Article:
Black, CJ, Yiannakou, Y, Guthrie, EA et al. (3 more authors) (2020) A Novel Method to Classify and Subgroup Patients With IBS Based on Gastrointestinal Symptoms and Psychological Profiles. American Journal of Gastroenterology. ISSN 0002-9270

10.14309/ajg.0000000000000975

Accepted for publication 4th September 2020

TITLE PAGE

Title: A Novel Method to Classify and Subgroup Patients with IBS Based on Gastrointestinal Symptoms and Psychological Profiles.

Short running head: Subgrouping People with IBS Using Symptoms and Psychological Profiles.

Authors: Christopher J. Black MBBS (Hons)[1, 2], Yan Yiannakou MD[3], Elspeth A. Guthrie PhD[4], Robert West DPhil[4], Lesley A. Houghton PhD[2], Alexander C. Ford MD[1, 2].

[1]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

[2]Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK.

[3]County Durham and Darlington NHS Foundation Trust, Durham, UK.

[4]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK.

Abbreviations:

ANOVA	analysis of variance
BSFS	Bristol stool form scale
BIC(LL)	Bayesian information criterion of the log-likelihood
CBT	cognitive behavioral therapy
CPSS	Cohen perceived stress scale
HADS	hospital anxiety and depression scale
IBS	irritable bowel syndrome

IBS-C	IBS with constipation
IBS-D	IBS with diarrhea
IBS-M	IBS with mixed stool pattern
IBS-U	IBS unclassified
IBS-SSS	irritable bowel syndrome severity scoring system
LCA	latent class analysis
MDCP	multi-dimensional clinical profile
PHQ-12	patient health questionnaire-12
PHQ-15	patient health questionnaire-15
QoL	quality of life
VSI	visceral sensitivity index

Correspondence: Professor Alexander C. Ford

Leeds Gastroenterology Institute

Room 125

4th Floor

Bexley Wing

St. James's University Hospital

Beckett Street

Leeds

United Kingdom

LS9 7TF

Email: alexf12399@yahoo.com

Telephone: +441132684963

Key words: irritable bowel syndrome; mood; somatization; latent class analysis; subgrouping

Word count: 4,578

ABSTRACT

Objectives: Conventionally, patients with IBS are subgrouped based on their predominant bowel habit. Given the relevance of psychological co-morbidity to IBS symptomatology, our aim was to explore an alternative approach to subgrouping by incorporating factors beyond stool form and frequency.

Methods: We collected demographic, symptom, and psychological health data from 1375 adult subjects in the community who self-identified as having IBS, identifying two cohorts meeting either Rome III or Rome IV criteria. In each cohort we performed latent class analysis (LCA), a method of model-based clustering, to identify specific subgroups (clusters). For each cluster, we drew a radar plot, and compared these by visual inspection, describing cluster characteristics.

Results: In total, 1080 individuals met Rome III criteria for IBS, and 811 met Rome IV criteria. In both cohorts, a seven-cluster model was the optimum solution and the characteristics of the clusters were almost identical between Rome III and IV. Four clusters were defined by pattern of gastrointestinal symptoms (loose stools and urgency or hard stools and bloating), further differentiated by presence of abdominal pain not relieved by defecation, and by extent of psychological co-morbidity. Two clusters had below-average gastrointestinal symptoms, differentiated by extent of psychological co-morbidity. The final cluster had well above-average gastrointestinal symptoms and high levels of psychological co-morbidity. The proportion of subjects with severe IBS symptom scores, high levels of perceived stress, and high levels of gastrointestinal symptom-specific anxiety was significantly higher in clusters with high psychological comorbidity ($p < 0.001$).

Conclusions: LCA identified seven distinct IBS subgroups characterized by varying degrees of gastrointestinal symptoms, extra-intestinal symptoms, and psychological co-morbidity. Further research is needed to assess whether they might be used to direct treatment.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder. [1, 2] Patients experience symptoms of abdominal pain associated with a change in either stool form or frequency. [3] The Rome Foundation recommends the use of symptom-based diagnostic criteria for IBS. [3] As well as facilitating a diagnosis, these allow subgrouping of patients, based entirely on stool form and frequency, to help direct treatment. Patients with predominantly loose or more frequent stools are classified as having IBS with diarrhea (IBS-D), and those with predominantly hard or less frequent stools IBS with constipation (IBS-C). Those with both stool types, or frequencies, an equal proportion of the time are classified as having IBS with mixed stool pattern (IBS-M), and those who do not meet criteria for any of the other three subgroups have IBS unclassified (IBS-U).

Although the aims of this classification system are laudable, using it to direct therapy is problematic for several reasons. First, even when patients with IBS with these subtypes are treated with novel drugs, which have more precise modes of action, only 20% to 30% report symptom improvement, [4-9] and there is little to choose between many of the available drugs, in terms of efficacy. [10-12] Second, predominant stool type in IBS fluctuates over time. [13, 14] Third, almost 50% of patients have IBS-M or IBS-U, [1, 15-17] but most new drugs are tested only in IBS-D or IBS-C, so treatment options for patients with these two subgroups are limited. Finally, and perhaps most importantly, because IBS is a brain-gut disorder, mood and psychological health play an important role in the development and persistence of symptoms. [18-22] Mood disorders are much more common in people with IBS than among healthy individuals. [23] Earlier use of psychological therapies in patients exhibiting substantial psychological co-morbidity might change the natural history of IBS. However, access to these is limited and, often, their use is advocated only in patients whose symptoms do not respond adequately to pharmacological treatment, [24] so they tend to be used only as a last

resort. [25] Indeed, recent studies have bolstered interest in the use of psychological therapies, such as cognitive behavioral therapy (CBT), as effective treatments for IBS with long-lasting benefits. [26-28] Unfortunately, current approaches to subgrouping patients with IBS offer no clinical guidance regarding who might derive the most benefit from these therapies.

A classification system based on stool type alone does not, therefore, reflect the complex composite nature of IBS adequately, nor does it allow equitable access of patients to either clinical trials of novel drugs, or existing drugs or psychological therapies with an evidence base for efficacy. In acknowledgment of the fact that IBS is a disorder of gut-brain interaction, with biopsychosocial influences, the Rome Foundation developed the multi-dimensional clinical profile (MDCP). This is a framework that, in addition to clinical symptoms, includes assessment of psychological factors, and impact of the illness, in order to build a unique clinical profile for each patient. [29] Although intended to help guide treatment, this approach has yet to be utilized in routine clinical practice, and is not incorporated into current diagnostic criteria. If it were possible to classify patients, not only by clinical symptoms, but also by psychological profiles, this may help optimize treatment selection, resulting in better outcomes, and reduced health service and societal costs of IBS. [30]

To date, only a few studies have examined this issue. [31-33] In two of these studies, conducted by the same group of investigators, distinct subgroups, or clusters, of patients appeared to exist. These subgroups consisted of those whose symptoms were predominantly intestinal, and who had only minimal psychological distress, and those for whom IBS symptoms were part of a broader picture, which included anxiety, depression, or extra-intestinal symptoms. [31, 32] These subgroups were not, however, reproducible across different patient cohorts or different iterations of the Rome criteria, and one study was conducted in only 172 patients in tertiary care. [31] A third study demonstrated clusters distinguished by low or high severity of intestinal and non-intestinal symptoms, which were further differentiated

by the extent of impairment in IBS-related quality of life (QoL), but combined patients meeting either the Rome II or Rome III criteria together. [33]

We hypothesized that we could derive subgroups of patients with IBS that were distinct and reproducible, irrespective of setting or diagnostic criteria. If feasible, these subgroups could change both the classification of, and management strategies for, IBS. For instance, those with predominantly gastrointestinal symptoms may respond best to a drug acting peripherally on the intestine, those with predominantly psychological or extra-intestinal symptoms to a centrally acting drug or psychological therapy, and those with both gastrointestinal and extra-intestinal symptoms to a combination of therapies.

METHODS

Participants and Setting

We recruited individuals who self-identified as having IBS registered with three UK organizations (see Supplementary Methods). This cohort has been described elsewhere. [34, 35]

Data Collection and Synthesis

Demographic and Symptom Data

We collected basic demographic data from all participants and captured lower gastrointestinal symptom data using the Rome III and Rome IV questionnaires. [36, 37] Further details are provided in the Supplementary Methods.

Assessment of Mood, Extra-Intestinal Symptoms, Gastrointestinal Symptom-specific Anxiety, and Perceived Stress.

We collected anxiety and depression data using the hospital anxiety and depression scale (HADS). [38] Extra-intestinal symptom data was collected using the patient health questionnaire-12 (PHQ-12). [39] The 15-item visceral sensitivity index (VSI) [40] was used to measure gastrointestinal symptom-specific anxiety. We utilized the 10-item version of the Cohen perceived stress scale (CPSS) to assess perceived stress, which is derived from the original 14-item instrument. [41] Further details are provided in the Supplementary Methods.

Statistical Analysis

We identified two cohorts of individuals who self-identified as having IBS and who met either the Rome III or Rome IV criteria for IBS. Many participants met both iterations of

the diagnostic criteria and were therefore represented in both cohorts. Consequently, we compared baseline characteristics of these two cohorts using a partially overlapping *t*-test for continuous data, and a partially overlapping *z*-test for comparison of proportions, [42] with the "partiallyoverlapping" package in R (version 3.6.2). [43, 44]

In each cohort, we performed latent class analysis (LCA) using LatentGOLD (version 5.1 Statistical Innovations, Belmont, MA, USA). [45] LCA is a method of structural equation modelling used to identify unobserved groups, or latent classes, within observed multivariate data. [46] A statistical model is postulated for the population from which the data sample is obtained, and it is assumed that a mixture of underlying probability distributions generates the data. [47] 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. [47] Finally, robust statistical criteria can be used to determine the best fit of the model, and the optimum number of clusters. [48] 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 that best fit the data. Details of the variables used in the model are provided in Supplementary Table 1.

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 compared the radar plots by visual inspection, describing the particular characteristics of each cluster.

In order to internally validate our analyses, we performed 10-fold cross-validation, [49] for both the Rome III and Rome IV models, using the *n*-validation capability of LatentGOLD. We compared the misclassification statistic for our original model derivation with that obtained from cross-validation, in order to understand how the model would

perform if applied to a different dataset. We also performed 10-fold cross-validation manually, by splitting the data randomly into 10 equally sized groups, or folds. We recombined these folds in all 10 possible permutations, omitting a different fold each time, and undertook LCA in each recombined dataset, using the same variables as were included in our original model. We again drew out the clusters for each derivation using radar plots and determined, by visual inspection, whether the subgroups appeared similar to the original model. We validated each derivation by applying the model to the fold that had been omitted each time, averaging the misclassification statistic across all 10 validation cycles to determine the overall misclassification statistic for the cross-validation process as a whole.

Finally, for both the Rome III and Rome IV cohorts, we compared characteristics of individuals in each cluster. We compared categorical variables, such as sex, consultation with a gastroenterologist, high levels of gastrointestinal symptom-specific anxiety or perceived stress, high symptom severity scores, IBS subtype according to the Bristol stool form scale (BSFS), and whether IBS onset followed an acute enteric infection, between individuals in each cluster using a χ^2 test. We compared differences in continuous variables between clusters using a one-way analysis of variance (ANOVA) test. Due to multiple comparisons, we considered a 2-tailed p value of <0.01 as statistically significant for these analyses, which we performed using SPSS for Windows (version 24.0 SPSS Inc., Chicago, IL, USA).

RESULTS

We recruited 1375 individuals who self-identified as having IBS into the study. The mean age of subjects was 49.2 years (range 18 to 86 years), 1157 (84.1%) were female, and 1293 (94.0%) were White Caucasian. Overall, 180 (13.1%) individuals stated their IBS symptoms commenced after an acute enteric infection, 1048 (95.5%) had previously seen their primary care physician with their IBS, and 633 (57.7%) had seen a gastroenterologist.

Characteristics of the Rome IV and Rome III Cohorts

There were 1373 individuals providing complete Rome IV data, of whom 811 (59.0%) met the Rome IV criteria for IBS. In total, 1368 individuals with IBS provided complete Rome III data, and 1080 (78.9%) met the Rome III criteria for IBS. The two cohorts overlapped, such that of the 1080 individuals who met Rome III criteria for IBS, 794 (73.5%) also met Rome IV criteria. Therefore, among 811 individuals meeting the Rome IV criteria for IBS, only 17 (2.1%) did not also meet Rome III criteria. The Rome IV cohort were significantly younger ($p < 0.001$), but there was no difference in the proportion of female participants between groups (Table 1). In both cohorts, over 95% of individuals had seen a primary care physician with IBS; however, those in the Rome IV cohort were significantly more likely to have seen a gastroenterologist ($p < 0.001$). IBS symptoms were significantly more severe in the Rome IV cohort ($p < 0.001$), and mood and psychological health were significantly worse ($p <0.001$). CPSS and VSI scores were also significantly higher among those with Rome IV IBS ($p < 0.001$).

Latent Class Analysis in the Rome IV and Rome III Cohorts

The best LCA solution was achieved with seven clusters, as indicated by the lowest value of the BIC(LL) (Supplementary Figure 1). An overview of the seven-cluster result is

provided in Figure 1, with descriptions of the clusters and their relative proportions. Each cluster was characterized by specific symptom profiles. Radar plots for each of these clusters are presented in Figure 2.

Two clusters were characterized by above-average scores for loose and watery stools and urgency, but were differentiated by the presence of below-average scores for abdominal pain that was not relieved by defecation and for extra-intestinal and mood-related symptoms, or above-average scores for abdominal pain that was not relieved by defecation and for extra-intestinal and mood-related symptoms. Similarly, another two of the clusters were characterized by above-average scores for hard and lumpy stools and bloating, and were again differentiated by the presence of below-average scores for abdominal pain that was not relieved by defecation and for extra-intestinal and mood-related symptoms, or above-average scores for abdominal pain that was not relieved by defecation and for extra-intestinal and mood-related symptoms. These clusters were described as diarrhea and urgency with low psychological burden (Figure 2A), diarrhea, abdominal pain, and urgency with high psychological burden (Figure 2D), constipation and bloating with low psychological burden (Figure 2G), and constipation, abdominal pain, and bloating with high psychological burden (Figure 2E).

Two clusters were characterized by below-average scores for all gastrointestinal symptoms, and were differentiated by the presence of either below-average or above-average scores for extra-intestinal and mood-related symptoms. These clusters were described as low overall gastrointestinal symptom severity with low psychological burden (Figure 2C) and low overall gastrointestinal symptom severity with high psychological burden (Figure 2B), respectively. The remaining cluster was characterized by a mixed profile of well above-average scores for gastrointestinal symptoms, including diarrhea, constipation, and abdominal pain, as well as well above-average scores for extra-intestinal and mood-related symptoms.

This cluster was described as high overall gastrointestinal symptom severity with high psychological burden (Figure 2F).

In the Rome III cohort, the best LCA solution was again achieved with seven clusters which were almost identical to those identified in the Rome IV cohort analysis (see Supplementary Results). 10-fold cross-validation of the Rome IV and Rome III LCA models showed that we could expect both models to perform similarly, if applied to a different dataset containing the same variables. Further details are provided in the Supplementary Results.

Characteristics of the Different Clusters in the Rome IV and Rome III Cohorts

The characteristics of the seven clusters in the Rome IV cohort are shown in Table 2. There was a difference in mean age between clusters, with those in cluster 1, defined as diarrhea, urgency and low psychological burden, being significantly older, and those in cluster 5, defined as constipation, abdominal pain, and high psychological burden, being significantly younger ($p < 0.001$). There was also a difference in sex distribution between clusters, with a significantly higher proportion of men in cluster 3, with low overall gastrointestinal symptoms and low psychological burden ($p = 0.003$). There were no significant differences in terms of the proportion of individuals who had seen a gastroenterologist, or the proportion who reported that their IBS symptoms started after an acute enteric infection. The proportion of participants with high CPSS scores and VSI scores, and the proportion of individuals with severe symptoms were significantly higher in clusters 2, 4, 5, and 6; those characterized by higher psychological burden ($p < 0.001$). Stool subtype according to the BSFS reflected the symptom-based characteristics of each cluster, and this trend was significant ($p < 0.001$). Clusters 1 and 4, which were those groups with above-average scores for diarrhea, had the largest proportions of subjects with IBS-D according to

the BSFS, with very few having IBS-C, and approximately one-third having IBS-M. Conversely, clusters 5 and 7, which had above-average scores for constipation, had the highest proportion of participants with IBS-C, and contained very few individuals with either IBS-D or IBS-M. The proportion of individuals with IBS-M was highest in clusters 2, 3, and 6; those characterized by a more mixed profile of gastrointestinal symptoms of varying severity. An identical analysis comparing clusters in the Rome III cohort demonstrated broadly similar findings (Supplementary Table 2).

DISCUSSION

We investigated whether it is possible to subgroup people with IBS using factors beyond stool form or frequency. We found seven unique clusters of individuals with IBS, distinguished by the pattern of gastrointestinal symptoms, extra-intestinal symptoms, and mood. Two of these were characterized by diarrhea and were differentiated based on the presence of abdominal pain that was not relieved by defecation, and high or low psychological burden. Two clusters were characterized by constipation and were again differentiated based on the presence of abdominal pain that was not relieved by defecation, and high or low psychological burden. A further two clusters exhibited mixed gastrointestinal symptoms of low overall intensity but were differentiated by the presence of high or low psychological burden. The final cluster was characterized by mixed gastrointestinal symptoms of high overall intensity with high psychological burden. These seven clusters were reproducible, irrespective of whether IBS was defined according to the Rome III or Rome IV criteria. We validated these models, demonstrating that they would be expected to perform similarly if applied to a different dataset. When we compared additional characteristics between clusters, we found a significantly higher proportion of men in the cluster with low overall symptoms and low psychological co-morbidity. We also found that groups characterized by high psychological co-morbidity had a significantly greater proportion of people with high scores using other measures of psychological health, such as the VSI and CPSS, which were not included in the model itself. Finally, stool subtype, as defined according to the BSFS, correlated significantly with the gastrointestinal symptom profile of each cluster. These results have the potential to change classification and treatment of IBS.

We recruited a large number of individuals, all of whom were in the community and self-identified as having IBS. Some individuals had consulted a primary care physician, some

a gastroenterologist, and some had never consulted a physician, meaning the participants are likely to be generalizable to many individuals living with IBS. This is further supported by the proportion of individuals with each IBS subtype, which is similar to other community based surveys. [1, 50] We used an online questionnaire, meaning data collection was near complete for many of the variables of interest. External validation of the Rome III and Rome IV latent class models in a different cohort of patients was not possible because no suitable data were available. In lieu of this, we were able to internally validate both models instead, in order to understand how they might apply to other groups of patients with IBS.

Weaknesses of the study include the fact that we did not confirm the diagnosis of IBS in all individuals in this study by looking at their medical records. This means that we relied on the fact that the people who took part believed that they had IBS as a means of confirming a diagnosis. This may have led to us including some people with disorders other than IBS, which may have different symptom profiles, and this may have affected the extent to which the results of our LCA are indicative of true IBS subgroups. However, given that almost 80% of those who responded did meet the Rome III criteria for IBS, more than 95% had previously seen a primary care physician with their IBS, and almost 60% had seen a gastroenterologist, we do not feel this is likely to have affected our results to any great degree. As the questionnaire we used was completed online, after visiting a website, we are unable to assess how many individuals visited the website but chose not to complete the questionnaire, or whether those who responded are broadly representative of all the people with IBS registered with these three organizations. In addition, because of the setting in which our study was conducted, and the fact that participants had to have internet access and be motivated to participate, they may not be generalizable to patients consulting with a gastroenterologist in secondary or tertiary care. However, given that almost 60% had previously consulted in this setting, we feel this is unlikely. Whether these subgroups are

stable, or fluctuate naturally, or with treatment, cannot be addressed in a cross-sectional survey such as this. Finally, we did not collect data to measure impact of symptoms, either gastrointestinal or psychological, on quality of life, so although it could be assumed that those in the groups with a higher psychological burden had worse quality of life, this is speculative.

To our knowledge, there have been only three previous studies examining approaches other than stool pattern to subgrouping people with IBS. [31-33] In the first of these studies, there appeared to be six distinct subgroups of people with Rome III-defined IBS; those whose symptoms were predominantly intestinal, including diarrhea, constipation, or abdominal pain, and who had only minimal psychological distress, and those for whom IBS symptoms were part of a broader picture, which included anxiety, depression, and extra-intestinal symptom reporting. [31] This Swedish study, however, included only 172 patients in tertiary care, so the findings may not be generalizable to the majority of people with IBS, who are seen in a primary or secondary care setting. In a second study conducted by the same group, again IBS subgroups characterized by a combination of gastrointestinal and extra-intestinal symptoms were identified, but these were not consistent between Rome III and Rome IV criteria. [32] The authors identified seven subgroups for Rome III-defined IBS, but only five with Rome IV. The latter were less distinct, with a preponderance of mixed-symptom profiles. Moreover, and in contrast to our study, this was a population-based cross-sectional survey, which classified participants as having IBS solely based on whether their responses fulfilled the Rome criteria, rather being included because they reported having IBS, or had received a diagnosis of IBS. The final study used an advertisement to recruit 332 patients who had received a diagnosis of IBS, and analysis of data concerning gastrointestinal symptoms, extra-intestinal symptoms, and IBS-related QoL identified four subgroups. [33] Two subgroups had low overall symptoms and were differentiated based on having either good or moderate QoL. The other two subgroups had high overall symptoms, with or without diarrhea, and

were further differentiated based on having poor or moderate QoL. This study defined IBS according to either the Rome II or Rome III criteria, but combined all participants together for analysis, so it is unclear how use of these different symptom-based definitions of IBS might have affected the characteristics of the subgroups.

Despite differences in their patient populations, and the variables used to define symptoms, all the studies conducted thus far have demonstrated that people with IBS appear to separate into distinct subgroups based on more than just stool form or frequency. The number of subgroups, however, and their precise characteristics, differs between studies. In part, this reflects differences in the choice of variables to be included in the model. Choosing different variables will change the results, a limitation of any such modelling analysis, which is why it is important to select relevant variables with a clear rationale. Although distinct IBS subgroups constructed using clinical symptoms, symptom severity, and psychological symptoms appear to exist, whether they are reproducible in other patient cohorts is unknown. This study is the first to demonstrate that the same IBS subgroups are reproducible irrespective of whether IBS is defined according to the Rome III or Rome IV criteria. This might partly reflect the overlap between the Rome III and Rome IV cohorts. However, previous studies, which also had similarly overlapping groups, failed to demonstrate this consistency. [32] Moreover, we validated the subgrouping model, demonstrating it could be expected to perform similarly if it were applied to a different cohort of patients with IBS. This is important because it suggests that we have not derived a model that is too specific and "overfitted" to the data, a risk in previous studies where model validation has not been undertaken. [31-33]

As all of these studies are cross-sectional in design, and in the absence of follow-up data, whether these subgroups can be used to guide treatment for the individual patient with IBS is uncertain. [51] Nonetheless, examining the diverse characteristics of the individuals

within the seven clusters identified in this study, which look beyond gastrointestinal symptoms, it becomes easier to understand why response to a drug targeted against a predominant stool form or frequency is so variable in clinical practice. It also supports the MDCP approach proposed by the Rome Foundation, but indicates that, rather than simply acting as a guide to clinicians for managing an individual patient, it could be more effective if incorporated formally into the stratification of all patients with IBS. This view is supported by a recent discussion paper, suggesting that conditions such as IBS should be classified as "functional somatic disorders", occupying a neutral territory between being considered purely somatic or purely mental. [52] Such a classification system aligns with the etiological construct that these disorders reflect the complex interaction between brain and body. Indeed, the results of our study indicate that some people are likely to respond well to drugs targeting their most troublesome gastrointestinal symptom, some may benefit from instituting a psychological therapy early on in their disease course and, in others, a combined approach targeting both physical and psychological symptoms may be more effective. People in cluster 3 could be provided with education about the condition and lifestyle advice, [53] cluster 1 or 7 treated with a drug targeting diarrhea or constipation, respectively, [54, 55] cluster 2 a psychological therapy, such as CBT, cluster 4 or 5 a drug targeting diarrhea or constipation, in combination with a central neuromodulator or psychological therapy to address pain and mood, [56] and cluster 6 augmentation of a central neuromodulator with a psychological therapy, a successful strategy in other functional somatic disorders, such as chronic headache and fibromyalgia. [57] This is supported by a recent observational study, which suggested that female patients with high somatization and depression should be prioritized for brain-gut psychological therapies. [58]

Overall, therefore, we believe that stratifying patients into these clusters has the potential to change the management paradigm for IBS, facilitating a more personalized

approach to treatment, by allowing clinicians to select the best treatment, or treatments, at the earliest opportunity for any individual patient. We therefore need to understand whether these clusters predict underlying pathophysiological mechanisms in IBS and, more importantly, whether they can be used to tailor treatment. The latter could be achieved in collaboration with other investigators by examining clinical trial datasets retrospectively to assess whether these subgroups predict response to a particular drug or psychological therapy. This study also provides guidance for a minimum dataset that future treatment trials in IBS should collect, to identify subgroups of patients who will respond best to a particular treatment. Lastly, given that our findings support the Rome Foundation's MDCP, it may be that future iterations of the Rome criteria consider incorporating the assessment of mood and extra-intestinal symptom reporting as part of their approach to subgrouping.

In summary, we show that, irrespective of whether IBS is defined according to the Rome III or Rome IV criteria, people with IBS could be divided into seven distinct and reproducible clusters. These were differentiated according to the presence of certain gastrointestinal symptoms, including stool form or frequency, and abdominal pain that was not relieved by defecation, as well as by the presence of extra-intestinal symptoms and abnormal mood. If these novel subgroups are reproducible in other settings, and are shown to predict response to specific therapies that are available to treat IBS, they could then be utilized to personalize treatment. This has the potential to change clinical practice by allowing gastroenterologists and patients to select the right therapy based on these subgroups, leading to improved symptom control, higher levels of patient satisfaction, better quality of life, and reduced health service and societal costs of managing IBS. In addition, for people whose IBS symptoms form part of a broader picture that includes substantial psychological co-morbidity, the subgroups could be used to prioritize access to psychological therapies, or to make the decision to institute combined therapy with both a drug and a psychological

therapy. Earlier use of psychological therapies in these particular subgroups of people, rather than after pharmacological therapies have failed, as is currently recommended, [24] may change the natural history of the condition.

ACKNOWLEDGEMENTS

We are grateful to the participants who gave their time freely to answer our questionnaire.

CONFLICTS OF INTEREST/STUDY SUPPORT

Guarantor of the article: ACF is guarantor.

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

Financial support: None.

Potential competing interests: Christopher J, Black: none. Yan Yiannakou: none. Elspeth A. Guthrie: none. Robert West: none. Lesley A. Houghton: none. Alexander C. Ford: none.

REFERENCES

1. Lovell RM, Ford AC. Global prevalence of, and risk factors for, irritable bowel syndrome: A meta-analysis. Clin Gastroenterol Hepatol 2012;10:712-721.

2. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. N Engl J Med 2017;376:2566-2578.

3. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. Gastroenterology 2016;150:1393-1407.

4. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: Lubiprostone in patients with constipation-associated irritable bowel syndrome - results of two randomized, placebo-controlled studies. Aliment Pharmacol Ther 2009;29:329-341.

5. Rao S, Lembo AJ, Shiff SJ, et al. 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol 2012;107:1714-1724.

6. Brenner DM, Fogel R, Dorn SD, et al. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: Results of two phase 3 randomized clinical trials Am J Gastroenterol 2018;113:735-745.

7. Chey WD, Lembo AJ, Rosenbaum DP. Tenapanor treatment of patients with constipation-predominant irritable bowel syndrome: A phase 2, randomized, placebo-controlled efficacy and safety trial. Am J Gastroenterol 2017;112:763-774.

8. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. N Engl J Med 2016;374:242-53.

9. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011;364:22-32.

10. 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.

11. 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 2019;doi: 10.1136/gutjnl-2018-318160.

12. Black CJ, Burr NE, Ford AC. Relative efficacy of tegaserod in a systematic review and network meta-analysis of licensed therapies for irritable bowel syndrome with constipation. Clin Gastroenterol Hepatol 2019;doi: 10.1016/j.cgh.2019.07.007.

13. Drossman DA, Morris CB, Hu Y, et al. A prospective assessment of bowel habit in irritable bowel syndrome in women: Defining an alternator. Gastroenterology 2005;128:580-589.

14. Palsson OS, Baggish JS, Turner MJ, et al. IBS patients show frequent fluctuations between loose/watery and hard/lumpy stools: Implications for treatment. Am J Gastroenterol 2012;107:286-95.

15. Andrews EB, Eaton SC, Hollis KA, et al. Prevalence and demographics of irritable bowel syndrome: Results from a large web-based survey. Aliment Pharmacol Ther 2005;22:935-942.

16. Khoshkrood-Mansoori B, Pourhoseingholi MA, Safaee A, et al. Irritable bowel syndrome: A population based study. J Gastrointestin Liver Dis 2009;18:413-418.

17. Lee S, Wu J, Ma YL, et al. Irritable bowel syndrome is strongly associated with generalized anxiety disorder: A community study. Aliment Pharmacol Ther 2009;30:643-651.

18. Koloski NA, Boyce PM, Talley NJ. Somatization an independent psychosocial risk factor for irritable bowel syndrome but not dyspepsia: A population-based study. Eur J Gastroenterol Hepatol 2006;18:1101-1109.

19. Koloski NA, Jones M, Kalantar J, et al. The brain--gut pathway in functional gastrointestinal disorders is bidirectional: A 12-year prospective population-based study. Gut 2012;61:1284-90.

20. Koloski NA, Jones M, Talley NJ. Evidence that independent gut-to-brain and brain-to-gut pathways operate in the irritable bowel syndrome and functional dyspepsia: A 1-year population-based prospective study. Aliment Pharmacol Ther 2016;44:592-600.

21. Jones MP, Tack J, Van Oudenhove L, et al. Mood and anxiety disorders precede development of functional gastrointestinal disorders in patients but not in the population. Clin Gastroenterol Hepatol 2017;15:1014-1020.e4.

22. Clevers E, Tack J, Tornblom H, et al. Development of irritable bowel syndrome features over a 5-year period. Clin Gastroenterol Hepatol 2018;16:1244-1251.e1.

23. 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.

24. Hookway C, Buckner S, Crosland P, et al. Irritable bowel syndrome in adults in primary care: Summary of updated NICE guidance. BMJ 2015;350:h701.

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.

26. 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.

27. Everitt HA, Landau S, O'Reilly G, et al. Cognitive behavioural therapy for irritable bowel syndrome: 24-month follow-up of participants in the ACTIB randomised trial. Lancet Gastroenterol Hepatol 2019;4:863-872.

28. Lackner JM, Jaccard J, Keefer L, et al. Improvement in Gastrointestinal Symptoms After Cognitive Behavior Therapy for Refractory Irritable Bowel Syndrome. Gastroenterology 2018;155:47-57.

29. Drossman DA. The multidimensional clinical profile for functional gastrointestinal disorders. Raleigh, NC: Rome Foundation, 2016.

30. Boeckxstaens GE, Drug V, Dumitrascu D, et al. Phenotyping of subjects for large scale studies on patients with IBS. Neurogastroenterol Motil 2016;28:1134-47.

31. 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.

32. Polster AV, Palsson OS, Tornblom H, et al. Subgroups of IBS patients are characterized by specific, reproducible profiles of GI and non-GI symptoms and report differences in healthcare utilization: A population-based study. Neurogastroenterol Motil 2019;31:e13483.

33. Han CJ, Pike K, Jarrett ME, et al. Symptom-based latent classes of persons with irritable bowel syndrome. Res Nurs Health 2019;42:382-391.

34. Black CJ, Yiannakou Y, Houghton LA, et al. Epidemiological, clinical, and psychological characteristics of individuals with self-reported irritable bowel

syndrome based on the Rome IV vs Rome III criteria. Clin Gastroenterol Hepatol 2019;doi: 10.1016/j.cgh.2019.05.037.

35. Black CJ, Yiannakou Y, Houghton LA, et al. Anxiety-related factors associated with symptom severity in irritable bowel syndrome. Neurogastroenterol Motil 2020:e13872.

36. Whitehead WE, and the Validation Working Team Committee in association with the Rome Questionnaire C. Development and validation of the Rome III diagnostic questionnaire. In: Drossman DA, editor.Rome III: The functional gastrointestinal disorders, 3rd edition.Virginia: Degnon Associates Inc 2006:835-853.

37. Palsson OS, Whitehead WE, van Tilburg MA, et al. Rome IV diagnostic questionnaires and tables for investigators and clinicians. Gastroenterology 2016;150:1481-1491.

38. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-370.

39. 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;32:811-20.

40. 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.

41. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24:385-96.

42. Derrick B, Dobson-McKittrick A, Toher D, et al. Tests for Comparing Two Proportions With Partially Overlapping Samples. Journal of Applied Quantitative Methods 2015;10:1-14.

43. Derrick B. Partiallyoverlapping: Partially Overlapping Samples Tests. R package version 2.0. Volume 2020, 2018.

44. R.Core.Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Volume 2020, 2020.

45. Magidson J, Vermunt J. Latent Class Models for Clustering: A Comparison with K Means. Canadian Journal of Marketing Research 2002;20.

46. Lanza ST, Rhoades BL. Latent class analysis: an alternative perspective on subgroup analysis in prevention and treatment. Prev Sci 2013;14:157-68.

47. Magidson J. Latent class cluster analysis. In: Hagenaars JaM, AL;, ed. Advances in Latent Class Analysis. Cambridge: Cambridge University Press, 2002.

48. 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;17:228-43.

49. Stone M. Cross-Validatory Choice and Assessment of Statistical Predictions. Journal of the Royal Statistical Society. Series B (Methodological) 1974;36:111-147.

50. Hungin APS, Whorwell PJ, Tack J, et al. The prevalence, patterns and impact of irritable bowel syndrome: An international survey of 40 000 subjects. Aliment Pharmacol Ther 2003;17:643-650.

51. Black CJ, Ford AC. Editorial: Subgroups in irritable bowel syndrome-more than just diarrhoea and constipation? Aliment Pharmacol Ther 2017;46:697.

52. Burton C, Fink P, Henningsen P, et al. Functional somatic disorders: discussion paper for a new common classification for research and clinical use. BMC Med 2020;18:34.

53. Ringström G, Störsrud S, Posserud I, et al. Structured patient education is superior to written information in the management of patients with irritable bowel syndrome: a randomized controlled study. Eur J Gastroenterol Hepatol 2010;22:420-8.

54. 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.

55. 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.

56. Drossman DA, Tack J, Ford AC, et al. Neuromodulators for Functional Gastrointestinal Disorders (Disorders of Gut-Brain Interaction): A Rome Foundation Working Team Report. Gastroenterology 2018;154:1140-1171.e1.

57. Holroyd KA, O'Donnell FJ, Stensland M, et al. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. Jama 2001;285:2208-15.

58. Riehl ME, Kinnucan JA, Chey WD, et al. Nuances of the psychogastroenterology patient: A predictive model for gastrointestinal quality of life improvement. Neurogastroenterol Motil 2019;31:e13663.

FIGURE LEGENDS

Figure 1. Latent Class Analysis in a Cohort of People with Rome IV IBS.

Figure 2. Profiles of the Seven Latent Class Clusters Identified in the Rome IV Cohort.

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.

Table 1. Comparison of Demographic Data, IBS Symptom Severity, and Psychological Comorbidity Between the Rome III and Rome IV Cohorts.

	Rome III cohort* **(n = 1080)**	**Rome IV cohort†** **(n = 811)**	***P* value‡**
Mean age (SD)	48.4 (15.3)	47.4 (15.2)	<0.001
Female (%)	915 (84.7)	697 (85.9)	0.06
IBS after acute enteric infection (%)	147 (13.6)	106 (13.1)	0.40
Seen a primary care physician with IBS (%)	1031 (95.5)	778 (95.9)	0.22
Seen a gastroenterologist with IBS (%)	620 (57.4)	492 (60.7)	<0.001
Mean IBS-SSS score (SD)	265 (102)	292 (96)	<0.001
Mean PHQ-12 score (SD)	9.6 (4.3)	10.3 (4.3)	<0.001
Mean HADS-A score (SD)	10.4 (4.7)	11.0 (4.7)	<0.001
Mean HADS-D score (SD)	7.1 (4.5)	7.6 (4.5)	<0.001
Mean CPSS score (SD)	20.5 (8.3)	21.6 (8.2)	<0.001
Mean VSI score (SD)	47.6 (17.5)	50.7 (16.8)	<0.001

*****Includes 794 individuals who also met the Rome IV criteria for IBS.

†Includes 17 individuals who did not meet Rome III criteria for IBS.

‡*P* value for overlapping samples *t*-test for continuous data and overlapping samples *z*-test for comparison of proportions.

Table 2. Characteristics of Latent Class Clusters in the Rome IV Cohort.

	Cluster 1 **Diarrhea and urgency with low psychological burden** **(n = 161)**	**Cluster 2** **Low overall GI symptom severity with high psychological burden** **(n = 170)**	**Cluster 3** **Low overall GI symptom severity with low psychological burden** **(n = 165)**	**Cluster 4** **Diarrhea, abdominal pain, and urgency with high psychological burden** **(n = 154)**	**Cluster 5** **Constipation, abdominal pain, and bloating with high psychological burden** **(n = 31)**	**Cluster 6** **High overall GI symptom severity with high psychological burden** **(n = 71)**	**Cluster 7** **Constipation and bloating with low psychological burden** **(n = 59)**	***P* value***
Mean age (SD)	51.7 (15.5)	44.6 (15.2)	49.3 (16.7)	45.3 (13.1)	40.7 (12.9)	46.9 (13.8)	47.6 (14.3)	<0.001
Female (%)	140 (87.0)	141 (82.9)	129 (78.2)	139 (90.3)	31 (100.0)	62 (87.3)	55 (93.2)	0.003
Seen a gastroenterologist with IBS (%)	92 (57.1)	104 (61.2)	97 (58.8)	98 (63.6)	18 (58.1)	48 (68.6)	35 (59.3)	0.726
High VSI scores (%)	46 (28.6)	80 (47.3)	32 (19.5)	87 (56.5)	23 (74.2)	53 (75.7)	10 (16.9)	<0.001
High CPSS scores (%)	18 (11.2)	81 (47.6)	20 (12.1)	86 (56.2)	18 (58.1)	57 (80.3)	10 (16.9)	<0.001
Severe symptoms on IBS-SSS (%)	63 (39.4)	87 (51.2)	27 (16.4)	90 (58.4)	25 (80.6)	63 (88.7)	24 (40.7)	<0.001
Subtype on BSFS								
IBS-C (%)	6 (3.7)	37 (21.9)	20 (12.1)	3 (1.9)	26 (83.9)	2 (2.8)	48 (81.4)	
IBS-D (%)	101 (62.7)	40 (23.7)	58 (35.2)	88 (57.1)	2 (6.5)	19 (26.8)	3 (5.1)	
IBS-M (%)	50 (31.1)	87 (51.5)	77 (46.7)	61 (39.6)	3 (9.7)	46 (64.8)	7 (11.9)	
IBS-U (%)	4 (2.5)	5 (3.0)	10 (6.1)	2 (1.3)	0 (0.0)	4 (5.6)	1 (1.7)	<0.001

IBS after acute enteric infection (%)	21 (13.0)	19 (11.2)	30 (18.2)	15 (9.7)	6 (19.4)	12 (17.1)	3 (5.1)	0.083

BSFS: Bristol stool form scale; GI: gastrointestinal; IBS-SSS: irritable bowel syndrome symptom severity score; CPSS: Cohen perceived stress scale; VSI: visceral sensitivity index.

*P value for Pearson χ^2 for comparison of categorical data and one-way ANOVA for comparison of means.