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Cumulative Impact of Comorbidity on Quality of Life in MS

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Abstract

Background—Little is known about the impact of comorbidity on HRQOL in multiple sclerosis (MS). We investigated the association of comorbidity and health-related HRQOL among participants in the North American Research Committee on Multiple Sclerosis (NARCOMS).

Materials & Methods—In 2006, we queried NARCOMS participants regarding physical and mental comorbidities and HRQOL, using the Short Form-12. We summarized physical HRQOL using the aggregate Physical Component Scale (PCS-12) score, and mental HRQOL using the aggregate Mental Component Scale (MCS-12) score. We assessed multivariable associations between comorbidity and HRQOL using a general linear model, adjusting for potential confounders.

Results—Among 8983 respondents, the mean (SD) PCS-12 was 36.9 (11.8) and MCS-12 was 45.6 (11.6). After adjustment for sociodemographic and clinical factors, participants with any physical comorbidity had a lower PCS-12 (37.2; 95% CI: 36.4-38.1) than those without any physical comorbidity (40.1; 95% CI: 39.0-41.1). As the number of physical comorbidities increased PCS-12 scores decreased (r = -0.25; 95% CI: -0.23- -0.27) indicating lower reported HRQOL. Participants with any mental comorbidity had a lower MCS-12 (40.7; 95% CI: 39.8-41.6) than those without any mental comorbidity (48.5; 95% CI: 47.7-49.4).

Conclusions—Comorbidity is associated with reduced HRQOL in MS. Further research should evaluate whether more aggressive treatment of comorbidities improves the HRQOL of MS patients.

Keywords

multiple sclerosis; epidemiology; comorbidity; quality of life

Introduction

Multiple sclerosis (MS) patients score lower on health-related quality of life (HRQOL) measures as compared to the general population.(1, 2) They also score lower on HRQOL measures when compared to patients with other chronic diseases such as inflammatory bowel disease.(3) Identification of modifiable factors which affect HRQOL could potentially improve the lives of MS patients.

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Conflict of Interest The authors have no conflicts of interest to declare.

In MS, factors which affect HRQOL are similar to those in other diseases and the general population and include age, sex, socioeconomic status, disability, and symptoms such as fatigue.(4) Although comorbidity is common in MS,(5) and comorbidity is associated with reduced HRQOL in other chronic diseases,(6) little is known about the impact of comorbidity on HRQOL in MS. One study suggested that MS patients with musculoskeletal and respiratory conditions had poorer physical HRQOL, but that small study was restricted to persons with relapsing-remitting MS.(7)

We investigated the association of comorbidity and HRQOL among participants in the North American Research Committee on Multiple Sclerosis (NARCOMS). We hypothesized that participants with comorbidities would have lower HRQOL than those without comorbidities, and that the magnitude of the effect would vary across comorbidities. We further hypothesized that physical comorbidities would predominantly affect physical rather than mental aspects of HRQOL based on reports in other disease populations.(8)

Materials & Methods

The methods for this study are detailed elsewhere.(5) Briefly, we surveyed active participants in the NARCOMS Registry, a voluntary self-report registry for patients with MS.(9) The NARCOMS registry is approved by the Institutional Review Board at the University of Alabama at Birmingham. At enrollment, participants provide demographic and clinical information, including date of birth; age of initial symptom onset; and age and year of MS diagnosis. Semiannually participants complete update questionnaires to update their information regarding disability, HRQOL, and treatment status. These update questionnaires also capture information about topics which vary from one questionnaire to the next.

In 2006, we queried NARCOMS participants about physical comorbidities, specifically hypertension, cancer (breast, lung, colon, rectal, skin), diabetes, heart disease, peripheral vascular disease, lung disease, cataracts, glaucoma, uveitis, peptic ulcer disease, liver disease, irritable bowel syndrome, inflammatory bowel disease, autoimmune thyroid disease, systemic lupus erythematosus, rheumatoid arthritis, Sjogren's disease, kidney disease, arthritis, fibromyalgia, anemia, and knee/hip replacements.(5) We also queried participants regarding mental comorbidities including depression, anxiety, bipolar disorder, and schizophrenia. Participants indicated the presence or absence of each comorbidity.

We measured HRQOL using the Short-Form 12 (SF-12) version 2.0, a shortened version of the Short-Form 36 (SF-36). The SF-12 consists of 12 items, each capturing an aspect of one of the eight subscales in the SF-36. The SF-12 captures approximately 90% of the variance of the SF-36,(10) is recommended for use in large surveys, and has been used in MS populations.(11) The generic nature of the SF-12 permits comparison of results regarding the impact of comorbidities on MS HRQOL with those of comorbidities on HRQOL in other patient populations. An aggregate Physical Component Scale (PCS-12) score summarizes physical HRQOL, with scores ranging from 0 (worst) to 100 (best). An aggregate Mental Component Scale (MCS-12) score summarizes mental HRQOL, with scores ranging from 0 (worst) to 100 (best). The PCS-12 and MCS-12 are standardized to reflect a general population mean of 50 and a standard deviation of 10. We calculated effect sizes for comorbidities under study by calculating the difference in mean scores in the affected and unaffected groups, and dividing by a standard deviation of 10.(4) Effect sizes are measures of the magnitude of effect in terms of standard deviation units which facilitate comparisons between populations.(12) As suggested elsewhere, we defined effect sizes of 0.2 as small, 0.5 as moderate, and 0.8 as large.(12)

We measured disability using Patient Determined Disease Steps, a validated self-report measure which correlates well with the Expanded Disability Status Scale (EDSS).(13) It is scored ordinally from 0 to 8, where a score of 0 approximates an EDSS score of 0, a score of 3 represents early gait disability without needing an assistive device and approximates an EDSS score of 4.0 to 4.5; and scores of 4, 5, and 6 represent EDSS scores of 6 to 6.5.

Of 18,000 active participants, 16037 met the inclusion criteria for the primary study: residence in the United States with complete data regarding date of birth, age of MS symptom onset, age of MS diagnosis; and age of symptom onset ≥16 years and <60 years. The inclusion criteria aimed to reduce heterogeneity in diagnostic testing and access to care, and to limit heterogeneity due to differences in prognosis among persons with very early or late onset MS.(14, 15)

Initially, we evaluated the association between reporting any of the physical comorbidities or any of the mental comorbidities queried and PCS-12 scores. Then we evaluated the association of individual comorbidities with a frequency of 5% or more in this population and PCS-12 scores, to focus on those conditions likely to be important at the population level. We summarized continuous variables using means and standard deviations (SD) or medians and interquartile ranges (IQR). Categorical variables were summarized using frequencies and percents. Wilcoxon rank sum tests were used to assess univariate associations between comorbidity and the PCS-12. Multivariable associations between comorbidity and the PCS-12 were assessed using a general linear model. We used the linear model to calculate mean SF-12 scores, adjusting for the following potential confounders derived from existing literature:(7) age; sex; race; socioeconomic status as measured by education, annual household income, and health insurance status; marital status; region of residence in the United States; disability status; year of symptom onset; and treatment status. We then repeated this analysis for MCS-12 scores.

Race was included as indicator variables for White (reference group), African-American, and Other. Education was included as indicator variables for <12 years (reference group), high school diploma, Associate's Degree or Technical Degree, Bachelor's Degree, post-graduate degree. Annual household income was included as indicator variables for <$15000 (reference group), $15000-30000, $30000-50000, $50000-100000, >$100000. Insurance status was included as indicator variables for private, public (reference group), or none. Region of residence was included as indicator variables for West (reference group), Midwest, South, and East as defined by the US Census bureau. Marital status was dichotomized as married/co-habiting versus single/divorced/widowed/living alone (reference group). Age was included as a continuous variable. Using PDDS, participants were classified as having mild (EDSS ≤3, reference group), moderate (EDSS 4 to 5.5), or severe (EDSS ≥ 6) disability.(16) Year of symptom onset was categorized as <1986, 1986-1995, ≥1996 because of non-linearity with HRQoL. Ever treatment with any of the approved disease-modifying therapies (IFNß-1a (Avonex), IFNß-1b (Betaseron), IFNß-1a (Rebif), Glatiramer Acetate (Copaxone), or Natalizumab (Tysabri)) was dichotomized as yes or no. Ever treatment with immunosuppressive therapies was dichotomized as yes or no.

All statistical analyses used SAS V9.2 (SAS Institute Inc., Cary, NC).

Results

As reported previously, 8983 (55.7%) of eligible participants responded to the questionnaire. (5) Their characteristics are outlined in Table 1, and were similar to other MS populations. (17) Survey responders were more likely to be white, women, and of higher socioeconomic status than non-responders.(5)

These participants frequently reported physical comorbidities,(5) including hypercholesterolemia (37.0%), hypertension (30.1%), arthritis (16%), irritable bowel syndrome (13.2%), chronic lung disease (13.0%), anemia (12.6%), cataracts (12.1%), thyroid disease (10.0%), peptic ulcer disease (7.8%), heart disease (6.9%), diabetes (6.1%), fibromyalgia (4.9%). The remaining comorbidities were reported by fewer than 5% of participants. Mental comorbidities were also common, particularly depression (46.0%) and anxiety (16.5%).(18)

Physical HRQOL

The mean (SD) PCS-12 was 36.9 (11.8). The mean PCS-12 was more than 5 points lower in participants with any physical comorbidity (35.7 (11.5)) than in participants without any physical comorbidity (40.9 (12.1), $p<0.0001$). The mean PCS-12 score was less than 1 point lower in participants with any mental comorbidity (36.5 (11.3)) than in participants without any mental comorbidity (37.3 (10.4), $p = 0.007$).

After adjustment for age, sex, socioeconomic status, region of residence, year of symptom onset, MS disability level, clinical course, and treatment status, participants with any physical comorbidity still had a lower PCS-12 (37.3; 95% CI: 36.4-38.2) than those without any physical comorbidity (39.8; 95% CI: 38.8-40.8). Participants with any mental comorbidity had a slightly lower PCS-12 (38.2; 95% CI: 37.3-39.2) than those without any mental comorbidity (38.9; 95% CI: 38.0-39.8), but of unlikely clinical significance. Race was not associated with HRQOL, and we did not identify any interaction between comorbidity and sex, nor between physical and mental comorbidity on HRQOL. There was an interaction between comorbidity and disability status such that the impact of physical comorbidity on HRQOL diminished with increasing disability. Among the mildly disabled the difference between PCS-12 scores in those with physical comorbidity as compared to those without physical comorbidity was 2.5, while among the severely disabled the difference was 1.7. Among the mildly disabled the difference between PCS-12 scores in those with mental comorbidity as compared to those without mental comorbidity was 1.6, while among the severely disabled the difference was -0.5.

We proceeded to evaluate the associations of individual comorbidities with physical HRQOL, focusing on comorbidities with a frequency of 10% or more in this population. All comorbidities evaluated were associated with reduced PCS-12 scores (all $p<0.0001$, Table 2). In a multivariable model simultaneously including individual comorbidities, hypertension, heart disease, lung disease, thyroid disease, peptic ulcer disease, arthritis, irritable bowel syndrome, anemia, and fibromyalgia were each independently associated with reduced PCS-12 scores. Depression and anxiety were not associated with reduced PCS-12 scores. In the multivariable model, the interaction noted previously between comorbidity and disability status remained evident for heart disease (**p = 0.015**), hypercholesterolemia (**p = 0.026**), and arthritis (**p = 0.0002**).

As the number of physical comorbidities increased PCS-12 scores decreased ($r = -0.25$; 95% CI: -0.23- -0.27) indicating lower reported HRQOL. This dose-response relationship remained after adjustment for age, sex, socioeconomic status, region of residence, year of symptom onset, disability, clinical course, and treatment status (Table 3, χ^2 for linear trend 207.3, $p<0.0001$).

Mental HRQOL

The mean (SD) MCS-12 was 45.6 (11.6). The unadjusted mean MCS-12 was only slightly lower in participants with any physical comorbidity (45.3 (11.7)) than in participants without any physical comorbidity (46.7 (11.3), $p<0.0001$). The mean MCS-12 score was

more than 8 points lower in participants with any mental comorbidity (41.4 (11.3)) than in participants without any mental comorbidity (49.6 (10.4), p<0.0001).

After adjustment for age, socioeconomic status, clinical course, and treatment status, participants with one or more physical comorbidities had a similar MCS-12 (44.5; 95% CI: 44.2-45.8) to those without any physical comorbidity (44.8; 95% CI: 45.8-47.7). Participants with any mental comorbidity had a lower MCS-12 (40.7; 95% CI: 39.8-41.6) than those without any mental comorbidity (48.5; 95% CI: 47.7-49.4). There was no interaction between physical and mental comorbidity, nor between comorbidity and disability status. We evaluated the associations of individual comorbidities with mental HRQOL. Fibromyalgia, irritable bowel syndrome, depression and anxiety were all independently associated with lower MCS-12 scores (Table 4).

Sensitivity Analyses

Our findings were unchanged when we repeated our analyses restricting them to participants reporting a relapsing course at onset, or to participants with an age of symptom onset between 16 and 50 years.

Discussion

With a mean PCS-12 score of 36.9, physical HRQOL in the NARCOMS population was similar to that reported by the Sonya Slifka Longitudinal Multiple Sclerosis Study (36.2),(4) and as expected, substantially lower than that reported for the general population. After accounting for potentially confounding sociodemographic and clinical characteristics,(4, 7) factors we found that participant reports of any physical comorbidity had an independent, negative impact on physical HRQOL, while mental comorbidity did not have a clinically significant impact.

Although not universally, similar findings are reported in other chronic diseases.(19) In a study of 15,000 patients from eight datasets, the presence of comorbidities was associated with poorer HRQOL regardless of the primary condition.(19) One study of 262 MS patients beginning disease-modifying therapy found that the concurrent presence of musculoskeletal and respiratory conditions reduced physical QOL.(7) When evaluated using effect sizes, the impact of comorbidity on **physical** HRQOL in the NARCOMS population was minimal for most individual conditions, with only heart disease having a small effect (effect size 0.20) and only fibromyalgia (effect size 0.42) having a moderate effect. In the general population, conditions such as angina have moderate to large effects on HRQOL (**effect size 0.70**), and fibromyalgia has large effects (**effect size 2.0**).(20-22) This suggests that these comorbid conditions impact HRQOL less in the MS population than in the general population, or at least that they do not have an additive effect. This may reflect a floor effect given the already substantial impact of MS on HRQOL. Similar observations have been made in a study of 615 persons with inflammatory bowel disease,(23) where the severity of the inflammatory bowel disease was the most important determinant of HRQOL. Similarly, we observed that the impact of comorbidity on physical HRQOL was greater in patients with mild to moderate disability than in patients with severe disability.

We observed a substantial dose-response relationship (Table 2) between comorbidity and quality of life, with physical HRQOL decreasing steadily with an increasing number of comorbidities. Studies of comorbidity in asthma, cancer and other chronic diseases have also observed such dose-response relationships.(8, 24, 25) The only previous study examining a dose-response relationship between comorbidity and HRQOL in MS was negative.(26) Warren *et al.* examined the association between comorbidity and HRQOL, as measured using the Health Utilities Index Mark 3 version, among 335 persons with MS responding to

the Canadian Community Health Survey. The mean HRQOL score of participants with no comorbidity was 0.12 points higher than the mean score of participants with any comorbidity, but there was no association with the number of comorbidities. That study differed from the present study in several important respects; it had a smaller sample size, was conducted solely in Canada, and did not distinguish between comorbidities and complications of disease.

Mental comorbidity adversely influenced mental HRQOL, as did irritable bowel syndrome and fibromyalgia. The impact of mental comorbidity is not surprising.(27) Turpin *et al.* reported that persons with relapsing remitting MS and digestive system problems had worse mental HRQOL.(7) Irritable bowel syndrome and fibromyalgia are both conditions which are frequently comorbid with depression and anxiety. Persons who seek care for irritable bowel syndrome are more likely to have psychiatric disorders than those who do not seek care and remain undiagnosed. Further, irritable bowel syndrome and mental comorbidity may share a common neurobiology.(28) Patients with fibromyalgia report worse mental HRQOL than patients with rheumatoid arthritis.(29) Our findings suggest that MS patients with any of depression, anxiety, irritable bowel syndrome or fibromyalgia should be considered at particular risk for poor mental HRQOL.

Physical and mental comorbidities are common in MS, and physical comorbidities increase in frequency with age. We evaluated comorbidities affecting 5% or more of the NARCOMS population to focus on comorbidities likely to be commonly identified in other MS populations. The finding that the effects of physical comorbidities were cumulative suggests that aggressively managing comorbidities may be an avenue for improving HRQOL in MS, and that integrated approaches to care should be given stronger emphasis. Emerging disease-modifying therapies for MS may increase the risk of developing comorbidities,(30) raising questions as to whether these comorbidities may ultimately negate expected improvements in HRQOL from these therapies. Studies of interventions designed to improve HRQOL in MS should measure comorbidities, and consider evaluating the impact of those interventions on the comorbidities and on MS.

An important analytic consideration was potential confounders of the association between comorbidity and HRQOL. After adjusting for confounders, the mean PCS-12 score improved among participants reporting comorbidities, but minimally worsened among participants without comorbidities. Persons with MS and physical comorbidities are more likely to be male, older, and of lower socioeconomic status than persons with MS who do not report physical comorbidities.(5) Persons with MS of lower socioeconomic status are at increased risk of mental comorbidity.(31) By identifying a person with MS and comorbidity the health care provider is likely identifying an individual who has multiple factors adversely affecting HRQOL. Future studies should consider examining the relative impact of the various determinants of HRQOL, and how the effects of these determinants are mediated,(32) as part of a broader strategy to improve HRQOL.

Limitations of this study should be noted. Our response rate was 55.7%, slightly lower than the mean response rate of 60% among published mail surveys.(33) Non-responders tended to have lower SES than responders, and the NARCOMS Registry is a volunteer registry which does not represent the entire MS population in the United States. Nonetheless, the registry population has similar characteristics to those reported for MS patients from the National Health Interview Survey.(34) The NARCOMS population is large, socio-demographically diverse, represents all regions of the US, and reflects MS patients with a broad range of disease duration and disability status. Comorbidity data were self-reported, but testing of the questionnaire among 404 persons with MS suggested that they can accurately report several common comorbidities.(35) Further, some studies suggest self-

report data predict HRQoL as well or better than comorbidity data from medical records.(36, 37) The study was cross-sectional thus we cannot establish a causal relationship between MS, comorbidity, and HRQOL.

Physical comorbidity is associated with substantially lower physical HRQOL in MS. Future studies in population-based cohorts are needed to determine if the impact of comorbidity differs by domain of HRQOL, to determine if changes in HRQOL over time differ in the presence of comorbidity, and to establish whether treating comorbidities can improve HRQOL in MS. We did not investigate the mechanisms by which comorbidity influences HRQOL, which could reflect either the effects of the comorbidity, or the effects of the treatment for the comorbidity on MS, or both. Little is known about the effects of concomitant therapy on the health and well being of MS patients, and this also deserves investigation.

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Table 1

Demographic and clinical characteristics of responders to the NARCOMS Fall 2006 questionnaire

Characteristic	Responders
Sex, n (%)	
Female	6811 (75.8)
Male	2172 (24.2)
Race, n (%)	
White	8442 (94.3)
Black	218 (2.4)
Other	293 (3.3)
Education, n (%)	
<12 yrs	165 (1.9)
High school diploma	3128 (35.0)
Associate's or Technical degree	1448 (16.2)
Bachelor's degree	2395 (26.8)
Post-graduate degree	1790 (20.1)
Annual Income, n (%)	
<$15000	888 (11.9)
$15000-30000	1292 (17.3)
$30000-50000	1605 (21.5)
$50000-100000	2418 (32.3)
>$100,000	1276 (17.1)
Health Insurance, n (%)	
Private	6601 (75.2)
Public	2057 (23.4)
None	126 (1.4)
Current age (years), mean (SD)	52.7 (10.4)
Age of symptom onset (years), mean (SD)	31.2 (9.0)
Age of diagnosis (years), mean (SD)	38.2 (9.5)
Clinical Course, n (%)	
Relapsing	7602 (88.5)
Progressive	991 (11.5)
Patient Determined Disease Steps (categorized), n (%)	
Mild	3178 (35.4)
Moderate	1067 (11.9)
Severe	4738 (52.7)

Table 2

Unadjusted mean (standard deviation) and adjusted mean Physical Component Scores (PCS-12) and 95% confidence intervals (CI) in NARCOMS participants with and without comorbidities (adjusted for age, sex, education, income, health insurance status, disability status, year of symptom onset, clinical course, and treatment status)

Comorbidity	Unaffected	Affected	Unaffected		Affected		Adjusted p-value	Effect Size[a]
	Unadjusted Mean (SD)	Unadjusted Mean (SD)	Adjusted Mean	95% CI	Adjusted Mean	95% CI		
Hypercholesterolemia[b]	38.2 (12.1)	34.8 (12.1)	31.2	29.8, 32.7	30.6	29.1, 32.0	0.027	0.06
Cataracts	37.6 (11.9)	32.4 (10.3)	31.2	29.8, 32.6	30.6	29.1, 32.1	0.16	0.06
Hypertension	38.2 (12.1)	33.7 (10.6)	31.2	29.8, 32.7	30.5	29.1, 32.0	0.013	0.07
Diabetes	37.3 (11.9)	32.0 (10.4)	31.0	29.7, 29.1	30.7	29.1, 32.4	0.57	0.03
Thyroid	37.1 (11.8)	35.6 (11.6)	31.4	30.0, 32.8	30.4	28.9, 31.9	0.019	0.10
Anemia	37.0 (11.9)	36.0 (11.6)	31.5	30.0, 32.9	30.3	28.8, 31.8	0.002	0.12
Irritable bowel syndrome	37.2 (11.8)	35.2 (11.7)	31.5	30.1, 32.9	30.3	28.8, 31.8	0.002	0.12
Lung disease	37.3 (11.9)	34.3 (11.2)	31.6	30.2, 33.1	30.2	28.7, 31.7	0.0004	0.14
Heart disease[b]	37.3 (11.9)	31.7 (10.1)	31.9	30.6, 28.2	29.9	28.2, 31.5	0.0007	0.20
Peptic ulcer disease	37.2 (11.8)	33.8 (11.7)	31.5	30.2, 32.9	30.2	28.7, 31.8	0.005	0.13
Arthritis[b]	37.7 (11.9)	33.0 (10.6)	31.7	30.3, 33.2	30.0	28.6, 31.5	<0.0001	0.17
Fibromyalgia	37.2 (11.8)	31.3 (10.3)	33.0	31.6, 34.3	28.8	27.2, 30.5	<0.0001	0.42
Depression[b]	37.3 (12.2)	36.4 (11.3)	31.1	29.6, 32.5	30.7	29.3, 32.1	0.23	0.04
Anxiety	36.9 (11.9)	37.1 (11.4)	30.7	29.3, 32.1	31.0	29.6, 32.5	0.36	0.03

[a]Difference of means divided by standard deviation of 10. Effect sizes of 0.2 are small, 0.5 are moderate, and 0.8 are large.(12)

[b]Interaction with disability status: heart disease (p = 0.015), hypercholesterolemia (p = 0.026), arthritis (p = 0.0002), depression (p <0.0001)

Table 3

Unadjusted mean (standard deviation) and adjusted mean Physical Component Scores (PCS-12) and 95% confidence intervals (CI) in NARCOMS participants according to the number of physical comorbidities reported

Number of Comorbidities	Number of Affected Participants	Unadjusted Mean (SD)	Adjusted Mean*	95% CI
0	2076	40.8 (12.1)	40.2	39.2, 41.1
1	2097	38.5 (12.1)	38.8	37.8, 39.8
2	1766	36.7 (11.3)	37.7	36.7, 38.7
3	1141	36.2 (10.9)	35.7	36.0, 38.2
4	789	33.5 (10.7)	34.6	34.6, 37.0
5	478	32.3 (10.2)	33.8	33.3, 35.9
≥6	636	30.3 (9.4)	34.3	32.5, 35.1

*adjusted for age, sex, education, income, health insurance status, year of symptom onset, clinical course, region of residence, disability status, and treatment status; all p <0.0001

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Table 4

Unadjusted mean (standard deviation) and adjusted mean Mental Component Scores (MCS-12) and 95% confidence intervals (CI) in NARCOMS participants with and without comorbidities (adjusted for age, sex, education, income, year of symptom onset, age of symptom onset, clinical course, and treatment status)

Comorbidity	Unaffected	Affected	Unaffected		Affected		Adjusted p-value	Effect Size*
	Unadjusted Mean (SD)	Unadjusted Mean (SD)	Adjusted Mean	95% CI	Adjusted Mean	95% CI		
Depression	49.7 (10.3)	41.1 (11.3)	45.0	43.9, 46.2	38.0	37.0, 39.1	<0.0001	0.70
Anxiety	47.0 (11.2)	39.1 (11.3)	43.7	42.6, 44.7	39.4	38.2, 40.6	<0.0001	0.43
Irritable bowel syndrome	46.1 (11.5)	42.8 (11.6)	42.1	41.1, 43.2	40.9	39.7, 42.1	0.006	0.12
Fibromyalgia	45.8 (11.5)	41.7 (11.9)	42.5	41.6, 43.5	40.5	39.0, 42.0	0.003	0.20