

# Clinical Determinants of Health-Related Quality of Life in Patients With Irritable Bowel Syndrome

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**Background:** Current guidelines recommend routine assessment of health-related quality of life (HRQOL) in patients with irritable bowel syndrome (IBS). However, physicians rarely have the time to measure HRQOL with the appropriate methodological rigor, and data suggest that HRQOL in patients with IBS is often estimated using inaccurate clinical gestalt. The identification of predictive factors could allow physicians to better assess HRQOL without using misleading clinical clues. We, therefore, sought to identify determinants of HRQOL in patients with IBS.

**Methods:** We examined 770 patients, 18 years or older, with IBS at a university-based referral center. Subjects completed a symptom questionnaire, the Symptoms Checklist–90 items psychometric checklist, and the 36-Item Short-Form Health Survey. The main outcome was HRQOL as measured by the mental and physical component scores of the 36-Item Short-Form Health Survey. We first developed a list of hypothesis-driven HRQOL predictors, and then performed multivariate regression analysis to measure the independent association of each predictor with HRQOL.

**Results:** Seven factors ( $r^2=0.39$ ) independently predicted physical HRQOL: (1) more than 5 physician visits per year, (2) tiring easily, (3) low in energy, (4) severe symptoms, (5) predominantly painful symptoms, (6) the feeling that there is “something seriously wrong with body,” and (7) symptom flares for longer than 24 hours. Eight factors ( $r^2=0.36$ ) independently predicted mental HRQOL: (1) feeling tense, (2) feeling nervous, (3) feeling hopeless, (4) difficulty sleeping, (5) tiring easily, (6) low sexual interest, (7) IBS symptom interference with sexual function, and (8) low energy.

**Conclusions:** Health-related quality of life in patients with IBS is primarily related to extraintestinal symptoms rather than traditionally elicited gastrointestinal symptoms. These findings suggest that rather than focusing on physiological epiphenomena (stool characteristics and subtype of IBS) and potentially misleading clinical factors (age and disease duration), physicians might be better served to gauge global symptom severity, address anxiety, and eliminate factors contributing to chronic stress in patients with IBS.

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**I**RRITABLE BOWEL SYNDROME (IBS) is a chronic disorder of gastrointestinal function characterized by recurrent abdominal pain and altered bowel habits in the absence of detectable organic disease.<sup>1</sup> Irritable bowel syndrome is a prevalent and expensive condition, affecting 15% of the general adult population, resulting in 3.6 million physician visits annually, and costing more than \$8 billion per year in direct and indirect expenditures.<sup>2,3</sup> Moreover, patients with IBS have a health-related quality of life (HRQOL) that is significantly worse than patients with diabetes mellitus or end-stage renal disease.<sup>4</sup> In light of this finding, a recent guideline<sup>5</sup> suggests routine HRQOL screening in patients with IBS, and recommends initiating treatment when the symptoms of IBS reduce functional status and diminish overall HRQOL.

However, the success of these guidelines rests on the implicit assumption that clinicians are capable of accurately assessing HRQOL in patients with IBS. To the contrary, data suggest that many physicians do a poor job of eliciting their patients' agendas, addressing their patients' fears and concerns, and accurately assessing the impact of IBS symptoms on health status.<sup>6-11</sup> Patients, in turn, indicate that this disconnect prompts dissatisfaction with care.<sup>6-11</sup> A practical limitation in the busy outpatient setting is that an accurate HRQOL assessment requires the evaluation of multiple patient domains, including biological, psychological, and social functioning.<sup>12</sup> Generic HRQOL measures, including the 36-Item Short-Form Health Survey (SF-36), are designed to capture information from each of these domains to establish a broad and balanced

portrait of a patient's unique HRQOL.<sup>13</sup> However, these measures are primarily designed for research purposes, and clinicians rarely have the time or inclination to assess HRQOL with such methodological rigor. Moreover, most primary care physicians and gastroenterologists have not received training in how to perform a complete biopsychosocial evaluation,<sup>14,15</sup> and observational data indicate that this inquiry is rarely performed.<sup>16</sup>

The identification of a concise and readily available set of clinical factors associated with HRQOL in patients with IBS might lead to more efficient and effective health care delivery. By establishing a convenient yet accurate list of clinical determinants, physicians may gain better insight into their patients' HRQOL without relying on inaccurate clinical clues and imperfect clinician gestalt. Although several studies<sup>4,17</sup> have evaluated HRQOL in patients with IBS compared with other medical conditions, there have been few attempts to identify specific clinical factors that predict HRQOL within IBS. Whereas researchers<sup>18-20</sup> have demonstrated that symptom severity and psychological component scores (as measured by the Symptoms Checklist-90 items) are independently associated with HRQOL, to our knowledge, there has been no attempt to determine specific clinical factors or symptoms that predict HRQOL. We, therefore, sought to identify determinants of mental and physical HRQOL in patients with IBS. Before conducting the study, we established 3 a priori hypotheses: (1) HRQOL in patients with IBS may be explained by a concise list of clinical variables; (2) HRQOL in patients with IBS is at least in part related to extraintestinal symptoms that physicians may neglect to ask about, including disease-specific fears or symptoms related to chronic stress; and (3) HRQOL in patients with IBS is not primarily related to traditionally elicited gastrointestinal symptoms, including IBS subtype or bowel habit characteristics.

## METHODS

### PATIENTS

We analyzed consecutive patients, 18 years or older, with Rome I or II-positive IBS examined at the Center for Neurovisceral Sciences and Women's Health, The David Geffen School of Medicine at UCLA, between January 1, 1995, and December 31, 2002. The Rome criteria provide a valid and reproducible definition of IBS, and are the most stringent criteria for accurately diagnosing IBS.<sup>1</sup> The diagnostic criteria are as follows. For at least 12 weeks, which need not be consecutive, in the preceding 12 months, persons must experience abdominal discomfort or pain that has 2 of the following 3 features: (1) relief with defecation, (2) onset associated with a change in the frequency of stool (abnormal frequency is >3 times per day and <3 times per week), and (3) onset associated with a change in form (ie, appearance of the stool, where abnormal stool is lumpy/hard or loose/watery). Supportive symptoms include the following: (1) fewer than 3 bowel movements a week, (2) more than 3 bowel movements a day, (3) hard or lumpy stools, (4) loose (mushy) or watery stools, (5) straining during a bowel movement, (6) urgency (having to rush to have a bowel movement), (7) feeling of an incomplete bowel movement, (8) passing mucus (white material) during a bowel movement, and (9) abdominal fullness, bloating, or swelling. "Diarrhea predominant" equals one

or more of items 2, 4, or 6 and none of items 1, 3, or 5. "Constipation predominant" equals one or more of items 1, 3, or 5 and none of items 2, 4, or 6.

The clinical arm of the Center for Neurovisceral Sciences and Women's Health is a university-based specialty clinic that focuses on the examination and treatment of patients with disorders of gastrointestinal function. One third of the patients examined at the center are self-referred, while two thirds are referred by primary care physicians, community gastroenterologists, and academic gastroenterologists. All subjects examined in this study completed a gastrointestinal symptom questionnaire, a psychological symptom checklist (Symptoms Checklist-90 items),<sup>21</sup> and the SF-36.<sup>13</sup>

The study was approved by the UCLA Institutional Review Board, and was conducted in accordance with the institutional guidelines regulating human subject research. All participants provided informed consent to participate in the study.

### STUDY OUTCOME MEASURE

The main outcome of our analysis was global HRQOL, as measured by the SF-36. The SF-36 is a widely used, validated, generic HRQOL instrument composed of 36 self-reported items.<sup>13</sup> The instrument has been tested in many patient populations and for many medical conditions, including IBS, and it was previously demonstrated that patients with IBS score significantly lower on the SF-36 than patients with other chronic medical conditions.<sup>4</sup> The SF-36 captures several health domains deemed important by patients with IBS, including bodily pain, energy/fatigue, and social functioning. In particular, the SF-36 contains several items pertaining to vital exhaustion, including the degree of feeling "full of life," feeling "worn out," and feeling "tired." Because vital exhaustion is regarded to be a critical component of health status in patients with IBS,<sup>22</sup> the SF-36 is an appropriate generic measure of HRQOL. The 36 items are organized into 8 discrete scales (physical functioning, physical role limitations, emotional role limitations, bodily pain, general health, emotional well-being, energy/fatigue, and social functioning) that are compiled into 2 summary scores: (1) the physical component score and (2) the mental component score. Each raw scale score is linearly transformed to *t* scores, with a mean of 50 and an SD of 10. The transformed scores range from 0 to 100, with higher scores indicating a better HRQOL. These physical and mental summary scores served as the dependent variables in our analysis. We performed a separate analysis for each score.

### CLINICAL PREDICTORS

In collaboration with members of the Center for Neurovisceral Sciences and Women's Health, we compiled a list of candidate independent predictors of HRQOL in patients with IBS (**Table 1**). We selected these hypothesis-driven predictors based on previous research and symptom assessments in IBS-specific HRQOL instruments,<sup>23</sup> along with the expert opinion and experience of the Center for Neurovisceral Sciences and Women's Health members. Each selected variable was supported by an a priori disease-specific hypothesis derived from this research and experience. To avoid circularity, we selected predictors that are not contained verbatim within the SF-36 itself. However, 3 of our predictors ("feel nervous," "tire easily," and "feel low in energy") are similar to items in the SF-36 ("very nervous," "feel tired," and "feel worn out"). Despite these similarities, each predictor overlaps with only 1 of the 36 items in the instrument. Therefore, it would be unlikely for one predictor to drive the results of global HRQOL based on overlap with a single item in the outcome measure. To simplify the interpretation and preserve the clinical utility of the character-

**Table 1. Hypothesized Independent Predictors of Health-Related Quality of Life in Patients With Irritable Bowel Syndrome (IBS)**

Independent Variable	Method of Dichotomization
<b>Demographic variables</b>	
Sex	Female vs male
Age	<50 y vs ≥50 y
Ethnicity	White vs nonwhite
Education	Beyond high school vs not beyond high school
Marital status	Married vs unmarried
Income	<\$30 000/y vs ≥30 000/y
<b>Bowel symptom variables</b>	
Duration of IBS	<2 y vs ≥2 y
Flare duration	Symptom flares for <24 h vs ≥24 h
Predominant bowel pattern	Diarrhea predominant vs constipation predominant (by Rome criteria)
Predominant bowel symptom	Pain vs discomfort predominant
Presence of bloating	Present vs absent
Severity of IBS symptoms	Mild or moderate vs severe or very severe
Presence of childhood bowel symptoms	Present vs absent
IBS symptom interference with sexual function	Present vs absent
Presence of concurrent nonreflux dyspepsia	Present vs absent
Presence of concurrent reflux-type dyspepsia	Present vs absent
<b>Psychological symptom variables</b>	
Feel low in energy	Not at all or moderately vs quite a bit or extremely
Feel nervous	Not at all or moderately vs quite a bit or extremely
Feel hopeless	Not at all or moderately vs quite a bit or extremely
Feel tense	Not at all or moderately vs quite a bit or extremely
Tire easily	Not at all or moderately vs quite a bit or extremely
Sleep difficulties	Not at all or moderately vs quite a bit or extremely
Loss of sexual interest	Not at all or moderately vs quite a bit or extremely
Feel that there is "something seriously wrong with body"	Not at all or moderately vs quite a bit or extremely
<b>Resource use variables</b>	
No. of physician visits within the past year	<5 vs ≥5 Visits
No. of different physicians seen within the past year	<3 vs ≥3 Different physicians
Previous flexible sigmoidoscopy performed	Yes vs no
Previous colonoscopy performed	Yes vs no
Previous upper endoscopy performed	Yes vs no
Patient interest in attending support group	Yes vs no

istics, each of the clinical predictors was expressed as a dichotomous variable.

### STATISTICAL ANALYSIS

We analyzed patient data using SAS statistical software (SAS Institute Inc, Cary, NC). To evaluate predictors for mental and physical health separately, we conducted separate analyses for the physical and mental component scores of the SF-36. We first performed bivariate analyses using the *t* test to evaluate the association of each predictor with HRQOL. To generate a parsimonious list of variables, and in acknowledgment of the fact that statistical significance does not always correspond with clinical significance, we limited our subsequent regression model to predictors fulfilling 2 explicit criteria in bivariate analysis: (1) the difference in SF-36 scores between patients with and without the variable exceeded 5 points (an effect size of 0.5, which is considered to be a medium effect in clinical studies<sup>24</sup> and corresponds with the proposed minimal SF-36 effect required for clinical significance<sup>25</sup>) and (2) the *P* value for the *t* test was highly significant (*P*<.001). By limiting our analysis to variables that were statistically and clinically significant, we attempted to guard against spurious and potentially noninformative results. The predictors selected from bivariate analysis were then entered as independent variables into a multiple linear regression model. Before conducting the multivariable analysis, we first performed collinearity testing between independent variables by constructing a correlation coefficient matrix.

This was performed to eliminate redundant variables from further analysis. If 2 variables correlated higher than *r*=0.8, then one of the pair was eliminated. Our final regression analysis evaluated the adjusted independent contribution of each clinical predictor to mental and physical HRQOL. We present the results of our final model in terms of the *P* value, the regression coefficient, the *t* value for the regression coefficient, and the percentage change in SF-36 score associated with each variable.

## RESULTS

### PATIENT CHARACTERISTICS

There were 770 patients with Rome I or II–positive IBS who completed the SF-36 during the study period. Their mean ± SD age was 48.0 ± 13.2 years, and 69.1% of the cohort was female. Of the cohort, 78.6% was white and 8.3% was African American. Of the patients, 47.2% had at least a high school education and 12.0% had attended college. Also, 40.7% of the cohort had diarrhea-predominant IBS, 32.1% had constipation-predominant IBS, and 27.2% had alternating IBS (by Rome II criteria<sup>1</sup>). The mean ± SD SF-36 physical component score was 43.6 ± 10.4, and the mean ± SD SF-36 mental component

**Table 2. Results of Bivariate Analyses for Independent Predictors and Physical Health-Related Quality of Life\***

Clinical Variable	SF-36 Score, Mean (SD)		SF-36 Score, /Δ in Mean /	P Value
	With Variable Present	With Variable Absent		
Low energy†	37.3 (10.0)	46.8 (9.1)	9.5‡	<.001§
Flare duration for >24 h†	40.9 (10.4)	50.4 (8.0)	9.5‡	<.001§
Tire easily†	40.3 (10.1)	49.7 (7.8)	9.4‡	<.001§
>5 Physician visits within the past year†	38.7 (10.4)	46.9 (8.9)	8.2‡	<.001§
Feel hopeless†	36.9 (11.0)	44.3 (10.0)	7.4‡	<.001§
Feel something is seriously wrong with body†	37.4 (10.2)	44.7 (10.0)	7.3‡	<.001§
High symptom severity†	40.9 (10.4)	47.8 (8.8)	6.9‡	<.001§
Predominant pain (vs discomfort)	39.8 (10.2)	44.8 (10.1)	5.0	<.001§
>3 Different physicians seen within the past year	39.7 (11.6)	44.6 (10.2)	4.9	<.001§
Feel nervous	39.8 (10.6)	44.2 (10.2)	4.4	<.001§
Sleep difficulties	42.3 (10.5)	46.6 (9.7)	4.3	<.001§
Female sex	42.5 (10.2)	46.0 (10.3)	3.5	<.001§
Symptoms interfere with sexual function	42.0 (10.4)	45.1 (10.0)	3.1	<.001§
Income <30 000/y	42.4 (10.4)	45.4 (10.0)	3.0	<.001§
Married	45.7 (10.0)	42.7 (11.0)	3.0	<.001§
Low sexual interest	41.4 (10.7)	44.2 (10.2)	2.8	.002
Feel tense	41.4 (10.8)	44.1 (10.2)	2.7	.004
Concurrent reflux-type dyspepsia	42.8 (10.6)	45.4 (9.6)	2.6	.002
Education beyond high school	43.8 (10.5)	41.6 (8.9)	2.2	.06
Age >50 y	42.5 (10.7)	44.7 (10.0)	2.2	.06
Previous sigmoidoscopy	42.0 (10.5)	43.9 (10.3)	1.9	.23
Diarrhea predominance (vs constipation)	42.9 (10.3)	44.7 (10.4)	1.8	.20
Previous upper endoscopy	42.6 (10.0)	43.7 (10.4)	1.1	.34
Childhood symptoms	44.0 (11.0)	43.1 (10.0)	0.9	.61
Time with symptoms >2 y	43.2 (10.3)	43.7 (10.4)	0.5	.64
Previous colonoscopy	43.2 (10.9)	43.7 (10.6)	0.5	.53
Interested in attending a support group	43.8 (10.5)	44.0 (10.1)	0.2	.95
White ethnicity	43.6 (10.2)	43.6 (10.5)	0.0	.98

Abbreviation: SF-36, 36-Item Short-Form Health Survey.

\*Variables are rank ordered according to their impact on SF-36 scores, as measured in column 4.

†These variables were selected for subsequent regression analysis based on achieving clinical and statistical significance. See the “Physical HRQOL Predictors” subsection of the “Results” section for additional information.

‡The difference is clinically significant, as defined by a difference in the absolute value of change in mean SF-36 scores of greater than 5 points.<sup>23</sup>

§Statistically significant, as defined by  $P < .001$ .

score was  $44.0 \pm 10.7$  (scale, 0-100, where 0 indicates the lowest HRQOL).

### PHYSICAL HRQOL PREDICTORS

**Table 2** displays the results of the bivariate analysis for each independent predictor in relation to physical HRQOL. Seven variables fulfilled our prespecified criteria for clinical and statistical significance. These variables were then entered into a linear regression analysis. The final model revealed 7 additive factors ( $r^2=0.39$ ) that independently predicted the SF-36 physical component score (in decreasing order of significance): (1) more than 5 physician visits within the past year, (2) tiring easily, (3) low in energy, (4) severe symptoms, (5) predominantly painful symptoms (vs discomfort), (6) the feeling that there is something seriously wrong with body, and (7) symptom flares for longer than 24 hours (**Table 3**).

**Figure 1** displays the percentage change in SF-36 physical component score independently associated with each predictor in the final regression model. For example, patients who tire easily had a 9.0% lower physical HRQOL compared with those who do not tire easily. Similarly, patients with symptom flares for 24 hours or

longer had a 3.7% lower physical HRQOL compared with those with flares for less than 24 hours. Because these factors are additive, patients who tire easily and have symptom flares for longer than 24 hours had a 12.7% lower physical HRQOL compared with those with neither characteristic.

### MENTAL HRQOL PREDICTORS

**Table 4** displays the results of bivariate analysis for each independent predictor in relation to mental HRQOL. Eight variables fulfilled our prespecified criteria for clinical and statistical significance. These variables were entered into a linear regression analysis. The final model revealed 8 additive factors ( $r^2=0.36$ ) that independently predicted the SF-36 mental component score (in order of significance): (1) feeling tense, (2) feeling nervous, (3) feeling hopeless, (4) difficulty sleeping, (5) tiring easily, (6) low sexual interest, (7) IBS symptom interference with sexual function, and (8) low energy (**Table 5**).

**Figure 2** displays the percentage change in SF-36 mental component score independently associated with each predictor in the final regression model. For example, patients who feel tense had a 13.6% lower mental HRQOL compared with those who do not feel tense.

**Table 3. Final Adjusted Linear Regression Model to Predict the SF-36 Physical Component Summary Score\***

Variable	Regression Coefficient (SE)	t Value	P Value
Intercept constant	55.95 (0.89)	62.58	<.001
No. of physician visits within the past year	-5.13 (0.81)	-7.13	<.001
Tire easily	-5.00 (0.81)	-6.19	<.001
Low in energy	-3.99 (0.84)	-4.74	<.001
Severity of IBS symptoms	-3.63 (0.72)	-5.05	<.001
Predominant bowel symptom (pain vs discomfort)	-2.74 (0.74)	-3.70	<.001
Feel something is seriously wrong with body	-2.46 (0.97)	-2.53	.01
Flare periodicity	-2.06 (0.74)	-2.80	.005

Abbreviations: IBS, irritable bowel syndrome; SF-36, 36-Item Short-Form Health Survey.

\* $r^2 = 0.39$ .

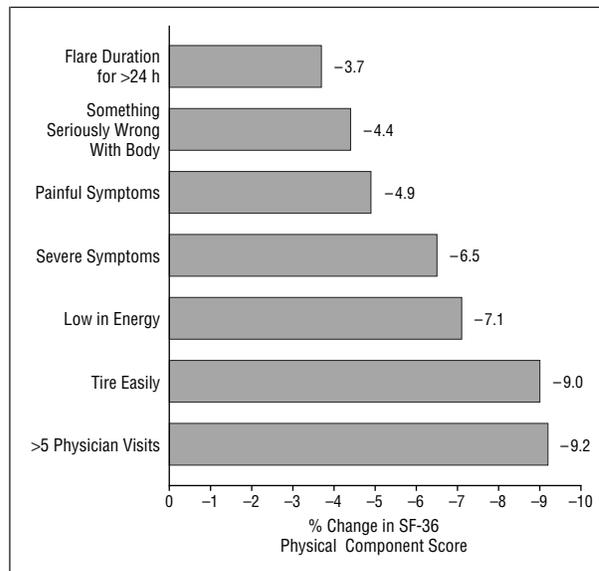
Similarly, patients whose IBS symptoms interfered with their sexual function had a 3.7% lower mental HRQOL compared with those without symptom interference with sexual function. Therefore, patients who both feel tense and have symptom interference with sexual function had a 17.3% lower mental HRQOL compared with those with neither characteristic.

### COMMENT

Because there is no consistent biological marker of IBS, to our knowledge, patients are identified based on their symptoms alone.<sup>1</sup> In this regard, the patients' perceived health not only defines their condition but also serves as the primary outcome to measure the impact of therapy. Therefore, an important goal of the physician-patient interaction in regard to IBS is to accurately and efficiently assess HRQOL by relying on clinical predictive factors. Behavioral models of health care suggest that addressing HRQOL allows clinicians to better understand patient needs, modify care-seeking patterns, and improve adherence to therapy.<sup>26</sup> Despite these conceptual underpinnings, data from clinical practice highlight a fundamental mismatch between patient and physician perception of health status in regard to IBS,<sup>6-11</sup> and this disconnect in the process of care may translate into suboptimal outcomes of care.

In light of this shortcoming, we have identified specific clinical predictors of mental and physical HRQOL that may facilitate efficient assessment and targeted treatment in patients with IBS. Our analysis reveals that much of the HRQOL variation in patients with IBS may be characterized by a parsimonious list of variables (Figures 1 and 2). Whereas physical HRQOL is associated with symptom severity, symptom periodicity, and pain, mental HRQOL is associated with abnormalities in sexuality, mood, and anxiety. Perhaps more important, both domains share a strong association with symptoms of chronic stress and vital exhaustion (eg, tire easily, low in energy, low sexual drive, and sleep difficulties), and neither is determined by the presence of specific gastrointestinal symptoms (eg, diarrhea, constipation, bloating, and dyspepsia), the degree of previous gastrointestinal evaluation (eg, previous flexible sigmoidoscopy or colonoscopy), or any demographic characteristics (eg, sex, age, or marital status).

The association of mental and physical HRQOL scores with symptoms of vital exhaustion is consistent with the emerging disease paradigm of IBS. Vital exhaus-



**Figure 1.** Impact of significant clinical predictors on physical health-related quality of life (HRQOL) in patients with irritable bowel syndrome, as measured by the percentage change in the 36-Item Short-Form Health Survey (SF-36) physical component score. For example, patients who think there is something seriously wrong with their body have a 4.4% lower physical HRQOL than those who do not.

tion refers to inappropriate fatigue, lack of energy, and ultimate demoralization in response to chronic physical or emotional stress.<sup>27</sup> Whereas healthy subjects maintain homeostasis in the face of acute stress through the precisely timed coordination of adaptive biological response systems, patients with IBS demonstrate an altered response to stress and inadequate physiological adaptation over time.<sup>28</sup> Chronic stress system activation in patients with IBS may manifest with exaggerated autonomic, neuroendocrine, or pain modulation responses that, in turn, lead to long-term altered bowel function and visceral perception. This evolving model of IBS has been corroborated by physiological data in animal and human studies.<sup>29-31</sup> Our analysis bolsters these laboratory findings by providing clinical evidence that symptoms of vital exhaustion are highly significant determinants of HRQOL in patients with IBS.

Therefore, our findings suggest that rather than focusing on physiological epiphenomena (stool frequency, stool characteristics, and subtype of IBS) and potentially misleading clinical factors (age and disease duration), phy-

**Table 4. Results of Bivariate Analyses for Independent Predictors and Mental Health-Related Quality of Life\***

Clinical Variable	SF-36 Score, Mean (SD)		SF-36 Score, /Δ in Mean/ P Value
	With Variable Present	With Variable Absent	
Feel hopeless†	31.8 (8.6)	45.5 (9.9)	13.7‡ <.001§
Feel tense†	33.8 (9.0)	46.6 (9.5)	12.8‡ <.001§
Feel nervous†	34.6 (9.6)	45.5 (10.1)	10.9‡ <.001§
Low sexual interest†	37.1 (10.8)	45.7 (9.8)	8.6‡ <.001§
Low energy†	38.8 (10.9)	46.6 (9.5)	7.8‡ <.001§
Feel something is seriously wrong with body†	37.4 (10.8)	45.2 (10.2)	7.8‡ <.001§
Tire easily†	41.9 (10.7)	48.0 (8.9)	6.1‡ <.001§
Sleep difficulties†	42.3 (10.7)	47.7 (9.6)	5.4‡ <.001§
Symptoms interfere with sexual function	41.4 (11.0)	46.0 (9.7)	4.6 <.001§
Age >50 y	46.2 (10.3)	42.7 (10.6)	3.5 <.001§
>3 Different physicians seen within the past year	41.5 (11.7)	44.9 (10.3)	3.4 <.001§
Income <30 000/y	45.8 (10.0)	42.5 (10.9)	3.3 <.001§
>5 Physician visits within the past year	42.2 (11.0)	45.4 (10.2)	3.2 <.001§
High symptom severity	42.9 (10.8)	45.9 (10.1)	3.0 <.001§
Married	42.7 (11.0)	45.7 (10.0)	3.0 <.001§
Education beyond high school	41.6 (10.9)	44.3 (10.6)	2.7 .02
Previous upper endoscopy	43.8 (11.2)	44.0 (10.6)	2.4 .95
Childhood symptoms	40.9 (11.5)	43.3 (10.2)	2.3 .20
Time with symptoms >2 y	42.1 (11.3)	44.4 (10.5)	2.3 .03
Flare duration for >24 h	42.9 (10.8)	45.1 (10.3)	2.2 .08
Female sex	43.4 (10.8)	45.3 (10.1)	1.9 .02
Previous sigmoidoscopy	43.3 (10.6)	45.2 (10.6)	1.9 .01
White ethnicity	44.3 (10.6)	42.7 (11.0)	1.6 .15
Diarrhea predominance (vs constipation)	43.4 (10.9)	44.9 (10.1)	1.5 .07
Interested in attending a support group	43.4 (10.6)	44.4 (10.7)	1.0 .18
Previous colonoscopy	44.4 (10.9)	43.9 (10.6)	0.5 .57
Predominant pain (vs discomfort)	44.0 (10.4)	44.1 (10.8)	0.1 .91
Concurrent reflux-type dyspepsia	44.0 (10.7)	44.0 (10.6)	0.0 .97

Abbreviation: See Table 2.

\*Variables are rank ordered according to their impact on SF-36 scores, as measured in column 4.

†These variables were selected for subsequent regression analysis based on achieving clinical and statistical significance. See the "Mental HRQOL Predictors" subsection of the "Results" section for additional information.

‡The difference is clinically significant, as defined by a difference in the absolute value of change in mean SF-36 scores of greater than 5 points.<sup>23</sup>§Statistically significant, as defined by  $P < .001$ .**Table 5. Final Adjusted Linear Regression Model to Predict the SF-36 Mental Component Summary Score\***

Variable	Regression Coefficient (SE)	t Value	P Value
Intercept constant	51.55 (0.74)	69.21	<.001
Feel tense	-7.01 (1.14)	-6.13	<.001
Feel nervous	-4.43 (1.19)	-3.72	<.001
Feel hopeless	-4.40 (1.40)	-3.13	.002
Sleep difficulties	-2.84 (0.79)	-3.59	<.001
Tire easily	-2.34 (0.83)	-2.82	.005
Low sexual interest	-2.12 (1.01)	-2.10	.04
Symptom interference with sexual function	-1.89 (0.74)	-2.56	.01
Low in energy	-1.88 (0.89)	-2.12	.03

Abbreviation: See Table 2.

\* $r^2 = 0.36$ .

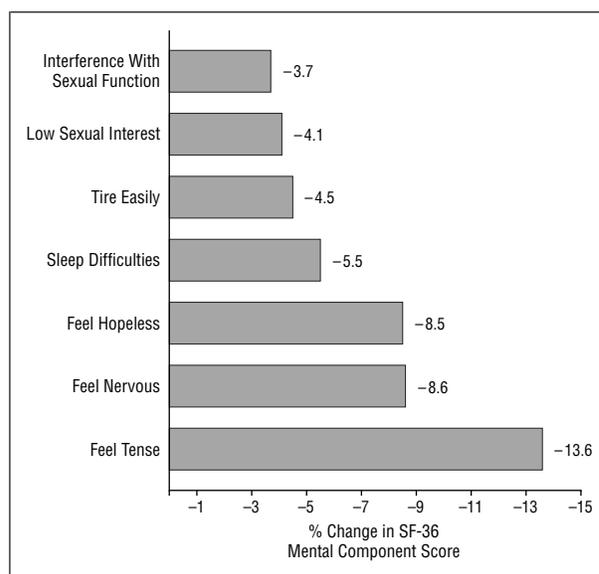
sicians might be better served to focus their brief patient encounter on gauging global symptom severity, addressing anxiety, and identifying and eliminating factors contributing to vital exhaustion in patients with IBS. This may occur through teaching coping mechanisms and relaxation skills, developing a greater sense of self-efficacy by encouraging control over IBS symptoms, promoting appropriate lifestyle modifications (diet, exercise, and quitting smoking), and allowing patients to recognize their own

limitations. In addition, a better understanding of the biological mechanisms underlying vital exhaustion may ultimately help identify targets for novel and more effective therapies. Through this process of targeting high-yield predictors of HRQOL in lieu of inaccurate clinical clues, physicians may be more capable of rapidly and accurately screening for diminished health status in patients with IBS and may, therefore, be in a position to initiate effective, timely, and self-empowering therapy.

Researchers<sup>19,20</sup> have demonstrated a strong correlation between psychological symptom scores (as measured by the Symptoms Checklist–90 items) and HRQOL in patients with IBS. The results of this analysis are consistent with the results of these studies. Whereas previous work<sup>19,20</sup> has evaluated the relationship between global psychological function and global HRQOL, this analysis identifies specific components of psychological function that seem highly predictive of HRQOL. Because primary care physicians face competing demands for their time that often preclude a full psychological evaluation,<sup>32</sup> our analysis acknowledges the practical need for a concise set of highly predictive symptoms. In particular, we found that much of the mental HRQOL variation in patients with IBS is determined by abnormalities in sexuality (“symptoms interfere with sexual function” and “low sexual interest”), mood (“feel hopeless”), and anxiety (“feel tense” and “feel nervous”). Therefore, a complete assessment in those with IBS requires not only an appreciation of the general relationship between psychophysiological factors and HRQOL but also an assessment of specific and highly predictive symptoms. These clinical predictors may ultimately provide a means for timely and accurate identification of psychological distress. This goal is particularly important in light of recent data<sup>33</sup> indicating that directed psychotherapy is effective and cost-effective in the management of IBS.

We found that patients who feel that there is something seriously wrong with their body had a significantly lower physical HRQOL than those who do not share this concern. In those with somatic pain conditions, pain-specific fear significantly impacts HRQOL and treatment response.<sup>34</sup> Irritable bowel syndrome symptom-specific fears may impact HRQOL by prompting avoidance of fear-producing contexts and activities (eg, restaurants, foods, and unfamiliar locations) and, in some cases, by reinforcing sick role behaviors.<sup>14,35,36</sup> From a neurobiological perspective, IBS symptom-specific fears may activate central stress mechanisms, including those underlying visceromotor responses and pain modulation. These responses are synergistic with responses to external psychosocial stressors in creating a sustained activation of the stress response and, in turn, promoting chronic gastrointestinal symptoms. Therefore, our results suggest that eliciting and addressing symptom-specific fears may improve the HRQOL assessment in those with IBS. When present, these fears may be partly offset through education regarding a realistic disease model of IBS, reassurance that IBS is not life threatening, and emphasis on coping skills to promote healthy behavior and decrease catastrophic thinking.<sup>35,36</sup> In addition, directed psychological treatments for pain-specific fear have been proposed and validated.<sup>37</sup>

Our study has several strengths. First, we recruited our study cohort from one of the largest functional-bowel disease specialty clinics in the United States. This referral setting allows for a cohort that is not only demographically and geographically diverse but also composed of patients from diverse practice settings. Moreover, there were more than 700 patients in the study. This large sample size extends the generalizability of our findings and reduces the probability of missing a true association (type II error). Second, each of our clinical predictors was selected based on



**Figure 2.** Impact of significant clinical predictors on mental health-related quality of life (HRQOL) in patients with irritable bowel syndrome (IBS), as measured by the percentage change in the 36-Item Short-Form Health Survey (SF-36) mental component score. For example, patients who report that their IBS symptoms interfere with their sexual function have a 3.7% lower mental HRQOL than those who do not.

an a priori disease-specific hypothesis derived from previous research, patient symptom assessments, and expert opinion, and this itemization occurred before conducting the analyses. In this regard, our analysis was hypothesis driven rather than hypothesis generating. Third, to compose a concise list of variables, we limited our analysis to the most highly predictive ( $P < .001$ ) determinants of HRQOL, and further required that each variable meet predefined levels of clinical significance (defined as an SF-36 difference of  $>5$  points) regardless of the degree of statistical significance. We believe that the generated list is, therefore, statistically significant and clinically relevant, and argue that its compact nature is preferable to an unwieldy catalogue of less significant variables.

Our study has potential shortcomings as well. In particular, the university-based referral setting may not be generalizable to all primary care settings. Although one third of the cohort was self-referred through advertising, two thirds were referred from primary care physicians, community gastroenterologists, and academic gastroenterologists. Therefore, many of our patients had already received first-line therapies for IBS; these therapies had failed. However, we hypothesize that even though severity and HRQOL impairment are likely to be higher in a tertiary referral setting, the determinants of HRQOL impairment in those with IBS should be similar, regardless of the precise health care setting. An additional limitation is that our analysis is a cross-sectional survey. Although this study design is capable of generating much information at one point in time, it is unable to track trends longitudinally. Therefore, our identified predictors of HRQOL are limited to observed associations (rather than causations), and are unable to predict HRQOL over time.

Although we selected a broad range of clinical predictors based on a priori hypotheses, our list may have omitted important variables. For example, we did not include

factors such as the number of comorbid conditions, current employment status, family dynamics, job satisfaction, or access to health care. In this regard, our analysis may commit a specification error by failing to include potentially important predictors. However, specification error is an inherent shortcoming of all multivariable analyses, and it can only be guarded against through careful selection of hypothesis-driven variables. Moreover, it is not only impossible to identify every potential predictor of HRQOL in those with IBS but also methodologically unsound to include an excess number of arbitrary variables. We limited our analysis to a discrete list of hypothesized variables and, therefore, attempted to minimize spurious findings and regression model overmatching.

In conclusion, much of the HRQOL variation in patients with IBS may be characterized by a concise list of clinical variables that can be related to specific underlying biopsychosocial mechanisms. Use of these determinants to help assess HRQOL may ultimately prove to be more accurate than reliance on potentially imperfect clinician gestalt. By effectively screening for and addressing poor HRQOL in those with IBS, clinicians may eventually improve their ability to target health services to those in greatest need, modify care-seeking patterns, reduce resource use, and improve adherence to prescribed therapy. However, firm conclusions regarding these hypothesized effects cannot be drawn until the clinical predictors are first prospectively and longitudinally validated in varying IBS populations, and then incorporated into a well-designed randomized trial comparing a multifactorial patient-centered intervention with usual care. Future studies should determine whether these predictive factors of HRQOL predict other clinically significant outcomes, including resource use, satisfaction with care, and specific treatment responses.

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