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A Closer Look at the Influence of Mood and Disability on Illness Intrusiveness in Multiple Sclerosis

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Purpose: Multiple sclerosis (MS) patients often report high levels of illness intrusiveness. The direct and indirect effects of disability and psychological symptoms on illness intrusiveness remain largely unknown, despite their pervasiveness. The present study aimed to examine how depression and anxiety can serve as mechanisms through which disability may impact illness intrusiveness in 3 life domains—instrumental activities, intimacy, and relationships and personal development. ***Method:*** Participants ($N = 72$) were adults ($M_{age} = 47.86$, $SD = 11.79$), predominantly female (73.6%) and diagnosed relapse-remitting MS (81.9%). The data was used from an archival neuropsychological database. Data on self-report measures were analyzed to examine the relationship between disability and illness intrusiveness, with depression and anxiety as mediators. Mediation models were run for total illness intrusiveness and the subscales. ***Results:*** Depression and anxiety were significant mediators through which disability may impact overall illness intrusiveness. When examining life domains, depression was a significant mediator in all domains. Anxiety was only a significant mediator between disability and relationships/personal development. ***Conclusions:*** Results suggest that greater disability both directly and indirectly interferes with illness intrusiveness via depression and anxiety. However, life domains are differentially impacted. Thus, this study helps to guide interventions on the best symptoms to target to improve illness intrusiveness and overall quality of life.

Impact and Implications

Disability is intrusive on the daily lives of MS patients, interfering with patients' participation in valued activities and interests. Depression and anxiety are highly prevalent in MS and can serve as mediators through which disability triggers perceived illness intrusiveness. The influence of depression and anxiety differs based on the life domain. Depression is related to illness intrusiveness across life domains (e.g., work, family, romance, diet, health, etc.), whereas anxiety is only associated with illness intrusiveness in relationships and personal development. Treating psychological symptoms can improve the perception of illness intrusiveness and enhance the overall quality of life for MS patients.

Keywords: disability, illness intrusiveness, quality of life, anxiety, depression

Introduction

Multiple sclerosis (MS) is a neurodegenerative, immune-mediated disease that leads to inflammatory demyelination and axonal loss within the central nervous system (CNS). MS has a detrimental impact on quality of life (QoL) due to its unpredictable course and symptom presentation, typically manifesting as an array of disabling physical, cognitive, and psychological symptoms (Opara et al., 2010). In particular, psychological comorbidity is pervasive in MS, with over 30% of patients having clinically significant depression and/or anxiety, often in the moderate to severe range (Boeschoten et al., 2017; Jones et al., 2012). Despite its pervasiveness, many MS patients do not receive adequate treatment for their psychological distress (Nathoo & Mackie, 2017). Failing to sufficiently address psychological symptoms is problematic as psychological distress is known to reduce disease-modifying behaviors, such as treatment adherence, while simultaneously contributing to poor health behaviors, including smoking, alcohol use, and physical inactivity, all of which are potential risk factors for worsening disability (Briggs et al., 2019; Feinstein et al., 2014). Further, psychological dysfunction adversely impacts patients' capacity to maintain employment, fulfill social roles, and partake in valued activities, thereby interfering with their QoL (Berrigan et al., 2016; Nourbakhsh et al., 2016).

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In addition to poor overall QoL, MS is frequently associated with a detriment in health-related QoL (HR-QOL), a multidimensional construct of quality of life that encompasses the patient's perspective on the extent physical, mental, and social components of their disease impact functioning (Revicki et al., 2000; Wilski & Tasiemski, 2016). Illness intrusiveness is an indicator of HR-QoL and involves disruption to lifestyle when illness-induced barriers, including treatment factors (e.g., medication side effects and cost/availability of treatment) and disease factors (e.g., disability, pain, fatigue), interfere with participation in previously valued interests and activities (Devins, 1994; 2010; Shawaryn et al., 2002). Illness intrusiveness is conceptualized as indirectly impacting HR-QOL by interfering with three key areas of life, (a) *instrumental activities,* including work, financial situation, active recreation, and health; (b) *intimacy*, including relationship with partner and sex life; and (c) *relationships and personal development*, including relationships with family and others, self-expression, religion, community and civic involvements, and passive recreation (Devins, 1994; 2010).

While illness intrusiveness has been studied in numerous chronic diseases, including MS, the majority of studies have focused on the unified construct and failed to examine its components (i.e. instrumental, intimacy, and relationships/personal development) independently. Studies that have focused on the components of illness intrusiveness have demonstrated that the specific domains of illness intrusiveness are differentially affected by chronic disease and that focusing on the impacted domains as therapeutic targets can be advantageous for effective psychological intervention (Edworthy et al., 2003; Sohl et al., 2014). For example, a study in MS examined sex differences in the three components of MS, indicating that men are particularly prone to perceived illness intrusiveness, especially in intimacy and relationship and personal development domains (Neto et al., 2019). Another study in systemic lupus erythematosus (SLE) demonstrated that group psychotherapy can be especially beneficial in reducing the perception of illness intrusiveness in intimacy and relationships (Edworthy et al., 2003). However, the extent to which illness-induced barriers (e.g., disability, psychological symptoms) may distinctly impact specific life domains in MS remains largely unknown.

The lack of research on the psychological determinants of illness intrusiveness, particularly in the MS population, is likely secondary to existing research mainly focusing on illness intrusiveness as a mediating variable on health outcomes (Shawaryn et al., 2002). One study by Snyder and colleagues (2013) that examined psychological factors as predictors of illness intrusiveness in MS found that higher levels of anxiety, depression, and disability were associated with increased overall illness intrusiveness. This study, however, did not examine how psychological factors interrelate with disease factors, such as disability, in impacting illness intrusiveness in MS (Snyder et al., 2013). Consistent with the biopsychosocial model, it is imperative to simultaneously consider biological (e.g., pathophysiology, disease symptoms), psychological (e.g., psychological/mood symptoms), and social (e.g., participation in valued activities) factors to entirely appreciate patients' experience of their disorder (Strober, 2018).

Understanding the mechanisms through which disability may impact illness intrusiveness is especially critical. Studies suggest that although disability status is a primary predictor of poor HR-QoL, there may be other critical factors that influence the relationship between disability and HR-QoL (Berrigan et al., 2016; Twork et al., 2010). For example, studies have shown patients with less advanced disability are more likely to perceive the impact of their symptoms (e.g., motor deficits) as intrusive on their QoL compared to those who already have more prominent deficits (Schmidt & Jöstingmeyer, 2019; Twork et al., 2010). A plausible explanation for this finding is that psychological functioning may change with disability progression and serve as a key mechanism through which disability is associated with QoL (Patti et al., 2003). That is, individuals with less advanced disability may experience a greater burden on their QoL as they experience elevated psychological distress, feel a loss of their identity, and attempt to conceal their disability. As disability progresses, QoL may improve as individuals develop effective psychological coping strategies, learn to accept their diagnosis, and identify as an individual with a disability (Bogart, 2015; Irvine et al., 2009).

The objective of the present study is to fill these gaps of knowledge by examining the role of disability, depression, and anxiety on MS patients' perception of illness intrusiveness. Specifically, the study hypothesized that depression and anxiety would be mediators through which disability indirectly affects illness intrusiveness. Moreover, the present study also aimed to contribute to existing research on illness intrusiveness, which has been largely examined as a unidimensional construct, by specifically examining how disability, depression, and anxiety relate to illness intrusiveness in three life domains—instrumental activities, intimacy, and relationships/personal development.

Method

Participants

The present study is a secondary analysis of a larger ongoing neuropsychological research project. Participants were recruited as part of an ongoing study at an outpatient clinic for MS at a suburban medical center in New Jersey. Inclusion criteria consisted of individuals diagnosed with MS and at least 18 years of age. Patients were excluded if they were in the midst of a relapsing episode or had substantial visual and/or hearing impairment that would interfere with the participant's ability to complete neuropsychological testing.

Procedure

All participants consented to participate in this study. The study was approved by the institutional review board (IRB) at Albert Einstein College of Medicine (Bronx, NY). Participants completed the following measures as part of a large neuropsychological study. Data collection for each participant was completed within one session that was comprised of standardized administration of neuropsychological measures and collection of self-report measures.

Materials

Demographics

Demographic information and disease characteristics, such as years since diagnosis, were collected via self-report. A subset of

participants (n = 31) had a recently updated medication list available for review; current psychotropic medication use was collected for this subset of participants.

Incapacity Status Scale (ISS)

The ISS is a 16-item, 5-point ordinal rating scale used to assess the severity of disability in MS (Mertin et al., 1984). This scale is completed by an MS specialty clinician, who rates an MS patient's disability with a higher score reflecting a higher degree of impairment. The items cover multiple areas of functioning, including ambulation, activities of daily living, mentation, fatigue, communication, mood and thought disturbances, and sexual functioning.

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14 item, 4-point measure (0–3) of anxiety and depression in the medical population, which has been validated in the MS population (Bjelland et al., 2002; Honarmand & Feinstein, 2009; Zigmond & Snaith, 1983). In the present study, the anxiety subscale (HADSA) was used to measure anxiety symptoms. Higher scores of this subscale indicate increased anxiety symptomology. A total subscale score at or above 8 on the HADSA has been found to be an indicator of clinically significant anxiety (88.5% sensitivity; 81% specificity; Honarmand & Feinstein, 2009).

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a valid, 9-item self-report measure used to quantify depressive symptoms (Kroenke et al., 2001). Higher scores indicate increased depressive symptoms. A total cut-off score of 10 or above has been shown to be indicative of clinical depression (sensitivity 88%; 85% specificity; Levis et al., 2019). The PHQ-9 was chosen as a measure of depression, given its robustness to MS confounds and high sensitivity relative to other validated depression scales in the MS population (Hind et al., 2016; Marrie, Zhang, et al., 2018).

Illness Intrusiveness Rating Scale (IIRS)

The IIRS is a 13-item, 7-point self-report instrument validated in chronic diseases, including MS (Devins, 1994, 2010). The scale asks respondents to rate the extent to which their illness and/or treatment has interfered with various aspects of their life. A high score indicates a higher degree of perception that respondents' disease is interfering and constraining their involvement in valued activities and interests central to QoL. The IIRS has three subscales: (a) a four-item *instrumental* subscale, (b) a two-item *intimacy* subscale, and (c) a six-item *relationships and personal development* subscale. In the present study, the sum of the 13-items was used to measure total illness intrusiveness, whereas the mean of the items in individual subscales was used to measure the subscales.

Data Analysis

Statistical analyses were conducted using SPSS 25.0. Little's missing completely at random (MCAR) test was insignificant (p = .78), revealing that the data were MCAR; list-wise deletion was subsequently used for missing values. Descriptive statistics were conducted to describe the sample characteristics (see Table 1).

Table 1
Descriptive Statistics for Demographics, Predictor, and Outcome Variables

Variable	Total (N = 72)	
	N	%
Gender		
Female	53	73.6
Male	19	26.4
Race/ethnicity		
White	55	76.4
Black	11	15.2
Hispanic	6	8.3
Marital status		
Single	19	26.4
Married	44	61.1
Divorced	7	9.7
Widowed	2	2.7
Employment status		
Unemployed—receiving disability	22	30.5
Unemployed—other	28	38.9
Part-time	4	5.5
Full-time	18	25.0
MS type		
Relapse-remitting	59	81.9
Secondary-progressive	8	11.1
Primary-progressive	5	6.9
Variable	*M*	*SD*
Age	47.86	11.97
Years of education	14.90	3.81
ISS total score	13.01	6.43
HADS anxiety	8.70	4.17
PHQ	10.21	6.21
IIRS total score	52.55	20.12
IIRS instrumental	5.09	1.76
IIRS intimacy	4.12	2.18
IIRS relationships/personal Development	3.53	1.63

Note. ISS = Illness Severity Scale; HADS = Hospital Anxiety and Depression Scale; IIRS = Illness Intrusiveness Rating Scale.

Pearson correlations examined the zero-order relationships between demographic variables, predictor, and the outcome variable (see Table 2). The data were examined to confirm that the data met the assumptions of normality, linearity, multicollinearity, and homoscedasticity.

Mediational analyses were conducted to examine the following mediational models (see Figures 1 & 2): (a) the relationship between disability and total illness intrusiveness through depression; (b) the relationship between disability and total illness intrusiveness through anxiety; (c–e) the relationship between disability and the three subtypes of illness intrusiveness through depression; (f–h) the relationship between disability and the three subtypes of illness intrusiveness through anxiety. Gender, age, and disability (ISS) were entered as covariates in each model. Separate mediational analyses were run for total illness intrusiveness and the three subscales, as each subscale captures a distinct construct of illness intrusiveness and there is a gap in the literature on the specific subscales, with existing studies having primarily examined total illness intrusiveness. It should be noted that running multiple mediation models heightens the risk of type I error. To address this risk, results that were no longer significant when applying a Bonferroni correction (α/n) were noted; the Bonferroni correction

Table 2
Zero-Order Correlations of Demographic and Predictor Variables

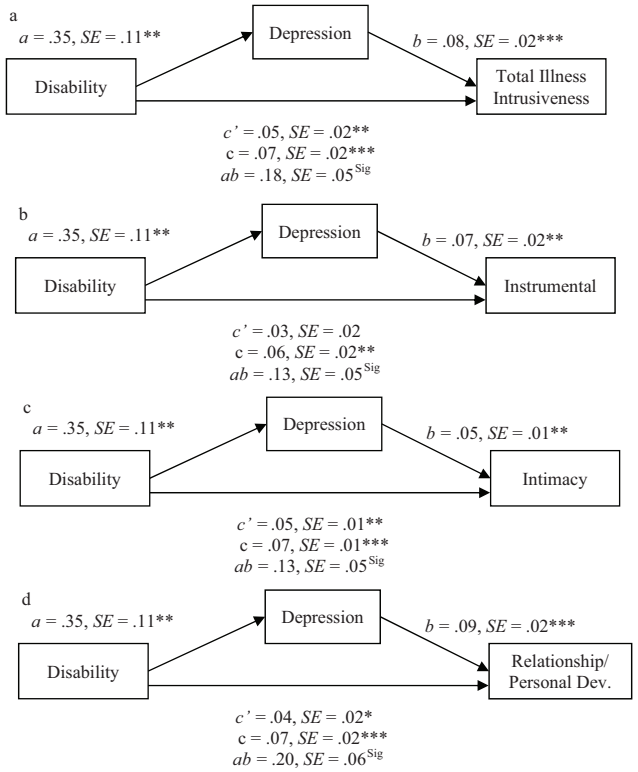
Variable	1	2	3	4	5	6	7	8	9
1. IIRS total score	—								
2. Relationship/personal devel	.869**	—							
3. Intimacy	.799**	.680**	—						
4. Instrumental	.726**	.621**	.609**	—					
5. PHQ	.608**	.629**	.483**	.446**	—				
6. HADS anxiety	.517**	.615**	.350**	.326**	.720**	—			
7. ISS	.488**	.421**	.481**	.322**	.321**	.246**	—		
8. Age	−.002	−.087	−.118	−.056	−.093	−.119	.127	—	
9. Years of diagnosis	−.063	−.053	−.051	−.122	−.164	−.022	.110	.261*	—

Note. IIRS = Illness Intrusiveness Rating Scale; PHQ = Patient Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; ISS = Illness Severity Scale.
*$p < .05$. ** $p < .01$.

set the significance cut-off at $\alpha = .0125$ ($\alpha = .05$; $n = 4$, the number of outcome variables).

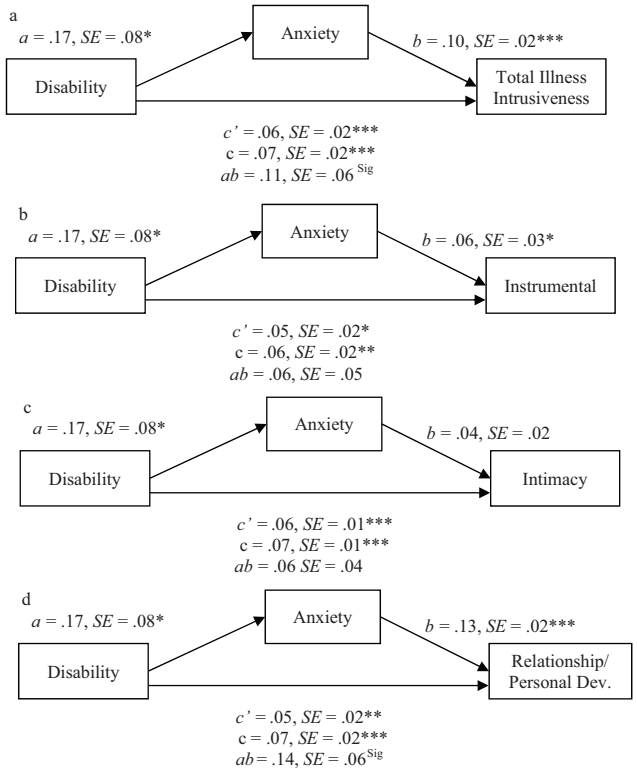
A method publicized by Hayes and Preacher that runs a series of ordinary least squares (OLS) regressions, using the PROCESS macro for SPSS, was used to examine the mediation models (Hayes, 2017). Specifically, the following OLS regressions were run to examine the mediation effect: (a) disability regressed on depression, the mediator (path a); (b) depression regressed on illness intrusiveness, controlling for disability (path b); (c) disability regressed on illness intrusiveness (path c, total effect); (d) disability regressed on illness intrusiveness, controlling for depression and control variables (path c', direct effect); and (e) the mediation, disability regressed on illness intrusiveness via depression (path ab, indirect effect). Total illness intrusiveness and each subscale

Figure 1
Depression Mediation Models



Note. Mediation analysis of the relationship between disability and illness intrusiveness through depression. Separate models are depicted for (a) total illness intrusiveness and the three subscales: (b) instrumental, (c) intimacy, (d) relationship/personal development. c' = direct effect; c = total effect; ab = indirect effect.
* $p < .05$. ** $p < .01$. *** $p < .001$. Sig = significant as determined by 95% CI.

Figure 2
Anxiety Mediation Models



Note. Mediation analysis of the relationship between disability and illness intrusiveness through anxiety. Separate models are depicted for (a) total illness intrusiveness and the three subscales: (b) instrumental; (c) intimacy; (d) relationship/personal development. c' = direct effect; c = total effect; ab = indirect effect.
* $p < .05$. ** $p < .01$. *** $p < .001$. Sig = significant as determined by 95% CI.

were entered in separate models. This process was then repeated with anxiety entered as the mediator. The indirect effects were calculated using a bootstrapping approach drawing from a sample of 10,000. A 95% confidence interval (CI) was fitted around the indirect effect estimates for each percentile-based confidence interval; mediation is present if this 95% CI does not contain zero. The completely standardized indirect effects were used as measures of effect size, such that .01 represented a small effect size, .09 represents a medium effect size, and .25 represents a large effect size (Preacher & Kelley, 2011). Unstandardized coefficient estimates were reported for direct and total effects.

Results

Participants

The results are based on 72 MS patients who met the eligibility criteria. The majority of participants were female (73.6%) and diagnosed with relapsing-remitting MS (81.9%). The ages ranged from 18 to 77 years (M = 47.86, SD = 11.97), and years since diagnosis ranged from 0 to 30 years (M = 7.74, SD= 7.41). See Table 1 for demographic and disease-related characteristics of participants. In the present study, 50.0% of the participants met the cut-off for moderate to severe depression (PHQ-9 ≥ 10), and 61.1% met the cut-off for clinically significant anxiety (HADSA≥ 8). Of the subset of participants who had available data on psychotropic medication use (n = 31), 48.5% were prescribed an antidepressant, and 25.8% were prescribed an antianxiety medication. When examining depression and anxiety in this subsample, 60.0% of those with moderate to severe depression were prescribed an antidepressant, while 35.3% of those with clinically significant anxiety were prescribed an antianxiety medication.

Correlations Among the Variables

Table 2 presents the zero-order correlations among the variables and demographics. Illness intrusiveness (total and subscales) was significantly associated with higher levels of depression, anxiety, and disability. The only demographic variable that was significantly associated with the study variables was gender, such that females (M = 5.18, SD = 1.70) had significantly higher instrumental illness intrusiveness compared to males (M = 4.19, SD = 2.08). Gender was not significantly associated with total illness intrusiveness or the other subscales—intimacy and relationship/personal development. Age and years since diagnosis were not associated with illness intrusiveness, depression, anxiety, or disability.

Mediation Analyses

Disability, Depressive Symptoms, and Illness Intrusiveness

The first series of mediational analyses examined the relationship between disability and illness intrusiveness with depression as the mediator (see Tables 3 and 4). Figure 1 depicts the mediation models.

Total Illness Intrusiveness. Higher disability was associated with a greater perceived total illness intrusiveness ($p < .001$). When examining the role of depression, higher disability was found to be significantly associated with a greater endorsement of depressive symptoms (p = .002). Greater depressive symptomology was associated with higher perceived illness intrusiveness ($p < .001$). There was a significant partial indirect effect of disability on perceived illness intrusiveness through depression (medium effect size: β = .18, SE = 05, 95% CI [.09, .30]). That is, when accounting for the indirect effect through depression, the direct effect between disability and total illness intrusiveness continues to be significant (p = .002). This indicates that depression only partly mediates the relationship. The total model accounted for 47% of the variance in total illness intrusiveness, R^2 = .47, F = 12.32, $p < .001$.

Instrumental. Higher disability was associated with greater illness intrusiveness in instrumental activities (p = .004). There was a significant indirect effect of disability on instrumental illness intrusiveness through depression (medium effect size: β = .13, SE = .05, 95% CI [.05, .25]). That is, higher depressive symptomology was predictive of greater instrumental illness intrusiveness (p = .001). When accounting for the indirect effect through

Table 3
Mediation Analyses for Total Illness Intrusiveness Using Ordinary Least Squares (OLS) Regression with (a) Anxiety (HADSA) and (b) Depression (PHQ) as Predictors

		Total illness intrusiveness			
Predictor	Path	*B*	*SE B*	*t*	95% CI
ISS (total effect)	*c*	.07	.02	4.66	[.04, .11]
(a) PHQ on:	*a*				
ISS		.35	.11	3.26	[.14, .56]
Age		−.05	.06	−.76	[−.17, .08]
Gender		−.14	1.61	−.09	[−3.36, 3.07]
Dx years		−.15	.10	−1.47	[−.34, .05]
			R^2 = .15		
(b) HADSA on:					
ISS	*a*	.17	.08	3.32	[.03, .32]
Age		−.05	.04	−1.28	[−.14, .03]
Gender		.87	1.13	.77	[−1.39, 3.12]
Dx years		−.01	.07	−.18	[−.15, .12]
			R^2 = .09		
IIRS on:					
(a) PHQ	*b*	.08	.02	5.24	[.05, .11]
ISS	*c′*	.05	.02	3.28	[.02, .08]
Age		−.03	.01	−.44	[−.02, .01]
Gender		.28	.20	1.40	[−.12, .68]
Dx years		−.01	.01	−.31	[−.03, .02]
			R^2 = .47		
(b) HADSA	*b*	.10	.02	4.13	[.05, .14]
ISS	*c′*	.06	.02	3.87	[.03, .09]
Age		−.01	.01	−.31	[−.02, .01]
Gender		.16	.22	.75	[−.27, .59]
Dx years		−.02	.01	−1.09	[−.04, .01]
			R^2 = .41		

Effect	Path	β	*SE* β	95% CI
Indirect				
Model 1	*ab*	.18	.05	[.09, .30]
Model 2	*ab*	.11	.06	[.02, .24]

Note. IIRS = Illness Intrusiveness Rating Scale; PHQ = Patient Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; ISS = Illness Severity Scale; Dx Years = diagnosis years. *B* = unstandardized coefficient; β = standardized coefficient; *c*' = direct effect; *c* = total effect; *ab* = indirect effect; *b* = Mediator→Y (controlling for X); *t* = *t*-test statistic.

Table 4

Mediation Analyses for Illness Intrusiveness Subscales Using Ordinary Least Squares (OLS) Regression With (a) Anxiety (HADSA) and (b) Depression (PHQ) as Predictors

		Instrumental				Intimacy				Relationships/personal development			
Predictor	Path	*B*	*SE B*	*t*	95% CI	*B*	*SE B*	*t*	95% CI	*B*	*SE B*	*t*	95% CI
ISS (Total Effect)	*c*	.06	.02	1.96	[.02, .10]	.07	.01	4.75	[.04, .09]	.07	.02	4.09	[.04, .10]
(a) PHQ	*b*	.07	.02	3.37	[.03, .11]	.05	.01	3.32	[.02, .08]	.09	.02	5.79	[.06, .12]
ISS	*c′*	.03	.02	1.80	[.00, .07]	.05	.01	3.60	[.02, .08]	.04	.02	2.58	[.01, .07]
Age		−.01	.01	−.91	[−.03, .01]	−.01	.01	−1.67	[−.03, .00]	−.01	.01	−1.31	[−.03, .01]
Gender		.63	.26	2.39	[.11, 1.16]	.14	.19	.72	[−.25, .53]	.39	.21	1.85	[−.03, .81]
Dx years		−.02	.02	−.89	[−.05, .02]	.00	.01	.01	[−.02, .02]	.00	.01	.20	[−.02, .03]
				R^2 = .30				R^2 = .37				R^2 = .48	
(b) HADSA	*b*	.06	.03	2.04	[.01, .12]	.04	.02	1.97	[.00, .09]	.13	.02	5.62	[.08, .17]
ISS	*c′*	.05	.02	2.36	[.01, .08]	.06	.01	4.13	[.03, .09]	.05	.02	3.22	[.02, .08]
Age		.00	.01	−.93	[−.03, .01]	−.01	.01	−1.61	[−.03, .00]	−.01	.01	−.99	[−.03, .01]
Gender		.54	.28	1.90	[−.03, 1.09]	.08	.21	.38	[−.34, .49]	.25	.22	1.14	[−.19, .68]
Dx years		−.02	.02	−1.39	[−.06, .01]	−.01	.01	−.52	[−.03, .02]	−.01	.01	−.69	[−.19, .68]
				R^2 = .23				R^2 = .31				R^2 = .47	
Effect	Path	β		*SE* β	95% CI	β		*SE* β	95% CI	β		*SE* β	95% CI
Indirect													
Model 1	*ab*	.13		.05	[.05, .25]	.13		.05	[.04, .23]	.20		.06	[.09, .33]
Model 2	*ab*	.06		.05	[−0.01, .18]	.06		.04	[−.01, .15]	.14		.06	[.02, .26]

Note. IIRS = Illness Intrusiveness Rating Scale; PHQ = Patient Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; ISS = Illness Severity Scale; Dx Years = diagnosis years. *B* = unstandardized coefficient; β = standardized coefficient; *c*' = direct effect; *c* = total effect; *ab* = indirect effect; *b* = Mediator → Y (controlling for X); *t* = *t*-test statistic.

depression, the direct effect between disability and instrumental illness intrusiveness was no longer significant (p = .076). This suggests that depression fully mediates the relationship between disability and instrumental illness intrusiveness. The total model accounted for 30% of the variance in instrumental illness intrusiveness, R^2 = .30, F = 5.92, $p < .001$.

Intimacy

Higher disability was associated with greater illness intrusiveness in the intimacy domain ($p < .001$). Disability had a significant indirect effect on intimacy illness intrusiveness through depression (medium effect size: β = .13, *SE* = .05, 95% CI [.04, .23]). When accounting for the indirect effect through depression, the direct effect between disability and intimacy illness intrusiveness remained significant (p = .001). As such, depression partially mediates the relationship between disability and intimacy illness intrusiveness. The total model accounted for 37% of the variance in intimacy illness intrusiveness, R^2 = .37, F = 8.05, $p < .001$.

Relationships/Personal Development

Higher disability was associated with greater illness intrusiveness in relationships/personal development ($p < .001$). Disability had a significant indirect effect on relationships/personal development illness intrusiveness through depression (small effect size: β = .03, *SE* = .20, 95% CI [.09, .33]). When accounting for the indirect effect through depression, the direct effect between disability and relationships/personal development illness intrusiveness remained significant (p = .012). As such, depression partially mediates the relationship between disability and illness intrusiveness in relationships/personal development. The total model accounted for 48% of the variance in relationships/personal development illness intrusiveness, R^2 = .48, F = 12.81, $p < .001$.

Disability, Anxiety, and Illness Intrusiveness

The second series of mediational analyses examined the relationship between disability and illness intrusiveness with anxiety as the mediator (Tables 3 and 4). Figure 2 depicts the mediation models.

Total Illness Intrusiveness

When examining the role of anxiety, higher disability was found to be significantly associated with a greater endorsement of anxiety symptoms (p = .023); this was no longer significant with the Bonferroni correction. Greater anxiety symptomology was associated with higher perceived illness intrusiveness, ($p < .001$). There was a significant partial indirect effect of disability on perceived illness intrusiveness through anxiety (medium effect size: β =.11, *SE* = .61, 95% CI [.02, .24]), such that the direct effect between disability and total illness intrusiveness continues to be significant ($p < .001$) when accounting for the indirect effect through anxiety. In sum, anxiety is a partial mediator through which disability affects perceived illness intrusiveness. The total model accounted for 41% of the variance in total illness intrusiveness, R^2 = .41, F = 9.24, $p < .001$.

Instrumental

Anxiety (p = .045) and disability (p = .021) were predictive of illness intrusiveness in instrumental activities; these relationships were no longer significant when applying the Bonferroni correction. The indirect effect of disability on instrumental illness intrusiveness through anxiety was insignificant (small effect size:

β = .06, *SE* = .05, 95% CI [−.01, .18]). Therefore, although higher anxiety and disability are predictive of greater instrumental illness intrusiveness, anxiety does not mediate the relationship between disability and instrumental illness intrusiveness. The total model accounted for 23% of the variance in instrumental illness intrusiveness, $R^2 = .23$, $F = 3.98$, $p = .003$.

Intimacy

Higher disability was predictive of greater illness intrusiveness in intimacy ($p < .001$) when accounting for anxiety. On the other hand, anxiety was not significantly predictive of intimacy illness intrusiveness ($p = .053$), nor was the indirect effect of disability through anxiety (small effect size: β = .06, *SE* = .04, 95% CI [−.01, .15]). As such, anxiety is not a significant mediator through which disability affects intimacy illness intrusiveness. The total model accounted for 31% of the variance in intimacy illness intrusiveness, $R^2 = .31$, $F = 5.92$, $p < .001$.

Relationships/Personal Development

Higher anxiety symptomology ($p < .001$) and disability ($p = .002$) were associated with greater perceived illness intrusiveness in relationships/personal development. Disability had a significant indirect effect on relationships/personal development illness intrusiveness through anxiety (medium effect size: β = .14, *SE* = .06, 95% CI [.02, .26]). In sum, anxiety is a partial mediator, given that the direct effect of disability on illness intrusiveness in relationships/personal development remained significant when taking into account the indirect effect through anxiety. The total model accounted for 47% of the variance in relationships/personal development illness intrusiveness, $R^2 = .47$, $F = 12.11$, $p = <001$.

Discussion

MS is a disabling immune-mediating disease that manifests as a wide range of physical, cognitive, and emotional symptoms and interferes with patients' HR-QoL. The present study contributed to the existing literature on HR-QoL by examining the direct and indirect effects of disability, depression, and anxiety on perceived illness intrusiveness in individuals with MS. Consistent with research by Snyder and colleagues (2013), higher disability was found to be associated with illness intrusiveness. The present study further expanded upon those findings to show that depression and anxiety are significant mediators through which disability may impact illness intrusiveness. Specifically, higher disability was associated with greater depressive and anxiety symptomology; greater depression and anxiety were associated with greater perceived overall illness intrusiveness.

The present study also added to current literature on illness intrusiveness by examining the individual domains of illness intrusiveness—instrumental activities, intimacy, and relationships and personal development. When examining the individual components, depression remained a significant mediator across all domains of illness intrusiveness. Depression was found to be a particularly important mechanism in instrumental activities, such as work, health, financial situation, as it fully accounts for the indirect effect of disability has on this domain of illness intrusiveness. This finding is in accordance with previous studies that have demonstrated that depression is a risk factor for unemployment (Povolo et al., 2019; Lauren B. Strober et al., 2012).

The risk for unemployment is an area warranting explicit attention as MS typically occurs in young adulthood, a time that is typically critical for building a career, yet 50% of MS patients are unemployed within 10 years of their diagnosis (Honarmand et al., 2011; Jones et al., 2016; Strober et al., 2012). Consistent with research suggesting the women with MS are particularly at risk for unemployment, the current study also indicated that women have a higher level of illness intrusiveness in instrumental activities, highlighting the importance of interventions targeting employment for women with MS (Grytten et al., 2017; Stimmel et al., 2020). In particular, the current study suggests that such interventions should aim to target depression, as depression is a mechanism through which disability may impact illness intrusiveness in instrumental activities, including work. In contrast to Neto and colleagues (2019), who found that men with MS were most susceptible to greater intimacy illness intrusiveness, the current study found that men and women largely did not differ in their perceptions of illness intrusiveness, with the exception of instrumental activities.

Regarding anxiety, although anxiety was a significant mediator for overall illness intrusiveness, when examining the individual components, anxiety was only a significant mediator for relationships and personal development. That is, the present study proposes that anxiety especially interferes with patients' relationships with family and others, community involvement, and passive recreation. This finding is congruent with studies that have similarly found significant associations between anxiety and problems with family relations and social functioning (Butler et al., 2016; Liu et al., 2009; Potagas et al., 2008). On the other hand, anxiety was not the mechanism through which disability asserts an indirect effect on instrumental activities or intimacy. Previous studies have indicated that anxiety in MS and other neurological disorders is predictive of reduced HR-QoL, although some studies suggest at a more modest level relative to depression (Hanna & Strober, 2020; Marrie, Patten, et al., 2018; Prisnie et al., 2018). A plausible explanation for this finding is that depressed individuals may be more likely to have cognitive distortions related to their health status (e.g., magnification of inadequacies and minimization of desirable qualities) and thus tend to report lower QoL compared to those with anxiety (Prisnie et al., 2018).

This study has some imperative treatment implications. The present study informs potential points of intervention in clinical practice by suggesting specific life domains that may be vulnerable to illness intrusiveness in MS patients with disability and mood symptoms. For instance, patients presenting with elevated anxiety may be at particular risk for reduced participation in social and recreational activities and may benefit from being screened for recreational participation. On the other hand, patients presenting with depression may benefit from being screened for illness intrusiveness across life domains. Targeting depressive and anxiety symptomology may help reduce perceived illness intrusiveness. Although the effectiveness of psychotherapy on illness intrusiveness has yet to be examined in MS, research in other medical populations have suggested self-management programs and brief psychological therapy may be advantageous in managing the perception of illness intrusiveness (Edworthy et al., 2003; Jonsdottir et al., 2015; Lorig et al., 2008; Renn et al., 2018). Future studies

are needed to better understand the use of evidence-based interventions for treatment of illness intrusiveness in the MS population, though the present study suggests depression and anxiety may be critical points of intervention.

The findings support the widely acknowledged understanding that mental health issues in MS are pervasive and an essential target of treatment. Specifically, 50% of the participants had moderate to severe depression, and 61.1% had clinically significant anxiety. These estimates are on the higher end of ranges previously published prevalence studies. For example, a relatively recent systematic review and meta-analysis indicated a 30.5% pooled mean prevalence for depression and 22.1% for anxiety (Boeschoten et al., 2017). Possible explanations for the higher rate of depression and anxiety in the present study are likely related to methodological aspects of the study design. For instance, it is plausible that the use of a clinic-based sampling approach in the current study led to a sample of individuals with MS who had greater disease severity (prompting more frequent medical appointments) compared to individuals with MS in the community. Moreover, the use of self-report scales to capture depression and anxiety (as were used in this study) may have additionally inflated the prevalence of clinical diagnoses relative to the use of a diagnostic interview to establish a formal diagnosis (Boeschoten et al., 2017).

Nonetheless, the extensiveness of psychological distress in MS reflected in the present study highlights the importance of adequate treatment of psychological symptoms to mitigate the potential effect disability may have on feelings of illness intrusiveness. With this in mind, the study also examined the use of pharmacological treatment in a small subset of the participants. The results indicated 60.0% of those with moderate to severe depression were prescribed an antidepressant. While this figure is promising, suggesting that many MS patients with depression are being pharmacologically treated, it is concerning that they continue to endorse moderate to severe symptoms. This finding is consistent with a Canadian survey that similarly indicated that although a high percentage of MS patients with depression were receiving psychopharmacological treatment, their depressive symptoms persisted (Nathoo & Mackie, 2017; Raissi et al., 2015).

In terms of anxiety, a smaller percentage of participants (35.3%) in the current study with clinically significant anxiety were prescribed an antianxiety medication. This indicates that a multimodal treatment approach that includes pharmacological management and conjunctive psychotherapy is likely imperative for effective management psychological symptoms. Particularly, evidence-based treatments, such as cognitive–behavioral therapy, have been demonstrated to be effective in ameliorating psychological symptoms in the individuals with MS (Dennison & Moss-Morris, 2010; Fiest et al., 2016; Raissi et al., 2015).

In sum, the present study contributed to the existing literature on HR-QoL by examining the direct and indirect effects of disability, depression, and anxiety on perceived illness intrusiveness in different life domains. However, there are some notable limitations. First, the principal limitation of the present study is its cross-sectional design, which limits the interpretability of the causal direction of the study variables. For example, the relationship between disability and psychological factors is likely bidirectional and it is plausible that disability may also serve as a mediator through which depression and anxiety impact illness intrusiveness. Examining the study variables longitudinally would be beneficial to better delineate the relationship among these factors to better pinpoint which mechanism drives the reduction in illness intrusiveness.

Additionally, this study recruited participants from an MS clinic, likely limiting the generalizability to individuals with MS in the community. This was most notable in the high prevalence of depression and anxiety captured in the present sample. Given that other studies have suggested that HR-QoL may vary based on disability severity, future studies that recruit a large, community-based sample will be important to examine whether depression and anxiety mediate the relationship between disability and illness intrusive across all levels of disability (Twork et al., 2010). Further, it is important to note that the present study was primarily comprised of Caucasian participants (∼75%) and future research examining factors that interfere with health outcomes, such as illness intrusiveness and HR-QoL, in a more ethnically diverse sample is critical. This is particularly important as current research suggests racial and ethnic minorities are often underrepresented in health research, and those with MS are more likely to have a higher degree of lesion burden, greater disability at an early age, and face barriers in accessing health care (Alsaeed et al., 2018; Rivas-Rodríguez & Amezcua, 2018). Moreover, there are a number of disease factors (e.g., fatigue, pain, motor deficits) that were not examined in the present study and may further influence illness intrusiveness in MS. As such, future research may investigate other disease factors, their relation to psychological distress and illness intrusiveness. Nonetheless, despite these limitations, findings provide key information to health care providers factors that influence illness intrusiveness in MS and may guide future research aimed at ameliorating HR-QoL.

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