

Anxiety-related factors associated with symptom severity in irritable bowel syndrome

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Abstract

Background: Gastrointestinal symptom-specific anxiety and somatization have both been associated with higher symptom severity in patients with irritable bowel syndrome (IBS); however, this relationship has not been explored fully. Moreover, the performance of the visceral sensitivity index (VSI) for measuring gastrointestinal symptom-specific anxiety has not been examined in a UK population. We conducted a cross-sectional survey to examine these issues.

Methods: Gastrointestinal symptom-specific anxiety was measured using the VSI, and somatization was measured via the patient health questionnaire-12 (PHQ-12) in adults from the UK community with Rome IV-defined IBS. Exploratory factor analysis was performed on the VSI, prior to subsequent analyses, to establish its factor structure. Multiple regression analysis was used to determine the relationship between demographic features, different factors of the VSI, somatization, and IBS symptom severity.

Key Results: A total of 811 individuals with IBS provided complete data. Factor analysis of the VSI revealed a three-factor structure, accounting for 47% of the variance. The first of these VSI factors and the PHQ-12 were both strongly and independently associated with IBS symptom severity, for the group as a whole and for all four IBS subtypes. Most VSI items concerned with overt gastrointestinal symptom-specific anxiety loaded onto the other two VSI factors that were not associated with symptom severity.

Conclusions and Inferences: The factor structure of the VSI requires further investigation. Our findings cast doubt on the central role of gastrointestinal symptom-specific anxiety as a driver for symptom severity in IBS. Awareness of both gastrointestinal and extra-intestinal symptoms, however, is strongly associated with symptom severity.

Abbreviations: CI, confidence interval; HADS, hospital anxiety and depression scale; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, IBS with mixed stool pattern; IBS-SSS, irritable bowel syndrome severity scoring system; IBS-U, IBS unclassified; OR, odds ratio; PHQ-12, patient health questionnaire-12; VSI, visceral sensitivity index.

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KEYWORDS

anxiety, irritable bowel syndrome, psychological health, Rome IV criteria, somatization, symptoms

1 | INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder, characterized by abdominal pain, in association with defecation or a change in bowel habit.¹ The prevalence in the community has previously been estimated to be 10%,² but in a recent study applying the Rome IV criteria in a UK and North American population, the prevalence was lower, at around 5%.³ The condition is commoner in women and younger individuals.^{2,4} IBS accounts for a considerable proportion of referrals to gastroenterology across both secondary and tertiary care settings,⁵ and direct costs in the USA have been estimated at almost \$1 billion, with another \$50 million in indirect costs.⁶

Although there are effective therapies available to treat some of the symptoms of IBS,⁷ there is no "cure" for sufferers. The chronicity of symptoms, which can fluctuate over time,⁸ may therefore impact on work and social functioning,⁹ and eating habits.¹⁰ This in turn may have deleterious consequences for both quality of life and mood.⁹⁻¹¹ The quality of life of people with IBS is impaired to a similar degree to individuals with organic bowel disorders, such as Crohn's disease,^{12,13} and co-existent mood disorders are common.¹⁴ This may be more pronounced for people with IBS with diarrhea (IBS-D) or IBS with mixed stool pattern (IBS-M).¹⁵ These patients often report a fear of incontinence due to loose stools and urgency¹⁶ and can therefore find working and socializing extremely challenging.¹⁷

General anxiety is common in IBS and is associated with increased severity of gastrointestinal symptoms.¹⁸ This may reflect the fact that IBS symptoms are worrisome for some patients, as with any other chronic disease, and that this anxiety is therefore secondary to the physical condition.¹⁹ Alternatively, anxiety may influence pain perception by interfering with central systems involved in processing and modulating noxious visceral afferent signals.²⁰

In recent years, there has been interest in a specific form of anxiety, termed gastrointestinal symptom-specific anxiety, which is the fear of the potential adverse consequences of gastrointestinal symptoms, as opposed to general anxiety, which involves a sense of unease and fear about a wide range of situations and issues (which may include IBS). Gastrointestinal symptom-specific anxiety has been measured with a validated questionnaire, the visceral sensitivity index (VSI).²¹ Support for gastrointestinal symptom-specific anxiety as a genuine concept in patients with IBS comes from the fact that its presence seems to predict a diagnosis of IBS with good accuracy and that it appears to mediate the observed relationship between measures of general anxiety and the severity of gastrointestinal symptoms.²² The VSI was developed and validated on a relatively small sample of subjects with IBS in the USA,²¹ recruited by advertisement, and a further validation study was conducted in a group of Japanese university students,²³ but its properties have not been confirmed in a UK population.

Key Points

- Gastrointestinal symptom-specific anxiety, measured using the visceral sensitivity index (VSI), and somatization have both been associated with higher symptom severity in patients with irritable bowel syndrome (IBS).
- This study in a large UK population of patients with IBS has revealed a three-factor structure of the VSI. Most VSI items concerned with overt gastrointestinal symptom-specific anxiety loaded onto the two VSI factors that were not associated with IBS symptom severity.
- Our findings cast doubt on the central role of gastrointestinal symptom-specific anxiety as a driver for symptom severity in IBS. However, awareness of both gastrointestinal and extra-intestinal symptoms is strongly associated with IBS symptom severity.

It is well recognized that patients with IBS often complain of other extra-intestinal symptoms,²⁴ the presence of which may be linked to mechanisms of central sensitization.²⁵ In IBS, somatization has been shown to predict both gastrointestinal symptom severity and patient consulting behavior,²⁶ and it is associated with most visceral sensitivity parameters.²⁷ In one study, general anxiety had an indirect effect on IBS symptom severity, via somatization and catastrophizing.²⁸ In the VSI validation study, the effects of general anxiety on IBS symptom severity were mediated via gastrointestinal symptom-specific anxiety.²¹ To our knowledge, the relationship between general anxiety, gastrointestinal symptom-specific anxiety, and somatization has not been fully explored, although there have been several relatively small cross-sectional studies that have examined the relationship between anxiety and gastrointestinal symptomatology.²⁹⁻³² In the present study, we first aimed to establish the factor structure of the VSI in a large UK cohort of individuals who meet the current gold standard for diagnosing IBS, the Rome IV criteria,¹ and then examined the relationship between IBS symptom severity, the VSI (and its different factors), general anxiety, and somatization.

2 | MATERIALS AND METHODS

2.1 | Participants and setting

The study was conducted among individuals who self-identified as having IBS and who were registered with three organizations in the

UK. The methodology has been described elsewhere.³³ Briefly, we approached individuals registered with the IBS network, the registered charity for people living with the condition; TalkHealth, an online social health community providing information about various medical conditions; and ContactMe-IBS, a dedicated register allowing individuals with IBS not receiving specialist care currently to participate in research. Individuals registered with these three organizations were provided with the opportunity to access a questionnaire electronically, between December 2017 and December 2018. There were no exclusion criteria, other than an inability to understand written English. The University of Leeds research ethics committee approved the study in November 2017.

2.2 | Data collection and synthesis

2.2.1 | Demographic and gastrointestinal symptom data

Participants provided basic demographic data, including age, gender, ethnicity, marital status, educational level, and lifestyle (tobacco and alcohol use). We also asked respondents to state whether they had seen a primary care physician or a gastroenterologist with their IBS symptoms. Lower gastrointestinal symptom data were collected using the Rome IV questionnaire.³⁴ The presence or absence of Rome IV-defined IBS among all individuals was assigned according to the scoring algorithms proposed for use with the Rome IV questionnaire,¹ which are detailed in Table S1. IBS subtypes (IBS with constipation [IBS-C], IBS-D, IBS-M, and IBS unclassified [IBS-U]) were assigned with the same questionnaire.

We assessed the severity of IBS symptoms using the IBS severity scoring system (IBS-SSS).³⁵ This seven-item self-administered questionnaire measures presence, severity, and frequency of abdominal pain, presence and severity of abdominal distension, satisfaction with bowel habit, and degree to which IBS symptoms are affecting, or interfering with, the person's life in general. The maximum score is 500 points: <75 indicates remission of symptoms; 75-174 mild symptoms; 175-299 moderate symptoms; and 300-500 severe symptoms.

2.2.2 | Assessment of mood and somatization

General anxiety and depression scores were collected using the hospital anxiety and depression scale (HADS).³⁶ The total HADS score ranges from 0 to 21 for either anxiety or depression. Severity for each was categorized into normal (total HADS-depression or HADS-anxiety score 0-7), borderline normal (8-10), or above threshold (≥ 11).³⁶ Somatization data were collected using the patient health questionnaire-12 (PHQ-12),²⁶ derived from the PHQ-15,³⁷ which in turn is derived from the validated full PHQ.³⁸ The PHQ-12 excludes three items from the PHQ-15 that refer to gastrointestinal symptoms. The total PHQ-12 score ranges from 0 to 24 and only includes extra-intestinal symptoms.

2.2.3 | Assessment of gastrointestinal symptom-specific anxiety

We used the VSI,²¹ which is a 15-item instrument to measure gastrointestinal symptom-specific anxiety. Replies to each of the questions are provided on a six-point scale from "strongly disagree" (scored as 0) to "strongly agree" (scored as 5). As mentioned previously, its developers reported a single factor structure in 100 patients with IBS who were recruited via advertising,²¹ which was confirmed by a Japanese study that used the measure on 349 university students.²³ As the VSI's factor structure has not been confirmed using a UK population, we undertook a preliminary factor analysis of the measure prior to any further analyses.

2.3 | Statistical analysis

Statistical analysis was performed using SPSS (version 26) and R (version 3.6.3). We used Pearson's correlation coefficients to determine the strength and direction of simple relationships between total IBS-SSS score and age, total HADS-anxiety score, total HADS-depression score, total PHQ-12 score, and total VSI score. We used exploratory factor analysis to investigate the potential multidimensionality of the VSI construct in our study dataset. We measured adequacy of exploratory factor analysis using the Kaiser-Meyer-Olkin test, which should be >0.60 .³⁹ We used parallel analysis, which is the most robust technique, to determine the number of retained extracted factors.⁴⁰ Since it is important to ensure distinct factor loading to interpret and name the factors, we applied factor rotation using oblique techniques to maximize factor loading on each factor. We deleted variables with loadings <0.30 from the corresponding factor.³⁹ We used Cronbach's alpha, the measure of internal consistency (or coefficient of reliability), to see how closely related the items were as a group for the VSI. Cronbach's alpha of 0.70 is a reasonable threshold for the scale to be reliable.⁴¹

We also used partial correlations to explore relationships between the key variables that may affect the performance of later regression analyses. We then carried out a series of multiple linear regression analyses to determine the relationship between gastrointestinal symptom-specific anxiety according to the VSI, general anxiety according to the HADS, somatization via the PHQ-12, and gastrointestinal symptom severity measured using the IBS-SSS. In every analysis, the IBS-SSS score was used as the dependent variable, and sex, age, marital status, White Caucasian ethnicity, and a university or postgraduate level of education were entered as co-founders in all analyses. As we found three different factors for the VSI, we entered each of the factors as a separate independent variable in the first series of analyses, together with HADS-anxiety score, PHQ-12 score, and relevant sociodemographic characteristics. We carried out the analyses on the group as whole and then for the four different IBS subtypes. In the second set of analyses, we used the total VSI score, instead of the three factors, and repeated the analyses as described above. We estimated both the unstandardized

regression coefficient (B), showing the effect of predictors, and the standardized coefficient (β), showing the relative magnitude of predictors. We checked model assumptions of residuals normality and homogeneity. We checked a model specification error for including irrelevant variables in the model or omitting relevant variables from the model.

We used path analysis to examine a potential mediating effect for the VSI on the relationship between HADS-anxiety score and IBS-SSS score, as has been reported previously.²¹ Similarly, we also examined a potential mediating effect for the PHQ-12 score on HADS-anxiety score and IBS-SSS score.

3 | RESULTS

Demographic data for the cohort are summarized in Table 1. The mean age of the 811 included individuals was 47.4 years, 697 (85.9%) were female, and 763 (94.3%) were White Caucasian.

Overall, 142 (17.5%) participants had IBS-C, 311 (38.3%) IBS-D, 331 (40.8%) IBS-M, and 26 (3.2%) IBS-U. There were 778 (95.9%) people who had seen their primary care physician with their IBS symptoms, and 492 (60.7%) who had seen a gastroenterologist. The mean IBS-SSS was 292, and 379 (46.8%) of the individuals had severe symptoms. The mean HADS-anxiety score was 11.0, and 442 (54.5%) had above threshold HADS-anxiety scores (≥ 11). The mean HADS-depression score was 7.7, and 186 (22.9%) had above threshold HADS-depression scores (≥ 11). The mean PHQ-12 score was 10.3, and the mean number of symptom items endorsed on the PHQ-12 was 7.1. Finally, the mean VSI score was 50.7; 369 (45.5%) participants agreed strongly with five or more of the 15 items on the VSI.

3.1 | Factor analysis of the VSI

The Kaiser-Meyer-Olkin measure of sampling adequacy of exploratory factor analysis was 0.94, above the recommended value of

TABLE 1 Demographics and psychosocial characteristics for all participants and for individual IBS subtypes

	Participants with Rome IV IBS (n = 811)	IBS-C (n = 142)	IBS-D (n = 311)	IBS-M (n = 331)	IBS-U (n = 26)
Mean age (SD)	47.4 (15.2)	46.1 (14.4)	47.9 (14.7)	46.6 (15.7)	57.5 (15.2)
Mean body mass index (SD)	28.4 (8.3)	25.9 (5.7)	29.6 (8.4)	28.2 (8.9)	27.8 (5.9)
Female gender (%)	697 (85.9)	126 (88.7)	258 (83.0)	291 (87.9)	21 (80.8)
Tobacco user (%)	79 (9.7)	19 (13.4)	29 (9.3)	31 (9.4)	0 (0)
Alcohol user (%)	442 (54.5)	72 (50.7)	184 (59.2)	175 (52.9)	11 (42.3)
Married or co-habiting (%)	526 (64.9)	96 (67.6)	199 (64.0)	215 (65.0)	15 (57.7)
University or postgraduate level of education (%)	315 (39.0)	56 (39.4)	133 (42.8)	117 (35.6)	9 (34.6)
White Caucasian ethnicity (%)	763 (94.3)	138 (97.2)	297 (95.5)	302 (91.5)	26 (100)
Seen a primary care physician with IBS (%)	778 (95.9)	133 (93.7)	300 (96.5)	318 (96.4)	26 (100)
Seen a gastroenterologist with IBS (%)	492 (60.7)	84 (59.2)	193 (62.1)	193 (58.5)	21 (80.8)
IBS-SSS symptom severity (%)					
Remission	8 (1.0)	1 (0.7)	3 (1.0)	2 (0.6)	2 (7.7)
Mild	90 (11.1)	9 (6.3)	38 (12.2)	40 (12.1)	3 (11.5)
Moderate	333 (41.1)	59 (41.5)	131 (42.1)	130 (39.4)	12 (46.2)
Severe	379 (46.8)	73 (51.4)	139 (44.7)	158 (47.9)	9 (34.6)
Mean IBS-SSS score (SD)	292.0 (95.8)	301.4 (86.9)	287.6 (96.3)	292.9 (96.9)	282.8 (122.8)
HADS-A categories (%)					
Normal	202 (24.9)	32 (22.5)	89 (28.6)	73 (22.1)	8 (30.8)
Borderline	167 (20.6)	33 (23.2)	60 (19.3)	65 (19.6)	9 (34.6)
Abnormal	442 (54.5)	77 (54.2)	162 (52.1)	193 (58.3)	9 (34.6)
Mean HADS-A score (SD)	11.0 (4.7)	11.3 (5.0)	10.6 (4.7)	11.3 (4.6)	9.8 (4.9)
HADS-D categories (%)					
Normal	434 (53.5)	80 (56.3)	177 (56.9)	159 (48.0)	18 (69.2)
Borderline	191 (23.6)	23 (16.2)	64 (20.6)	101 (30.5)	2 (7.7)
Abnormal	186 (22.9)	39 (27.5)	70 (22.5)	71 (21.5)	6 (23.1)
Mean HADS-D score (SD)	7.7 (4.5)	7.8 (4.8)	7.4 (4.7)	7.9 (4.1)	6.2 (4.5)
Mean PHQ-12 score (SD)	10.3 (4.3)	10.7 (4.6)	9.5 (4.0)	11.0 (4.4)	9.2 (4.9)

TABLE 2 Items of the VSI according to a three-factor solution, using oblique rotation techniques, with corresponding factor loadings, Kaiser-Meyer-Olkin measure and Cronbach's alpha

Factors and items	Loadings for Factor 1	Loadings for Factor 2	Loadings for Factor 3
Factor 1: worry and/or awareness of abdominal discomfort			
Item 1: I worry that whenever I eat during the day, bloating and	0.55		
Item 3: I often worry about problems in my belly distension in my belly will get worse	0.66		
Item 4: I have a difficult time enjoying myself because I cannot get my mind off of discomfort in my belly	0.65		
Item 7: No matter what I eat, I will probably feel uncomfortable	0.73		
Item 10: I am constantly aware of the feelings I have in my belly	0.68		
Factor 2: fear of serious illness			
Item 11: I often feel discomfort in my belly could be a sign of serious illness		0.69	
Item 12: As soon as I awake, I worry that I will have discomfort in my belly during the day		0.60	
Item 13: When I feel discomfort in my belly, it frightens me		0.91	
Item 15: I constantly think about what is happening inside my belly		0.62	
Factor 3: Fear of new experiences			
Item 2: I get anxious when I go to a new restaurant			0.88
Item 6: Because of fear of developing abdominal discomfort, I seldom try new foods			0.48
Item 9: When I enter a place I haven't been before, one of the first things I do is look for a bathroom			0.39
Proportion variation	21.1%	16.5%	10.0%
Kaiser-Meyer-Olkin measure	0.94		
Cronbach's alpha	0.86	0.89	0.74
	0.92 (overall)		

0.60. Using parallel analysis, three factors were found to account for 47% of the variance. One main factor (VSI factor one) accounted for 21.1% of the variance, with the second factor (VSI factor two) accounting for 16.5%, and the third factor (VSI factor three) 10.0%. Table 2 shows the items and loadings for each of the factors. VSI factor one comprised items 1, 3, 4, 7, and 10 of the VSI, with factor loadings from 0.55 to 0.73, and appeared to be best described as "awareness of abdominal discomfort". VSI factor two consisted of items 11, 12, 13, and 15 with loadings from 0.60 to 0.91 and included factors that predominantly related to worry and fear that gastrointestinal symptoms may have a serious underlying cause. VSI factor three consisted of items 2, 6, and 9 with loadings between 0.39 and 0.88, which were all concerned with worries or fears of how new experiences may impact on gastrointestinal symptoms. Items 5, 8, and 14 were problematic, since they showed either indistinct or low

factor loading (<0.3), and hence, they were not included in any of the three factors. The reliability of the overall VSI and the three extracted factors was above 0.70.

3.2 | Results of the regression analyses

In the univariate analyses, using simple correlation (r), the following variables were associated with total IBS-SSS score: total HADS-anxiety score ($r = .262$, P -value <.001); total HADS-depression score ($r = .335$, P -value <.0001); PHQ-12 score ($r = .408$, P -value <.001); total VSI score ($r = .364$, P -value <.001); and age ($r = -.130$, P -value <.001). Partial correlations involving the main variables and IBS-SSS showed no major differences to the full correlation matrix, with the exception of the effects of total HADS-depression score on total

TABLE 3 Regression models for all participants with IBS, and according to subtype, with IBS-SSS score as the dependent variable and the three-factor VSI included as an independent variable^a

	B	β	t	P-value	95% CI for B
All participants meeting Rome IV criteria for IBS (n = 811)					
VSI factor one: worry and/or awareness of abdominal discomfort	6.03	0.42	8.17	<.001	4.58 to 7.48
VSI factor two: fear of serious illness	-0.41	-0.025	-0.54	.586	-1.87 to 1.06
VSI factor three: fear of new experiences	-2.08	-0.09	-2.21	.27	-3.93 to -0.23
PHQ-12	6.79	0.31	8.87	<.001	5.29 to 8.30
HADS-anxiety	-4.55	-0.04	-1.15	.253	-12.34 to 3.25
Constant	109.31		4.15	<.001	57.66 to 161
$R^2 = 28.5\%$ R^2 -adjusted% = 27.6% F (ANOVA) = 31.63 P-value <.001					
Participants with IBS-C (n = 142)					
VSI factor one: worry and/or awareness of abdominal discomfort	4.89	0.37	3.05	.003	1.72 to 8.07
VSI factor two: fear of serious illness	-0.31	-0.02	-0.18	.86	-3.66 to 3.04
VSI factor three: fear of new experiences	-1.88	-0.095	-0.96	.34	-5.78 to 2.01
PHQ-12	7.90	0.42	4.15	<.001	4.39 to 11.41
HADS-anxiety	-11.33	-0.11	-1.19	.24	-30.23 to 7.57
Constant	114.59		1.75	.08	-14.73 to 244
$R^2 = 28.1\%$ R^2 -adjusted% = 22.6% F (ANOVA) = 5.11 P-value <.001					
Participants with IBS-D (n = 311)					
VSI factor one: worry and/or awareness of abdominal discomfort	7.24	0.49	5.98	<.001	4.86 to 9.63
VSI factor two: fear of serious illness	-0.20	-0.01	-0.18	.86	-2.43 to 2.03
VSI factor three: fear of new experiences	-0.87	-0.037	-0.575	.565	-3.86 to 2.12
PHQ-12	5.75	0.24	4.52	<.001	3.25 to 8.25
HADS-anxiety	-1.70	-0.015	-0.29	.77	-13.21 to 9.82
Constant	88.71		1.75	.08	-14.73 to 244
$R^2 = 37.8\%$ R^2 -adjusted% = 35.7% F (ANOVA) = 18.25 P-value <.001					
Participants with IBS-M (n = 331)					
VSI factor one: worry and/or awareness of abdominal discomfort	5.09	0.35	4.27	<.001	2.74 to 7.44
VSI factor two: fear of serious illness	-0.96	-0.06	-0.76	.45	-3.46 to 1.53
VSI factor three: fear of new experiences	-2.50	-0.10	-1.50	.13	-5.77 to 0.78
PHQ-12	6.73	0.30	5.40	<.001	4.28 to 9.19
HADS-anxiety	-1.20	-0.01	-0.18	.86	-14.45 to 12.05
Constant	108.79		2.35	.02	17.79 to 200
$R^2 = 22.4\%$ R^2 -adjusted% = 20.0% F (ANOVA) = 9.11 P-value <.001					
Participants with IBS-U (n = 26)					
VSI factor one: worry and/or awareness of abdominal discomfort	19.29	0.93	3.56	.003	7.79 to 30.80
VSI factor two: fear of serious illness	-5.05	-0.28	-1.12	.28	-14.63 to 4.54
VSI factor three: fear of new experiences	-7.59	-0.22	-1.43	.17	-18.89 to 3.70
PHQ-12	13.88	0.55	3.99	.001	6.51 to 21.25
HADS-anxiety	-62.44	-0.42	-2.03	.06	-127.5 to 2.63
Constant	-11.99		-0.09	.93	-290 to 266
$R^2 = 79.2\%$ R^2 -adjusted% = 67.5% F (ANOVA) = 6.79 P-value <.001					

^aControl variables are: sex, age, marital status, White Caucasian ethnicity, and university or postgraduate education.

HADS-anxiety score. The presence of HADS-depression reduced the correlation between total HADS-anxiety and total IBS-SSS ($r = .067$, P -value = .57), whereas HADS-anxiety appeared to have little effect on the relationship between total HADS-depression and total IBS-SSS ($r = .226$, P -value <.001). Checking model specification error for omitting variables, total HADS-depression was irrelevant to the model. For this reason, in the main regression analyses, this was excluded.

The results of the main regression analyses, for all individuals and by IBS subtype, are shown in Table 3. For each model, the three factors of the VSI were entered separately, plus HADS-anxiety score and the PHQ-12 score. Sociodemographic characteristics (gender, age, ethnicity, and educational level) were included as cofounders. VSI factor one and PHQ-12 were the only variables that had an

independent significant association with IBS-SSS, and this was true for the group as a whole and for all four IBS subtypes. Neither VSI factor two nor VSI factor three showed any significant association with IBS-SSS. The results for the 26 individuals in the IBS-U subtype were less robust than for the other three, as the 95% confidence intervals for the B coefficients were very wide, which probably relates to the smaller number of participants, in comparison with the other three subtypes.

All the above analyses were then re-run for the group as a whole and for all four IBS subtypes, with the total VSI score included, instead of the three-factor version (Table 4). The total VSI score and the PHQ-12 score were independently associated with the IBS-SSS score for the group as a whole and each of the individual IBS subtypes. The variance explained using VSI factor one

TABLE 4 Regression models for all participants with IBS, and according to subtype, with IBS-SSS score as the dependent variable and total VSI included as an independent variable^a

	<i>B</i>	β	<i>t</i>	<i>P</i> -value	95% CI for <i>B</i>
All participants meeting Rome IV criteria for IBS (n = 811)					
VSI	1.88	0.29	8.16	<.001	1.43 to 2.33
HADS-anxiety	-0.456	-0.02	-0.60	.55	-1.96 to 1.04
PHQ-12	6.84	0.31	8.57	<.001	5.27 to 8.40
Constant	133.330		5.01	<.001	81.09 to 186
$R^2 = 25.2\%$ R^2 -adjusted% = 24.5% F (ANOVA) = 33.65 P -value <.001					
Participants with IBS-C (n = 142)					
VSI	1.76	0.30	3.13	.002	0.65 to 2.89
HADS-anxiety	-2.72	-0.16	-1.60	.11	-6.09 to 0.65
PHQ-12	7.39	0.39	4.15	<.001	3.87 to 10.91
Constant	149.64		2.25	.03	18.15 to 281
$R^2 = 25.5\%$ R^2 -adjusted% = 21.1% F (ANOVA) = 5.70 P -value <.001					
Participants with IBS-D (n = 311)					
VSI	2.79	0.425	7.74	<.001	2.08 to 3.50
HADS-anxiety	-0.80	-0.039	-0.69	.49	-3.09 to 1.48
PHQ-12	6.43	0.26	4.90	<.001	3.85 to 9.01
Constant	117.17		2.93	.004	38.55 to 196
$R^2 = 34.7\%$ R^2 -adjusted% = 33.0% F (ANOVA) = 20.10 P -value <.001					
Participants with IBS-M (n = 331)					
VSI	1.13	0.17	3.06	.002	0.41 to 1.86
HADS-anxiety	1.03	0.049	0.81	.42	-1.47 to 3.53
PHQ-12	6.44	0.29	4.97	<.001	3.89 to 8.90
Constant	122.88		2.64	.009	31.33 to 214
$R^2 = 20.0\%$ R^2 -adjusted% = 18.0% F (ANOVA) = 9.92 P -value <.001					
Participants with IBS-U (n = 26)					
VSI	3.79	0.48	2.47	.024	0.57 to 7.02
PHQ-12	-2.20	-0.09	-0.37	.72	-14.76 to 10.36
HADS-anxiety	14.68	0.58	3.41	.003	5.63 to 23.73
Constant	184.84		1.47	.16	-78.64 to 448
$R^2 = 65.5\%$ R^2 -adjusted% = 52.1% F (ANOVA) = 4.88 P -value = .003					

^aControl variables are: sex, age, marital status, White Caucasian ethnicity, and university or postgraduate education.

was slightly better than using total VSI score for the group as a whole (27.6% vs 24.5%) and the individual subtypes (IBS-C 22.6% vs 21.1%; IBS-D 35.7% vs 33.0%; IBS-M 20.0% vs 18.0%). General anxiety, as measured by the HADS-anxiety score, was not significant in any of the models. The results of path analysis indicated that there was no mediating effect for total VSI, VSI factor one, or PHQ-12 on the HADS-anxiety score and the IBS-SSS score.

4 | DISCUSSION

IBS is a chronic disease, which is now viewed as a disorder of gut-brain interaction,⁴² and patients often exhibit psychological comorbidity,^{14,18,43,44} although whether this is a cause or consequence of gastrointestinal symptoms is unclear.^{45,46} It is reasonable to expect that patients with the highest symptom burden will have the highest levels of psychological problems. However, there is increasing evidence that mood problems can drive IBS symptoms,^{45,46} and therapies designed to improve psychological health, such as cognitive behavioral therapy,^{7,47} or gut-directed hypnotherapy,⁴⁸ can lead to symptom improvement for some patients. It is therefore important to understand these interactions and to better elucidate the relationship between anxiety, both general and gastrointestinal symptom-specific, and symptoms of IBS.

We have done this in a large cohort of individuals with IBS, defined according to the Rome IV criteria. Almost 50% of participants endorsed five or more of the 15 items on the VSI, 54.5% had above threshold HADS-anxiety scores, and more than one in five had above threshold HADS-depression scores, with mean HADS-anxiety and depression scores of 11.0 and 7.7, respectively. The mean IBS-SSS score was 292, and almost 50% of participants had a score of ≥ 300 , indicating severe symptoms. These findings are consistent with a clinical population of IBS sufferers.

Our factor analysis of the VSI found a three-factor solution, rather than a single factor structure. VSI factor one included three items concerned with discomfort ("I am constantly aware of the feelings I have in my belly," "No matter what I eat, I will probably feel uncomfortable," and "I have a difficult time enjoying myself because I cannot get my mind off of discomfort in my belly") and two items concerned with worry about gastrointestinal symptoms ("I worry that whenever I eat during the day, bloating and distension in my belly will get worse" and "I often worry about problems in my belly"). The second and third factors included items much more overtly related to anxiety and fear. VSI factor two consisted of items concerned with worry and fear about the potential serious consequences of gastrointestinal symptoms, and VSI factor three consisted of three items concerned with worries about coping with gastrointestinal symptoms in new environments. The three items which were not included in any of the three factors (items 5, 8, and 14) were concerned with worry, fear, and stress ("I often fear that I won't be able to have a normal bowel movement," "As soon as I feel abdominal discomfort I begin to worry and feel anxious," and "In stressful situations my belly bothers me a lot").

The further analyses we conducted suggest that only VSI factor one was independently associated with IBS symptom severity. As with other investigators, we found that general anxiety was not an independent predictor of IBS symptom severity.²¹ We did not find any evidence that either total VSI or VSI factor one mediated the relationship between HADS-anxiety scores and total IBS-SSS, which is in contrast to previous investigators.²¹ Our findings question the strength of the association between so-called gastrointestinal-specific anxiety and IBS symptom severity, as the items most overtly associated with fear and anxiety about gastrointestinal symptoms in the total VSI were not included in VSI factor one, which was the only factor that was significantly associated with IBS symptom severity in the regression analyses. It appears that neither general anxiety nor most of the items on the VSI are independently associated with IBS symptom severity. An awareness of gastrointestinal symptoms and feelings of discomfort from gastrointestinal symptoms, rather than overt fear and anxiety, appear to be more likely to be associated with IBS symptom severity and may therefore reflect a tendency to focus on more severe physical symptoms, rather than a fear of their consequences or recurrence.

The PHQ-12 was independently associated with IBS symptom severity in all the analyses, whether total VSI score or the three-factor VSI was used, and for all the IBS subtypes. This instrument records the tendency to report extra-intestinal symptoms and is used as a measure of somatization. However, there is increasing evidence that IBS is associated with atopic and immune disorders,^{49,50} so in some cases, this may represent overlap between IBS and these other conditions, rather than somatoform-behavior per se. Although other investigators have found that depressed and anxious patients with IBS are more likely than non-depressed or anxious patients to have higher IBS severity scores, higher PHQ-12 scores, and higher total VSI scores,⁵¹ the central driver of IBS symptom severity appears to be the tendency to report or experience both gastrointestinal and extra-intestinal symptoms. Both general anxiety, measured by HADS, and gastrointestinal symptom-specific anxiety, as measured by the total VSI score, were highly prevalent in our large sample of people with IBS. Although general anxiety and anxiety and/or fear about IBS may not be independently associated with the severity of gastrointestinal symptoms, evidence suggests that they still play an important role in the impact IBS has on coping²⁹ and quality of life.^{30,31}

As our study is cross-sectional in nature, we are unable to comment on the direction of the associations we have observed. Other studies of identical design have demonstrated similar associations between gastrointestinal symptom-specific anxiety and IBS symptom severity,^{22,29,31} but these did not examine the factor structure of the VSI prior to their analysis. In the only longitudinal study conducted, to date, which recruited 276 patients with Rome II-defined IBS, gastrointestinal symptom-specific anxiety predicted future deterioration in both symptom severity and quality of life, whereas mood did not appear to impact on either symptoms or quality of life.⁵² An alternative hypothesis is that these effects are bidirectional, as has been observed in studies examining the relationship

between psychological health and symptoms in patients with both functional and organic gastrointestinal disorders.^{45,46,53}

Strengths of this study include the sample size and representativeness of the population. A large number of individuals were recruited, all of whom were in the community and met the Rome IV criteria for IBS. Because some individuals had consulted a primary care physician, some a gastroenterologist, and some had never consulted a physician, the participants are likely to be generalizable to many individuals living with IBS in the UK. Due to our use of an online questionnaire, data collection was near complete for many of the variables of interest, even in our logistic regression models. We used parallel analysis in our factor analysis of the VSI to determine number of extracted factors. We also removed three gastrointestinal symptoms from the PHQ-15,³⁷ converting it to the PHQ-12,²⁶ to ensure it was not measuring gastrointestinal symptomatology. Finally, we used validated questionnaires to collect gastrointestinal symptoms, mood, and gastrointestinal symptom-specific anxiety and utilized the Rome IV criteria to define IBS, the current gold standard.¹

Weaknesses of the study include the fact that we did not confirm the diagnosis of IBS in all individuals in this study by looking at their medical records. Instead, we relied on the fact that people who met the Rome IV criteria were likely to have IBS as a cause of their lower gastrointestinal symptoms. This may mean that we included some people with organic diseases such as celiac disease or inflammatory bowel disease,⁵⁴⁻⁵⁶ rather than true IBS, although as the prevalence of these conditions in the community is much lower than IBS, this is unlikely to have had any major impact on our results. Although this is a limitation, our methodology is similar to that used in numerous population-based studies that have estimated the prevalence of IBS in community subjects,² and even studies examining yield of colonoscopy in patients meeting criteria for IBS in secondary care report a low prevalence of organic disease.^{57,58} In addition, given that the respondents in this survey believed they had IBS, were registered with three organizations that provide services to people living with IBS, and as a high proportion had seen either a primary care physician or a gastroenterologist with their IBS, we feel it is likely that the vast majority of respondents genuinely had IBS. As the questionnaire was completed online, we are unable to assess how many individuals chose not to complete the questionnaire or whether those who responded are broadly representative of all the people with IBS registered with these three organizations. It is possible that individuals choosing to register with these organizations might have more troublesome IBS symptoms than average, but alternatively their involvement may indicate that they are more engaged with their illness, and therefore actively seeking treatment. Indeed, only patients who are bothered by their symptoms are likely to seek the advice of a doctor, and these are the most relevant patients to understand for clinical practice. Moreover, these patients are drawn from a community setting, rather than being identified using a hospital-based survey and, consequently, are likely to be more representative of the spectrum of IBS patients as a whole. Indeed, 40% of patients had not seen a gastroenterologist. Due to the setting in which this study was conducted, and the fact that participants had to have internet

access, the individuals taking part may not be generalizable to patients consulting with a gastroenterologist in secondary or tertiary care. We feel this is unlikely, as a large proportion had previously consulted in this setting. Finally, as the vast majority of respondents were White Caucasians, the results cannot be extrapolated to individuals with IBS of other ethnicities.

Our findings suggest that further work is required to establish the factor structure of the VSI. We recommend that future investigators who use this instrument assess its factor structure prior to any further analysis, at least until a consistent structure can be established. The direction of the associations we have found in this study between the PHQ-12 score, VSI factor one, and IBS-SSS score can only be addressed by future longitudinal studies. Additionally, greater attention should be played to extra-intestinal symptoms in IBS, particularly in relation to overall treatment outcomes. It is possible that stratifying patients using questionnaire tools such as the PHQ-12 or the VSI, in addition to gastrointestinal symptoms, might be useful in tailoring treatment, but this concept requires further investigation. Our findings question the previously reported key role of gastrointestinal-specific anxiety as a driver of symptom severity in IBS. The number of extra-intestinal symptoms and an awareness of, or focus on, abdominal symptoms were most strongly associated with IBS symptom severity in the present study. We suggest that interventions designed to treat gastrointestinal symptom-specific anxiety may be less helpful in reducing IBS symptom severity than previously supposed, although they may still help with improving quality of life.

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DISCLOSURES

CJB, YY, LAH, FS, RW, EG, and ACF: None to declare.

AUTHOR CONTRIBUTIONS

CJB, YY, LAH, and ACF conceived and drafted the study; CJB collected all data; ACF, FS, RW, and EG analyzed and interpreted the data; ACF, FS, CJB, and EG drafted the manuscript; All authors have approved the final draft of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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