



## Original article

## Measuring productivity loss in early relapsing-remitting multiple sclerosis

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## ABSTRACT

**Background:** Multiple sclerosis is one of the most common causes of neurological disability in young adults with major consequences for their autonomy and capacity to maintain employment.

**Objective:** The aim of this study was to assess the impact on work productivity in early-stage relapsing-remitting multiple sclerosis (RRMS).

**Methods:** A multicenter, non-interventional study was conducted. Adult patients with a diagnosis of RRMS, a disease duration  $\leq 3$  years, and an Expanded Disability Status Scale (EDSS) score of 0–5.5 were included. Absenteeism, presenteeism, and unpaid work loss due to RRMS were measured using the Valuation of Lost Productivity (VOLP) questionnaire. The EDSS, SymptoMScreen, 5-item Modified Fatigue Impact Scale, Hospital Anxiety and Depression Scale, Symbol Digit Modalities Test, and Multiple Sclerosis Work Difficulties Questionnaire were used to gather information on disability, patients' perception of symptom severity, fatigue, mood/anxiety, cognition, and problems in the workplace, respectively. Associations between the VOLP and clinical and work outcomes were analyzed using Spearman's rank correlations.

**Results:** A total of 189 patients were included. Mean age (SD) was  $36.1 \pm 9.4$  years and 71.4% were female. Mean disease duration was  $1.2 \pm 0.8$  years. Median EDSS score was 1.0 (IQR 0, 2.0). One hundred thirty patients

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(68.8%) were working for pay or self-employed. Fifty-three patients (40.8%) reported absence from work in the past 3 months with an average of 14.3 absent workdays. Their health problems resulted in the loss of 3.4% of their actual work time in the past 7 days. Thirty patients got help (11.8 h) with their unpaid work activities in the past 7 days. Absenteeism was significantly correlated with anxiety and depression ( $\rho=0.298$  and  $0.291$ ,  $p<0.001$ ), fatigue ( $\rho=0.214$ ,  $p=0.014$ ), and symptom severity ( $\rho=0.213$ ,  $p=0.015$ ). Presenteeism was significantly correlated with fatigue ( $\rho=0.375$ ,  $p<0.001$ ), symptom severity ( $\rho=0.373$ ,  $p<0.001$ ), depression ( $\rho=0.263$ ,  $p=0.008$ ), and disability ( $\rho=0.215$ ,  $p=0.031$ ).

**Conclusions:** Productivity loss even in a RRMS population with short disease duration stresses the need for more efficient treatment control of disease activity from earlier stages.

## 1. Introduction

Multiple sclerosis (MS) causes a huge socioeconomic impact from productivity loss due to the age of onset, chronic course, and caregiver burden (Kobelt et al., 2017; Sicras et al., 2017; Paz-Zulueta et al., 2020; Lehmann et al., 2020).

Older age at onset, progressive course, fatigue, pain, mobility problems, visual impairment, bladder and bowel incontinence, cognitive impairment, and anxiety and depression are the factors most commonly found to be associated with difficulties in the workplace (Raggi et al., 2016; Chen et al., 2019; Lehmann et al., 2020). A suboptimal disease activity control with disease-modifying therapy was associated with higher medical, sick leave, and short-term disability costs (Hersh et al., 2021).

Fatigue, depression, cognitive impairment, and subtle motor deficits are common problems affecting quality of life of patients with MS even in the early stage of the disease course (Nourbakhsh et al., 2016; Cattaneo et al., 2021; Thruue et al., 2021). However, productivity loss have been mainly studied in patients with longstanding MS. Therefore, the aim of this study was to assess absenteeism, presenteeism, and unpaid work loss in patients with early-stage relapsing-remitting multiple sclerosis (RRMS).

## 2. Methods

We conducted a multicenter, non-interventional, cross-sectional study (MS ONSET study). Key eligibility criteria included age 18 years and older, a diagnosis of RRMS according to the 2017 revised McDonald criteria, and an Expanded Disability Status Scale (EDSS) score from 0 to 5.5 (Thompson et al., 2018; Kurtzke, 1983). Patients were consecutively recruited in the context of their follow-up visits at 21 hospital-based Neuroimmunology Clinics between November 2020 and March 2021. This study was conducted in accordance with the Good Clinical Practice Guidelines of the International Conference on harmonization and with the ethical principles of the Declaration of Helsinki and was approved by the investigational review board of the Hospital Universitari Arnau de Vilanova (Lleida, Spain). All participants provided written informed consent.

### 2.1. Outcome measures

Absenteeism refers to the number of missed workdays for employed people and presenteeism to the reduced intensity and/or quality of labor input caused by health problems while working (Zhang et al., 2011). Absenteeism, presenteeism, and unpaid work loss due to RRMS were measured using the Valuation of Lost Productivity (VOLP) questionnaire (Zhang et al., 2012). The VOLP is a validated, generic questionnaire assessing the labor input loss due to health (any physical, mental, or emotional problems or symptoms). It consists of 36 questions exploring employment status, job characteristics, absenteeism, work performance, unpaid work, and working environment. This questionnaire was developed in English and has been translated into 11 languages (<https://www.thevolp.com/>).

The EDSS, SymptomScreen (SyMS), 5-item Modified Fatigue Impact

Scale (MFIS-5), Hospital Anxiety and Depression Scale (HADS), Symbol Digit Modalities Test (SDMT), and 23-item Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ-23) were used to gather information on disability, symptom severity, fatigue, mood/anxiety, cognition, and problems in the workplace, respectively. The SyMS is a validated, self-report questionnaire assessing MS symptom severity across twelve neurologic domains: mobility, hand function/dexterity, spasticity and stiffness, pain, sensory symptoms, bladder control, fatigue, vision, dizziness, cognition, depression, and anxiety (Green et al., 2017; Meca-Lallana et al., 2020). Each item is assessed on a seven-point Likert scale: 0 (not at all affected) to 6 (total limitation). The total score ranges from 0 to 72, with higher scores indicating more severe symptom endorsement. The MFIS-5 is a brief self-assessment tool for measuring the impact of fatigue on cognitive, physical and psychosocial function (Meca-Lallana et al., 2019). It scores each item on a five-point Likert scale from 0 (never) to 4 (almost always). The total score ranges from 0 to 20, with higher scores indicating more severe fatigue. The HADS is a fourteen-item, self-assessment scale to measure symptoms of anxiety and depression (Zigmond et al., 1983). Each item is scored on a four-point Likert scale from 0 to 3. A total subscale score of  $>10$  points out of 21 indicates a probable case of anxiety or depression, respectively. The SDMT measures patient attention, concentration, and speed of information processing and is a sensitive screening tool to evaluate cognitive impairment in patients with MS (Sandry et al., 2021). Participants are required to use a coded key to match nine abstract symbols paired with numerical digits. The final score is the correct number of substitutions in 90 s (range between 0 and 110). A cut-off of  $\leq 49$  correct substitutions was used to identify participants with cognitive problems (López-Góngora et al., 2015). The MSWDQ-23 is a self-report measure to assess the extent of physical, psychological/cognitive, and external difficulties experienced by patients with MS in the workplace (Honan et al., 2014; Martínez-Ginés et al., 2018). Each item is scored on a five-point Likert scale from 0 (never) to 4 (almost always). All the subscales and the total scale are scored as a percentage by summing the observed item scores, divided by the total possible item scores in each subscale, then multiplying the value by 100, to give a maximum total score in each subscale of 100, with higher scores indicating greater difficulties.

### 2.2. Methodological approach

Demographic and clinical characteristics were summarized using frequencies (percentages) and mean (standard deviations) or median (interquartile range) as appropriate. According to the VOLP questionnaire, absenteeism was measured by the number of absent workdays due to any symptoms of RRMS in the past 3 months. Presenteeism was measured asking participants to think of the work they completed during the past 7 days and answer whether they would complete the same work in less time if they did not experience any health problems. If the answer is positive, they were asked to indicate the time in hours they actually used to do all the work during the past 7 days, and the supposed time they would use to do the same work if they did not experience any health problems. The percentage time loss while working due to RRMS in the past 7 days was calculated by dividing the difference between

hours actually used to complete work with health problems and hours used to complete the same work without health problems by hours actually used to complete work with health problems. Unpaid work loss was measured by the number of hours of getting help on unpaid work activities due to RRMS in the past 7 days.

Associations between the VOLP and clinical and work outcomes were analyzed using Spearman's rank correlations.

### 3. Results

A total of 189 patients were included in the study. The mean age was 36.1 years and 71.4% were female. The mean disease duration was 1.2 years and the median EDSS score was 1.0. Symptom severity was low (mean SyMS score = 12.0) with fatigue, sensory symptoms, and anxiety being the most affected dimensions. Nineteen patients (10.1%) were receiving disease-modifying therapy. Sociodemographic and clinical characteristics of the sample are shown in Table 1.

One hundred thirty patients (68.8%) were working for pay or self-employed. Fifty-three patients (40.8%) reported absence from work in the past 3 months because of their disease with an average of 14.3 absent workdays (Table 2). Their health problems resulted in the loss of 3.4% of their actual work time in the past 7 days. Thirty patients got help (11.8 h) with their unpaid work activities from relatives, friends or neighbors because of health problems in the past 7 days.

Absenteeism was significantly correlated with anxiety and depression ( $\rho=0.29$ ,  $p<0.001$ ), fatigue ( $\rho=0.21$ ,  $p = 0.01$ ), symptom severity ( $\rho=0.21$ ,  $p = 0.01$ ), and cognition ( $\rho=-0.17$ ,  $p = 0.04$ ). Presenteeism was significantly correlated with fatigue ( $\rho=0.37$ ,  $p<0.001$ ), symptom severity ( $\rho=0.37$ ,  $p<0.001$ ), depression ( $\rho=0.26$ ,  $p = 0.008$ ), and disability ( $\rho=0.21$ ,  $p = 0.03$ ). Spearman's rank correlations are shown in Table 3.

### 4. Discussion

The analysis of work outcomes and labor economic burden in MS is an area of increasing interest. However, little is known about the work productivity loss in early MS. In our study, absenteeism and

**Table 2**

Value of productivity outcomes.

	N	Mean (SD)
Among patients who were working for pay or self-employed	130	
Hours worked per week		33.5 (11.8)
Absenteeism (in the past 3 months)		
Number of absent workdays due to RRMS	53	14.3 (30.6)
Among patients who went to work in the past 7 days	105	
Presenteeism (in the past 7 days)		
Time in hours used to complete all the work	35	28.9 (16.4)
Time in hours would use to do the same work not suffering RRMS	35	26.7 (15.7)
Percentage time loss while working due to RRMS among actual work time	101	3.4 (8.8)
Unpaid work loss (in the past 7 days)		
Number of hours of getting help with unpaid work due to RRMS	30	11.8 (13.3)

RRMS: Relapsing-remitting multiple sclerosis; SD: Standard deviation.

**Table 3**

Spearman correlations between value of productivity and clinical and work outcomes.

	Absent workdays due to RRMS rho (p-value)	Percentage time loss while working due to RRMS among actual work time rho (p-value)
Disability	0.05 (0.54)	0.21 (0.03)
Symptom severity	0.21 (0.01)	0.37 (<0.001)
Fatigue	0.21 (0.01)	0.37 (<0.001)
Anxiety	0.29 (<0.001)	0.15 (0.11)
Depressive symptoms	0.29 (<0.001)	0.26 (0.008)
Cognition	-0.17 (0.04)	-0.14 (0.14)
Difficulties in the workplace		
Psychological-cognitive barriers	0.33 (<0.001)	0.35 (<0.001)
Physical barriers	0.24 (0.006)	0.19 (0.05)
External barriers	0.28 (<0.001)	0.24 (0.01)

RRMS: Relapsing-remitting multiple sclerosis.

**Table 1**

Sociodemographic and clinical characteristics.

	N = 189
Age, years, mean (SD)	36.1 (9.4)
Sex (female), n (%)	135 (71.4)
Education, n (%)	
University	151 (79.9)
Living status, n (%)	
With a partner/family members	164 (86.8)
Time since diagnosis, mean (SD)	1.2 (0.8)
Number of relapses since first attack, mean (SD)	1.8 (8.4)
Number of relapses in the last year, mean (SD)	0.9 (1.0)
Treatment naïve-patients, n (%)	170 (89.9)
EDSS score, median (IQR)	1.0 (0–2.0)
SDMT score, mean (SD)	51.7 (14.7)
≤49 correct answers, n (%)	77 (41.0)
SyMS score, mean (SD)	12.0 (10.8)
MFIS-5 global score, mean (SD)	6.2 (5.1)
HADS	
Anxiety global score, mean (SD)	7.8 (4.3)
Depression global score, mean (SD)	4.1 (3.9)
Anxiety categorized (probable cases), n (%)	47 (24.9)
Depression categorized (probable cases), n (%)	13 (6.9)
MSWDQ-23 total score, mean (SD)	17.9 (19.3)
Psychological/cognitive barriers, mean (SD)	17.9 (19.3)
Physical barriers, mean (SD)	15.1 (17.8)
External barriers, mean (SD)	23.3 (26.4)

EDSS: Expanded Disability Status Scale; HADS: Hospital Anxiety and Depression Scale; IQR: Interquartile range; MFIS-5: 5-item Modified Fatigue Scale; MSWDQ-23: 23-item Multiple Sclerosis Work Difficulties Questionnaire; SD: Standard deviation; SDMT: Symbol Digit Modalities Scale; SyMS: SymptoMScreen.

presenteeism were a common phenomenon even in a RRMS population with short disease duration (1.2 years) and low physical disability (median EDSS score=1.0). Absenteeism was mainly associated with anxiety, depression, and self-perception of symptom severity, whereas presenteeism was associated with fatigue, depression, and self-perception of symptom severity.

Fourteen percent of employed patients reported absenteeism and 47% reported presenteeism in a sample of 377 subjects in the US with a clinically isolated syndrome or RRMS and a mean disease duration of 12.4 years (Glanz et al., 2012). The mean work time lost was 12% and was associated with disability, fatigue, depression, anxiety, and poor quality of life. Salter et al. studied absenteeism in a cohort of 5887 patients with RRMS and primary progressive MS (PPMS) from the North American Research Committee on Multiple Sclerosis Registry (Salter et al., 2017). The proportion of participants reporting absent workdays in the past six months were similar between RRMS and PPMS patients (26.6% and 30.8%, respectively;  $p = 0.5076$ ). Mean absent workdays were higher in RRMS patients with moderate-to-severe disability (10.0 days) compared with those with mild disability (6.0 days). Older age, number of comorbidities, fatigue, cognitive impairment, and problems in hand function were associated with an increased risk of absenteeism. In a sample of 740 employed patients in Australia with a MS mean duration of 11.2 years, 56% experienced any work productivity loss in the past month (Chen et al., 2019). Mean absent workdays was 1.1 (2.9) and their health problems resulted in the loss of 19.7% of their actual

work time. Work productivity was mainly determined by the severity of different symptoms, including fatigue and cognitive impairment, pain and sensory symptoms, and mobility problems (OR= 3.31, 2.32, and 1.74, respectively;  $p < 0.001$ ). More recently, the same group reported that individual changes in work productivity were mainly driven by the changes in symptom severity over time rather than the absolute severity (B Bessing et al., 2021a, 2021b).

Unemployment and productivity losses in RRMS also occur without overt physical disability (Giovannoni, 2017; García-Domínguez et al., 2019). Less visible symptoms and difficulties including cognitive impairment, fatigue, anxiety and depression are reasons for a low productivity and difficulties to keep a job (Kobelt et al., 2017; Raggi et al., 2018; Chen et al., 2019; van Gorp et al., 2019; Maurino et al., 2020; van der Hiele et al., 2021). The perception of cognitive difficulties in the workplace was found to predict unemployment and reduced work hours since MS diagnosis (Honan et al., 2015; McNicholas et al., 2018; van Gorp et al., 2019). In a register-based cohort study of 1988 working patients with MS in Sweden spanning from 4 years prior to 4 years after the diagnosis, Murley et al. found excess healthcare costs and productivity losses occurring already before the diagnosis and increasing over time (Murley et al., 2021). Productivity losses were higher than healthcare costs. The mean annual productivity losses increased over the study period, with a sharp increase at the first year of diagnosis. The productivity losses pre-diagnosis suggest that patients may experience early symptoms, such as fatigue, that even affect their work capacity.

Our results are similar to previous reports and may advocate a more effective control of disease activity from earlier stages of the disease (Chen et al., 2018; Chalmer et al., 2020; Simonsen et al., 2021; Thruue et al., 2021). Treating earlier in the course of the disease showed a trend towards lower total, indirect and treatments costs, and a better quality of life compared to those patients receiving a late treatment according to the IMPRESS study (Tinelli et al., 2018). Patients receiving high-efficacy disease-modifying therapy reported significant increases in work participation, attendance, and productivity compared with those under first-generation injectable treatments (Chen et al., 2018). In addition, the finding of symptom severity as a predictor of both work participation and productivity loss emphasizes the need for improved management of symptoms (Honan et al., 2015; Chen et al., 2019; Murley et al., 2021).

Our study has some limitations. First, productivity information was collected using a self-report questionnaire without objective measures. Second, the study population may not be representative of the entire spectrum of patients with early RRMS (e.g., EDSS scores  $>5.5$ ). Third, we acknowledge a potential selection bias given that those people most motivated to collaborate or with a better relationship with their physicians may have enrolled in the study.

## 5. Conclusions

Work participation and job retention are critical objectives to reduce the economic burden that MS imposes on both the patient and the society. Anxiety, depression, fatigue, and cognitive impairment are common problems already existing at earlier stages of the disease with a substantial impact on work outcomes.

A more proactive management strategy from the disease onset is necessary to prevent disability progression and improve symptom control.

## Authorship contribution statement

S.S-M., J.M., M.B. and T.C-T. developed the research question and co-designed the study. All authors contributed to the analysis and interpretation of the results. All authors contributed to and approved the final manuscript.

## Declaration of Competing Interest

S.S-M. received payment for lecturing or travel expenses from Merck-Serono, Biogen, Sanofi-Genzyme, Roche, and Novartis. M.C. C-A received compensation from Sanofi-Genzyme, Roche, Novartis, and Biogen for service as consultant. L.B. received funding for research projects or in the form of conference fees, mentoring, and assistance for conference attendance from Bayer, Biogen, Roche, Merk, Novartis, Almirall, Celgen, and Sanofi. J.M., R.G-B., and L.R-A. are employees of Roche Pharma Spain. M.B., J.M-M., J.S., A.A., A.B.C., L.B., J.L.S-M., F.J. B-H., C.C., M.R.B., J.D-GS., L.N—C., E.A., M.G-R., O.C., L.G-T., L.F., M. H., and T.C-T. declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The study was funded by Roche Medical Department, Spain (ML42064). The funding source had no role in the design, analysis and interpretation of the data, review or approval of the manuscript, and decision to submit for publication.

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