A literature review of cost-of-illness studies on the economic burden of multiple sclerosis.

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Abstract

Background Multiple sclerosis has both high healthcare and social impacts.

Objective The purpose of this article is to analyse the available literature describing the economic burden of multiple sclerosis and to compare costs among studies examining main cost drivers.

Methods A literature search on studies published in English on cost-of-illness of multiple sclerosis included in this review using PubMed, the Cochrane Library, SCOPUS and Web of Science includes a retrospective horizon and it describes direct and indirect costs in patients categorized into severity groups.

Results Several papers were obtained from the database search (n=37). Additionally, results from "hand searching" were also included, where a wider horizon was considered. Cost estimates were compared among studies that used a societal perspective on costs, time-period studied, and year of price level used. The estimated total annual cost per patient in Europe is on average 40,300€ (n=20). In addition, differences by geographic areas and severity groups are also considered. All in all, the higher the severity, the higher the associated costs.

Conclusions This systematic review provides one clear finding: multiple sclerosis places a huge economic burden on healthcare models and societies due to productivity losses and caregiver burden. Moreover, costs of drugs were main cost determinants for less severe cases of multiple sclerosis and informal care and production losses for the most severe cases of multiple sclerosis.

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system and causes pathological inflammatory, demyelinating and neurodegenerative changes. MS usually affects young adults, with a mean age of onset ranging from 20 to 40 years, and is more common in women than in men [1].

MS is a clinical-pathological entity of unknown aetiology in which there is an autoimmune attack on the myelin antigens, causing an inflammatory, demyelinating and neurodegenerative process [1]. Thus, MS has variable clinical effects and an unpredictable evolutionary course. The prevalence of MS has been increasing in recent decades and there was no disease-modifying treatment for MS until the 1990s because relevant scientific advances in MS have taken place in recent years [2].

Management of the disease consisted of treatment of acute relapses with corticosteroids, symptom control, physiotherapy, psychiatric and social support and disability aids. In recent years, pharmaceutical drugs have been improved in order to slow down progression of this disease. In this regard, it could be useful to develop more models to improve the natural history, the effects of treatment and costs of different strategies for MS [3].

Hence, interest in the overall cost of MS and the cost to patients with different stages of MS has increased. On one hand, direct costs include inpatient care, outpatient care, drugs, diagnostics, surgical interventions, nursing care, social services, and patients´ travel costs in order to get to health care. On the other hand, indirect costs are losses of production due to short- or long-term sick leave, disability pension, early retirement due to health problems, permanent losses due to premature death, and sometimes time spent by next of kin to care for the patient. Besides, there are intangible costs understood as humanitarian losses due to, for instance, pain, anxiety, and suffering.

Therefore, the economic burden of MS includes medical and non-medical direct costs, indirect costs from increased morbidity, early mortality, and impact on family and friends, and intangible costs.

The purpose of this article is to analyse the available literature describing the economic burden of MS and to compare costs among studies examining main cost drivers.

Methods

A systematic review was performed for economic burden studies in cost-of-illness of MS using four electronic databases: PubMed, the Cochrane Library, SCOPUS and Web of Science. The search strategy was based on a broad combined search string "Cost*" OR "Cost Analysis or Cost of Illness" "Economic burden" AND "multiple sclerosis" in the title or abstract fields to retrieve potentially relevant publications. They were employed both in free text and controlled vocabulary. The search was limited to English-language studies published between January 1, 2013 and May 22, 2018 (in order to capture 5 full years of literature). Search strategies were limited to humans only. Reference lists from the remaining studies were hand searched to identify any additional articles meeting the above-mentioned criteria.

Methodological approach

The study design was classified as a cross-sectional retrospective, a review, a systematic review, and systematic review and meta-analysis. To quantify the resources used, approaches commonly used are the state/publicly funded health services; third-party/private sector/not-for-profit organizations, and patient and family and/or societal perspective. The payer approach estimates economic costs by using aggregate data on mortality, morbidity, hospital admissions, general practice consultations, disease-related costs, and other health-related indicators. The societal approach calculates resources utilization and productivity loss at the level of the patient or individual. In Table 1, the selected articles are given, describing their most relevant characteristics: study design, country, year of data, and perspective.

An additional manual search was also performed to identify other potentially relevant studies. See Appendix Table I for the search strategy/search terms used.

Table 1. Selected articles and their most relevant characteristics: study design, country, year of data, and perspective.

Author	Study desing	Country	Year of data	Perspective
Buijs et al. [4]	CS	Netherlands	2006-2014	PB
Carney et al. [5]	CS	Ireland	2015	S
Gyllensten et al. [6]	CS	Sweden	2006/2009/2012	S
Svendsen et al. [7]	CS	Norway	2013-2014	S
Battaglia et al. [8]	CS	Italy	2015	S
Berger et al. [9]	CS	Austria	2015	S
Boyko et al. [10]	CS	Russia	2015-2016	S
Brundin et al. [11]	CS	Sweden	2015	S
Calabrese et al. [12]	CS	Switzerland	2015	S
Dubois et al. [13]	CS	Belgium	2015	S
Fernandez et al. [14]	R	Spain	2000-2016	S
Flachenecker et al. [15]	CS	Germany	2015	S
Havrdova et al. [16]	CS	Czech Republic	2015	S
Kobelt et al. [17]	CS	International	2015-2016	S
Lebrun-Frenay et al. [18]	CS	France	2015	S
Oreja-Guevara et al. [19]	CS	Spain	2015	S
Péntek et al. [20]	CS	Hungary	2015	S
Rasmussen et al. [21]	CS	Denmarck	2015	S
Sá et al. [22]	CS	Portugal	2015	S
Selmaj et al. [23]	CS	Poland	2015	S
Thompson et al. [24]	CS	United Kingdom	2015	S
Uitdehaag et al. [25]	CS	Netherlands	2015	S
da Silva et al. [26]	CS	Brazil	2011-2012	SP
Ernstsson et al. [27]	SR	International	1969-2014	S
Hawton et al. [28]	CS	United Kingdom	2012	SP
Ruutiainen et al.[29]	CS	Finland	2014	S
Stawowczyk et al. [30]	SR	International	1993-2015	S
Fogarty et al. [31]	CS	Ireland	2011-2012	S
Ma et al. [32]	SR	USA	2008-2013	PB
Zettl et al. [33]	CS	Germany	2011	S
Adelman et al. [34]	SR	International	2007-2012	S
Coleman et al. [35]	CS	USA	2010	S
Karampampa et al. [36]	CS	Netherlands	2011	S
Kolasa et al. [37]	SR	International	2002-2012	S
Palmer et al. [38]	CS	Australia	2010	S
Parisé et al. [39]	CS	USA	1999-2011	S
Svensson et al. [40]	CS	Sweden	2010	S

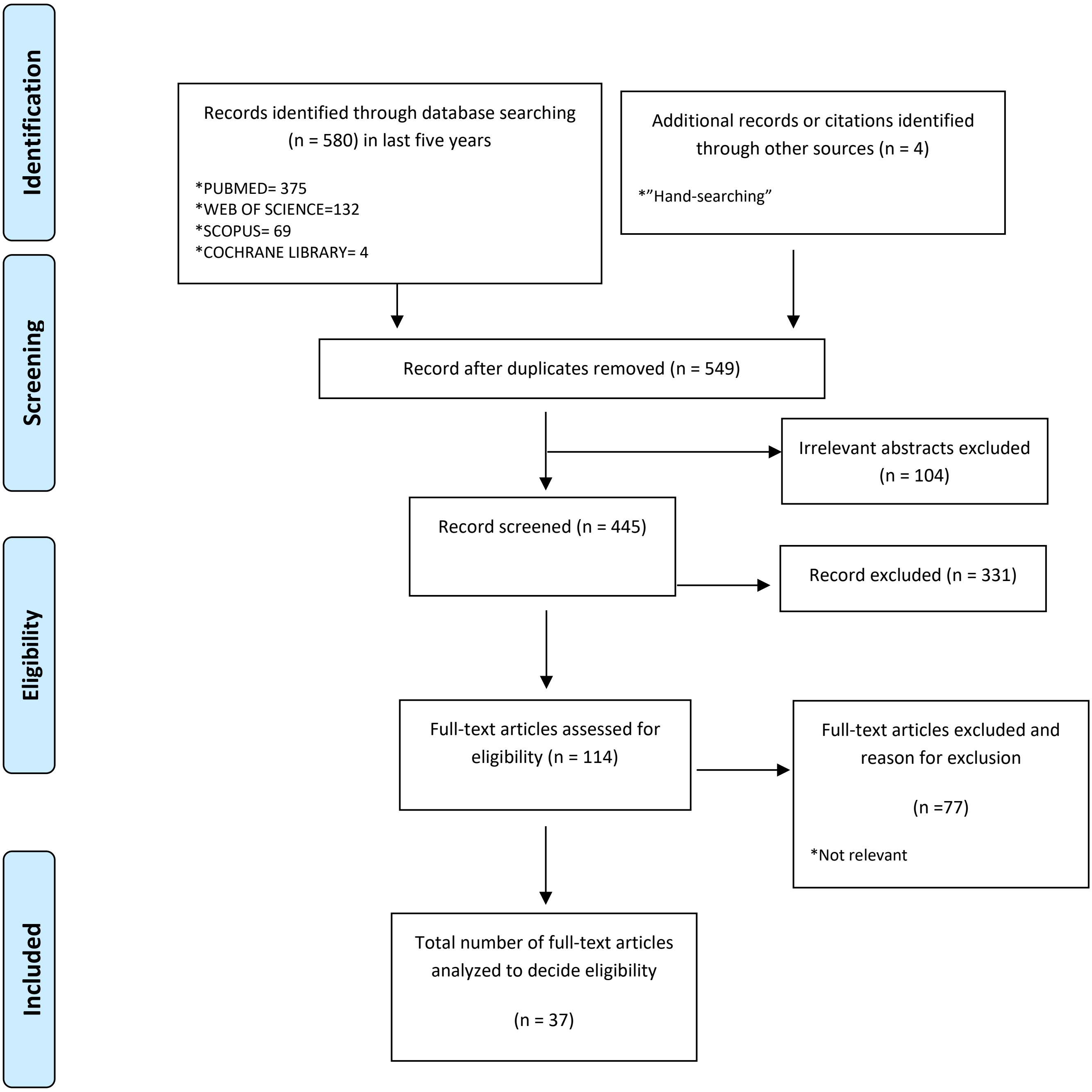
Source: Authors' own elaboration. Notes: Cross-sectional retrospective (CS); Review (R); Systematic Review (SR). State/ publicly funded health services (SP); Private sector/ not-for-profit organizations (PB); Societal (S).

Results

Study selection

The inclusion criteria were review, systematic review, and original research that: 1) reported cost of illness, economic burden, health care expenditure, or resource utilization for MS, 2) provided information on data sources, and 3) studied population that included MS patients. Excluded were duplicate articles, studies which were not cost focused, studies which were not relevant, and studies which only focused on pharmacy costs, or comparison of treatment costs. Thereafter, the full text of all potentially relevant studies was reviewed. A flow chart that illustrates the selection process is shown in Figure 1.

Figure 1. Flow diagram (PRISMA, 2009).



The search criteria resulted in 580 articles being identified: 375 articles from the PubMed database, 4 articles from the Cochrane Library, 69 articles from the SCOPUS, and 132 from Web of Science. Moreover, four additional citations were identified through hand-searching. 104 irrelevant abstracts were excluded.

The abstracts for each of these 445 citations were then reviewed and compared against the previously mentioned inclusion and exclusion criteria, after which 114 articles remained. Seventy-two studies which were not relevant, 3 studies which only focused on pharmacy costs, and 2 studies which focused on comparison of treatment costs were all excluded.

The 37 remaining articles were included in this literature review. From these selected studies, we have thirty-one cross-sectional retrospective studies, one review, four systematic reviews, and one systematic review and meta-analysis. Three major cost groups were identified in 34 studies: direct healthcare costs, direct non-healthcare costs, and indirect costs. There is a direct relationship between disease progression and increased costs, mainly direct non-healthcare costs (greater need for informal care) and indirect costs (greater loss of productivity).

Cost components and data sources

The economic burden of MS can be reported as direct (medical and non-medical), indirect costs, and intangible costs. Table 2 describes the economic aspects of the articles: currency, direct health costs (direct health care costs and/or direct non-medical costs), indirect costs, and totals.

Table 2. Economic aspects of the articles: currency, direct health costs (Direct health care costs and/or Direct non-medical costs), indirect costs, and totals.

Author	Direct cost	Indirect cost	Total costs
Buijs et al. [4]; €/2014	2006= 9011; 2007=8595; 2008= 8227; 2009= 8482; 2010= 8201; 2011=7563; 2012= 11833; 2013=11543; 2014=7177	Not included.	Total healthcare costs (medication and hospital) 10.930,593
Carney et al. [5]; €/2015	Mild= 14,269; Moderate= 13,696; Severe= 26,298	Mild= €5,470; Moderate= 32,671; Severe= 46,232 *Intangible costs: Mild= 5,202; Moderate= 11,490; Severe= 28,033	Average annual cost for those with mild, moderate, and severe MS calculated as 34,942, 57,857, and 100,554, respectively.
Gyllensten et al. [6]; €/2012	2006=8,367.09; 2009=9,891.10; 2012=11,208.69	2006=23,156.12; 2009=22,390.38; 2012=20,982.39	Average direct and indirect costs per MS patient in 2006=31,523.21; 2009=32,281.48 and 2012=32,191.08.
Svendsen et al. [7]; €/2014	3,931	7,672	Mean annual total economic costs for the patients and their families were 11,603.
Battaglia et al. [8]; €/2015	Mild= 21,175 (15,798); Moderate= 30,605 (40,492); Severe= 35,245 (44,543)	Mild= 1717 (5915); Moderate= 9542 (15,324); Severe= 18,045 (18,997)	Cost of a relapse for patients = 2620; Total cost Mild=22,900; Moderate= 40,100; Severe= 53,300.
Berger et al. [9]; €/2015	Mild= 18,358 (15,019); Moderate= 29,224 (28,798); Severe= 55,107 (44,505)	Mild= 6735 (12,854); Moderate= 14,924 (16,417); Severe= 18,676 (17,350)	Cost of a relapse for patients = €2563; Total cost Mild=25,100; Moderate= 44,100; Severe=73,800.
Boyko et al. [10]; €/2015	Mild= 7,321.06 (6,076.97); Moderate= 8,295.44 (6,582.49); Severe= 8,767.40 (9,804.53)	Mild= 1,170.72 (2,729.42); Moderate= 3,844.71 (4,041.37); Severe= 6,109.41 (3,166.12)	Cost of a relapse for patients = 484,77; Total cost Mild=8490.82; Moderate= 12,133.94; Severe= 14,880.97.
Brundin et al. [11]; €/2015	Mild= 16,861.58 (20,611.12); Moderate= 25,199.99 (33,737.27); Severe= 76,424.69 (70,585.72)	Mild= 9,227.73 (16,822.82); Moderate= 15,819.22 (20,694.42); Severe= 18,401.32 (22,621.63)	Cost of a relapse for patients = 3,364.20; Total cost Mild= 26,091.24; Moderate= 41,021.88; Severe= 94,827.72).
Calabrese et al. [12]; CHF/2015	Mild= 20,867 (16,786); Moderate= 44,124 (59,422); Severe= 70,136 (69,220)	Mild= 8724 (21,894); Moderate= 22,668 (32,696); Severe= 40,706 (36,400)	Cost of a relapse for patients = 7643; Total cost Mild=29,600; Moderate=66,800; Severe=110,800.
Dubois et al. [13]; €/2015	Mild= 14,845 (15,220); Moderate= 26,577 (27,135); Severe= 43,617 (36,516)	Mild= 11,560 (19,142); Moderate= 18,700 (22,427); Severe= 18,424 (22,756)	Cost of a relapse for patients = 2976; Total cost Mild=26,400; Moderate=45,300; Severe=62,000.

Author	Direct cost	Indirect cost	Total costs
Fernandez et al. [14]; €/2016	20,966	9,084	Annual cost per patient. Total cost per patient per year= 30,050.
Flachenecker et al. [15]; €/2015	Mild= 20,024 (14,225); Moderate= 25,752 (20,458); Severe= 41,149 (31,618)	Mild= 8190 (15,022); Moderate= 18,238 (18,814); Severe= 21,586 (19,392)	Cost of a relapse for patients = 2468; Total cost Mild=28,200; Moderate=44,000; Severe=62,700.
Havrdova et al. [16]; €/2015	Mild= 8,237.92 (7,411.96); Moderate= 8,908.41 (8,755.27); Severe= 9,416.07 (8,863.41)	Mild= 1,276.63 (3,929.72); Moderate= 6837.58 (7,097.59); Severe= 8,687.59 (7,247.35)	Cost of a relapse for patients = 466.29; Total cost Mild=9,510.77; Moderate= 15,746.43; Severe= 18,096.37.
Kobelt et al. [17]; €/2015	Non- disaggregated	Non- disaggregated	Mean costs for patients with mild=22,800 (12,600–27,300), moderate= 37,100 (22,500–54,700) and severe 57,500 (27,500–77,600).
Lebrun-Frenay et al. [18]; €/2015	Mild= 18,067 (12,128); Moderate= 25,706 (19,674); Severe= 33,420 (29,567)	Mild= 4562 (10,816); Moderate= 12,438 (15,227); Severe= 14,681 (16,269)	Cost of a relapse for patients= €2305; Total cost Mild=22,600; Moderate= 38,100; Severe= 48,100.
Oreja-Guevara et al. [19]; €/2015	Mild= 16,611 (9821); Moderate= 31,550 (23,932); Severe= 52,069 (36,218)	Mild= 3997 (10,307); Moderate= 16,901 (15,920); Severe= 16,645(16,258)	Cost of a relapse for patients= €2044; Total cost Mild=20,600; Moderate= 48,500; Severe= 68,700.
Péntek et al. [20]; €/2015	Mild= 8,717.14 (7,478,92); Moderate= 11,009.16 (9,300.53); Severe= 11,610.34 (8,222.90)	Mild= 2,363.92 (4,609.11); Moderate= 5,977.12 (6,240.28); Severe= 8,518.39 (6,099.37)	Cost of a relapse for patients= 776.43; Total cost Mild=11,079.90; Moderate= 16,987.89; Severe= 20,129.14.
Rasmussen et al. [21]; €/2015	Mild= 16,352.69 (16,273.90); Moderate= 20,385.69 (20,153.87); Severe= 48,522 (52,841.29)	Mild= 9,916 (16,446.76); Moderate= 18,112.78 (18,974.53); Severe= 22,933.43 (18,989.27)	Cost of a relapse for patients= 2,550.96; Total cost Mild=26,264; Moderate= 38,458; Severe= 71,422.
Sá et al. [22]; €/2015	Mild= 12,873 (15,204); Moderate= 19,412 (21,305); Severe= 23,278 (22,793)	Mild= 3585 (6323); Moderate= 9323 (7408); Severe= 11,122 (6934)	Cost of a relapse for patients= €2931; Total cost Mild=16,500; Moderate= 28,700; Severe= 34,400.
Selmaj et al. [23]; €/2015	Mild= 10,191.20 (6,073.71); Moderate= 8,523.70 (7,061.97); Severe=9,695.27 (37,531.13)	Mild=1,445.95 (3,714.30); Moderate= 5,630.60 (6,588.04); Severe=9,814.30 (6,237.42)	Cost of a relapse for patients=932.10; Total cost Mild=11,639.30; Moderate= 14,148,80; Severe= 19,502.40.
Thompson et al. [24]; GBP/2015	Mild= 6953 (10,715); Moderate= 12,435 (13,531); Severe= 24,662 (21,895)	Mild= 4480 (9989); Moderate= 10,284 (12,871); Severe= 11,875 (13,831)	Cost of a relapse for patients= 792; Total cost Mild=11,400; Moderate=22,700; Severe= 36,500.
Uitdehaag et al. [25]; €/2015	Mild= 10,626 (13,415); Moderate= 16,239 (32,316); Severe= 30,716 (39,987)	Mild= 12,428 (16,251); Moderate= 16,045	Cost of a relapse for patients= €2977; Total cost Mild=23,100; Moderate= 32,300; Severe= 50,500.

		(16,737); Severe= 19,771 (19,123)	
Author	**Direct cost**	**Indirect cost**	**Total costs**
da Silva et al. [25]; USD/2012	Mild= 18,475.08 (8,256.02); Moderate= 19,370.84 (7509.87); Severe= 19,545.57 (19,445.75)	Not included.	Mean annual cost of MS according to disability level. USD 19,012.32 (SD = 10,465.96).
Ernstsson et al. [27]; USD/2011	Non- disaggregated	Non- disaggregated	Mild= 22,719; Moderate= 40,153; Severe= 64,853
Hawton et al. [28]; £/2012	Non- disaggregated	Non- disaggregated	Health/social care cost for individuals who reported a relapse was £519 vs those who did not report a relapse being £229 (six-monthly).
Ruutiainen et al.[29]; €/2013	26,493	20,501 Productivity losses)	Mean total annual cost of MS was 46,994. Patients with Expanded Disability Status Scale (EDSS) score of 0 = 10,835 vs EDSS score of 8-9 = €109,901.
Stawowczyk et al. [30]; USD/2014	Non- disaggregated	Scenario 1: was as high as US$20,167 with US$22,197 in Europe, US$17,382 in North America and US$153 in Asia. scenario 2: equal to US$16,939, with US$19,612 in Europe, US$11,592 in North America and US$899 in Asia.	Overall indirect costs varied from 3726 for patients with EDSS score less than 3 to 19,264 for patients with EDSS score greater that 7.
Fogarty et al. [31]; €/2012	Mild= 10,249 (8,856–11,685); Moderate= 13,045 (10,119–16,238); Severe= 56,528 (43,160–72,067)	Mild= 9,447 (6,465–12,681); Moderate=31,806 (25,287–38,452); Severe= 39,440 (27,229–52,005)	Total direct medical=11,946; Total direct non-medical=5,157; Total direct costs =17,103; Total indirect costs=20,858.
Ma et al. [32]; USD/2013	Non- disaggregated	Non- disaggregated	Annual health care costs for patients with MS have been reported: 18,000 - 39,000.
Zettl et al. [33]; €/2011	TPP perspective Mild= 1,172 (1,735); Moderate= 2,364 (2,639); Severe= 4,106 (3,569) Patient perspective Mild= 991 (4,634); Moderate= 1,717 (7,021); Severe= 4,319 (9,262)	Mild= 105 (535); Moderate= 281 (1,388); Severe= 264 (1,139)	Mild= 2,268 (4,917); Moderate= 4,362 (7,609); Severe= 8,688 (10,031) Mean MS spasticity management resource costs were 4794/patient/year.

Author	**Direct cost**	**Indirect cost**	**Total costs**
Adelman et al. [34]; $/2011	6,144–34,511	1,896–19,733	Mean cost ranged 8528-54,244 per patient/ year.
Coleman et al. [35]; USD/2011	Not included.	30,601 (31,184)	18,000 - 36,000 compared to a referent category of mobility impairment, depending on the WTP threshold used.
Karampampa et al. [36]; €/2011	Mild= 16,225; Moderate= 28,635; Severe= 66,281	Mild= 14,714 (19,828); Moderate= 22,421 (20,707); Severe= 34,188 (15,881)	Total cost Mild=30,938; Moderate= 51,056; Severe= 100,469.
Kolasa et al. [37]; USD/2011	Non-desagregated.	Non-desagregated.	The mean cost for one patient from studies under analysis was 41,133.
Palmer et al. [38]; €/2010	Mild= 16,778.34; Moderate=24,425.04; Severe= 29,260.27	Mild= 13,698.70; Moderate= 24,924.49; Severe= 25,464.99	Total cost Mild=30,475; Moderate= 49,346; Severe= 54,727.
Parisé et al. [39]; USD/2011	No relapse= 4434 (15,883); Less frequent relapses=4476 (19,531); More frequent relapses=5623 (20,012)	No relapse= 1652 (6023); Less frequent relapses=1487 (5463); More frequent relapses=2204 (9477)	Per caregiver per year costs, mean (SD). Total cost no relapse= 6085 (19,161); Less frequent relapses=5963 (22,394); More frequent relapses=7827 (25,166).
Svensson et al. [40]; €/2010	76,407	37,885 (22,771)	Total cost= 114,293 (104,897).

Source: Authors' elaboration.

Discussion

This review has focused on total costs of MS. Firstly, we have collected and summarized all current data on different study design, country, and perspectives. Secondly, economic aspects of the articles have been summarized. Thus, in this section we will analyze all comparable results from the abovementioned review. Some general findings have been shown previously to provide a suitable framework.

Regarding international studies, we should highlight a systematic review of 15 studies that was conducted in the United Stated by Adelman et al. [34]. Total mean costs for patients with MS ranged from $8,528–$54,244 per patient per year in 2011. Direct costs ranged from $6,144–$34,511 in the same year. On average, direct costs comprised 77% (range 64–91%) of total costs. The two lowest direct cost estimates were derived from studies that did not consider MS medication costs. Indirect costs ranged from $1,896-$19,733 depending on the study. On average, indirect costs comprised 23% (range 9–36%) of total costs.

Coleman el al. [35] studied the impact of mobility impairment on indirect costs and health-related quality of life in MS. This cross-sectional retrospective study was conducted in the Unites States, and the total indirect costs of MS were estimated to exceed $30,000 per participant per year. Moreover, the largest relative increases in indirect costs were seen at earlier mobility impairment stages.

In addition, Parisé et al. [39] estimated the direct and indirect cost burden associated with MS relapses. Their results indicate that, after a 12-month period of monitoring, the average annual all-cause direct cost of MS patients ranged from $17,545 to $41,969. MS relapses were associated with greater direct and indirect costs for MS patients. In addition, higher rates of MS relapses were associated with an increased direct medical and indirect work loss cost burden for spouse caregivers. The average total cost per caregiver per year was $6,085 for cases where there was no relapse, $5,963 where there were less frequent relapses, and $7,827 for more frequent relapses.

Concerning European studies, we should highlight a cross-sectional study that was conducted in 16 countries by Kobelt et al. [17] in collaboration with national MS societies and local clinical and economic experts. The countries included were Austria, Belgium, the Czech Republic, Denmark, France, Germany, Hungary, Italy, the Netherlands, Poland, Portugal, Russia, Spain, Sweden, Switzerland and the United Kingdom. Patients reported on their disease, health-related quality of life (HRQoL) and resource consumption. Descriptive analyses were performed by disease severity (mild, moderate, and severe). All costs were reported from a societal perspective. Costs and utility were highly correlated with disease severity, but resource consumption was heavily influenced by healthcare system and availability of services. There was a wide variation ?? among countries, leading to very different mean annual costs per patient and making inter-country cost comparisons meaningless. Costs were related to disease severity (EDSS score) in all countries and were dominated by production losses, and non-healthcare costs.

Ruutiainen et al. [29] published the DEFENSE study. It aimed to estimate the costs and health-related quality-of-life (HRQoL) of patients with MS in Finland. The mean total annual cost of MS was 46,994€. The cost increased with advancing disease: mild disease 10,835€ - severe disease 109,901€. Karampampa et al. [36] published similar results. The mean cost per patient per year increased with worsening disability and was estimated at 30,938€ for patients with mild disease, 51,056€ for thoses with moderate disease, and 100,469€ for those with severe disability.

In Spain, Fernandez et al. [14] estimated the cost of MS by literature review. The total cost associated with MS for this country is 1,395€ million per year, and the mean annual cost per patient is 30,050€. Beyond costs, a large impact on the quality of life of patients has been observed, with an annual loss of up to 13,000 quality-adjusted life years also being estimated.

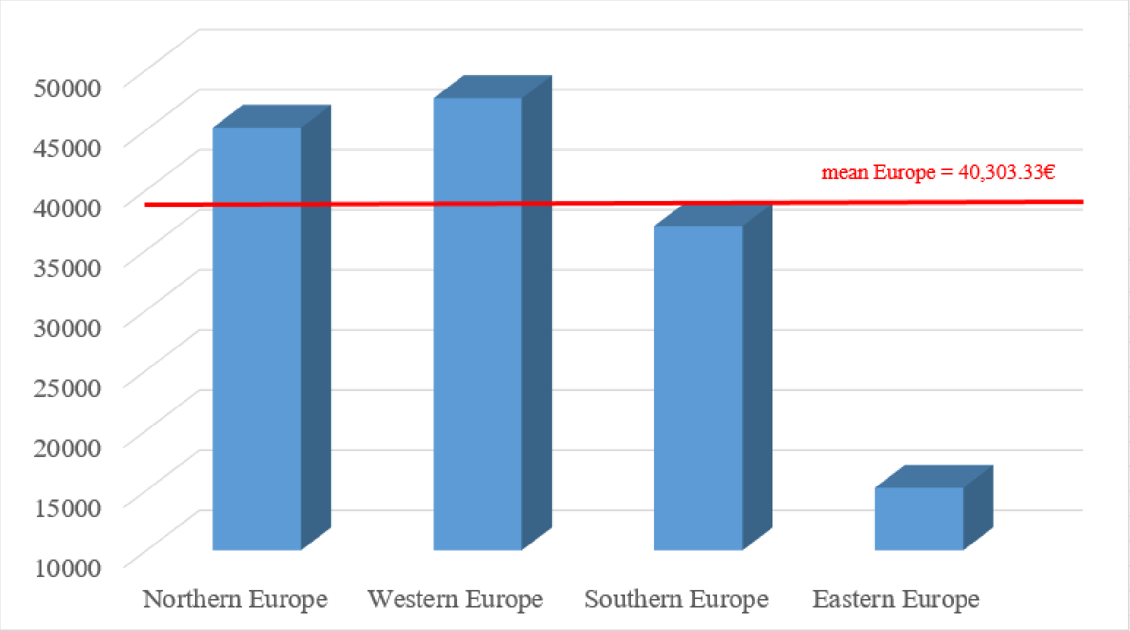
In addition, Oreja et al. [19] published part of a cross-sectional retrospective study of 16 countries collecting data on resource consumption, work capacity, health-related quality of life (HRQoL) and prevalent symptoms for patients with MS. Descriptive analyses are presented by level of severity, from a societal perspective with the cost of a relapse for patients being 2,044€. The total cost for patients with mild MS was 20,600€; for those with moderate MS it was 48,500€, and for those with severe MS it was 68,700€.

Summary of comparable results from the review

From the above-mentioned 37 studies, we aim to provide a general overview regarding final estimates of MS. In order to summarize comparable costs we first focused on the research studies that consider a societal perspective (n=33). Secondly, those that provide a cross-sectional retrospective analysis (n=28), and finally we emphasized possible heterogeneity among areas (n=23 of them were for European countries). However, ultimately, three were not eligible due to particularities in the sample costs (n=20).

Mean total costs for the selected European studies are 40,303€. All in all, some differences, as expected, are appreciated by macro areas. Figure 2 plots the comparative of total MS costs from a societal perspective considering differences by European macro-areas whereas Table 3 shows cost per patient and year.

Figure 2. European cross-sectional retrospective studies that consider a societal perspective. Cost per patient and year, (€, 2015).



Source: Authors' own elaboration.
Notes: Northern Europe (Denmark, Finland, Ireland, Sweden, and United Kingdom); Western Europe (Austria, Belgium, France, Germany, Netherlands, and Switzerland); Southern Europe (Italy, Portugal, and Spain), and Eastern Europe (Czech Republic, Hungary, and Poland).

Table 3. Total MS costs from a societal perspective. Cost per patient and year, (€, 2015).

MACRO-AREA	AUTHOR(S)	COST PER PATIENT AND YEAR, (€, 2015)
Northern Europe	Carney et al. [5]; Gyllensten et al. [6]; Brundin et al. [11]; Rasmussen et al. [21]; Thompson et al. [24]; Ruutiainen et al. [29]; Fogarty et al. [31].	44,589
Western Europe	Berger et al. [9]; Calabrese et al. [12]; Dubois et al. [13]; Flachenecker et al. [15]; Lebrun-Frenay et al. [18]; Uitdehaag et al. [25]; Karampampa et al. [36].	47,619
Southern Europe	Battaglia et al.[8]; Oreja-Guevara et al. [19]; Sá et al. [22].	36,978
Eastern Europe	Havrdova et al. [16]; Péntek et al. [20]; Selmaj et al. [23].	15,205

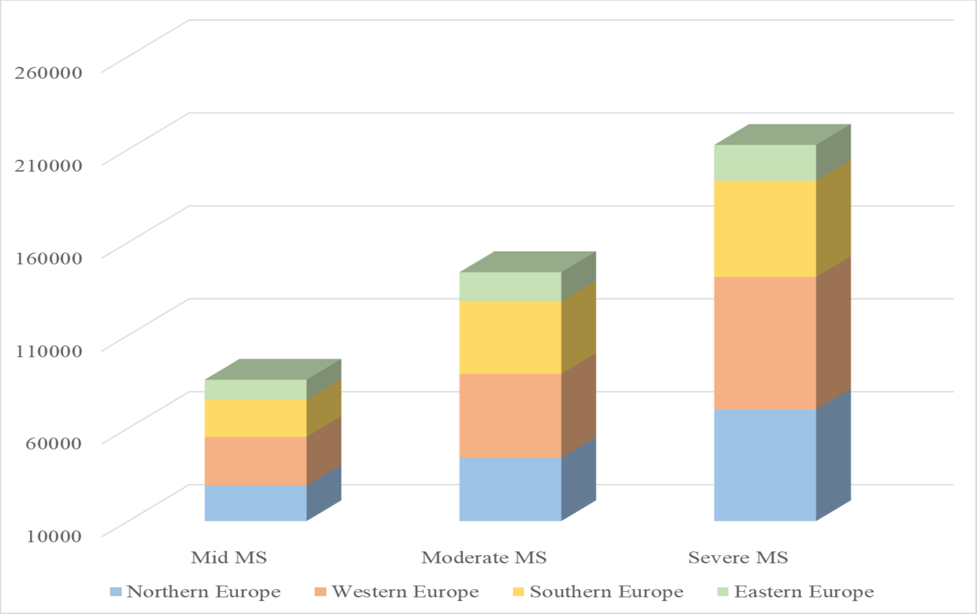
Source: Authors' elaboration.

Notes: Northern Europe (Denmark, Finland, Ireland, Sweden, and United Kingdom); Western Europe (Austria, Belgium, France, Germany, Netherlands, and Switzerland); Southern Europe (Italy, Portugal, and Spain), and Eastern Europe (Czech Republic, Hungary, and Poland).

On the one hand, it is observed that Northern and Western European countries face higher costs. On the other hand, Southern European countries are somehow slightly above the on mean European amounts, but Eastern European countries have less than half the cost in relation to their European partners.

Furthermore, most of the studies mentioned above (n=19) also estimated the cost per patient according to disease severity: Mild MS, Moderate MS, and Severe MS. Figure 3 plots the comparative of total MS costs by severity from a societal perspective considering differences by European macro-areas whereas Table 4 shows the corresponding amounts.

Figure 3. European cross-sectional retrospective studies that consider a societal perspective. Cost per patient and year by disease severity, (€, 2015).



Source: Authors' elaboration.
Notes: Northern Europe (Denmark, Ireland, Sweden, and United Kingdom); Western Europe (Austria, Belgium, France, Germany, Netherlands, and Switzerland); Southern Europe (Italy, Portugal, and Spain), and Eastern Europe (Czech Republic, Hungary, and Poland).

Table 4. Total MS costs from a societal perspective. Cost per patient and year by disease severity, (€, 2015)

MACRO-AREA	**AUTHOR(S)**	**Mid MS**	**Moderate MS**	**Severe MS**
Northern Europe	Carney et al. [5]; Gyllensten et al. [6]; Brundin et al. [11]; Rasmussen et al. [21]; Thompson et al. [24]; Fogarty et al. [31].	29,087	43,970	69,925
Western Europe	Berger et al. [9]; Calabrese et al. [12]; Dubois et al. [13]; Flachenecker et al. [15]; Lebrun-Frenay et al. [18]; Uitdehaag et al. [25]; Karampampa et al. [36].	26,237	45,215	71,404
Southern Europe	Battaglia et al.[8]; Oreja-Guevara et al. [19]; Sá et al. [22].	20,000	39,100	51,833
Eastern Europe	Havrdova et al. [16]; Péntek et al. [20]; Selmaj et al. [23].	10,743	15,628	19,243

Source: Authors' elaboration.
Notes: Northern Europe (Denmark, Ireland, Sweden, and United Kingdom); Western Europe (Austria, Belgium, France, Germany, Netherlands, and Switzerland); Southern Europe (Italy, Portugal, and Spain), and Eastern Europe (Czech Republic, Hungary, and Poland).

As expected, the higher the severity, the higher the associated costs. From 23,706€ per year in patients with mild disability to 59,611€ in patients with severe disability (on average), and which represented practically 49% of the total cost of the disease in the latter group. Overall, the highest cost is obtained for Western European countries whereas the lowest costs are found among Eastern European ones.

Publication bias represents a particular threat to the validity of a systematic review. Because of our comprehensive search strategy, omission of important published trials seems unlikely.

A systematic review of the literature, if used correctly, is an extremely suitable tool for combining the results of different studies when presented with large amounts of information. However, since they are retrospective research studies, they can lead to biased conclusions from imperfect studies that in isolation would have been confusing. Therefore, and with the aim of minimizing this bias, we have clearly defined the criteria for inclusion and exclusion of studies in the review, and these have been as objective as possible.

Heterogeneity among the combined different studies can affect the results of the systematic review of the literature in a very important way. These are usually research studies carried out in different economic contexts, with patients not necessarily with similar characteristics or even with very different results, which implies that it is not always advisable to carry out a comparison. In our case, we have investigated the possible sources of heterogeneity, its influence on the results, and the possibility of carrying out an analysis by subgroups; and due to heterogeneity, a standardization of costs (currency) or an adjustment per year has not been possible.

Conclusions

Published literature on MS is characterized by many papers advocating for increasing health care needs and its corresponding affect on health expenditures, which would determine the future sustainability of health care systems. The aim of this review was to determine the average annual cost of MS while also compare costs among studies and perspectives.

In this regard, this study confirmed that MS puts forward a very important challenge for both health care systems and worldwide society. What is true is that different types of analysis produce very different results on final costs. However, this societal perspective has been applied in the most recently-included studies, appearing to make comparisons among studies feasible.

Precisely, from the literature analysis, our findings support the raised concern that total cost per patient and year varies among studies and countries. Overall, our outcomes claim that the higher the severity, the higher the associated cost. Indeed, mean total costs for the selected European studies stand at 40,303€ (ranging from 23,707€ for Mild MS to 59,611€ for Severe MS). Eastern European countries face the lowest costs.

Therefore, the conducted review has provided a general perspective on the huge economic burden of MS and possible heterogeneity among studies, main cost drivers, and areas. Also seen is the relationship between the severity of the disease and costs.

Notwithstanding, there are some limitations to this review that we should consider. First, the literature search was limited to the four databases. Secondly, we only considered a 5-year retrospective horizon. Future reviews should also include other relevant sources and expand the period under analysis.

All in all, the conclusions from this analysis are intended to be the basis and contextualization for recommendations for future researchers of the topic who would like to conduct MS cost study. However, more studies on these issues are still needed. An effort should be made by the scientific community to estimate the economic burden of MS. This would provide information to allow better decision-making about public-health priorities in MS.

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Appendix

Table I. Search strategy: PubMed, the Cochrane Library, SCOPUS and Web of Science.

#	Search term
PubMed	
#1	Cost* AND “multiple sclerosis” [title/abstract]
#2	"Cost of Illness" AND “multiple sclerosis” [title/abstract]
#3	"Economic burden" AND “multiple sclerosis” [title/abstract]
#4	Limit to: journal article; review; year of publication ≥ 2013; English; Humans subjects.
Cochrane Library	
#1	Cost* AND “multiple sclerosis” [title/abstract]
#2	“Cost Analysis” OR “Economic burden” AND “multiple sclerosis” [title/abstract]
#3	“Cost of Illness” OR “Economic burden” AND “multiple sclerosis” [title/abstract]
#4	Limit to: review; year of publication ≥ 2013; English; Humans subjects.
SCOPUS	
#1	“Cost Analysis” AND “multiple sclerosis” [title]
#2	“Cost of Illness” AND “multiple sclerosis” [title]
#3	“Economic burden” AND “multiple sclerosis” [title]
#4	Limit to: journal article; review; year of publication ≥ 2013; English; Humans subjects.
Web of Science	
#1	Cost* AND “multiple sclerosis” [title]
#2	"Economic burden" AND “multiple sclerosis” [title]
#3	“Cost of Illness” AND “multiple sclerosis” [title]
#4	Limit to: journal article; review; year of publication ≥ 2013; English; Humans subjects.

Source: Authors’ elaboration.