

## **Averting multiple sclerosis long-term societal and healthcare costs: the Value of Treatment (VoT) project**

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## **Abstract**

**Background and purpose:** The recent report on Value-of-Treatment (VoT) project highlights the need for early diagnosis-intervention; integrated, seamless care underpinning timely care pathways; and access to best treatments. The VoT-multiple-sclerosis (MS) economic case study analysis aimed to estimate the effectiveness/cost-effectiveness of both early treatment and reducing MS risk factors (e.g. smoking and vitamin D insufficiency).

**Methods:** A series of decision analytical modelling were developed and applied to estimate the cost-effectiveness of: (1) reducing the conversion from clinically-isolated-syndrome (CIS) to clinically-definite-MS (CDMS); (2) smoking cessation and increase of 25 hydroxy vitamin D (25(OH)D) serum level. Both (1) and (2) considered socioeconomic impact on averted MS disability progression. Costs were reported for societal and healthcare provider perspectives (pending on data across nations; Euros). Effectiveness was expressed as Quality-Adjusted-Life-Years (QALYs) gains. Long term (25-30-40-50-years) and short (one-year) timelines were considered for (1) and (2), respectively.

**Results:** Early treatment was cost-effective for the health care provider and both cost-effective/cost-saving for the society across time-horizons and nations. Smoking cessation and increase of 25(OH)D in MS patients were both cost-effective/cost-saving across nations.

**Conclusions:** 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.

## **Introduction**

Multiple sclerosis (MS), an immune-mediated inflammatory and neurodegenerative disorder of the central nervous system, is likely triggered by the action of exogenous factors in genetically susceptible people. Modifiable lifestyle factors, such as cigarette smoking, 25 hydroxy vitamin D (25(OH)D) serum levels' insufficiency have been consistently found in association with increased risk of MS onset in the general population and with disease worsening (Hempel S, et al. 2017(a)).

To date, there is no cure for MS, yet the disease has become a treatable condition. In the clinically isolated syndrome (CIS) speeding up referral to specialist care and diagnosis, and early intervention with disease modifying drugs (DMDs) are associated to better outcomes of both CIS and relapsing-remitting MS (RRMS) and are recommended to maximize lifelong brain health of people with MS (PwMS)(Giovannoni G, et al. 2016). In particular, in CIS DMDs delay the time to a second relapse (i.e., conversion to RRMS) and improves magnetic resonance imaging (MRI) outcomes, including brain atrophy rate (Comi G, et al. 2012; De Stefano N, et al. 2014; Edan G, et al. 2014). Yet, the actual access to DMDs for PwMS is very heterogeneous across populations in Europe (Kobelt G, et al. 2016), it is often delayed and/or subject to restrictions in licensing, and prescription and reimbursement policies.

The evidence of lifestyle risk factors found to be associated to MS progression may translate into secondary prevention interventions, such as smoking cessation and vitamin D supplementation and the promotion of a 'brain-healthy' lifestyle as part of a comprehensive approach to treatment to also be initiated at the time of diagnosis (Giovannoni G, et al. 2016).

This study is part of the larger Value of Treatment Project (VoT; European Brain Council 2017, promoted by the European Academy of Neurology (EAN) and funded by the European Brain Council (EBC) aimed to define the 'value' of treatment approaches and strategies of nine different brain disorders in Europe. Specifically the MS case study was undertaken to analyse the MS care pathway describing the major challenges and needs accompanying the patient's disease course from onset to later stages. In addition key treatment gaps identified from the patient journey analysis (such as the detrimental impact of some lifestyle factors and late intervention with DMDs) were considered for further in-depth economic analyses aimed at identifying the economic benefit of closing such gaps.

No data are available to showcase that early diagnosis and start of DMDs have an economic impact besides the health one, and mostly that interventions aimed to reduce exposure to detrimental risk factors such as cigarette smoking habit or 25(OH)D serum levels' insufficiency in MS patients also have an economic impact in preventing or slowing disability.

The focus of this paper was to build the economic case of treating MS in terms of cost-effectiveness of early treatment and, for the first time to our knowledge, of intervention on lifestyle factors such as cigarette smoking habit and insufficient 25(OH)D serum levels on disease progression and disability.

## Methods

Relevant evidence on the cost-effectiveness of early treatment was searched from peer-reviewed scientific literature with regards to European countries and long time horizon (at least 25 years) especially looking at the pharmacoeconomics of early treatment of MS in Europe using interferon beta (IFNB; Castrop F, et al. 2013). Economic data are presented for Italy, Spain and Sweden. When comparing costs and Quality-Adjusted-Life-Years (QALY) of treatment with beta-interferon 1b (IFNB-1b) between treatment initiation at diagnosis of CIS versus at diagnosis of clinically definite MS, the probability of conversion was higher among Italian patients untreated (85%) than treated (73%) from CIS diagnosis ( $p < 0.0001$ ) with a 25 year-long model-based cost-utility analysis following the Italian National Health Service (INHS) and societal perspectives (Lazzaro C, et al. 2009). Early treatment with IFNB-1b was highly cost-effective for the INHS (Incremental Cost-effectiveness Ratio (ICER): Euros 2,574.94) and dominant from the societal perspective. Based on the BENEFIT study a cohort of 1000 Spanish patients with CIS and health status measured with EDSS included patients who received early IFNB-1b treatment and those who did not (Piñol C.2016) The ICER of IFNB-1b versus no treatment in CIS patients were more effective and less costly (dominant) from a societal perspective. From the perspective of the Spanish Health System, the ICER was € 13/relapse avoided. In Sweden IFNB-1a 44 mcg three-times-per-week (tiw) was found to be 'dominant' vs no treatment in CIS over a 40-year time horizon (Fredrikson S, et al. 2013). Gains in QALYs were 0.53 and projected cost savings were 270,263 SEK. IFN beta-1a 44 mcg (tiw) remained dominant from a payer perspective.

Evidence on increased risk of MS disability progression from exposure to cigarette smoking and insufficient 25(OH)D serum levels was extracted from a recent systematic review by Hempel S, et al. (2017(a)), presenting the empirical evidence of modifiable risk factors related to MS progression measured with EDSS scores, time to conversion from RRMS to secondary progressive MS (SPMS) and probability of reaching EDSS 6. An increased risk of MS progression among smokers than non-smokers was reported based on 14 studies (HR = 1.55; CI = 1.10, 2.19; I<sup>2</sup> = 72%; 7 studies. In the same review, a negative Standardised Mean Difference (SMD) was obtained for 25(OH)D serum levels and EDSS scores across 15 studies of -0.22 (CI = -0.32, -0.12; 11 studies; I<sup>2</sup> = 66%).

Additional searches for the most updated socio-economic impact of the MS disease in Europe were undertaken in PubMed and Google Scholar looking at systematic reviews of the MS literature published between January and December 2016. The focus of the searches were the most updated European-based data on MS related direct and indirect costs and quality of life stratified according to severity of the disease (expressed as MS Expanded Disability Status Scale (EDSS)). When systematic reviews were not available we looked at individual population based studies collecting primary data in Europe.

Economic modelling for early treatment. Data on the cost-effectiveness of early treatment covered case studies in Italy, Spain and Sweden (Lazzaro C, et al. 2009; Piñol C. 2016; Fredrikson S, et al. 2013) were extracted from the individual studies related to different type of economic models, with different assumptions, different sources of evidence, and describing different time horizons (Table 1). The statistical and design heterogeneity of the individual studies did not allow to compare evidence across country settings; however for each individual case study we reported the cost-effectiveness of early intervention at long term (at 25 years or beyond). Cost estimates were reported for the healthcare provider (and also from the societal perspectives when available); Euros were updated to 2020 figures. Effectiveness was expressed as QALYs gains. ICERs, ie., cost to be invested per QALY gain, were calculated for the healthcare provider perspective. In addition, disaggregated costs (for the health care provider and societal perspective) and outcomes (QALYs) were also presented to allow readers to form their own opinion on relevance and relative importance of cost types to their decision making context. The individual case studies covered different time horizons (25, 40 and 50 years for Italy, Sweden and Spain, respectively).

Additional modelling included the calculation of long-term effects for the same time points across the three case studies looking at 25, 30, 40, and 50 years and adapting same economic model to the three settings to allow for comparability of results. The novelty of this economic analysis is the fact that it allowed to monitor the variation of cost-effectiveness across time and cover longer term impacts (up to 50 years) across the three nations.

allowed to monitor the variation of cost-effectiveness across time. In doing so, we took the case study with the longest time frame (Spain, 50 years) as referent case and re-run the Markov model presented by Piñol (2016) (see Table 1 and Appendix 1) to track changes in costs and effectiveness across time. For Sweden (Fredrikson S, et al. 2013), the time frame pictured in the original Markov model was 40 years (see Table 1). For our study we wanted to predict the differences in costs and effectiveness across alternatives at 40 years but also at three additional time points, 25, 30 and 50 years. In doing so, we adapted the Markov model used for the Spanish analyses to include the Swedish clinical, QALY and economic data (Ernstsson O, et al. 2016) and we calculated updated outcome estimates for the different time points. For Italy the original study was an epidemiological 25 years-long model and the costs effectiveness of the intervention was evaluated at 25 years. In our study we updated the Markov model by Piñol (2016) to include Italian clinical data, QALY and economic estimates (Lazzaro C, et al. 2009).

The data considered for the economic modelling are presented in Figure 1. Different sensitivity analyses were undertaken to test the robustness of the model according to a series of assumptions (see Appendix 2).

Economic modelling for lifestyle risk factors. Additional decision analytical models were developed and applied to assess the economic impact of: cigarette smoking cessation assumed as non-smokers vs ever smokers<sup>1</sup> and looking at decrease in mean EDSS score % (Kobelt G and Pugliatti M 2013); increase of

25(OH)D serum level on MS disability progression vs status quo (Hempel S, et al. 2017(a)). Decision analytic tree structures and epidemiological estimates are reported in Tables 2 and 3, respectively. Cost and effectiveness data extracted from the literature were categorised according to EDSS score (Figure 1; Ernstsson O, et al. 2016). A population of 1000 MS individuals was considered for each analysis. The economic and utility estimates were reported for 10 country settings (Czech Republic, Sweden, France, Germany, Spain, UK, Italy, The Netherlands, Poland) with a societal perspective on annual costs (Euros), and effectiveness in terms of QALY figures (Hawton A and Green C, 2016). A one-year timeline was considered. Deterministic sensitivity analyses were applied to test the robustness of the models according a range of effectiveness' levels (Hempel S, et al. 2017(a); see details in Tables 2 and 3). Despite the heterogeneous economic evidence from different methodologies used in original work prevented from a direct comparison of the estimates across settings, we could still evaluate whether smoking cessation and increase of 25(OH)D serum level had an effective impact when looking at case studies with different healthcare systems, access to care, and level of income.

## **Results**

Economic modelling for early treatment. Results from the economic analyses showed that early treatment to reduce conversion from CIS to CDMS is cost-effective from health care provider perspective across time (ICER of euros 2,579- 3,099 and 40,668 - 45,729 per QALY in Italy and Spain respectively). Figure 2 reports on the ICERs for the baseline scenario and sensitivity analyses. In Italy early intervention is highly cost effective for any scenario considered (all under euros 3000 per QALY). The Spanish sensitivity data analyses confirmed a variation of ICER between 29,966 and 52,285 euros per QALY. From a societal perspective early intervention was always dominant (compared with conversion from CIS to CDMS), which means it was more effective and less costly (Figure 3). The longer the time frame the more effective and cost saving was the early intervention. The same results were confirmed across healthcare settings. Our sensitivity analyses showed that early intervention was always cost saving and more effective across the different scenarios (Figure 3).

Economic modelling for lifestyle risk factors. As partial predictors of MS progression, cigarette smoking and low 25(OH)D serum levels with their impact on disease progression as graded by Hempel et al (2017, a) were selected for our economic modelling (Table 3). Consistent and significant annual QALY gains and cost savings (negative difference in costs) are recurrent outcomes for smoking cessation across cases (Hazard Ratio, HR = 1.55: 0.11 QALYs and euros saved 2,500-16,400 per case across country settings; Figure 4). The same positive outcomes were reported when looking at increased 25(OH)D serum levels (Standardised Mean Difference, SDM = - 0.22 (Hempel S, et al. 2017(a)): 0.15 QALYs and euros saved 435-6,210; Figure 4). Sensitivity analyses for both smoking and 25(OH)D serum level models showed that significant cost-effectiveness of both lifestyle interventions is already evident when using conservative estimates for clinical effectiveness (see figure 3, smoking: HR

range between 1.10 to 2.19, and Figure 5, 25(OH)D serum levels: SMD range between -0.32 to -0.12, respectively).

## **Discussion**

The economic analyses confirmed that early treatment and a brain healthier lifestyle slow MS progression and indeed reduce the disease societal and healthcare costs (Ernstsson O, et al. 2016; Kobelt, G, et al. 2017; Tinelli M, et al. 2018). The longer is the time frame the more successful is early treatment in terms of both economic (decreased health care provider investments and increased saving for society) and health outcomes. MS is nowadays diagnosed more frequently in the population, not only in relation to the disease increasing incidence, but also for the use of new diagnostic criteria (Shirani A, et al. 2012; Banwell B, et al. 2013; Cutter GR, et al. 2015) which allow to detect the disease earlier as CIS or even radiologically isolated syndrome (RIS), i.e., as isolated or subclinical demyelinating events of the central nervous system likely prone to convert to MS over time. DMDs are recommended to be started early at the CIS stage (Montalban X, et al. 2018). This attitude inflates the direct health care costs of MS, but will have an impact in reducing long-term costs especially from the societal perspective.

The impact of lifestyle factors has been investigated in terms of both disease epidemiological (i.e. incidence) and clinical outcomes (e.g., disease activity and accumulation of disability (McKay KA, et al. 2015; McKay KA, et al. 2017)). However, to the best of our knowledge, this work for the first time provides an economic evidence (value) of the impact of two such factors (cigarette smoking and insufficient 25(OH)D serum level) on disease worsening. Our work provide first economic evidence in terms of both cost-effective and cost-saving results to reflect on the introduction of appropriate public health interventions to reduce the MS burden in Europe, by promotion of early treatment also by means of controlling modifiable lifestyle factors in disease worsening.

The successful economic results of averting MS long-term societal and healthcare consequences featured in this paper were aligned with the overall positive outcomes emerging from the analyses of the brain disease case studies included in the VoT project (European Brain Council, 2017). The VoT project findings confirmed that bridging the treatment gaps is widely beneficial – for patients, families, providers, payers, and policy-makers – and this is recurrent across brain disorders. The methodology applied for the VoT economic case study analyses (including the MS analyses presented here) proved to be robust and adequate to provide, for the first time, the overall a measure of the benefit of closing treatment gaps for MS and other brain disorders.

A limitation of the VoT methodology relates to the lack of primary data and this may have had impact on some areas of uncertainty relating to the economic results of the project.

For the MS economic analyses presented in this paper economic modelling was chosen given the lack of primary data on cost and outcomes in both (i) MS early interventions across country settings and long term horizons as well as (ii) smoking cessation and increase in 25(OH)D serum levels in MS patients.

Unfortunately, the statistical and design heterogeneity of the published studies reporting on early intervention effects caused uncertainty around the correct value for health state costs and utilities to be used in modelling across the different country settings. As a consequence, we felt that the direct comparison of the effectiveness and cost-effectiveness of early intervention across healthcare systems was compromised. We tried ourselves to re-run previous Spanish model and adapt it to cover also the lack of long term data in the other settings (beyond the published time horizons).

There are also limitations related to the risk factor analyses. They are mainly associated with the methods of estimating association of clinical risk factors with treatment outcomes, allocating different health status and economic outcomes according to the patients' EDSS score. We feel that more work is needed to better capture the dose-response relationships for smoking status, 25(OH)D serum levels on MS socioeconomic impact, in terms also of MS relapses, and disease severity.

The choice of the risk factors analysed was made to include those factors presenting the most robust evidence across European settings (Hempel S, et al. 2017(a)). The economic analysis considered their etiological effect on the progression of MS. Evidence on the effects of risk factor interventions is less robust, but still supporting the same direction of results on decreased disability progression (Hempel S, et al. 2017(b)). However, the same review underscores that since these findings are based on associations at a single time point and there is no evidence of a causal effect (nor any data to support that an intervention to modify these risk factors would translate into effects on disease progression). Any estimates of economic benefits therefore have to be presented and interpreted with great caution. Additional cost-effectiveness studies would be needed to evaluate the health outcomes and economics associated with the current national guidance relating to smoking cessation (or 25(OH)D serum levels) through the introduction of suggested smoking cessation (or vitamin D supplementation) interventions. Our proposal for new research would include also exploring the economic impact of other MS risk factor (such as over nutrition and obesity) and the extension of the prediction modelling to the overall population.

Lastly more robust research would be welcome to better design the MS patient care pathway according to patient experience and preferences of care management. An health economic technique, such discrete choice experiments (Clark MD, et al. 2014) could find a new use to support the development of person-centered care pathways in MS according to patient preferences and experience of care (Anagnostou D, et al. 2017). A DCE-based patient relevant outcome indicator could also be developed and applied to evaluate the benefits attached to new person-centered care pathways compared to current care (for example see application to diabetes (Tinelli M, et al. 2017) and also monitor their performance (alongside other clinical and health status indicators) against defined benchmarks (Tinelli M, et al. 2016).



## **CRedit author statement**

Michela Tinelli and Maura Pugliatti: Conceptualization, Methodology, Formal analysis, Data Curation, Writing - Original Draft, review and editing, Visualization, Project administration, and Funding acquisition.

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