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Predictors of Ability to Work in Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronic disorder that typically shows accumulation of disability, affecting the ability to work. The disease severity is usually graded by physicians with the expanded disability status scale (EDSS) in the clinic, but patient-reported outcome questionnaires are also available, like the Multiple Sclerosis Impact Scale (MSIS-29) or Fatigue Scale for Motor and Cognitive Functions (FSMC). The aim of this work was to investigate the quantitative link between disease severity and the number of days with MS-related sickness benefits from registry data (the Swedish MS registry and the Swedish Social Insurance Agency's Micro Data for Analyzes of Social Insurance registry). An item response theory model for the disability was built, linking the EDSS, MSIS-29, and FSMC to the same underlying disease construct through five correlated latent variables. A Markov state model for the level of sickness benefits was also developed, in which the disease severities from the disability model were tested as covariates, on top of age. The latent variable for EDSS was the most important predictor of work ability. Patients with low disability (EDSS < 3) hardly had any sickness benefit days, while patients with severe disability (EDSS ≥ 6) were found to spend over 50% of their time with sickness benefits. Physical aspects of the disease were found to be more important than psychological aspects in predicting work ability. This underlines the patient-specific nature of MS, and the need for predictive models such as these to evaluate treatment effects, make risk assessments, and calculate societal and individual costs.

1 | Introduction

Being able to work can be a source of identity, economic independence, and socialization. Losing this ability due to a debilitating disease is a major disruptor in any person's life and bears high societal costs. Multiple sclerosis (MS) is a chronic degenerative disease that is estimated to affect over 2.9 million people globally and is considered one of the leading causes of disability in young adults [1]. Over time, increased lesion burden, brain atrophy, reduced repair capacity, and neurodegenerative processes leading to disability occur [2]. While the etiology of MS has not yet been fully understood, there has been encouraging progress in the development of novel treatments during the past 30 years [3]. Today, an increasing number of disease-modifying therapies

are available for patients, and multiple innovative drugs are in the pipeline [4–6]. With this growing choice of available treatments and considering an increasing number of even more costly biologic drugs, the need for robust evidence regarding the cost-effectiveness of a treatment is growing too. Public agencies require justifications that the available resources are being efficiently used, and pharmaceutical companies desire arguments to justify their pricing structure. However, the collection of the data necessary to estimate the societal costs of a disease is extremely challenging. In most cases, models on cost-effectiveness rely entirely on data from clinical trials [7]. Only recently have attempts been made to use more real-world-like data in the determination of MS-associated costs. In a survey conducted in 16 European countries, the annual societal costs per person

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Study Highlights

- What is the current knowledge on the topic?
 - Multiple sclerosis (MS) may lead to impaired ability to work. There are different questionnaires to evaluate MS disease severity.
- What question did this study address?
 - How does the disease severity, as reported by clinicians and self-reported by the patient, relate to the number of days with sickness benefits within MS?
- What does this study add to our knowledge?
 - The number of sickness benefit days varies considerably, heavily depending on disease severity. The EDSS was best at predicting MS-related sickness benefits. Physical factors also seem more important than psychological factors for this prediction.
- How might this change drug discovery, development, and/or therapeutics?
 - The model approach could be used to gain a better understanding of who will be at risk of disability to work, and to evaluate treatments with respect to individual and societal costs.

with MS have been estimated to range from 22,800€ in mild to 57,500€ in severe disease [8]. While this collected data does not suffer from the same limitations inherent to clinical trial data, it still does not represent observational real-world data.

In this work, we aim to combine two unique data sources to develop a quantitative link between various measures of disability in MS and the requirement for sickness benefits. We use registry data from the Swedish Neuro Registries to obtain real-world clinical MS data and data on the payment of sickness benefits from the Swedish Social Insurance Agency.

The Swedish Neuro Registries, a Swedish national quality registry, aims to improve the equity and quality of neurological care as well as ensure adherence to national guidelines. MS is one of several neurological diagnosis groups included in the registry. The Swedish MS registry (SMSreg) was officially launched in 2001 [9], and today, more than 70 centers from all counties of Sweden participate in the data collection. The registry contains data on more than 24,000 Swedish MS patients, representing a coverage of over 80%, with a total number of recorded visits exceeding 230,000 [9]. In this work, SMSreg was used as a data source for longitudinal information on patient disability as assessed by the Kurtzke expanded disability status scale (EDSS), the Multiple Sclerosis Impact Scale (MSIS-29), and the Fatigue Scale for Motor and Cognitive Functions (FSMC). While the EDSS is physician-assessed, both MSIS-29 and FSMC are patient-reported outcome measures (PRO).

The Swedish Social Insurance Agency (Försäkringskassan) administers the areas of social insurance that provide financial security in the event of illness, disability, and for families with children. The agency covers essentially all persons who live and work in Sweden [10]. For this analysis, data on the payment of sickness benefits in the Micro Data for Analyzes of Social

Insurance (MiDAS) registry from the Swedish Social Insurance Agency were used.

With the overall goal of creating a quantitative link between measures of disability and sickness benefits, we proceeded in three steps. First, we developed an MS disability model capturing the relationship between a set of hypothetical latent disability variables and the observed assessment scores (i.e., EDSS, MSIS-29, FSMC). In the second step, a sickness-benefit model was developed to capture the variation in benefits. Finally, we included the disability variables from step one in the sickness benefit model to evaluate their predictive value.

2 | Methods

2.1 | Disability Assessments

2.1.1 | EDSS

The EDSS is the most widely used measure of disease progression in MS. The score is based on seven functional systems, including vision, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, mental (cerebral), as well as ambulation (500-m walk) and reliance on walking aid [11]. The EDSS is a summarized measure that ranges from 0 (normal neurological exam) to 10 (death due to MS) in incremental steps of 0.5. In the SMSreg database, only the EDSS total score assessed during routine visits is available and was used in this analysis.

2.1.2 | MSIS-29

The MSIS-29 consists of 29 statements, in which the patients are asked to rate their views about the impact of their disease on day-to-day life during the past 2 weeks. The patients rank the statements according to a Likert-type scale from 1 to 5, where 1 represents “Not at all,” and 5 “Extremely,” with the total score of the test ranging from 29 to 145, but the score is typically presented as the mean [12]. The 29 items can be split into two scales: physical impact (20 items) and psychological impact (nine items). Patients can report the MSIS-29 via an online patient portal. For this work, the item-level data were used.

2.1.3 | FSMC

The FSMC aims to assess MS-related cognitive and motor fatigue, where the patients are asked to rate 20 questions related to problems in everyday life associated with an extreme form of tiredness (fatigue). The questions are rated according to a Likert-type 5-point scale, ranging from “does not apply at all” to “applies completely,” producing a score between 1 and 5 for each scored question. The total score ranges between a total minimum value of 20 (no fatigue at all) and a total maximum value of 100 (most severe grade of fatigue) [13]. Like the MSIS-29, the FSMC is made up of two subscales: motor-related and cognitive-related fatigue. The score can also be reported by the patient via an online patient portal. In this analysis, the item-level data of the FSMC were utilized.

2.2 | Data

2.2.1 | EDSS & PRO Data

The study population was identified through SMSreg and consisted of all individuals with at least one record in the registry in the 5-year period starting from the beginning of 2014 to the end of 2018. Records from individuals younger than 18 years and those older than 65 years were excluded. Data extracted from the SMSreg included the MS disability assessments (i.e., EDSS, MSIS-29, and FSMC scores), patient and clinical characteristics. For the disability model, at least an EDSS measurement was required, such that data from 9611 patients with a total of 81,079 records of disability assessment were included in the analysis. The number of records and records/patient for each assessment were (33,640, 3.5) (EDSS), (35,187, 3.66) (MSIS-29), and (12,252, 1.27) (FSMC), respectively.

2.2.2 | Sickness Benefit Data

MiDAS was used as a data source for work capacity. MiDAS includes data for benefits provided in the event of reduced work capacity because of sickness (e.g., sickness cash benefit, rehabilitation benefit, activity and sickness compensation). For this work, all records regarding sickness benefits from the beginning of 2014 to the end of 2018 for the subjects included in SMSreg were requested from the Swedish Social Insurance Agency. Records of reimbursements from the first 14 days of any sickness period, paid by the employer, were not included.

The data obtained contained records of sickness benefit periods, encoded as start date, stop date, associated disease, and compensation level (25%, 50%, 75%, or 100%). For the analysis, only records corresponding to MS-related sickness periods (ICD-10 codes: G35, G36, G37, and H46), from all subjects between 18 and 62 (as this is the start of the governmental retirement age range) years of age were considered. For each subject, the sickness benefit period data were transformed to daily observations of sickness benefits at levels of either 0%, 25%, 50%, 75%, and 100%. A level of 0% was assumed for a day without any recorded MS-related sickness benefit.

Overall data from 14,626 individuals were utilized for the analysis, with a total of 20,840,662 days, including subjects without EDSS measurements. On 62% of the days considered, subjects did not receive any benefits due to MS; on 7% of the days, they received benefits for reasons other than MS, while on 31% of the days, they did receive benefits related to MS.

2.3 | Models

2.3.1 | Disability Model

Let Y_{ij}^k denotes an item-level score for subject i and item j of subscale k (EDSS, MSIS-29 physical, MSIS-29 psychological, FSMC motor, FSMC cognitive). The probability of observing a score of s was modeled according to

$$P\left(Y_{ij}^k = s\right) = P\left(Y_{ij}^k \geq s\right) - P\left(Y_{ij}^k \geq s + 1\right)$$

$$P\left(Y_{ij}^k \geq s\right) = \frac{e^{a_j^k\left(\Psi_i^k - b_{js}^k\right)}}{1 + e^{a_j^k\left(\Psi_i^k - b_{js}^k\right)}}$$

where Ψ_i^k is the subject-specific disability latent variable (LV) for subscale k , and a_j^k, b_{js}^k are the item-specific discrimination and threshold parameters, respectively. The LVs were modeled as random effects only, i.e.,

$$\Psi_i^k = \eta_i^k \quad \eta_i^k \sim N(0, 1)$$

and their correlation was freely estimated, that is,

$$\text{Corr}\left(\eta_i^k, \eta_i^l\right) = \rho_{kl}$$

2.3.2 | Sickness Benefit Model

Let $X_{i1}, X_{i2}, \dots, X_{id}, \dots$ with $X_{id} \in \{0, 0.25, 0.5, 0.75, 1\}$ denote the sequence of MS-related sickness benefits for subject i on day d . The probability for a subject to have sickness benefit level m on day $d + 1$ given the sickness benefit level n on the previous day, was modeled as

$$P\left(X_{i,d+1} = m \mid X_{id} = n\right) = P\left(X_{i,d+1} \geq m \mid X_{id} = n\right) - P\left(X_{i,d+1} \geq m + 1 \mid X_{id} = n\right)$$

$$P\left(X_{i,d+1} \geq m \mid X_{id} = n\right) = \frac{e^{\Phi_{i,d} - b_{n,m}}}{1 + e^{\Phi_{i,d} - b_{n,m}}}$$

where $b_{n,m}$ is the threshold parameter for a transition from sickness benefit level n to m and $\Phi_{i,d}$ is a time-varying subject-specific sickness propensity. For the first day, the observed sickness benefit level was used; that is, the probability was not modeled.

Sickness benefit predictors were investigated on the sickness propensity according to

$$\Phi_{i,d} = \theta_1(z_{age} - 18) + \theta_2\Psi_{i,d}^1 + \theta_3\Psi_{i,d}^2 + \dots + \eta_i$$

where the LV values $\Psi_{i,d}^k$ were estimated using maximum a posteriori (MAP) estimation based on the EDSS-PRO model for days with assessments and then carried forward and η_i is the disability model a random effect.

2.4 | Simulations

The sickness benefit model with all five disability variables (EDSS, MSIS-29 physical, MSIS-29 psychological, FSMC motor, FSMC cognitive) as well as age was used as a simulation model to calculate the expected number of days with sickness benefits per year for different scores and age ranges, using a full model approach. Correlations between scores and age were maintained by sampling score-age combinations from the observed data, and LVs were also sampled from the observed distribution.

2.5 | Software

Model development and parameter estimation for the EDSS-PRO model were performed using the mirt package in R [14].

Sickness benefit modeling was performed in NONMEM 7.4 using the LAPLACE estimation algorithm for parameter estimation [15].

3 | Results

3.1 | Disability Model

The final EDSS-PRO model consisted of five correlated LVs. Each LV represented one score; that is, LV one was associated with the EDSS, LV two with the MSIS-29 physical, LV three with the MSIS-29 psychological, LV four with the FSMC motor, and LV five with the FSMC cognitive score. Fewer LVs (including a bifactor model) were tested, but did not describe the data as well (not shown). A schematic of the model is shown in Figure 1. Model evaluations showed that the model was able to accurately describe the relationship between each of the LVs and the associated item-level scores, as well as between different scores (Figure S1). A detailed model evaluation can be found in the appendix (Figures S2–S7), and the parameters are shown in Supplemental Code 1.

In the chosen parameterization, the estimated correlation between LVs represents the similarity of the measured constructs assessed by each of the scores. These correlations are shown in Table 1. All correlations were estimated to be positive but markedly differed in magnitude. High correlations (>0.7) were found between the two subscores of MSIS-29 and FSMC, between EDSS and MSIS-29 physical, and between MSIS-29 physical and FSMC motor. The lowest correlations (≤ 0.30) were estimated between EDSS and MSIS-29 psychological, as well as between EDSS and FSMC cognitive.

3.2 | Sickness Benefit Model

The structure of the final five-state Markov model postulates five states corresponding to various levels of sickness linked to MS (Supplemental Code 2). The model assumes that on a given day, a subject can be either 0%, 25%, 50%, 75%, or 100% sick due to MS. Subjects can transition freely between states from 1 day to the next. The transition probabilities are freely estimated but

linked to a subject-specific sickness propensity, quantifying a subject's tendency to be sick. Furthermore, it is assumed that the transition probabilities to change in a coherent manner, that is, an increasing sickness propensity will increase all transition probabilities to higher percentages of sickness and decrease the transition probabilities to lower percentages. In consequence, the inclusion of a predictor on the sickness propensity will affect all transition probabilities jointly.

A model with age included as a covariate on the sickness propensity formed the basis for the evaluation of the predictive value of the individual disability assessments. Model evaluations showed that the base model was able to reasonably characterize the relationship between age and the percentage of days spent in each state (Figure 2). The linear age relation was deemed parsimonious, and age did not show nonlinear trends with any LV (Figure S8).

Starting from the base model, including age, the LV values from the different disability assessments were included as additional predictors in a stepwise manner, testing first one predictor at a time. Each LV was included as a time-varying relationship, with the LV values being carried forward until the next assessment. A selection of the tested relationships and the resulting improvement in objective function value is shown in Table 2. The inclusion of the LV for EDSS yielded the largest improvement in the first step, followed by the LVs for MSIS-29 physical and the FSMC motor. The simultaneous inclusion of both MSIS-29 subscales or both FSMC subscales resulted in larger improvement than each subscale alone (difference in objective function value (dOFV) -1592.1 and -1260.6 , respectively), but not as high as the EDSS.

3.3 | Simulations

For simulations, a full model was used. Figure 3 shows the expected number of benefit days per year for different scores and age ranges in a univariate manner. For all assessments considered, the figure highlights a strong difference in the number of days with compensation between low and high values. Similarly,

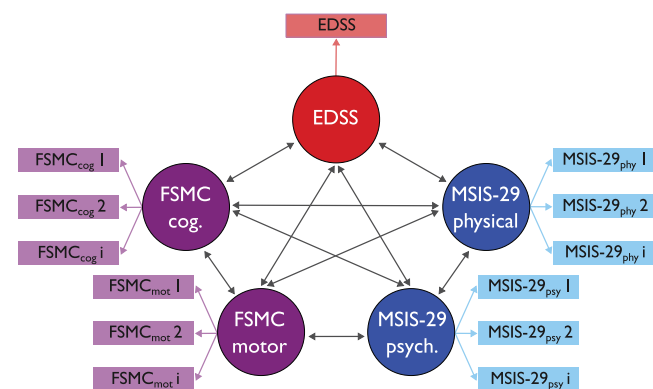


FIGURE 1 | Schematic representation of the EDSS-PRO score model. Numbers indicate items, black arrows indicate the estimated correlations, and colors indicate the different scales.

TABLE 1 | Correlation between latent variables.

	EDSS	MSIS-29 phy	MSIS-29 PSY	FSMC mot	FSMC cog
EDSS	1				
MSIS-29 phy	0.73	1			
MSIS-29 psy	0.30	0.71	1		
FSMC mot	0.47	0.72	0.59	1	
FSMC cog	0.28	0.57	0.60	0.92	1

Abbreviations: COG, cognitive; EDSS, expanded disability status scale; FSMC, fatigue scale for motor and cognitive functions; MOT, motor; MSIS-29, multiple sclerosis impact scale; PHY, physical; PSY, psychological.

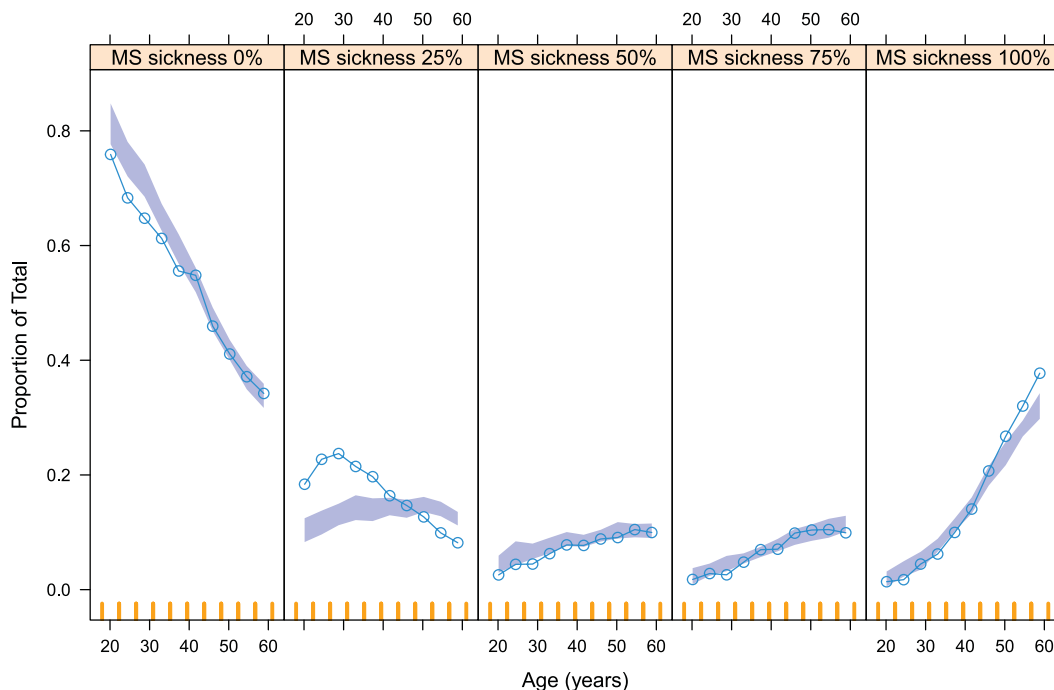


FIGURE 2 | Visual predictive check comparing observed (solid blue line) and model simulated (shaded blue area) fraction of days spent in each benefit level as a function of age. The proportion of the total adds up to 1 for each age bin across the strata.

TABLE 2 | Overview of the predictors tested in the sickness-benefit model and the corresponding drop in objective function value (OFV).

Step	Model	OFV	dOFV
0	Base (age)	388083.8	
1	Base + LV EDSS		-1661.6
	Base + LV MSIS-29 PHY		-1589.8
	Base + LV MSIS-29 PSY		-786.4
	Base + LV FSMC MOT		-1044.2
	Base + LV FSMC COG		-747.5
2	Base + LV EDSS + LV MSIS-29 PHY		-222.6
	Base + LV EDSS + LV MSIS-29 PSY		-322.7
	Base + LV EDSS + LV FSMC MOT		-232.6
	Base + LV EDSS + LV FSMC MOT		-251.9
3	Base + LV EDSS + LV MSIS-29 PSY + LV MSIS-29 PHY		-0.3
	Base + LV EDSS + LV MSIS-29 PSY + LV FSMC MOT		-40.0
	Base + LV EDSS + LV MSIS-29 PSY ± LV FSMC COG		-46.4

Abbreviations: COG, cognitive; dOFV, difference in OFV; EDSS, expanded disability status scale; FSMC, fatigue scale for motor and cognitive functions; LV, latent variable; MOT, motor; MSIS-29, multiple sclerosis impact scale; OFV, objective function value; PHY, physical; PSY, psychological.

there is a large difference for the three age groups. Among the assessments, EDSS shows the biggest differences, with 21 expected benefit days for patients with an EDSS value between 0 and 2.5 and 262 expected benefit days for patients with a value between 6 and 9.

Figure 4 provides a view of the same simulated data as in Figure 3, but stratified by EDSS score and age group. The figure stresses the large differences in the expected number of days with compensation between different groups of patients even more. While patients under 30 years of age, in the lowest EDSS group, with low MSIS-29 or FSMC values have only 1 expected day with compensation, patients at the opposite extreme have more than 300 expected days. For the lowest EDSS group (0 to 2.5), MSIS-29 physical provides the biggest difference, that is, a patient with an MSIS-29 physical of more than 2.5 has more than three times the expected number of compensation days than a patient with a value below 2.5. For larger EDSS values, this difference diminishes. Thus, MSIS-29 physical is a strong predictor for assessing the disease severity while the EDSS is low.

4 | Discussion

In this work, we combined two real-world data sources to develop a model quantifying the link between various measures of disability in MS and MS-related sickness benefits. Our model enables a patient-level prediction of the expected number of benefit days in the period of interest based on age, EDSS, MSIS-29, and FSMC. The data sources utilized here, SMSreg and the MiDAS database from the Swedish Social Insurance Agency, provide purely observational data on disability assessments and sickness benefits for a very large fraction of the Swedish MS population.

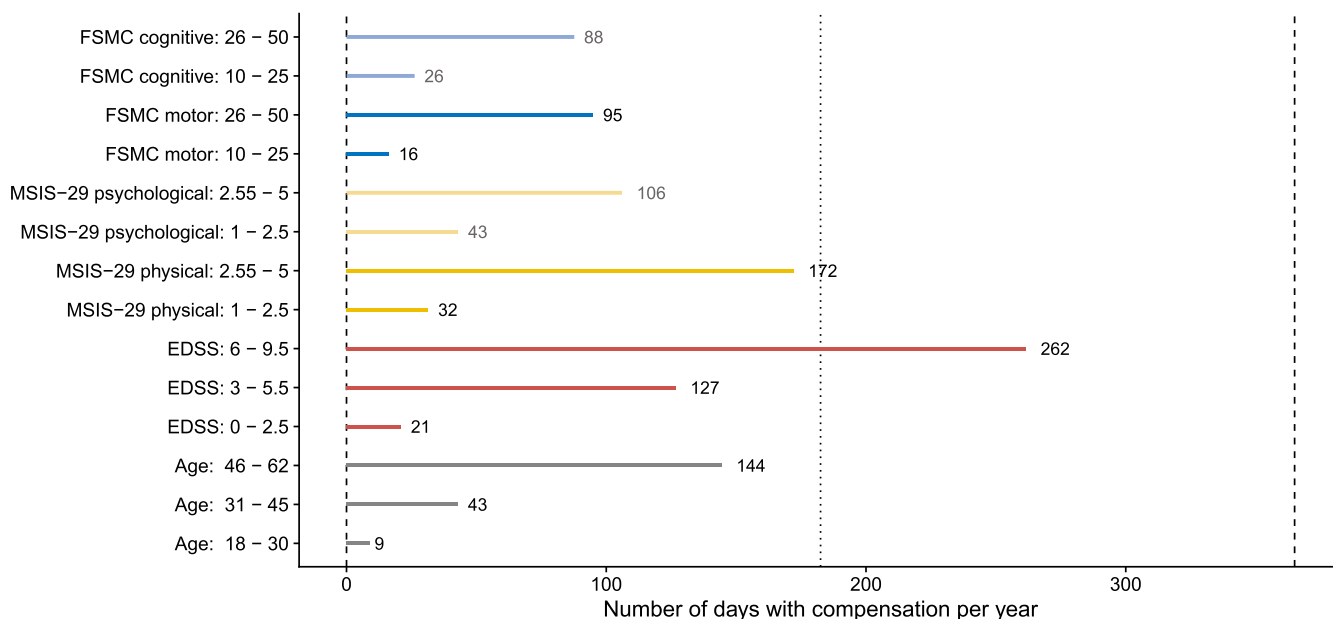


FIGURE 3 | Expected number of days with benefits per year for different scores and age ranges. The dashed lines indicate 0 and 365 days; the dotted line indicates 182.5 days, that is, half a year. Colors indicate different covariates and hues separate subscales.

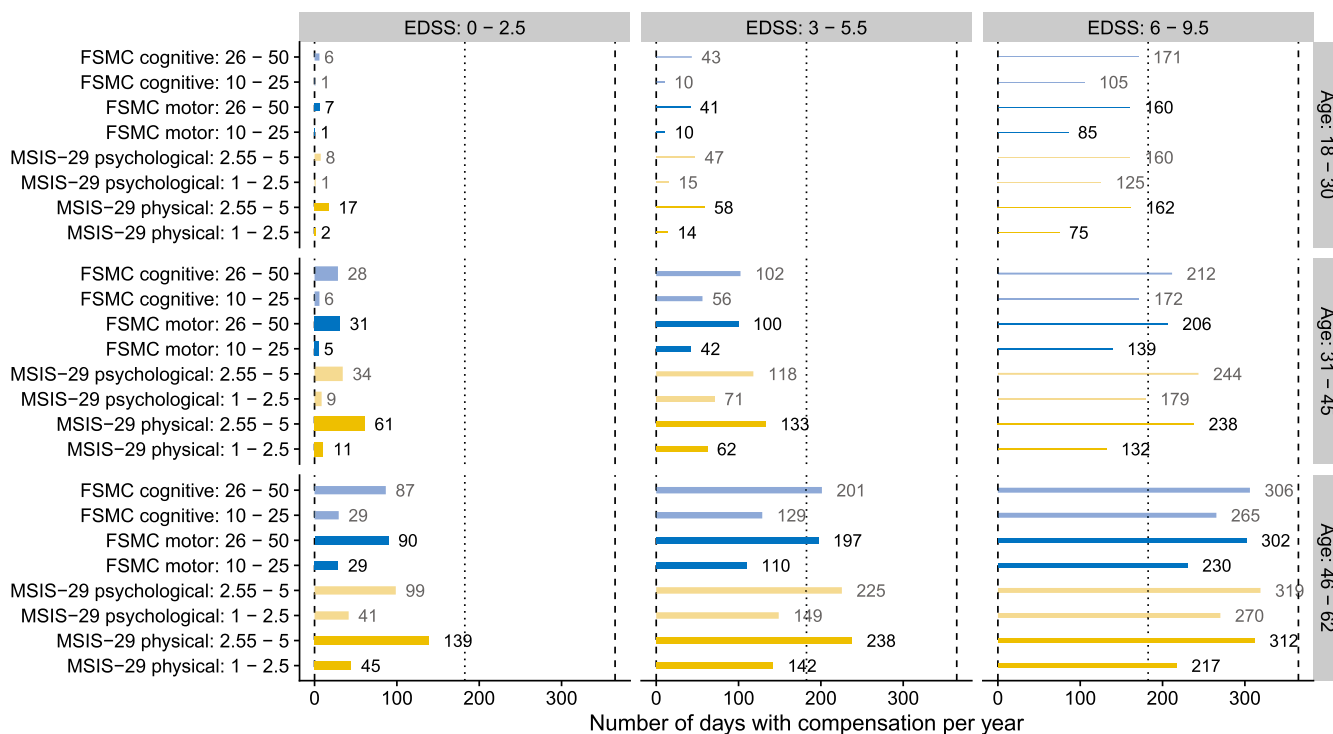


FIGURE 4 | Expected number of days with benefits per year for different PRO score ranges, stratified by EDSS value and age. The dashed lines indicate 0 and 365 days, the dotted line indicates 182.5 days, that is, half a year. The widths of the bars are proportional to the number of observations of each scenario. The colors and hues indicate the different subscales.

The large differences in the expected number of days with sickness compensation between people with mild and severe MS are remarkable and highlight the high personal and socio-economic burden of the disease. People with mild MS hardly have any expected number of days with sickness benefits, while those with severe MS are expected to spend more than 50% of the time on sickness benefits. People with MS have been found to have a high prevalence of sickness absence and disability pension

previously [16]. Compared to matched controls, they had considerably lower incomes and higher summed social benefits [17], leading to a high societal and socioeconomic burden [18, 19]. Socioeconomic status itself was also found to be a strong predictor of disability pension [20]. In a study in Denmark, the disposable income within the first 4 years after diagnosis was similar to, but comprised substantially of much more sick-leave and disability pension in people with MS than in controls [21].

In one review, the authors found that most determinants of reduced workforce participation in people with MS could be impacted positively by rehabilitation [22], suggesting that there are measures that can be taken from an early time point to improve the likelihood of being able to work. Thus, the current work provides a basis to evaluate the cost–benefit of such interventions.

Age is well known to affect disability and work capacity [23–26], and was therefore included in the base model. In our investigation, the LV value for EDSS was the best predictor for MS-related sickness benefits when age had been accounted for. This suggests that disability evaluated by the physician is the most relevant measure for a patient's ability to work. In general, the measures of physical disability (i.e., EDSS, MSIS-29 physical, and FSMC motor) appeared to be of higher predictive value than the psychological disability measures (i.e., MSIS-29 psychological and FSMC cognitive). However, it should be noted that the EDSS is the only disability measure evaluated here that is directly assessed in the clinic, while both MSIS-29 and FSMC are self-assessed. This difference in assessment is a potential source of systematic bias, as it is also the physician who needs to support sickness leave and sickness pension requests. A physician might be more inclined to put in such a request for a patient with a high EDSS score. The importance of the two other measures of physical disability could then merely be a consequence of the strong correlation with the EDSS seen in Table 1, but may be of importance if the EDSS is low (see Figure 4).

Others have also attempted to predict sickness benefits in MS, with other methods. A cluster analysis showed trends that trajectories of disease progression were linked to the number of days with sickness absence [27]. From the opposite perspective, the historical number of days on sickness absence and disability pension was predictive of the disease projection trajectory [28]. Lower incomes and more sickness benefits have been observed to strongly correlate with disability, as assessed by EDSS, in people with MS [29]. Machine learning is an option that has been used to build predictive models for levels of sickness benefits in other disease areas [30]. However, to our knowledge, this work is the first analysis assessing the MS disability by linking EDSS, MSIS-29, and FSMC to a common latent variable through item response modeling, to predict the outcome of sickness benefits.

In this work, only periods of sickness benefits related to MS, as identified through ICD-10 coding, were considered. While these periods are expected to be most closely related to the measures of disability investigated here, the actual number of sickness benefit days is possibly underestimated. An analysis of the total number of sickness benefits (MS related and unrelated) could be a complementing extension of the present work. The disability might also have a different impact on shorter periods of sickness benefits, which may be masked since the first 14 days of sick leave, paid by the employer, were not included. The developed model predicts the number of sickness benefit days as a function of different disability measures. A translation to the economic impact, in Euros or Swedish crowns, would also be a natural extension. Such a model would allow relating the improvement in a disability measure for a novel treatment to the expected savings in terms of sickness benefits and, hence, facilitate price selection for that treatment. Similar analyses have been done, but only on group aggregate levels [31] and not with IRT methodology.

In conclusion, this work investigated the relation between disability status and its impact on the ability to work, as measured through the number of days on sickness benefits, where the EDSS was the most important predictor, along with age. The self-assessed FSMC and MSIS-29 were not as predictive as EDSS, but could also be useful, as a complement for patients with low EDSS.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Item characteristic curves diagnostic—The solid lines represent the estimated item characteristic curves from the model, and the shaded area is a 95% confidence interval from a GAM smooth fitted to disability estimates and observed data. Lines that lie within the shaded area of the same color indicate a satisfactory model fit. **Figure S2:** Visual predictive check comparing 2.5th, 50th, and 97.5th percentile of the observed data (red lines) with a 95% confidence interval of the corresponding quantities from model simulations (gray shaded area). **Figure S3:** Visual predictive check comparing observed (blue line) and simulated (blue shaded area) fraction of time spent in each benefit state as a function of the LV for EDSS. **Figure S4:** Visual predictive check comparing observed (blue line) and simulated (blue shaded area) fraction of time spent in each benefit state as a function of the LV for MSIS-29 physical. **Figure S5:** Visual predictive check comparing observed (blue line) and simulated (blue shaded area) fraction of time spent in each benefit state as a function of the LV for MSIS-29 psychological. **Figure S6:** Visual predictive check comparing observed (blue line) and simulated (blue shaded area) fraction of time spent in each benefit state as a function of the LV for FSMC motor. **Figure S7:** Visual predictive check comparing observed (blue line) and simulated (blue shaded area) fraction of time spent in each benefit state as a function of the LV for FSMC cognitive. **Figure S8:** Correlation plot for the LVs and age. The Empirical Bayes Estimates for the LVs are shown. The red dashed line and shaded area represent a linear model fit with a 95% confidence interval. The green dashed line and shaded area represent a GAM smooth fit with a 95% confidence interval. The diagonal shows the density plot for each variable. **Data S2:** Supporting Information. **Data S1:** Supporting Information. **Data S3:** Supporting Information.