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TITLE PAGE

Title: Longitudinal Follow-up of a Novel Classification System for Irritable Bowel Syndrome: Natural History and Prognostic Value.

Short running title: Natural History of Novel Subgroups in Irritable Bowel Syndrome.

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Abbreviations:

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 bowel habit
IBS-U	IBS unclassified
IBS-SSS	IBS severity scoring system
LCA	latent class analysis
PHQ-12	patient health questionnaire-12

MDCP multi-dimensional clinical profile

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STRUCTURED SUMMARY

Background: Conventionally, irritable bowel syndrome (IBS) is subgrouped using predominant stool form, yet it is a complex disorder, with multiple biopsychosocial contributors. We previously derived and validated a latent class model subgrouping people with IBS into seven clusters based on gastrointestinal and extra-intestinal symptoms and psychological profile.

Aims: To conduct longitudinal follow-up examining the natural history and prognostic value of these clusters.

Methods: Participants completed a 12-month follow-up questionnaire. We applied our model to these data, comparing cluster membership between the two time points in those still meeting Rome IV criteria at follow-up, including stratifying the analysis by predominant stool pattern, and level of psychological burden, at baseline. We examined whether baseline cluster predicted the course of IBS, and whether starting new treatment was associated with changing cluster.

Results: 811 participants met Rome IV criteria for IBS at baseline, of whom 452 (55.7%) responded, and 319 (70.6%) still met Rome IV criteria for IBS at follow-up. Of these, 172 (53.9%) remained in the same IBS cluster as at baseline and 147 changed cluster. Cluster membership stratified according to psychological co-morbidity was more stable; 84% of those in a cluster with high psychological burden at baseline remained in such a cluster at follow-up. People in clusters with high psychological burden at baseline had more severe symptoms (p<0.001), received a higher mean number of subsequent treatments (p<0.001), and were more likely to consult a doctor than people in clusters with low psychological burden (p<0.001*)*. There was no significant association between starting a new treatment and changing cluster at follow-up

Conclusions: Longitudinal follow-up demonstrated little transition between clusters with respect to psychological burden, and these appeared to predict disease course. Directing treatment according to cluster, including earlier use of psychological therapies, and exploring how this approach influences outcomes in IBS, should be examined.

Keywords: irritable bowel syndrome; mood; somatisation; latent class analysis; subgrouping

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common functional bowel disorders. It is characterised by a specific pattern of gastrointestinal symptoms, namely altered stool form or frequency in association with abdominal pain, [1] and is diagnosed using the Rome criteria. These criteria have been revised three times since their inception, to make them more specific for diagnosing IBS, [2] and the latest iteration, Rome IV, was published in 2016. [1] Rome IV also redefined IBS as a disorder of gut-brain interaction, in recognition of the complex interplay between biological, psychological, and social factors in its pathogenesis.

Conventionally, IBS is categorised into four subtypes based on the predominant stool form or frequency reported by the patient: IBS with constipation (IBS-C); IBS with diarrhoea (IBS-D); IBS with mixed bowel habit (IBS-M); or IBS unclassified (IBS-U), where stool form or frequency cannot classify the patient accurately into one of the other three subtypes. [1] Assigning patients with IBS to the appropriate subtype is the mainstay of management, as treatment is symptom-based, and directed according to the patient's predominant stool pattern. [3-6] However, longitudinal studies demonstrate that these stool subtypes are not stable over time, [7-11] with a change in subtype occurring in up to one-third of people during follow-up. [11] Moreover, in a recent study, fluctuation between IBS subtypes did not depend solely on whether a new treatment was initiated, or whether the choice of treatment was deemed appropriate based on IBS stool subtype at baseline. [11]

Importantly, although relied upon for classifying patients with IBS, stool form is only one element of this complex, multi-faceted disorder. Mood and psychological health, for example, play an important role in the development and persistence of symptoms. [12-16] Moreover, mood disorders are much more common in people with IBS than among healthy individuals. [17] Conceivably, therefore, alternative approaches, integrating factors other than

stool form, may offer a more nuanced means of classifying people with IBS, and directing treatment. The Rome Foundation has proposed the multi-dimensional clinical profile (MDCP), a framework that, in addition to the cardinal gastrointestinal symptoms needed to make a diagnosis of IBS, includes assessment of additional clinical features, psychological factors, and impact of the illness, in order to build a unique clinical profile for each patient. [18] This approach is intended to help clinicians optimise the management of individual patients, aiming to address sometimes overlooked dimensions of the illness experience, but it is not incorporated into current diagnostic criteria for subgrouping patients. Awareness of the MDCP is also likely to be limited to those gastroenterologists with a subspecialist interest in disorders of gut-brain interaction. If the approach advocated by the MDCP is to be translated into a formal classification system for IBS, being able to demonstrate that incorporating factors other than gastrointestinal symptoms can be used to derive new and distinct patient subgroups, and that those additional factors are of relevance to clinical management, would provide useful supporting evidence.

In keeping with this approach, we have previously demonstrated that, irrespective of whether IBS is defined according to the Rome III or Rome IV criteria, people with IBS can be divided into seven distinct and reproducible clusters using latent class analysis (LCA). [19] These were characterised by a pattern of gastrointestinal symptoms (predominantly diarrhoea-related, predominantly constipation-related, or mixed symptoms) further differentiated by the presence or absence of abdominal pain not relieved by defaecation, and by the presence of high or low levels of both extra-intestinal symptom reporting and psychological co-morbidity. These clusters are described in Box 1. If gastroenterologists and patients were to personalise their treatment choices based on these subgroups, for example making earlier use of psychological therapies in clusters with high psychological co-morbidity, this has the potential to improve outcomes. To explore this theory further, we

conducted a follow-up study to understand the evolution of IBS according to this novel classification system, and to assess whether these clusters were predictive of differing disease courses. We also examined if commencing new treatments was associated with a change in cluster membership. Although other groups have performed similar studies, these have important limitations, and none have conducted any follow-up of their proposed models to assess their behaviour or prognostic value. [20-22]

METHODS

Participants and Setting

This was a 12-month follow-up study of individuals who self-identified as having IBS registered with three organisations in the UK, and who agreed to participate in a previous study published elsewhere. [19, 23, 24] These were the IBS network, the registered charity for people living with the condition, TalkHealth, an online social health community providing information about various medical conditions, and ContactMe-IBS, a dedicated register allowing individuals with IBS not receiving specialist care currently to participate in research. Briefly, we contacted participants via email and post, inviting them to complete an online questionnaire. All non-responders were sent a reminder. The questionnaire collected demographic data, and data about lower gastrointestinal symptoms, extra-intestinal symptoms, and psychological health. We sent out invitations to complete a follow-up questionnaire a minimum of 12 months later, using the same methods. Although all participants self-identified as having IBS, we used the baseline data to identify two cohorts of people meeting the Rome IV and Rome III diagnostic criteria for IBS. In both cohorts we used latent class analysis, which is a method of model-based clustering, to derive novel subgroups of people with IBS, and we validated these models internally. Comprehensive details regarding this methodology are provided in our previous study. [19]

The latent class modelling using baseline data identified seven distinct IBS clusters, which were almost identical, in both the Rome IV and Rome III cohorts, and which are detailed in Supplementary Figure 1. To examine the natural history of these clusters, we applied the same model to participant follow-up data, and we compared cluster membership at baseline with that at 12-month follow-up. The University of Leeds research ethics committee approved the study in November 2017.

Data Collection and Synthesis

Baseline Data

We collected demographic data at baseline, as well as lower gastrointestinal symptom data using both the Rome IV and Rome III questionnaires. [25, 26] We assigned presence or absence of either Rome IV or Rome III-defined IBS among all individuals according to the scoring algorithms proposed for these questionnaires. [1, 27] Symptom severity was measured using the validated IBS severity scoring system (IBS-SSS), [28] and we measured the impact of symptoms, in terms of the proportion of time that they limited normal daily activities, as per the Rome questionnaire. We collected anxiety and depression data using the hospital anxiety and depression scale (HADS), [29] and extra-intestinal symptom data using the patient health questionnaire-12 (PHQ-12), [30] derived from the validated PHQ-15. [31]

Natural History and Prognosis During 12-month Follow-up

At 12 months, we asked participants to complete identical questionnaires. In order to assess the natural history of the clusters we used these data to assign cluster membership at 12 months, as well as applying the algorithms for Rome IV or Rome III-defined functional bowel disorders at 12 months, including functional constipation, functional diarrhoea, functional abdominal bloating or distension, or unspecified functional bowel disorder, to assess their stability by baseline cluster. [1] Again, we assessed symptom severity at 12 months using the IBS-SSS, and impact of symptoms, in terms of the proportion of time that they limited normal daily activities, according to the Rome questionnaire. We also asked participants to record any new treatments (dietary, drugs, and/or psychological, but not complementary or alternative medicines) that they commenced, as well as general

practitioner (GP) visits, or consultations with a gastroenterologist, after the baseline questionnaire.

Statistical Analysis

We compared categorical variables between individuals responding to the 12-month questionnaire, and those who did not, using a χ^2 test. We compared mean age using an independent samples *t*-test. We compared IBS cluster at baseline with IBS cluster at follow-up in those still meeting criteria for Rome IV-defined IBS and Rome III-defined IBS, respectively. In addition, we compared IBS cluster membership between the two time points stratified according to predominant stool pattern, and level of psychological burden, at baseline. We also compared proportions of individuals with Rome IV or Rome III IBS at baseline who fluctuated to another functional bowel disorder at 12 months, analysed according to their IBS cluster at baseline. Due to multiple comparisons a 2-tailed P value of <0.01 was considered statistically significant for all analyses. We examined whether baseline cluster influenced subsequent disease behaviour by comparing proportions of people in each cluster who commenced a new treatment, saw their GP, or consulted a gastroenterologist, using a χ^2 test, and the mean number of new treatments commenced, and mean IBS-SSS at follow-up, using a one-way ANOVA. *Post-hoc* analysis using the Bonferroni correction for multiple comparisons was used to explore any differences in mean values between clusters at the 0.05 significance level. Finally, we examined what treatments participants received, according to their baseline cluster, and whether commencing new treatment(s) was associated with changing to a different cluster at follow-up. We performed all analyses 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 at baseline with a mean age of 49.2 years (range 18 to 86 years). 1157 (84.1%) were female, and 1293 (94.0%) were White Caucasian. 784 participants (57.0%) were successfully followed up and provided complete data at 12 months. Significant differences between responders and non-responders related to demographic characteristics (Table 1). There were no differences in the proportion who met either the Rome IV or Rome III criteria at baseline, IBS symptom severity, or psychological co-morbidity between those successfully followed up, and those who were not. There was also no difference in the proportion of individuals in each baseline cluster between responders and non-responders. There were 811 participants who met Rome IV criteria for IBS at baseline, of whom 452 (55.7%) responded to the 12-month questionnaire, and 319 (70.6%) of these individuals still met Rome IV criteria for IBS at follow-up. In total, 631 (58.4%) of 1080 participants who met Rome III criteria for IBS at baseline responded to the 12-month questionnaire, and 527 (83.5%) still met the Rome III criteria for IBS at follow-up. Results for the cohort of participants meeting Rome III criteria were very similar to those reported below and are provided in the Supplement.

Natural History of IBS Clusters Among Individuals Continuing to Meet Rome IV Criteria for IBS at Follow-up

Of the 319 individuals still meeting Rome IV criteria for IBS at follow-up, 172 (53.9%) remained in the same IBS cluster as at baseline and 147 (46.1%) changed cluster. Fluctuation in each individual cluster is detailed in Figure 1. The proportion of people who remained in the same cluster between baseline and follow-up varied from 47.5% for cluster 4 (diarrhea, abdominal pain, and urgency with high psychological burden) to 72.2% for cluster 7 (constipation and bloating with low psychological burden) (p<0.001).

Of the 140 people who were in a diarrhoea-related cluster (clusters 1 or 4) at baseline, 87 (62.1%) remained in a diarrhoea-related cluster at follow-up and 50 (35.7%) moved to a mixed gastrointestinal symptom cluster (clusters 2, 3, or 6), whilst only three individuals (2.1%) moved to a constipation-related cluster (clusters 5 or 7) (Figure 2). Similarly, although the number of people was smaller, of 28 individuals in a constipation-related cluster at baseline, 19 (67.9%) remained in a constipation-related cluster at follow-up, seven (25.0%) moved to a mixed gastrointestinal symptom cluster, and only two individuals (7.1%) moved to a diarrhoea-related cluster. Lastly, of the 151 individuals in a mixed gastrointestinal symptom cluster at baseline, 115 (76.2%) remained in a mixed gastrointestinal symptom cluster at follow-up. The proportion of individuals who remained in a mixed gastrointestinal symptom cluster at follow-up was significantly higher than the proportion who remained in either a diarrhoea-related cluster or a constipation-related cluster ($p<0.001$). Stool subtype according to the Bristol stool form scale reflected the symptom-based characteristics of each cluster, and this trend was significant ($p < 0.001$).

Of the 131 people who were in a cluster with low psychological burden at baseline (clusters 1, 3, or 7), 104 (79.4%) remained in a cluster with low psychological burden at follow-up (Figure 3). Similarly, of the 188 people who were in a cluster with high psychological burden at baseline (clusters 2, 4, 5, or 6), only 30 individuals (16.0%) moved to a cluster with low psychological burden at follow-up ($p<0.001$). Mean IBS-SSS scores at follow-up were significantly higher in clusters with high psychological burden at baseline assessment (299.2, 315.5, 389.0, and 367.7 in clusters 2, 4, 5, and 6 respectively, versus 278.5 in cluster 1, 220.1 in cluster 3, and 285.2 in cluster 7, $p<0.001$) (Table 2). Additional *post-hoc* analysis using the Bonferroni correction showed that the mean IBS-SSS score in cluster 3 was significantly lower than in clusters 1, 2, 4, 5, and 6. Mean scores were also

significantly higher in cluster 5 compared with cluster 1, and in cluster 6 compared with clusters 1, and 2.

Change in Functional Bowel Disorder Diagnosis and IBS Cluster Membership Among Those No Longer Meeting Rome IV Criteria for IBS at Follow-up

Among the 133 (29.4%) individuals with Rome IV IBS at baseline who no longer met Rome IV criteria for IBS at 12-month follow-up, 48 (36.1%) met Rome IV criteria for functional diarrhoea, 39 (29.3%) functional abdominal bloating or distension, 32 (24.1%) unspecified functional bowel disorder, and 14 (10.5%) functional constipation. Change in functional bowel disorder diagnosis at 12 months according to baseline IBS cluster is shown in Figure 4. Although these individuals no longer met Rome IV criteria for IBS, when we applied the baseline Rome IV cluster model to these individuals at 12 months, 93 (69.9%) were assigned to clusters with low overall gastrointestinal symptoms (clusters 2 or 3), compared with 68 (51.1%) at baseline, reflecting a greater proportion fluctuating to having milder symptoms that, overall, did not meet criteria for IBS.

Commencement of New Treatment and Consultation Behaviour According to Baseline IBS Cluster Among those with Rome IV IBS at Baseline and Follow-up

Overall, of the 319 individuals who continued to have Rome IV IBS at follow-up, 243 (76.2%) had commenced at least one new treatment during the 12-month follow-up period, of whom 112 (46.1%) changed IBS cluster at follow-up. Similarly, of the 76 people who did not commence any new treatment, 35 (46.1%) changed IBS cluster at follow-up. There was no significant association between commencing a new treatment and changing IBS cluster at follow-up ($p = 1.00$). This remained the case when subcategories of treatment were examined, including commencing any medication for diarrhoea ($p = 0.23$), any medication for

constipation ($p = 1.00$), any medication for pain, including a central neuromodulator ($p = 0.35$), or any psychological therapy ($p = 0.84$).

New treatments commenced by baseline IBS cluster are shown in Supplementary Table 1. Only 25 individuals with Rome IV IBS at baseline and follow-up reported receiving any form of psychological therapy, of whom 13 (52%) were in baseline clusters characterised by low psychological burden (clusters 1, 3, or 7). Overall, the mean number of treatments commenced was significantly higher in clusters with a high psychological burden (1.71, 2.10, 2.20, and 2.21 in clusters 2, 4, 5, and 6 respectively, *vs.* 1.42, 1.08, and 1.09 in clusters 1, 3, and 7 respectively, $p<0.001$) (Table 2). Additional *post-hoc* analysis using the Bonferroni correction showed that this difference was driven by a significantly lower number of mean treatments in cluster 3 compared with clusters 4, and 6. Clusters with high psychological burden also had significantly higher rates of consultation with both GPs ($p<0.001$) and gastroenterologists (30.4%, 35.0%, 40.0%, and 58.6% in clusters 2, 4, 5, and 6 respectively *vs.* 20.0%, 24.5%, and 16.7% in clusters 1, 3, and 7 respectively, $p = 0.007$) (Table 2). The impact of symptoms at follow-up, in terms of patients reporting that they limited activities at least 50% of the time, was also significantly greater in clusters with high psychological burden at baseline (65.2%, 87.5%, 90.0%, and 93.1% in clusters 2, 4, 5, and 6 respectively, *vs.* 66.7%, 41.5%, and 44.4% in clusters 1, 3, and 7 respectively, $p<0.001$) (Table 2). Although it was the combination of troublesome gastrointestinal symptoms and high psychological burden that was the most debilitating (clusters 4, 5, and 6), and also most likely to result in consultation with a gastroenterologist, it should be noted that the proportion of individuals with diarrhoea and urgency with low psychological burden (cluster 1) reporting marked limitation of activities was slightly greater than the proportion of those with low overall gastrointestinal symptom severity and high psychological burden (cluster 2), and much greater than the proportion of people with low psychological burden in association with

constipation and bloating (cluster 7). Diarrhoea and urgency therefore appear to be important symptoms with respect to the impact they can have on daily life.

As would be expected, a significantly higher proportion of people in clusters with diarrhoea-related symptoms (clusters 1 or 4) commenced medication for diarrhoea ($p<0.0001$) and, similarly, a significantly higher proportion of people in clusters with constipation-related symptoms (clusters 5 or 7) commenced medication for constipation ($p<0.0001$). Finally, a significantly higher proportion of people in clusters characterised by high psychological burden (clusters 2, 4, 5, or 6) commenced medication for pain, including prescription of central neuromodulators ($p = 0.001$).

DISCUSSION

In a previous study we derived and validated a model to classify people with IBS into seven novel subgroups based on their pattern of gastrointestinal symptoms, extra-intestinal symptoms, and psychological profiles. [19] The current longitudinal follow-up study has examined the natural history of these subgroups, investigating whether they are of prognostic value, and explored changes in cluster membership, by applying the baseline model to longitudinal data, collected after 12-months, in the same cohort of people. Of those who provided follow-up data, 46% changed cluster at 12 months. Commencing a new treatment was not associated with a change in cluster membership. When cluster membership was stratified according to gastrointestinal symptoms, of those in a diarrhoea-predominant or constipation-predominant cluster at baseline, around two-thirds remained in such a cluster at follow-up. Of those who changed cluster, this was almost exclusively to a mixed-gastrointestinal symptom cluster; transition between diarrhoea-predominant and constipation-predominant clusters, or *vice versa*, was rare. Of those in a mixed gastrointestinal symptoms cluster at baseline, three-quarters remained in such a cluster at follow-up. Cluster membership stratified according to psychological co-morbidity was more stable; of those in a cluster with high psychological co-morbidity at baseline, 84% remained in a cluster with high psychological co-morbidity at follow-up. Findings with respect to those in a cluster with low psychological co-morbidity at baseline were similar. This stratification was useful from a prognostic perspective. People in clusters with high psychological burden had more severe symptoms at follow-up, which had a significantly greater impact on daily activities. They also commenced a higher mean number of treatments and were more likely to consult with a doctor about their IBS, compared with people in clusters with low psychological burden. This was irrespective of whether the Rome IV or III criteria were used to define IBS.

This study recruited a large number of individuals in a community setting who self-identified as having IBS. Most had consulted a primary care physician, some a gastroenterologist, and a small proportion had never sought medical advice for their symptoms. This implies that the participants, and the model we derived from their data, will be generalisable to many individuals living with IBS. Moreover, and in contrast to other subgroup modelling studies in IBS, [20-22] we validated our model in our previous study, showing that it was likely to perform similarly if applied to other cohorts of patients with IBS. [19] In addition, our questionnaire was completed using a web-based portal meaning that, for most variables of interest, data collection at baseline and 12-months was complete.

Weaknesses include the fact that we were unable to confirm the diagnosis of IBS in all individuals in this study using medical records. Consequently, because those participating believed that they had IBS, and met diagnostic criteria, we assumed that they had the condition. It is important to acknowledge that some organic gastrointestinal disorders, such as coeliac disease or inflammatory bowel disease, can mimic IBS; [32-35] however, the community prevalence of these disorders in comparison to IBS is considerably lower. Moreover, over 95% of study subjects had consulted with a doctor regarding their symptoms. It is likely, therefore, that the majority of participants had undergone some investigation, in addition to clinical assessment, to rule out organic disease and did, therefore, genuinely have IBS. The response rate to the 12-month questionnaire was 57%, which is similar to other longitudinal follow-up studies of gastrointestinal disorders conducted over a similar time frame. [36-40] However, this resulted in some clusters having low numbers of participants for comparison at follow-up. Responders were older, less likely to smoke, more likely to be married or co-habiting, to have attained a university or postgraduate level of education, to be White Caucasian, and to have seen a doctor about their IBS symptoms. This indicates that the population we studied at follow-up may not be representative of the original cohort of people

we recruited. Although these differences may have affected the validity of comparing clusters at baseline and follow-up, it should be emphasised that comparison between responders and the original study participants in terms of symptoms, symptom severity, psychological co-morbidity, and baseline cluster membership revealed no significant differences. Moreover, absolute differences in demographic data observed were relatively modest.

Other investigators have also examined the possibility of subgrouping people with IBS using factors beyond stool form.[20-22] Although there is a consensus that people with IBS can be separated into distinct groups using a combination of gastrointestinal symptoms and psychological factors, the specific characteristics and number of subgroups varies between studies. The current treatment paradigm for IBS advocates targeting therapy according to predominant gastrointestinal symptom; however, extra-intestinal symptoms and psychological co-morbidity, which are recognised as playing an important role in IBS symptomatology, are not considered as part of the current classification system for the condition. Consequently, knowing how best to tailor multimodal treatment, including use of psychological therapies, to the needs of the individual patient is difficult, and yet it seems likely that the pursuit of more personalised treatment in the care of those with IBS will be increasingly desirable. Crucially, to our knowledge, no previous study investigating novel IBS subgroups has examined their natural history, in order to understand the clinical evolution of IBS, or whether they can be used to identify those with a worse disease course. If alternative approaches to subgrouping IBS, such as we are proposing, are to be incorporated into clinical practice and used to guide treatment, understanding these issues is key.

Overall, our findings show that cluster membership changed in some individuals over time; however, rather than being a disadvantage, this flexibility is a desirable feature of a classification system that could be used to direct treatment. Indeed, one would hope that

patients could transition from clusters with a high symptom burden to those with a lower symptom burden, a trend that was observed among those individuals no longer meeting criteria for IBS at follow-up. Nevertheless, the reasons for changes in cluster membership are unclear. There was no association with commencing a new treatment and changes may, therefore, reflect natural fluctuations of symptoms over time. However, it is also important to consider that, due to experiencing improvements in their symptoms, some participants may not have responded to the follow-up questionnaire, and this will have affected assessment of natural history of the clusters. In contrast to studies investigating the stability of IBS stool subtypes alone, which have suggested that IBS-M is the least stable subtype, [7, 8, 41] we found that three-quarters of individuals remained in a mixed gastrointestinal symptoms cluster between baseline and follow-up. This was higher than the proportion remaining in either a diarrhoea-predominant or constipation-predominant cluster, although almost two-thirds of individuals remained in one of these predominant symptom clusters. In keeping with the findings of these previous stool subtype stability studies, [7, 8, 41] very few participants transitioned from a diarrhoea-predominant cluster to a constipation-predominant cluster, or *vice versa*. The fact that Bristol stool form scale reflected the symptom-based characteristics of each cluster underlines its usefulness in helping subgroup people with IBS.

Treatments commenced appeared broadly appropriate for each cluster, but, interestingly, were not associated with a change in cluster membership. It is important to emphasise, however, that, although we can examine treatment according to cluster, it was not directed in this way. Instead, it was prescribed by the participants own clinicians, or obtained over the counter, presumably according to predominant gastrointestinal symptoms. Of note, when we have previously investigated the effect of treatment on IBS stool subtype stability specifically, in the same cohort, no association was found. [11] Moreover, because we only have data at two distinct time points, we cannot assess the temporal relationship between

treatment and symptoms, or cluster membership. It is also difficult to assess the appropriateness of treatment for any individual, and whether this influences a change in cluster membership. Some participants who were in a baseline cluster with diarrhoea, for example, received secretagogue drugs for constipation. This seems an inappropriate choice of drug therapy, but an individual's symptoms might have changed from baseline to the point of commencing this treatment. In addition, it is difficult to assess the effects of different combinations of treatment.

Regarding psychological co-morbidity, it is interesting to note that those individuals in a cluster characterised by high psychological co-morbidity at baseline largely remained in such a cluster at follow-up. Compared with a change in cluster membership stratified by gastrointestinal symptoms, cluster membership stratified by level of psychological co-morbidity was more stable, and predicted higher numbers of subsequent treatments, as well as consultation behaviour and disease impact. Of note, despite there being 188 people in a cluster with high psychological co-morbidity at baseline, the number of people receiving psychological therapies was very low, the emphasis being mainly on first line drug therapies, such as anti-diarrhoeals and laxatives. This might partly reflect difficulties accessing these therapies, particularly for those individuals managed solely in a primary care setting. Moreover, half of those who reported receiving psychological therapies were in clusters with low psychological burden at baseline. This might indicate poor assessment of psychological health in this group of people with IBS, or poor acceptance of the role of psychological factors in IBS, and a reluctance among those with psychological co-morbidity to accept psychological therapies. Nevertheless, these findings raise the question of whether addressing psychological health needs earlier, in conjunction with physical symptoms, might prove to be a more effective approach, which could have resulted in changes to cluster membership and reduced consumption of medical resources.

In summary, this study has explored the natural history and prognostic value of a novel method of subgrouping people with IBS, which uses a combination of gastrointestinal symptoms, extra-intestinal symptoms, and psychological co-morbidity. Overall, approximately half of those responding to the follow-up questionnaire remained in the same cluster, and further analysis revealed that there was little transition with respect to psychological co-morbidity. Most people who were in a cluster with high psychological co-morbidity at baseline remained in such as cluster at follow-up, and these appeared to predict disease course. These findings support the MDCP and suggest that it should be incorporated into clinical practice and, perhaps, used to help subgroup patients with IBS. Despite this, very few people reported receiving psychological therapies. To better understand whether formal approaches to subgrouping patients with IBS using factors beyond stool are helpful in directing treatment, a prospective study is needed. Such a study would allocate patients to a cluster at baseline using the model, which is a mathematical equation that can be easily applied in clinical practice, and then randomise them to receive targeted treatment according to cluster, or conventional physician-directed management according to the patient's predominant symptoms, with symptoms, quality of life, and resource use compared between groups. Clusters with low gastrointestinal symptoms and high psychological co-morbidity would likely receive a psychological therapy, clusters with high gastrointestinal symptoms and low psychological co-morbidity a peripherally acting drug, and clusters with high gastrointestinal symptoms and high psychological co-morbidity a combination of psychological therapy and drugs, including centrally acting neuromodulators. Further investigation of this potential approach for the management of IBS is warranted as we strive for ways to deliver high-quality and high-value personalised care, with the potential to improve outcomes, for people suffering with this chronic, and frequently debilitating, condition.

REFERENCES

1. Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel Disorders. Gastroenterology. 2016;150(6):1393-407.

2. Black CJ, Craig OF, Gracie DJ, Ford AC. Comparison of the Rome IV Criteria with the Rome III Criteria for the Diagnosis of Irritable Bowel Syndrome in Secondary Care. Gut. 2020;doi: 10.1136/gutjnl-2020-322519.

3. Black CJ, Burr NE, Camilleri M, Earnest DL, Quigley EM, Moayyedi P, 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.

4. 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. 2020;18:1238-9.

5. Black CJ, Burr NE, Quigley EMM, Moayyedi P, Houghton LA, Ford AC. Efficacy of secretagogues in patients with irritable bowel syndrome with constipation: Systematic review and network meta-analysis. Gastroenterology. 2018;155:1753-63.

6. Black CJ, Yuan Y, Selinger CP, Camilleri M, Quigley EMM, Moayyedi P, et al. Efficacy of soluble fibre, antispasmodic drugs, and gut-brain neuromodulators in irritable bowel syndrome: A systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2020;5:117-31.

7. Drossman DA, Morris CB, Hu Y, Toner BB, Diamant N, Leserman J, et al. A prospective assessment of bowel habit in irritable bowel syndrome in women: defining an alternator. Gastroenterology. 2005;128(3):580-9.

8. Garrigues V, Mearin F, Badia X, Balboa A, Benavent J, Caballero A, et al. Change over time of bowel habit in irritable bowel syndrome: A prospective, observational, 1-year follow-up study (RITMO study). Aliment Pharmacol Ther. 2007;25:323-32.

9. Palsson OS, Baggish JS, Turner MJ, Whitehead WE. IBS patients show frequent fluctuations between loose/watery and hard/lumpy stools: implications for treatment. Am J Gastroenterol. 2012;107(2):286-95.

10. Palsson OS, Baggish J, Whitehead WE. Episodic nature of symptoms in irritable bowel syndrome. Am J Gastroenterol. 2014;109(9):1450-60.

11. Barberio B, Houghton LA, Yiannakou Y, Savarino EV, Black CJ, Ford AC. Symptom Stability in Rome IV vs. Rome III Irritable Bowel Syndrome. Am J Gastroenterol. 2020;doi: 10.14309/ajg.0000000000000946.

12. 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(10):1101-9.

13. Koloski NA, Jones M, Kalantar J, Weltman M, Zaguirre J, Talley NJ. The brain--gut pathway in functional gastrointestinal disorders is bidirectional: A 12-year prospective population-based study. Gut. 2012;61(9):1284-90.

14. 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(6):592-600.

15. Jones MP, Tack J, Van Oudenhove L, Walker MM, Holtmann G, Koloski NA, et al. Mood and anxiety disorders precede development of functional gastrointestinal disorders in patients but not in the population. Clin Gastroenterol Hepatol. 2017;15(7):1014-20.e4.

16. Clevers E, Tack J, Tornblom H, Ringstrom G, Luyckx K, Simren M, et al. Development of irritable bowel syndrome features over a 5-year period. Clin Gastroenterol Hepatol. 2018;16(8):1244-51.e1.

17. 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(2):132-43.

18. Drossman DA. The multidimensional clinical profile for functional gastrointestinal disorders. 2nd ed ed. Raleigh, NC: Rome Foundation; 2016.

19. Black CJ, Yiannakou Y, Guthrie EA, West R, Houghton LA, Ford AC. A Novel Method to Classify and Subgroup Patients with IBS Based on Gastrointestinal Symptoms and Psychological Profiles. Am J Gastroenterol. 2020;doi: 10.14309/ajg.0000000000000975.

20. Polster A, Van Oudenhove L, Jones M, Ohman L, Tornblom H, Simren M. Mixture model analysis identifies irritable bowel syndrome subgroups characterised by specific

profiles of gastrointestinal, extraintestinal somatic and psychological symptoms. Aliment Pharmacol Ther. 2017;46(5):529-39.

21. Polster AV, Palsson OS, Tornblom H, Ohman L, Sperber AD, Whitehead WE, 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(1):e13483.

22. Han CJ, Pike K, Jarrett ME, Heitkemper MM. Symptom-based latent classes of persons with irritable bowel syndrome. Res Nurs Health. 2019;42(5):382-91.

23. Black CJ, Yiannakou Y, Houghton LA, Ford AC. 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. 2020;18:392-8.

24. Black CJ, Yiannakou Y, Houghton LA, Shuweihdi F, West R, Guthrie E, et al. Anxiety-related factors associated with symptom severity in irritable bowel syndrome. Neurogastroenterol Motil. 2020;32(8):e13872.

25. 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, editorRome III: The functional gastrointestinal disorders, 3rd editionVirginia: Degnon Associates Inc. 2006:835-53.

26. Palsson OS, Whitehead WE, van Tilburg MA, Chang L, Chey W, Crowell MD, et al. Rome IV diagnostic questionnaires and tables for investigators and clinicians. Gastroenterology. 2016;150(6):1481-91.

27. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006;130:1480-91.

28. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: A simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther. 1997;11(2):395-402.

29. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.

30. Spiller RC, Humes DJ, Campbell E, Hastings M, Neal KR, Dukes GE, 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(6):811-20.

31. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med. 2002;64(2):258-66.

32. Kamp EJ, Kane JS, Ford AC. Irritable bowel syndrome and microscopic colitis: A systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2016;14(5):659-68.

33. Slattery SA, Niaz O, Aziz Q, Ford AC, Farmer AD. Systematic review with meta-analysis: The prevalence of bile acid malabsorption in the irritable bowel syndrome with diarrhoea. Aliment Pharmacol Ther. 2015;42:3-11.

34. Irvine AJ, Chey WD, Ford AC. Screening for celiac disease in irritable bowel syndrome: An updated systematic review and meta-analysis. Am J Gastroenterol. 2017;112(1):65-76.

35. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: Systematic review and meta-analysis. Am J Gastroenterol. 2012;107(10):1474-82.

36. Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of brain-gut interactions in patients with inflammatory bowel disease. Gastroenterology. 2018;154(6):1635-46.e3.

37. Gracie DJ, Hamlin PJ, Ford AC. Longitudinal impact of IBS-type symptoms on disease activity, healthcare utilization, psychological health, and quality of life in inflammatory bowel disease. Am J Gastroenterol. 2018;113(5):702-12.

38. Nicholl BI, Halder SL, MacFarlane GJ, Thompson DG, O'Brien S, Musleh S, et al. Psychosocial risk markers for new onset irritable bowel syndrome - Results of a large prospective population-based study. Pain. 2008;137(1):147-55.

39. Bolling-Sternevald E, Aro P, Ronkainen J, Storskrubb T, Talley NJ, Junghard O, et al. Do gastrointestinal symptoms fluctuate in the short-term perspective? The Kalixanda study. Dig Dis. 2008;26(3):256-63.

40. Wong RK, Palsson O, Turner MJ, Levy RL, Feld AD, Von Korff M, et al. Inability of the Rome III criteria to distinguish functional constipation from constipation-subtype irritable bowel syndrome. Am J Gastroenterol. 2010;105(10):2228-34.

41. Ersryd A, Posserud I, Abrahamsson H, Simrén M. Subtyping the irritable bowel syndrome by predominant bowel habit: Rome II versus Rome III. Aliment Pharmacol Ther. 2007;26(6):953-61.

FIGURE LEGENDS

Figure 1. Comparison of IBS Cluster Membership Between Baseline and Follow-up Among 319 Individuals with Rome IV IBS.

Cluster 1: Diarrhoea and urgency with low psychological burden.

Cluster 2: Low overall gastrointestinal symptom severity with high psychological burden.

Cluster 3: Low overall gastrointestinal symptom severity with low psychological burden.

Cluster 4: Diarrhoea, abdominal pain, and urgency with high psychological burden.

Cluster 5: Constipation, abdominal pain, and bloating with high psychological burden.

Cluster 6: High overall gastrointestinal symptom severity with high psychological burden.

Cluster 7: Constipation and bloating with low psychological burden.

FU, follow-up.

Each bar represents one baseline cluster. The coloured segments and percentages in each bar indicate the proportion of individuals in each of the 7 clusters at follow-up.

Figure 2. Comparison of IBS Cluster Membership According to Pattern of Gastrointestinal Symptoms Between Baseline and Follow-up Among 319 Individuals with Rome IV IBS.

The proportion of individuals who remained in a mixed gastrointestinal symptom cluster at follow-up was significantly higher than the proportion who remained in either a diarrhoea-related cluster or a constipation-related cluster ($p<0.001$).

Figure 3. Comparison of Cluster Membership According to Degree of Psychological Burden Between Baseline and Follow-up Among 319 Individuals with Rome IV IBS.

The proportion of individuals who remained in a cluster characterised by high psychological burden at follow-up was significantly higher than the proportion who transitioned to a cluster characterised by low psychological burden ($p<0.001$). The converse was true for those in a cluster with low psychological burden at baseline.

Figure 4. Change in Functional Bowel Disorder at Follow-up According to Baseline IBS Cluster Among 133 Individuals with Rome IV IBS at Baseline.

Cluster 1: Diarrhoea and urgency with low psychological burden.

Cluster 2: Low overall gastrointestinal symptom severity with high psychological burden.

Cluster 3: Low overall gastrointestinal symptom severity with low psychological burden.

Cluster 4: Diarrhoea, abdominal pain, and urgency with high psychological burden.

Cluster 5: Constipation, abdominal pain, and bloating with high psychological burden.

Cluster 6: High overall gastrointestinal symptom severity with high psychological burden.

Cluster 7: Constipation and bloating with low psychological burden.

FU, follow-up.

Each bar represents one baseline cluster. The coloured segments and percentages in each bar indicate the proportion of individuals with Rome IV IBS at baseline whose symptoms fluctuated to another functional bowel disorder.

Box 1. Descriptions of the Seven Clusters Identified at Baseline.

Cluster 1: Diarrhoea and urgency with low psychological burden.
Cluster 2: Low overall gastrointestinal symptom severity with high psychological burden.
Cluster 3: Low overall gastrointestinal symptom severity with low psychological burden.
Cluster 4: Diarrhoea, abdominal pain, and urgency with high psychological burden.
Cluster 5: Constipation, abdominal pain, and bloating with high psychological burden.
Cluster 6: High overall gastrointestinal symptom severity with high psychological burden.
Cluster 7: Constipation and bloating with low psychological burden.

Note: The terms “high” or “low” are made with reference to the adjustment of variables with respect to the cohort average for each variable using *z*-scores. More detail is provided in our previous paper. [19]

Table 1. Characteristics of Individuals Responding to the 12-month Questionnaire Compared with Non-responders.

	Responded to Questionnaire at 12 months (n=784)	**Did not Respond to Questionnaire at 12 months (n = 591)**	**P value***
Mean age (SD)	50.7 (14.4)	47.1 (16.4)	<0.001
Female gender (%)	660 (84.2)	497 (84.1)	0.96
Married or co-habiting (%)	535 (68.2)	363 (61.4)	0.009
University or postgraduate level of education (%)	369 (47.1)	218 (37.2)	<0.001
Smoker (%)	49 (6.3)	71 (12.0)	<0.001
White Caucasian ethnicity (%)	754 (96.2)	539 (91.7)	<0.001
IBS after acute enteric infection (%)	102 (13.0)	78 (13.2)	0.90
Previously seen a GP regarding IBS at study entry (%)	754 (96.2)	548 (92.9)	0.007
Previously seen a gastroenterologist regarding IBS at study entry (%)	475 (60.6)	314 (53.2)	0.006
Rome IV criteria for IBS met (%)	452 (57.7)	359 (60.8)	0.24
Rome III criteria for IBS met (%)	631 (80.7)	449 (76.6)	0.07
IBS subtype (%)			
Constipation	146 (18.6)	124 (21.0)	
Diarrhoea	310 (39.5)	207 (35.1)	
Mixed stool pattern	296 (37.8)	220 (37.3)	
Unclassified	32 (4.1)	35 (5.9)	0.03

Severity on IBS-SSS (%)			
Remission	27 (3.4)	28 (4.8)	
Mild	183 (23.3)	110 (18.7)	
Moderate	314 (40.1)	231 (39.2)	
Severe	260 (33.2)	220 (37.4)	0.09
HADS anxiety categories (%)			
Normal	251 (32.0)	177 (29.9)	
Borderline	167 (21.3)	118 (20.0)	
Abnormal	366 (46.7)	296 (50.1)	0.46
HADS depression categories (%)			
Normal	480 (61.2)	329 (55.7)	
Borderline	164 (20.9)	130 (22.0)	
Abnormal	140 (17.9)	132 (22.3)	0.07
PHQ-12 severity high (%)	166 (21.2)	142 (24.0)	0.21
Rome IV latent class baseline cluster (%) †‡			
Cluster 1	135 (17.2)	109 (18.4)	
Cluster 2	167 (21.3)	127 (21.5)	
Cluster 3	277 (35.3)	188 (31.8)	
Cluster 4	105 (13.4)	70 (11.8)	
Cluster 5	14 (1.8)	20 (3.4)	
Cluster 6	34 (4.3)	40 (6.8)	
Cluster 7	52 (6.6)	37 (6.3)	0.15

*P value for independent samples *t*-test for continuous data and Pearson χ^2 for comparison of categorical data.

†Based on applying Rome IV model to all participants, not only those with Rome IV IBS.

‡Analysis comparing Rome III Latent Class Baseline Cluster also showed no significant difference between responders and non-responders ($p = 0.52$).

Table 2. Symptom Severity, Consultation Behaviour, and Commencement of New Treatment According to Baseline IBS Cluster Assignment Among 319 Individuals with Rome IV IBS.

	Rome IV IBS latent class cluster at baseline								
	Cluster 1 Diarrhoea and urgency with low psychological burden (n = 60)	**Cluster 2 Low overall GI symptom severity with high psychological burden (n = 69)**	**Cluster 3 Low overall GI symptom severity with low psychological burden (n = 53)**	**Cluster 4 Diarrhoea, abdominal pain, and urgency with high psychological burden (n = 80)**	**Cluster 5 Constipation, abdominal, and bloating with high psychological burden (n = 10)**	**Cluster 6 High overall GI symptom severity with high psychological burden (n = 29)**	**Cluster 7 Constipation and bloating with low psychological burden (n = 18)**	**Total (n = 319)**	***P* value**
Mean IBS-SSS score at follow-up (SD)	278.5 (97.9)	299.2 (93.8)	220.1 (92.9)	315.5 (105.8)	389.0 (76.1)	367.7 (88.1)	285.2 (74.7)	294.5 (104.2)	<0.001
Symptoms limiting activities ≥50% of the time at follow-up (%)	40 (66.7)	45 (65.2)	22 (41.5)	70 (87.5)	9 (90.0)	27 (93.1)	8 (44.4)	221 (69.3)	<0.001

Seen a GP regarding IBS during follow-up (%)	24 (40.0)	31 (44.9)	23 (43.3)	47 (58.8)	9 (90.0)	24 (82.8)	7 (38.9)	165 (51.7)	<0.001
IBS stool subtype based on BSFS (%)									
IBS-C	1 (1.7)	11 (15.9)	7 (13.2)	1 (1.3)	9 (90.0)	1 (3.4)	16 (88.9)	46 (14.4)	
IBS-D	43 (71.7)	20 (29.0)	19 (35.8)	48 (60.0)	0 (0)	5 (17.2)	0 (0)	135 (42.3)	
IBS-M	15 (25.0)	35 (50.7)	25 (47.2)	31 (38.8)	1 (10.0)	21 (72.4)	2 (1.1)	130 (40.8)	
IBS-U	1 (1.7)	3 (4.3)	2 (3.8)	0 (0)	0 (0)	2 (6.9)	0 (0)	8 (2.5)	<0.001
Seen a gastroenterologist regarding IBS during follow-up (%)	12 (20.0)	21 (30.4)	13 (24.5)	28 (35.0)	4 (40.0)	17 (58.6)	3 (16.7)	98 (30.7)	0.007

Any new treatment commenced during follow-up (%)	41 (68.3)	50 (72.5)	32 (60.4)	72 (90.0)	9 (90.0)	23 (79.3)	16 (88.9)	243 (76.2)	0.002
Mean number of new treatments commenced during follow-up (SD)	1.42 (1.37)	1.71 (1.62)	1.08 (1.05)	2.10 (1.38)	2.20 (1.03)	2.21 (1.59)	1.67 (1.09)	1.71 (1.43)	<0.001

*Adds up to >100%, as some people commenced more than one treatment during 12-month follow-up.

BSFS, Bristol stool form scale; IBS-SSS, IBS severity scoring system; GI, gastrointestinal