

Health and Economic Impact of Relapsing Forms of Multiple Sclerosis in Greece: The Storms Study

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Abstract

Background: Little information on costs and quality of life (QoL) of patients with Multiple Sclerosis (MS) has been published for Greece so far.

Objective: The objective of the study was to assess the socio-economic burden that MS imposes to Greek patients with relapsing forms of multiple sclerosis.

Methods: Information on demographics, disease history, resource consumption and productivity losses was collected from 200 patients recruited in six MS centres throughout Greece. Annual costs were estimated in 2011 unit costs. Health-related QoL (HRQoL) was measured with the EQ-5D questionnaire. Using the Expanded Disability Status Scale (EDSS), patients were stratified into those with mild (EDSS 0-3), moderate (EDSS 3.5-6.0) and severe (EDSS 6.5-7.5) disability. The perspective of the analysis was that of the national security fund (EOPYY).

Results: The mean annual cost per patient was estimated at €26,118. Higher disability increased costs substantially; €20,702 for mild, €32,126 for moderate and €45,442 for high severity patients. HRQoL was considerably impaired by disease progression. Patients with Secondary Progressive (SPMS) as expected had higher costs and lower HRQoL than Relapsing Remitting Multiple Sclerosis (RRMS) subjects, attributed to higher mean disability.

Conclusion: In accordance with other studies, MS imposes a considerable health and economic burden in Greece, which increases significantly with advancing disability.

Keywords: Multiple sclerosis; Economic impact; Health, Quality of life; EQ-5D; Greece

Introduction

Multiple sclerosis (MS) is the second most common non-traumatic cause of neurological disability in adults worldwide, with a considerable socioeconomic impact, which is disproportionate to the relatively limited prevalence of the disease [1]. In Greece, the estimated prevalence varies with location, ranging between 10.2/100,000 individuals in southern areas [2] and 119.61/100,000 people in western areas [3], with the most recent estimation being 23 cases per 100,000 individuals in northern areas [4]. Several epidemiological studies have demonstrated a gradual increase in prevalence and incidence of MS in Greece, placing most geographical areas in the medium and high-risk zone [3-7]. This gradual increase has been ascribed to the advances in diagnostic modalities and overall improved awareness [4].

The socio-economic burden of MS is particularly high both for patients, their families, as well as the national health system. The average annual cost per patient with MS is higher than for patients with many other, more common, chronic conditions [8,9]. The economic burden of MS is largely driven by the progression of disability and relapses, while MS-related symptoms of fatigue, depression, cognitive deterioration and behavioral disorders, pain, urinary and sexual

dysfunction and comorbidities are also factors in the overall economic impact [10-15]. MS typically starts in early adulthood, so the disease has considerable economic consequences through lifelong decreased work capacity and productivity [16-20].

Furthermore, MS patients have lower health-related quality of life (HRQoL) than the general population, with the magnitude being similar to that of other chronic diseases [21,22]. Greater disability and relapses [16-20], other MS-related symptoms (fatigue, depression, cognitive deterioration and behavioral disorders, pain, urinary and sexual dysfunction), as well as treatment side effects and injection problems for some therapies, have been found to exert a detrimental

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influence on patients' quality of life (QoL) [23-24]. Additionally, MS has an adverse impact on the social and family life of patients, as well as on the lives of their caregivers [25].

Although information about costs and QoL of MS patients is available for a number of European countries, no such data have been published for Greece so far. The objective of the study was to assess the health and economic burden that relapsing forms of MS impose to Greek MS patients and the Greek social security fund (EOPYY), respectively.

Materials and Method

Study design and data collection

This was a multicentre, cross-sectional, retrospective, burden of disease study. The subjects were identified from six MS centres from various areas of the country. Adult patients suffering from either relapsing-relapsing or secondary progressive MS with relapses were included in the study, provided they had given written informed consent. Patients that had limited capacity to participate in the study procedures, due to cognitive impairment or other factors, or were participating in another clinical study were excluded.

During a single visit, trained researchers completed a case report form by interviewing each patient on: i) demographics, ii) disease data (year of diagnosis, year of first symptoms, type of MS, Expanded Disability Status Scale [EDSS] score, number of relapses), iii) MS related comorbidities, iv) treatment-related information, v) resource utilization (inpatient and outpatient care, diagnostic and laboratory tests, medication, disability equipment, productivity loss and informal caregiving). Additionally, patients self-assessed their HRQoL with the EQ-5D questionnaire.

Costs calculation

This study adopts a bottom-up approach to estimate the mean annual costs per MS patient in Greece, from a social security fund perspective. Since MS is a chronic disease, a prevalence-based approach was selected, taking into account the use of resources during the previous year, using information which was gathered at a single point in time. A prevalence-based economic evaluation provides estimates of costs and health benefits of a certain population for a specific time horizon. Only MS specific resource utilization was collected. Costs were computed as the monetary value of resource utilization, i.e. the number of resource units consumed multiplied by the respective unit cost. Unit costs were obtained from publicly available sources in Greece (Table 1). MS related comorbidities' economic burden was estimated as the total mean annual cost per patient related to each comorbidity, based on previous relevant literature [9,26]. Productivity loss of patients was approximated as the income reduction due to MS and the cost related to the early disability pension. The informal care cost was estimated by taking into account the total weekly hours spent for informal care (extrapolated to year), and using the mean gross income for Greece in 2011 (€19,018), divided by the number of hours worked, equally for working and non-working caregivers.

Costs were grouped as: 1) direct medical costs (inpatient and outpatient care, consultations, investigations, treatments and MS-related comorbidities), 2) direct non-medical costs (equipment investment, professional assistance, informal care) and 3) indirect costs (productivity loss, i.e., disability pension, percentage of income reduction).

QoL

The EQ-5D [27] is a widely used generic instrument for measuring HRQoL. It consists of a descriptive health state classification system with five dimensions, including: 1) mobility, 2) self-care, 3) usual activities, 4) pain/discomfort and 5) anxiety/depression, and a Visual Analogue Scale (VAS) assessing the overall perception of the subject's health state. Each dimension of the descriptive system is measured with an ordinal three-point scale describing three levels of severity: i) no problems, ii) some problems, and iii) extreme problems. Together, these five dimensions with three levels for each dimension define a total of 243 health states, ranging from full to worst health. Health utilities were obtained based on time trade-off valuations from a general population study conducted at the United Kingdom, which have been found applicable in the Greek setting [28].

Analysis

Descriptive statistics (frequency, percentage, mean, standard deviation, median and interquartile range) were used for the analysis of the demographic and clinical characteristics of the sample, as well as the resource utilization and costs. To assess the effect of disability on costs and QoL of MS, along with demographic and clinical data, three categories were created based on EDSS score, as in previous studies [10-13,15], i.e., those with mild (EDSS 0-3), moderate (EDSS 3.5-6) and severe disability (EDSS 6.5-7.5). We conducted Jonckheere trend tests to examine whether a significant trend existed (ordered pattern of alternatives) in continuous data with advancing severity of the disease, as it was measured with the EDSS groups described; Cochran-Armitage tests were used for categorical responses. Similarly, the differences between MS type groups were compared with Mann-Whitney and χ^2 tests, for continuous and categorical data respectively. All comparisons were evaluated on the $\alpha=5\%$ level. Confidence intervals (95%) of the costs were estimated by non-parametric bootstrapping. Statistical analysis was carried out with IBM SPSS Statistics 21 software package.

Results

Patient demographics and disease information

A total of 200 patients completed the study and were included in the analysis. Patients' socio-demographics and disease information are presented in (Table 2). The sample had a mean age of 39.5 years, with 70.4% being females. The overall mean EDSS level was 3.1 (± 2.0), and the majority of subjects (62.5%) belonged to the mild disability subgroup (EDSS ≤ 3). Patients with less severe disease were younger ($p<0.001$); also the time period since first appearance of symptoms and diagnosis was shorter for less afflicted subjects (both $p<0.001$). A proportion of 86.5% was diagnosed as having RRMS, and 13.5% with SPMS. Finally, only 32% of the participants were employed or self-employed at the time of the study.

The most frequently reported comorbidities were depression (50%), urinary problems (34.5%), sleep disturbance (27.5%) and cognitive impairment (21.5%). Urinary tract infections and osteoporosis increased with the EDSS disability level ($p<0.05$). On average, RRMS patients were experiencing comorbidities to a lesser extent, though the difference was found statistically significant only for osteoporosis ($p<0.05$).

Resource utilisation

About 30% of the patients had required a hospital admission due to MS during the previous year (Table 3); a proportion of 46% had received outpatient care in a hospital and 4.5% in a rehabilitation centre, while 64.5% had consulted a specialist. The majority of patients

	Cost (€)	Source
Disability pension (per month)	500	I.K.A. (https://www.ika.gr/gr/infopages/asf/pensions/handicap_sub/handicap_a.cfm)
Mean annual gross income per capita	19,018	Hellenic Statistical Authority
Inpatient and outpatient care		
Inpatient care (hospitalization; per day)	70.43	Joint Ministerial Decision Y4a/oik 1320/3-2-98 FEK B 99/10-2-1998
Out patient care (rehabilitation centre; 10 sessions)	150	Joint Ministerial Decision Y4a/oik 1320/3-2-98 FEK B 99/10-2-1998
Outpatient care (hospital; per visit)	54	Joint Ministerial Decision Y4a/oik 1320/3-2-98 FEK B 99/10-2-1998
Consultations (per visit)		
General practitioner (EOPYY)	10	Law 4052/1-3-2012
Neurologist	75	Joint Ministerial Decision Y4a/G.P. oik 40620/6.12.2001 FEK B 1643/10-12-2001
Other specialist	60	Joint Ministerial Decision Y4a/G.P. oik 40620/6.12.2001 FEK B 1643/10-12-2001
Nurse	10	Law 4052/1-3-2012
Physiotherapist	15	Joint Ministerial Decision Y4a/G.P. oik 40620/6.12.2001 FEK B 1643/10-12-2001
Psychologist	45	Joint Ministerial Decision Y4a/G.P. oik 40620/6.12.2001 FEK B 1643/10-12-2001
Ergotherapist	15	Joint Ministerial Decision Y4a/G.P. oik 40620/6.12.2001 FEK B 1643/10-12-2001
Optician	60	Joint Ministerial Decision Y4a/G.P. oik 40620/6.12.2001 FEK B 1643/10-12-2001
Investigations (per exam)		
Magnetic Resonance Imaging	237	Presidential Decree 163/88 FEK A 75/22-4- 88
Computerized Tomography	71.11	Presidential Decree 163/88 FEK A 75/22-4- 88
Lumbar Puncture	3.43	Presidential Decree 157/91 FEK A 62/30-4-91
Multiple Sclerosis related investments		
Gait aids	206	I.K.A., DECISION 391/SYN. 39/13-12-01 Board IKA (IKA Ref. Circular 107/2001)
Manual wheelchair	890	I.K.A., DECISION 391/SYN. 39/13-12-01 Board IKA (IKA Ref. Circular 107/2001)
Electric wheelchair	5600	I.K.A., DECISION 391/SYN. 39/13-12-01 Board IKA (IKA Ref. Circular 107/2001)
Disease Modifying Treatments (yearly cost)		
AVONEX	8449.61	Ministry of Health, Price List of Medicines for Human Use, May 2012 (D.T. 5/2012)
BETAIFERON	7279	Ministry of Health, Price List of Medicines for Human Use, May 2012 (D.T. 5/2012)
COPAXONE	5823	Ministry of Health, Price List of Medicines for Human Use, May 2012 (D.T. 5/2012)
REBIF 44	8942	Ministry of Health, Price List of Medicines for Human Use, May 2012 (D.T. 5/2012)
REBIF 22	7513	Ministry of Health, Price List of Medicines for Human Use, May 2012 (D.T. 5/2012)
TYSABRI	17011.15	Ministry of Health, Price List of Medicines for Human Use, May 2012 (D.T. 5/2012)

* Source: Prices reimbursed by social security funds (www.eopyy.gov.gr) accessed on 28 Dec 2014

Table 1: Unit costs (in euros) for hospitalization, patient follow-up, lab and imaging tests and health aid material.

	Overall (n=200)	Severity			p-value*	Type of MS		p-value†
		EDSS 0-3 (n=125)	EDSS 3.5-6 (n=58)	EDSS 6.5-7.5 (n=17)		RRMS (n=173)	SPMS (n=27)	
Subjects (female: male ratio)	200 (70.0:30.0)	125 (26.4:73.6)	58 (36.2:63.8)	17 (35.3:64.7)	0.198	172 (72.7:27.3)	27 (55.6:44.4)	0.078
Age, years								
Mean ± SD	39.5 ± 10.3	35.9 ± 8.7	44.4 ± 9.9	49.8 ± 9.1		37.9 ± 9.5	50.3 ± 8.6	
Median (IQR)	39.5 (14.7)	35 (13.5)	43.5 (12.0)	50 (12.0)	<0.001	38.0 (13.0)	50.0 (12.0)	<0.001
Cohabits with family/spouse, n (%)	177 (88.5%)	111 (89.5%)	53 (91.4%)	13 (76.5%)		154 (89.0%)	23 (85.2%)	0.503
Employment status, n (%)								
Full time	53 (26.5%)	34 (27.2%)	17 (29.3%)	2 (11.8%)	0.868	49 (28.3%)	4 (14.8%)	0.347
Part time	11 (5.5%)	8 (6.4%)	2 (3.4%)	1 (5.9%)		11 (6.4%)	0 (0%)	
Employed	44 (22.0%)	25 (20.0%)	17 (29.3%)	2 (11.8%)	0.841	41 (23.7%)	3 (11.1%)	0.142
Self-employed	20 (10.0%)	17 (13.6%)	2 (3.4%)	1 (5.9%)	0.058	19 (11.0%)	1 (3.7%)	0.241
Housekeeping	29 (14.5%)	16 (12.8%)	9 (15.5%)	4 (23.5%)	0.256	24 (13.9%)	5 (18.5%)	0.524
Student	15 (7.5%)	14 (11.2%)	1 (1.7%)	0 (0%)	0.014	15 (8.7%)	0 (0%)	0.112
Unemployed	27 (13.5%)	21 (16.8%)	5 (8.6%)	1 (5.9%)	0.083	25 (14.5%)	2 (7.4%)	0.319
Type of MS, n (%)								
RRMS	173 (86.5%)	124 (99.2%)	45 (77.6%)	4 (23.5%)	<0.001	n.a.	n.a.	
SPMS	27 (13.5%)	1 (0.8%)	13 (22.4%)	13 (76.5%)		n.a.	n.a.	
Years since first diagnosis								
Mean ± SD	9.2 ± 5.9	7.4 ± 5.2	11.7 ± 6.1	14.2 ± 5.2		8.5 ± 5.7	14.1 ± 5.2	
Median (IQR)	8.0 (7.0)	6.0 (7.0)	11.0 (9.0)	12.0 (5.0)	<0.001	8.0 (7.0)	13.0 (7.0)	<0.001
Years since first symptoms								
Mean ± SD	11.9 ± 6.7	9.9 ± 6.1	15.1 ± 6.7	16.2 ± 5.5		11.1 ± 6.5	17.2 ± 5.6	

Median (IQR)	11.0 (10.0)	9.0 (8.5)	15.0 (11.3)	15.5 (9.0)	<0.001	10.0 (9.0)	17.0 (10.3)	<0.001
EDSS								
Mean ± SD	3.1 ± 2.0	1.7 ± 0.8	4.8 ± 1.0	6.8 ± 0.4		2.7 ± 1.7	5.9 ± 1.4	
Median (IQR)	2.5 (2.9)	2.0 (1.0)	4.5 (2.0)	6.5 (0.8)	<0.001	2.0 (2.3)	6.0 (2.5)	<0.001
Relapses in previous year								
Mean ± SD	1.5 ± 1.0	1.4 ± 0.8	1.8 ± 1.2	1.8 ± 1.0		1.6 ± 1.0	1.3 ± 0.7	
Median (IQR)	1.0 (1.0)	1.0 (1.0)	1.5 (1.0)	1.5 (2.0)	0.070	1.0 (1.0)	1.0 (0)	0.223
Relapses requiring steroids in previous year								
Mean ± SD	0.9 ± 0.9	0.8 ± 1.0	1.2 ± 1.0	0.5 ± 1.0		1.0 ± 1.0	0.6 ± 0.8	
Median (IQR)	1.0 (1.0)	1.0 (1.0)	1.0 (2.0)	0 (1.0)	0.351	1.0 (2.0)	0 (1.0)	0.128
MS related Comorbidities, n (%)								
Depression/Anxiety	100 (50%)	59 (47.2%)	32 (55.2%)	9 (52.9%)	0.382	85 (49.1%)	15 (55.6%)	0.535
Urinary tract infection	69 (34.5%)	26 (20.8%)	34 (58.6%)	9 (52.9%)	<0.001	57 (32.9%)	12 (44.4%)	0.243
Sleep disturbances	55 (27.5%)	30 (24.0%)	18 (31.0%)	7 (41.2%)	0.101	45 (26.0%)	10 (37.0%)	0.233
Mental problems	43 (21.5%)	25 (20.0%)	13 (22.4%)	5 (29.4%)	0.392	35 (20.2%)	8 (29.6%)	0.269
Osteoporosis	15 (7.5%)	3 (2.4%)	8 (13.8%)	4 (23.5%)	<0.001	9 (5.2%)	6 (22.2%)	0.002
Hypertension	9 (4.5%)	5 (4.0%)	4 (6.9%)	0 (0%)	0.943	7 (4.0%)	2 (7.4%)	0.433
Arthritis	6 (3.0%)	2 (1.6%)	3 (5.2%)	1 (5.9%)	0.151	4 (2.3%)	2 (7.4%)	0.149

* Comparing patients with mild, moderate and severe disability; Jonckheere–Terpstra or Cochran-Armitage test for examination of trend.

† Comparing patients with RRMS and SPMS type of MS; Mann-Whitney or X2 test for examination of difference.

MS: Multiple Sclerosis; EDSS: Expanded Disability Status Scale; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; SD: Standard deviation; IQR: Interquartile range; n.a.: Not Applicable.

Table 2: Socio-demographics and disease information of the sample by EDSS level and MS type.

	Overall (n=200)	Severity			p-value*	Type of MS		p-value†
		EDSS 0-3 (n=125)	EDSS 3.5-6 (n=58)	EDSS 6.5-7.5 (n=17)		RRMS (n=173)	SPMS (n=27)	
Inpatient care (length of stay in days)								
Hospital, n (%)	60 (30.0%)	36 (28.8%)	23 (39.7%)	1 (5.9%)	0.535	57 (32.9%)	3 (11.1%)	0.021
Mean ± SD	1.8 ± 3.7	1.7 ± 3.4	2.5 ± 4.3	0.8 ± 3.2		2.0 ± 3.8	0.9 ± 2.8	
Median (IQR)	0 (3.0)	0 (3.0)	0 (4.0)	0 (0)	0.945	0 (3.0)	0 (0)	0.033
Hospital due to relapses								
Mean ± SD	2.2 ± 3.4	2.0 ± 3.3	2.9 ± 3.5	1.3 ± 4.1		2.3 ± 3.4	1.5 ± 3.4	
Median (IQR)	0 (4.0)	0 (3.0)	3.0 (5.0)	0 (0)	0.631	0 (4.0)	0 (2.0)	0.148
Outpatient care (visits)								
Hospital, n %	92 (46.0%)	49 (39.2%)	32 (55.2%)	11 (64.7%)	0.010	77 (44.5%)	15 (55.6%)	0.284
Mean ± SD	3.8 ± 6.8	3.6 ± 7.5	4.2 ± 5.9	4.0 ± 4.5		3.9 ± 7.1	3.3 ± 4.2	
Median (IQR)	0 (4.0)	0 (4.0)	4.0 (4.0)	4.0 (4.0)	0.035	0 (4.0)	4.0 (4.0)	0.615
Rehabilitation centre, n %	9 (4.5%)	1 (0.8%)	5 (8.6%)	3 (17.6%)	<0.001	7 (4.0%)	2 (7.4%)	0.433
Mean ± SD	1.2 ± 9.1	0 ± 0.4	3.7 ± 16.7	0.7 ± 1.6		1.3 ± 9.8	0.3 ± 1.1	
Median (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0.001	0 (0)	0 (0)	0.452
Consultations (public & private), n %								
Physiotherapist,	129 (64.5%)	79 (63.2%)	41 (70.7%)	9 (52.9%)	0.938	115 (66.5%)	14 (51.9%)	0.140
Mean visits ± SD	12.4 ± 38.0	3.9 ± 19.4	24.6 ± 48.6	33.2 ± 71.2		11.9 ± 37.5	15.4 ± 41.6	
Median visits (IQR)	0 (0)	0 (0)	0 (34.0)	0 (16.0)	0.001	0 (0)	0 (0)	0.530
Ergotherapist								
Mean visits ± SD	0.7 ± 10.2	0 ± 0	2.5 ± 18.9	0 ± 0		0.8 ± 10.9	0 ± 0	
Median visits (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0.274	0 (0)	0 (0)	0.639
Neurologist								
Mean visits ± SD	3.7 ± 5.7	3.9 ± 6.2	3.5 ± 4.9	2.4 ± 4.0		3.8 ± 5.9	2.8 ± 4.0	
Median visits (IQR)	0 (4.0)	0 (6.0)	0 (5.0)	0 (6.0)	0.388	0 (6.0)	0 (4.0)	0.620
Psychologist								
Mean visits ± SD	0.7 ± 4.2	0.2 ± 1.6	1.7 ± 7.3	0.7 ± 2.1		0.7 ± 4.4	0.7 ± 2.7	
Median visits (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0.019	0 (0)	0 (0)	0.343
Other specialist								
Mean visits ± SD	2.0 ± 4.9	1.9 ± 5.4	2.5 ± 4.2	1.4 ± 2.8		2.1 ± 5.2	1.5 ± 3.0	
Median visits (IQR)	0 (4.0)	0 (0)	0 (4)	0 (2.0)	0.150	0 (4.0)	0 (0)	0.598
General practitioner								

Mean visits ± SD	0.2 ± 1.3	0.2 ± 1.3	0.2 ± 1.6	0 ± 0		0.2 ± 1.4	0 ± 0	
Median visits (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0.557	0 (0)	0 (0)	0.426
Nurse (hospital)								
Mean visits ± SD	0.1 ± 1.4	0.2 ± 1.8	0 ± 0	0 ± 0		0.1 ± 1.5	0 ± 0	
Median visits (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0.447	0 (0)	0 (0)	0.693
Optician								
Mean visits ± SD	0.1 ± 0.7	0.1 ± 0.5	0.2 ± 1.2	0 ± 0		0.1 ± 0.8	0 ± 0	
Median visits (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0.729	0 (0)	0 (0)	0.426
Investigations (tests)								
Magnetic Resonance Imaging, n (%)	152 (76.0%)	95 (76.0%)	47 (81.0%)	10 (59.8%)	0.455	138 (79.8%)	14 (51.9%)	0.002
Mean number ± SD	1.1 ± 0.9	4.8 ± 3.6	4.4 ± 3.2	2.8 ± 2.4		1.2 ± 0.9	0.5 ± 0.5	
Median number (IQR)	1.0 (1.0)	4.0 (4.0)	4.0 (0)	4.0 (4.0)	0.176	1.0 (1.0)	1.0 (1.0)	<0.001
Computerized Tomography, n (%)	1 (0.5%)	1 (0.8%)	0 (0%)	0 (0%)	0.476	1 (0.6%)	0 (0%)	0.692
Mean number ± SD	0.1 ± 0.1	0 ± 1.6	0 ± 0	0 ± 0		0 ± 0.1	0 ± 0	
Median number (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0.447	0 (0)	0 (0)	0.693
Lumbar Puncture, n (%)	11 (5.5%)	9 (7.2%)	2 (3.4%)	0 (0%)	0.143	10 (5.8%)	1 (3.7%)	0.660
Mean number ± SD	0.1 ± 0.2	0.4 ± 1.2	0 ± 0.8	0 ± 0		0.1 ± 0.2	0 ± 0.2	
Median number (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0.150	0 (0)	0 (0)	0.681
MS Treatment, n (%)								
On DMT	168 (84%)	103 (82.4%)	50 (86.2%)	15 (88.2%)	0.417	145 (83.8%)	23 (85.2%)	0.857
Not currently treated, but have received DMT in the past	46 (23%)	27 (36.5%)	16 (64.0%)	3 (60.0%)	0.023	42 (24.3%)	4 (14.8%)	0.476
Prescribed drugs, n (%)								
Antidepressants	48 (24.0%)	19 (15.2%)	22 (37.9%)	7 (41.2%)	<0.001	37 (21.4%)	11 (40.7%)	0.029
Immunosuppressant's	3 (1.5%)	0 (0%)	1 (1.7%)	2 (11.8%)	0.001	0 (0%)	3 (11.1%)	<0.001
Anti-spasticity drugs	40 (20.0%)	9 (7.2%)	24 (41.4%)	7 (41.2%)	<0.001	29.1 (16.8%)	11 (40.7%)	0.004
Urological drugs	29 (14.5%)	12 (9.6%)	14 (24.1%)	3 (17.6%)	0.039	25.1 (14.5%)	4 (14.8%)	0.960
Analgesic drugs	46 (23.0%)	25 (20%)	16 (27.6%)	5 (29.4%)	0.209	38.9 (22.5%)	7 (25.9%)	0.698
Steroids	24 (12.0%)	11 (8.8%)	12 (20.7%)	1 (5.9%)	0.319	22 (12.7%)	2 (7.4%)	0.430
Sleep disturbances treatment	17 (8.5%)	5 (4.0%)	9 (15.5%)	3 (17.6%)	0.005	11.9 (6.9%)	5 (18.5%)	0.045
Fatigue drugs	19 (9.5%)	6 (4.8%)	10 (17.2%)	3 (17.6%)	0.007	13 (7.5%)	6 (22.2%)	0.015
Cognitive dysfunction drugs	2 (1.0%)	1 (0.8%)	1 (1.7%)	0 (0%)	0.929	1 (0.6%)	1 (3.7%)	0.129
OTC drugs, n %	58 (29.0%)	38 (30.4%)	15 (25.9%)	5 (29.4%)	0.686	54 (31.2%)	4 (14.8%)	0.081

* Comparing patients with mild, moderate and severe disability; Jonckheere–Terpstra or Cochran-Armitage test for examination of trend.
† Comparing patients with RRMS and SPMS type of MS; Mann-Whitney, or X2 test for examination of difference.
‡ The recall period for outpatient care, consultations and MS treatment was 3 months, and for prescribed and OTC drugs was one month, which were linearly extrapolated to a year.
MS: Multiple Sclerosis; EDSS: Expanded Disability Status Scale; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; OTC: over-the-counter drugs; SD: Standard deviation; IQR: Interquartile range.

Table 3: Annual direct medical resource utilisation of the sample by EDSS level and MS type[‡].

had received a Disease Modifying Treatment (DMT; 84%), and 29% non-prescription medicines in the previous 3 months and 1 month of the study, respectively; a proportion of 76% had at least one Magnetic Resonance Imaging Scan and 5.5% a Lumbar Puncture performed, in the previous 3 months. Advancing disability appears to increase significantly the utilisation of outpatient care (both hospital and rehabilitation centre) and co-medication, though statistical significance is not established in all cases. RRMS patients utilise medical resources to a greater extent compared with SPMS subjects (with the exception of most prescribed drugs), though again the level of statistical significance is not reached in most items.

Modification of living space or vehicle or use of walking aids due to MS was necessary for 14% of the subjects (Table 4). The frequency of patients reporting any MS-related investment ($p < 0.001$) and use of professional or informal care due to MS (both $p < 0.001$) increased significantly with worsening severity of the disease; notably, utilization

of informal care was much more frequently reported (39%) than professional care (6.5%). RRMS patients were receiving less informal and professional assistance (both $p < 0.001$), and had less overall MS-related modifications and equipment investments than the SPMS subjects ($p < 0.001$). Apparently, due to higher disability level and lower relapse rate, SPMS patients require more informal care support rather than health care services utilisation.

About one third of the patients (31%) had been retired due to MS, and 33.5% reported receiving MS-related disability benefits during the time of the study (Table 5); both percentages were higher for patients experiencing SPMS ($p < 0.005$). 14% of the subjects reported that they had taken a sick leave due to MS during the previous 3 months of the study; patients in a more severe condition recorded more sick days on average, though not statistically significant. A proportion of 9% of the sample reported a permanent reduction in work hours, and 5% listed a work change and/or income reduction due to the disease.

	Overall (n=200)	Severity			p-value*	Type of MS		
		EDSS 0-3 (n=125)	EDSS 3.5-6 (n=58)	EDSS 6.5-7.5 (n=17)		RRMS (n=173)	SPMS (n=27)	p-value†
MS related investments previous 12 months, n (%)	28 (14.0%)	4 (3.2%)	15 (25.9%)	9 (52.9%)	<0.001	18 (10.4%)	10 (37.0%)	<0.001
House modifications, n (%)	10 (5.0%)	2 (1.6%)	3 (5.2%)	5 (29.4%)	<0.001	6 (3.5%)	4 (14.8%)	0.012
Car modifications, n (%)	6 (3.0%)	1 (0.8%)	3 (5.2%)	2 (11.8%)	0.007	4 (2.3%)	2 (7.4%)	0.149
Gait aids, n (%)	20 (10.0%)		11 (19.0%)	7 (41.2%)	<0.001	13 (7.5%)	7 (25.9%)	0.003
Manual wheelchair, n (%)	3 (1.5%)	0 (0%)	2 (3.4%)	1 (5.9%)	0.018	1 (0.6%)	2 (7.4%)	0.007
Electric wheelchair, n (%)	2 (1.0%)	0 (0%)	1 (1.7%)	1 (5.9%)	0.022	1 (0.6%)	1 (3.7%)	0.129
Professional assistance, n (%)	13 (6.5%)	4 (3.2%)	3 (5.2%)	6 (35.3%)	<0.001	7 (4.0%)	6 (22.2%)	<0.001
Nurse at home								
Mean hours per week ± SD	2.0 ± 0	2.0 ± 0	0 ± 0	0 ± 0		2.0 ± 0	0 ± 0	
Median hours per week (IQR)	2.0 (0)	2.0 (0)	0 (0)	0 (0)	1.000	2.0 (0)	0 (0)	1.000
Home helper								
Mean hours per week ± SD	16.5 ± 24.8	5.5 ± 4.1	4.7 ± 4.6	29.8 ± 32.6		5.1 ± 4.0	29.8 ± 32.6	
Median hours per week (IQR)	8.0 (23.0)	5.0 (8.0)	2.0 (0)	25.0 (46.0)	0.158	2.0 (8.0)	25.0 (46.0)	0.138
Personal assistant								
Mean hours per week ± SD	34.7 ± 22.5	0 ± 0	0 ± 0	34.7 ± 22.5		0 ± 0	34.7 ± 22.5	
Median hours per week (IQR)	40.0 (0)	0 (0)	0 (0)	40.0 (0)	1.000	0 (0)	40.0 (0)	1.000
Informal care, n (%)	78 (39.0%)	28 (22.4%)	36 (62.1%)	14 (82.4%)	<0.001	57 (32.9%)	6 (77.8%)	<0.001
Mean hours per week ± SD	7.08 ± 16.2	2.1 ± 5.8	11.7 ± 20.3	28.2 ± 27.7		4.7 ± 12.5	22.4 ± 26.1	
Median hours per week (IQR)	0 ± 7.0	0 (0)	5.5 (13)	24.0 (38.0)	<0.001	0 (4.0)	13.0 (30.0)	<0.001

* Comparing patients with mild, moderate and severe disability; Jonckheere–Terpstra or Cochran–Armitage test for examination of trend.
† Comparing patients with RRMS and SPMS type of MS; Mann–Whitney, or X² test for examination of difference.
‡ The recall period for professional assistance and informal care was 3 months.
MS: Multiple Sclerosis; EDSS: Expanded Disability Status Scale; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; SD: Standard deviation; IQR: Interquartile range.

Table 4: Indirect resource utilisation data of the sample by EDSS level and MS type*.

	Overall (n=200)	Severity			p-value*	Type of MS		
		EDSS 0-3 (n=125)	EDSS 3.5-6 (n=58)	EDSS 6.5-7.5 (n=17)		RRMS (n=173)	SPMS (n=27)	p-value†
Retired due to age, n (%)	3 (1.5%)	0 (0%)	3 (5.2%)	0 (0%)	0.145	2 (1.2%)	1 (3.7%)	0.311
Retired due to MS, n (%)	62 (31.0%)	32 (25.6%)	21 (36.2%)	9 (52.9%)	0.013	47 (27.2%)	15 (55.6%)	0.003
On disability payment, n (%)	67 (33.5%)	34 (27.2%)	23 (39.7%)	10 (58.8%)	0.005	51 (29.5%)	16 (59.3%)	0.002
Sick leave due to MS past 3 months, n (%)	28 (14%)	18 (14.4%)	8 (13.8%)	2 (11.8%)	0.782	26 (15%)	2 (7.4%)	0.288
Mean days ± SD	2.6 ± 11.7	1.9 ± 9.0	2.9 ± 12.6	6.5 ± 22.1		2.9 ± 12.5	0.5 ± 2.0	
Median days (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0.939	0 (0)	0 (0)	0.278
Reduction in work hours, n (%)	18 (9.0%)	13 (10.4%)	4 (6.9%)	1 (5.9%)	0.384	16 (9.2%)	2 (7.4%)	0.758
Work change and income reduction, n (%)	10 (5.0%)	7 (5.6%)	2 (3.4%)	1 (5.9%)	0.763	10 (5.8%)	0 (0%)	0.200
Percentage of income reduction								
Mean ± SD	2.2 ± 11.1	2.5 ± 12.3	1.7 ± 9.2	1.8 ± 7.3		2.5 ± 11.9	0 ± 0	
Median (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0.850	0 (0)	0 (0)	0.229

* Comparing patients with mild, moderate and severe disability; Jonckheere–Terpstra or Cochran–Armitage test for examination of trend.
† Comparing patients with RRMS and SPMS type of MS; Mann–Whitney, or X² test for examination of difference.
MS: Multiple Sclerosis; EDSS: Expanded Disability Status Scale; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; SD: Standard deviation; IQR: Interquartile range.

Table 5: Productivity loss of the sample by EDSS level and MS type.

Costs

The mean cost per patient per year was estimated at €26,118, with MS treatments being the largest contributor to the overall cost (48.4%) and for all disability and MS type subgroups (Tables 6 and 7). Total cost increased significantly ($p < 0.001$) across the EDSS disability level groups; €20,702 for mild disability (EDSS 0-3), €32,126 for moderate disability (EDSS 3.5-6) and €45,442 for high disability patients (EDSS 6.5-7.5). Total direct medical and non-medical, and indirect costs all increased significantly with advancing disability (all $p < 0.05$).

The component costs of outpatient care, MS treatments, MS-related comorbidities, MA-related investments, professional and informal assistance and economic burden due to early retirement (disability pension) all enlarged significantly (all $p < 0.05$) with increasing disability. Notably, the share of informal care in the total cost rose from 5.7% in patients with mild condition to 32.6% in subjects with severe disability (14.6% overall contribution).

RRMS subjects were on average less disabled than SPMS patients (EDSS mean score 2.7 vs. 5.9 respectively; Table 2), which is reflected

	Severity												p-value*	
	EDSS 0-3 (n=125)				EDSS 3.5-6 (n=58)				EDSS 6.5-7.5 (n=17)					
	Mean ± SD	95% CI	Median (IQR)	Mean ± SD	95% CI	Median (IQR)	Mean ± SD	95% CI	Median (IQR)	Mean ± SD	95% CI	Median (IQR)		
Overall (n=200)														
Inpatient care	129 ± 261	98-164	0 (211)	117 ± 241	78-159	0 (211)	175 ± 305	105-261	0 (282)	54 ± 222	54-215	0 (0)	0.937	
Outpatient care	294 ± 626	218-380	216 (216)	206 ± 404	143-280	0 (216)	495 ± 969	302-732	216 (486)	254 ± 244	165-368	216 (432)	0.002	
Consultations	630 ± 868	512-754	300 (900)	483 ± 642	379-594	300 (720)	902 ± 1127	663-1176	480 (1260)	791 ± 1091	346-1302	240 (1440)	0.099	
Investigations	261 ± 211	231-291	237 (237)	274 ± 224	237-314	237 (237)	266 ± 194	221-315	237 (62)	153 ± 144	98-209	237 (237)	0.138	
MS treatments	12643 ± 4982	11947-13401	17011 (8562)	11701 ± 5223	10844-12671	8942 (8562)	14023 ± 4177	12879-15062	17011 (8069)	14859 ± 4010	13056-16439	17011 (4281)	0.001	
MS related Comorbidities	5644 ± 6290	4778-6534	3377 (10210)	4606 ± 5494	3717-5567	3377 (5946)	7091 ± 7323	5379-8995	5156 (10989)	8349 ± 6587	4960-11512	10216 (12681)	0.002	
OTC	17 ± 76	9-28	0 (10)	14 ± 50	7-21	0 (12)	22 ± 118	4-53	0 (6)	26 ± 51	0-51	0 (35)	0.806	
Direct medical costs	19618 ± 8161	18525-20818	19459 (10207)	17399 ± 7322	16087-18702	17961 (9474)	22973 ± 8474	20898-25006	21457 (13361)	24486 ± 7243	20480-27883	24847 (12565)	<0.001	
MS related Investments	68 ± 648	2-135	0 (0)	0 ± 0	0-0	0 (0)	119 ± 852	4-350	0 (0)	394 ± 1572	12-1157	0 (0)	0.002	
Professional assistance	188 ± 1214	64-363	0 (0)	28 ± 173	4-60	0 (0)	28 ± 155	4-79	0 (0)	1904 ± 3818	498-3856	0 (2860)	0.001	
Informal care	3816 ± 8393	2830-4885	0 (4123)	1171 ± 3106	725-1707	0 (515)	6299 ± 10500	3988-8885	2834 (7343)	14793 ± 14263	8611-20908	12883 (19582)	<0.001	
Direct non-medical costs	4072 ± 8677	2947-5300	0 (4638)	1199 ± 3101	750-1740	0 (515)	6446 ± 10522	4063-9065	3607 (7730)	17091 ± 14228	10530-23462	16315 (19011)	<0.001	
Income reduction	418 ± 2109	166-708	0 (0)	472 ± 2341	155-844	0 (0)	328 ± 1750	164-920	0 (0)	336 ± 1384	336-1007	0 (0)	0.850	
Retirement due to MS*	2010 ± 2839	1590-430	0 (6000)	1632 ± 2681	1200-2064	0 (6000)	2379 ± 2961	1759-3000	0 (6000)	3529 ± 3044	2471-4588	6000 (6000)	0.008	
Indirect costs	2428 ± 3324	1988-2908	0 (6000)	2104 ± 3388	1538-2656	0 (6000)	2707 ± 3200	1880-3509	0 (6000)	3865 ± 2943	2453-5277	6000 (6000)	0.020	
Total costs	26118 ± 14922	24297-28084	22090 (17302)	20702 ± 9813	19003-22466	20625 (12309)	32126 ± 16110	28376-35711	27231 (20017)	45442 ± 18486	36929-54179	42809 (21954)	<0.001	

* Comparing patients with mild, moderate and severe disability; Jonckheere-Terpstra test for examination of trend. MS:Multiple Sclerosis; EDSS:Expanded Disability Status Scale; OTC: over-the-counter drugs; SD: Standard deviation; IQR: Interquartile range.

Table 6: Costs per patient per year by EDSS level (in € 2011), 95% CI.

	RRMS (n=173)			SPMS (n=27)			p-value [†]
	Mean ± SD	95% CI	Median (IQR)	Mean ± SD	95% CI	Median (IQR)	
Inpatient care	139 ± 268	99-185	0 (211)	60 ± 196	10-115	0 (0)	0.033
Outpatient care	308 ± 667	226-412	216 (216)	200 ± 231	112-291	216 (216)	0.791
Consultations	641 ± 883	516-763	300 (900)	564 ± 778	302-871	300 (960)	0.458
Investigations	283 ± 214	254-313	237 (237)	123 ± 121	79-167	237 (237)	<0.001
MS treatments	12418 ± 5062	11584-13210	17011 (8562)	14082 ± 4241	12165-15736	17011 (8069)	0.168
MS related comorbidities	5202 ± 5802	4421-6129	3377 (7173)	8480 ± 8396	5676-11452	5946 (12780)	0.061
OTC	18 ± 81	9-31	0 (13)	9 ± 30	1-20	0 (0)	0.131
Direct medical costs	19009 ± 7839	17829-20192	19267 (10181)	23518 ± 9214	20057-27080	23674 (13870)	0.025
MS related Investments	39 ± 494	0-114	0 (0)	256 ± 1247	8-729	0 (0)	0.002
Professional assistance	30 ± 172	8-60	0 (0)	1199 ± 3139	324-2343	0 (0)	<0.001
Informal care	2562 ± 6523	1629-3621	0 (2061)	11852 ± 13419	7710-16953	7214 (15975)	<0.001
Direct non-medical costs	2630 ± 6559	1675-3710	0 (2061)	13307 ± 13755	9163-18223	7730 (15460)	<0.001
Income reduction	484 ± 2262	176-896	0 (0)	0 ± 0	0-0	0 (0)	0.227
Retirement due to MS	1769 ± 2744	1353-2150	0 (6000)	3556 ± 3004	2222-4667	6000 (6000)	0.002
Indirect costs	2252 ± 3345	1756-2782	0 (6000)	3556 ± 3004	2222-4667	6000 (6000)	0.020
Total costs	23892 ± 12570	21809-25851	21655 (15070)	40381 ± 20365	33806-47552	39321 (32361)	<0.001

†Comparing patients with RRMS and SPMS type of MS; Mann-Whitney test for examination of difference.
MS: Multiple Sclerosis; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; SD: Standard deviation; IQR: Interquartile range.

Table 7: Costs per patient per year by MS type (in € 2011), 95% CI.

	Overall (n=200)	Severity			p-value*	Type of MS		p-value [†]
		EDSS 0-3 (n=125)	EDSS 3.5-6 (n=58)	EDSS 6.5-7.5 (n=17)		RRMS (n=173)	SPMS (n=27)	
EQ-5D dimensions, subjects reporting problems (%)								
Mobility * †	135 (67.5%)	61 (48.8%)	57 (98.3%)	17 (100%)	<0.001	108 (62.4%)	27 (100%)	<0.001
Self-care * †	54 (27.0%)	9 (7.2%)	29 (50.0%)	16 (94.1%)	<0.001	33 (19.1%)	21 (77.8%)	<0.001
Usual activities* †	118 (59.0%)	50 (40.0%)	51 (87.9%)	17 (100%)	<0.001	93 (53.8%)	25 (92.6%)	<0.001
Pain/ discomfort	90 (45.0%)	54 (43.2%)	28 (48.3%)	8 (47.1%)	0.567	76 (43.9%)	14 (51.9%)	0.442
Anxiety/ depression	148 (74.0%)	86 (68.8%)	50 (86.2%)	12 (70.6%)	0.140	128 (74.0%)	20 (74.1%)	0.992
EQ-5D utility index * †								
Mean ± SD	0.601 ± 0.287	0.683 ± 0.255	0.508 ± 0.266	0.316 ± 0.309		0.639 ± 0.263	0.359 ± 0.318	
Median (IQR)	0.689 (0.296)	0.735 (0.228)	0.620 (0.525)	0.260 (0.583)	<0.001	0.725 (0.298)	0.516 (0.553)	<0.001
VAS * †								
Mean ± SD	67.9 ± 21.0	75.2 ± 18.5		53.2 ± 10.0		70.5 ± 19.7	51.6 ± 22.3	
Median (IQR)	70 (30)	80.0 (21.0)	60.0 (31.0)	60.0 (35.0)	<0.001	75.0 (25.0)	50.0 (40.0)	<0.001

*Comparing patients with mild, moderate and severe disability; Jonckheere–Terpstra or Cochran–Armitage test for examination of trend.
†Comparing patients with RRMS and SPMS type of MS; Mann-Whitney, or X2 test for examination of difference.
MS: Multiple Sclerosis; EDSS: Expanded Disability Status Scale; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; VAS: Visual analogue scale; SD: Standard deviation; IQR: Interquartile range.

Table 8: HRQoL results by EDSS level and MS type.

in the lower costs observed in the RRMS subgroup; the mean cost per patient per year was €23,892 for RRMS and €40,381 for SPMS subjects respectively. Direct medical and non-medical as well as indirect costs all were significantly different between groups (all p<0.05); component costs of inpatient care and investigations were statistically significantly larger in RRMS patients (p<0.05), whereas economic burden due to MS-related investments, informal care and early retirement (disability pension) was greater in participants with SPMS (all p<0.05).

QoL

Anxiety/depression problems were reported by 74% of the patient population, while 67.5% had at least some mobility issues, 59% were experiencing usual activities limitations, 45% were complaining of pain/discomfort and 27% had at least some self-care difficulties (Table 8). The frequency of patients reporting problems with mobility, self-care and

usual activities was increasing significantly with worsening disability (all p<0.001), and it was found higher in patients with SPMS (all p<0.001).

The mean utility score of the sample was 0.601 (± 0.287); HRQoL index decreased significantly with worsening disability (p<0.001), i.e., 0.683 (± 0.255) in mild, 0.508 (± 0.266) in moderate, and 0.316 (± 0.309) in high disability patients. SPMS group's HRQoL was more impaired than that of the RRMS (p<0.001); the mean EQ-5D index was 0.359 (± 0.318) and 0.639 (± 0.263) for SPMS and RRMS subjects respectively. VAS results concerning self-assessed health were in congruence with these findings; the mean VAS score of the whole sample was 67.9 (± 21.0), and a decreasing trend was again established with increasing severity (p<0.001). Finally, the SPMS group was associated with a significantly lower mean VAS score compared with the RRMS group (51.6 vs. 70.5, respectively; p<0.001).

Discussion

The objective of this study was to estimate the health and economic burden of MS in Greece, while offering valuable insights into the way disease severity and MS type affect the related costs.

The mean annual cost per patient was estimated at €26,118. This is comparable to the results of a recent study across 5 European countries, in which the mean annual cost per patient ranged between €20,738 and €29,400 [10-15]. Worsening disability was associated with a substantially increased economic impact of the disease, which is in accordance with the findings of most published studies [10-13,15, 19,29-36]. According to the existing literature [10-20], severe disability, when compared to mild, is associated with increased costs for hospitalizations, consultations, laboratory tests and other drugs, although the cost of immunomodulatory drugs is reduced. In our research, total direct medical and non-medical as well as indirect costs indeed increased considerably with advancing disability, with statistical significances established for the majority of their components. Furthermore, treatment cost retained its prominence in all disability and MS type subgroups, though its share in the total cost gradually decreased, which may be attributed to the patient recruitment, as it is discussed subsequently. Informal care contributed significantly to the total cost (14.6%); its contribution increased from 5.7% in patients with mild to 32.6% in subjects with severe disability, confirming the importance of informal care for MS patients, which is strongly associated with the severity of the disease [10-15,18,19,29-36]. Higher mean disability in patients with SPMS compared with RRMS subjects resulted in almost doubled total costs, in congruence with what is observed in other European countries [10,12-15]; total direct medical and non-medical as well as indirect costs all were significantly different between the 2 groups.

HRQoL was found considerably impaired by MS. Psychological and mobility problems and difficulties related to usual activities were reported by the majority of the patients. The mean utility score in the sample was 0.601 (VAS mean score 67.9), which is lower than the corresponding value in the general population, though somewhat higher than in other similar reports [16-20,37], which could be attributed to the lower mean EDSS level of this study. Finally, higher severity and SPMS type of MS decreased HRQoL, which is consistent with the international literature [10-15,18,19,29-36].

There are several limitations related to the recruitment of patients from hospital MS centres, as it might result in a sample of subjects with higher mean disability [38]. Nevertheless, in our study, the number of patients which were assigned to the high disability group (EDSS 6.5-7.5) was relatively low (n=17). In fact, patients with EDSS >7.5 were not represented in our study, hence costs might have been actually underestimated due to the lack of high resource consuming patients. Currently, there are no country-scale studies of MS in Greece with epidemiological data concerning different patient disability categories, which could have been used as a demographic guide in the study design. Additionally, we approximated the productivity loss due to MS by the patient-reported reduction in their income, which may not be an appropriate proxy for estimating productivity losses, if there is a benefit to mitigate the fall in income.

Furthermore, the questionnaire explicitly requested resource utilization due to MS, but it still might have captured consumption unrelated to MS, thus yielding inflated costs. This possible limitation is particularly relevant to the comorbidities' economic burden, which was estimated as the total mean annual cost per patient, and not only as co-medication costs. Nevertheless, MS is a well-defined condition,

and unrelated comorbidity is relatively low due to the young age of the patients [19,38]. A degree of recall bias introduced by participants regarding their reports about past events or experiences may also be present, as it is a common peril among studies with a retrospective design [41]. Finally, the sample size of patients without a recent relapse was not large enough to estimate the specific cost related to relapses, which would have been a valuable piece of information.

In conclusion, the STORMS study contributes to the scarce information on costs and health of MS patients in Greece. In view of the increasing economic and HRQoL burden with worsening disability, the use of MS treatments that can effectively delay the progression of the disease may reduce the detrimental impact of the disease on patient and caregiver lives, as well as on society as a whole.

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