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Secondary progressive multiple sclerosis: a systematic review of costs and health state utilities

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Transparency

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Declaration of financial/other relationships

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Author contributions

VK conducted the original systematic review searches, and VK, HS and JF conducted the updated systematic review searches. HS and JF drafted the manuscript and all authors critically reviewed the manuscript. All authors gave final approval of the version to be published and all authors agree to be accountable for all aspects of the work.

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Data availability statement

There is no data set for this review.

Abstract

Objective: To identify evidence in the literature presenting the economic and humanistic (based on health state utility values [HSUVs]) burden of multiple sclerosis (MS) and report the incremental burden of secondary progressive MS (SPMS) compared with relapsing–remitting MS (RRMS).

Methods: Electronic databases (Embase®, MEDLINE®, MEDLINE® In-Process, Cochrane Library) and other relevant repositories were systematically searched from the date of inception until November 2019 for evidence on the economic burden of MS, or HSUVs in patients with MS. Data were extracted from studies investigating cost data or HSUVs for patients with SPMS compared with RRMS.

Results: In total, 25 studies were identified that reported data on the economic and HSUV burden of SPMS versus RRMS: 18 studies reported cost data and nine presented HSUVs. Overall, costs associated with SPMS were consistently higher than those for RRMS. Major cost drivers appeared to shift following transition from RRMS to SPMS, with higher direct medical costs associated with RRMS than with SPMS, while the opposite was true for direct non-medical costs and indirect costs. In all studies presenting HSUVs specifically in patients with SPMS, the disease burden was greater (indicated by lower HSUV scores or a negative regression coefficient vs RRMS) for patients with SPMS than for those with RRMS. Fatigue and psychological stress (including depression) were identified as key drivers of this reduced health-related quality of life (HRQoL).

Conclusions: Our findings indicate that SPMS is associated with higher costs and more substantial HRQoL decrements than RRMS. These results highlight the substantial unmet need for effective treatments that can slow disease progression in patients with SPMS, which, in turn, would reduce the rate of HRQoL deterioration and increasing healthcare costs.

Keywords: secondary progressive multiple sclerosis; cost of illness; economic value of life; systematic review

Short title: Health state utilities and costs in SPMS

Introduction

Secondary progressive multiple sclerosis (SPMS) is characterized by irreversible disability progression that occurs independently of relapses [1,2]. Approximately two-thirds of patients initially diagnosed with relapsing–remitting multiple sclerosis (RRMS) will eventually transition to a SPMS disease course [2]. The estimated prevalence of SPMS varies considerably by study design, country (from 0.2 per 100,000 in Brazil [3] to 95.5 per 100,000 in Scotland [4]) and geographic latitude [5,6]. One reason for the variation is the difficulty in identifying when the transition from RRMS to SPMS occurs. Furthermore, disability worsening caused by relapses from which patients may fully or partially recover is hard to distinguish in the short term from chronic disability progression associated with progressive disease [1,7,8]. The problem of identifying this transition is compounded by the absence of a full consensus for the definition of SPMS and the lack of validated, objective diagnostic criteria [8].

Overall, SPMS is associated with a greater symptomatic burden than RRMS. Mobility is generally significantly more affected with SPMS than with RRMS, and other physical aspects of health-related quality of life (HRQoL) are also more impaired in SPMS than in RRMS [9,10]. Bowel [10], bladder [11,12], and sexual dysfunction, as well as fatigue, occur more frequently with SPMS than with RRMS [10,12,13]. Cognitive and memory impairment are more common and are usually more severe in patients with SPMS than in those with RRMS [14-16].

Despite the development of numerous disease-modifying therapies for RRMS, few treatments are approved for SPMS, particularly those that can slow disability progression [17,18]. The paucity of treatments as well as concerns about reimbursement may cause neurologists to be cautious about diagnosing progression to SPMS, and this may also contribute to the wide estimated prevalence ranges [7].

For many reasons it is important that payers and healthcare systems fully understand the economic impact and humanistic burden of SPMS [19]. Humanistic burden, defined as the effect of SPMS on HRQoL, may be examined through consideration of health state utility values (HSUVs). These are important measures of HRQoL because they provide a single weighted value based on patients' preference of different health states that can be compared between disease areas [20,21]. Economic and HRQoL aspects of SPMS are generally less well described than the symptomatic burden of the disease. Accordingly, the aim of the present study was to identify systematically the available evidence of the economic burden and HSUVs associated with multiple sclerosis (MS) and report the burden of SPMS compared with RRMS.

Methods

This systematic review was designed to identify published studies that included information on the economic burden and HSUVs associated with MS and report the incremental burden of SPMS compared with RRMS. Searches were conducted according to a pre-specified protocol and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. The following data sources were interrogated using comprehensive search strings that included a mixture of free text and Medical Subject Heading terms: Embase®, MEDLINE®, MEDLINE® In-Process, the Cochrane Library, and the Health Technology Assessment Database. Finally, Health Technology Assessment websites were searched and reference lists from relevant appraisals were screened (see Supplemental Files 1 and 2).

Supplementary searches of abstracts published between 2017 and 2019 were carried out for annual congresses/meetings of the American Academy of Neurology, European Academy of Neurology, European Committee for Treatment and Research in Multiple Sclerosis, Americas

Committee for Treatment and Research in Multiple Sclerosis, Consortium of Multiple Sclerosis Centers, Association of British Neurologists, and International Society for Pharmacoeconomics and Outcomes Research (US and EU).

Initial searches to identify evidence on the economic burden of MS and on HSUVs were conducted on November 15, 2018 and January 18, 2019, respectively. Additional searches to augment the initial results were conducted on November 22, 2019.

Study selection

Once publications had been identified, they were screened based on their titles and abstracts by one reviewer against predefined eligibility criteria (Table 1). Decisions were then validated by a second reviewer. Publications meeting the eligibility criteria were then obtained as full texts and these were reassessed against the eligibility criteria.

[Table 1 near here]

Data extraction

Relevant data were extracted and checked by an independent reviewer. Where more than one publication describing a single study was identified the data were compiled into a single summary to avoid double counting of patients. All cost data were converted to purchasing power parity adjusted € 2021 using the Campbell and Cochrane Economics Methods Group and Evidence for Policy and Practice Information and Co-ordinating Centre cost converter (version 1.6) [23,24]. No adjustments were made to economic outcomes that were reported as ratios or percentages.

Results

Among 25 publications selected, 18 reported economic data [25-42], and nine reported humanistic data (based on HSUVs) on the burden of SPMS [29,40,43-49]; two provided both economic and humanistic data [29,40]. An overview of the study designs, patient populations, cohort sizes, outcomes, and objectives reported in these publications is given in Supplemental Table S1.

Economic burden of SPMS

In total, 18 publications presented data on costs and health resource use for patients with SPMS (see Supplemental Figure S1 for PRISMA diagram) [25-42]. Of these, nine studies estimated direct and indirect costs separately in RRMS and SPMS [26,27,29,31-35,40], four estimated direct costs only by multiple sclerosis (MS) type [28,36-38], and three provided estimates of total cost (direct and indirect costs combined) [25,30,39] (Tables 2 and 3).

[Tables 2 and 3 near here]

Almost all studies found higher total costs with SPMS than with RRMS. The treatment experience, burden, and unmet needs (TRIBUNE) studies (all 2009 data) reported findings from five European countries (France, Germany, Italy, Spain, and the UK) [31-35]. Overall, the TRIBUNE studies found that total costs associated with SPMS were 1.7–2.2-fold higher than those with RRMS. Among more recent analyses, a study in Ireland by Carney et al. (2015 data) found the total annual costs of SPMS to be about 70% greater than those for RRMS [29], and a study in Finland by Purmonen et al. (2017 data) estimated that total costs in SPMS were approximately twice those in RRMS [40].

In almost all cases where both direct and indirect costs were provided, costs associated with SPMS were greater than those associated with RRMS (Finland [40], France [31], Germany [33], Ireland [29], Italy [34], Spain [32], Sweden [26]). Among studies reporting sufficient data to derive proportional costs, a higher mean total cost for SPMS than for RRMS was observed, and SPMS was associated with greater proportions contributed by direct non-medical and indirect costs compared with RRMS (Figure 1). Of the remaining nine studies [25,27,28,30,35-39], only four (conducted in France [38] and Italy [28,30,39]) estimated higher direct or overall costs associated with RRMS than SPMS.

[Figure 1 near here]

Indirect costs

In the TRIBUNE studies, indirect costs were two (France [31,33]) to nine (Italy [34]) times higher for SPMS than RRMS. The costs of early retirement from work due to MS among patients with SPMS was calculated in the TRIBUNE studies as the mean number of annual working hours across countries enrolled in the Organization for Economic Co-operation and Development multiplied by the gross salary per hour. In general, retirement from work due to MS was associated with a 3–4-fold rise in costs with SPMS compared with RRMS, except in Italy, where the cost increased 10-fold [34]. Carney et al. reported that the increase in costs with SPMS compared with RRMS was largely due to indirect costs such as lost productivity and informal care [29], and Purmonen et al. also found lost productivity to have a large impact on costs [40].

Direct non-medical costs were found to be approximately two (UK [35]) to eight (Italy [34]) times higher with SPMS than with RRMS in the TRIBUNE studies, and Purmonen et al.

reported that direct non-medical costs, such as modifications to the home and informal care, were major cost drivers [40].

Direct costs

Direct medical costs contributed a greater proportion of the total spend in RRMS than in SPMS, largely because of the cost of treatment. Ten studies looked at treatment costs and all found that the cost of drugs (particularly immunomodulatory therapies, such as disease-modifying treatments [DMT]) was higher in patients with RRMS than in those with SPMS [27,28,31-35,37,38,40]. In the French study by Bruno et al., overall monthly costs were slightly higher for patients with RRMS than for those with SPMS; this was attributed largely to medication, which was more than twice the cost in RRMS than in SPMS (2013–2014 data) [38]. In the TRIBUNE studies, drug costs accounted for 36–80% of total costs in patients with RRMS compared with 12–39% in those with SPMS [31-35]. In three of the identified studies from Germany [27], Australia [37], and Italy [28], spending on immunomodulatory drugs was higher for patients with RRMS than for those with SPMS, reaching statistical significance in the studies from Germany and Australia (both $p<.01$) [27,37]. The most recent treatment costs reported (2017 data) were from the Finnish study by Purmonen et al., which determined that immunomodulatory drugs contributed to 23% of healthcare costs in RRMS and only 6% in SPMS [40].

Some other direct costs also appeared to be greater in SPMS than in RRMS. Indeed, Bruno et al. found that hospitalization costs with SPMS were 55% higher, and costs contributing to community care (nurse and physiotherapist consultations, medical devices, and transportation, but not medication costs) and disability benefits were 3–9-fold higher with SPMS than with RRMS [38]. The French arm of the TRIBUNE study found that other direct medical costs

(excluding the cost of MS treatments and investigations) were at least 2–3-fold greater, and inpatient care was over 7-fold greater, in SPMS than in RRMS [31]. Only three studies reported total direct costs to be higher in RRMS than in SPMS [28,38,39].

Cost of progressive MS

Two recent studies were identified that presented statistical comparisons between patients with progressive MS and reference groups in place of numerical cost data [41,42]. In an analysis of two longitudinal, observational studies in Germany by Ness et al., the societal economic impact was significantly greater for patients in the transitional period between RRMS and SPMS (as defined by disability progression independent of relapse activity [PIRA]) than for individuals with no evidence of disease activity (NEDA) [42]. Indeed, total costs, direct medical costs, and indirect costs in patients with PIRA were 26%, 40%, and 23% higher, respectively, than in those with NEDA (all $p<.05$; Figure 2a) [42]. A further study by Blinkenberg et al. reported outcomes from Denmark, with costs of SPMS or RRMS being compared with those of PPMS over a 10-year follow-up period (5 years before or after diagnosis) [41]. Overall, RRMS (7012 patients) was associated with significantly lower total health costs and homecare costs and significantly higher income than PPMS (1099 patients); estimates for SPMS (1542 patients) were closer to those for PPMS for all outcomes (Figure 2b) [41].

[Figure 2 near here]

HSUVs in patients with SPMS

In total, nine studies were identified that reported HSUVs in patients with SPMS (Table 4 and Supplemental Figure 2 [PRISMA diagram]) [29,40,43-49]. These studies derived HSUVs based

on responses to patient questionnaires encompassing the single-level or three-level version of the EuroQoL five-dimension instrument (EQ-5D, EQ-5D-3L), or from the 36-item (six-dimension) Short-Form Health Survey (SF-6D). Responses were converted to a value between 0 and 1, with 1 representing full health and 0 considered equivalent to death; negative values represent a heath state considered worse than being dead [44].

[Table 4 near here]

In the nine studies, the disease burden was consistently observed to be greater (indicated by lower HSUV scores or a negative regression coefficient vs RRMS) for patients with SPMS than for those with RRMS (Table 4). Two studies also reported HSUVs for patients with SPMS stratified by Expanded Disability Status Scale (EDSS) score states [40,44]. When mean HSUV scores were assessed using the EQ-5D-3L in patients with SPMS, they decreased from 0.481 at EDSS score 6 to 0.397 and 0.021 at EDSS scores 7 and 8, respectively [44]. Similar results were obtained using the SF-6D: mean HSUV scores decreased from 0.569 at EDSS score 6 to 0.517 at EDSS score 7 [44]. This reduction in HSUVs with increasing disability was also observed in the study by Purmonen et al., ranging from 0.688 (EDSS scores 0–3) to 0.315 (EDSS scores 7–9) [40].

Four of the studies identified also presented further information regarding the key drivers of the observed reduction in HRQoL [40,46,47,49]. Across these studies, fatigue was the most commonly reported symptom contributing to reduced HRQoL in patients with MS. An extensive comparison of fatigue prevalence and impact between patients with progressive MS and those with non-progressive MS was undertaken by Rooney et al. (UK, USA and Australia) [47]. The prevalence and severity of fatigue were significantly greater for patients with progressive MS

than for those with non-progressive MS. Progressive MS was also associated with a greater physical and psychological impact of fatigue in addition to a higher depression and physical impact of MS compared with non-progressive MS [47]. Similar results were found in the study by Purmonen et al. (Finland); individuals with SPMS consistently reported a greater physical and psychological burden than those with RRMS [40]. Furthermore, in patients with a relatively low level of disability (EDSS score 0–3), a higher proportion of those with SPMS than RRMS reported fatigue (80.8% vs 48.6%) [40].

Discussion

It is necessary to understand the economic and humanistic burden of SPMS in order to carry out an accurate evaluation of the cost-effectiveness of future treatments. Our systematic review found SPMS to be associated with a high economic burden, which is greater than that for RRMS. Higher costs for SPMS than for RRMS were particularly apparent for inpatient and outpatient care, professional and informal care, and retirement owing to MS. SPMS was also associated with a high humanistic burden, indicated by lower HSUVs than RRMS.

Overall, the studies identified consistently found that costs (both direct and indirect) for SPMS were higher than those for RRMS; however, it should be noted that there was a degree in variation between studies in the components included in direct and indirect costs. Major drivers of direct costs included costs of hospitalization and the cost of care. Major drivers of indirect costs included retirement owing to MS. These costs may be higher because patients with SPMS have greater levels of disability than those with RRMS [10]. High EDSS scores have been shown to be associated with greater mean overall costs per patient and a shift toward an increased use of health services [50]. The reasons for the differences in retirement due to MS between European

countries was unclear, with factors such as retirement age, life-expectancy and disability benefits all potentially playing a role. In addition, the methods used to estimate the cost of productivity lost from early retirement in the TRIBUNE study were not specific to the country for which the data were obtained and so there may be a degree of uncertainty in this evidence.

Only two studies found comparable overall costs for SPMS and RRMS [28,39]. However, for the study in which cost components were reported and were consistent with those from other investigations, the cost of hospitalization for reasons other than MS was higher in SPMS than in RRMS [28]. Furthermore, the greatest difference in cost between SPMS and RRMS was for immunomodulatory drugs; such costs were significantly higher in RRMS [28]. This finding was consistent with that of several other studies identified by the systematic review that reported higher costs of immunomodulatory drugs for RRMS than SPMS. The reason for this is likely to be the relative lack of approved, effective treatments for SPMS compared with RRMS.

The economic burden of SPMS reported across studies may be an underestimate owing to the challenges of definitive diagnosis in this group of patients [51]. Uncertainty surrounding diagnosis may also contribute to the small sample sizes of patients with SPMS seen in the majority of studies and the observation that a number of studies not included here reported costs for MS as a whole.

The studies identified in this review specifically highlighted the fact that that patients with SPMS reported lower HSUVs than those with RRMS. This is likely to be because of the higher symptomatic burden and greater levels of disability in SPMS than in RRMS. These findings are consistent with those from other investigations of HRQoL, which show that patients

with SPMS have a significantly worse HRQoL, which declines at a faster rate, than individuals with RRMS [25,45].

Across a number of the studies identified as part of this review, fatigue appears to be a major driver of observed HRQoL reductions [40,46,47,49]. This observation is in agreement with results of an extensive analysis of the humanistic and economic burden of MS in Europe, in which cognitive decline and fatigue were the most common drivers of HRQoL decrements and reductions in work productivity [50]. These are notable findings given that EuroQoL instruments are commonly used to derive HSUVs for cost-effectiveness analyses; however, confounders for the self-reporting of cognitive impairments including fatigue [52] and depression [53] have been reported. These issues may in turn lead to factors that have a fundamental impact on the HRQoL of patients with MS not being adequately captured and the value of new therapies being underestimated [54].

Evidence gaps

The studies identified during this systematic review highlight important evidence gaps and areas in which future analyses are warranted. In particular, there was a relative lack of relevant evidence generated outside Europe, including from the USA. In addition, a large proportion of the data discussed were from the TRIBUNE study, which provided cost data from 2009. Many DMTs for RRMS and one DMT for active SPMS have become available since 2009 and the cost of these treatments would not have been captured by this study.

Only one study reporting economic outcomes and one providing HSUVs for patients with SPMS were conducted outside Europe (Australia and Brazil, respectively) [37,48]. Furthermore, robust studies reporting information about cost drivers in addition to overall cost data were typically

older, being based on data from before 2010. Studies giving HSUVs for patients with SPMS also highlighted key drivers of reduced HRQoL (e.g. fatigue and depression), which may not be adequately captured by self-reported assessments. These findings suggest that assessments of outcomes that drive HRQoL in SPMS would be useful to enable full investigation of the value of new therapeutic options. Finally, while the trends were consistent in terms of differences between SPMS and RRMS, some of the variation observed may have been due to differences in the definitions of study populations and outcomes used. Potential differences in MS subtype definitions might be alleviated by conducting analyses in patient groups defined by clinical characteristics, as in the study by Ness et al. (Germany) [42].

Conclusions

This review found that SPMS is associated with a substantially higher economic and humanistic burden than RRMS. There is some evidence that major cost drivers shift following the transition from RRMS to SPMS, with higher direct medical costs being associated with RRMS than with SPMS, while the opposite is true for direct non-medical costs and indirect costs. This shift is most likely driven by the increasing symptomatic burden observed in patients with SPMS, which leads to a gradual and constant decrease in HRQoL compared with individuals with RRMS.

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Tables

Table 1. Eligibility criteria.

	Economic SLR	HSUV SLR
Population	Adults with MS[a]	
Study design	Any study reporting cost and HRU data	Any studies reporting HSUVs[b]
Language	English	
Search timeframe	Database inception to present	
Country	No restriction on country	
Other specific exclusion criteria	• Studies evaluating impact of any treatment/disease management program on cost/HRU, medical utilization/treatment pattern only and associated cost, DMT price evaluation studies, and out-of-pocket expenditures only • Studies aiming to compare the cost/HRU among different types of disease cohorts, i.e. treatment types, insurance types, comorbidity yes vs. no, adherent vs. non-adherent etc.[c] • Studies evaluating specific cohort of MS patients i.e. patients with any comorbidity • Conference abstracts published in 2016 and before	• Studies assessing impact of other variables (e.g. disease symptoms, medication adherence, employment status, education level) on HRQoL • Studies assessing cognitive/symptom burden • Psychometric studies of different patient reported outcomes • Conference abstracts published in 2016 and before

[a]The systematic review included all studies reporting cost, HRU and HSUV data for patients with MS; this publication only includes studies reporting data for patients with SPMS.

[b]The protocol specified that HRQoL and HSUV studies will be included, but owing to a high number of included studies after second screening, only studies reporting HSUVs were included in the SLR.

[c]Studies comparing patient specific characteristics including gender, race and disease severity were included.

Abbreviations: DMT, Disease-modifying treatment; HRQoL; health-related quality of life; HSUV, health state utility value; HRU, health resource use; MS, multiple sclerosis; SLR, systematic literature review; SPMS, secondary–progressive multiple sclerosis.

Table 2. Studies reporting annual total and cost breakdown summaries in SPMS and RRMS.

Reference	Country	Year of cost data	Methodology of cost derivation	Costs included in analysis	Costs for SPMS, per patient per year[a] (€)	Costs for RRMS, per patient per year[a] (€)
Carney et al.[29]	Ireland	2015	Estimated based on resources given by a sample of patients with MS and extrapolated to national level	**Direct** (measured via CSRI)[b]	18,714	16,089
				Indirect (including productivity losses and informal care)[c]	40,480	20,874
				Total	76,182	44,013
Johansson et al.[31]	France	2009	Healthcare and non-medical resources, as well as productivity losses, were annualized[d]	**Direct medical** (including inpatient and outpatient care, consultations, investigations and medications)	23,426	16,256
				Direct non-medical (including investments/modifications, professional care, informal care)	6188	1640
				Indirect (including sick leave and retirement due to MS)	4831	2817
				Total	34,445	20,712
Karampampa et al.[32]	Spain	2009	Healthcare and non-medical resources, as well as productivity losses, were annualized[e]	**Direct medical** (including inpatient and outpatient care, consultations, investigations and medications)	22,217	16856
				Direct non-medical (including investments/modifications, professional care, informal care)	20,198	3782
				Indirect (including sick leave and retirement due to MS)	17,752	6677
				Total	60,168	27,316
Karampampa et al.[33]	Germany	2009	Healthcare and non-medical resources, as well as productivity losses, were annualized[d]	**Direct medical** (including inpatient and outpatient care, consultations, investigations and medications)	26,437	21,620

				Direct non-medical (including investments/modifications, professional care, informal care)	16,434	3671
				Indirect (including sick leave and retirement due to MS)	11,790	5416
				Total	54,661	30,708
Karampampa et al.[34]	Italy	2009	Healthcare and non-medical resources, as well as productivity losses, were annualized[d]	**Direct medical** (including inpatient and outpatient care, consultations, investigations and medications)	43,448	25,866
				Direct non-medical (including investments/modifications, professional care, informal care)	8949	1075
				Indirect (including sick leave and retirement due to MS)	8455	914
				Total	60,854	27,856
Karampampa et al.[35]	UK	2009	Healthcare and non-medical resources, as well as productivity losses, were annualized[d]	**Direct medical** (including inpatient and outpatient care, consultations, investigations and medications)	8069	12,109
				Direct non-medical (including investments/modifications, professional care, informal care)	20,276	9007
				Indirect (including sick leave and retirement due to MS)	18,640	6346
				Total	46,986	27,462
Purmonen et al.[40]	Finland	2017	MS-related cost and resource use and need for additional resources were surveyed and valued to the year 2017 using official indices from Finland	**Direct** (including inpatient and outpatient, rehabilitation, other professional services, tests and medicine costs)	14,521	13,066
				Direct non-medical (including informal costs and home modifications)	25,198	6593
				Productivity (including	36,310	19,320

	sick leave, reduced income and early retirement)		
	Total mean annual	76,030	38,980

[a]Annual cost unless stated otherwise. All costs converted to € and inflated to 2021 values using the Campbell and Cochrane Economics Methods Group and Evidence for Policy and Practice Information and Co-ordinating Centre cost converter [23,24].

[b]Information on direct resource utilization was collected through questions based on the Client Service Receipt Inventory (CSRI), and adapted to the study setting. The CSRI is a research instrument applied for the collection of information on costs [29].

[c]Productivity losses covered early retirement due to MS, absenteeism, reduced working hours and presenteeism. Informal care covers hours of care, and whether the caregiver had officially reduced their working week or given up their own job in order to provide care [24].

[d]It was assumed that the recall period of each resource is representative of similar recall periods throughout the year, then multiplied by the relevant unit cost. Unit costs were derived from country-specific price lists or from published literature and were inflated to 2009 prices using harmonized price indices reported by EUROSTAT [31,33-35].

[e]It was assumed that the recall period of investment and the cost per hour of professional help that were reported in the most recent cost-of-illness study in Spain were used. Unit costs were derived from country-specific price lists or from published literature and were inflated to 2009 prices using harmonized price indices reported by EUROSTAT [32].

Abbreviations. MS, multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table 3. Studies reporting other economic outcomes for SPMS and RRMS

Reference	Country	Year of cost data	Costs included in analysis	Costs for SPMS, per patient per year[a] (€)	Costs for RRMS, per patient per year[a] (€)
Amato et al.[30]	Italy	1996	**Direct** (hospital admissions, medical visits, nurse interventions tests and investigations, physical therapy, medicines, technical aids and travel) **Indirect** (patients and caregivers' time off work and informal care)	11,849	5642
Bruno et al.[38]	France	2013–2014	**Direct** (inpatient and outpatient care, including long term condition cover, low income cover, practitioner visits, medical acts, medicines, healthcare provider costs, transportation, daily and disability allowances and hospital resources)	1046 (monthly average)[b]	1149 (monthly average)[b]
Fogarty et al.[36]	Ireland	2012	**Annual direct** (inpatient and outpatient care, rehabilitations, nursing home care, primary healthcare and respite, investigations and medications, mobility and living aids, investments and home adaptations and professional home help)	30,311	12,473
Gyllensten et al.[26]	Sweden	2006–2013	**Direct taken at year of diagnosis[c]** (including medicine cost and inpatient and outpatient healthcare)	11,753	10,369
			Indirect taken at year of diagnosis[c] (including loss of productivity and disability pension)	9479	7378
McCrone et al.[25]	UK	2006–2007	**Total mean including indirect** (including tests and investigations, aids and adaptations to home, informal care, medicines, lost employment costs including retirement as a consequence of illness, days off work or reduced hours)	21,083	13,390
Moccia et al.[39]	Italy	2017	**Total annualized** (healthcare services including DMTs, general hospital costs, neurological visits and special consultations, tests and investigations)	13,610	15,495
Patti et al.[28]	Italy	2004	**Overall per MS classification** (including hospitalisation,	17,656	20,025

			consultations, immunomodulatory drugs, steroids, immunosuppressant drugs, other medicines, and tests and investigations)		
			Extrapolated annual direct (per MS classification, disease course, and EDSS score)	21,472	23,755
Reese et al.[27]	Germany	2009	**Indirect** (including premature retirement, disablement, unemployment or sick leave)	8506 (3 monthly cost)[d]	4375 (3 monthly cost)[d]
			Drug (including medication, inpatient and outpatient care, non-medical treatment and medical aids.)	3317 (3 monthly cost)[d]	4982 (3 monthly cost)[d]
			Total	14,582 (3 monthly cost)[d]	11,544 (3 monthly cost)[d]
Taylor et al.[37]	Australia	2002[e]	**Overall direct** (including hospitalization, consultations, medicines, testing and transport)	13,126 (6 monthly cost)[f]	8547 (6 monthly cost)[f]
			Annual direct per patient	22,904	15,976

[a]Annual cost unless stated otherwise. All costs converted to € and inflated to 2021 values using the Campbell and Cochrane Economics Methods Group and Evidence for Policy and Practice Information and Co-ordinating Centre cost converter [23,24].

[b] Patients were derived from a regional MS registry (Registre Lorrain des Scléroses En Plaques). On average, patients were documented every 6 months during routine visits.

[c]Costs converted using Swedish krona 2013 value.

[d]As reported in publication.

[e]Year for costs is not reported; enrollment concluded in 2002.

[f]Patients were recruited on presentation to a MS clinical of the Royal Hobart Hospital, and the study population was considered representative of a cross-section of the MS population in the area. Data were collected retrospectively over a 6-month period for all factors except for hospitalization, which was collected over 12 months, then halved to give a more accurate average cost over 6 months.

Abbreviations. DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RRMS, relapsing–remitting MS; SPMS, secondary progressive MS.

Table 4. Studies reporting HSUV data in SPMS and RRMS.

Reference	Country	SPMS definition	HSUV outcomes	
			SPMS	RRMS
Carney et al.[29]	Ireland	MS type reported by patient	EQ-5D: 0.338	EQ-5D: 0.673
Eriksson et al.[55]	Western Europe[a]	MS type reported by patient[50]	SPMS regression coefficient (95% CI) vs RRMS: UK −0.01 (−0.022 to 0.001); *p*=.069 Sweden −0.007 (−0.012 to −0.003); *p*=.0009 France −0.019 (−0.029 to −0.008); *p*=.0004	
Hawton & Green [44]	UK	MS type reported by patient with guidance in questionnaire	EQ-5D-3L: 0.421 ± 0.334 SF-6D: 0.570 ± 0.100	EQ-5D-3L: 0.623 ± 0.294 SF-6D: 0.657 ± 0.128
Orme et al.[45]	UK	MS type reported by patient with guidance in questionnaire	SPMS regression coefficient (95% CI): −0.045 (−0.076 to −0.014); *p*=.005	
Purmonen et al.[40]	Finland	According to Lublin et al.[1]	EQ-5D: 0.52	EQ-5D: 0.76
Reese et al.[27]	Germany	MS type recorded by physician	EQ-5D: 0.64 ± 2.78	EQ-5D: 0.83 ± 0.18
Rooney et al.[47]	UK, USA, Australia	MS type reported by patient	$EQ\text{-}5D_{index}$: 0.33 ± 0.36[b]	$EQ\text{-}5D_{index}$: 0.58 ± 0.30[b]
Takemoto et al.[48]	Brazil	MS type reported by patient during interview	EQ-5D-3L: Brazil, 0.440 ± 0.21 UK, 0.380 ± 0.33[c]	EQ-5D-3L: Brazil, 0.635 (0.21) UK, 0.606 ± 0.30[c]
Tinelli et al.[49]	International	NR	EQ-5D, mean: 0.510	EQ-5D, mean: 0.620

Data are mean (± standard deviation) unless stated otherwise.

[a]Austria, Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, the Netherlands, Poland, Portugal, Russia, Spain, Sweden, Switzerland, and the UK.

[b]Data quoted for SPMS are from a mixed progressive MS (SPMS and PPMS; *n* = 105) population; data quoted for RRMS are from a mixed non-progressive MS (benign, RRMS, unknown type; *n* = 270) population.

[c]UK values derived from Brazilian data using UK value set [48,56].

Abbreviations. CI, confidence interval; EQ-5D, five-dimension EuroQoL instrument; EQ-5D-3L, three-level EQ-5D; EQ-$5D_{index}$, health index based on EQ-5D-3L; HSUV, health state utility value; MS, multiple sclerosis; NR, not reported; PPMS, primary progressive MS; RRMS, relapsing–remitting MS; SF-6D, six-dimension Short-Form Health Survey; SPMS, secondary progressive MS.

Figures

Figure 1

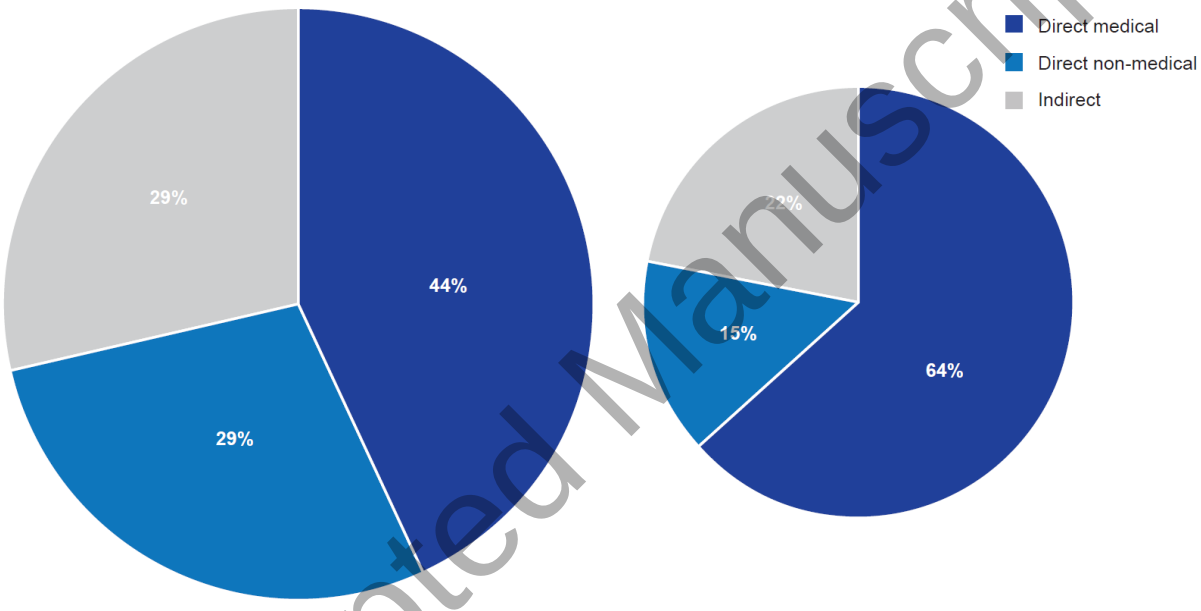


Figure 2

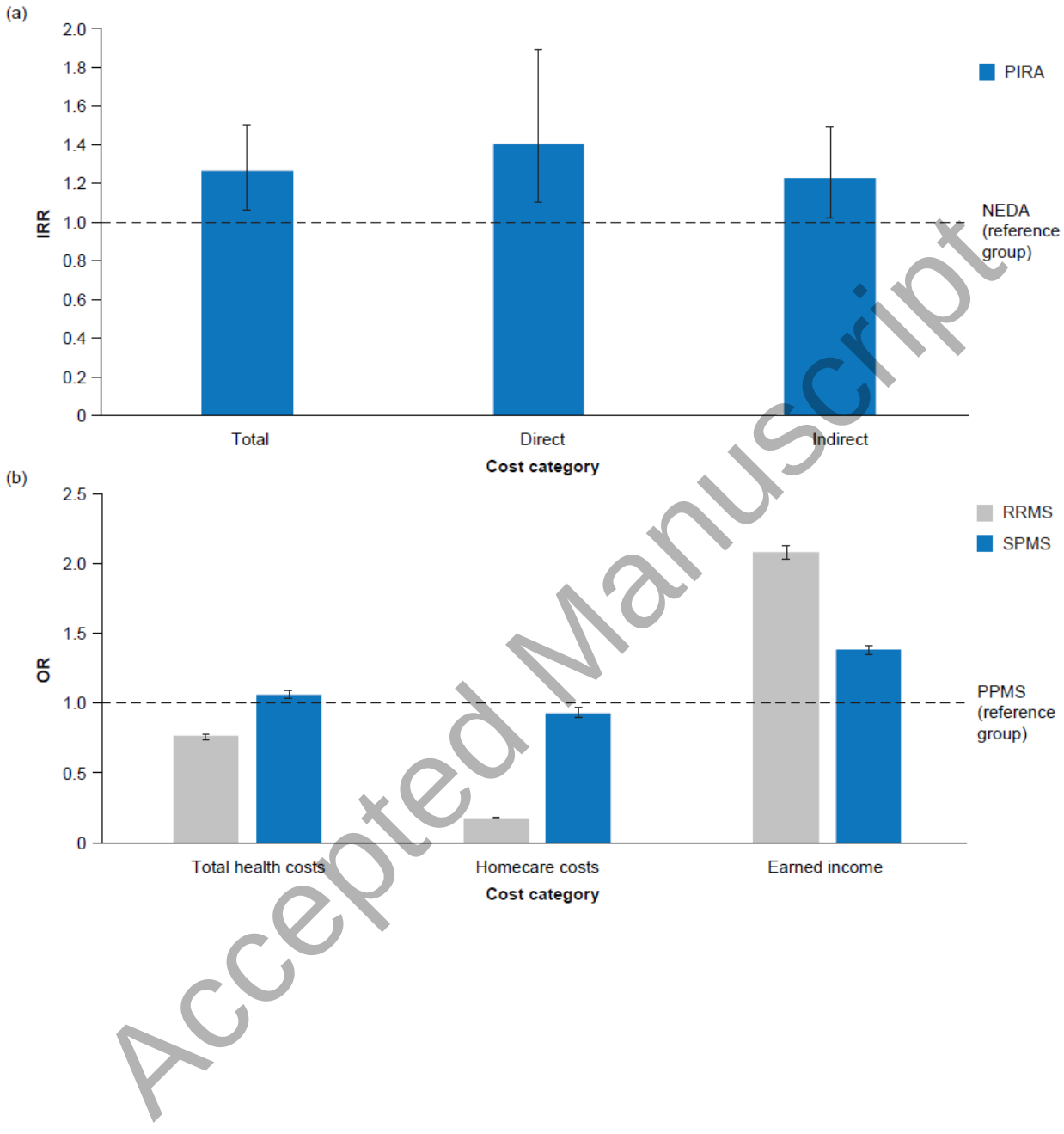


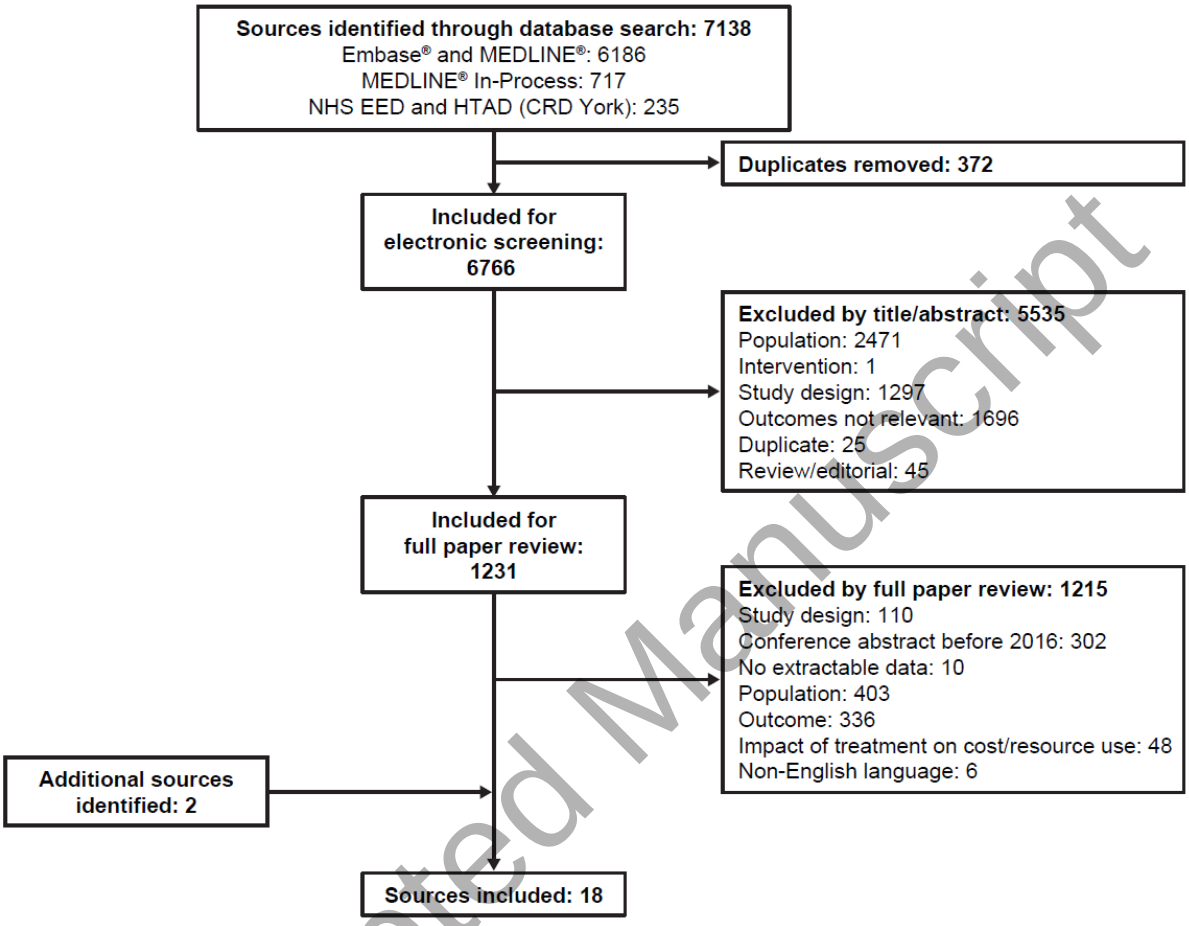
Figure captions

Figure 1. Mean total costsa and cost category proportions (of total costs) associated with SPMS and RRMS [29,31-35,40]. aDifference in mean total costs represented by the area of the circles and values do not sum to 100% as a result of rounding. Abbreviations. RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Figure 2. Relative cost outcomes reported by (a) Ness et al. [42] and (b) Blinkenberg et al. [41]. (a) IRR of costs associated with patients who displayed PIRA as determined by roving Expanded Disability Status Scale score analysis with confirmation over at least 6 months (bars) relative to a reference group of patients displaying NEDA (dashed line). (b) OR of costs associated with patients with RRMS (gray bars) or SPMS (orange bars) versus a reference group of patients with PPMS (dashed line). Error bars represent 95% confidence intervals. Abbreviations. IRR, incidence rate ratio; NEDA, no evidence of disease activity; OR, odds ratio; PIRA, disability progression independent of relapse activity; PPMS, primary progressive multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

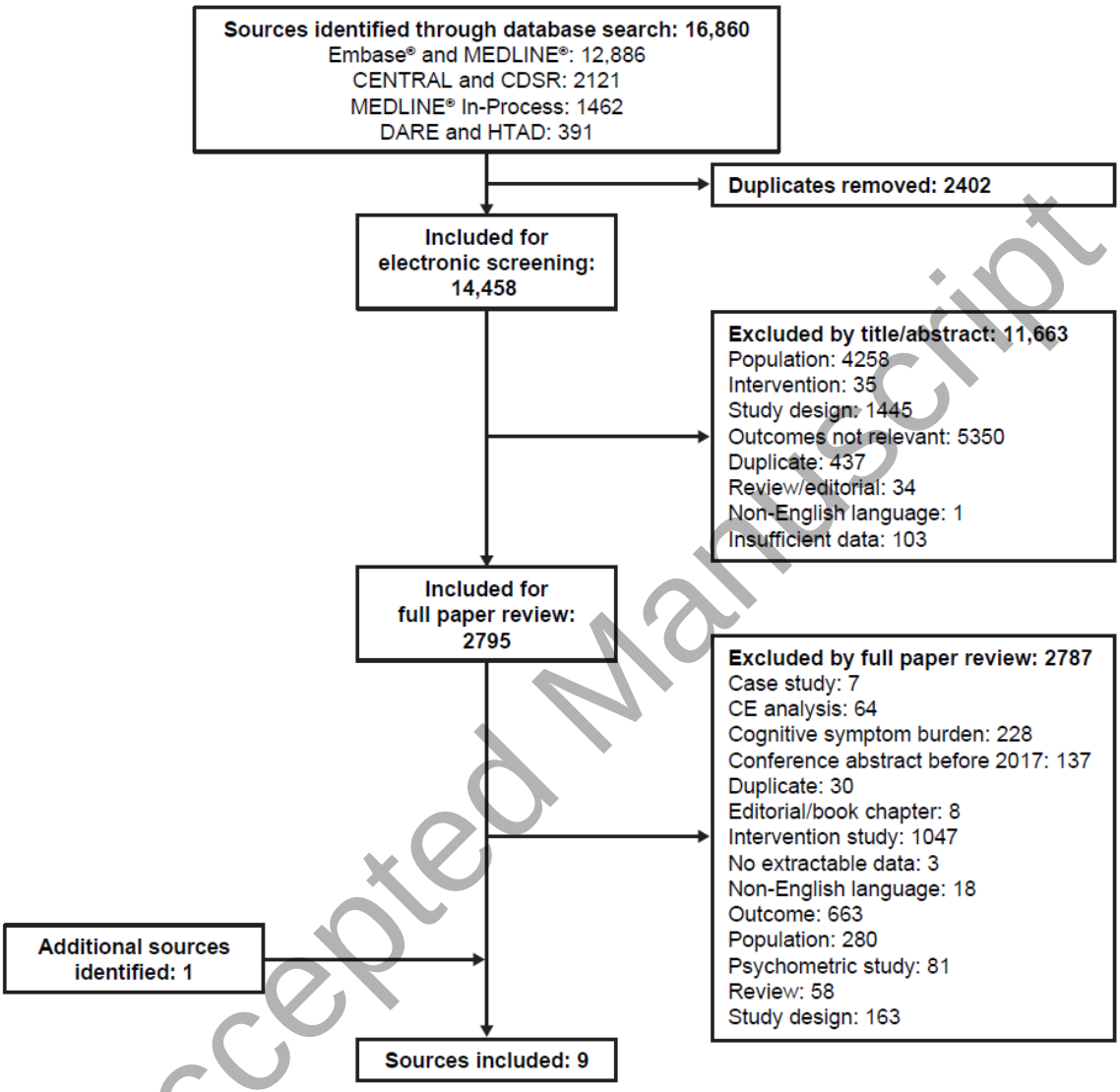
Supplemental information

Supplemental Figure S1. Flow of articles through the systematic review process for economic studies.



Abbreviations. CRD, Centre for Reviews and Dissemination; Embase®, Excerpta Medica Database; HTAD, Health Technology Assessment Database; MEDLINE®, Medical Literature Analysis and Retrieval System Online; NHS EED, National Health Service Economic Evaluation Database.

Supplemental Figure S2. Flow of articles through the systematic review process for health state utility values studies.



Abbreviations. CDSR, Cochrane Database of Systematic Reviews; CE, cost-effectiveness; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; Embase®, Excerpta Medica Database; HTAD, Health Technology Assessment Database; MEDLINE®, Medical Literature Analysis and Retrieval System Online.

Supplemental Table S1. Summary of studies systematically identified for inclusion in the review.

Reference	Country; study design; population; comparator	Cohort size	Outcomes reported	Objective
Amato et al. [30]	Italy; questionnaire and weekly expense diary for 3 months; outpatients at 44 centers; N/A	*N* = 515 RRMS, *n* = 264 SPMS, *n* = 198 PPMS, *n* = 53	Sociodemographic EDSS	Estimate socioeconomic impact of MS
Blinkenberg et al. [41]	Denmark; retrospective registry analysis (1998–2015); costs calculated each year in 5-year period before and after patient index diagnosis date	*N* = 9563 RRMS, *n* = 7012 SPMS, *n* = 1452 PPMS, *n* = 1099	Economic outcomes	Assess whether global measures of socioeconomic burden of PPMS and SPMS are increased compared with RRMS
Bruno et al. [38]	France; retrospective registry and claims analysis; outpatients aged >18 years in ReLSEP 2013–2014; N/A	*N* = 4373 CIS, *n* = 171 RRMS, *n* = 1110 rSPMS, *n* = 373 nrSPMS, *n* = 226 PPMS, *n* = 289 Excluded, *n* = 2207	Sociodemographic EDSS Disease history	Estimate direct healthcare costs of MS in France and identify risk factors of high costs
Carney et al. [29]	Ireland; retrospective, cross-sectional internet-based survey during 1 month in 2015; patients registered with MS Ireland (MS type self-reported); N/A	*N* = 594 Benign, *n* = 13 CIS, *n* = 7 RRMS, *n* = 374 SPMS, *n* = 97 PPMS, *n* = 66 Not known, *n* = 37	Sociodemographic Client Service Receipt Inventory EDSS severity Disease history EQ-5D-5L (*n* = 542)	Estimate societal costs of MS in Ireland and variation in cost by disease type and severity
Eriksson et al. [43]	Western Europe[a]; cross-sectional, observational, internet/postal questionnaire over 15 months until April 2016; patients aged ≥18 years with MS identified by national MS societies;[50] N/A	*N* = 16,808 RRMS, *n* = 8148 SPMS, *n* = 4280 PPMS, *n* = 3133 Not reported, *n* = 1247	Sociodemographic Disease history Patient-rated EDSS Fatigue Cognitive impairment EQ-5D-3L	Study the relationship of disability, fatigue, cognitive difficulties to EQ-5D domains, and utility with different Western European value sets
Fogarty et al. [36]	Ireland; questionnaire-based interview; outpatients with a confirmed MS diagnosis at a single center in Dublin,	*N* = 214 Benign, *n* = 4 RRMS, *n* = 113	Sociodemographic Client Service Receipt Inventory EDSS	Investigate the economic consequences of increasing MS disability from the perspectives of

	September 2011–February 2012	SPMS, *n* = 72 PPMS, *n* = 25	Disease history EQ-5D	the Irish healthcare payer, patients, and society
Gyllensten et al. [26]	Sweden; retrospective registry analysis; patients aged 21–64 years newly registered in SMSreg during 2006–2013; N/A	*N* = 15,449 RRMS, *n* = 3528[b] SPMS, *n* = 847[b] PPMS, *n* = 252 Excluded, *n* = 10,973	Sociodemographic EQ-5D	Explore progression of annual direct and indirect costs and HRQoL among people with MS of working age
Hawton & Green [44]	UK; SWIMS study: longitudinal, prospective, questionnaire-based cohort study; patients with MS aged ≥18 years returning questionnaires by October 2012; N/A	*N* = 1441 Benign, *n* = 45 RRMS, *n* = 572 SPMS, *n* = 231 PPMS, *n* = 264 Combination or not known, *n* = 251 NR, *n* = 78	Demographic Disease history EDSS EQ-5D-3L SF-6D	Estimate HSUVs for MS by demographic and clinical characteristics, including disease severity and relapses
Johansson et al. [31]	France; TRIBUNE:[57] cross-sectional, retrospective burden-of-illness survey; patients aged ≥18 years with clinically definite MS at treatment centers in the study nations; N/A	*N* = 248 RRMS, *n* = 138 SPMS, *n* = 48 PPMS, *n* = 24 Unknown, *n* = 38	Sociodemographic Disease history Patient-rated EDSS[c]	Update cost information and examine the impact of relapses and disease severity on direct medical costs, informal care, and productivity losses in France
Karampampa et al. [32]	Spain; TRIBUNE[57] (see above)	*N* = 324 RRMS, *n* = 238 SPMS, *n* = 42 PPMS, *n* = 13 Unknown, *n* = 31	Sociodemographic Disease history Patient-rated EDSS[c]	Measure the economic burden of MS in Spain and the impact of MS on direct healthcare and non-medical costs, and productivity losses
Karampampa et al. [33]	Germany; TRIBUNE[57] (see above)	*N* = 244 RRMS, *n* = 158 SPMS, *n* = 32 PPMS, *n* = 20 Unknown, *n* = 34	Sociodemographic Disease history Patient-rated EDSS[c]	Estimate the economic burden of MS in Germany and the impact of MS on direct healthcare costs, informal care, and productivity losses
Karampampa et al. [34]	Italy; TRIBUNE[57] (see above)	*N* = 251 RRMS, *n* = 186 SPMS, *n* = 18 PPMS, *n* = 11 Unknown, *n* = 36	Sociodemographic Disease history Patient-rated EDSS[c]	Measure the socioeconomic burden of MS in Italy, focusing on the costs of relapses and disease severity
Karampampa et al. [35]	UK; TRIBUNE[57] (see above)	*N* = 194	Sociodemographic	Measure the economic

		RRMS, *n* = 140 SPMS, *n* = 33 PPMS, *n* = 11 Unknown, *n* = 10	Disease history Patient-rated EDSS[c]	burden of MS in the UK and the impact of MS on direct medical costs, informal care, and productivity losses
McCrone et al. [25]	UK; cross-sectional study by questionnaire; patients from the MS Society of Great Britain and Northern Ireland (no age restriction); N/A	*N* = 1942 RRMS, *n* = 651 SPMS, *n* = 618 PPMS, *n* = 358 Other, *n* = 12	Sociodemographic Client Service Receipt Inventory EQ-5D GNDS	Investigate links between service use, costs, HRQoL, and disability
Moccia et al. [39]	Italy; retrospective analysis of prospective observational medical and claims data; patients aged ≥18 years diagnosed with MS attending the same one of two MS centers during 2015–2017; N/A	*N* = 277 RRMS, *n* = 230 SPMS, *n* = 33 PPMS, *n* = 14	Demographic Disease history EDSS	Evaluate differences in healthcare resource utilization and costs between two MS centers, representing a centralized or local-service healthcare model, and associations between costs and MS clinical features
Ness et al. [42]	Germany; pooled analysis based on two longitudinal observational multicenter studies	*N* = 1305 Comparison data presented for patients characterized as PIRA vs those with NEDA (patient numbers not stated)	Socioeconomic	Quantify the impact of PIRA on societal economic burden in patients with MS relative to individuals with stable disease
Orme et al. [45]	UK: cross-sectional postal survey-based study	*N* = 2048 RRMS, *n* = 727 SPMS, *n* = 762 PPMS, *n* = 559	Sociodemographic Disease history APDDS EDSS EQ-5D	Estimate the disutility of disease progression in MS and quantify disutility associated with acute relapses
Patti et al. [28]	Italy; retrospective study based on a neurological questionnaire; patients aged ≥18 years in hospitals and outpatient clinics ≥1 year since diagnosis; N/A	*N* = 510 RRMS, *n* = 293 SPMS, *n* = 139 PPMS, *n* = 63 Missing, *n* = 15	EDSS, health status Previous 3 months: consultations, steroid use; non-MS drugs, non-pharmacological therapy, laboratory, or radiological tests Previous 12 months: hospitalization, MS-related drugs/DMTs	Estimate direct costs of MS in the national health system
Purmonen et al. [40]	Finland; retrospective, cross-sectional mail survey; random sample of patients from the	*N* = 498 RRMS, *n* = 244	Sociodemographic Disease history	Building on the DEFENSE study,[58] to quantify further how MS

	Finnish Neuro Society (national MS patient association) aged ≥18 years in 2015; N/A	SPMS, *n* = 160 PPMS, *n* = 94	EDSS EQ-5D-VAS MSIS-29 FSS	types differ in respect of costs and HRQoL
Reese et al. [27]	Germany; 3-month cost-sample period and questionnaire or interview; patients with clinically definite MS at an outpatient clinic (no age restriction stipulated); N/A	*N* = 144 RRMS, *n* = 97 SPMS, *n* = 39 PPMS, *n* = 8	Socioeconomic EDSS MSFC BDI MFIS EuroQoL FAMS	Estimate costs of MS according to severity of disease and clinical symptoms
Reese et al. [46]	Germany: 12-month prospective analysis of patient and physician case-report forms at an MS center; a sample of patients with MS admitted during October–December 2007; N/A	*N* = 137 RRMS, *n* = 92 SPMS, *n* = 38 PPMS, *n* = 7	Sociodemographic Clinical status EDSS MSFC EQ-5D FAMS MFIS BDI	Explore systematically factors associated with MS and their contribution to decreases in patient-reported health status
Rooney et al. [47]	UK, USA, Australia; 1-month cross-sectional, open-access, online survey in 2018; patients with MS, aged ≥18 years; N/A	*N* = 412[d] Benign, *n* = 2 RRMS, *n* = 291 SPMS, *n* = 74 PPMS, *n* = 37 Unknown, *n* = 8	Demographic Disease history PDDS	Estimate the prevalence of self-reported fatigue in MS, evaluate the relationship between fatigue severity and impact and clinical features of MS, and compare the prevalence of fatigue and these relationships in progressive and non-progressive MS
Taylor et al. [37]	Australia; data from a questionnaire were collected retrospectively over 6 months or 12 months for hospitalization; sequential patients with clinically definite MS from a single center	*N* = 100 RRMS, *n* = 61 SPMS, *n* = 27 PPMS, *n* = 8 Other, *n* = 4	Sociodemographic characteristics, health status, concomitant health conditions, disease course and severity, hospitalizations, resource consumption, medical resource consumption, adaptations and services, social impact	Provide information about direct and indirect costs of MS in Australia
Takemoto et al. [48]	Brazil; cross-sectional, multicenter study based on structured interviews in eight	*N* = 210 RRMS, *n* = 166	Sociodemographic Clinical status	Compare utility scores from Brazilian and British value sets and

	centers specializing in MS diagnosis and treatment, between November 2011 and May 2012; outpatients with MS aged ≥18 years; N/A	SPMS, *n* = 44	Disease history EDSS EQ-5D-3L MFIS	determine the roles of MS disability, fatigue, and patients' sociodemographic and clinical MS characteristics on utility scores reported by Brazilians
Tinelli et al.[49]	International[e]; IMPrESS: observational study based on online surveys; patients recruited through national and international MS organizations and centers; N/A	*N* = 856 RRMS, *n* = 542 SPMS, *n* = 110 PPMS, *n* = 61 Unknown, *n* = 113 NR, *n* = 30	Sociodemographic Clinical characteristics Disease history EQ-5D-5L Barthel severity score	Produce new international evidence on the socioeconomic burden and HRQoL of people affected by MS

[a]Austria, Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, the Netherlands, Poland, Portugal, Russia, Spain, Sweden, Switzerland, the UK.

[b]Among the patients with RRMS, 109 converted to SPMS on study and were counted in both groups.

[c]The patient-rated EDSS score ranged from 0 to 9, with lower scores corresponding to lower levels of disability.

[d]Patients were grouped for analysis as progressive (SPMS and PPMS; *N* = 111) or non-progressive (benign, RRMS, unknown type; *N* = 301).

[e]Responses were from 34 nations; most were from Australia, Croatia, France, Greece, Italy, Poland, Romania, Serbia, Slovenia, Spain, the UK, and the USA.

Abbreviations. APDDS, Adapted Patient Determined Disease Steps; BDI, Beck Depression Inventory; CIS, clinically isolated syndrome; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; EQ-5D, five-dimension EuroQoL instrument; EQ-5D-3L, three-level EQ-5D; EQ-5D-5L, five-level EQ-5D; FAMS, Functional Assessment in MS; FSS, Fatigue Severity Scale; GNDS, Guy's Neurological Disability Scale; HRQoL, health-related quality of life; HSUV, health state utility value; IMPrESS, International MultiPlE Sclerosis Study; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; MSFC, MS Functional Composite; MSIS-29, 29-item MS Impact Scale; N/A, not applicable; NEDA, no evidence of disease activity; NR, not reported; nrSPMS, non-relapsing secondary progressive MS; PDDS, Patient Determined Disease Steps scale; PIRA, disability progression independent of relapse activity; PPMS, primary progressive MS; ReLSEP, Registre Lorrain des Scléroses en Plaques; RRMS, relapsing–remitting MS; rSPMS, relapsing secondary progressive MS; SF-6D, six-dimension Short-Form Health Survey; SMSreg, Swedish nationwide clinical register for MS; SPMS, secondary progressive MS; SWIMS, South West Impact of Multiple Sclerosis; TRIBUNE, treatment experience, burden, and unmet needs; VAS, visual analog scale.