	
EDSS changes over 2013 2014 period	0.1 (1.0)	0.1 (0.8)	0.3 (0.6)	0.2 (0.6)	0.4 (0.6)	0.2 (0.8)	< 0.0001
Number of relapses over 2013–2014							n.a.
0	75.4%	71.4%	99.6%	82.0%	96.5%	79.8%	
1	19.3%	22.6%	0.4%	12.9%	3.5%	15.8%	
2	5.3%	4.7%	–	4.0%	–	3.5%	
3+	–	1.4%	–	1.1%	–	0.9%	
At least one MS treatment at study entry	73.1%	78.3%	45.6%	36.7%	28.7%	60.8%	< 0.0001
Immuno-modulators	92.0%	93.0%	76.7%	67.9%	41.5%	85.8%	n.a.
Oral treatment	6.4%	0.2%	–	0.7%	–	0.8%	n.a.
Immuno-suppressor	0.8%	6.0%	22.3%	30.7%	50.0%	12.1%	n.a.
Other treatment	0.8%	0.8%	1.0%	0.7%	8.5%	1.3%	n.a.
Number of MS treatment 2013–2014							n.a.
1	63.5%	67.2%	87.1%	86.3%	88.7%	71.9%	
2	33.8%	28.9%	11.3%	11.2%	10.3%	24.9%	
3	2.7%	3.0%	1.6%	1.9%	1.9%	2.6%	
4	*	0.8%	–	0.6%	1.0%	0.6%	

n.a. Not available.

Table 2
Total annual healthcare costs and breakdown, societal perspective (€2013 and €2014, respectively), year 2013 and 2014. Average ± standard deviation [min;median;max].

	2013	2014
Hospitalization costs	1 527.7 ± 3 491.9 [0;0;62 165.9]	1 490.5 ± 3 048.0 [0;0;38 182.6]
*Community care costs**	9 052.4 ± 7 000.1 [0;8 722.4;40 873.6]	10 805.5 ± 8 593.5 [0:10 286.8;116 251.6]
General practitioner	211.5 ± 345.0	229.6 ± 356.3
Neurologist	51.0 ± 130.3	49.5 ± 130.1
Nurse	310.4 ± 2 127.7	340.8 ± 2 225.0
Physiotherapist	381.8 ± 1 225.6	424.8 ± 1 283.9
Other	400.2 ± 2 385.0	448.2 ± 2 539.1
Medication	6 074.2 ± 6 436.2	6 543.5 ± 7 311.5
Dental care	194.4 ± 770.4	170.2 ± 824.4
Biological testing	131.9 ± 258.5	138.2 ± 260.4
Medical devices	479.3 ± 2 064.1	603.2 ± 2 524.9
Transportation	626.5 ± 2 592.2	661.9 ± 2 729.9
Other	78.2 ± 167.2	83.2 ± 163.8
TOTAL	10 580.1 ± 8 059.3 [15.0;10 224.6;69 192.1]	12 296.1 ± 9 292.6 [0;11 550.1;116 251.6]
Daily allowance	451.5 ± 1 709.1	344.5 ± 1 431.0
Disability benefits	2 258.7 ± 4 582.9	2 508.0 ± 4 752.4

* Breakdown of community care costs does not include all components.

costs (€6 074–€6 543), followed by hospitalization (€1 528–€1 491), and transportation (€627–€662). While hospitalization costs remained nearly stable over the 2013–2014 period, drugs increased by €469, disability benefits by €249, and medical devices by €123.

Table 3 described the total monthly healthcare cost according to disability severity.

Overall, there was a strong positive association between MS severity and costs ($p < 0.0004$). While community care costs increased by about 18% between mild and severe disability patients, hospitalization costs were almost doubled. However, moderate disability patients had the lowest total cost likely due to a "decrease" in drug cost not completely compensated by handicap management. When considering community care, cost breakdown was different in MS with more severe cluster compared to mild cluster. Indeed, in mild disability MS patients, most of the costs were due to medications and represented 3-fold higher costs than those of patients with severe disability. In the contrary, paramedical care, medical devices use, and transportation were the biggest contributor to costs in patients with severe disability MS. Daily allowances related to sick leave were much higher in patients with mild disability compared to those with a more severe disease. Conversely, disability benefits increased substantially from mild to severe disease patients. As for practitioner costs, they remained stable across the EDSS groups.

Table 4 describes the total monthly healthcare costs according to type of MS.

Patient with progressive disease, whether primary or secondary, had a healthcare cost profile very similar to that of severe disabled patients in terms of hospitalization, paramedical care, medical devices use, transportation, and disability benefits (Table 3). Moreover, CIS and RR-MS patients had higher medication and daily allowance costs similar to mild patients (Table 3).

Fig. 2 reports the results of the relapse cost estimated with a general linear model.

There were few patients with more than one relapse in 2014, therefore, they did not participate to the analysis. Age and gender were eliminated during the stepwise process. R-square of the two presented models were quite low and less than 3% of the total variance was explained. Patients with EDSS score 4–6 were associated with a negative value, in line with results reported in Table 3. Cost of relapse was estimated at €2193 ($p < 0.015$) and €1681($p < 0.065$) when 2011–2013 previous relapse were added to the model suggesting a high level of auto-correlation of relapses with MS evolution.

According to Foulon et al. (2017), 99,123 patients were identified as affected by MS in France. Considering an annual cost of €12,296, based on our findings in 2014, the burden of MS to the health sickness fund would be €1218m, representing 0.6% of overall annual health care expenses in France.

4. Discussion

This study, to our knowledge, was the first attempt at using patient charts along with claims data to estimate cost of MS in France. These longitudinal data allowed population exhaustivity at a regional level. We found that average total cost (out and inpatient care) was €12,296, social allowances summed up to €2853, and cost of relapse ranged from €1681 to €2193 in 2014. High costs were reported in the most disabled patients, and in the progressive forms of MS. Cost of MS at a national level was estimated at €1.2m and is now available for modelling activities.

These results are quite similar to previous estimates in France. However, this study is different in terms of design, data sources, and economic perspective, among others.

Fromont et al. (2014) reported an annual cost of €9506 from the SNIIRAM database in 2004. This lower cost could probably be explained by the low use of DMTs at that time.

Costs reported by Karampampa et al. (2012) were much higher than

Table 3
Total monthly healthcare cost and breakdown according to Expanded Disability Status Scale (EDSS) score, societal perspective, average 2013 and 2014, Average ± standard deviation.

	Mild disability (EDSS 0–3)	Moderate disability (EDSS 4–6)	Severe disability (EDSS 7–9)	*P*-value
Hospitalization costs	101.3 ± 169.6	133.5 ± 263.0	195.8 ± 343.6	0.0258
*Community care costs**	890.4 ± 572.2	819.9 ± 665.8	1 053.0 ± 1 273.7	0.0002
General practitioner	18.7 ± 26.7	19.6 ± 31.7	22.7 ± 35.4	0.7433
Neurologist	5.3 ± 11.7	4.0 ± 10.2	3.9 ± 21.6	0.0429
Nurse	6.4 ± 22.4	22.5 ± 146.7	146.5 ± 448.9	0.7380
Physiotherapist	8.7 ± 31.5	37.8 ± 94.1	135.6 ± 219.3	< 0.0001
Other	4.6 ± 21.6	37.9 ± 147.0	182.0 ± 525.6	< 0.0001
Medication	687.1 ± 563.9	498.1 ± 591.2	183.1 ± 257.8	< 0.0001
Dental care	16.8 ± 58.1	15.4 ± 54.7	10.0 ± 29.8	0.0152
Biological testing	11.4 ± 19.7	12.3 ± 23.2	9.8 ± 16.9	0.4920
Medical devices	8.5 ± 49.8	54.4 ± 204.8	226.3 ± 730.0	< 0.0001
Transportation	13.6 ± 61.6	66.1 ± 180.0	200.9 ± 524.7	< 0.0001
Other	8.5 ± 13.8	6.7 ± 13.5	3.2 ± 7.6	< 0.0001
TOTAL	991.7 ± 611.3	953.4 ± 725.3	1 248.8 ± 1 355.7	0.0004
Daily allowance	47.6 ± 134.0	31.4 ± 116.3	6.3 ± 38.7	< 0.0001
Disability benefits	71.1 ± 195.1	254.9 ± 394.4	453.7 ± 660.9	< 0.0001

* Breakdown of community care costs does not include all components.

Table 4
Total monthly healthcare cost and breakdown according to type of multiple sclerosis (MS), societal perspective, average 2013 and 2014, Average ± standard deviation.

	Clinically isolated syndrome	Relapsing-remitting MS	Secondary progressive MS	Primary progressive MS	*P*-value
Hospitalization costs	87.6 ± 164.4	102.8 ± 172.1	159.3 ± 309.0	153.1 ± 322.8	< 0.0001
*Community care costs**	778.0 ± 449.3	956.1 ± 614.5	804.8 ± 943.6	664.9 ± 582.5	< 0.0001
General practitioner	15.0 ± 29.3	19.2 ± 28.1	18.6 ± 28.1	22.9 ± 35.9	0.2835
Neurologist	5.1 ± 12.4	5.4 ± 11.4	3.1 ± 8.6	2.0 ± 6.3	0.0186
Nurse	3.5 ± 9.4	10.3 ± 71.5	47.6 ± 250.4	59.3 ± 288.2	0.2895
Physiotherapist	7.0 ± 28.5	10.8 ± 39.7	61.7 ± 139.1	78.3 ± 158.1	< 0.0001
Other	4.4 ± 25.2	8.0 ± 45.5	51.2 ± 168.2	131.8 ± 473.4	< 0.0001
Medication	629.9 ± 416.7	721.8 ± 598.4	335.7 ± 457.2	222.6 ± 387.6	< 0.0001
Dental care	9.6 ± 39.4	19.3 ± 79.9	16.4 ± 51.5	7.2 ± 25.7	0.0043
Biological testing	11.0 ± 27.4	12.0 ± 19.5	12.7 ± 21.8	10.1 ± 20.8	0.1237
Medical devices	6.5 ± 19.0	13.6 ± 80.8	111.7 ± 470.3	88.9 ± 266.8	0.0316
Transportation	5.8 ± 33.9	20.3 ± 81.2	80.7 ± 201.9	158.3 ± 471.2	< 0.0001
Other	8.6 ± 19.4	8.5 ± 13.6	5.5 ± 11.5	5.9 ± 12.8	0.0003
TOTAL	865.6 ± 493.3	1 058.9 ± 650.4	964.1 ± 1 021.9	818.0 ± 694.3	< 0.0001
Daily allowance	42.7 ± 142.1	47.2 ± 132.2	16.4 ± 73.6	26.7 ± 111.1	< 0.0001
Disability benefits	28.7 ± 126.8	113.3 ± 250.1	347.7 ± 491.2	281.0 ± 489.7	< 0.0001

* Breakdown of community care costs does not include all components.

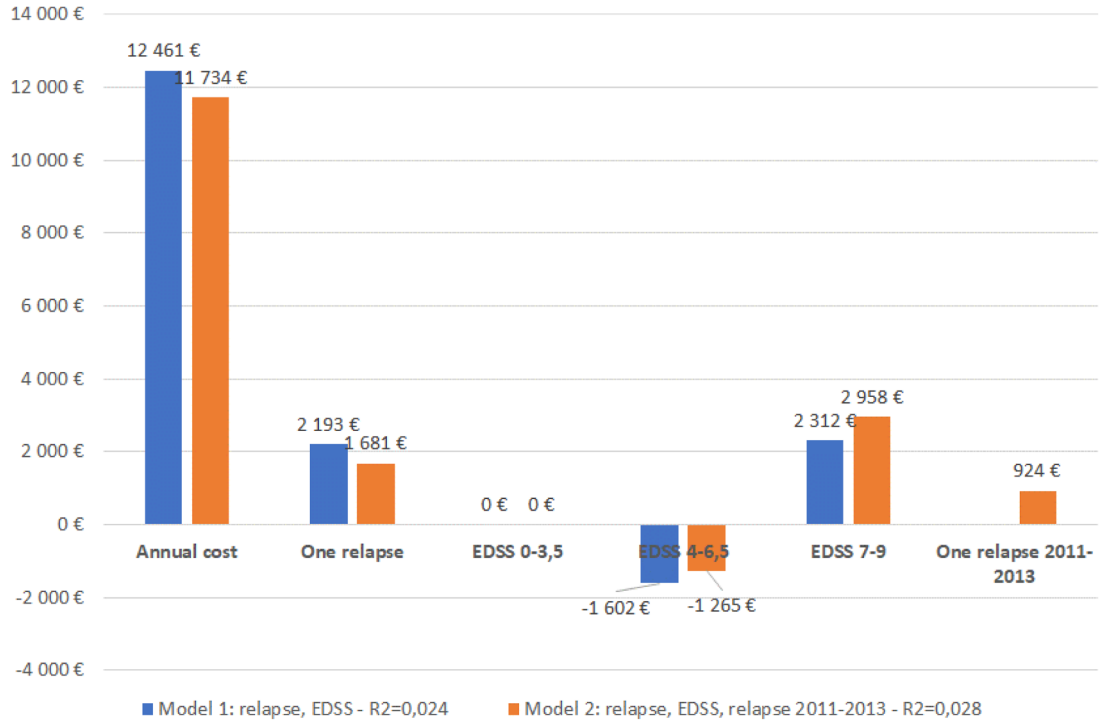

Fig. 2. Relapse cost estimates adjusted through a general linear model.

ours. However, this international study could not cope with country specificities which are especially important when managing handicap. The medical and economic information were collected on a self-administered web-based questionnaire whose validity was considered to minimise recall bias. However, this study used a cross-sectional design rather than longitudinal, and measured exposure and consequences simultaneously, which exposed to a high risk of endogeneity and biased estimates.

The study reported by Lebrun-Frenay et al. (2017) was part of an international study including 16 countries (Kobelt et al., 2017a,b). Data were collected from a questionnaire validated at a country level, completed online by patients from MS associations. The economic scope of this study was quite large including caregivers, and home modifications on resources usually not covered by the French sickness fund. This could explain partially the cost estimates reported in this study which are much higher than ours. Furthermore, patients from MS associations could be more severe and better informed about their social rights, leading to higher costs as compared to data from an exhaustive registry.

We believe that our approach with high external and internal validity on cost estimates will reduce uncertainty and help decision makers.

It is important to note that MS exhaustivity is one of the key benefits of our approach. Furthermore, knowing the status of a financial system at any time and being able to replicate the analysis once a decision has been implemented will facilitate risk sharing implementation and management. However, we must acknowledge that in our study, exhaustivity was limited to one region in the context of known heterogeneity of costs and prevalence of MS. Moreover, difficulties in identifying some patients in the claim database may have had some impact on our cost estimates. Excluding for age and age at disease onset, no characteristics difference was observed between patients from the

ReLSEP registry who were identified in the ambulatory and hospital claim databases and those who were not retrieved in these databases and therefore, we did not expect this resulted in major selection bias.

Using claims data and patient charts in a retrospective manner avoid observational and recall bias. Also, access to longitudinal data with a strong medical and economic validity over time is critical to control endogeneity.

Claims data have some limitations and do not suffice to adequately answer the economic perspective requested by the HAS when performing economic analysis. Typical missing information is loss of productivity related to MS. In addition, daily allowances and disability benefits are biased estimates of indirect costs. We were not able to collect variables such as time spent by the relatives, loss of patient productivity due to MS (absenteeism, loss of productivity at work and unemployment), and management of handicap not covered by the French health funds. This information should be collected at the family level with validated specific questionnaire and then aggregated through models. An important limitation of our study is therefore that it does not include the costs associated with loss of productivity related to MS as well as informal assistance provided by caregivers that are highly relevant contributors to MS costs.

The model developed to estimate the cost of one relapse could explain only a very small amount of total variance, i.e. less than 3%. Although we believe that the stepwise general linear model is the right approach, we faced several difficulties. First, very few patients experienced 2 or more relapses in 2014 which limits the anchoring of our estimate when excluding these patients. Secondly, the structure of total cost breakdown was very different between mild and severe patients, but total cost did not reflect it; therefore, this information was not brought to the model. Finally, model copying with endogeneity over one single year are difficult to implement, and longer period of follow-up would be required. Nevertheless, more analysis needs to be conducted to get more accurate estimates of relapses.

In our results, costs of patients with moderate MS were similar to those observed in mild MS. However, structure of costs was different between these two groups of patients. From an economic perspective, patients with moderate MS were at the crossroad of decreasing outpatient care but increasing inpatient care and disability.

Interestingly, we found an increase of total cost from 2013 to 2014, mainly driven by drugs, disability benefits, and medical devices, which reflected potential treatment intensification during that period. However, dimethyl fumarate was available in France since 2013 but only through a restricted temporary authorization before its final reimbursement decision on June 25, 2015. Teriflunomide was marketed on Nov 1, 2014. Natalizumab, fingolimod were not marketed in France at the time of the study and mitoxantrone only used in few patients.

We have also observed an increase in patient disability over the study which had impacted both drugs and devices. This was likely reinforced by excluding death and lost to follow-up patients, which would usually lower the cost. Use of uncomplete longitudinal data including death and lost to follow-up could be an alternative approach.

5. Conclusion

The average total annual direct cost of a MS patient is about €12,296 in France leading to an overall healthcare cost of €1.2 billion. Costs were mainly driven by drugs and highly related to disease severity. Patient charts and claims data are now available in France and could be used to better understand the efficiency of care used in MS and make the best outcome of current economic resources.

Declaration of Competing Interest

This study was supported by an unrestricted grant from Biogen.

Acknowledgements

We thank Drs G. Berdeaux and M Coulibaly for their support in the writing of the manuscript.

References

ATIH. ScanSante, National Cost Study by DRG: https://www.scansante.fr/applications/enc-mco. 2019.

Chevalier J., Chamoux C., Hammès F., Chicoye A. PLoS One.201617;11Mar (3):e0150703. doi: 10.1371/journal.pone.0150703. eCollection 2016.

Confavreux, C., Compston, D.A., Hommes, O.R., McDonald, W.I., Thompson, A.J, 1992. EDMUS, a European database for multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 55 (8), 671–676.

El Adssi, H., Debouverie, M., Guillemin, F., 2012. LORSEP group. estimating the prevalence and incidence of multiple sclerosis in the Lorraine region, France, by the capture-recapture method. Mult. Scler. 18 (Sep (9)), 1244–1250.

Fantoni-Quinton, S., Kwiatkowski, A., Vermersch, P., Roux, B., Hautecoeur, P., Leroyer, A, 2016. Impact of multiple sclerosis on employment and use of job-retention strategies: the situation in France in 2015. J. Rehabil. Med. 48 (Jun (6)), 535–540 13.

Flachenecker, P., Buckow, K., Pugliatti, M., Kes, V.B., Battaglia, M.A., Boyko, A., Confavreux, C., Ellenberger, D., Eskic, D., Ford, D., Friede, T., Fuge, J., Glaser, A., Hillert, J., Holloway, E., Ioannidou, E., Kappos, L., Kasilingam, E., Koch-Henriksen, N., Kuhle, J., Lepore, V., Middleton, R., Myhr, K.M., Orologas, A., Otero, S., Pitschnau-Michel, D., Rienhoff, O., Sastre-Garriga, J., Schyns-Liharska, T., Sutovic, D., Thalheim, C., Trojano, M., Vlasov, Y.V., Yaldizli, O., 2014. EUReMS consortium. multiple sclerosis registries in Europe - results of a systematic survey. Mult. Scler. 20 (11), 1523–1532.

Foulon, S., Maura, G., Dalichampt, M., Alla, F., Debouverie, M., Moreau, T., Weill, A, 2017. Prevalence and mortality of patients with multiple sclerosis in France in 2012: a study based on French health insurance data. J. Neurol. 264 (Jun (6)), 1185–1192.

Fromont, A., Binquet, C., Rollot, F., Despalins, R., Weill, A., Clerc, L., Bonithon-Kopp, C., 2013. Moreau TComorbidities at multiple sclerosis diagnosis. J. Neurol. 260 (Oct (10)), 2629–2637.

Fromont, A., Binquet, C., Sauleau, E.A., Fournel, I., Bellisario, A., Adnet, J., Weill, A., Vukusic, S., Confavreux, C., Debouverie, M., Clerc, L., Bonithon-Kopp, C., Moreau, T, 2010. Geographic variations of multiple sclerosis in France. Brain 133 (Pt 7), 1889–1899 Jul.

Fromont, A., Lehanneur, M.N., Rollot, F., Weill, A., Clerc, L., Bonithon Kopp, C., Binquet, C., Moreau, T, 2014. [Cost of multiple sclerosis in France]. Rev. Neurol. (Paris) 170 (6–7), 432–439 Jun-Jul.

Gold, R., Toumi, M., B3, Meesen, Fogarty, E, 2016. The payer's perspective: what is the burden of MS and how should the patient's perspective be integrated in health technology assessment conducted for taking decisions on access to care and treatment? Mult. Scler. 22 (2 Suppl), 60–70 Aug.

Guide affection longue durée, 2006. Scléroses en Plaques. HAS. Saint Denis, France SepAt: https://www.has-sante.fr/portail/upload/docs/application/pdf/07-024_sclerose-guide_sans_lap.pdf.

HAS. Guide méthodologique, 2011. Choix Méthodologiques Pour L'évaluation économique à la HAS. Haute Autorité de la Santé, Saint Denis, France OctobreAvailable at. https://www.has-sante.fr/portail/upload/docs/application/pdf/2011-11/guide_methodo_vf.pdf.

Jasse, L., Vukusic, S., Durand-Dubief, F., Vartin, C., Piras, C., Bernard, M., Pélisson, D., Confavreux, C., Vighetto, A., Tilikete, C, 2013. Persistent visual impairment in multiple sclerosis: prevalence, mechanisms and resulting disability. Mult. Scler. 19 (Oct (12)), 1618–1626.

Karampampa, K., Gustavsson, A., Miltenburger, C., Eckert, B, 2012. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries. Mult. Scler. 18 (2 Suppl), 7–15 Jun.

Kobelt, G., Eriksson, J., Phillips, G., Berg, J, 2017a. The burden of multiple sclerosis 2015: methods of data collection, assessment and analysis of costs, quality of life and symptoms. Mult. Scler. 23 (2_suppl), 4–16 Aug.

Kobelt, G., Giovannoni, G., 2017. Tackling comorbidity in multiple sclerosis. Mult. Scler. Relat. Disord. 17 (Oct), 144–145. https://doi.org/10.1016/j.msard.2017.07.010. Epub 2017 Jul 13.

Kobelt, G., Thompson, A., Berg, J., Gannedahl, M., Eriksson, J., MSCOI Study Group; European Multiple Sclerosis Platform, 2017. New insights into the burden and costs of multiple sclerosis in Europe. Mult. Scler. 23 (Jul (8)), 1123–1136.

Kurtze, J., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33 (11), 1444–1452.

Lebrun, C., Vermersch, P., Brassat, D., Defer, G., Rumbach, L., Clavelou, P., Debouverie, M., de Seze, J., Wiertlevsky, S., Heinzlef, O., Tourbah, A., Fromont, A., Frenay, M, 2011. Cancer and multiple sclerosis in the era of disease-modifying treatments. J. Neurol. 258 (Jul (7)), 1304–1311.

Lebrun-Frenay, C., Kobelt, G., Berg, J., Capsa, D., 2017. Gannedahl m and the European multiple sclerosis platform new insights into the burden and costs of multiple sclerosis in Europe: results for France. Mult. Scler. J. 23 (2S), 65–77.

Le Pen, C., Coyle, P., Vollmer, T., Blumhardt, L., Lilliu, H., Beresniak, A, 2003. Long-Term cost effectiveness of interferon-beta-1a in the treatment of relapsing-remitting multiple sclerosis: an econometric model. Clin. Drug Investig. 23 (9), 571–581.

Leray, E., Moreau, T., Fromont, A., Edan, G, 2016. Epidemiology of multiple sclerosis. Rev. Neurol. (Paris) 172 (Jan (1)), 3–13.

Leray, E., Morrissey, S., Yaouanq, J., Coustans, M., Le Page, E., Chaperon, J., Edan, G, 2007. Long-term survival of patients with multiple sclerosis in West France. Mult.

Scler. 13 (Aug (7)), 865–874.
McDonald, W.I., Compston, D.A.S., Edan, G., et al., 2001. Recommended diagnostic criteria for MS: guidelines from the international panel on the diagnosis of MS. Ann. Neurol. 50, 121–127.
Moisset, X., Ouchchane, L., Guy, N., Bayle, D., Dallel, R., et al., 2013. Migraine headaches and pain with neuropathic characteristics: comorbid conditions in patients with multiple sclerosis: migraine and neuropathic pain in multiple sclerosis. Pain 154. pp. 2691–2699 Elsevier.
Pivot, D., Debouverie, M., Grzebyk, M., Brassat, D., Clanet, M., Clavelou, P., Confavreux, C., Edan, G., Leray, E., Moreau, T., Vukusic, S., Hédelin, G., Guillemin, F, 2016. Geographical heterogeneity of multiple sclerosis prevalence in France. PLoS One 11 (Dec (12)), e0167556 9.
Polman, C.H., Reingold, S.C., Banwell, B., et al., 2010. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol. 69, 292–302.
Polman, C.H., Reingold, S.C., Edan, G., et al., 2005. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald criteria". Ann. Neurol. 58, 840–846.
Poser C.M., Paty D.W., Scheinberg L., et al. Ann. Neurol.. 1983; 13 (3): 227–31.
Pugliattia, M., Rosatia, G., Cartonc, H., Riiseb, T., Drulovicd, J., Vecseie, L., Milanov, I, 2006. The epidemiology of multiple sclerosis in Europe. Eur. J. Neurol. 13, 700–722.
WHO, 2017. Collaborating center for drug statistics methodology. ATC Classification Available at. https://www.whocc.no/atc/structure_and_principles.