

Functional gastrointestinal disorders negatively affect health-related quality of life in MS

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Abstract

Objective

To determine the prevalence of functional gastrointestinal disorders, the demographic and clinical characteristics associated with the presence of functional gastrointestinal disorders, and the effects of these disorders with health-related quality of life (HRQOL) in a large, diverse population of persons with MS.

Methods

In 2014, we surveyed participants in the North American Research Committee on Multiple Sclerosis registry regarding functional gastrointestinal disorders using the Rome III questionnaire. Participants also reported their sociodemographic characteristics, disability status using Patient Determined Disease Steps, the presence of comorbid depression and anxiety, health behaviors, and HRQOL using the RAND-12. We determined the prevalence of each gastrointestinal disorder using the Rome III criteria. Using multivariable logistic regression models, we assessed the factors associated with the presence of each bowel disorder. Using linear regression, we evaluated the association between functional gastrointestinal disorders and HRQOL.

Results

Of 6,312 eligible respondents, 76.5% were female, with a mean (SD) age of 58.3 (10.2) years. Forty-two percent of respondents ($n = 2,647$) had a functional gastrointestinal disorder, most often irritable bowel syndrome (IBS), which affected 28.2% of participants. The prevalence of all functional gastrointestinal disorders increased with greater disability, and the prevalence of IBS increased with longer disease duration. After adjusting for sociodemographic and clinical characteristics, functional gastrointestinal disorders were associated with lower physical and mental HRQOL (both $p < 0.0001$).

Conclusions

Functional gastrointestinal disorders are common in MS and are associated with reduced HRQOL.



Functional gastrointestinal disorders are common in the general population, affecting up to 1 in 3 people.¹ Functional gastrointestinal disorders are characterized by persistent symptoms referable to the middle or lower abdomen in the absence of other diseases or structural abnormalities, which account for the symptoms.² Symptoms may include abdominal pain,

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diarrhea, constipation, bloating, and irregular stool. The Rome III criteria classified these disorders as irritable bowel syndrome (IBS), functional bloating, functional constipation, functional diarrhea, and functional bowel disorders not otherwise specified.³ Functional dyspepsia affects the upper gastrointestinal tract, and symptoms may include early satiety, epigastric pain, and postprandial fullness.⁴ These functional gastrointestinal disorders associated with reduced health-related quality of life (HRQOL), increased health care utilization and impaired work productivity.⁵⁻⁷

MS is a disease of the CNS, which causes a plethora of symptoms, including bowel dysfunction. Little is known about the prevalence of functional gastrointestinal disorders in MS; most previous studies have focused on IBS, suggesting that 9.40%–19.3% of persons with MS are affected.⁸⁻¹¹ Only 1 study has reported the prevalence of other functional gastrointestinal disorders in MS,⁹ and the clinical and demographic characteristics associated with these disorders remain poorly understood. The contribution of comorbid functional gastrointestinal disorders to HRQOL in MS is also unknown.

Therefore, we aimed to determine the prevalence of functional gastrointestinal disorders, demographic and clinical characteristics associated with the presence of functional gastrointestinal disorders, and the effects of these disorders with HRQOL in a large, diverse population of persons with MS.

Methods

Study population

The North American Research Committee on Multiple Sclerosis (NARCOMS) registry is a self-report registry for persons with MS, which has been enrolling participants since 1996. Participants share information regarding their socio-demographic characteristics and clinical aspects of their MS at enrollment and update this information semiannually through surveys. Participants may complete questionnaires on paper or online.

Standard protocol approvals, registrations, and patient consents

Participants allow the use of their de-identified information for research purposes. At the time of the spring 2014 survey, the NARCOMS registry was approved by the Institutional Review Board of the University of Alabama at Birmingham.

Participant characteristics

For this study, we obtained information from the enrollment and spring 2014 questionnaires. We obtained date of birth, sex, race, education level, region of residence, and ages at MS symptom onset and diagnosis from the enrollment questionnaire. We categorized race as white or nonwhite and education level as <high school, high school/GED, and postsecondary (associate's degree, bachelor's degree,

postgraduate education, and technical degree). From the spring 2014 questionnaire, we obtained annual household income, marital status, disability status, and health behaviors. Annual household income was reported as ≤\$50,000, \$15,001–\$30,000, \$30,001–\$50,000, \$50,001–\$100,000, >\$100,000 and “I do not wish to answer”. Marital status was categorized as single (never married, divorced, widowed, or separated) and married (married or cohabiting). Disease duration was categorized based on time from symptom onset (<10, 10–19, ≥20 years).

Participants reported disability status using Patient Determined Disease Steps (PDDS), a single-item measure with 9 potential responses ranging from 0 (normal) to 8 (bedridden). The PDDS is highly correlated with the Expanded Disability Status Scale score.¹² We categorized PDDS as mild (0–1), moderate (2–4), and severe (5–8).¹³

With respect to health behaviors, we captured smoking status, physical activity, and alcohol intake. Using a question from the Behavioral Risk Factor Surveillance Survey, participants reported their current smoking status as No, Yes Some days, and Yes Every day; we collapsed these responses to yes/no.¹⁴ They also reported whether they had participated in any physical activity or exercise during the past month (yes/no). We captured alcohol intake using 1 question from the Alcohol Use Disorders Identification Test.¹⁵ The question was modified to ask about alcohol intake over the past 6 months instead of the past 12 months and was reported as never, monthly or less, 2 to 4 times a month, 2 to 3 times a week, or 4 or more times a week.

Gastrointestinal symptoms

In the spring 2014 survey, participants responded to 26 questions from the Rome III Diagnostic Questionnaire regarding adult functional gastrointestinal disorders aimed at identifying IBS, functional bloating, functional constipation, functional diarrhea, and functional dyspepsia.¹⁶ The Rome III criteria were the prevailing diagnostic criteria at the time the survey was conducted. Participants also reported whether a physician had ever diagnosed them (yes/no) with inflammatory bowel disease, depression, or anxiety.

Health-related quality of life

We measured HRQOL using the RAND-12, a shortened version of the RAND-36, which has been used in the MS population.¹⁷ The RAND scoring has been proposed to better assess mental health in MS than the scoring used for the Short Form-12 and Short Form-36.¹⁷ The RAND-12 generates aggregate physical component (PCS-12) and mental component (MCS-12); standardized scores range from 0 (worst HRQOL) to 100 (best HRQOL), with a mean of 50 and SD of 10.

Statistical analysis

We excluded individuals who reported inflammatory bowel disease (IBD, n = 194) from the analysis because IBD is an

exclusion to diagnosing functional bowel disorder. We also excluded individuals who did not provide complete responses to the questions regarding functional gastrointestinal disorders ($n = 1,415$).

We summarized the characteristics of the respondents using mean (SD), median (interquartile range), and frequency (percent). We examined correlations between continuous variables using Spearman correlations. First, we report the prevalence of functional gastrointestinal disorders overall and stratified by sex, age (18–34, 35–54, and ≥ 55 years), and disease duration (<10, 10–19, and ≥ 20 years) and disability status (mild, moderate, and severe). Second, we examined factors associated with the presence or absence of functional gastrointestinal disorders using a series of binary logistic regression models. Covariates included in the models were sex, age (as defined above), disease duration (as defined above), race, educational level, income, smoking status, alcohol intake, physical activity, disability status, depression, and anxiety disorder. We used standard methods to assess model assumptions and assessed model fit using the Hosmer Lemeshow Goodness of Fit Statistic.¹⁸ We report the c -statistic for each model.

Third, we examined the association between the presence of any functional bowel disorder and HRQOL (PCS-12 and MCS-12) using multivariable linear regression, adjusting for all the covariates described above. Model assumptions were assessed using standard methods. Statistical analyses were conducted using SAS V9.4 (SAS Institute Inc., Cary, NC).

Data availability

The data sets generated and analyzed during the current study are held by the NARCOMS registry (narcoms.org).

Results

Participants

Of 13,609 participants to whom the survey was sent, 7,921 (58.2%) responded. Compared with responders, nonresponders were younger at MS symptom onset (mean [SD] 30.30 [10.4] vs 31.1 [9.8], $p < 0.0001$), more likely to be nonwhite (1505 [26.4%] vs 1131 [14.3%], $p < 0.0001$), and were more likely to have attained \leq high school education (1893 [34.3%] vs 2304 [29.9%], $p < 0.0001$). Sex and disability status at enrollment did not differ between responders and nonresponders. After applying the exclusion criteria, 6,312 of the responders were eligible for the analyses. Participants who were eligible were less likely to be female, more likely to have attained more than a high school education, and had a lower level of disability than those who were ineligible (all $p < 0.0001$).

Over three-quarters of participants were women, most were white, of mean (SD) age 58.2 (10.2) years at the time of the survey (table 1). Age was moderately correlated with disease

duration ($r = 0.56$; 95% confidence interval [CI]: 0.55, 0.58), but more weakly correlated with disability status ($r = 0.34$; 95% CI: 0.32, 0.36). Disability and disease duration were weakly correlated ($r = 0.34$; 95% CI: 0.32, 0.36).

Functional gastrointestinal disorders

Overall, 2,647 participants (41.9%) met the criteria for a functional bowel disorder. Compared with participants with no functional bowel disorder, those with any disorder were younger, had an earlier age at symptom onset, were more likely to be female, to have a lower annual household income, more disability, be more likely to smoke, and more likely to report a diagnosis of anxiety or depression (table 2). Functional bloating affected 8.5% of participants, whereas functional constipation and diarrhea were uncommon. Stratified analyses indicated that women had a higher prevalence of IBS or functional bloating than men, whereas men had a higher prevalence of functional constipation or diarrhea than women. The prevalence of each disorder consistently increased with disease duration and was higher in participants with moderate or severe disability than those with mild disability.

On multivariable analysis, women had increased odds of IBS and functional bloating but decreased odds of functional constipation or diarrhea. Older age was associated with reduced odds of IBS, but increased odds of functional diarrhea. Longer disease duration was associated with increased odds of IBS, but was not associated with the odds of the other functional gastrointestinal disorders. Severe, compared with mild, disability was associated with increased odds of IBS, functional diarrhea, and functional bloating. Depression was associated with increased odds of IBS, functional diarrhea, and functional dyspepsia. Anxiety was associated with increased odds of IBS and functional dyspepsia. Race, level of education, marital status, smoking status, physical activity, and amount of alcohol intake were not associated with increased odds of having any of the functional gastrointestinal disorders (table 3).

Health-related quality of life

After adjustment for sociodemographic and clinical characteristics and health behaviors, participants with any functional gastrointestinal disorder reported lower physical HRQOL on average [SD] (PCS-12 35.5 [0.30]) than participants without a functional gastrointestinal disorder (38.1 [0.29], $p < 0.0001$, table 4). Similarly, participants with any functional gastrointestinal disorder reported lower mental HRQOL (42.9 [0.40]) than those without a functional gastrointestinal disorder (45.4 [0.38], $p < 0.0001$, table 4).

Discussion

In this large cross-sectional study, we found that 2 in 5 participants with MS had a functional gastrointestinal disorder, most often IBS, followed by functional bloating. In North

Table 1 Clinical and demographic characteristics of study participants^a

Characteristics	All participants N = 6312	No functional gastrointestinal disorder N = 3665	Any functional gastrointestinal disorder N = 2647	p Value
Age at the time of the study, mean (SD)	58.25 (10.25)	58.66 (10.22)	57.67 (10.28)	0.0001
Age at MS symptom onset, mean (SD)	31.19 (10.34)	31.91 (10.47)	30.20 (10.07)	<0.0001
Age at MS diagnosis, mean (SD)	38.97 (9.79)	39.20 (9.87)	38.66 (9.68)	0.0630
Disease duration, mean (SD)	27.00 (12.18)	26.68 (12.24)	27.44 (12.07)	0.0096
Female, n (%)	4816 (76.47)	2650 (72.42)	2166 (82.08)	<0.0001
White race, n (%)	5381 (85.45)	3116 (85.18)	2265 (85.83)	0.49
Education, n (%)				0.16
High school/GED	1778 (28.89)	1007 (28.20)	771 (29.85)	
Postsecondary	4376 (71.11)	2564 (71.80)	1812 (70.15)	
Annual household income, n (%)				0.011
Less than \$15,000	490 (7.79)	253 (6.92)	237 (8.99)	
\$15,001–\$30,000	848 (13.48)	502 (13.73)	346 (13.13)	
\$30,001–\$50,000	970 (15.42)	542 (14.82)	428 (16.24)	
\$50,001–\$100,000	1585 (25.19)	928 (25.38)	657 (24.92)	
Over \$100,000	1045 (16.61)	625 (17.10)	420 (15.93)	
I do not wish to answer	1354 (21.52)	806 (22.05)	548 (20.79)	
Marital status, n (%)				0.91
Married/common law	4153 (69.55)	2384 (69.48)	1769 (69.65)	
Single/widowed/divorced	1818 (30.45)	1047 (30.52)	771 (30.35)	
PDDS, median (p25–p75)	4.00 (1.00–6.00)	4.00 (1.00–6.00)	4.00 (2.00–6.00)	0.012
PDDS, n (%)				<0.0001
Mild (0–1)	1802 (28.66)	1199 (32.82)	603 (22.88)	
Moderate (2–4)	2091 (33.25)	1074 (29.40)	1017 (38.60)	
Severe (5–8)	2395 (38.09)	1380 (37.78)	1015 (38.52)	
Current smoker, n (%)	644 (10.48)	328 (9.26)	316 (12.14)	0.0003
Physical activity (yes), n (%)	3716 (59.39)	2186 (60.25)	1530 (28.20)	0.11
Alcohol intake, n (%)				0.14
Never	1961 (34.91)	1099 (34.32)	862 (35.69)	
Monthly or less often	1425 (25.37)	789 (24.64)	636 (26.34)	
Two to 4 times a month	986 (17.55)	577 (18.02)	409 (16.94)	
Two to 3 times a week	583 (10.38)	335 (10.46)	248 (10.27)	
Four or more times a week	662 (11.79)	402 (12.55)	260 (10.77)	
Anxiety, n (%)	1097 (17.38)	462 (12.61)	635 (23.99)	<0.0001
Depression, n (%)	1841 (29.17)	836 (22.81)	1005 (37.97)	<0.0001
PCS-12	37.2 (11.8)	38.9 (11.8)	34.8 (11.4)	<0.0001
MCS-12	48.4 (11.2)	50.2 (10.7)	46.0 (11.4)	<0.0001

Abbreviations: MCS-12 = Mental Component Score; PCS-12 = Physical Component Score; PDDS = Patient Determined Disease Step.

^a Because of missing responses, the sum across variable categories may add to less than column totals.

America, the most common functional gastrointestinal disorder is IBS, which is estimated to affect 12% of the general population.¹⁹ This estimate is substantially lower than we observed. Only a few studies have examined the prevalence of IBS among persons with MS.^{8–11} These studies used a variety of methods including surveys and administrative data. The sole population-based study relied on administrative data and found a prevalence of 12.2%,¹¹ which was nearly two-fold higher than in age, sex, and geographically matched controls. However, the administrative definition was insensitive (39.1%) despite high specificity (96.6%) and also would only capture individuals who sought medical care for their symptoms, potentially underestimating the prevalence of IBS. Another study, conducted by Levinthal et al.,⁹ also examined the prevalence of other functional gastrointestinal disorders among 218 persons with MS using the Rome III questionnaire. In that study, 19.3% of participants had IBS, over 30% had functional constipation, and >15% had functional dyspepsia; the prevalence of functional diarrhea was not reported. These estimates differ from ours, identifying a lower prevalence of IBS, but higher prevalence of the other functional gastrointestinal disorders. The reason for these differences is uncertain but may reflect differences in the characteristics of the study populations. On average, our sample was 10 years older, with a disease duration that was about 14 years longer than the sample in the Levinthal study. Disability status may have differed as well, but the disability

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measures used in the 2 studies are not directly comparable. These differences are relevant, given that age, disability, and disease duration influenced the prevalence of functional gastrointestinal disorders in our sample.

Female sex was associated with a higher prevalence of IBS, and functional bloating, but a lower prevalence of functional constipation and diarrhea. Our findings regarding female sex and functional constipation and diarrhea should be viewed with caution, given the small number of participants affected. Greater disability and disease duration were also associated with a higher prevalence of IBS, whereas comorbid anxiety and depression were associated with a higher prevalence of most of the functional gastrointestinal disorders. Women are recognized to be at increased risk of IBS.²⁰ In the previous

Table 2 Prevalence of functional bowel disorders

	Irritable bowel syndrome N (%; 95% CI)	Functional constipation N (%; 95% CI)	Functional diarrhea N (%; 95% CI)	Functional bloating N (%; 95% CI)	Functional dyspepsia N (%; 95% CI)
Overall	1777 (28.15; 27.05–29.28)	83 (1.31; 1.05–1.63)	134 (2.12; 1.78–2.51)	537 (8.51; 7.83–9.22)	140 (2.22, 1.87–2.61)
Sex					
Female	1474 (30.61; 29.31–31.93)	54 (1.12; 0.84–1.46)	88 (1.83; 1.47–2.25)	459 (9.53; 8.72–10.40)	109 (2.26, 1.86–2.72)
Male	296 (19.97; 17.96–22.10)	29 (1.96; 1.31–2.80)	46 (3.10; 2.28–4.12)	78 (5.26; 4.18–6.53)	30 (2.02, 1.37–2.88)
Age group (y)					
18–34	30 (29.41; 20.80–39.25)	1 (0.98; 0.02–5.34)	0 (0)	8 (7.84; 3.45–14.87)	2 (1.96, 0.24–6.90)
35–54	590 (29.77; 27.76–31.83)	28 (1.41; 0.94–2.04)	38 (1.92; 1.36–2.62)	195 (9.84; 8.56–11.24)	47 (2.37, 1.75–3.14)
≥55	1150 (27.30; 25.96–28.67)	54 (1.28; 0.96–1.67)	96 (2.28; 1.85–2.78)	334 (7.93; 7.13–8.79)	90 (2.14, 1.72–2.62)
Disease duration (y)					
<10	75 (21.68; 17.45–26.40)	4 (1.16; 0.32–2.93)	6 (1.73; 0.64–3.74)	33 (9.54; 6.66–13.13)	6 (1.73, 0.64–3.74)
11–19	390 (26.10; 23.89–28.41)	16 (1.07; 0.61–1.73)	31 (2.07; 1.41–2.93)	138 (9.24; 7.82–10.82)	35 (2.34, 1.64–3.24)
≥20	1275 (29.26; 27.91–30.63)	63 (1.45; 1.11–1.85)	95 (2.18; 1.77–2.66)	361 (8.28; 7.48–9.14)	97 (2.23, 1.81–2.71)
Disability status					
Mild	386 (21.42; 19.55–23.39)	16 (0.89; 0.51–1.44)	35 (1.94; 1.36–2.69)	134 (7.44; 6.27–8.75)	38 (2.11, 1.50–2.88)
Moderate	698 (33.38; 31.36–35.45)	26 (1.24; 0.81–1.82)	38 (1.82; 1.29–2.49)	206 (9.85; 8.61–11.21)	56 (2.68, 2.03–3.46)
Severe	686 (28.64; 26.84–30.50)	41 (1.71; 1.23–2.32)	59 (2.46; 1.88–3.17)	194 (8.10; 7.04–9.27)	46 (1.92, 1.41–2.55)

Abbreviation: CI = confidence interval.

Table 3 Adjusted odds ratios (95% confidence intervals) for the association of demographic and clinical characteristics with functional gastrointestinal disorders

Variable	IBS (n = 5217)	Functional constipation (n = 5217)	Functional diarrhea (n = 5217)	Functional bloating (n = 5217)	Functional dyspepsia (n = 5217)
Sex					
Male	1.0	1.0	1.0	1.0	1.0
Female	1.76 (1.49, 2.07)	0.57 (0.35, 0.94)	0.56 (0.37, 0.86)	1.92 (1.45, 2.55)	1.19 (0.73, 1.93)
Age	0.984 (0.976, 0.991)	0.997 (0.973, 1.02)	1.03 (1.01, 1.05)	0.997 (0.985, 1.008)	1.02 (0.99, 1.04)
Race					
White	1.0	1.0	1.0	1.0	1.0
Nonwhite	0.91 (0.76, 1.08)	0.92 (0.47, 1.81)	1.05 (0.60, 1.84)	1.04 (0.80, 1.37)	0.60 (0.32, 1.12)
Education level					
High school/GED	1.0	1.0	1.0	1.0	1.0
Postsecondary	1.04 (0.90, 1.20)	1.24 (0.57, 2.67)	0.90 (0.57, 1.41)	0.90 (0.71, 1.12)	0.92 (0.60, 1.43)
Annual household income					
<\$15,000	1.0	1.25 (0.65, 2.41)	1.0	1.0	1.0
\$15,001–\$30,000	0.87 (0.66, 1.14)	1.69 (0.38, 7.53)	2.00 (0.55, 7.26)	0.90 (0.58, 1.39)	1.33 (0.59, 2.99)
\$30,001–\$50,000	0.92 (0.70, 1.21)		4.32 (1.26, 14.7)	0.86 (0.55, 1.33)	1.01 (0.43, 2.37)
\$50,001–\$100,000	0.97 (0.74, 1.26)	1.0	2.28 (0.65, 8.04)	0.85 (0.55, 1.31)	1.33 (0.59, 3.01)
Over \$100,000	0.80 (0.59, 1.08)	1.02 (0.33, 3.09)	3.54 (0.96, 13.1)	1.17 (0.73, 1.86)	0.74 (0.30, 1.78)
I do not wish to answer	0.76 (0.58, 0.99)	0.88 (0.28, 2.77)	3.37 (0.97, 11.7)	1.12 (0.74, 1.72)	1.30 (0.52, 3.22)
Marital status					
Married/cohabiting	1.14 (0.99, 1.33)	1.48 (0.51, 4.26)	0.88 (0.56, 1.39)	1.15 (0.90, 1.46)	0.81 (0.52, 1.25)
Single/divorced/widowed	1.0	1.06 (0.35, 3.18)	1.0	1.0	1.0
Disability					
Mild (0–1)	1.0	0.93 (0.53, 1.63)	1.0	1.0	1.0
Moderate (2–4)	1.66 (1.40, 1.96)	1.0	0.94 (0.56, 1.58)	1.32 (1.02, 1.71)	1.05 (0.66, 1.68)
Severe (5–8)	1.58 (1.31, 1.90)		0.83 (0.47, 1.46)	1.40 (1.05, 1.87)	0.85 (0.49, 1.47)
Disease duration (y)^a					
<10	1.0	—	1.0	1.0	1.0
10–19	1.65 (1.20, 2.26)		0.80 (0.32, 2.02)	1.02 (0.65, 1.62)	1.17 (0.47, 2.87)
≥20	1.44 (1.21, 1.71)		0.66 (0.26, 1.64)	0.97 (0.61, 1.54)	0.95 (0.38, 2.36)
Smoking					
No	1.0	1.0	1.0	1.0	1.0
Yes	1.19 (0.98, 1.44)	0.72 (0.30, 1.69)	0.89 (0.45, 1.74)	1.19 (0.88, 1.60)	1.09 (0.62, 1.92)
Any physical activity					
No	1.0	1.0	1.0	1.0	1.0
Yes	0.93 (0.81, 1.06)	1.17 (0.70, 1.95)	0.95 (0.61, 1.47)	1.09 (0.87, 1.35)	1.42 (0.93, 2.19)
Alcohol use					
Never	1.0	1.0	1.0	1.0	1.0

Continued

Table 3 Adjusted odds ratios (95% confidence intervals) for the association of demographic and clinical characteristics with functional gastrointestinal disorders (continued)

Variable	IBS (n = 5217)	Functional constipation (n = 5217)	Functional diarrhea (n = 5217)	Functional bloating (n = 5217)	Functional dyspepsia (n = 5217)
Monthly or less often	1.02 (0.87, 1.20)	1.08 (0.60, 1.96)	0.87 (0.53, 1.45)	1.22 (0.95, 1.57)	0.85 (0.52, 1.41)
Two to 4 times a month	1.01 (0.84, 1.21)	0.37 (0.14, 0.98)	0.60 (0.31, 1.15)	1.15 (0.86, 1.55)	1.17 (0.47, 2.87)
Two or more times a week	0.98 (0.82, 1.17)	1.44 (0.79, 2.62)	0.86 (0.50, 1.46)	1.11 (0.84, 1.48)	0.89 (0.52, 1.53)
Depression					
No	1.0	1.0	1.0	1.0	1.0
Yes	1.38 (1.19, 1.60)	1.75 (1.03, 2.98)	1.19 (0.73, 1.94)	1.25 (0.99, 1.58)	1.55 (1.00, 2.41)
Anxiety					
No	1.0	1.0	1.0	1.0	1.0
Yes	1.44 (1.21, 1.71)	0.59 (0.28, 1.24)	0.95 (0.52, 1.73)	1.18 (0.90, 1.55)	1.69 (1.06, 2.72)
c-Statistic	0.63	0.67	0.64	0.60	0.64
HLGOF	7.09, <i>p</i> = 0.53	8.8, <i>p</i> = 0.36	3.28, <i>p</i> = 0.91	9.71, <i>p</i> = 0.29	10.4, <i>p</i> = 0.24

Abbreviations: HLGOF = Hosmer Lemeshow Goodness of Fit; IBS = irritable bowel syndrome

Bold indicates statistical significance.

^a Disease duration excluded from the functional constipation model because of poor model fit when this variable was introduced.

study by Levinthal et al.,⁹ greater severity of gastrointestinal symptoms was associated with greater impairment of physical function as assessed by the MSIS-29, which would be consistent with our findings regarding disability. In systemic lupus erythematosus, the prevalence of functional gastrointestinal disorders has also been reported to be higher with longer disease duration. Depression and anxiety disorders are associated with functional gastrointestinal disorders in the general population²¹ and may precede or follow the development of gastrointestinal symptoms.²² Treatment of psychiatric comorbidities in functional gastrointestinal disorders is associated with reduced severity of gastrointestinal symptoms.²³

The presence of a comorbid functional gastrointestinal disorder was associated with reduced HRQOL, although the effects were modest, with effect sizes at the minimum threshold for clinical importance (0.2).²⁴ Although we were unable to identify other studies that evaluated the effects of functional

gastrointestinal disorders on HRQOL in MS, some studies have evaluated the effect of bowel symptoms on HRQOL. In a study of 56 persons with MS from Hordaland County, Norway, the presence of bowel symptoms including flatus, constipation, and incontinence was associated with lower HRQOL scores as measured using the Short Form-36.^{25,26} Similarly, a study of 223 persons with MS found that more severe bowel symptoms, as assessed using the Bowel Control Scale, were correlated with lower physical and mental HRQOL as measured using the Short Form-36.²⁵ Satisfaction with treatment of bowel symptoms is modest, but treatment of such symptoms has been reported to improve HRQOL,²⁷ emphasizing the clinical importance of recognizing and addressing gastrointestinal symptoms and disorders.

The reasons for the high prevalence of functional gastrointestinal disorders in MS are unknown, but several reasons can be postulated. First, MS-related immune dysregulation may play a role. A case-control study of 23,471 persons captured in the Health Improvement Network database found that the prevalence of any autoimmune disease was higher among persons with a functional gastrointestinal disorder (odds ratio [OR] 1.35; 95% CI: 1.12–1.63).²⁸ The odds of any immune-mediated rheumatologic disorder were higher among persons with functional dyspepsia (OR 1.44; 95% CI: 1.15–1.80). In a study of 86 persons with systemic lupus erythematosus, 76.7% had at least 1 functional gastrointestinal disorder, most often functional dyspepsia.²⁹ Several studies suggest that immune dysregulation and inflammation may underlie these disorders in some cases. In IBS, altered cytokine profiles and T-cell population and increased

Female sex was associated with a higher prevalence of IBS, and functional bloating, but a lower prevalence of functional constipation and diarrhea.

Table 4 Multivariable linear regression of association between any functional gastrointestinal disorder and health-related quality of life

Variable	PCS-12	MCS-12
	β (SE)	β (SE)
Any functional gastrointestinal disorder		
No		
Yes	-2.57 (0.22)	-2.44 (0.29)
Sex		
Male		
Female	1.02 (0.26)	-0.21 (0.35)
Age		
	-0.11 (0.01)	0.056 (0.02)
Race		
White		
Nonwhite	-0.058 (0.30)	0.13 (0.40)
Education level		
High school/GED		
Postsecondary	0.23 (0.25)	1.41 (0.33)
Annual household income		
<\$15,000		
\$15,001-\$30,000	-0.50 (0.49)	1.72 (0.64)
\$30,001-\$50,000	1.14 (0.49)	1.90 (0.64)
\$50,001-\$100,000	0.96 (0.48)	3.11 (0.63)
Over \$100,000	2.77 (0.53)	3.22 (0.70)
I do not wish to answer	1.76 (0.48)	3.15 (0.64)
Marital status		
Married/cohabiting	-0.79 (0.26)	-0.089 (0.34)
Single/divorced/widowed		
Disability		
Mild (0-1)		
Moderate (2-4)	-12.4 (0.28)	-1.40 (0.37)
Severe (5-8)	-18.0 (0.31)	-0.13 (0.41)
Disease duration (y)		
<10		
10-19	-0.39 (0.51)	1.24 (0.67)
≥20	-0.34 (0.51)	0.80 (0.67)
Smoking		
No		
Yes	-1.26 (0.34)	-2.39 (0.45)
Any physical activity		

Table 4 Multivariable linear regression of association between any functional gastrointestinal disorder and health-related quality of life (*continued*)

Variable	PCS-12	MCS-12
	β (SE)	β (SE)
No		
Yes	2.16 (0.24)	1.68 (0.31)
Alcohol		
Never		
Monthly or less often	0.79 (0.28)	0.98 (0.37)
Two to 4 times a month	1.81 (0.32)	1.48 (0.42)
Two or more times a week	1.95 (0.30)	0.47 (0.40)
Depression		
No		
Yes	-0.17 (0.27)	-6.17 (0.35)
Anxiety		
No		
Yes	-0.26 (0.32)	-3.72 (0.42)

Abbreviations: MCS-12 = Mental Component Score; PCS-12 = Physical Component Score; SE = standard error. For the PCS-12 and MCS-12 higher scores indicate higher health-related quality of life. Bold indicates statistical significance.

immune activation^{30,31} are recognized. Altered immune activation has also been reported in functional dyspepsia.³² Second, psychiatric comorbidity may increase the risk of functional gastrointestinal disorders. The prevalence of depression and anxiety disorders is higher in the MS population than in the general population.³³ Also, depression and anxiety disorders are associated with functional gastrointestinal disorders in the general population, which is postulated to reflect dysregulation of the gut-brain axis.³⁴

We acknowledge several study limitations. Study participants are volunteers, and the response rate was 58%, which is slightly lower than the mean response rate of 60% in the medical literature.³⁵ Responders differed with respect to race and educational status from nonresponders, and responders who were eligible for inclusion differed from those with incomplete responses with respect to sex (less likely to be female), education (higher education level), and disability at enrollment (less disability). Thus, our findings may not be representative of the entire MS population. Specifically, those eligible for the analysis had a lower proportion of the characteristics that are positively associated with functional gastrointestinal disorders, which could reduce the estimated prevalence compared with the larger MS population. Although our sample averaged 58 years old, this falls within the range of the peak age-specific prevalence of MS in the United States.³⁶ Like several other studies, we relied on a

questionnaire to establish diagnoses of functional gastrointestinal disorders. Although we excluded self-reported inflammatory bowel disease, participants may have had other underlying disorders that could account for their gastrointestinal symptoms; thus, our estimates of functional gastrointestinal disorders may be slightly elevated. Strengths of the study included the large sample size and evaluation of the association of a broad range of demographic factors, health behaviors, and clinical characteristics with functional gastrointestinal disorders.

Our findings indicate that functional gastrointestinal disorders are common in MS and increase in frequency with increasing disability and disease duration. The association of anxiety and depression with functional gastrointestinal disorders suggests that effectively diagnosing and treatment psychiatric comorbidities may reduce the burden of functional gastrointestinal disorders. These disorders are associated with reduced HRQOL, suggesting that improved management of these disorders may offer a means of improving HRQOL in persons with MS.

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Stella Leung, MSc	University of Manitoba, Winnipeg	Author	Data analysis and revision of the manuscript
Tuula Tyry, PhD	St. Joseph's Hospital and Medical Center, Phoenix	Author	Acquisition and interpretation of the data and revision of the manuscript
Gary Cutter, PhD	University of Alabama at Birmingham, Birmingham	Author	Acquisition of data and critical review of the manuscript
Robert Fox, MD, MSc	Mellen Center for Multiple Sclerosis, Neurological Institute, Cleveland Clinic, Cleveland	Author	Acquisition of data and critical review of the manuscript
Amber Salter, PhD	Washington University in St. Louis, St. Louis	Author	Conception and design of the study, acquisition of data, and revision of the manuscript

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