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Novel Irritable Bowel Syndrome Subgroups are Reproducible in the Global Adult Population

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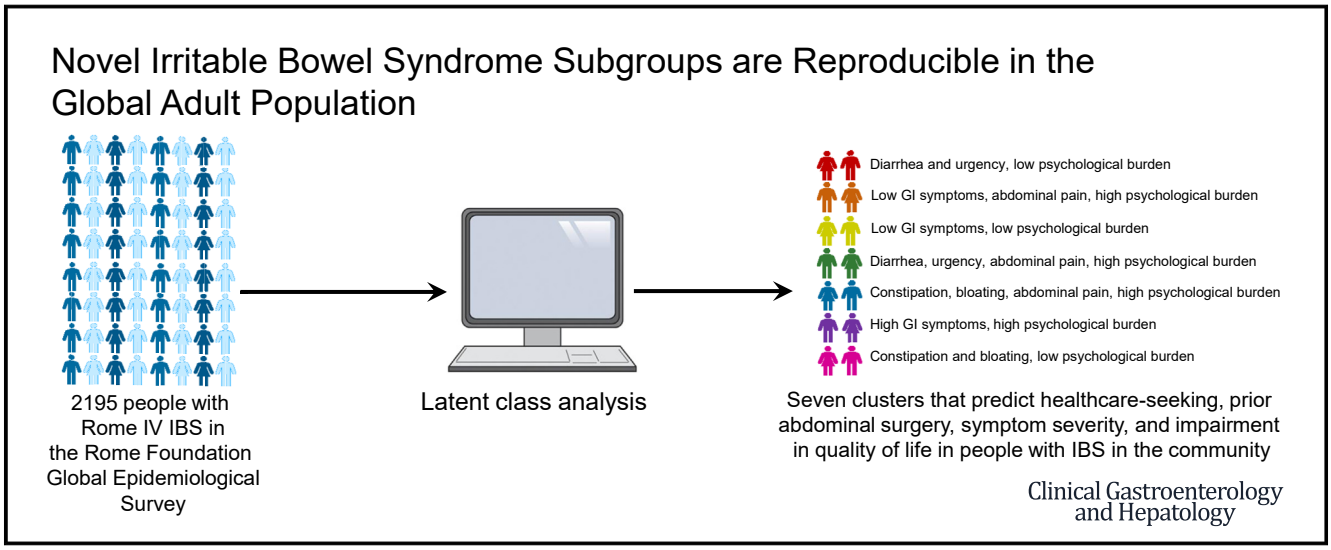

BACKGROUND & AIMS: **Current classification systems for irritable bowel syndrome (IBS) based on bowel habit do not consider psychological impact. We validated a classification model in a UK population with confirmed IBS, using latent class analysis, incorporating psychological factors. We applied this model in the Rome Foundation Global Epidemiological Survey (RFGES), assessing impact of IBS on the individual and the health care system, and examining reproducibility.**

METHODS: **We applied our model to 2195 individuals in the RFGES with Rome IV–defined IBS. As described previously, we identified 7 clusters, based on gastrointestinal symptom severity and psychological burden. We assessed demographics, health care–seeking, symptom severity, and quality of life in each. We also used the RFGES to derive a new model, examining whether the broader concepts of our original model were replicated, in terms of breakdown and characteristics of identified clusters.**

RESULTS: **All 7 clusters were identified. Those in clusters with highest psychological burden, and particularly cluster 6 with high overall gastrointestinal symptom severity, were more often female, exhibited higher levels of health care–seeking, were more likely to have undergone previous abdominal surgeries, and had higher symptom severity and lower quality of life**

Abbreviations used in this paper: BIC(LL), Bayesian information criterion of the log-likelihood; IBS, irritable bowel syndrome; LCA, latent class analysis; PROMIS, Patient-Reported Outcomes Measurement Information System; RFGES, Rome Foundation Global Epidemiological Survey.

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($P < .001$ for trend for all). When deriving a new model, the best solution consisted of 10 clusters, although at least 2 seemed to be duplicates, and almost all mapped on to the previous clusters.

CONCLUSIONS: **Even in the community, our original clusters derived from patients with physician-confirmed IBS identified groups of individuals with significantly higher rates of health care–seeking and abdominal surgery, more severe symptoms, and impairments in quality of life.**

Keywords: Irritable Bowel Syndrome; Latent Class Analysis; Subgrouping; Quality of Life; Surgery.

Irritable bowel syndrome (IBS) is a chronic disorder,[1] diagnosed using symptom-based criteria, with Rome IV representing the current gold standard.[2] These consist of abdominal pain at least once per week with 2 or more of the following: related to defecation, associated with a change in stool frequency, or associated with a change in stool form. Using these criteria, prevalence of IBS in the community is 4%.[3] There is no unifying pathophysiologic explanation for IBS,[4] and no associated increase in mortality.[5] Nevertheless, patients demonstrate impairment in quality of life,[6] ability to work, and social functioning.[7] In addition, IBS represents a considerable financial burden to health care systems.[8]

Although IBS is a gut-brain disorder, patients are subtyped exclusively according to bowel symptoms, based on predominant stool form. There are 4 subtypes: (1) IBS with diarrhea, (2) IBS with constipation, (3) IBS with mixed bowel habits, and (4) IBS unclassified. However, psychological comorbidity is common in IBS. Symptoms compatible with anxiety or depression affect 30%–40% of patients,[9] and somatization scores are elevated.[10] These associated features are not included in current subtyping systems. Nor do subtypes based on stool form predict disease impact or burden of IBS.[11] Over the past 7 years, several studies have used a statistical technique called latent class analysis (LCA) to subgroup patients with IBS using gastrointestinal and psychological symptoms.[12–14] The results are relatively consistent, demonstrating clusters of people with IBS with high levels of gastrointestinal symptoms, clusters with high levels of psychological symptoms, and clusters with high levels of both gastrointestinal and psychological symptoms.

In our own study,[12] LCA identified 7 clusters consisting of diarrhea and urgency with low psychological burden (cluster 1); low overall gastrointestinal symptom severity with abdominal pain and high psychological burden (cluster 2); low overall gastrointestinal symptom severity with low psychological burden (cluster 3); diarrhea, abdominal pain, and urgency with high psychological burden (cluster 4); constipation, abdominal pain, and bloating with high psychological burden (cluster 5); high overall gastrointestinal symptom severity with high psychological burden (cluster 6); and constipation and bloating with low psychological burden (cluster 7). During longitudinal follow-up,[15] these clusters predicted disease course. Clusters with the highest psychological burden at baseline had more severe symptoms subsequently, received more drugs, and were more likely to consult a doctor with symptoms than clusters with lower psychological burden. Applying our model to a separate cohort of patients, individuals in clusters with the highest psychological burden had substantial impairment in quality of life, earning potential, and ability to work and function socially, and were higher users of health care.[14]

However, these studies have mainly been performed in patients with a physician-confirmed diagnosis of IBS in the United Kingdom and Europe. The Rome Foundation Global Epidemiological Survey (RFGES) represents a unique opportunity to examine the epidemiology of clusters globally in a community setting. We, therefore, aimed to examine impact of the clusters identified by our previous model in the RFGES, in terms of health care–seeking behavior, symptom severity, and quality of life. However, because the RFGES population differs from our original study cohort with respect to geography and clinical setting, we also used it to derive a new LCA model to assess whether the broader concepts of our initial model could be replicated, in terms of the breakdown and characteristics of identified clusters. If confirmed, this provides external validity for using this approach to subgroup patients with IBS across community and specialist clinical settings.

Methods

Participants and Setting

Methodology of the RFGES has been described elsewhere.[3] It was conducted under the auspices of the Rome Foundation Research Institute. Participants from 26 countries were invited to complete an online symptom survey and were selected according to demographic characteristics. Further details are provided in the Supplementary Methods.

Data Collection and Synthesis

The online survey included the entire Rome IV Adult Diagnostic Questionnaire; sociodemographic items; and questions on prior medical diagnoses, health care utilization (frequency of doctor visits, medications for

gastrointestinal and other symptoms, prior abdominal surgeries), and concern about, and impact of stress on, bowel function. It also included the Irritable Bowel Syndrome Severity Scoring System,[16] the Patient Health Questionnaire-12,[17] a screening tool for somatoform symptom-reporting, the Patient Health Questionnaire-4 for anxiety and depression,[18] and the Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10 questionnaire.[19] The latter is a publicly available global health assessment tool measuring health care–related quality of life for various chronic diseases and conditions.

Statistical Analysis

We applied the LCA model that we derived and validated previously to all individuals meeting Rome IV criteria for IBS.[12] LCA is a method of structural equation modeling used to identify unobserved groups, or latent classes, within observed multivariate data.[20] Because the syntax for our LCA model derived previously is stored as syntax, it can be applied easily to other datasets that collect the same variables. We compared categorical variables of the 7 clusters identified previously, including sex, IBS subtype, most bothersome symptom, health care utilization, whether IBS had been confirmed by a doctor, other related medical diagnoses, prior surgeries, prescribed medications, concern about bowel function, impact of stress on bowel function, and IBS symptom severity between each of the 7 clusters using a chi-square test. We compared differences in continuous variables, such as age and PROMIS Global-10 scores, using a 1-way analysis of variance test. Because of multiple comparisons, we considered a 2-tailed P value of $<$ .01 as indicating statistical significance for these analyses, which we performed using SPSS for Windows version 29.0 (SPSS Inc, Chicago, IL).

We performed a second LCA using LatentGOLD version 6.0 (Statistical Innovations, Belmont, MA) in all respondents with Rome IV IBS to derive a new model and assess whether our previously observed clusters were generally reproducible. A statistical model was postulated for the population from which the data sample was obtained, and it was assumed a mixture of underlying probability distributions generated the data.[21] The use of LCA for this purpose is called model-based clustering and 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.[21] Robust statistical criteria are used to determine the best fit of the model and the optimum number of clusters.[22] We used the Bayesian information criterion of the log-likelihood (BIC[LL]) for this purpose, selecting the cluster solution with the lowest BIC(LL) value as the one best fitting the data.

What You Need to Know

Background

We applied our novel classification system for patients with irritable bowel syndrome (IBS), incorporating gastrointestinal and psychological symptoms, to the Rome Foundation Global Epidemiological Survey, assessing impact and burden of IBS.

Findings

The clusters derived from our latent class analysis model identified individuals in the community with IBS with higher rates of healthcare-seeking and prior abdominal surgery, more severe symptoms, and worse quality of life.

Implications for patient care

These clusters could be used to tailor treatment approaches for patients with IBS, based on whether gastrointestinal symptoms, psychological symptoms, or both, predominate.

In this second model, for each cluster, we drew a radar plot, using z-values for each variable. We calculated these by adjusting the cluster mean for each variable to the cohort mean and standard deviation for that variable. We crosstabulated clusters derived in the new LCA model with clusters from the existing model to see if they were broadly corroborative of the groups of individuals identified previously.

Results

Of 54,127 RFGES participants, 2195 (4.1%) met Rome IV criteria for IBS (1390 [63.3%] female; mean age, 39.2 years [standard deviation, 13.8 years]). Overall, 319 (14.5%) stated their IBS symptoms commenced after an acute enteric infection, 1180 (53.8%) had seen a primary care physician with IBS, and 813 (37.0%) a gastroenterologist. Applying the 7-cluster solution from the existing LCA model, there were 140 (6.4%) individuals in cluster 1 (diarrhea and urgency with low psychological burden), 717 (32.7%) in cluster 2 (low overall gastrointestinal symptom severity with abdominal pain and high psychological burden), 783 (35.7%) in cluster 3 (low overall gastrointestinal symptom severity with low psychological burden), 212 (9.7%) in cluster 4 (diarrhea, abdominal pain, and urgency with high psychological burden), 56 (2.6%) in cluster 5 (constipation, abdominal pain, and bloating with high psychological burden), 91 (4.1%) in cluster 6 (high overall gastrointestinal symptom severity with high psychological burden), and 196 (8.9%) in cluster 7 (constipation and bloating with low psychological burden) (Figure 1). There were more individuals in cluster 2 in Eastern Europe, more

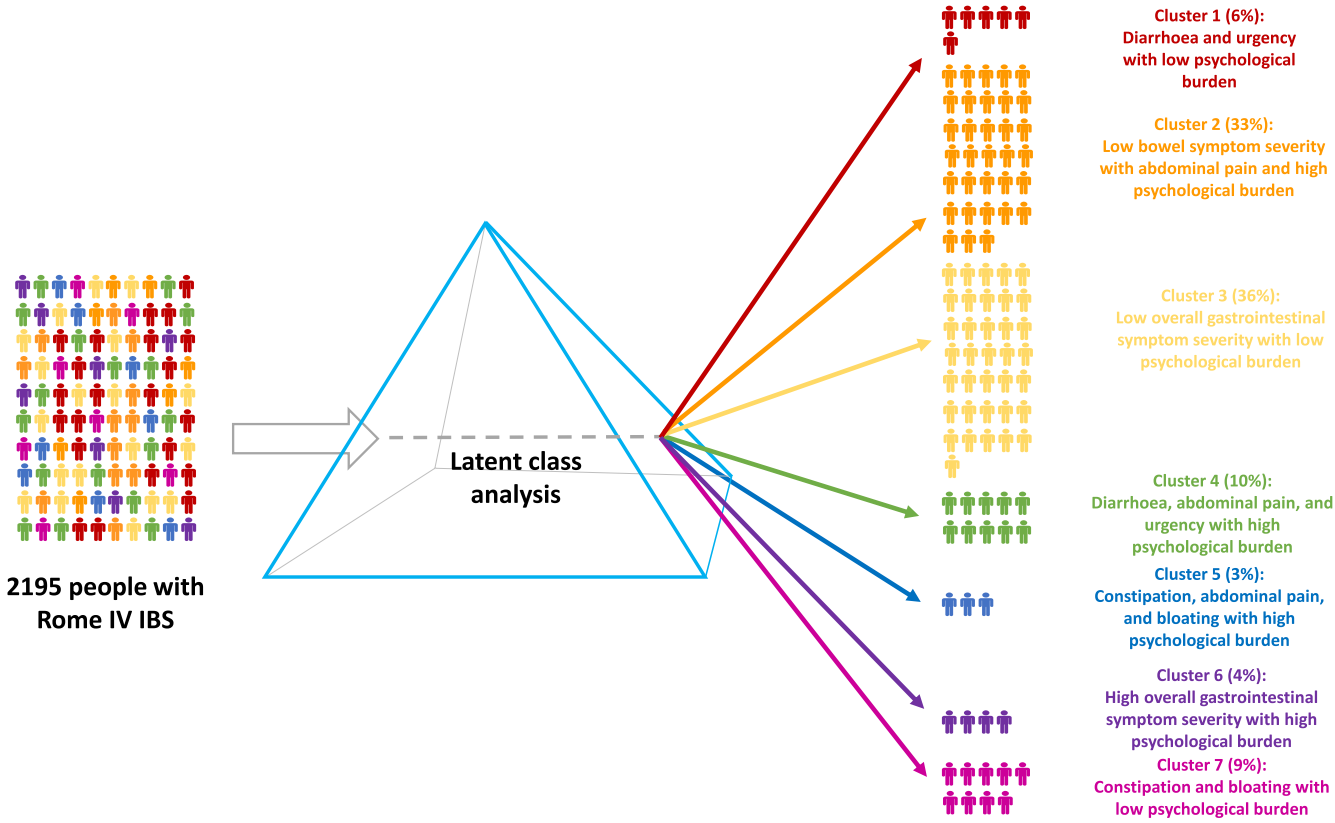

Figure 1. Latent class analysis using the existing 7-cluster model in 2195 people with Rome IV IBS in the community in the Rome Foundation Global Epidemiology Survey.

individuals in cluster 3 in Asia, and more individuals in cluster 6 in North America ($P < .001$) (Figure 2).

Characteristics of Individuals According to Cluster in the Existing Latent Class Analysis Model

Similar to the original derivation and validation study, those in clusters 2, 4, and 5, with the highest psychological burden, and those with constipation in cluster 7, were more likely to be female ($P < .001$) (Table 1). Those with diarrhea in clusters 1 and 4, and those with high overall gastrointestinal symptom severity with high psychological burden in cluster 6 were more likely to report acute gastroenteritis triggering their IBS. There was no significant difference in body mass index across clusters. As would be expected, IBS

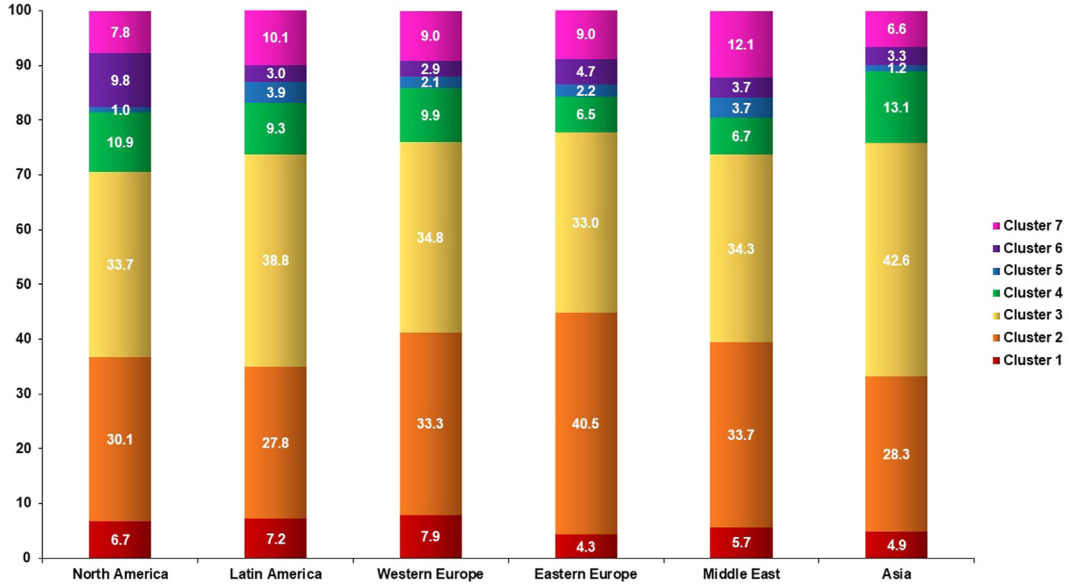

Figure 2. Distribution of clusters in the existing 7-cluster model according to geographical region.

Table 1. Demographic Characteristics of Individuals in Each of the 7 Clusters and Association of the Clusters with Health Care Utilization, Other Related Medical Diagnoses, Previous Surgeries, Medication Use, IBS Symptom Severity, and Quality of Life

	Cluster 1 Diarrhea and urgency with low psychological burden (n = 140)	Cluster 2 Low bowel symptom severity with abdominal pain and high psychological burden (n = 717)	Cluster 3 Low overall gastrointestinal symptom severity with low psychological burden (n = 783)	Cluster 4 Diarrhea, abdominal pain, and urgency with high psychological burden (n = 212)	Cluster 5 Constipation, abdominal pain, and bloating with high psychological burden (n = 56)	Cluster 6 High overall gastrointestinal symptom severity with high psychological burden (n = 91)	Cluster 7 Constipation and bloating with low psychological burden (n = 196)	*P* value[a]
Mean age, *y* (SD)	38.9 (13.7)	38.9 (13.7)	39.8 (14.7)	38.8 (12.6)	38.0 (12.3)	38.2 (10.7)	39.8 (14.1)	.76
Mean body mass index (SD)	26.2 (6.6)	26.2 (6.9)	25.6 (6.2)	26.4 (7.8)	26.3 (5.4)	26.1 (7.3)	24.9 (5.6)	.22
Female	75 (53.6)	469 (65.4)	450 (57.5)	150 (70.8)	44 (78.6)	49 (53.8)	153 (78.1)	< .001
IBS after acute gastroenteritis	30 (21.4)	88 (12.3)	85 (10.9)	45 (21.2)	7 (12.5)	32 (35.2)	32 (16.3)	< .001
IBS subtype on BSFS								
IBS-C	14 (10.0)	236 (32.9)	216 (27.6)	22 (10.4)	44 (78.6)	23 (25.3)	157 (80.1)	
IBS-D	80 (57.1)	174 (24.3)	251 (32.1)	103 (48.6)	0 (0.0)	19 (20.9)	2 (1.0)	
IBS-M	45 (32.1)	260 (36.3)	233 (29.8)	86 (40.6)	10 (17.9)	48 (52.7)	30 (15.3)	
IBS-U	1 (0.7)	47 (6.6)	83 (10.6)	1 (0.5)	2 (3.6)	1 (1.1)	7 (3.6)	< .001
Most bothersome symptom in last 3 mo								
Abdominal pain	33 (23.6)	221 (30.8)	292 (37.3)	63 (29.7)	16 (28.6)	38 (41.8)	51 (26.0)	
Diarrhea	69 (49.3)	113 (15.8)	150 (19.2)	82 (38.7)	0 (0.0)	19 (20.9)	5 (2.6)	
Constipation	9 (6.4)	152 (21.2)	125 (16.0)	13 (6.1)	17 (30.4)	14 (15.4)	89 (45.4)	
Bloating or distention	26 (18.6)	206 (28.7)	190 (24.3)	50 (23.6)	21 (37.5)	19 (20.9)	50 (25.5)	< .001
Other	3 (2.1)	25 (3.5)	26 (3.3)	4 (1.9)	2 (3.6)	1 (1.1)	1 (0.5)	
How often do you see a doctor for your health								
Once a month or more	34 (24.3)	204 (28.5)	131 (16.7)	70 (33.0)	26 (46.4)	45 (49.5)	46 (23.5)	
A few times a year	64 (45.7)	373 (52.0)	441 (56.3)	92 (43.4)	24 (42.9)	38 (41.8)	104 (53.1)	
Once a year	22 (15.7)	58 (8.1)	88 (11.2)	17 (8.0)	2 (3.6)	1 (1.1)	17 (8.7)	
Less than once a year	15 (10.7)	68 (9.5)	106 (13.5)	25 (11.8)	2 (3.6)	6 (6.6)	26 (13.3)	
Never	5 (3.6)	14 (2.0)	17 (2.2)	8 (3.8)	2 (3.6)	1 (1.1)	3 (1.5)	< .001
Seen a primary care physician with bowel problems	74 (52.8)	391 (54.5)	382 (48.8)	124 (58.5)	33 (58.9)	64 (70.3)	112 (57.1)	.0015
Seen a gastroenterologist with bowel problems	64 (45.7)	263 (36.7)	258 (33.0)	79 (37.3)	24 (42.9)	49 (53.8)	76 (38.8)	< .001

Table 1. Continued

	Cluster 1 Diarrhea and urgency with low psychological burden (n = 140)	Cluster 2 Low bowel symptom severity with abdominal pain and high psychological burden (n = 717)	Cluster 3 Low overall gastrointestinal symptom severity with low psychological burden (n = 783)	Cluster 4 Diarrhea, abdominal pain, and urgency with high psychological burden (n = 212)	Cluster 5 Constipation, abdominal pain, and bloating with high psychological burden (n = 56)	Cluster 6 High overall gastrointestinal symptom severity with high psychological burden (n = 91)	Cluster 7 Constipation and bloating with low psychological burden (n = 196)	*P* value[a]
Diagnosed by a doctor as having IBS	59 (42.1)	232 (32.6)	202 (25.8)	89 (42.0)	18 (32.1)	52 (57.1)	64 (32.7)	< .001
Diagnosed by a doctor as having gastroesophageal reflux	41 (29.3)	242 (33.8)	224 (28.6)	80 (37.7)	23 (41.1)	51 (56.0)	55 (28.1)	< .001
Diagnosed by a doctor as having fibromyalgia	7 (5.0)	50 (7.0)	18 (2.3)	18 (8.5)	7 (12.5)	12 (13.2)	16 (8.2)	< .001
Previous cholecystectomy	24 (17.1)	52 (7.3)	42 (5.4)	27 (12.7)	4 (7.1)	21 (23.1)	7 (3.6)	< .001
Previous appendectomy	15 (10.7)	117 (16.3)	104 (13.3)	33 (15.6)	7 (12.5)	29 (31.9)	31 (15.8)	< .001
Previous hysterectomy	10/75 (13.3)	30/469 (6.4)	22/450 (4.9)	12/150 (8.0)	0/44 (0.0)	13/49 (26.5)	11/153 (7.2)	< .001
Medication for constipation at least once weekly	34 (24.3)	173 (24.1)	106 (13.5)	40 (18.9)	25 (44.6)	49 (53.8)	60 (30.6)	< .001
Medication for diarrhea at least once weekly	47 (33.6)	109 (15.2)	104 (13.3)	57 (26.9)	2 (3.6)	42 (46.2)	14 (7.1)	< .001
Medication for pain (prescribed) at least once weekly	48 (34.3)	289 (40.3)	196 (25.0)	79 (37.3)	31 (55.4)	64 (70.3)	77 (39.3)	< .001
Medication for gas or bloating at least once weekly	43 (30.7)	213 (29.7)	184 (23.5)	66 (31.1)	27 (48.2)	53 (58.2)	61 (31.1)	< .001
Medication for anxiety at least once weekly	28 (20.0)	216 (30.1)	97 (12.4)	64 (30.2)	22 (39.3)	40 (44.0)	35 (17.9)	< .001
Medication for depression at least once weekly	20 (14.3)	190 (26.5)	76 (9.7)	56 (26.4)	22 (39.3)	40 (44.0)	30 (15.3)	< .001
Medication for sleeping at least once weekly	28 (20.0)	204 (28.5)	93 (11.9)	60 (28.3)	22 (39.3)	43 (47.3)	35 (17.9)	< .001

Table 1. Continued

	Cluster 1 Diarrhea and urgency with low psychological burden (n = 140)	Cluster 2 Low bowel symptom severity with abdominal pain and high psychological burden (n = 717)	Cluster 3 Low overall gastrointestinal symptom severity with low psychological burden (n = 783)	Cluster 4 Diarrhea, abdominal pain, and urgency with high psychological burden (n = 212)	Cluster 5 Constipation, abdominal pain, and bloating with high psychological burden (n = 56)	Cluster 6 High overall gastrointestinal symptom severity with high psychological burden (n = 91)	Cluster 7 Constipation and bloating with low psychological burden (n = 196)	*P* value[a]
How concerned are you about your bowel functioning								
Not at all	9 (6.4)	79 (11.0)	119 (15.2)	10 (4.7)	4 (7.1)	1 (1.1)	17 (8.7)	
Somewhat	84 (60.0)	463 (64.6)	547 (69.9)	113 (53.3)	19 (33.9)	36 (39.6)	114 (58.2)	
Very	47 (33.6)	175 (24.4)	117 (14.9)	89 (42.0)	33 (58.9)	54 (59.3)	65 (33.2)	< .001
Does stress, tension, or pressure affect your bowel function								
Not at all	19 (13.6)	38 (5.3)	104 (13.3)	13 (6.1)	2 (3.6)	5 (5.5)	25 (12.8)	
Somewhat	58 (41.4)	314 (43.8)	380 (48.5)	71 (33.5)	19 (33.9)	24 (26.4)	90 (45.9)	
Greatly	63 (45.0)	365 (50.9)	299 (38.2)	128 (60.4)	35 (62.5)	62 (68.1)	81 (41.3)	< .001
Symptom severity on IBS-SSS								
Remission	1 (0.7)	23 (3.2)	76 (9.7)	2 (0.9)	0 (0.0)	0 (0.0)	7 (3.6)	
Mild	18 (12.9)	118 (16.5)	260 (33.2)	14 (6.6)	0 (0.0)	5 (5.5)	29 (14.8)	
Moderate	66 (47.1)	365 (50.9)	351 (44.8)	77 (36.3)	12 (21.4)	25 (27.5)	87 (44.4)	
Severe	55 (39.3)	208 (29.0)	91 (11.6)	116 (54.7)	44 (78.6)	61 (67.0)	72 (36.7)	< .001
Mean physical health score on PROMIS-10 (SD)	12.8 (2.4)	10.9 (2.3)	13.2 (2.3)	10.6 (2.6)	9.0 (2.2)	9.6 (2.5)	12.2 (2.6)	< .001
Mean mental health score on PROMIS-10 (SD)	12.6 (3.0)	10.1 (3.0)	12.6 (3.0)	9.6 (3.3)	8.8 (2.7)	9.9 (3.8)	12.0 (3.3)	< .001

NOTE. Values are number (%) or (SD).
BSFS, Bristol Stool Form Scale; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, IBS with mixed bowel habits; IBS-SSS, Irritable Bowel Syndrome Severity Scoring System; IBS-U, IBS unclassified; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.
[a]*P* value for Pearson chi-square test for comparison of categorical data and 1-way analysis of variance for comparison of means.

subtype and most troublesome symptom reported varied significantly by cluster. Most of those in clusters 1 and 4, where diarrhea was the predominant gastrointestinal symptom, met criteria for IBS with diarrhea or IBS with mixed bowel habits. In clusters 5 and 7, where constipation was a predominant symptom, most met criteria for IBS with constipation. In clusters 2, 3, and 6, with mixed gastrointestinal symptoms, no one subtype predominated ($P < .001$). The highest proportion of people reporting abdominal pain as the most bothersome symptom was in cluster 6 (41.8%; $P < .001$), with the highest levels of both gastrointestinal and psychological symptoms.

People in cluster 6 were also more likely than other clusters to see a doctor at least once a month (49.5%; $P < .001$); to have seen a primary care physician (70.3%; $P = .0015$) or gastroenterologist (53.8%; $P < .001$); or to have been diagnosed with IBS (57.1%), gastroesophageal reflux (56.0%), or fibromyalgia (13.2%) ($P < .001$ for all). They were also more likely to have undergone cholecystectomy (23.1%), appendectomy (31.9%), or hysterectomy (26.5%) ($P < .001$ for all) and more likely to be taking medication at least once weekly for constipation (53.8%), diarrhea (46.2%), pain (70.3%), gas or bloating (58.2%), anxiety (44.0%), depression (44.0%), or to help sleep (47.3%) ($P < .001$ for all). Concerns about bowel function were highest in clusters 5 and 6, and reporting that stress affected bowel function highest in clusters 4, 5, and 6 ($P < .001$ for all). Rates of severe IBS symptoms on the Irritable Bowel Syndrome Severity Scoring System were highest in clusters 5 and 6 (78.6% and 67.0%, respectively; $P < .001$). Finally, physical and mental health scores on the PROMIS-10 were lowest in clusters 2, 4, 5, and 6, the 4 clusters with the highest psychological burden ($P < .001$ for all).

Clusters Derived in the New Latent Class Analysis Model

The best solution was achieved with 10 clusters, with the lowest value of the BIC(LL) (Supplementary Table 1). Radar plots for each new cluster, and the existing 7 clusters, are presented in Supplementary Figures 1 and 2. Crosstabulation of the 10 clusters against those from the existing 7-cluster model is provided in Supplementary Table 2. In the new 10-cluster model, clusters 1 and 9 seemed to represent cluster 3 (low overall gastrointestinal symptom severity with low psychological burden) in the existing model. Clusters 2 and 6 mapped onto existing cluster 2 (low overall gastrointestinal symptom severity with abdominal pain and high psychological burden). Cluster 3 consisted of a combination of individuals in existing cluster 1 (diarrhea and urgency with low psychological burden) and cluster 3 (low overall gastrointestinal symptom severity with low psychological burden). Cluster 4 was a mixture of existing cluster 2 (low overall gastrointestinal symptom severity with abdominal pain and high psychological burden) and cluster 3 (low overall gastrointestinal symptom severity with low psychological burden). Cluster 5 was a combination of existing cluster 2 (low overall gastrointestinal symptom severity with abdominal pain and high psychological burden) and cluster 6 (high overall gastrointestinal symptom severity with high psychological burden). Cluster 7 seemed to represent existing cluster 7 (constipation and bloating with low psychological burden). Cluster 8 was mainly made up of individuals in existing cluster 4 (diarrhea, abdominal pain, and urgency with high psychological burden). Finally, most individuals in cluster 10 in the new model were from existing cluster 6 (high overall gastrointestinal symptom severity with high psychological burden). The only cluster from the existing model that did not seem to map onto any of the new clusters was cluster 5 (constipation, abdominal pain, and bloating with high psychological burden), the smallest cluster when the existing model was applied in the RFGES. Most individuals in this cluster, however, were found in clusters 5 and 7 in the new model. Assignment of people in the 7 clusters in the existing model across the 10 clusters derived from the new model was greater than expected by chance ($P < .001$).

Given the BIC(LL) for 7–10 cluster models were very similar, indicating little difference in degree of model fit, we assessed the new 7-cluster model in the Supplementary Results.

Discussion

We applied our existing LCA model for IBS to 2195 individuals meeting Rome IV criteria for the condition in the RFGES dataset. We confirmed the existence of all 7 clusters previously identified in patients with IBS in this large multinational community-based dataset. We examined characteristics of individuals according to cluster. As in our previous studies, the proportions of female individuals were greatest in clusters with the highest psychological burden and, as would be expected, stool subtypes and predominant symptom reported varied by cluster. In addition, health care–seeking behavior was significantly higher in clusters with the highest psychological burden, as were the proportion of individuals with a formal diagnosis of IBS from their doctor. In the high psychological burden clusters, rates of medication use for gastrointestinal and psychological symptoms, IBS symptom severity scores, and self-reported concern about bowel symptoms were highest and quality of life scores lowest. Because the RFGES collected other information, we demonstrated associations between clusters with the highest levels of psychological burden and other chronic diseases, including gastroesophageal reflux and fibromyalgia, and consistently, and significantly, higher rates of prior abdominal surgeries in cluster 6, the cluster with the highest levels of both gastrointestinal and psychological symptoms. Cluster membership differed significantly by

geographical region, with a higher proportion of individuals in Asia found in cluster 3, the cluster with low overall gastrointestinal symptom severity with low psychological burden, and a higher proportion of individuals in North America in cluster 6. Finally, when we used the RFGES to derive a new LCA model, the best solution consisted of 10 clusters, although at least 2 of these seemed to be duplicate clusters, and almost all mapped on to the clusters we reported previously. In a new 7-cluster model, which had a similar BIC(LL), 6 of 7 clusters mapped on to clusters in the existing model.

Limitations of the study are those reported elsewhere in publications arising from the RFGES. Although nationally representative samples of individuals were drawn, and uniform methods used to obtain data, a diagnosis of IBS was not confirmed. They were, however, asked to report coexistence of any organic gastrointestinal diseases that may present with similar symptoms to IBS, such as celiac disease or inflammatory bowel disease,[23,24] and those with these conditions were excluded from the definition of IBS. This may, of course, be subject to bias because it was by self-report. In addition, some geographical regions were not well-represented in the online survey, including Africa and South Asia. In terms of the LCA analysis, because this was a cross-sectional study, we can only report associations between the clusters and the data collected in the RFGES, not the direction of any effects. It is, therefore, unclear whether health care–seeking behavior, medication use, and poor quality of life drives individuals into these clusters, or whether the converse is true.

As in previous studies we demonstrated that, even in a community-based dataset where there are more likely to be individuals with milder symptoms, the 7 clusters predicted disease burden and impact. However, the new 10-cluster model we derived in the RFGES differed somewhat from our previous model. This may relate, in part, to the fact that there were 26 separate countries taking part and, therefore, there are likely to be ethnic, cultural, or dietary variations influencing gastrointestinal and psychological symptom reporting, and severity. This is supported, to some degree, by the geographical differences observed in cluster membership. On that note, there is likely to be a much wider range of gastrointestinal and psychological symptom severities in a community sample of individuals meeting Rome IV criteria for IBS, such as this, compared with cohorts of people known to have IBS that prior LCA studies have been conducted in. This is reflected in the observation that at least 4 of the clusters observed in the new 10-cluster model seemed to derive mainly from the 2 clusters with the lowest gastrointestinal symptom severity in the previous 7-cluster model. In addition, cluster 5, the constipation, abdominal pain, and bloating with high psychological burden cluster, was not replicated in this model. However, this was the smallest group in the RFGES, with only 56 individuals; most of these participants were in clusters 5 or 7 in the new 10-cluster model; and it has been shown previously that core symptoms of constipation in IBS with constipation may differ globally, particularly in Asia.[25] Finally, although a 10-cluster model was the optimum solution in the new LCA, there was actually very little separating models of 7–10 clusters assessed using numerical measures of model fit. Hence, although a higher number of clusters was preferred mathematically, it is debatable whether this additional statistical discrimination is either clinically relevant or useful. This is highlighted by the way in which the new clusters map onto those of our original model. Moreover, visual inspection of clusters to establish whether they are clinically intuitive is an important aspect of model validation.

Despite some differences, our study results provide further support for a subgrouping system based on combinations of gastrointestinal and psychological symptoms, which perhaps better reflects the complex construct that IBS represents. This supports the multidimensional clinical approach proposed by the Rome Foundation, a framework that, in addition to clinical symptoms, includes assessment of psychological factors, and impact of the illness, to build a unique clinical profile for each patient.[26] There are clearly groups of people with IBS with low levels of gastrointestinal and psychological symptoms, who may be best managed with simple dietary advice, first-line drugs, or reassurance. There are also individuals with predominantly gastrointestinal symptoms, in whom use of a peripherally acting drug targeting predominant gastrointestinal symptom would be the optimal approach, and those with mainly abdominal pain and psychological symptoms who may benefit from a brain-gut behavioral therapy. For those with a combination of gastrointestinal and psychological symptoms, combination therapy with a peripherally acting drug and either a gut-brain neuromodulator or a brain-gut behavioral therapy may be required. Finally, there is a group with high levels of gastrointestinal and psychological symptoms, and in whom there is a high prevalence of other chronic medical conditions and previous abdominal surgery, who may be best served by psychological input and a multidisciplinary approach.

Biomarkers or mechanistic insights that provide evidence for response of subsets of patients with IBS to a particular drug or dietary or brain-gut behavioral therapy remain sparse, and even when drugs are targeted to bowel habit, most of patients do not experience improvement in symptoms.[27,28] Future studies examining different treatment approaches, such as those described previously, in individual clusters of patients, rather than subtyping all patients according to stool pattern and treating them accordingly, may yield valuable insights into the optimal management of IBS.

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 http://doi.org/10.1016/j.cgh.2024.05.042.

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Conflicts of interest
The authors disclose no conflicts.

Supplementary Methods

The Rome Foundation Global Epidemiological Survey (RFGES) included at least 2000 participants in each country, 50% females and 50% males, 40% aged 18–39 years, 40% aged 40–64 years, and 20% aged 65 years or older, and with a representative national geographic distribution. The 26 countries were Argentina, Australia, Belgium, Brazil, Canada, China, Colombia, Egypt, France, Germany, the Netherlands, Israel, Italy, Japan, Mexico, Poland, Romania, Russia, South Africa, South Korea, Singapore, Spain, Sweden, Turkey, United Kingdom, and United States. The online survey was conducted using an Internet survey platform (Qualtrics, LLC, Provo, UT).

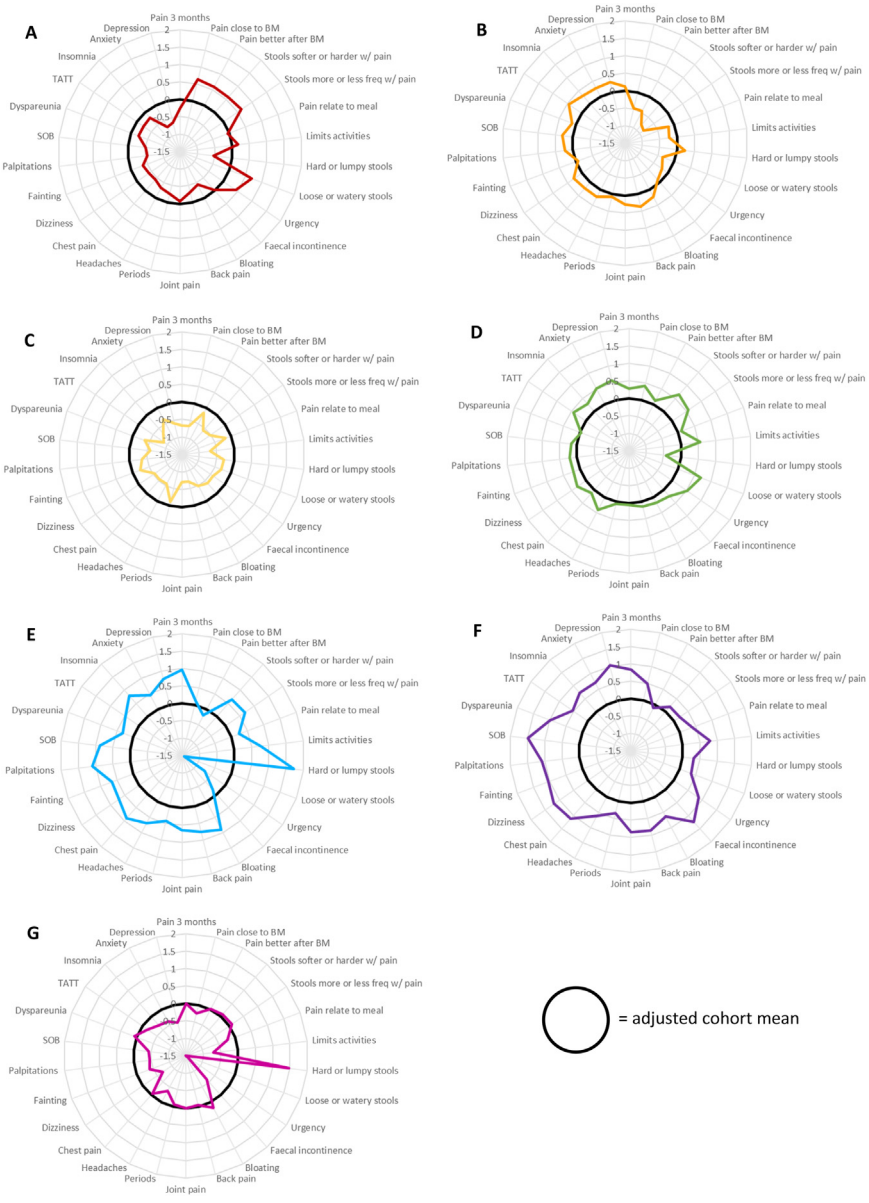
An ethical review was performed for all participating countries. Formal ethical approval was waived by the institutional review board of the University of North Carolina at Chapel Hill, where data collection was coordinated, given the data collected were anonymous to investigators with no means of identification either in the present or future. The survey had multiple built-in quality-assurance measures to exclude poor-quality responders to reduce the risk of missing data or incorrect values. The online questionnaire included electronic informed consent. Only individuals meeting Rome IV criteria for IBS were included in the present analysis. As in prior papers from the RFGES, individuals who self-reported a diagnosis of known organic bowel disorders, such as celiac disease, inflammatory bowel disease, gastrointestinal cancer, diverticulitis, or previous intestinal resection were excluded from meeting criteria for IBS.

Supplementary Results

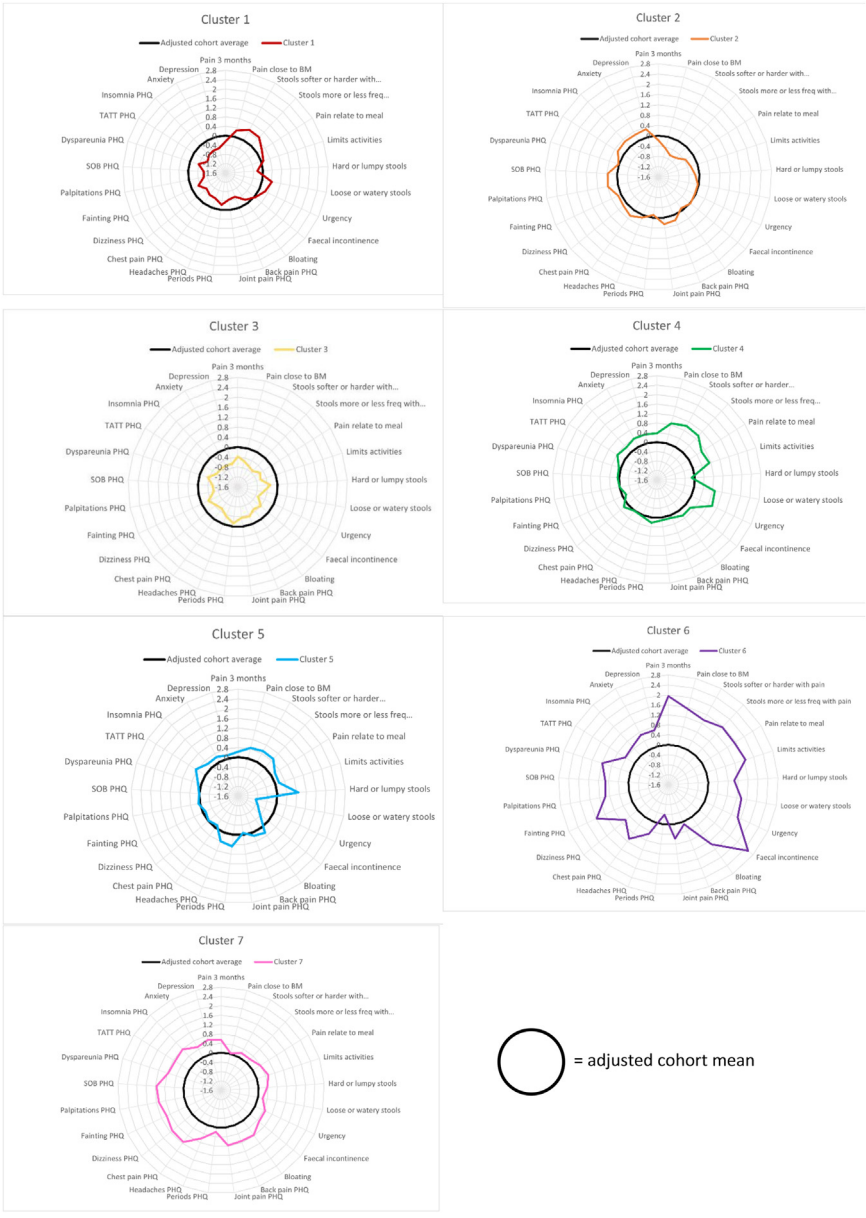
Given the BIC(LL) for models 7–10 were all very similar, indicating that there was little difference in the degree of model fit (Supplementary Table 1), we also assessed the new 7-cluster model, drawing radar plots (Supplementary Figure 3) and crosstabulating the 7 new clusters against those from the existing 7-cluster model (Supplementary Table 3). Overall, the new 7-cluster model (Supplementary Figure 3) seemed to produce clusters with diarrhea and urgency with low psychological burden (most individuals from cluster 1 in the existing model were in cluster 1 in the new model); diarrhea, abdominal pain, and urgency with high psychological burden (most individuals from cluster 4 in the existing model were in cluster 4 in the new model); low overall gastrointestinal symptom severity with low psychological burden (most individuals in cluster 3 in the new model were from cluster 3 in the existing model); low overall gastrointestinal symptom severity with abdominal pain and high psychological burden (most individuals in cluster 2 in the new model were from cluster 2 in the existing model); and high overall gastrointestinal symptom severity with high psychological burden (most individuals in cluster 6 in the new model were from cluster 6 in the existing model). There seemed to be only 1 constipation and bloating cluster with relatively high psychological burden (cluster 5 in the new model consisting of a mixture of individuals from clusters 5 [constipation, abdominal pain, and bloating with high psychological burden] and 7 [constipation and bloating with low psychological burden] in the existing model). Finally, the last cluster, cluster 7, in the new model did not map onto any of the previous clusters and seemed to consist of high levels of both mixed gastrointestinal symptoms and psychological symptoms and consisted of a mixture of individuals from clusters 2 (low overall gastrointestinal symptom severity with abdominal pain and high psychological burden), 5 (constipation, abdominal pain, and bloating with high psychological burden), and 6 (high overall gastrointestinal symptom severity with high psychological burden) in the existing model. Again, the assignment of people in the 7 clusters in the existing model across the 7 clusters derived from the new model was greater than would be expected by chance ($P < .001$).

= adjusted cohort mean

Supplementary Figure 1. Profiles of the 10 clusters identified in the new LCA model. BM, bowel movement; PHQ, patient health questionnaire; SOB, shortness of breath; TATT, tired all the time.



Supplementary Figure 2. Profiles of the 7 clusters in the existing LCA model. (*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 Figure 3. Profiles of the 7 clusters identified in the new LCA model. BM, bowel movement; PHQ, patient health questionnaire; SOB, shortness of breath; TATT, tired all the time.

Supplementary Table 1. Values of BIC(LL) for Each Specification of the Number of Clusters in the Rome Foundation Global Epidemiology Survey

Model	No. of clusters	BIC(LL)
Model 1	1-cluster	152193.0831
Model 2	2-cluster	148356.0330
Model 3	3-cluster	147133.8732
Model 4	4-cluster	146372.4599
Model 5	5-cluster	146090.5229
Model 6	6-cluster	145827.9081
Model 7	7-cluster	145633.7288
Model 8	8-cluster	145529.7227
Model 9	9-cluster	145449.5019
Model 10	10-cluster	145425.0211
Model 11	11-cluster	145446.5884
Model 12	12-cluster	145459.9001
Model 13	13-cluster	145494.1144
Model 14	14-cluster	145477.4531
Model 15	15-cluster	145569.7548

NOTE. The lowest value of BIC(LL) indicates the optimum number of clusters. The model converges on a 10-cluster solution being the best fit for the model. BIC(LL), Bayesian information criterion of the log-likelihood.

Supplementary Table 2. Crosstabulation of the New 10-Cluster LCA Model with the Clusters from the Existing 7-Cluster LCA Model

	Cluster 1 Diarrhea and urgency with low psychological burden (n = 140)	Cluster 2 Low bowel symptom severity with abdominal pain and high psychological burden (n = 717)	Cluster 3 Low overall gastrointestinal symptom severity with low psychological burden (n = 783)	Cluster 4 Diarrhea, abdominal pain, and urgency with high psychological burden (n = 212)	Cluster 5 Constipation, abdominal pain, and bloating with high psychological burden (n = 56)	Cluster 6 High overall gastrointestinal symptom severity with high psychological burden (n = 91)	Cluster 7 Constipation and bloating with low psychological burden (n = 196)
Cluster 1	0 (0.0)	38 (5.3)	452 (57.7)	0 (0.0)	0 (0.0)	0 (0.0)	54 (27.6)
Cluster 2	0 (0.0)	261 (36.4)	52 (6.6)	4 (1.9)	0 (0.0)	0 (0.0)	20 (10.2)
Cluster 3	90 (64.3)	1 (0.1)	125 (16.0)	4 (1.9)	0 (0.0)	0 (0.0)	12 (6.1)
Cluster 4	32 (22.9)	112 (15.6)	46 (5.9)	32 (15.1)	0 (0.0)	1 (1.1)	0 (0.0)
Cluster 5	0 (0.0)	90 (12.6)	0 (0.0)	16 (7.5)	30 (53.6)	61 (67.0)	0 (0.0)
Cluster 6	0 (0.0)	170 (23.7)	5 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.0)
Cluster 7	5 (3.6)	41 (5.7)	21 (2.7)	2 (0.9)	18 (32.1)	0 (0.0)	96 (49.0)
Cluster 8	12 (8.6)	4 (0.6)	0 (0.0)	140 (66.0)	6 (10.7)	5 (5.5)	1 (0.5)
Cluster 9	0 (0.0)	0 (0.0)	82 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	11 (5.6)
Cluster 10	1 (0.7)	0 (0.0)	0 (0.0)	13 (6.1)	2 (3.6)	24 (26.4)	0 (0.0)

NOTE. Values are n (%).
LCA, latent class analysis.

Supplementary Table 3. Crosstabulation of the New 7-Cluster LCA Model with the Clusters from the Existing 7-Cluster LCA Model

	Cluster 1 Diarrhea and urgency with low psychological burden (n = 140)	Cluster 2 Low bowel symptom severity with abdominal pain and high psychological burden (n = 717)	Cluster 3 Low overall gastrointestinal symptom severity with low psychological burden (n = 783)	Cluster 4 Diarrhea, abdominal pain, and urgency with high psychological burden (n = 212)	Cluster 5 Constipation, abdominal pain, and bloating with high psychological burden (n = 56)	Cluster 6 High overall gastrointestinal symptom severity with high psychological burden (n = 91)	Cluster 7 Constipation and bloating with low psychological burden (n = 196)
Cluster 1	91 (65.0)	9 (1.3)	239 (30.5)	0 (0.0)	0 (0.0)	0 (0.0)	29 (14.8)
Cluster 2	2 (1.4)	462 (64.4)	103 (13.2)	4 (1.9)	0 (0.0)	0 (0.0)	8 (4.1)
Cluster 3	0 (0.0)	4 (0.6)	420 (53.6)	0 (0.0)	0 (0.0)	0 (0.0)	44 (22.4)
Cluster 4	44 (31.4)	37 (5.2)	4 (0.5)	172 (81.1)	4 (7.1)	5 (5.5)	1 (0.5)
Cluster 5	2 (1.4)	96 (13.4)	17 (2.2)	1 (0.5)	24 (42.9)	0 (0.0)	114 (58.2)
Cluster 6	1 (0.7)	0 (0.0)	0 (0.0)	15 (7.1)	3 (5.4)	25 (27.5)	0 (0.0)
Cluster 7	0 (0.0)	109 (15.2)	0 (0.0)	20 (9.4)	25 (44.6)	61 (67.0)	0 (0.0)

NOTE. Values are n (%).
LCA, latent class analysis.