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Sex differences in predictors of illness intrusiveness in persons with multiple sclerosis

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Abstract

Purpose Multiple sclerosis (MS) is a complex, chronic disease that can have debilitating effects on daily activities and well-being, compromising health-related quality of life. One underlying determinant of quality of life (QOL) is perceived illness intrusiveness, which examines the disruptiveness of the condition and/or its related treatment on engagement in interest and activities, in turn affecting psychological functioning. There is evidence that persons with MS (PwMS) have higher level of illness intrusiveness compared to those with other chronic conditions; however, limited research exists on differences by sex. This study aimed to explore these possible differences between men and women, hypothesizing that men with MS will have overall higher illness intrusiveness (lower QOL) when compared to women with MS.

Methods A total of 922 PwMS were primarily recruited through the North American Research Committee on MS Registry. The participants completed a one-time anonymous online survey. Illness intrusiveness was measured using the Illness Intrusiveness Ratings Scale (IIRS) total score and three subscales. Independent *t*-tests determined differences in demographics, disease characteristics, and IIRS outcomes. Hierarchical regressions were then used to further assess whether sex was a significant predictor of illness intrusiveness.

Results Men exhibited greater overall, intimacy, and relationship and personal development-related perceived illness intrusiveness. However, sex was only a significant predictor of the Intimacy IIRS subscale after accounting for age, disability, and depression.

Conclusions These findings highlight the intrusiveness of MS on intimacy and sexual functioning, particularly among men. Potential clinical implications and future directions are discussed.

Keywords Multiple sclerosis · Illness intrusiveness · Sex differences · Quality of life

Introduction

Multiple sclerosis (MS) is a complex, chronic disease that targets the central nervous system and is one of the most common causes of non-traumatic neurological disability in younger adults [1, 2]. Disease onset typically occurs between 20 and 50 years of age, during the most productive time of life [2]. Women are affected by MS approximately three times more often than men [3] with a highly variable disease course seen clinically among individuals. Persons with MS (PwMS) may experience a diverse number of symptoms as a consequence of the disease, ranging from physical, cognitive, sensory, motor, bladder/bowel, and visual disturbances to fatigue, pain, and sexual dysfunction among others. While some PwMS may be affected by mild impairments, others endure severe limitations in the ability to independently carry out activities of daily living. Considering PwMS

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are commonly diagnosed at a relatively young age with an unpredictable, symptomatic chronic disease that has no current cure, PwMS are often faced with many disruptions in their everyday life due to their MS [4].

The heterogeneity of MS has led to great interest in defining and understanding the overall health perceptions of PwMS and determinants of health-related quality of life (HRQOL) in this population. It has been reported that PwMS have a lower HRQOL compared to those with any other chronic diseases [5–7]. Furthermore, lower HRQOL scores have been shown to be a prognostic factor in future disability progression [8]. Both clinical aspects of the disease and socio-demographic variables are thought to influence HRQOL in MS [9]. Most notably, disease course, disease severity, duration of disease, physical disability, cognitive impairment, depression, fatigue, sexual and bladder disturbances, and pain are thought to have a major impact on HRQOL [5, 7, 9–12], while employment status, educational level, marital status, age, and gender [9, 13–15] are socio-demographic variables that have been shown to influence HRQOL.

It is evident that out of these variables, biological sex has a considerable role in many aspects of the disease process including MS risk and susceptibility, disease course, inflammatory activity, as well as progression of disability [16, 17]. Although biological sex is frequently considered in HRQOL research studies, detailed analysis focusing specifically on sex differences in HRQOL outcomes in MS is limited. The few studies that have focused on this topic have found that physical limitations of the disease and disability level have a greater negative impact on HRQOL in men than women [15, 18]. A study conducted by Casetta and colleagues revealed that men reported lower HRQOL scores in sexual function and satisfaction with sexual function and that an increased disability level correlated with a lower HRQOL in men in domains such as physical function, social function, mental health, emotional well-being, and vitality when compared to women [18]. Women, conversely, were better able to mentally and emotionally adjust to their physical disability, resulting in higher HRQOL scores in most domains when compared to men with similar disability levels [15, 18]. Miller and colleagues concluded that the HRQOL of men is more susceptible to changes in physical condition when compared to women [15].

Inconsistent results are noted in studies that do not focus explicitly on sex differences but rather on disease characteristics or socio-demographic variables collectively [14, 19–23]. The majority of these studies do have some methodological limitations, such as a small sample size or utilization of non-MS-specific HRQOL assessments. Each had some variation in study design making a clear interpretation or comparison challenging. Despite the lack of research studies that focus specifically on sex differences in HRQOL

in the MS population, it remains clear that HRQOL is multidimensional and influenced by several patient and disease factors [14, 15]. In addition, the need to identify what affects HRQOL remains important in understanding the burden MS places on the individual.

Equally important and to more comprehensively describe the impact of MS on HRQOL, it is crucial to understand the extent to which individuals perceive their MS to be disruptive to their lives [24]. Illness intrusiveness is an underlying determinant of HRQOL in those faced with chronic disease like MS [25]. This construct examines how the disease and/or its related treatments disrupt individuals' engagement and perceived control in interests and activities, which in turn affects psychological functioning [25]. Devins explains that there is a fine interplay between disease progression and an increase in illness intrusiveness resulting from reduced personal control [25]. This has an effect on subjective well-being which in turn negatively affects HRQOL [25].

Illness intrusiveness is therefore reflective of the psychosocial impact MS may have on HRQOL [25, 26] and has been shown to correlate with many HRQOL indicators in MS [24, 27]. Previous research has indicated that physical disability, fatigue, anxiety, and depression may be determinants of illness intrusiveness in the MS population [24, 28–30]. These determinants have also been noted to be independent predictors of HRQOL in MS [5, 10]. It would seem, therefore, that because there are trends that show sex differences in HRQOL in the MS population, there may also be differences in the way men and women perceive MS to be disruptive. Evidence suggests that PwMS do experience higher levels of illness intrusiveness compared to other individuals with chronic conditions [31]; however, there has been limited research on differences by sex especially in the MS population. Thus, this study aims to bring awareness to the issues burdening the lives of men and women living with MS by exploring possible sex differences in illness intrusiveness in PwMS. Based on the current literature, it is hypothesized that men with MS will exhibit overall higher illness intrusiveness or worse HRQOL when compared to women with MS.

Methods

Participants

Participants were primarily recruited through the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry as part of a larger study. Inclusion criteria included (1) a diagnosis of MS, (2) being English-speaking, and (3) having no history of another major medical condition (i.e., another neurological condition). PwMS with a diagnosis of a mood or anxiety disorder could participate if their

symptoms began after their MS diagnosis. NARCOMS staff sent a recruitment email to a random sample of 3000 registry participants with a link to the study. A total of 1038 PwMS signed the electronic consent; 114 of these participants were not included due to significant missing data (e.g., omission of MS diagnosis, sex, or full measures). As only two individuals identified as transgender, they were excluded from these analyses due to small sample size. The study was approved by the Institutional Review Board at Albert Einstein College of Medicine of Yeshiva University.

Measures

Age, sex, ethnicity, years of education completed, and self-reported MS subtype and disease duration were collected from all participants. Depression was measured by the Hospital Anxiety and Depression Scale (HADS), a 14-item questionnaire that has been validated in the MS population and has been found to have a good reliability with Cronbach's alpha of 0.82 in the MS population [32–34].The measure's reliability within the current sample was 0.79. Level of disability was quantified using the Patient Determined Disease Steps (PDDS), a 9-point self-report version of the Disease Steps that has been modified by NARCOMS to expand the response options [35–38]. The primary outcome, perceived illness intrusiveness, was measured using the Illness Intrusiveness Ratings Scale (IIRS), a 13-item self-report questionnaire [25]. Using a Likert scale ranging from 1 (not very much) to 7 (very much), participants rated the impact of their MS and/or related treatments on several aspects of their daily life. Besides an overall total score, these life domains were broken down into three subscales: (a) Relationship and Personal Development subscale, which includes family relations, other social relations, self-expression/self-improvement, religious expression, community and civic involvements, and passive recreation; (b) Intimacy subscale, which includes relationship with partner and sex life; and (c) Instrumental subscale, which includes health, work, financial situation, and active recreation. The IIRS has also been shown to have good reliability in the MS population with the total score having a Cronbach's alpha of 0.87 and subscales ranging from 0.74 to 0.77 [39]. The data collected in this sample have similar reliability with the IIRS total score having a Cronbach's alpha of 0.89 and subscales ranging from 0.76 to 0.83.

Statistical analysis

Analyses were conducted using the IIRS Total Score and three subscales (Relationship and Personal Development, Instrumental, and Intimacy), which were converted to z-scores using published MS norms [25]. As such, higher IIRS scores indicate increased illness intrusiveness when compared to other individuals with MS. Sex differences in demographics and IIRS outcomes were determined using the independent samples t-test, median test, and chi-squared test. The independent variables were coded as follows: age and HADS were coded as continuous, PDDS was coded as ordinal, and sex was coded as categorical. The assumptions for conducting t-tests were met, as the outcome data were approximately normally distributed, based on examination of the Q–Q plots, histograms, and values of skew and kurtosis, given the large size of the dataset [40]; independent; measured at least at the interval level; and variances were roughly equal, with the exception of the IIRS Total Score, though the Hartley's F_{Max} was 1.26. Hierarchical regression was then run to further assess whether sex was a significant predictor after accounting for age, level of disability and depression. An alpha level was set at 0.05 and a p-value < 0.05 was deemed significant for all statistical analyses. All assumptions for linear regressions were met, as there was a linear relationship, residuals in the model were independent and normally distributed, and there was no multicollinearity.

Results

Demographics

A total of 922 participants were included in this analysis. The majority of the sample was female (82.2%) and Caucasian (94%), with relapsing remitting MS (62.4%) (Table 1). Males in this sample were significantly older, had significantly more disability, and higher depression scores than females. A total of 19.2% of women and 26.9% of men were at the clinical cut off of ≥ 8 on the HADS as reported by Honarmand and Feinstein [32]. Disease duration and years of education were not different between men and women.

Independent samples *t*-test

Positive z-scores indicated an increase in illness intrusiveness compared to the general MS population. Significant differences between men and women were found on the IIRS Total Score, Intimacy Subscale, and Relationship and Personal Development subscale (Table 2). The Instrumental subscale was close to significant (Table 2). The overall trend observed is that men report higher levels of intrusiveness across all aspects of their lives as presented in Table 2.

Multivariate analysis

As detailed in Table 3, the hierarchical regression for the IIRS Total Score revealed that age, PDDS, and depression

Table 1 Demographic and clinical characteristics of the sample

	N (%) or mean (s.d.) or median	Min–max	IQR	t/χ²	df	p-value
Age, mean (s.d.)						
Female	55.81 (9.40)	26–83		− 3.43	205.9	0.001*
Male	58.85 (10.05)	34–82				
Sex, n (%)						
Female	766 (82.2)					
Male	156 (16.7)					
Ethnicity, n (%)						
White	867 (94.0)					
African American/Black	15 (1.6)					
Asian/Alaska Native	1 (0.1)					
Hispanic/Latino	23 (2.5)					
American Indian	5 (0.5)					
Other	3 (0.3)					
Years of education completed, mean (s.d.)						
Female	15.76 (2.87)	3–27		− 1.14	917.0	0.255
Male	16.05 (2.83)	5–25				
PDDS, median						
Female	3		1–5	7.25	1	0.007*
Male	4		3–6			
MS subtype, n (%)						
Relapsing remitting MS	575 (62.4)					
Secondary progressive MS	237 (25.7)					
Primary progressive MS	88 (9.5)					
Progressive relapsing MS	22 (2.4)					
Duration of disease, mean (s.d.)						
Female	17.86 (9.32)	0–54		− 0.835	918.0	0.404
Male	18.54 (8.60)	3–41				
HADS-D, mean (s.d.)						
Female	4.75 (3.42)	0–17		− 2.96	894.0	0.003*
Male	5.66 (3.38)	0–13				

s.d. standard deviation, *IQR* interquartile range, *PDDS* patient determined disease steps, *MS* multiple sclerosis, *HADS* hospital anxiety and depression scale

*p-value < 0.05

were significant predictors; however, sex was not. The final model accounted for 54.7% of the total variance.

As detailed in Table 4, the hierarchical regression for IIRS Instrumental Subscale revealed that age, PDDS, depression, were all significant predictors. Sex was not a significant predictor. The final model accounted for 48.3% of the variance.

As detailed in Table 5, the hierarchical regression for IIRS intimacy subscale revealed that age, PDDS, depression, and sex were all significant predictors. After controlling for age, disability, and depression, sex accounted for 1.6% of the variance. Together, these four predictors accounted for 30.5% of the variance.

As detailed in Table 6, the hierarchical regression for IIRS Relationship and Personal Development Subscale revealed that age, PDDS, depression, were all significant predictors. Sex was not a significant predictor. The final model accounted for 46.5% of the variance.

Discussion

HRQOL is often affected in PwMS and can be influenced by a number of socio-demographic variables. Sex has been noted to play a considerable role in several aspects of the MS disease process. Previous HRQOL studies in the MS population have determined that men with increased disability have lower HRQOL scores when compared to women [5, 7, 9–12]. However, there is a dearth of research examining sex differences in HRQOL outcomes, using perceived illness

Table 2 Independent samples *t*-test results comparing sex to IIRS subscale *z*-scores

	Mean (s.d.)	*t*	*df*	*p*-value
IIRS total score				
Female	− 0.170 (0.888)	− 3.41	216.3	0.001*
Male	0.086 (0.791)			
IIRS instrumental subscale				
Female	− 0.085 (0.985)	− 1.85	893.0	0.065
Male	0.078 (0.950)			
IIRS intimacy subscale				
Female	0.167 (0.770)	− 5.70	894.0	< 0.001*
Male	0.555 (0.732)			
IIRS relationship and personal development subscale				
Female	− 0.398 (0.839)	− 2.19	884.0	0.023*
Male	− 0.234 (0.789)			

s.d. standard deviation, *IIRS* illness intrusiveness rating scale

*p-value < 0.05

Table 3 Final step of the hierarchical regression analysis for variables predicting IIRS Total scores

	R^2		*B* (SE)	*β*	*p*
Step 4	0.55	Constant	− 0.63 (0.14)		
		Age	− 0.01 (0.00)	− 0.13	< 0.001*
		PDDS	0.11 (0.01)	0.28	< 0.001*
		HADS depression score	0.15 (0.01)	0.60	< 0.001*
		Sex	0.06 (0.06)	0.03	0.282

PDDS patient determined disease steps, *MS* multiple sclerosis, *HADS* hospital anxiety and depression scale

*p-value < 0.05

Table 4 Final step of the hierarchical regression analysis for variables predicting IIRS instrumental subscale scores

	R^2		*B* (SE)	*β*	*p*
Step 4	0.49	Constant	− 0.42 (0.16)		
		Age	− 0.02 (0.00)	− 0.14	< 0.001*
		PDDS	0.16 (0.01)	0.39	< 0.001*
		HADS depression score	0.13 (0.01)	0.47	< 0.001*
		Sex	− 0.02 (0.07)	− 0.01	0.729

PDDS patient determined disease steps, *MS* multiple sclerosis, *HADS* hospital anxiety and depression scale

*p-value < 0.05

Table 5 Final step of the hierarchical regression analysis for variables predicting IIRS intimacy subscale scores

	R^2		*B* (SE)	*β*	*p*
Step 4	0.31	Constant	− 0.33 (0.15)		
		Age	− 0.01 (0.00)	− 0.10	0.001*
		PDDS	0.08 (0.01)	0.22	< 0.001*
		HADS depression score	0.09 (0.01)	0.41	< 0.001*
		Sex	0.27 (0.06)	0.13	< 0.001*

PDDS patient determined disease steps, *MS* multiple sclerosis, *HADS* hospital anxiety and depression scale

*p-value < 0.05

Table 6 Final step of the hierarchical regression analysis for variables predicting IIRS relationship and personal development subscale scores

	R^2		*B* (SE)	*β*	*p*
Step 4	0.47	Constant	− 0.87 (0.14)		
		Age	− 0.01 (0.00)	− 0.09	0.001*
		PDDS	0.05 (0.01)	0.15	< 0.001*
		HADS depression score	0.15 (0.01)	0.62	< 0.001*
		Sex	− 0.00 (0.06)	− 0.00	0.944

PDDS patient determined disease steps, *MS* multiple sclerosis, *HADS* hospital anxiety and depression scale

*p-value < 0.05

intrusiveness. This study aimed to explore these possible differences between men and women, hypothesizing that men with MS will have overall higher illness intrusiveness (lower HRQOL) when compared to women with MS.

In this large, nation-wide sample of PwMS, we did find that there are differences in the way men and women view the impact of their MS on their lives. Overall, univariate analyses showed that men had higher illness intrusiveness scores than women in the total score, intimacy and relationship and personal development subscales. The instrumental subscale fell just short of significant, though the same trend emerged of higher illness intrusiveness among men. Even after controlling for age, disease severity, and depression, men exhibited greater perceived illness intrusiveness from their MS on aspects of intimacy, which includes relationships with their partners and their sex life, compared to women. However, sex was no longer a significant predictor for the total IIRS subscale as well as the relationship and personal development subscale after accounting for age, PDDS, and HADS depression scale.

To our knowledge, this study is one of the first looking at sex differences in perceived illness intrusiveness among

PwMS. Although there is a limited literature specific to this topic, some of the findings here are in line with previous research conducted by Casetta and colleagues, which demonstrated that men with MS have lower HRQOL scores in sexual function and satisfaction when compared to women [18]. In our study, when controlling for age, disability, and depression, men reported that their sex life and relationships with partner were still influenced by their MS, leading to the conclusion that sexual dysfunction is a larger issue for men regardless of age, physical limitations, and emotional distress.

Sexual dysfunction is highly prevalent in the MS population with estimates of 50–90% of males and 40–80% of females reporting problems with sexual function at some point during the disease course [41–44]. Males with MS show higher levels of sexual dysfunction when compared to males in the general population [44] and males with other chronic diseases [45]. Sexual dysfunction in itself may arise from the neurological impairments caused by MS [41]. Physiologic and physical symptoms as well as psychosocial issues all can have a role in sexual dysfunction in PwMS [43, 46]. Several studies focusing on sexual dysfunction and HRQOL in PwMS have noted its negative effect on HRQOL in both men and women [12, 47, 48]. It has been reported that sexual dysfunction affects all aspects of HRQOL [49], but has more of an adverse impact on mental aspects of HRQOL versus physical aspects [47, 48]. It has also been shown that sexual dysfunction can reduce those mental aspects of HRQOL even early in the disease course [48]. While sexual dysfunction in males with MS may include erectile dysfunction, a decrease in libido, MS symptoms, disability accumulation, psychological symptoms, and psychosocial and cultural issues such as performance anxiety, and low self-esteem due to role changes [50], further qualitative research may help to determine what is contributing to the higher perceived illness intrusiveness in males with MS on aspects of intimacy. It is likely that there is both a psychological component as well as a physical component, but without further research it is hard to determine the exact cause of this increased trend.

One potential implication of these findings, however, is that the higher intimacy-related illness intrusiveness among men may be indicative that sexual dysfunction is still an overlooked problem in the health management and treatment of men with MS. It has been previously reported that issues with sexual function in MS are often underdiagnosed and undertreated [51–53], adding to the burden of disease. Furthermore, surveys of MS specialists have shown that health care providers do not routinely assess for sexual dysfunction, instead waiting for the patient to initiate the conversation due to a myriad of reasons including time constraints and lack of training or knowledge of treatment options [51, 52]. The current findings are further evidence of the perceived effects of MS on sexual functioning in men, highlighting the need for providers to be more attentive to and encourage open communication around this issue. As previously suggested by Shawaryn et al. [24], providers may potentially consider utilizing the IIRS as an initial screen for HRQOL. Should patients report higher levels of intimacy-related illness intrusiveness, focused follow-up should be considered, potentially using measures that are specific to MS-related sexual dysfunction, such as the MS Intimacy and Sexuality Questionnaire [46]. However, further research is needed to warrant the use of the IIRS in this way especially for sexual dysfunction, to determine if it can be used as a more streamlined approach to discussing sexual dysfunction with patients.

While the current study has several strengths, including tapping a large nation-wide sample of PwMS, there are a number of limitations that should be acknowledged. Given the nature of the data collection, all demographic data, including MS diagnosis and their meeting of other inclusion criteria, were self-reported and could not be confirmed with individuals prior to their participation. Also, since the survey was only offered online and only in English, the sample included only those who had indicated a preference for completing surveys online rather than by mail and excluded non-English-speaking individuals. As the measures used were self-report scales, there is the possibility of measurement errors, which may have potentially resulted in an underestimation of the relationships between variables; however, this is true for all subjective measures. This study also just reported on a one-time indication of the participant's current perceptions and did not take into account if the participant was experiencing a relapse or other health condition at the time of response, as this could influence a person's perception of their well-being. In addition, antidepressant use and level of fatigue were not collected, which are factors that have been linked to an increase in sexual dysfunction in PwMS [43, 53, 54]. Finally, given the larger proportion of Caucasians in relation to previously published NARCOMS demographics [55, 56], these results may not be fully reflective of other PwMS' experiences.

Even with these limitations, this study provides data that offer a valuable look into the different perceptions of men and women living with MS and how impactful MS is on their lives. It should also be noted that the statistically significant difference in depression between men and women was less than one point on the HADS, which may not be a clinically meaningful difference. Since depression was significant in all the models and was therefore controlled for, perhaps even subtle differences in depression scores may be important in understanding HRQOL. The findings highlight a need for interventions that both bring awareness to issues with intimacy and sexual dysfunction in men diagnosed with MS and protect their psychosocial well-being.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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