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FUNCTIONAL DISORDERS

Novel Symptom Subgroups in Individuals With Irritable Bowel Syndrome Predict Disease Impact and Burden

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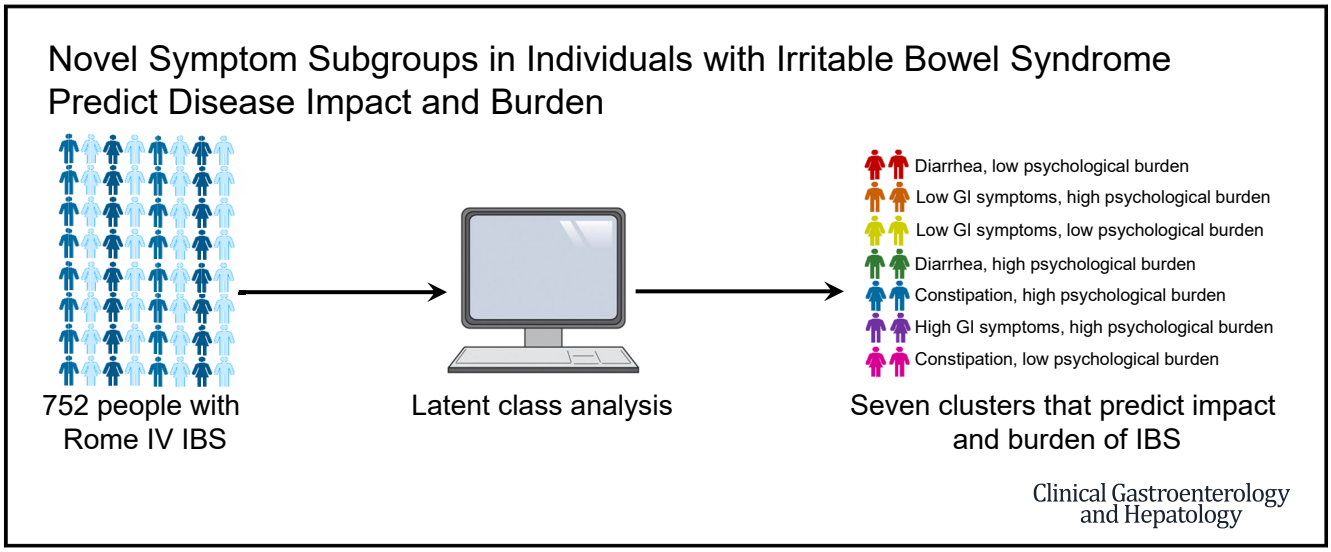

BACKGROUND & AIMS: **Current classification systems based on bowel habit fail to capture the multidimensional nature of irritable bowel syndrome (IBS). We previously derived and validated a classification system, using latent class analysis, incorporating factors beyond bowel habit. We applied this in another cohort of people with IBS to assess its ability to capture the impact of IBS on the individual, the health care system, and society.**

METHODS: **We collected demographic, symptom, and psychological health data from adults in the community self-identifying as having IBS, and meeting Rome IV criteria. We applied our latent class analysis model to identify the 7 subgroups (clusters) described previously, based on overall gastrointestinal symptom severity and psychological burden. We assessed quality of life, health care costs (£1 = $1.20), employment status, annual income, work productivity, and ability to perform work duties in each cluster.**

RESULTS: **Of 1278 responders, 752 (58.8%) met Rome IV criteria. The 7-cluster model fit the data well. The patients in the 4 clusters with the highest psychological burden, and particularly those in cluster 6 with high overall gastrointestinal symptom severity and high psychological burden, showed lower educational levels, higher gastrointestinal symptom–specific anxiety, were more likely to have consulted a gastroenterologist, and used more drugs for IBS. IBS-related and generic quality of life were impaired significantly in these 4 clusters and significantly fewer individuals reported earning ≥£30,000 per year. Productivity and the ability to work, manage at**

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Abbreviations used in this paper: IBS, irritable bowel syndrome; IBS-M, IBS with mixed bowel habits; LCA, latent class analysis.

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home, engage in social and private leisure activities, and maintain close relationships all were impacted significantly, and IBS-related health care costs over the previous 12 months were highest in these 4 clusters. In those in cluster 6, costs were more than £1000 per person per year.

CONCLUSIONS: **Our clusters identify groups of individuals with significant impairments in quality of life, earning potential, and ability to work and function socially, who are high utilizers of health care.**

Keywords: Irritable Bowel Syndrome; Latent Class Analysis; Subgrouping; Quality Of Life; Costs; Work.

See editorial on page 237.

Irritable bowel syndrome (IBS) is a chronic fluctuating disorder of the lower gastrointestinal tract,[1] which is conceptualized as a disorder of gut–brain interaction.[2,3] The condition is characterized by abdominal pain that is related to defecation, in the presence of a change in stool frequency or consistency.[4] It is diagnosed based on limited investigation and symptom-based diagnostic criteria,[5] with the current gold standard being the Rome IV criteria.[6] Using these criteria, 5% of the global population is affected by symptoms compatible with IBS.[7,8] Patients are subtyped, according to predominant bowel habit, into 4 subtypes, IBS with diarrhea, IBS with constipation, IBS with mixed bowel habits (IBS-M), and IBS unclassified. The aim of this subtyping system is to guide successful treatment.[9,10]

However, IBS is considered to be a gut–brain disorder. Patients with IBS have reported significantly more psychological comorbidity than those without IBS.[11] Symptoms compatible with common mental disorders, such as anxiety and depression, are more common in IBS,[12] and rates of somatoform symptom reporting also are higher.[13] A classification system based on bowel habit alone, therefore, seems insufficient to capture the complex composite nature of IBS adequately. Recently, we, and others, have used a statistical technique called latent class analysis (LCA) to classify patients according to not only gastrointestinal, but also psychological, symptoms.[14–16] These studies showed, relatively consistently, that there are clusters of people with IBS in whom gastrointestinal symptoms predominate, some in whom psychological symptoms predominate, and some for whom IBS symptoms are part of a broader picture, which included anxiety, depression, or extraintestinal symptoms. Longitudinal follow-up evaluation of one of these studies showed little transition between clusters with respect to psychological burden,[17] and these appeared to predict disease course, with those in clusters with the highest psychological burden at baseline having more severe symptoms, receiving more drugs, and being more likely to consult a doctor about their symptoms than those in clusters with low psychological burden.

These studies only examined demographic characteristics of, and symptom severity in, individuals in these clusters. They did not assess other factors, such as their ability to capture the impact of IBS on the individual, the health care system, or society as a whole. Therefore, we applied our previous LCA model in a new cohort of individuals with IBS, examining the association of the clusters with IBS-specific and generic health-related quality of life, health care costs, employment status, annual income, work productivity, and ability to perform work duties, as well as willingness to accept risk in return for cure of symptoms. We hypothesized that the clusters we identified previously would be reproducible, and that clusters with the highest psychological burden would show the strongest associations with these markers of disease impact and burden.

Methods

Participants and Setting

We approached 4280 individuals registered with ContactME-IBS, a national UK registry of people with IBS who have expressed an interest in volunteering for research. The registry is run by County Durham and Darlington National Health Service Foundation Trust. Individuals self-identify with the registry via primary care physicians, specialist hospital clinics, posters in pharmacies, or social media. They enroll online by completing a short questionnaire about bowel symptoms and provide their contact details. All registrants have a documented diagnosis of IBS according to either a primary or secondary care physician, of whom 1455 (34%) have seen a gastroenterologist about IBS, and 2268 (53%) have seen their primary care physician, with the remainder (13%) recruited via pharmacies or social media. We contacted all individuals registered with ContactME-IBS, via electronic mailout, in July 2021. There were no exclusion criteria apart from an inability to understand written English. The correspondence directed them to a website where they could access further study information. Those willing to participate completed an online questionnaire, with responses stored in an online database. Nonresponders received a reminder in August 2021. Participants were given a chance to win 1 of 3 gift cards (worth £200, £100, or £50) in return for completing the questionnaire. The University of Leeds research ethics committee approved the study in March 2021 (Medical and Health Research Ethics Committee, University of Leeds [MREC 20-051]).

Data Collection and Synthesis

We collected demographic data, including age, sex, lifestyle (tobacco and alcohol consumption), ethnicity,

marital status, educational level, employment status, and annual income (in £UK; £1 = $1.20). Respondents stated whether their IBS symptoms commenced after an acute enteric infection. We defined IBS according to the Rome IV questionnaire,[18] and categorized subtype according to the proportion of time stools looked abnormal according to the Bristol Stool Form Scale. We asked all participants to choose their most troublesome symptom from a list of 5 possibilities, including abdominal pain, constipation, diarrhea, bloating, or urgency. We questioned participants about drug use for their IBS symptoms, as well as severity of IBS symptoms, mood, somatic symptom reporting, gastrointestinal symptom–specific anxiety, impact of IBS symptoms on productivity and ability to work, and IBS-specific and generic health-related quality of life using validated questionnaires (see Supplemnetary Methods). We collected data on IBS-related health care use in the 12 months before study recruitment and applied costs in £UK and used a standard gamble to evaluate risk of death that participants would be willing to accept in return for a permanent cure of their IBS symptoms (see Supplementary Methods). Finally, we asked participants to choose a pill they would prefer to take from a list of eight hypothetical pills. Four pills relieved one symptom (pill A, pain; pill B, bloating; pill C, diarrhea; or pill D, constipation) almost completely, but hardly relieved other symptoms, whereas the other 4 pills relieved 1 symptom (pill E, pain; pill F, bloating; pill G, diarrhea; or pill H, constipation) well and relieved other symptoms a little.

Statistical Analysis

Among all respondents with IBS, we identified a cohort of individuals who met Rome IV criteria. We applied the LCA model that we derived and validated previously to these individuals.[14] LCA is a method of structural equation modeling used to identify unobserved groups, or latent classes, within observed multivariate data.[19] In our original study,[14] and a subsequent longitudinal follow-up study,[17] a statistical model was postulated for the population from which the data sample was obtained, and it was assumed that a mixture of underlying probability distributions generated the data.[20] The use of LCA for this purpose is referred to as model-based clustering. LCA is a flexible technique, enabling inclusion of a range of variable types within the same model. Analysis is iterative, whereby, for any given number of clusters, multiple solutions are evaluated to determine the best output.[20] Finally, robust statistical criteria can be used to determine the best fit of the model, and the optimum number of clusters.[21] Variables used in the original model are provided in Supplementary Table 1. The 7 clusters generated are detailed in the Supplementary Figure 1.

We compared categoric variables, such as sex, IBS subtype, or most troublesome symptom between individuals in each of the 7 clusters using the χ^2 test. We compared differences in continuous variables between clusters using a 1-way analysis of variance test. For nonparametric data, we compared medians using a Kruskal–Wallis test. Because of multiple comparisons, we considered a 2-tailed P value $<.01$ as statistically significant for these analyses, which we performed using SPSS for Windows (version 26.0; SPSS, Inc, Chicago, IL).

What You Need to Know

Background

Current bowel habit–based classification systems fail to capture the multidimensional nature of irritable bowel syndrome. We examined whether latent class analysis incorporating factors beyond bowel habit predicted the impact and burden of irritable bowel syndrome.

Findings

The clusters derived from latent class analysis identify groups of individuals with significant impairments in quality of life, earning potential, and ability to work and function socially, who are high utilizers of health care.

Implications for patient care

A multidimensional treatment approach tailored to the characteristics of patients in each cluster may be preferable to the use of peripheral drugs targeted toward the predominant bowel habit.

Results

In total, 1278 (29.9%) of 4280 registered individuals agreed to participate. The mean age of respondents was 47.2 years (range, 18–89 y), and 1086 (85.0%) were female. Of these 1278 individuals, 752 (58.8%) met the Rome IV criteria for IBS with a mean age of 45.3 years (range, 18–81 y), of whom 665 (87.1%) were female, and only these individuals were included in the LCA model. Overall, 91 (12.1%) individuals stated their IBS symptoms commenced after an acute enteric infection, 294 (39.1%) had seen a primary care physician with IBS in the prior 12 months, and 147 (19.5%) had seen a gastroenterologist. Characteristics of those with Rome IV IBS, compared with those with IBS by self-report, are provided in Supplementary Table 2. Those with Rome IV IBS were significantly younger, more likely to smoke, more likely to have IBS-M, and less likely to report constipation as their most troublesome symptom. They were also more likely to have seen a primary care physician or a gastroenterologist, to have used more drugs for their IBS in the past 12 months, and to have severe symptoms. More individuals with Rome IV IBS had abnormal anxiety or depression scores, and higher somatoform symptom-reporting scores. Levels of

gastrointestinal symptom–specific anxiety, productivity at work, and IBS-related costs all were significantly higher, and levels of IBS-related and generic quality of life were significantly lower, in those with Rome IV IBS. Finally, the median level of risk of death accepted in return for cure from a hypothetical drug was significantly higher in Rome IV IBS.

By applying the 7-cluster solution to this data set, there were 140 (18.6%) individuals in cluster 1, 195 (25.9%) individuals in cluster 2, 143 (19.0%) individuals in cluster 3, 147 (19.5%) individuals in cluster 4, 24 (3.2%) individuals in cluster 5, 56 (7.4%) individuals in cluster 6, and 47 (6.3%) individuals in cluster 7 (Figure 1).

Demographic and Psychological Characteristics of Individuals According to Cluster

Those in cluster 6 with high overall gastrointestinal symptom severity and high psychological burden were more likely to smoke (25.0%; $P = .003$) (Table 1), and those in clusters 4, 5, and 6, which consisted of gastrointestinal symptoms with the highest psychological burden, were less likely to have achieved a university level of education (29.3%, 20.8%, 28.6%, respectively; $P < .001$), but there were no other significant differences in demographics by cluster. As would be expected, IBS subtype and most troublesome symptom reported varied significantly by cluster. The majority of those in clusters 1 and 4, in which diarrhea was the predominant gastrointestinal symptom, met criteria for IBS with diarrhea or IBS-M, in clusters 5 and 7, in which constipation was a predominant symptom, most met criteria for IBS with constipation, and in clusters 2, 3, and 6, with mixed gastrointestinal symptoms, no one subtype predominated ($P < .001$). Urgency was reported as the most troublesome symptom in more people in clusters 1 and 4, in which diarrhea was a key symptom, as well as in those in cluster 6, with high overall gastrointestinal symptom severity and high psychological burden (42.9%, 37.4%, and 39.3%, respectively; $P < .001$). The highest proportion of people reporting abdominal pain as the predominant symptom were in cluster 6 (30.4%) ($P < .001$). Those in cluster 6 also were more likely to have seen a gastroenterologist (37.5%) and have tried more drugs for IBS (mean, 2.8 drugs) in the previous 12 months ($P < .001$ and $P = .002$, respectively). Those in clusters 4, 5, and 6 were more likely to report severe symptoms (67.3%, 66.7%, and 87.5%, respectively; $P < .001$). Only clusters 4 and 6, with diarrhea, abdominal pain, and urgency with high psychological burden, and high overall gastrointestinal symptom severity with high psychological burden, respectively, contained significantly higher proportions of individuals with high levels of gastrointestinal symptom–specific anxiety (55.1% and 67.9%, respectively; $P < .001$).

Impact of Clusters on Quality of Life, Irritable Bowel Syndrome–Related Health Cre Costs, Employment Status, Income, Work and Productivity, and Median Risk of Death Accepted in Return for Cure of Symptoms According to Cluster

The proportion of people with lower levels of IBS-related quality of life was highest in clusters 4, 5, and 6 (55.1%, 50.0%, and 85.7%, respectively; $P < .001$), which consisted of gastrointestinal symptoms with the highest psychological burden, and mean IBS quality-of-life scores were significantly lower in these 3 groups ($P < .001$) (Table 2). Mean EuroQol 5-dimension 5-level version (EQ-5D-5L) scores were lowest in the 4 clusters with a high psychological burden ($P < .001$). For comparison, reported reference scores for other chronic diseases are provided in Supplementary Table 3.

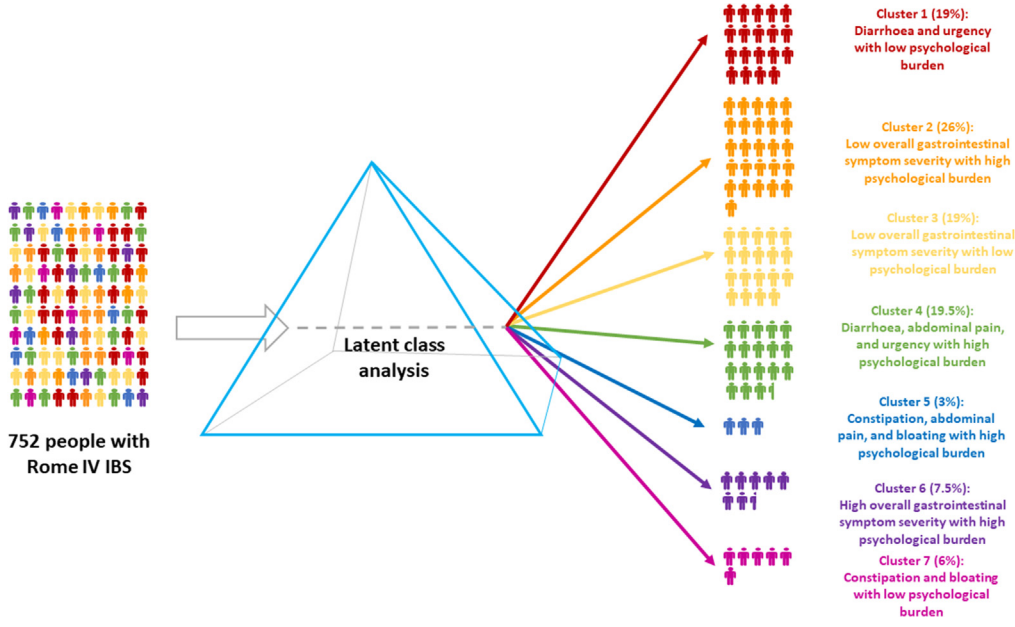

Figure 1. Latent class analysis in 752 people with Rome IV IBS. IBS, irritable bowel syndrome.

Table 1. Demographic and Psychological Characteristics of Individuals in Each of the Latent Class Clusters

	Cluster 1: diarrhea and urgency with low psychological burden (n = 140)	Cluster 2: low overall gastrointestinal symptom severity with high psychological burden (n = 195)	Cluster 3: low overall gastrointestinal symptom severity with low psychological burden (n = 143)	Cluster 4: diarrhea, abdominal pain, and urgency with high psychological burden (n = 147)	Cluster 5: constipation, abdominal pain, and bloating with high psychological burden (n = 24)	Cluster 6: high overall gastrointestinal symptom severity with high psychological burden (n = 56)	Cluster 7: constipation and bloating with low psychological burden (n = 47)	*P* value[a]
Mean age, *y* (SD)	48.9 (14.6)	45.1 (14.7)	45.4 (16.9)	42.3 (13.7)	48.0 (13.6)	44.2 (12.7)	44.9 (13.5)	.015
Female, n (%)	118 (84.3)	172 (88.2)	119 (83.2)	129 (87.8)	23 (95.8)	49 (87.5)	45 (95.7)	.24
Smoker, n (%)	8 (5.7)	25 (12.8)	10 (7.0)	19 (12.9)	1 (4.2)	14 (25.0)	5 (10.6)	.003
White Caucasian ethnicity, n (%)	135 (96.4)	190 (97.4)	139 (97.2)	143 (97.3)	24 (100.0)	51 (91.1)	47 (100.0)	.17
Married or cohabiting, n (%)	97 (69.3)	115 (59.0)	102 (71.3)	93 (63.3)	15 (62.5)	31 (55.4)	34 (72.3)	.11
University or postgraduate level of education, n (%)	61 (43.6)	80 (41.0)	88 (61.5)	43 (29.3)	5 (20.8)	16 (28.6)	21 (44.7)	<.001
IBS subtype, n (%)								
IBS-C	5 (3.6)	44 (22.6)	20 (14.0)	9 (6.1)	16 (66.7)	3 (5.4)	39 (83.0)	
IBS-D	89 (63.6)	38 (19.5)	54 (37.8)	99 (67.3)	0 (0.0)	25 (44.6)	1 (2.1)	
IBS-M	46 (32.9)	108 (55.4)	66 (46.2)	38 (25.9)	8 (33.3)	28 (50.0)	7 (14.9)	
IBS-U	0 (0.0)	5 (2.6)	3 (2.1)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	<.001
Most troublesome symptom, n (%)								
Abdominal pain	24 (17.1)	49 (25.1)	31 (21.7)	30 (20.4)	5 (20.8)	17 (30.4)	13 (27.7)	
Constipation	4 (2.9)	17 (8.7)	8 (5.6)	3 (2.0)	5 (20.8)	1 (1.8)	15 (31.9)	
Diarrhea	35 (25.0)	11 (5.6)	23 (16.1)	41 (27.9)	0 (0.0)	7 (12.5)	0 (0.0)	
Abdominal bloating or distension	17 (12.1)	88 (45.1)	57 (39.9)	18 (12.2)	12 (50.0)	9 (16.1)	17 (36.2)	
Urgency	60 (42.9)	30 (15.4)	24 (16.8)	55 (37.4)	2 (8.3)	22 (39.3)	2 (4.3)	<.001
IBS after acute enteric infection, n (%)	18 (12.9)	12 (6.2)	18 (12.6)	26 (17.7)	5 (20.8)	8 (14.3)	4 (8.5)	.049
Seen a primary care physician with IBS in past 12 months, n (%)	40 (28.6)	79 (40.5)	51 (35.7)	66 (44.9)	13 (54.2)	29 (51.8)	16 (34.0)	.014
Seen a gastroenterologist for IBS in past 12 months, n (%)	12 (8.6)	45 (23.1)	15 (10.5)	36 (24.5)	6 (25.0)	21 (37.5)	12 (25.5)	<.001

Table 1. Continued

	Cluster 1: diarrhea and urgency with low psychological burden (n = 140)	Cluster 2: low overall gastrointestinal symptom severity with high psychological burden (n = 195)	Cluster 3: low overall gastrointestinal symptom severity with low psychological burden (n = 143)	Cluster 4: diarrhea, abdominal pain, and urgency with high psychological burden (n = 147)	Cluster 5: constipation, abdominal pain, and bloating with high psychological burden (n = 24)	Cluster 6: high overall gastrointestinal symptom severity with high psychological burden (n = 56)	Cluster 7: constipation and bloating with low psychological burden (n = 47)	*P* value[a]
Mean number of drugs for IBS in past 12 months (SD)	2.0 (1.5)	2.3 (1.7)	1.8 (1.4)	2.2 (1.5)	2.2 (1.7)	2.8 (1.9)	2.4 (1.5)	.002
Symptom severity on IBS-SSS, n (%)								
Remission	3 (2.1)	0 (0.0)	4 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Mild	13 (9.3)	21 (10.8)	36 (25.2)	9 (6.1)	1 (4.2)	1 (1.8)	5 (10.6)	
Moderate	68 (48.6)	73 (37.4)	82 (57.3)	39 (26.5)	7 (29.2)	6 (10.7)	25 (53.2)	
Severe	56 (40.0)	101 (51.8)	21 (14.7)	99 (67.3)	16 (66.7)	49 (87.5)	17 (36.2)	<.001
Mean IBS-SSS score (SD)	278.8 (88.0)	297.2 (84.0)	223.4 (81.6)	329.8 (85.6)	341.0 (96.3)	387.6 (79.6)	278.8 (79.3)	<.001
Gastrointestinal symptom–specific anxiety on VSI, n (%)								
Low	46 (32.9)	62 (31.8)	88 (61.5)	22 (15.0)	3 (12.5)	4 (7.1)	22 (46.8)	
Medium	61 (43.6)	69 (35.4)	36 (25.2)	44 (29.9)	12 (50.0)	14 (25.0)	11 (23.4)	
High	33 (23.6)	64 (32.8)	19 (13.3)	81 (55.1)	9 (37.5)	38 (67.9)	14 (29.8)	<.001
Mean VSI score (SD)	49.9 (15.9)	51.7 (15.3)	41.2 (16.1)	58.7 (13.1)	57.1 (14.4)	65.0 (12.8)	47.4 (16.5)	<.001

IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; IBS-M, irritable bowel syndrome with mixed bowel habits; IBS-SSS, irritable bowel syndrome severity scoring system; IBS-U, irritable bowel syndrome unclassified; VSI, visceral sensitivity index.

[a]*P* value for Pearson χ^2 for comparison of categoric data and 1-way analysis of variance for comparison of means.

Table 2. Association of Clusters With Quality of Life, Irritable Bowel Syndrome–Related Health Care Costs, Employment Status, Income, Work and Productivity, and Median Risk of Death Accepted in Return for Cure of Symptoms

	Cluster 1: diarrhea and urgency with low psychological burden (n = 140)	Cluster 2: low overall gastrointestinal symptom severity with high psychological burden (n = 195)	Cluster 3: low overall gastrointestinal symptom severity with low psychological burden (n = 143)	Cluster 4: diarrhea, abdominal pain, and urgency with high psychological burden (n = 147)	Cluster 5: constipation, abdominal pain, and bloating with high psychological burden (n = 24)	Cluster 6: high overall gastrointestinal symptom severity with high psychological burden (n = 56)	Cluster 7: constipation and bloating with low psychological burden (n = 47)	*P* value[a]
Disease-specific health-related quality of life on IBS-QOL, n (%)								
Low	29 (20.7)	57 (29.2)	8 (5.6)	81 (55.1)	12 (50.0)	48 (85.7)	4 (8.5)	
Medium	53 (37.9)	78 (40.0)	37 (25.9)	50 (34.0)	10 (41.7)	4 (7.1)	20 (42.6)	
High	58 (41.4)	60 (30.8)	98 (68.5)	16 (10.9)	2 (8.3)	4 (7.1)	23 (48.9)	<.001
Mean IBS-QOL score (SD)	53.5 (19.4)	47.7 (19.3)	66.8 (17.3)	35.1 (17.9)	36.4 (17.6)	23.3 (18.7)	56.9 (17.1)	<.001
Mean EQ-5D-5L score (SD)	0.689 (0.185)	0.516 (0.256)	0.776 (0.114)	0.455 (0.276)	0.389 (0.374)	0.186 (0.305)	0.717 (0.132)	<.001
Mean IBS-related costs in £UK[b] (SD)	92.42 (262.85)	265.76 (593.25)	110.89 (308.22)	250.02 (504.12)	274.79 (522.98)	590.23 (1058.53)	250.85 (931.22)	<.001
Appointments								
Investigations	116.13 (340.12)	189.78 (379.53)	92.90 (245.78)	204.19 (389.77)	92.86 (222.36)	251.87 (474.66)	120.91 (250.74)	.012
Inpatient admissions	77.59 (339.41)	55.70 (289.43)	21.70 (182.87)	116.12 (409.69)	0.00 (0.00)	221.68 (547.92)	33.02 (226.35)	.003
Drugs	52.54 (66.92)	74.16 (88.38)	66.94 (90.68)	83.66 (100.83)	93.17 (130.86)	80.22 (97.71)	89.24 (157.97)	.076
Total	359.16 (865.70)	622.73 (1151.32)	298.60 (544.35)	702.00 (1068.28)	479.20 (767.57)	1179.44 (1425.61)	498.70 (1053.42)	<.001
Currently employed, n (%)	93 (66.4)	122 (62.6)	98 (68.5)	95 (64.6)	14 (58.3)	25 (44.6)	37 (78.7)	.015
Annual income of ≥£30,000,[b] n (%)	51 (41.5)	41 (22.8)	48 (37.2)	30 (21.7)	2 (10.5)	8 (17.0)	17 (38.6)	<.001
Mean WPAI percentages (SD)								
Absenteeism	4.8 (12.5)	4.9 (13.2)	0.5 (1.9)	8.0 (16.7)	10.5 (21.6)	12.5 (18.9)	2.1 (7.1)	<.001
Presenteeism	38.5 (26.4)	35.4 (26.9)	23.9 (22.0)	50.9 (29.9)	46.4 (29.8)	52.8 (34.7)	27.0 (21.2)	<.001
Work impairment	38.1 (28.3)	34.7 (27.6)	23.9 (22.3)	50.6 (30.6)	38.9 (29.4)	48.6 (30.5)	25.4 (21.0)	<.001
Activity impairment	41.0 (26.5)	43.3 (24.9)	26.2 (22.8)	59.7 (27.4)	56.3 (28.1)	71.4 (26.9)	33.0 (24.5)	<.001
Any absenteeism on WPAI, n (%)	31/91 (34.1)	35/119 (29.4)	10/94 (10.6)	34/90 (37.8)	5/14 (35.7)	13/25 (52.0)	5/34 (14.7)	<.001

Table 2. Continued

	Cluster 1: diarrhea and urgency with low psychological burden (n = 140)	Cluster 2: low overall gastrointestinal symptom severity with high psychological burden (n = 195)	Cluster 3: low overall gastrointestinal symptom severity with low psychological burden (n = 143)	Cluster 4: diarrhea, abdominal pain, and urgency with high psychological burden (n = 147)	Cluster 5: constipation, abdominal pain, and bloating with high psychological burden (n = 24)	Cluster 6: high overall gastrointestinal symptom severity with high psychological burden (n = 56)	Cluster 7: constipation and bloating with low psychological burden (n = 47)	*P* value[a]
Any presenteeism on WPAI, n (%)	74/84 (88.1)	93/110 (84.5)	68/91 (74.7)	79/83 (95.2)	11/13 (84.6)	20/22 (90.9)	28/33 (84.8)	.014
Any work impairment on WPAI, n (%)	75/91 (82.4)	95/119 (79.8)	70/94 (74.5)	80/90 (88.9)	12/14 (85.7)	22/25 (88.0)	28/34 (82.4)	.27
Any activity impairment on WPAI, n (%)	127 (90.7)	181 (92.8)	115 (80.4)	144 (98.0)	23 (95.8)	54 (96.4)	40 (85.1)	<.001
Mean WSAS score (SD)	10.1 (6.9)	14.1 (8.9)	6.8 (6.4)	18.5 (9.5)	19.0 (11.1)	26.1 (9.9)	9.2 (6.2)	<.001
IBS affects home management on WSAS, n (%)	21 (15.0)	63 (32.3)	8 (5.6)	70 (47.6)	11 (45.8)	42 (75.0)	5 (10.6)	<.001
IBS affects social leisure activities on WSAS, n (%)	67 (47.9)	115 (59.0)	37 (25.9)	118 (80.3)	16 (66.7)	51 (91.1)	19 (40.4)	<.001
IBS affects private leisure activities on WSAS, n (%)	25 (17.9)	50 (25.6)	11 (7.7)	64 (43.5)	11 (45.8)	42 (75.0)	4 (8.5)	<.001
IBS affects close relationships on WSAS, n (%)	19 (13.6)	56 (28.7)	14 (9.8)	54 (36.7)	11 (45.8)	41 (73.2)	8 (17.0)	<.001
Median risk of death (%) accepted in return for cure of symptoms (IQR)	2.0 (0.0–5.0)	3.0 (0.0–10.0)	1.0 (0.0–5.0)	4.0 (0.0–10.0)	2.0 (0.0–7.5)	5.0 (0.0–20.0)	1.0 (0.0–5.0)	<.001

IBS-QOL, irritable bowel syndrome quality of life; IQR, interquartile range; WPAI:IBS, Work Productivity and Activity Impairment questionnaire for irritable bowel syndrome; WSAS, Work and Social Adjustment Scale.
[a]*P* value for Pearson χ^2 for comparison of categoric data, 1-way analysis of variance for comparison of means, and Kruskal–Wallis for comparison of medians.
[b]£1 = $1.20.

Mean IBS-related costs in the previous 12 months were higher in clusters 2, 4, 5, and 6, which all were associated with a high psychological burden, and were highest in cluster 6 (£1179.44; $P < .001$) the cluster with high overall gastrointestinal symptom severity and high psychological burden. There was a trend toward those in cluster 6 being less likely to be currently employed (44.6%; $P = .015$), and significantly lower proportions of individuals in all 4 clusters with a high psychological burden were earning ≥£30,000 per year (22.8%, 21.7%, 10.5%, and 17.0%, respectively; $P < .001$). Among those who were working, the mean work productivity and activity impairment questionnaire percentages and rates of absenteeism and activity impairment all were higher among those in clusters with a high psychological burden ($P < .001$ for all analyses), although these also were high in cluster 1, which consisted of diarrhea and urgency with low psychological burden. Mean work and social adjustment scale scores were highest in the 3 clusters with gastrointestinal symptoms with the highest psychological burden, as were the proportions in whom IBS affected home management, social and private leisure activities, and close relationships ($P < .001$ for all analyses). Finally, those in clusters 4 and 6 were prepared to accept a median risk of death of 4% and 5%, respectively, in return for cure of their symptoms with a hypothetical medication ($P < .001$).

Pill Choice By Cluster

The proportion of individuals in each of the 7 clusters choosing each one of the 8 hypothetical pills is provided in Figure 2. As would be expected, those in clusters 1 and 4, characterized by diarrhea, were more likely to choose either pill C or G, whereas those in clusters 5 or 7, characterized by constipation, were more likely to choose pills D or H. Pills that relieved pain (A or E) or bloating (B or F) were more likely to be chosen by individuals in clusters 2 or 3. Individuals in cluster 6 were spread more evenly across the pill choices.

Discussion

We report data from a cohort of individuals who met Rome IV criteria for IBS, and in whom we performed LCA to apply a previously validated model to classify people according to both gastrointestinal symptom severity and psychological burden. The proportion of individuals in each cluster was almost identical to those in our previous study,[14] as were the basic demographic data. Individuals in the clusters with the highest psychological burden, and particularly those in cluster 6, with high overall gastrointestinal symptom severity and high psychological burden, showed lower educational levels, higher gastrointestinal symptom–specific anxiety, and were more likely to have consulted a gastroenterologist and used a higher number of drugs in the previous 12 months. In addition, both IBS-related and generic quality of life were impaired significantly among individuals in these clusters. In cluster 6 the level of impairment in generic quality of life was far worse than seen in many other chronic disease states. There was a trend toward individuals in this cluster being less likely to be

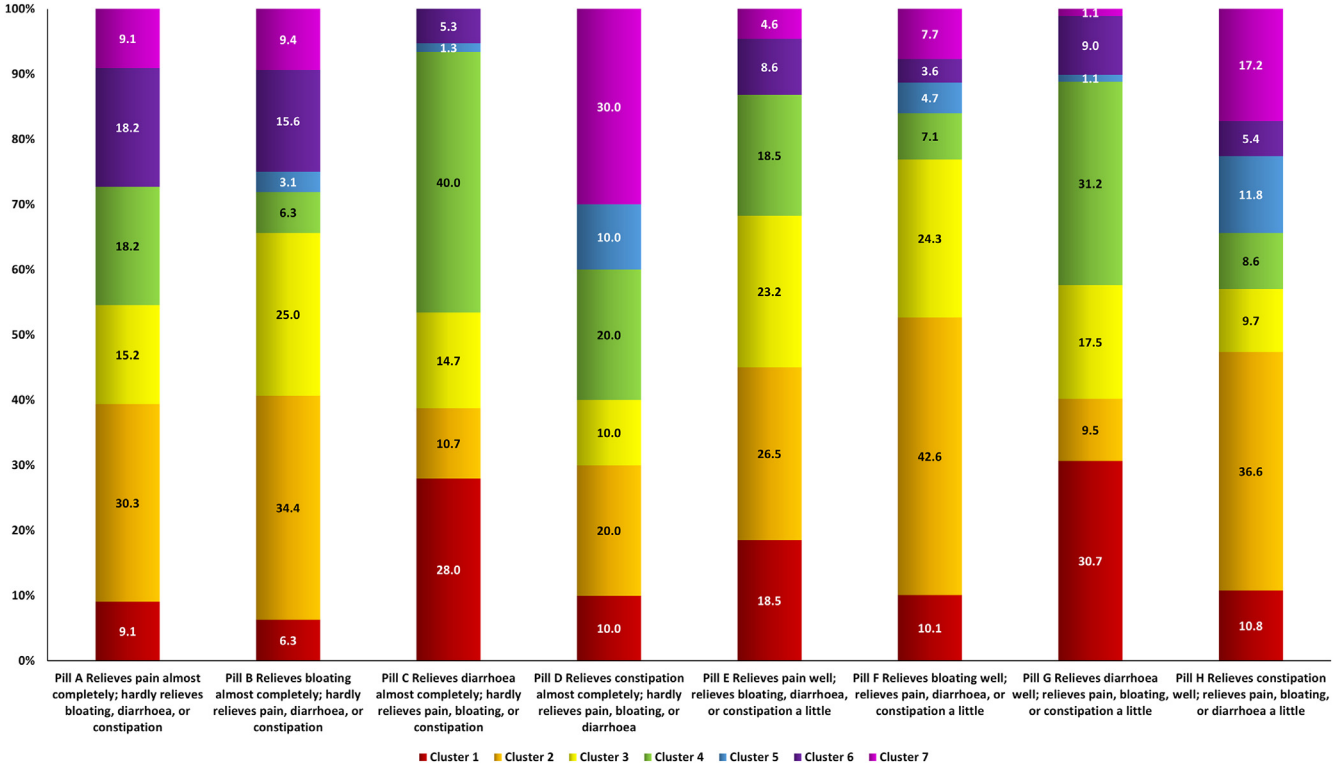

Figure 2. Hypothetical pill choice according to cluster.

employed, and fewer individuals in the 4 clusters with the highest psychological burden reported earning ≥£30,000 per year. Productivity and ability to work, manage at home, engage in social and private leisure activities, and maintain close relationships all were impacted significantly, and IBS-related health care costs over the previous 12 months were highest in these 4 clusters. In those in cluster 6, costs were >£1000 per person per year. Finally, those in the clusters with high psychological burden were willing to accept between a 3% and 5% risk of death in return for symptom cure. These clusters, therefore, identify groups of individuals with significant impairments in quality of life, earning potential, and ability to work and function socially, who are high utilizers of health care, and who would accept up to a 1 in 20 chance of death with a new hypothetical medication in return for a cure of their symptoms.

Although we used a national UK IBS registry, we could not check participants' medical records to rule out organic gastrointestinal diseases presenting with similar symptoms, such as celiac disease or inflammatory bowel disease.[22,23] However, we believe our participants genuinely had IBS, given that IBS is more prevalent than these conditions, UK national guidance recommends these conditions are ruled out before a diagnosis of IBS,[24] and almost 90% of the ContactME-IBS registrants have a physician's diagnosis of IBS. All involved individuals were UK residents and 97% were White, so our findings cannot be generalized to other countries or ethnicities. Nevertheless, even in the United States with its diverse population, the LCA model can be applied to any group of people with Rome IV IBS, although demographics of those in each cluster may differ from those seen in our study. Because we used an online questionnaire, we are unable to report the number and characteristics of individuals who accessed but did not complete the questionnaire, meaning we cannot exclude volunteer bias. However, the proportion of individuals included in this study who met Rome IV criteria for IBS and the proportion of individuals in each of the 7 clusters is almost identical to our previous study.[14] Because this was a cross-sectional study, we can only report associations, not the direction of any effects, so it is unclear whether these clusters influence future quality of life, work productivity, or health care costs, or whether the reverse is true.

Other investigators have applied LCA to people with IBS.[15,16] The results differ but are broadly corroborative of the clusters we describe. Polster et al[15] reported 6 distinct subgroups of people with Rome III–defined IBS; those whose symptoms were predominantly intestinal, including diarrhea, constipation, or abdominal pain; with minimal psychological distress; and those in whom IBS symptoms co-existed with anxiety, depression, and extraintestinal symptom reporting. However, because the investigators included only 172 patients in tertiary care, the findings may not be generalizable to most people with IBS who are seen in primary or secondary care. More recently, a study using the Mayo Clinic biobank, applying LCA in more than 4000 patients with Rome III IBS, reported 7 clusters.[16] These were characterized based on the degree of perceived health impairment, presence of neuropsychological factors, or predominant bowel symptom. Results of physiological testing were available in a subset of patients but did not reveal significant differences between clusters, although those with a higher degree of health impairment were significantly more likely to undergo investigation. Importantly, however, neither of these studies assessed whether these clusters could identify individuals with a higher disease impact or burden.

Medical treatment for IBS is based on tailoring a drug to the patient's most troublesome symptom(s). Although there are efficacious drugs available, they do not work in all patients, even when a drug targeting a particular pathophysiological mechanism that may underlie the abnormality in a predominant bowel habit is used.[9,10] In addition, up to one third of patients with IBS will have IBS-M or IBS unclassified, yet there are no licensed drugs for these subtypes. Gut–brain behavioral therapies, such as IBS-specific cognitive behavioral therapy or gut-directed hypnotherapy, are efficacious in some people with IBS,[25] but in many countries access to these is limited and they are used as a last resort when all other medical approaches have failed.

Given the multifaceted nature of the symptoms in the clusters with the highest disease impact and burden seen in this study, it seems unlikely that a drug directed against peripheral symptoms alone will improve quality of life, reduce health care utilization, or increase work productivity and activity in all individuals. Rather, the clusters that we describe, and the evidence of their impact, suggest that there is a group of people with IBS with mild symptoms who may be best managed by reassurance, explanation of the disorder, and lifestyle and dietary advice; other groups whose symptoms predominantly are intestinal, who may be best treated with a peripherally acting drug; a group whose symptoms who predominantly are extraintestinal and psychological, who may respond best to behavioral therapies; and groups with both gastrointestinal and psychological symptoms who may need combinations of peripherally and centrally acting drugs or peripherally acting drugs and gut–brain behavioral therapies. Future studies should assess whether such approaches can alter the natural history of these clusters and their impact on quality of life, health care utilization, and work productivity and activity.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.02.016.

References

1. Ford AC, Forman D, Bailey AG, et al. Irritable bowel syndrome: a 10-year natural history of symptoms, and factors that influence consultation behavior. Am J Gastroenterol 2008;103:1229–1239.
2. Black CJ, Drossman DA, Talley NJ, et al. Functional gastrointestinal disorders: advances in understanding and management. Lancet 2020;396:1664–1674.
3. Drossman DA, Hasler WL. Rome IV-functional GI disorders: disorders of gut-brain interaction. Gastroenterology 2016; 150:1257–1261.
4. Ford AC, Sperber AD, Corsetti M, et al. Irritable bowel syndrome. Lancet 2020;396:1675–1588.
5. Black CJ, Craig O, Gracie DJ, et al. Comparison of the Rome IV criteria with the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. Gut 2021;70:1110–1116.
6. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. Gastroenterology 2016;150:1393–1407.
7. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation global study. Gastroenterology 2021;160:99–114.
8. Oka P, Parr H, Barberio B, et al. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:908–917.
9. Black CJ, Burr NE, Quigley EMM, et al. Efficacy of secretagogues in patients with irritable bowel syndrome with constipation: systematic review and network meta-analysis. Gastroenterology 2018;155:1753–1763.
10. Black CJ, Burr NE, Camilleri M, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: systematic review and network meta-analysis. Gut 2020;69:74–82.
11. Henningsen P, Zimmermann T, Sattel H. Medically unexplained physical symptoms, anxiety and depression: a meta-analytic review. Psychosom Med 2003;65:528–533.
12. Zamani M, Alizadeh-Tabari S, Zamani V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. Aliment Pharmacol Ther 2019;50:132–143.
13. Patel P, Bercik P, Morgan DG, et al. Irritable bowel syndrome is significantly associated with somatisation in 840 patients, which may drive bloating. Aliment Pharmacol Ther 2015;41:449–458.
14. Black CJ, Yiannakou Y, Guthrie EA, et al. A novel method to classify and subgroup patients with IBS based on gastrointestinal symptoms and psychological profiles. Am J Gastroenterol 2021;116:372–381.
15. Polster A, Van Oudenhove L, Jones M, et al. Mixture model analysis identifies irritable bowel syndrome subgroups characterised by specific profiles of gastrointestinal, extraintestinal somatic and psychological symptoms. Aliment Pharmacol Ther 2017;46:529–539.
16. Byale A, Lennon RJ, Byale S, et al. High-dimensional clustering of 4000 irritable bowel syndrome patients reveals seven distinct disease subsets. Clin Gastroenterol Hepatol. Published online September 27, 2022. https://doi.org/10.1016/j.cgh.2022.09.019.
17. Black CJ, Yiannakou Y, Guthrie E, et al. Longitudinal follow-up of a novel classification system for irritable bowel syndrome: natural history and prognostic value. Aliment Pharmacol Ther 2021;53:1126–1137.
18. Palsson OS, Whitehead WE, van Tilburg MA, et al. Rome IV diagnostic questionnaires and tables for investigators and clinicians. Gastroenterology 2016;150:1481–1491.
19. Lanza ST, Rhoades BL. Latent class analysis: an alternative perspective on subgroup analysis in prevention and treatment. Prev Sci 2013;14:157–168.
20. Magdison J. Latent class cluster analysis. In: Hagenaars JA, McCutcheon AL, eds. Advances in latent class analysis. Cambridge: Cambridge University Press, 2002.
21. Vrieze SI. Model selection and psychological theory: a discussion of the differences between the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). Psychol Methods 2012;17:228–243.
22. Irvine AJ, Chey WD, Ford AC. Screening for celiac disease in irritable bowel syndrome: an updated systematic review and meta-analysis. Am J Gastroenterol 2017;112:65–76.
23. Fairbrass KM, Costantino SJ, Gracie DJ, et al. Prevalence of irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease in remission: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:1053–1062.
24. Vasant DH, Paine PA, Black CJ, et al. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. Gut 2021;70:1214–1240.
25. Black CJ, Thakur ER, Houghton LA, et al. Efficacy of psychological therapies for irritable bowel syndrome: systematic review and network meta-analysis. Gut 2020;69:1441–1451.

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Supplementary Methods

Irritable Bowel Syndrome Symptom Severity

We assessed the severity of symptoms using the IBS severity scoring system,[1] which measures the presence, severity, and frequency of abdominal pain, the presence and severity of abdominal distension, satisfaction with bowel habits, and the degree to which IBS symptoms are affecting, or interfering with, the individual's life. The IBS severity scoring system carries a maximum score of 500 points, with more than 75 points indicating remission; 75 to 174 points indicating mild symptoms; 175 to 299 points indicating moderate symptoms; and 300 to 500 points indicating severe symptoms.

Mood and Somatic Symptoms

We used the Hospital Anxiety and Depression Scale to collect anxiety and depression data.[2] The total Hospital Anxiety and Depression Scale score ranges from 0 to 21 for either anxiety or depression. We categorized the severity for each into normal (total Hospital Anxiety and Depression Scale depression or anxiety score, 0–7), borderline normal (score, 8–10), or abnormal (score, $\geq$11). We collected somatic symptom data using the Patient Health Questionnaire-12,[3] derived from the validated Patient Health Questionnaire-15.[4] The total Patient Health Questionnaire-12 score ranges from 0 to 24. We categorized the severity into high (total Patient Health Questionnaire-12 score, $\geq$13), medium (score, 8–12), low (score, 4–7), or minimal (score, $\leq$3).

Gastrointestinal Symptom–Specific Anxiety

We used the Visceral Sensitivity Index to determine gastrointestinal symptom–specific anxiety.[5] Replies to each of the 15 items are provided on a 6-point scale from 0 to 5, with higher scores indicating more severe gastrointestinal symptom–specific anxiety. We divided these data into equal-sized tertiles, both for all individuals and for those with only Rome IV IBS, because there are no validated cut-off values to define low, medium, or high levels of gastrointestinal symptom–specific anxiety.

Irritable Bowel Syndrome–Specific and Generic Health-Related Quality of Life

We used the irritable bowel syndrome quality of life questionnaire, which is a validated IBS-specific questionnaire.[6,7] The IBS quality of life consists of 34 items, each ranked on a 5-point Likert scale ranging from 0 to 4, with a total possible score of 0 to 136, and lower scores indicating better quality of life. The 34 items are based on the following 8 variables: dysphoria, interference with activity, body image, health worry, food avoidance, social reactions, sexual activity, and relationships. Score were transformed to a scale of 0 to 100 points, with zero indicating worst quality of life and 100 indicating best quality of life. We divided these data into equal-sized tertiles because there are no validated cut-off values to define low, medium, or high levels of quality of life. Again, we did this both for all individuals and for those with only Rome IV IBS. We also administered the EuroQOL,[8] a generic health-related quality-of-life questionnaire used widely in health care. We used the EuroQOL 5-dimension 5-level (EQ-5D-5L) instrument,[9] one of the 3 versions of EuroQOL, consisting of 5 items capturing different aspects of health, including mobility, self-care, ability to perform usual activities, pain/discomfort, and anxiety/depression. Each item has 5 levels of responses, for a total of 3125 possible health states. We mapped each health state to obtain a utility score for a UK population using a cross-walk calculator,[10] a mapping function recommended by the National Institute for Health and Care Excellence.[11]

Impact of Irritable Bowel Syndrome on Productivity and Ability to Work

We assessed the impact of IBS on the ability to work using the Work Productivity and Activity Impairment questionnaire for IBS,[12] which is a validated questionnaire to assess the level of work productivity loss in people with IBS who are employed, as well as activity impairment in their activities of daily living. The Work Productivity and Activity Impairment questionnaire for IBS measures 4 domains: absenteeism, which is the percentage of work hours missed because of IBS; presenteeism, which is the percentage of impairment experienced while working because of IBS; overall work impairment, which is the percentage of work productivity loss; and activity impairment, which is the percentage of impairment in activities of daily living. We also used the Work and Social Adjustment Scale,[13] which has been used by other investigators to measure the effect of IBS on individuals' ability to work, manage at home, engage in social and private leisure activities, and maintain close relationships.[14–16] The 5 domains are scored on a 9-point scale from "not at all" (score, 0) to "very severely" (score, 8). We dichotomized the presence ($\geq$1%) or absence (0%) of absenteeism, presenteeism, overall work impairment, or activity impairment on the Work Productivity and Activity Impairment and presence (score, $\geq$4; "definitely" impacting) or absence (score, $<$4) of an impact of IBS on home management activities, social leisure activities, private leisure activities, or maintaining close relationships on the Work and Social Adjustment Scale.

Irritable Bowel Syndrome–Related Health Care Use

We asked participants to record the number of appointments with health care professionals (primary care

physicians, gastroenterologists, specialist nurses, dietitians, and psychologists), investigations (blood tests, stool tests, endoscopies, abdominal ultrasounds, computed tomography scans, magnetic resonance imaging scans, hydrogen breath tests, or 23-seleno-25-homotauro-cholic acid scans), unplanned hospital attendances or admissions (including length of stay for inpatient admissions), and drug usage (in months). We applied costs (in £UK) for primary care physician appointments from Unit Costs of Health and Social Care 2020[17]; and for appointments, investigations, and unplanned inpatient days in secondary care using the NHS 2019/2020 National Cost Collection Data (Supplementary Table 4).[18] We assumed all appointments for IBS were follow-up appointments, which cost less than a new patient appointment. We applied the lowest price for a 1-month supply of each IBS-related drug using the British National Formulary online (Supplementary Table 5).[19]

Risk of Death in Return for Permanent Cure of Irritable Bowel Syndrome Symptoms

In the standard gamble,[20] each question offered participants a choice of a chance of a permanent cure of their IBS symptoms with a hypothetical pill or a risk of a painless death in their sleep from the same pill. As the participants moved from one question to the next, the chance of cure titrated down from 100% and risk of death titrated up from 0%. Therefore, we were able to estimate the maximum risk of death that participants would be willing to accept for the corresponding minimum chance of cure.

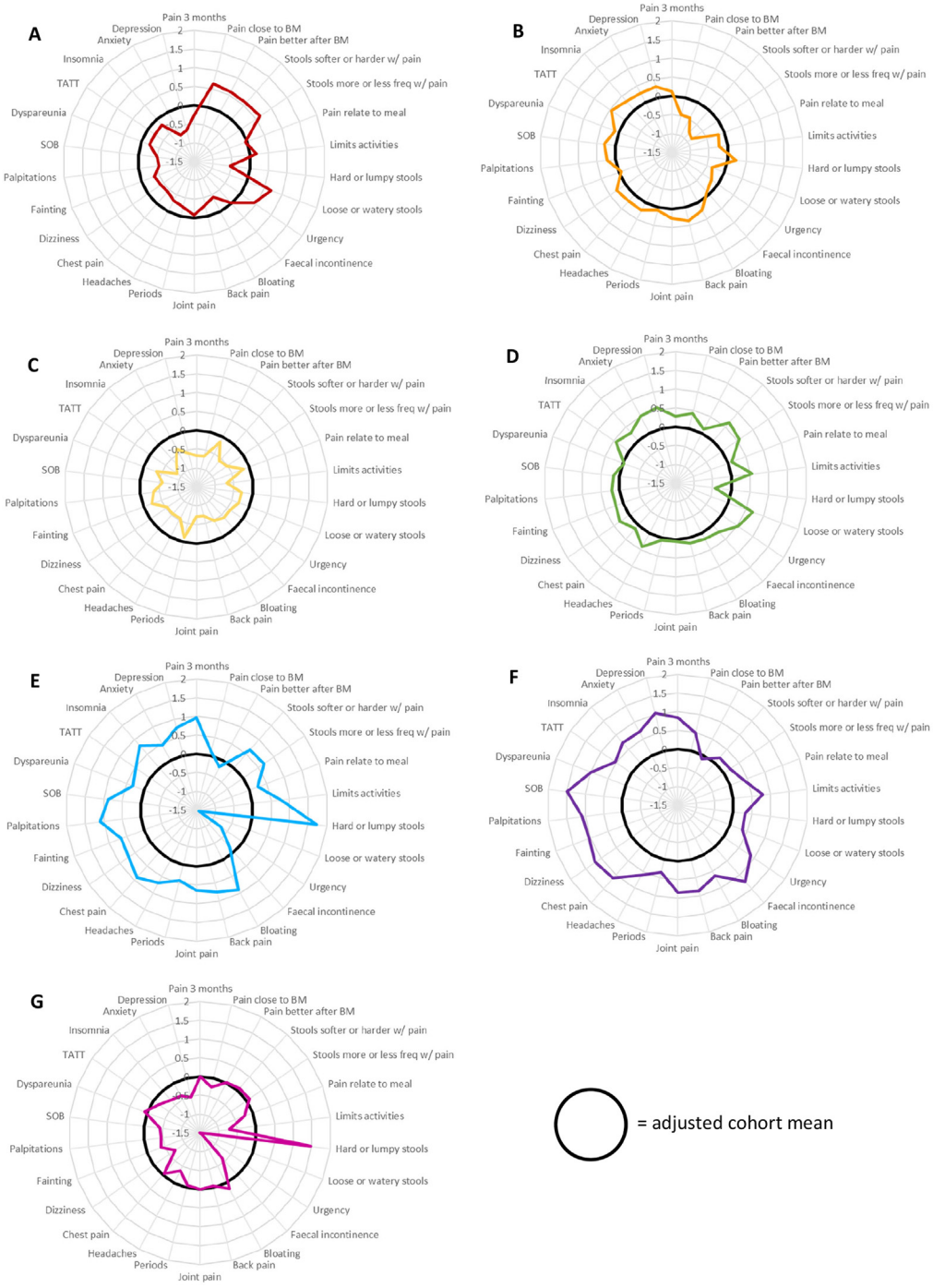
The 7-Cluster Model Derived in the Previous Study

In our original study this model generated 7 clusters,[21] as detailed in Supplementary Figure 1. These were as follows: diarrhea and urgency with low psychological burden (cluster 1, Supplementary Figure 1*A*); diarrhea, abdominal pain, and urgency with high psychological burden (cluster 4, Supplementary Figure 1*D*); constipation and bloating with low psychological burden (cluster 7, Supplementary Figure 1*G*); constipation, abdominal pain, and bloating with high psychological burden (cluster 5, Supplementary Figure 1*E*); low overall gastrointestinal symptom severity with low psychological burden (cluster 3, Supplementary Figure 1*C*); low overall gastrointestinal symptom severity with high psychological burden (cluster 2, Supplementary Figure 1*B*); and high overall gastrointestinal symptom severity with high psychological burden (cluster 6, Supplementary Figure 1*F*).

References

1. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997;11:395–402.
2. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression scale. Acta Psychiatr Scand 1983;67:361–370.
3. Spiller RC, Humes DJ, Campbell E, et al. The Patient Health Questionnaire 12 Somatic Symptom scale as a predictor of symptom severity and consulting behaviour in patients with irritable bowel syndrome and symptomatic diverticular disease. Aliment Pharmacol Ther 2010;32:811–820.
4. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med 2002;64:258–266.
5. Labus JS, Bolus R, Chang L, et al. The Visceral Sensitivity Index: development and validation of a gastrointestinal symptom-specific anxiety scale. Aliment Pharmacol Ther 2004;20:89–97.
6. Drossman DA, Patrick DL, Whitehead WE, et al. Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire. Am J Gastroenterol 2000;95:999–1007.
7. Patrick DL, Drossman DA, Frederick IO, et al. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. Dig Dis Sci 1998;43:400–411.
8. EuroQol Group. EuroQol–a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.
9. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–1736.
10. Hernández Alava M, Pudney S, Wailoo A, Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English population study. Policy Research Unit in Economic Evaluation of Health and Care Interventions. Universities of Sheffield and York, 2020.
11. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. NICE, 2022. https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation#measuring-and-valuing-health-effects-in-cost-utility-analyses. Accessed August 16, 2022.
12. Reilly MC, Bracco A, Ricci JF, et al. The validity and accuracy of the Work Productivity and Activity Impairment questionnaire–irritable bowel syndrome version (WPAI:IBS). Aliment Pharmacol Ther 2004;20:459–467.
13. Mundt JC, Marks IM, Shear MK, et al. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry 2002;180:461–464.
14. Everitt HA, Landau S, O'Reilly G, et al. Assessing telephone-delivered cognitive-behavioural therapy (CBT) and web-delivered CBT versus treatment as usual in irritable bowel syndrome (ACTIB): a multicentre randomised trial. Gut 2019;68:1613–1623.
15. Kennedy TM, Chalder T, McCrone P, et al. Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial. Health Technol Assess 2006;10:1–67.
16. Zhao J, Chen M, Wang X, et al. Efficacy of acupuncture in refractory irritable bowel syndrome: study protocol for a randomised controlled trial. BMJ Open 2021;11:e045655.
17. Curtis L, Burns A. Unit costs of health & social care 2020. Unit costs of health and social care canterbury: Personal Social Services Research Unit (PSSRU), University of Kent. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020. Accessed January 3, 2023.
18. National Health Service. National cost collection for the NHS. 2019-20. https://www.england.nhs.uk/national-cost-collection. Accessed January 3, 2023.

19. Joint Formulary Committee. British National Formulary. (online). London: BMJ Group and Pharmaceutical Press, 2021. https://bnf.nice.org.uk. Accessed January 3, 2023.
20. Ross PL, Littenberg B, Fearn P, et al. Paper standard gamble: a paper-based measure of standard gamble utility for current health. Int J Technol Assess Health Care 2003;19:135–147.
21. Black CJ, Yiannakou Y, Guthrie EA, et al. A novel method to classify and subgroup patients with IBS based on gastrointestinal symptoms and psychological profiles. Am J Gastroenterol 2021;116:372–381.
22. Brazier J, Roberts J, Tsuchiya A, et al. A comparison of the EQ-5D and SF-6D across seven patient groups. Health Econ 2004;13:873–884.
23. Barton GR, Sach TH, Doherty M, et al. An assessment of the discriminative ability of the EQ-5D index, SF-6D, and EQ VAS, using sociodemographic factors and clinical conditions. Eur J Health Econ 2008;9:237–249.
24. Szentes BL, Schultz K, Nowak D, et al. How does the EQ-5D-5L perform in asthma patients compared with an asthma-specific quality of life questionnaire? BMC Pulm Med 2020;20:168.
25. Gallagher AM, Lucas R, Cowie MR. Assessing health-related quality of life in heart failure patients attending an outpatient clinic: a pragmatic approach. ESC Heart Fail 2019;6:3–9.
26. Hernández Alava M, Wailoo A, Wolfe F, et al. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. Rheumatology (Oxford) 2013;52:944–950.



Supplementary Figure 1. Profiles of the 7 clusters. (*A*) Cluster 1: diarrhea and urgency with low psychological burden. (*B*) Cluster 2: low overall gastrointestinal symptom severity with high psychological burden. (*C*) Cluster 3: low overall gastrointestinal symptom severity with low psychological burden. (*D*) Cluster 4: diarrhea, abdominal pain, and urgency with high psychological burden. (*E*) Cluster 5: constipation, abdominal pain, and bloating with high psychological burden. (*F*) Cluster 6: high overall gastrointestinal symptom severity with high psychological burden. (*G*) Cluster 7: constipation and bloating with low psychological burden. BM, bowel movement; SOB, shortness of breath; TATT, tired all the time.

Supplementary Table 1. Variables Used in the Latent Class Analysis

	Variable	Type of variable	Measurement scale	Reason for including in the model
Gastrointestinal symptoms	Frequency of abdominal pain anywhere in the abdomen in the past 3 months	Ordinal	9-point scale from never (score, 0) to multiple times per day or all the time (score, 8)	All of these variables for quantifying gastrointestinal symptoms were taken from Rome Foundation questionnaires These are the recognized gold standard for diagnosing IBS and are used widely
	Frequency of abdominal pain being closely related to a bowel movement	Ordinal	11-point scale from 0% (never) to 100% (always)	
	Frequency with which abdominal pain improved or resolved after a bowel movement	Ordinal	11-point scale from 0% (never) to 100% (always)	
	Frequency with which stools became softer or harder than usual in association with abdominal pain	Ordinal	11-point scale from 0% (never) to 100% (always)	
	Frequency with which stools became more or less frequent than usual in association with abdominal pain	Ordinal	11-point scale from 0% (never) to 100% (always)	
	Frequency with which abdominal pain started or got worse after a meal	Ordinal	11-point scale from 0% (never) to 100% (always)	
	Frequency with which abdominal pain restricted usual activities	Ordinal	11-point scale from 0% (never) to 100% (always)	
	Frequency of hard or lumpy stools in the past 3 months	Ordinal	5-point scale from 0% (never or rarely) to 100% (always)	
	Frequency of loose, mushy, or watery stools in the past 3 months	Ordinal	5-point scale from 0% (never o rarely) to 100% (always)	
	Frequency of fecal urgency over the past 3 months	Ordinal	9-point scale from never (score, 0) to multiple times per day or all the time (score, 8)	
	Frequency of fecal incontinence over the past 3 months	Ordinal	9-point scale from never (score, 0) to multiple times per day or all the time (score, 8)	
	Frequency of abdominal bloating or distension over the past 3 months	Ordinal	9-point scale from never (score, 0) to multiple times per day or all the time (score, 8)	
Extraintestinal symptoms	All individual items of the PHQ-12 and the frequency experienced in the past 4 weeks: Back pain Arm, leg, joint pain Period pain/period problems Headaches Chest pain Dizziness Fainting spells Heart pounding/racing Shortness of breath Pain/problems during sex Feeling tired or low in energy Trouble sleeping	Ordinal	3-point scale: never (score, 0), a little (score, 1), or a lot (score, 2)	Reporting symptoms referable to multiple body systems, also referred to as *somatization*, is recognized as being associated with IBS and other functional GI disorders The PHQ-12 questionnaire is a widely used and validated method for measuring this

Supplementary Table 1. Continued

	Variable	Type of variable	Measurement scale	Reason for including in the model
Mood	Presence of anxiety, as measured by the total score of the HADS-Anxiety questionnaire	Ordinal	3-point scale: normal (score, 0), borderline (score, 1), or abnormal (score, 2)	Abnormal mood is well recognized as being an important factor in IBS
	Presence of depression, as measured by the total score of HADS-Depression questionnaire	Ordinal	3-point scale: normal (0), borderline (1), or abnormal (2)	The HADS questionnaire for quantifying the presence of anxiety and/or depression are used widely and validated for this purpose

GI, gastrointestinal; HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; PHQ-12, patient health questionnaire-12.

Supplementary Table 2. Demographic and Psychological Characteristics, Employment Status, Income, Work and Productivity, IBS-Related Health Care Costs, Quality of Life, and Median Risk of Death Accepted in Return for Cure of Symptoms of Individuals With Rome IV–Defined IBS Vs Individuals With Self-Reported IBS

	Rome IV–defined IBS (n = 752)	Self-reported IBS (n = 524)	*P* value[a]
Mean age, *y* (SD)	45.3 (14.8)	49.9 (15.7)	<.001
Female, n (%)	655 (87.1)	429 (81.9)	.010
Smoker, n (%)	82 (10.9)	31 (5.9)	.002
White Caucasian ethnicity, n (%)	729 (96.9)	504 (96.2)	.46
Married or cohabiting, n (%)	487 (64.8)	373 (71.2)	.016
University or postgraduate level of education, n (%)	314 (41.8)	224 (42.7)	.72
IBS subtype, n (%)			
IBS-C	136 (18.1)	120 (22.9)	
IBS-D	306 (40.7)	207 (39.5)	
IBS-M	301 (40.0)	174 (33.2)	
IBS-U	9 (1.2)	23 (4.4)	<.001
Most troublesome symptom, n (%)			
Abdominal pain	169 (22.5)	97 (18.5)	
Constipation	53 (7.0)	66 (12.6)	
Diarrhea	117 (15.6)	93 (17.7)	
Abdominal bloating or distension	218 (29.0)	146 (27.9)	
Urgency	195 (25.9)	122 (23.3)	.006
IBS after acute enteric infection, n (%)	91 (12.1)	57 (10.9)	.34
Seen a primary care physician for IBS in the past 12 months, n (%)	294 (39.1)	148 (28.2)	<.001
Seen a gastroenterologist for IBS in the past 12 months, n (%)	147 (19.5)	68 (13.0)	.002
Mean number of drugs for IBS in the past 12 months (SD)	2.2 (1.6)	1.7 (1.4)	<.001
Symptom severity on IBS-SSS, n (%)			
Remission	7 (0.9)	40 (7.6)	
Mild	86 (11.4)	188 (35.9)	
Moderate	300 (39.9)	203 (38.7)	
Severe	359 (47.7)	93 (17.7)	<.001
Mean IBS-SSS score (SD)	293.1 (95.1)	205.6 (100.8)	<.001
HADS Anxiety category, n (%)			
Normal	200 (26.6)	225 (42.9)	
Borderline abnormal	173 (23.1)	139 (26.5)	
Abnormal	378 (50.3)	160 (30.5)	<.001
Mean HADS Anxiety score (SD)	10.7 (4.8)	8.6 (4.4)	<.001
HADS Depression category, n (%)			
Normal	404 (53.7)	401 (76.5)	
Borderline abnormal	165 (21.9)	73 (13.9)	
Abnormal	183 (24.3)	50 (9.5)	<.001
Mean HADS Depression score (SD)	7.6 (4.5)	5.2 (3.8)	<.001
PHQ-12 severity, n (%)			
Minimal	36 (4.8)	77 (14.7)	
Low	176 (23.4)	182 (34.7)	
Medium	307 (40.8)	199 (38.0)	
High	233 (31.0)	66 (12.6)	<.001
Mean PHQ-12 score (SD)	10.3 (4.3)	7.8 (3.9)	<.001

Supplementary Table 2. Continued

	Rome IV–defined IBS (n = 752)	Self-reported IBS (n = 524)	*P* value[a]
Gastrointestinal symptom–specific anxiety on VSI, n (%)			
Low	182 (24.2)	245 (46.8)	
Medium	257 (34.2)	178 (34.0)	
High	313 (41.6)	101 (19.3)	<.001
Mean VSI score (SD)	51.6 (16.5)	39.7 (18.8)	<.001
Disease-specific health-related quality of life on IBS-QOL, n (%)			
Low	308 (41.0)	102 (19.5)	
Medium	274 (36.4)	166 (31.7)	
High	170 (22.6)	256 (48.9)	<.001
Mean IBS-QOL score (SD)	48.4 (22.3)	64.4 (21.4)	<.001
Mean EQ-5D-5L score (SD)	0.570 (0.283)	0.723 (0.220)	<.001
Mean IBS-related costs in £UK[b] (SD)			
Appointments	224.48 (575.33)	110.45 (329.69)	<.001
Investigations	157.69 (352.33)	116.39 (306.72)	.026
Inpatient admissions	101.85 (434.88)	63.80 (323.99)	.074
Drugs	72.62 (96.29)	52.45 (92.24)	<.001
Total	556.64 (1023.92)	343.09 (694.02)	<.001
Currently employed, n (%)	484 (64.4)	336 (64.1)	.93
Annual income of ≥£30,000[b], n (%)	197 (29.0)	134 (28.8)	.94
Mean WPAI percentages (SD)			
Absenteeism	5.0 (13.2)	2.4 (10.6)	.003
Presenteeism	38.5 (27.4)	21.7 (24.7)	<.001
Work impairment	36.4 (28.6)	20.9 (25.0)	<.001
Activity impairment	44.7 (28.7)	26.0 (26.4)	<.001
Any absenteeism on WPAI, n/N (%)	133/467 (28.5)	43/320 (13.4)	<.001
Any presenteeism on WPAI, n/N (%)	373/436 (85.6)	193/299 (64.5)	<.001
Any work impairment on WPAI, n/N (%)	382/467 (81.8)	198/320 (61.9)	<.001
Any activity impairment on WPAI, n (%)	684 (91.0)	376 (71.8)	<.001
Mean WSAS score (SD)	13.6 (9.9)	7.7 (8.2)	<.001
IBS affects home management on WSAS, n (%)	220 (29.3)	65 (12.4)	<.001
IBS affects social leisure activities on WSAS, n (%)	423 (56.3)	153 (29.2)	<.001
IBS affects private leisure activities on WSAS, n (%)	207 (27.5)	61 (11.6)	<.001
IBS affects close relationships on WSAS, n (%)	203 (27.0)	61 (11.6)	<.001
Median risk of death (%) accepted in return for cure of symptoms (IQR)	2.0 (0.0–9.0)	0.0 (0.0–4.75)	<.001

HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; IBS-M, irritable bowel syndrome with mixed bowel habits; IBS-QOL, irritable bowel syndrome quality of life; IBS-SSS, irritable bowel syndrome severity scoring system; IBS-U, irritable bowel syndrome unclassified; IQR, interquartile range; PHQ-12, Patient Health Questionnaire-12; VSI, visceral sensitivity index; WPAI:IBS, Work Productivity and Activity Impairment questionnaire for irritable bowel syndrome; WSAS, Work and Social Adjustment Scale.

[a]*P* value for independent-samples *t* test for continuous data, Pearson χ^2 for comparison of categoric data, and Kruskal–Wallis for comparison of medians.

[b]£1 is equal to $1.20.

Supplementary Table 3. EQ-5D-5L Score Among Individuals with Other Chronic Diseases[22–26] Compared With Each Rome IV IBS Cluster in the Present Study

Chronic disease	Mean EQ-5D-5L score (SD)
Asthma	0.840 (0.200)
Rome IV IBS cluster 3	0.776 (0.114)
Menopause	0.729 (0.262)
Rome IV IBS cluster 7	0.717 (0.132)
Rome IV IBS cluster 1	0.689 (0.185)
Diabetes mellitus	0.673 (0.283)
Rheumatoid arthritis	0.660 (0.270)
Heart failure	0.640 (0.270)
Low back pain	0.636 (0.266)
Elderly, age, >75 y	0.614 (0.299)
Stroke	0.612 (0.318)
Rome IV IBS	0.570 (0.283)
Leg ulcers	0.552 (0.307)
Chronic obstructive pulmonary disease	0.540 (0.309)
Rome IV IBS cluster 2	0.516 (0.256)
Rome IV IBS cluster 4	0.455 (0.276)
Osteoarthritis	0.442 (0.336)
Rome IV IBS cluster 5	0.389 (0.374)
Rome IV IBS cluster 6	0.186 (0.305)

EQ-5D-5L, EuroQOL 5-dimension 5-level version; IBS, irritable bowel syndrome.

Supplementary Table 4. Unit Costs (in £UK) for IBS-Related Appointments, Investigations, and Unplanned Hospital Attendances or Admissions

	Cost, £
Follow-up appointment with a GP	33.00
Follow-up appointment with a gastroenterologist	148.12
Follow-up appointment with a specialist nurse	127.91
Follow-up appointment with a dietician	83.03
Follow-up appointment with a psychologist	179.84
Blood test	1.81
Stool test	8.09
Gastroscopy	482.23
Colonoscopy	559.35
Hydrogen breath test	57.96
Abdominal ultrasound	62.39
Abdominal computed tomography	114.36
Abdominal magnetic resonance imaging	144.29
23-seleno-25-homo-tauro-cholic acid scan	367.73
Emergency department attendance	220.53
Inpatient admission under gastroenterology	1551.77

GP, general practitioner; IBS, irritable bowel syndrome.

Supplementary Table 5. Unit Costs (in £UK) for a 1-Month Supply of IBS-Related Medications

	Cost, £
Loperamide	1.68
Sodium picosulfate	4.62
Bisacodyl	1.67
Polyethylene glycol	2.99
Hyoscine	9.63
Alverine	7.64
Mebeverine	4.39
Dicycloverine	30.00
Ispaghula	3.24
Peppermint oil	4.95
Amitriptyline	1.08
Nortriptyline	1.00
Imipramine	2.15
Fluoxetine	0.50
Paroxetine	1.26
Sertraline	0.80
Citalopram	1.02
Escitalopram	1.55
Lubiprostone	53.48
Linaclotide	37.56
Prucalopride	47.62
Eluxadoline	88.20

IBS, irritable bowel syndrome.