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Depressive symptoms and fatigue as predictors of objective-subjective discrepancies in cognitive function in multiple sclerosis

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Abstract

Objective—To examine the degree to which depressive symptoms and fatigue in individuals with multiple sclerosis (MS) are associated with discrepancies between subjective and objective cognitive impairment.

Methods—Ninety-nine adults with MS who were receiving care in a university-affiliated MS center completed the Patient Health Questionnaire-8 (PHQ-8), Fatigue Severity Scale (FSS), MS Neuropsychological Screening Questionnaire (MSNQ), and Brief International Cognitive Assessment for MS (BICAMS). Participants were classified as “Accurates,” “Underestimators,” or “Overestimators” based on discrepancies between their MSNQ (subjective) and BICAMS (objective) scores. Underestimators were individuals whose subjective scores were significantly worse than their objective scores. Overestimators exhibited the opposite profile.

Results—The PHQ-8 ($r = 0.58$) and FSS ($r = 0.48$) significantly correlated with the MSNQ, but not with the BICAMS ($rs < 0.07$). Underestimators (i.e., participants who underestimated their objective cognitive functioning) exhibited higher PHQ-8 and FSS scores compared to Accurates ($ps < 0.01$) and Overestimators ($ps < 0.01$). Optimal cut-scores of ≥6on the PHQ-8 and ≥36 on the FSS provided fair accuracy (78% and 74%) for identifying Underestimators. Identification of Underestimators based on PHQ-8 and FSS scores was not moderated by any demographic or MS clinical variables.

Conclusions—In the presence of mild levels of depression or significant fatigue, subjective cognitive measures are unlikely to provide accurate estimates of objective cognitive functioning. Objective cognitive measures are required for accurate identification of cognitive impairment.

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Supplementary materials

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Keywords

Multiple sclerosis; Cognitive function; Neuropsychology; Fatigue; Depression

1. Introduction

Research has shown discrepancies between subjective and objective measures of cognitive function in individuals with multiple sclerosis (MS), with some individuals underestimating, and others over-estimating, their cognitive function (Julian et al., 2007; Kinsinger et al., 2010). Such discrepancies pose challenges for providers with regard to: (1) selecting valid screening measures of cognition, and; (2) determining the need for further neuropsychological evaluations and interventions. In MS, it is not uncommon for individuals to perceive their cognitive function as being worse than their objective performance on cognitive testing; and this underestimation of their cognitive abilities is believed to be related to two other common MS symptoms: depression and fatigue. (Julian et al., 2007) Compared to the general population, individuals with MS are three times more likely to experience depression in their lifetime, (Koch et al., 2015; Berzins et al., 2017) and fatigue is also among the most common MS symptoms, affecting up to 90% of the population (Berger et al., 2013; Parmenter et al., 2003). Given that depressive symptoms and fatigue have been linked to underestimation of cognitive function, these symptoms must be considered when assessing cognition, especially when using subjective rating scales (Kinsinger et al., 2010).

Although prior studies of cognitive function in MS have shown objective-subjective discrepancies to be correlated with depressive symptoms and fatigue, the measures used to assess these discrepancies have varied. To date, objective-subjective discrepancies and their associations with depression and fatigue have not been investigated using the objective Brief International Cognitive Assessment for MS (BICAMS) (Benedict et al., 2012; Langdon et al., 2012). This is particularly notable given that the BICAMS is among the most widely validated screening measures for MS and is designed to assess the cognitive domains most commonly affected in MS: processing speed, verbal learning, and visuospatial learning. Past studies of objective-subjective discrepancies have typically examined measures of other cognitive domains (e.g., memory, executive function); thus, it remains unclear whether subjective-objective discrepancies would also be observed for the BICAMS in the presence of depression or fatigue. Additionally, no studies to date have examined the degree to which demographic or clinical variables may moderate the associations between objective-subjective discrepancies and symptoms of depression and fatigue. For example, older patients or those with progressive disease types may be more or less vulnerable to the effects of fatigue and depression on cognitive accuracy. These potential moderating effects could have implications for appropriate use (or non-use) of subjective cognitive screening tools in diverse MS clinics.

Given the need for additional work in this area, the present study aimed to: (1) examine the degree to which depressive symptoms and fatigue are associated with objective-subjective discrepancies in cognitive function based on the objective BICAMS and the subjective MS Neuropsychological Screening Questionnaire (MSNQ); (Benedict et al., 2004) (2) propose

optimal cut-off scores on depression and fatigue measures for classifying patients who under -or overestimate their cognitive impairment; and (3) identify potential moderators of these predictive associations.

2. Methods

2.1. Participants and procedures

This cross-sectional study featured a secondary analysis of data collected from a previous investigation of cognitive assessment in persons with MS. (Beier et al., 2017) The original study, which was approved by the Institutional Review Board at an academic medical center in the Pacific Northwest, was conducted at the university's MS center. The measures of the study were administered by a psychologist and research coordinator in a single assessment session that lasted approximately 30 min.

Participants included in this study were required to: (1) be 18 years of age or older; (2) have a physician-confirmed MS diagnosis in their medical record; and (3) have the ability to read and write in English. Participants were excluded if they had a neurological disorder other than MS or had severe dexterity issues or cognitive impairment that impeded completion of testing procedures (e.g., a figure copy task). A total of 100 participants were enrolled in the original study; however, one participant withdrew before completing the testing session, yielding a final sample of 99.

2.2. Measures

2.2.1. Demographics and dinical characteristics—Participants provided demographic and clinical information to include: age; gender; race; ethnicity; years of education; employment status; marital status; use of disease modifying therapies (DMTs); disease duration; and MS type.

2.2.2. Patient Health Questionnaire-8 (PHQ-8) (Spitzer et al., 1999; Kroenke et al., 2009)—The PHQ-8 is used to assess the severity of depressive symptoms over the past two weeks and has been applied to research with a number of rehabilitation populations, including MS. (Kroenke et al., 2009) Responses range from 0 (not at all; 0 to 1 day) to 3 points (nearly every day; 12–14 days) and total scores range from 0 to 24 points. The PHQ-8 demonstrated high internal consistency (Cronbach's α = 0.87) for this sample.

2.2.3. Fatigue Severity Scale (FSS) (Krupp et al, 1989)—The 9-item FSS measures fatigue symptoms in persons with chronic medical conditions, including MS. (Krupp et al., 1989) Each of the 9 items has responses ranging from 1 (strongly disagree) to 7 (strongly agree) and the total score is obtained by summing the items. Total scores range from 9 to 63. The FSS demonstrated high internal consistency (α = 0.91) for this sample.

2.2.3.1. MSNQ (Benedict et al., 2003): The 15-item MSNQ is a self-report measure of cognitive dysfunction. (Benedict et al., 2003) Items assess the degree to which symptoms have interfered with daily activities over the past three months. Each item contains responses ranging from 0 ("Never, does not occur") to 4 ("Very often, very disruptive"), resulting in a total score that ranges from 0 to 60. The instrument demonstrated high internal consistency

(a = 0.94) in the current sample. In addition to a raw total score, a standardized (z) score was calculated for the MSNQ based on normative mean and standard deviation data published in the measure's original validation study. (Benedict et al., 2004) That score was then multiplied by −1 such that higher scores indicated better subjective functioning.

2.2.4. BICAMS (Benedict et al., 2012; Langdon et al., 2012)—The BICAMS was developed by an international expert consensus committee to assess cognitive domains frequently affected in MS (Benedict et al., 2012). It includes the following components: the total score from the Symbol Digit Modalities Test (SDMT); (Smith, 1982) the total score from the five learning trials of the California Verbal Learning Test-II (CVLT-II); (Delis et al., 2000) and the total score from the five learning trials of the Brief Visuospatial Memory Test —Revised (BVMT-R) (Benedict, 1997). The BICAMS demonstrates strong psychometric properties, where impairment on one or more of the instruments indicates cognitive impairment with excellent sensitivity (94%) and good specificity (86%) (Dusankova et al., 2012). In addition to each raw score, a standardized (z) score was generated for each measure based on norms published in each measure's respective manual. The three z scores were then averaged to produce a composite BICAMS z score, where higher scores indicated better cognitive functioning.

2.3. Data analysis

Discrepancies between subjective scores on the MSNQ and objective scores on the BICAMS were calculated based on previously reported methods (Julian et al., 2007; Kinsinger et al., 2010). Continuous discrepancy scores were calculated by subtracting MSNQ z scores from composite BICAMS z scores. Participants who exhibited discrepancy scores ≤−1.0 were labeled as "Overestimators," as their subjective responses overestimated their objective cognitive performance. Participants who exhibited discrepancy scores ≥1.0 were labeled as "Underestimators," as their subjective responses underestimated their objective performance. All others participants were labeled as "Accurates."

Preliminary Pearson's r correlations were calculated to determine the significance and strength of relationships between: potential demographic and clinical covariates; scores on the PHQ-8 and FSS; raw scores on the MSNQ and BICAMS; and BICAMS-MSNQ discrepancy scores. Any demographic or clinical characteristic that correlated with the PHQ-8, FSS, or discrepancy score was retained as a covariate for subsequent analyses. Next, separate univariate analyses of variance (ANOVAs) were performed to compare Accurates, Underestimators, and Overestimators on the covariates, PHQ-8, and FSS. *Post hoc* group differences were identified using Bonferonni tests. Because Accurates did not differ significantly from Overestimators (i.e., those who rated their perceived cognitive function as better than their objective performance), these groups were merged into a single "Non-underestimators" group for subsequent analyses.

For Aim 1, three binary logistic regression analyses were conducted to assess whether Underestimators could be accurately classified based on PHQ-8 and FSS scores. For each regression, significant covariates were entered into Step 1 and either the PHQ-8 (first regression), FSS (second regression), or both (third regression) were entered in Step 2. For

Aim 2, receiver operating characteristic (ROC) analyses and Youden's index (Youden, 1950) were used to identify optimal PHQ-8 and FSS cut-off scores for distinguishing Underestimators from Non-underestimators. ROC analyses also yielded values for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). For Aim 3, a series of binary logistic regression analyses were performed to test whether age, gender, education, or MS duration moderated the relationship between PHQ-8 and FSS scores and underestimation of cognitive function. These variables were selected based on previous findings that depression and fatigue in MS may vary as a function of demographic and clinical characteristics (Bakshi et al., 2000). For moderation analyses, all variables were standardized to reduce multicollinearity. The same regression models were run from Aim 2, but with an interaction term (e.g., Age x PHQ-8) entered into Step 3.

3. Results

3.1. Sample descriptive statistics

Table 1 presents descriptive statistics for all study variables. The sample was predominately female, white/Caucasian, and had high levels of education. Over half of the participants were married or living with a partner. Approximately three-quarters of the sample had relapsing-remitting MS, while the remainder had one of the progressive subtypes. The infusion medication, natalizumab, was the most commonly prescribed DMT, followed by oral medications, then injectables. The overall mean PHQ-8 score for the sample fell in the mild range, with 28% of the sample endorsing moderate (≥10) or greater levels of depressive symptomatology (Amtmann et al., 2014; Sjonnesen et al., 2012). The mean FSS score fell below the clinical cut-off (≥36), with 54% of the sample endorsing clinically significant fatigue. Mean scores on all cognitive measures—subjective and objective—were numerically lower than the normative sample means. Using a criterion of 1.5 *SD* below the normative mean, 25%, 21%, and 15% were impaired on the SDMT, BVMT-R, and CVLT-II, respectively. Although the mean BICAMS-MSNQ discrepancy score ($z = 0.72$) fell within the "Accurate" range, Underestimators were the majority group within the sample (43%).

3.2. Correlations between study variables

Table 2 presents correlations among study variables. Regarding potential covariates, gender and years of education were significantly negatively correlated with BICAMS-MSNQ discrepancy scores ($ps < 0.01$), where women and individuals with lower education exhibited higher discrepancy scores and were more likely to underestimate their objective cognitive function. Additionally, younger age, female gender, fewer years of education, and shorter MS duration correlated with higher PHQ-8 scores; and fewer years of education also correlated with higher FSS scores ($ps < 0.05$). These demographic and clinical characteristics were retained as covariates in subsequent analyses. The PHQ-8 correlated significantly and strongly with the MSNQ, and with the BICAMS-MSNQ discrepancy score; however, correlations between the PHQ-8 and objective BICAMS measures were nonsignificant and minimal in strength ($rs < 0.06$). Similarly, the FSS correlated significantly and moderately with the MSNQ and BICAMS-MSNQ discrepancy score, but correlations with objective measures were non-significant for the BVMT-R and CVLT-II, and significant but small for the SDMT.

3.3. Differences between Accurates, Underestimators, and Overestimators

Results of univariate analyses comparing diagnostic accuracy groups are presented in Table 3. There were no statistically significant differences between the three groups based on age, years of education, MS duration, or MS type (all *ps* > 0.05). However, the Underestimators group exhibited a higher proportion of women relative to the other groups. Underestimators also exhibited significantly higher PHQ-8 and FSS scores relative to Accurates and Overestimators. As indicated in the analytic plan, because Overestimators and Accurates did not differ on any study measures, these groups were combined for subsequent regression and ROC analyses.

3.4. Depression and fatigue aspredictors of underestimation

Results from the three logistic regression analyses are presented in Table 4. After adjusting for covariates (i.e., age, gender, education, and MS duration), the PHQ-8 significantly distinguished Underestimators from Non-underestimators, where higher PHQ-8 scores predicted greater likelihood for underestimation ($p < 0.001$). Similarly, after adjusting for gender and education, the FSS also distinguished Underestimators from Non-underestimators ($p < 0.001$). A third logistic regression that included both the PHQ-8 and the FSS demonstrated independent and significant contributions of the PHQ-8 ($p < 0.01$) and FSS ($p < 0.05$) to predicting underestimation.

3.4.1. Cut-off scores for the PHQ-8 and FSS—ROC analyses, including optimal cut-off scores for the PHQ-8 and FSS, are presented in Table 5. For the PHQ-8 and FSS, analyses yielded fair AUCs of 0.78 ($p < 0.001$, 95% CI: 0.69, 0.87) and 0.74 ($p < 0.001$, 95% CI: 0.64, 0.84), respectively. Cut-off scores identified through Youden's index showed fair sensitivity, poor specificity, poor PPV, and good NPV for both the PHQ-8 and FSS.

3.4.2. Moderators ofdiagnostic accuracy—Age, gender, years of education, and MS duration were tested as potential moderators of the relationship between Underestimation and symptoms of depression and fatigue. None of the variables assessed emerged as significant moderators (all *ps* > 0.05).

4. Discussion

Discrepancies between objective and subjective cognitive function are common in individuals with MS, and the present study aimed to examine depressive symptoms and fatigue as they relate to these observed discrepancies. Sixty-one percent of the present sample exhibited objective-subjective discrepancies, with the majority (43%) underestimating their objective cognitive abilities. Importantly, depressive symptoms and fatigue, as measured by the PHQ-8 and FSS, respectively, were moderately correlated with objective-subjective discrepancies, with Underestimators (i.e., individuals who evidenced worse subjective than objective function) exhibiting significantly higher PHQ-8 and FSS scores than Accurates or Overestimators. Although the PHQ-8 and FSS were moderately correlated with the MSNQ, neither measure was associated with BICAMS measures, with the exception of the SDMT, which exhibited a small but statistically significant correlation with FSS. Depression and fatigue were examined separately and together in terms of their

accuracy in distinguishing Underestimators from Non-underestimators. Multiple regression analyses showed that the PHQ-8 and FSS each contributed unique variance for classifying Underestimators. Additional analyses showed that these associations were not moderated by any of the demographic (e.g., age) or diseaserelated variables (e.g., MS duration) assessed. These findings are generally consistent with the literature (Kinsinger et al., 2010), though, studies involving severely depressed individuals with MS have found stronger correlations between depressive symptoms and objective cognitive functioning (Golan et al., 2017; Niino et al., 2014).

In addition to supporting prior findings, the present study proposed novel cut-off scores on the PHQ-8 and FSS for predicting the likelihood that a participant would underestimate their objective cognitive functioning. A cut-off score of ≥6 on the PHQ-8 yielded fair sensitivity for identifying Underestimators. The recommended cut-off score on this measure for identifying depression among individuals with MS is ≥10 (Amtmann et al., 2014; Sjonnesen et al., 2012); thus, the present study suggests that even mild levels of depressive symptomatology can confer risk for underestimating cognitive function. A cut-off score of ≥36 on the FSS demonstrated fair sensitivity for identifying Underestimators. This is the same recommended cut-score typically employed for identifying clinically significant fatigue in MS (Krupp et al., 1989).

The limitations of this study are important to consider when applying the findings in research and clinical settings. With regard to assessment, objective cognitive performance was assessed using the BICAMS. Although the BICAMS is among the most commonly used and validated measures for assessing cognition in MS, it is a brief screening tool that does not capture potential deficits in delayed memory, reasoning, problem-solving, or complex attention. It is possible that individuals classified as Underestimators did have cognitive impairment that was not captured by the battery. Thus, the classification pattern observed in the present study may differ for a full neuropsychological battery. Another assessment limitation included use of the FSS, which has been shown to have moderate ceiling effects compared to other measures of fatigue in MS. (Amtmann et al., 2012) Elevated responses on the FSS may indicate other symptoms (e.g., sleep disturbance) that may have implications for assessing cognitive impairment. A third assessment limitation was the lack of assessment of premorbid functioning, which could have implications for interpreting scores that fell within the average range for a patient but nonetheless represented a decline from prior function and thus led to elevations on the MSNQ. Thus, the proposed cut-off scores for the PHQ-8 and FSS should not solely be used to determine overall rehabilitation interventions and recommendations, but rather as screeners to determine if further assessment and/or intervention is warranted. In addition to assessment measures, the present study was limited by a relatively homogenous sample. Although the sample was representative of individuals with MS in the Pacific Northwest, it is nonetheless essential to practice caution when applying the findings to other populations due to the variability in disease progression and other healthcare factors that vary across subpopulations (Khan et al., 2015).

5. Conclusions

In the presence of mild to moderate depressives symptoms and fatigue, subjective cognitive measures like the MSNQ are unlikely to provide accurate or incrementally beneficial diagnostic data. In terms of clinical implications, providers may consider using measures of fatigue and depression to determine if administration of a subjective cognitive screener would be clinically useful. Objective cognitive measures are required for accurate identification of cognitive impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest

We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which they are associated and we certify that all financial and material support for this research and work are clearly identified in the title page of the manuscript.

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Table 1

Sample descriptive statistics.

	N (%)	*M*	*SD*	Min	Max
Age (years)		46.20	12.96	19	72
Gender					
Female	73 (74%)				
Male	24 (24%)				
Not reported	2 (2%)				
Ethnicity					
Hispanic	7 (90%)				
Non-Hispanic	89 (7%)				
Not reported	3 (3%)				
Race					
White	95 (96%)				
Black/African American	0 (0%)				
Asian	5 (5%)				
American Indian/Alaska native	0 (0%)				
Native Hawaiian/Pacific Islander	11 (11%)				
Multi-racial	10 (10%)				
Not reported	2 (2%)				
Education (years)		15.47	2.47	10	22
MS duration (years)		10.69	8.41	1	37
MS type					
RRMS	76 (77%)				
SPMS	8 (8%)				
PPMS	3 (3%)				
PRMS	1 (1%)				
Not reported	11 (11%)				
DMT status					
None	3 (3%)				
Interferon beta-1a	4 (4%)				
Peginterferon beta-1a	1 (1%)				
Interferon beta-1b	2 (2%)				
Glatiramer acetate	7 (7%)				
Fingolimod	10 (10%)				
Natalizumab	42 (42%)				
Dimethyl fumarate	22 (22%)				
Not reported	8 (8%)				
Marital status					
Married/partnered	52 (53%)				
Divorced/separated	16 (16%)				
Single/never married	28 (21%)				

	N (%)	*M*	*SD*	Min	Max
Widowed	1 (1%)				
Not reported	2 (2%)				
Employment status					
Employed	45 (46%)				
Not employed	52 (53%)				
PHQ-8		6.91	5.39	0	23
FSS		37.96	14.37	9	63
MSNQ (raw)		23.15	11.42	1	58
MSNQ (*z*)		−1.15	1.84	−6.77	2.42
BICAMS (raw)					
SDMT		48.73	12.33	20	79
CVLT-II		49.06	11.82	19	74
BVMT-R		23.16	7.88	3	36
BICAMS (*z*)		−0.44	1.01	−3.12	1.80
SDMT		−0.95	1.14	−4.30	1.59
CVLT-II		−0.08	1.29	−3.10	2.7
BVMT-R		−0.27	1.42	−3.10	2.5
BICAMS (*z*) – MSNQ (*z*) Discrepancy		0.72	1.96	−4.31	5.71
Discrepancy status					
Accurates	38 (38%)				
Underestimators (worse subjective)	43 (43%)				
Overestimators (worse objective)	18 (18%)				

Notes. *N* = 99 participants. Race variable not mutually exclusive.

Abbreviations: BICAMS = Brief International Cognitive Assessment of Multiple Sclerosis; BVMT-R = Brief Visuospatial Memory Test-Revised; CVLT-II = California Verbal Learning Test-Second Edition; DMT = disease-modifying therapy; FSS = fatigue severity scale; MS = multiple sclerosis; MNSQ = Multiple Sclerosis Neuropsychological Screening Questionnaire; PHQ-8 = Patient Health Questionnaire-8; PPMS = primary progressive MS; PRMS = progressive relapsing MS; RRMS = relapsing remitting MS; SDMT = Symbol Digit Modalities Test; SPMS = secondary progressive MS.

Table 2

Correlations between potential covariates, depression, fatigue, cognitive measures, and objective-subjective discrepancy scores.

	PHQ-8	FSS	MSNQ(raw)	SDMT (raw)	BVMT (raw)	CVLT (raw)	BICAMS-MSNQ discrepancy
Age	−0.25*	−0.09	−0.19	−0.31**	−0.26*	−0.10	−0.16
Gender	−0.19	−0.13	−0.31**	0.05	0.03	−0.01	−0.28**
Education (years)	−0.26*	−0.24*	−0.40***	0.20*	0.08	0.18	−0.26**
MS duration	−0.22*	−0.05	−0.06	−0.14	−0.06	0.03	< 0.01
MS type	−0.16	−0.07	−0.12	−0.28*	−0.08	−0.11	−0.16
PHQ-8	–	0.52***	0.58***	−0.02	0.06	0.04	0.52***
FSS	–	–	0.48***	−0.21*	0.10	0.11	0.47***

Notes.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

Gender coded as 0 = female and 1 = male. MS type coded as 0 = RRMS and 1 = progressive MS.

Abbreviations: BICAMS = Brief International Cognitive Assessment of Multiple Sclerosis; BVMT-R = Brief Visuospatial Memory Test—Revised; CVLT-II = California Verbal Learning Test—Second Edition; FSS = Fatigue Severity Scale; MS = multiple sclerosis; MNSQ = Multiple Sclerosis Neuropsychological Screening Questionnaire; PHQ-8 = Patient Health Questionnaire-8; SDMT = Symbol Digit Modalities Test.

Table 3

Univariate analyses comparing diagnostic accuracy groups on potential covariates, depression, and fatigue.

	Accurates (*n* = 38)		**Underestimators (*n* = 43)**		**Overestimators (*n* = 18)**			
	M	***SD***	***M***	***SD***	***M***	***SD***	**F or χ^2**	**Post-hoc**
Age	45.70	14.37	44.55	11.16	51.06	13.38	1.65	NS
Gender (F/M)	24/13		37/5		12/6			U > A
Education (years)	15.30	2.58	15.17	2.25	16.56	2.57	2.20	NS
MS duration	10.28	8.74	11.17	8.55	10.39	7.82	0.12	NS
MS type (RR/P)	27/5		37/3		12/4		3.14	NS
PHQ-8	5.11	4.09	9.83	5.79	3.89	3.25	14.13***	U > A
								U > O
FSS	35.39	13.26	44.56	12.76	27.61	12.95	12.00***	U > A
								U > O

Notes.

*** $p < .001$.

Gender coded as 0 = female and 1 = male. MS type coded as 0 = relapsing-remitting and 1 = progressive MS.

Abbreviations: A = Accurates; FSS = Fatigue Severity Scale; MS = multiple sclerosis; O = Overestimators; P = progressive MS; PHQ-8 = Patient Health Questionnaire-8; RR = relapsing remitting MS; U = Underestimators.

Table 4

Binary logistic regression models of depression and fatigue as predictors of underestimation.

	χ^2	*B*	*SE* (*B*)	*Wald*	Exp (B)
PHQ-8					
Step 1	9.91*				
Age		−0.39	0.02	3.25	0.96
Gender		−1.47	0.60	6.06*	0.23
Education (years)		−0.26	0.09	0.08	0.98
MS duration		0.04	0.03	1.36	1.04
Step 2	22.04***				
Age		−0.03	0.03	1.76	0.97
Gender		−1.18	0.66	3.22	0.31
Education (years)		0.64	0.10	0.39	1.07
MS duration		0.07	0.04	3.81	1.07
PHQ-8		0.25	0.07	15.02***	1.29
FSS					
Step 1	7.55*				
Gender		−1.32	0.56	5.59*	0.27
Education (years)		−0.07	0.09	0.57	0.94
Step 2	15.21***				
Gender		−1.29	0.59	4.75*	0.28
Education (years)		0.01	0.10	0.01	1.01
FSS		0.07	0.02	12.66***	1.07
PHQ-8 & FSS					
Step 1	9.91*				
Age		−0.39	0.02	3.25	0.96
Gender		−1.47	0.60	6.06*	0.23
Education (years)		−0.26	0.09	0.08	0.98
MS duration		0.04	0.03	1.36	1.04
Step 2	26.12***				
Age		−0.04	0.03	2.01	0.96
Gender		−1.25	0.67	3.46	0.29
Education (years)		0.92	0.11	0.73	1.10
MS duration		0.07	0.04	3.57	1.07
PHQ-8		0.21	0.07	9.18**	1.23
FSS		0.42	0.02	3.88*	1.04

Notes.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

Gender coded as 0 = female and 1 = male.

Abbreviations: FSS = Fatigue Severity Scale; PHQ-8 = Patient Health Questionnaire-8.

Table 5

ROC analyses identifying optimal cut-off scores for the PHQ-8 and FSS with regard to identifying Underestimators.

Test	Cut-Off*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PHQ-8	≥6	74	66	49	85
FSS	≥36	77	64	49	86

Notes. N = 99 participants.

*Cut-off scores represent optimal balance between sensitivity and specificity based on Youden's index.

Abbreviations: FSS = Fatigue Severity Scale; NPV = negative predicted value; PHQ-8 = Patient Health Questionnaire-8; PPV = positive predicted value.