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Patient-reported outcomes associated with transition to secondary progressive multiple sclerosis

Brian C. Healy[1,2,3] · Jonathan Zurawski[1,2] · Tanuja Chitnis[1,2] · Howard L. Weiner[1,2] · Bonnie I. Glanz[1,2]

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Abstract

Purpose To investigate patient-reported outcome (PRO) measures in patients with relapsing–remitting multiple sclerosis (RRMS) who transition to secondary progressive multiple sclerosis (SPMS).

Methods Subjects enrolled in the Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women's Hospital (CLIMB) who completed PRO measures in the RRMS and SPMS phases were identified ($n = 52$). The PRO measures were Medical Outcomes Study Short-Form 36 Health Survey (SF-36), the Modified Fatigue Impact Scale (MFIS), and the Center for Epidemiologic Studies Depression Scale (CESD). Two control groups of RRMS CLIMB patients who did not progress to SPMS were identified based on different matching criteria related to age, sex, disease duration and Expanded Disability Status Scale (EDSS). Summary statistics for each PRO were calculated at the last RRMS measurement and first SPMS measurement, and the change over this transition was calculated using a paired *t*-test. Patients who transitioned were compared to the control groups using linear regression to adjust for age, disease duration and EDSS and a mixed model to further account for the matching with a random effect for matched group.

Results Patients who transitioned from RRMS to SPMS had noticeable deficits in terms of Quality of Life (QOL) and fatigue at the visit prior to the transition. Patients worsened in terms of SF-36 Role Physical (−3.6 [−6.6, −0.7]), Social Functioning (−3.7 [−6.4, −1.0]), and Physical Component Summary (−2.3 [−4.5, −0.1]) during the transition from RRMS to SPMS. When patients who transitioned were compared to the matched subjects, they had worse scores on several outcomes, including Physical Functioning (adjusted mean difference = −10.8 [−14.1, −7.5]), Physical Component Summary (−5.2 [−9.3, −1.0]), fatigue (8.9 [1.7, 16.1]), and depression (3.1 [0.3, 5.9]).

Conclusions Patients in the period closely preceding transition from RRMS to SPMS have worse physical QOL and fatigue compared to subjects who remain RRMS.

Keywords Fatigue · Multiple sclerosis · Patient-reported outcomes · Quality of life · Secondary progression

Introduction

Multiple sclerosis (MS) has a heterogeneity of clinical presentation and course, but most commonly begins with a relapsing–remitting (RR) phase followed by a secondary progressive (SP) phase [1, 2]. In the RR phase, patients experience relapses, which are short periods of reduced/loss of function, and these relapses are followed by periods of remission. Some relapses are associated with residual disability [3], but the RR phase is not associated with the constant disease worsening that occurs in the progressive forms of the MS. An important clinical distinction occurs in MS when a patient moves from the RR to SP phase of the disease. The majority of RRMS patients will transition to SPMS, and the timing of the transition depends on the patient's disease course [4, 5]. In the SP phase, patients experience steady disability accumulation with fewer or no associated relapses [6]. At this stage of the disease, moderate-to-severe disability is common, often impacting ambulatory status and spinal cord function. Nearly all treatments for MS reduce the relapse rate and are effective during the RR phase, but the impact on disease progression especially

✉ Brian C. Healy
bchealy@mgh.harvard.edu

[1] Partners MS Center, Brigham and Women's Hospital, Boston, MA, USA

[2] Department of Neurology, Harvard Medical School, Boston, MA, USA

[3] Biostatistics Center, Massachusetts General Hospital, 60 Fenwood Rd, Boston, MA 02115, USA

during the SP phase is less clear [7, 8]. Over the past 15 years, the time to SPMS has increased, which may be related to the impact of treatment [9].

One of the key challenges in treating MS patients is understanding the clinical and pathological hallmarks defining transition from RRMS to SPMS. Many studies have investigated predictors of development of SPMS [10, 11]. These studies have shown that older age, longer disease duration and male sex are all associated with increased chance of transitioning from RRMS to SPMS. These analyses have focused on the natural history of the disease to identify early predictors of development of SPMS. At the same time, the definition of SPMS is still uncertain with several potential definitions recently proposed in the literature [12]. At a histopathological level, among patients who ultimately reach SPMS, there is likely gradual subclinical accumulation of disease burden during the RRMS stage that eventually manifests clinically as SPMS, and there is no single hallmark indicating RRMS-to-SPMS transition [13].

An alternative approach to understanding the disease transition is to investigate the changes that occur in patients in the period closely preceding the transition from RRMS to SPMS. The main challenge in this type of study is that subjects who are about to transition cannot be identified using a cross-sectional study design. Rather, a large number of subjects must be followed longitudinally with consistent data collection in order to find subjects who transition during the follow-up period. This type of design has been used to identify predictors of development of MS using nested case–control studies in the Nurse's Health Study and the Department of Defense Serum Repository [14, 15]. There are multiple longitudinal MS studies that have followed patients for more than 20 years. This type of longitudinal study design can now be used to identify characteristics of subjects who are about to transition from RRMS to SPMS.

In this paper, we identify RRMS patients who transition to SPMS who completed patient-reported outcome (PRO) measures during both the RRMS and SPMS phases of the disease. The first goal of the paper is to understand how PROs change when a patient transitions from RRMS to SPMS to better understand how the patient experiences the transition. The second goal of the paper is to identify specific PROs that are different in patients who are about to transition from RRMS to SPMS by comparing subjects who transition to subjects with similar age, sex, disease duration and disability level who remain RRMS.

Methods

Participants

The Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women's Hospital (CLIMB) began enrolling subjects in 2000 [16]. 2356 MS subjects were enrolled in the study by 10/25/18 when the database for this study was locked, and 808 of these subjects had available PRO information. Among the CLIMB subjects, 1846 were RRMS at the first CLIMB visit, and an additional 99 were clinically isolated syndrome or suspected MS. Subjects have clinical visits with a complete neurologic exam every 6 months, including measurement of the Expanded Disability Status Scale, EDSS [17]. At each clinical visit, the physician classifies the subject's disease category as relapsing–remitting, secondary progressive, primary progressive, or progressive relapsing. In addition to the clinical visits, a subset of CLIMB participants was enrolled in the Quality of Life (QOL) subgroup, and all subjects who enrolled in CLIMB prior to 2009 were enrolled in the QOL subgroup so that this group has extensive longitudinal follow-up. These subjects completed a set of PRO questionnaires annually until 2011, and then biennially until 2015, and the measures that are the focus of this analysis are described in more detail below.

For this study, CLIMB subjects who completed PRO questionnaires both during the RRMS phase and SPMS phase of the disease were identified ($n = 53$). In total 156 CLIMB subjects were observed to transition from RRMS to SPMS, but the remaining 103 did not have sufficient QOL data to contribute to this analysis. One patient who transitioned from RRMS to progressive relapsing MS to SPMS was removed so the final dataset included 52 subjects. The last available PRO measurement during the RRMS phase and the first available PRO measurement during the SPMS phase were chosen for the analysis. The mean (SD; range) time between measurements was 1.5 years (1.0; range 0.8, 4.4). The demographic characteristics of the subjects at the last RRMS visit with PRO data and the first SPMS visit with PRO data are provided in Supplementary Table 1.

For this analysis, we also identified two comparison groups. First, we identified all CLIMB subjects who met the following matching criteria for each subject who transitioned: (1) diagnosis of RRMS, (2) EDSS score within 0.5 points, (3) age within 5 years, (4) disease duration within 5 years, (5) available PRO measurement, (6) sex and (7) subsequent PRO measurement with the patient remaining RRMS. Using this approach, we chose up to three matches for each subject who transitioned. If multiple measurements from a potential control subject were

available, the measurement that matched closest by age was included in the analysis. Once a control subject was matched to a subject who transitioned, this subject was not included as a potential match for any other subjects who transitioned so that all the matched subjects were distinct. 42 Subjects who transitioned were matched using these criteria; subjects with high EDSS values were the most likely to not be included in this matched set. In the second analysis, we used the same matching criteria except we required the EDSS score to be equal for the match, which led to 37 subjects being matched. The demographic characteristics of the two groups of matched subjects are provided in Supplementary Tables 2 and 3.

Patient-reported outcomes

The CLIMB battery of PROs was chosen to include a generic measure of health-related QOL as well as instruments assessing specific domains commonly affected in patients with MS. Three PROs were the focus of our analysis to investigate QOL, fatigue and depression. The QOL measure was the Medical Outcomes Study Short-Form 36 Health Survey (SF-36) [18], which is a generic QOL measure. Eight component scales were derived from the SF-36: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. Two summary scores, Physical Component Summary and Mental Component Summary, were also derived from this measure. Fatigue was assessed using the Modified Fatigue Impact Scale (MFIS), which is a 21-item measure of physical, mental and psychosocial fatigue [19]. Our analysis focused on the total score. Depression was assessed using the Center for Epidemiologic Studies Depression Scale, CESD [20]. The CESD is a 20-item self-report measure of depression focusing on the cognitive and affective rather than somatic components of depression. For the SF-36 and MFIS, the scoring from the Multiple Sclerosis Quality of Life Inventory was used. For each scale, subjects with missing data for one or more questions were considered missing and removed from the analysis.

Statistical methods

Summary statistics for PROs at the time of the last RRMS measurement and the time of the first SPMS measurement were calculated. To investigate the change with time, we calculated the annualized change as the change in each PRO measurement divided by the change in time, and we performed a one sample *t*-test on the annualized change. In order to compare the subjects who transitioned to the matched subjects who did not transition, we used four methods for each comparison group. The first two approaches compared the mean PRO score between the groups using linear regression with (1) conversion status as the only predictor and (2) including EDSS, age and disease duration as covariates. The second two approaches compared the mean PRO between the groups using linear mixed model with the same outcomes and predictors including a matched group random effect to account for the correlation within a matched group. These approaches were used with both comparison groups. All statistical analysis was completed in the statistical package R version 3.6.3 (www.r-project.org).

Results

The summary statistics for each of the PROs in subjects who transitioned from RRMS to SPMS are provided in Table 1. At the last measurement prior to conversion from RRMS to SPMS, subjects demonstrated impairment on several PRO measures. In terms of QOL, subjects reported the lowest scores for Physical Functioning, Role Physical, Vitality, and the Physical Composite Score. In addition, subjects had high fatigue scores. In terms of change in PRO during the transition, three QOL scores worsened over the transition (Role Physical, Social Functioning, and Physical Component Summary).

Table 2 presents the comparison of the subjects who transitioned to the first matched group in terms of the PROs at the measurement prior to transition using the random effects model. The results showed many differences between the subjects who were about to transition to SPMS even though the groups were similar in terms of EDSS, age and disease duration. In both unadjusted analysis and after adjusting for EDSS, age and disease duration, patients who were about to transition had worse Physical Function, Role Physical, General Health, Vitality, Physical Component Summary, fatigue (MFIS) and depression (CESD). All these results were essentially unchanged in the analysis using the linear regression model (data not shown).

Table 3 presents the comparison of subjects who transition to the other matched group using the random effects model. Subjects who converted had worse Physical Function, Role Physical, General Health, Vitality, Social Functioning, Role Emotional, Physical Component Summary and fatigue (MFIS) in both unadjusted and adjusted analyses. In the adjusted analysis, there was also a difference in depression (CESD). All of these results were essentially unchanged in the analysis using linear regression (data not shown).

Discussion

Our study investigated PRO measures in patients who transitioned from RRMS to SPMS. These patients had important impairments in QOL even while still clinically

Table 1 Summary statistics for patient-reported outcomes at the last RRMS measurement and first SPMS measurement

	Last measurement during RR phase	First measurement during SP phase	Paired *t*-test
SF-36 Physical functioning	34.3 (9.8); $n=49$	31.2 (9.9); $n=51$	−1.8; 95% CI −4.1, 0.5; $p=0.126$
SF-36 Role physical	37.2 (10.9); $n=50$	32.5 (9.7); $n=51$	−3.6; 95% CI −6.6, −0.7; $p=0.017$
SF-36 Bodily pain	47.8 (11.3); $n=50$	45.7 (11.9); $n=52$	−1.6; 95% CI −4.0, 0.7; $p=0.176$
SF-36 General health	39.9 (11.2); $n=49$	40.7 (10.7); $n=51$	0.9; 95% CI −0.8, 2.5; $p=0.293$
SF-36 Vitality	39.2 (9.1); $n=50$	39.9 (7.2); $n=52$	1.1; 95% CI −0.6, 2.7; $p=0.189$
SF-36 Social functioning	44.5 (11.5); $n=47$	40.0 (12.1); $n=52$	−3.7; 95% CI −6.4, −1.0; $p=0.009$
SF-36 Role emotional	42.4 (13.5); $n=51$	41.3 (12.9); $n=52$	−0.5; 95% CI −3.5, 2.5; $p=0.748$
SF-36 Mental health	46.9 (10.6); $n=51$	46.7 (9.8); $n=51$	0.0; 95% CI −1.4, 1.4; $p=0.98$
SF-36 Physical composite score	37.0 (9.5); $n=45$	34.4 (8.8); $n=49$	−2.3; 95% CI −4.5, −0.1; $p=0.043$
SF-36 Mental composite score	47.3 (10.9); $n=45$	46.5 (10.1); $n=49$	0.3; 95% CI −1.8, 2.4; $p=0.783$
MFIS	43.0 (15.0); $n=31$	42.9 (16.7); $n=39$	−0.6; 95% CI −3.4, 2.3; $p=0.693$
CESD	33.5 (9.4); $n=50$	33.2 (9.7); $n=50$	−0.4; 95% CI −2.0, 1.2; $p=0.626$

SF-36 Medical Outcomes Study Short-Form 36 Health Survey, *MFIS* Modified Fatigue Impact Scale, *CESD* Center for Epidemiologic Studies Depression

Table 2 Comparison of subjects who convert to SPMS and those who remain RRMS using first matched cohort

	Converted	Did not convert	Unadjusted comp	Adjusted comp
SF-36 Physical functioning	35.1 (9.9); $n=39$	47.8 (9.5); $n=108$	**−12.7; 95% CI −16.2, −9.2; $p<0.001$**	**−11.3; 95% CI −14.5, −8.0; $p<0.001$**
SF-36 Role physical	37.6 (10.4); $n=40$	44.1 (12.2); $n=109$	**−6.5; 95% CI −10.7, −2.4; $p=0.002$**	**−5.5; 95% CI −9.6, −1.5; $p=0.009$**
SF-36 Bodily pain	48.3 (11.8); $n=40$	49.1 (9.2); $n=108$	−0.8; 95% CI −4.1, 2.5; $p=0.626$	0.2; 95% CI −3.1, 3.5; $p=0.895$
SF-36 General health	40.6 (11); $n=40$	46.6 (10.4); $n=107$	**−6.2; 95% CI −9.7, −2.6; $p=0.001$**	**−6.2; 95% CI −9.7, −2.6; $p=0.001$**
SF-36 Vitality	40.2 (8.9); $n=41$	45.0 (11.0); $n=108$	**−4.9; 95% CI −8.6, −1.1; $p=0.01$**	**−4.6; 95% CI −8.2, −0.8; $p=0.015$**
SF-36 Social functioning	46.2 (9.8); $n=38$	48.7 (8.8); $n=102$	−2.5; 95% CI −5.8, 0.8; $p=0.135$	−2.3; 95% CI −5.7, 1.0; $p=0.174$
SF-36 Role emotional	43.1 (13.3); $n=41$	47.7 (11.5); $n=109$	**−4.6; 95% CI −8.9, −0.3; $p=0.037$**	−3.8; 95% CI −8.1, 0.5; $p=0.090$
SF-36 Mental health	47.6 (10.5); $n=41$	50.6 (8.1); $n=108$	−3.1; 95% CI −6.2, 0.1; $p=0.059$	**−3.3; 95% CI −6.5, −0.1; $p=0.048$**
SF-36 Physical composite score	37.7 (10.1); $n=36$	46.0 (10.1); $n=99$	**−8.2; 95% CI −11.8, −4.5; $p<0.001$**	**−6.6; 95% CI −10.1, −3.0; $p<0.001$**
SF-36 Mental composite score	48.8 (10.4); $n=36$	49.7 (8.9); $n=99$	−0.9; 95% CI −4.5, 2.6; $p=0.614$	−1; 95% CI −4.7, 2.7; $p=0.6$
MFIS	41.0 (15.3); $n=23$	30.4 (15.8); $n=82$	**10.6; 95% CI 3.4, 17.9; $p=0.004$**	**9.9; 95% CI 2.8, 17.0; $p=0.007$**
CESD	33.0 (9.4); $n=40$	29.4 (7.3); $n=108$	**3.6; 95% CI 0.7, 6.4; $p=0.015$**	**3.7; 95% CI 0.9, 6.6; $p=0.011$**

SF-36 Medical Outcomes Study Short-Form 36 Health Survey, *MFIS* Modified Fatigue Impact Scale, *CESD* Center for Epidemiologic Studies Depression, *EDSS* Expanded Disability Status Scale

Matching criteria were (1) diagnosis of RRMS, (2) EDSS score within 0.5 points, (3) age within 5 years, (4) disease duration within 5 years, (5) available PRO measurement, (6) sex, and (7) subsequent PRO measurement with the patient remaining RRMS. Differences that are bolded have a *p*-value less than 0.05. A Bonferroni corrected α level for this table would be $0.05/12=0.0042$

classified as RRMS, and their disease continued to worsen during the transition from RRMS to SPMS. Prior to physician-determined disability worsening over the transition period, patients who are about to transition from RRMS to SPMS reported worse QOL and fatigue compared to subjects who remained relapsing using two groups for

Table 3 Comparison of subjects who convert to SPMS and those who remain RRMS using second matched cohort

	Converted	Did not convert	Unadjusted comp	Adjusted comp
SF-36 Physical functioning	35.8 (10.4); $n=34$	47.6 (9.1); $n=89$	**−11.8; 95% CI −15.3, −8.4; $p<0.001$**	**−11.8; 95% CI −15.2, −8.3; $p<0.001$**
SF-36 Role physical	38.4 (10.7); $n=35$	44.5 (12.3); $n=90$	**−6.0; 95% CI −10.7, −1.4; $p=0.011$**	**−6.2; 95% CI −10.8, −1.7; $p=0.008$**
SF-36 Bodily pain	50.0 (11.4); $n=35$	49.5 (9.6); $n=88$	0.4; 95% CI −3.3, 4.1; $p=0.834$	0.4; 95% CI −3.3, 4.2; $p=0.829$
SF-36 General health	41.3 (10.5); $n=35$	47.2 (9.7); $n=89$	**−5.9; 95% CI −9.8, −2.0; $p=0.003$**	**−6.1; 95% CI −9.9, −2.3; $p=0.002$**
SF-36 Vitality	40.0 (9.3); $n=36$	46.1 (10.6); $n=90$	**−6.1; 95% CI −10.0, −2.2; $p=0.002$**	**−6.3; 95% CI −10.2, −2.5; $p=0.001$**
SF-36 Social functioning	46.0 (10.1); $n=33$	49.6 (8.1); $n=88$	**−3.6; 95% CI −7.1, −0.1; $p=0.042$**	**−3.6; 95% CI −7.0, −0.2; $p=0.039$**
SF-36 Role emotional	43.3 (13.5); $n=36$	48.5 (11.1); $n=90$	**−5.2; 95% CI −9.7, −0.6; $p=0.027$**	**−5.2; 95% CI −9.7, −0.7; $p=0.026$**
SF-36 Mental health	47.7 (10.5); $n=36$	50.8 (7.4); $n=90$	−3.0; 95% CI −6.3, 0.2; $p=0.068$	−3.0; 95% CI −6.3, 0.2; $p=0.072$
SF-36 Physical composite score	39.0 (10.1); $n=31$	46.4 (9.4); $n=85$	**−7.5; 95% CI −11.2, −3.8; $p<0.001$**	**−7.2; 95% CI −10.8, −3.5; $p<0.001$**
SF-36 Mental composite score	48.6 (10.3); $n=31$	50.4 (8.3); $n=85$	−1.8; 95% CI −5.5, 1.9; $p=0.337$	−1.8; 95% CI −5.5, 1.9; $p=0.347$
MFIS	40.1 (15.4); $n=20$	28.1 (15.8); $n=69$	**11.8; 95% CI 4.3, 19.3; $p=0.002$**	**11.8; 95% CI 4.4, 19.6; $p=0.002$**
CESD	32.2 (8.6); $n=35$	29.4 (6.9); $n=88$	2.8; 95% CI −0.1, 5.7; $p=0.056$	**3.0; 95% CI 0.1, 5.9; $p=0.045$**

SF-36 Medical Outcomes Study Short-Form 36 Health Survey, *MFIS* Modified Fatigue Impact Scale, *CESD* Center for Epidemiologic Studies Depression, *EDSS* Expanded Disability Status Scale

Matching criteria were (1) diagnosis of relapsing–remitting MS, (2) EDSS score within 0 points, (3) age within 5 years, (4) disease duration within 5 years, (5) available PRO measurement, (6) sex and (7) subsequent PRO measurement with the patient remaining relapsing–remitting MS. Differences that are bolded have a p-value less than 0.05. A Bonferroni corrected α level for this table would be $0.05/12=0.0042$

comparison. These results show that patients who are about to transition to the progressive phase of the disease have characteristics that are measurable using PROs but are not observed using the EDSS alone.

When PRO measures were compared before and after the transition to SPMS, there were changes observed in Role Physical, Social Functioning, and Physical Component Summary. The largest change was observed for the Social Functioning subscale, and the estimated change was a third of a standard deviation decrease per year. This change shows that the transition from RRMS to SPMS may lead to both social and physical consequences for the patient. The questions related to Social Functioning specifically ask how physical health or emotional problems impact an individual's interactions with others. Therefore, the observed change in the Social Functioning subscale may show that the disease transition also impacts social interactions. The limited changes observed on other measures may be driven by the level of disability already impacting patients at the last RRMS measurement. Even though all patients were classified as RRMS, the mean scores across all of the PROs showed noticeable disability. Future work on these patients will compare the change in PROs at the end of the RRMS phase and the beginning of the SPMS to understand if the transition leads to an inflection point.

The comparisons of the patients who were about to transition from RRMS to SPMS and the matched subjects demonstrated many important differences in PROs despite the similarities between the groups in terms of age, sex, disease duration and disability level. The largest difference between the groups was observed on the Physical Functioning subscale of the SF-36. The questions for the physical functioning subscale ask, "Does your health limit you in these activities?" Given the large differences between the groups, patients may observe that MS is limiting their ability to participate in certain activities even if their level of disability as measured by the EDSS does not highlight these limitations. The Physical Functioning subscale has shown very strong correlations with the EDSS in previous analyses [21, 22], but the result in this analysis demonstrates that the Physical Subscale provides additional information regarding the impact of disease that goes beyond the physician rated EDSS.

Additional subscales that showed the most consistent differences between patients who transitioned to SPMS and those who remained RRMS were the Role Physical subscale and the General Health subscale. The Role Physical subscale asks whether the patient experiences problems with regular

daily activities due to problems with physical health. The lower scores on the Role Physical subscale could indicate that patients who were about to transition to SPMS observed limitations in daily activities more than patients who were not about to transition. The General Health subscale questions ask patients to rate their health relative to others. Lower scores on this scale among patients who transition to SPMS indicate that a patient's subjective impression of disease worsening may help identify increased clinical risk of RRMS-to-SPMS transition.

In addition to differences in QOL, differences in fatigue and the Vitality subscale of the SF-36 were also observed between patients who transition and those who remain RRMS. Fatigue is the most common MS symptom [23], and several interventions for treating fatigue have been proposed. In addition to being a highly common MS symptom, a recent analysis found that fatigue is predictive of worsening disease [24]. Our analysis found that patients who are about to transition to SPMS had higher mean fatigue scores by 8–9 points, which corresponds to an effect size of about 0.5 using the within group standard deviation of 16. This effect size corresponds to an important difference between groups. The difference between groups in terms of self-reported fatigue is confirmed by the consistent group difference seen on the Vitality subscale of the SF-36. It is possible that patients with similar levels of disability, but different fatigue profiles may differ in terms of future disease progression.

A difference between the patients who transition and those who remain RRMS was observed for depression as well. Depression is a common symptom in individuals with MS and has been shown to be elevated in SPMS patients compared to RRMS patients in some studies but not others [25]. Although there was a difference between the groups in terms of the mean depression score, the difference in the means was only about 3–4 points on the CESD, which would not be considered a large effect size. At the same time, the difference in depression on average demonstrates that patient-reported measures distinguish subjects about to transition from patients who will remain RRMS.

Our study has several limitations that warrant further discussion. First, the transition from RRMS to SPMS is based on the clinician classification of the disease category. Some of the patients classified as RRMS may have already transitioned to SPMS at the time of the last RRMS visit. Although this might have changed the disease category for some patients, our results were consistent across a set of matching criteria with regards to disability, which should reduce the bias introduced by this potential limitation. Further, all data were collected prospectively so the patient responses to the questionnaires could not have been biased by any errors in the disease category classification. Second, the CLIMB enrolled subjects at a tertiary care MS center so that the results from our sample may not be generalizable to all MS patients. At the same time, it seems likely that any bias due to the sampling of the CLIMB study would impact both patients who transition and those who remain RRMS so the estimated difference between the groups would have limited bias.

In conclusion, our study demonstrates that patients who are about to transition from RRMS to SPMS report worse functioning on PRO measures compared to matched subjects who remain RRMS. This finding suggests that MS patients may be recognizing and reporting disease worsening on PRO measures even when this worsening is not captured on the EDSS. Clinicians may want to consider patient-reported disease status in addition to the clinical exam when determining the approach for monitoring and treating patients.

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Data availability Anonymized data related to the findings of this analysis are available from the corresponding author, upon reasonable request from qualified investigators.

Code availability R code for this analysis is available from the corresponding author, upon reasonable request from qualified investigators.

Declarations

Conflict of interest Brian Healy has received grant support from Analysis Group, Celgene (Bristol-Myers Squibb), Verily, Novartis, Merck Serono, and Genzyme. Jonathan Zurawski reports no disclosures relevant to the manuscript. Tanuja Chitnis has provided advisory board/consulting services to Biogen-Idec, Merck Serono, Novartis, Sanofi, Bayer, Celgene (Bristol-Myers Squibb), and Alexion and has received research support from Verily, Merck Serono, and Novartis. Howard Weiner has received grant support from National Institutes of Health, National Multiple Sclerosis Society, Verily, Google Life Sciences, EMD Serono, Biogen, Teva, and Novartis, has received grant support and provided consulting services to Sanofi and Genentech, has provided personal, consulting, and/or advising services to Tilos, Tiziana, IM Therapeutics, vTv Therapeutics, and MedDay. Bonnie Glanz has received research support from Merck Serono and Verily.

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