>It is estimated that these costs could be reduced by 25 % if only Indicated prevention services were adopted (policy change 1), 33 % if only Indicated prevention services were adopted (policy change 2) and 40 % if both, Indicated prevention and EI services, were adopted (policy change 3) in the country. This means an annual cost savings of about 2,000-2,800-3,300 Euro per patient when introducing policy changes1-2-3 respectively.

These estimates are very conservative in terms of that only health care costs and costs associated with reduced work productivity, and do not include costs associated with other sectors, e.g. social care, informal care, criminal justice, housing arrangements.

Conclusions

Overall, the UK economic analyses showed early detection and early intervention services for people with early psychosis had the potential for cost-savings from a societal perspective. Our results suggest that adopting Indicated prevention and EI services in the Czech Republic would be highly cost saving due to decrease in hospitalizations and better employment outcomes of people with psychoses. Uncertainty was tested in multiple sensitivity analyses which demonstrated robustness of the results across settings.

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Averting multiple sclerosis long-term societal and healthcare costs

Early intervention and lifestyle choices as key to success

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Background

Multiple sclerosis (MS) is a chronic, inflammatory demyelinating and degenerative disease of the central nervous system (CNS) with typical onset between age 20-40 years. Over 2 million people have MS worldwide, with 770.000 people in Europe affected. MS is the commonest cause of non-traumatic neurological disability in young adults [1]. MS imposes a high burden on society, in terms of production losses as well as on families, with a very high need for informal care. All types of costs increase with increasing disease severity. MS is an acquired immune-mediated inflammatory and degenerative disease due to an abnormal immune response to environmental triggers in people who are genetically predisposed. The actual cause is unknown [2]. The MS course is unpredictable, with some people minimally affected and others rapidly accumulating disability. To date, there is no cure for MS, but a number of disease modifying treatments (DMTs). Early diagnosis and treatment may delay, or even prevent, the previously inevitable disability [3]. The course of MS implies different stages, from the clinical onset and clinically isolated syndrome (CIS), to later stages of life featuring severe cognitive decline and physical disability. Also economic and patient related outcomes, vary across these stages of the disease. We therefore aimed to define the MS 'patient journeys' capturing the main unmet needs on the different life domains.

Methods

In order to perform a 'MS patient journeys'analysis, scientific and lay literature was scrutinized for the disease relevant clinical features, disease course, prognostic factors, available DMTs, guidelines for the management of a person with MS, and implications for his/her quality of life and social functioning. Also the economic burden of the different stages of the disease was considerd. The 'MS patient's voice' was listened to, through the wealth of material from the European MS Platform and its initiatives. In particular, semistructured interviews were conducted by EMSP with two MS patients advocates each representing a separate journey.

Treatment Gaps

In Europe patients with MS face three significant treatment gaps in their care pathway: (1) **poor access to treatment** (first treatment, switch therapy); (2) non- or reduced adherence specific to the DMTs; and (3) **poor treatment of fatigue**. Recent economic crisis has exacerbated the **unequal access to medicines**. The increasingly cost of DMTs and shrinking of public health budgets

jeopardies access to essential medicines. In 2014, considerable variations were detected in the access to DMTs for people with RR MS: 13% in Poland, 21% in UK and other Eastern Europe countries and 69% in Germany to give examples. Difference in access can be explained by healthcare infrastructure, number of neurologists, access to a neurologist, restrictive reimbursement and price of medicines and affordability as well as lack of awareness in the value of treatment [4]. Nearly half of the currently available DMTs involve self-injection, and all cause adverse events of varying degrees of severity. **This affect treatment adherence in patients with MS** (eg., forgetting the medication, injection anxiety, perceived lack of efficacy, coping with adverse events). **Fatigue** is reported in ca 96% of patients [5]. As an 'invisible' symptom of MS, fatigue can sometimes be confused with depression or just not "trying hard enough". Fatigue is a major cause of stopping working or reducing working hours. People with MS are missing out on an estimated 18 years of their working lives. While some of the symptomatic treatments are fairly good, treatment of fatigue needs to be urgently addressed.

Recommendations

Patient Journey 1: In this stage of the disease the **MS patient's needs** concerns (1) **diagnosis**: an early diagnosis through lab and instrumental examinations, (2) **therapy**: treatment of the acute phase; (3) **information and psychological support**: communication of diagnosis. **The diagnosis** of MS is based on spatial and temporal dissemination criteria which are searched for by means of clinical, lab and instrumental (neuroimaging) tests. Avoiding misdiagnosis or delaying MS diagnosis becomes crucial to ensure a correct and comprehensive management of the person with MS. The Centre for Diagnosis and Treatment of MS ('MS Centre'), including Day Hospital and Day Service, or even hospitalization represents the adequate **health care setting**, wherein the patient care pathway, incl., treatment choices and monitoring, should be coordinated. **The communication of the diagnosis** – a very delicate phase – should involve the patient and his/her direct relatives, the neurologist and when possible – also a psychological support. This communication must be correct and comprehensive, adequate to the patient's level of bio-psycho-social specificity, extended in time. **Information** in this phase is in general a priority for most patients. **Patient Journey 2:** Some health care needs are in common with Patient Journey 1 (DMTs continuation, symptomatic treatment, their monitoring, multidisciplinary approach at the MS Centre), but **rehabilitation and palliative care** may feature this stage. This person would need **documentation to start insurance procedures for disability**, adequate working conditions (changes), prescription for aids/devices, home and means of transportation adjustment. He or she **should be managed at home,** hence

the need of home care integrated with the territory primary level health care. Health care should pivot on the **General Practitioner** (GP), on the r**ehabilitation specialist**, and on the **nursing staff** (eg., a case manager), social services and residential structure to integrate health care (including palliative care) or admit the person.

The experience of a young patient with RRMS

"I started treatment (DMT) immediately after diagnosis…The most common symptoms for me are walking and gait difficulties, leg's spasticity, bladder problems, balance problems and fatigue… I think that the most important thing receiving an MS diagnosis is to take your time to understand what's happening; then you have to learn to live with MS and all that it can mean.... Sure it affects many aspects. At first it is a shock. I think that nobody can accept a chronic disease but you can learn to live with it in the best way you can".

The experience of a patient with progressive MS

"There was no DMD at the time I was diagnosed… I now manage my progressive condition with DMD medication, rehabilitation, physical training plan to maintain the undamaged part of my body, I also take nutrition and vitamin supplement as needed… My conclusions, in agreement with my neurologist, and seconded by several other researchers/neurologists is to continue what has been a very positive treatment experience. A multidisciplinary health team including psychosocial assistance with good communication is essential…"

Conclusions

MS imposes a high burden on patients and society, due to production losses, and a very high need for informal care. All types of costs increase with increasing severity of the disease. MS incidence is increasing, particularly among women. Lifestyle factors (eg., cigarette smoking, vitamin D insufficiency) have been consistently found in association to increased risk for MS onset in the general population and disease worsening. To date, there is no cure for MS, yet MS has become a treatable disease. Early diagnosis and start of DMTs may delay, or prevent, the previously inevitable disability. Once the diagnosis is confirmed, a coordinated multidisciplinary approach is needed, with MS nurses and MS psychologists, and physiotherapists for rehabilitation [6]. Two MS 'patient journeys' are defined, based on specific

needs, challenges and preferences: (1) the person with a new diagnosis of CIS fearing to develop defined MS, or with new MS diagnosis of MS, relapsing-remitting phase, fearing prognostic uncertainty towards worsening and disability accumulation; (2) the person with progressive MS experiencing accumulating disability, limitations in work and social life, dependence from others in daily activities; reduced response to most treatments (EDSS 4 to 9.5). Treating MS nowadays should aim to preserve brain and cognitive reserve through the early use of DMTs and by adopting a 'brain-healthy' lifestyle, which implies considering patients' values and preferences. Patients with MS face three main unmet needs, ie, gaps in access to treatment, DMT-specific non-adherence, treatment of fatigue. In addition, we need a more holistic approach to care. Awareness-raising on the fluctuating nature and often invisible symptoms of the disease together with small adaptations can help keep people in work.

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Averting multiple sclerosis long-term societal and healthcare costs

Early intervention and lifestyle choices as key to success

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Background

Multiple sclerosis (MS) is a progressive neuro-inflammatory and -degenerative disease typically affecting young adults in the prime of life, causing irreversible physical and mental disability. It is the leading cause of non-traumatic disability in young adults in many developed countries [1]. The burden of MS to society include direct (medical and non-medical) and indirect costs. In Europe, such burden amounts to €15.5 billion, and €37,000/case/year [2,3]: higher for other long-term conditions such as asthma, chronic obstructive pulmonary disease and diabetes [4]. MS societal costs increase significantly with disability: from €23,000 for mild MS to €77,000 for severe MS [3], as well as indirect costs (productivity losses for sick leave, incapacity to work and early retirement), and also informal care costs largely falling outside of the health and social care systems, borne by PwMS and families. Modifiable lifestyle factors seem to modulate the risk of MS in the population, as well as its worsening [1]. We aimed to analyse the economic gain of MS early treatment on the long-term societal costs, as well as the potential role of reducing the prevalence of two common modifiable lifestyle factors (ie., cigarette smoking habit, low vitamin D serum levels) to avert MS worsening based on identified clinical outcomes.

Methods

Efficacy data on early treatment reducing conversion from CIS to MS, and on increased risk of MS progression or disability from exposure to cigarette smoking and low vitamin D serum levels were taken from meta-analyses or systematic reviews [5-7].

Early treatment - Published data on the cost-effectiveness of CIS early treatment to conversion to MS were updated to 2017 figures and used to compare the economic evidence across different healthcare systems (Italy, Spain, Sweden [8-10]). Cost estimates were reported for both societal and healthcare provider perspectives (Euros). Effectiveness was expressed as Quality Adjusted Life-Years (QALYs) gains. Cost-effectiveness was reported as incremental cost-effectiveness ratio (ICER).

Lifestyle risk factors - Decision analytical tree modeling was developed and applied to assess the economic impact of:

- **Smoking cessation** [11] vs ever smokers (decrease in mean EDSS score % [5] and conversion from RRMS to SPMS [6]; model 1);
- **Increase of vitamin D (25(OH)D) serum level** on MS progression [2] vs status quo [11] (model 2).

The estimates were compared between the 10 country settings (Czech Republic, Sweden, France, Germany, Spain, UK, Italy, The Netherlands, Poland) with a societal perspective on annual costs [12] inflated to 2017 figures (Euros), and effectiveness in terms of QALY figures [13]. Sensitivity analyses were applied to test the robustness of the models according a range of effectiveness' levels [5,6]. Smoking analyses included additional model (model 3) to evaluate the economic impact of shifting from current [11] to target smoking prevalence levels as proposed by WHO [14].

Results

Early treatment - Early treatment to reduce conversion from CIS to MS is cost-effective from health care provider perspective across EU healthcare systems (ICER of EUR 3,000-41,000 per QALY). From a societal perspective it was always dominant, which means it was more effective and less costly (table 1).

Lifestyle risk factors - Consistent and significant annual QALY gains and savings have been shown from smoking cessation (0.11 QALYs and EUR 2,500-16,400 per case across country settings; figure 1) and increase of vitamin D serum levels (0.13 QALYs and EUR 435-6,210; figure 2). Significant cost effectiveness of both lifestyle interventions is already evident when using conservative clinical effectiveness data. Such QALY gains and savings are more remarkable in patients with increased disability. When considering the prevalence-based model (smoking only) the shift from current to WHO target smoking levels brings savings and QALY gains (cost-effective and cost saving approaches as per NICE; table 2).

Country	Time horizon (years)	Groups	NHS costs pp (euro)	Societal costs pp (euro)	QALY	ICER
Spain	50	CIS CDMS	371,452 340,992	654,772.75 664,811.74	15.42 14.68	NHS 41,162 SOCIETY - 13,566
Italy	25	CIS CDMS	199,247 198,379	258,367.89 264,939.15	7.84 7.49	NHS 2,994 SOCIETY - 18,775
Sweden	40	CIS CDMS	N/A	821,013.52 849,716.63	13.79 13.26	N/A SOCIETY - 54,157

Table 1: **Early treatment to reduce conversion of CIS to CDMS**
(Clinically Definite Multiple Sclerosis): cost effectiveness analysis; pp=per person

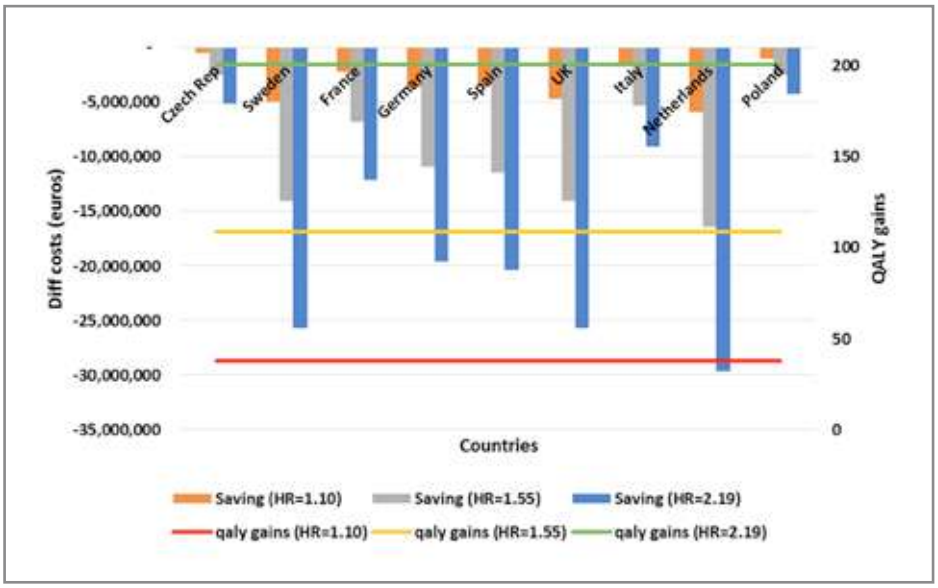

Figure 1: **Smoking cessation:** difference in costs (negative sign = saving) and QALY gains according to different adjusted estimate of risk (HR, Hazard Ratio) when considering a pop. of 1000 MS no smokers (compared with 1000 MS smokers)

Country	Outcome indicator (measure of risk)	Diff cost per 1000 MS patients	QALY gained per 1000 MS patient	ICER
Italy	progression EDSS score (HR=1.55)	- 607,459	19.43	- 31,260
	progression EDSS score (HR=1.10)	13,716	7.87	1,744
	conversion from RR to SP (RR= 1.88)	- 375,221.58	17.18	- 21,839
	conversion from RR to SP (RR=1.47)	- 200,402	9.18	- 21,839
Sweden	progression EDSS score (HR=1.55)	- 1,489,370	15.85	- 93,945
	progression EDSS score (HR=1.10)	- 275,054	6.42	- 42,860
	conversion from RR to SP (RR= 1.88)	- 433,383	19.84	- 21,839
	conversion from RR to SP (RR=1.47)	- 231,466	10.60	- 21,839

Table 2: **Smoking cessation: shift from current to WHO target smoking levels**

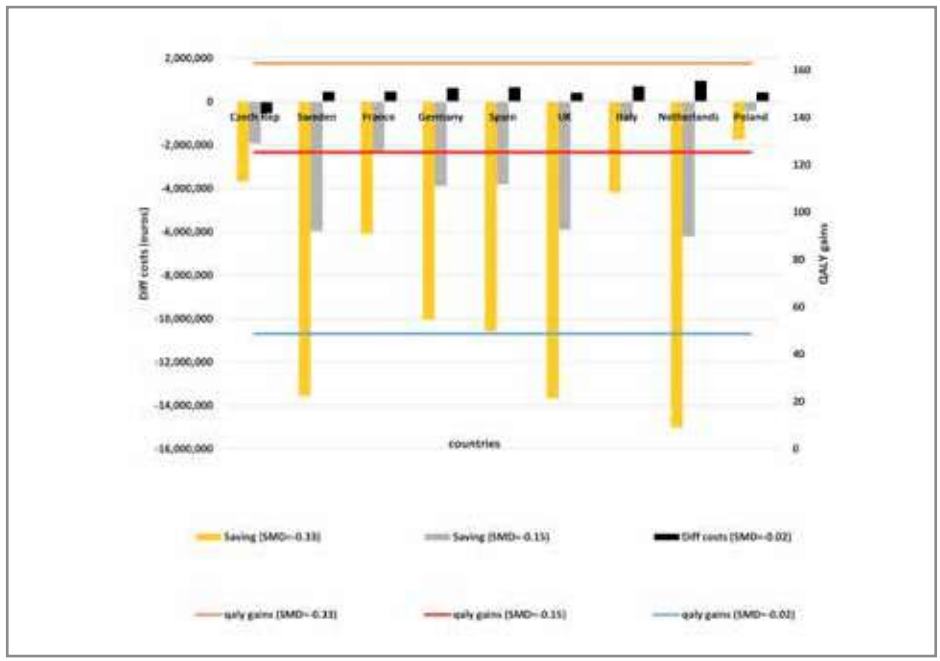

Figure 2: **Increase of vitamin D serum levels:** difference in costs (if negative sign = saving) and QALY gains according to different adjusted estimate of risk (SDM, Standardised Mean Difference) when considering a pop. of 1000 MS increase of vitamin D serum levels (from <20 mmol/l to 20+ mmol/l), compared with 1000 MS no increase of vitamin D serum levels.

Conclusions

Early treatment and a brain healthier lifestyle slow MS progression and indeed reduce the disease societal and healthcare costs. To the best of our knowledge, our work provide first economic evidence to base appropriate public health interventions to reduce the MS burden in Europe, also by means of controlling modifiable lifestyle factors in disease worsening. Further research is needed to overcome methodological limitations (eg., CIS economic models and evidence from available from the literature).

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NOTES

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