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TITLE PAGE

Title: Characteristics of, and Natural History Among, Individuals with Rome IV Functional Bowel Disorders.

Short running head: History of Functional Bowel Disorders.

Authors: Vivek C. Goodoory^{1,2} MBChB, Lesley A. Houghton¹ PhD, Christopher J. Black^{1,2} MBBS(Hons)*, Alexander C. Ford^{1,2} MD*.

*Denotes joint last author.

¹Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK.

²Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

Abbreviations:	CI	confidence interval
	CPSS	Cohen perceived stress scale
	FABD	functional abdominal bloating or distension
	FC	functional constipation
	FDr	functional diarrhoea
	HADS	hospital anxiety and depression scale
	IBS	irritable bowel syndrome
	OR	odds ratio
	PHQ-12	patient health questionnaire-12
	UFBD	unspecified functional bowel disorder

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: alex12399@yahoo.com
Telephone: +441132684963

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ABSTRACT

Background: Little is known about the natural history of functional bowel disorders using Rome IV criteria. We examined these issues in a longitudinal follow-up study.

Methods: We collected complete demographic, gastrointestinal symptom, and psychological comorbidity data at baseline from 1372 adults who met Rome IV criteria for one of the five functional bowel disorders. At 12 months, we collected data regarding gastrointestinal symptoms, psychological comorbidity, consultation behavior, and treatment commenced. We examined prognosis and stability of all five functional bowel disorders.

Key results: At baseline, 811 (59.1%) individuals met Rome IV criteria for IBS, 76 (5.5%) functional constipation (FC), 199 (14.5%) functional diarrhea (FDr), 130 (9.5%) functional abdominal bloating or distension (FABD), and 156 (11.4%) unspecified functional bowel disorder (UFBD). In total, 782 (57.0%) were successfully followed up. Individuals with IBS at baseline were significantly more likely to report symptoms compatible with anxiety, depression, or somatoform-type behavior ($p < 0.001$ for all analyses) at baseline and follow-up compared with those with the other four functional bowel disorders. IBS was the most stable functional bowel disorder; 319 (70.6%) of 452 participants still met criteria for IBS at 12 months, compared with 14 (34.1%) of 41, 43 (35.5%) of 121, 26 (33.8%) of 77, and 37 (40.7%) of 91 for FC, FDr, FABD, and UFBD respectively ($p < 0.001$).

Conclusions & Inferences: Individuals with Rome IV-defined IBS exhibited higher levels of anxiety, depression, or somatoform-type symptom reporting. IBS was the most stable and the likeliest disorder that the other four functional bowel disorders would fluctuate to.

Key words: functional bowel disorders; Rome IV criteria; natural history; stability; irritable bowel syndrome

INTRODUCTION

Functional bowel disorders are chronic gastrointestinal conditions. Individuals report symptoms attributable to the small and large intestine. Their underlying pathophysiology is incompletely understood but, due to involvement of disordered communication between the gut and brain, they are classed as disorders of gut-brain interaction (DGBI).¹ They affect more than 1 in 4 individuals and account for at least one-third of referrals to gastroenterology clinics.^{2,3} A diagnosis is usually made using symptom-based criteria, in the absence of red flag symptoms, and limited investigations.⁴ The clusters of symptoms used to diagnose functional bowel disorders have been refined over the last 30 years, for clinical and research purposes, the latest iteration being the Rome IV criteria.⁵

These criteria recognize six functional bowel disorders, one of which, opioid-induced constipation, has a clear etiology. The other five consist of irritable bowel syndrome (IBS), functional constipation (FC), functional diarrhea (FDr), functional abdominal bloating or distension (FABD), and unspecified functional bowel disorder (UFBD).⁵ The changes made from the Rome III to the Rome IV criteria were to the definitions of IBS and FDr. The more stringent Rome IV criteria for IBS require individuals to experience abdominal pain, rather than abdominal discomfort or pain, for at least 1 day per week, rather than 3 days per month. In contrast, these updated criteria are more permissive for the definition of FDr, requiring only >25%, rather than >75%, of stools to be loose in the past 3 months.⁶

Although the Rome Foundation recognizes that these functional bowel disorders exist on a continuum, rather than as distinct entities, most therapeutic trials still segregate individuals according to individual functional bowel disorder. As a result, evidence-based therapies are only available to treat IBS and FC,⁷⁻¹² despite previous longitudinal follow-up studies, using prior iterations of the Rome criteria, suggesting that functional bowel disorders are not stable and fluctuate considerably during extended follow-up.¹³⁻¹⁶ A recent study,

using the Rome IV criteria, demonstrated that individuals with IBS have higher levels of psychological comorbidity than those with FC or FDr.¹⁷ However, the authors recruited patients referred to secondary care who warranted a colonoscopy, and did not include those with FABD or UFBD. In addition, as this study was cross-sectional, the authors could not examine the natural history of these conditions.

Previous studies examining the stability of functional bowel disorders have, for the most part, only examined IBS,^{15, 18-25} or IBS, FDr, and FC,¹³ rather than all five functional bowel disorders simultaneously, and most have used prior iterations of the Rome criteria. The characteristics and natural history of individuals with functional bowel disorders according to the Rome IV criteria is, therefore, unclear. Given that assigning patients with bowel symptoms to appropriate functional bowel disorder categories is the mainstay of current management, as treatment is symptom-based, it is important to understand this. This is of particular relevance as, with the changes made in the Rome IV criteria, one of the disorders that is the least well-understood or studied, UFBD, is now one of the most prevalent of these conditions.³ We examined these issues in a longitudinal follow-up study conducted over 12 months.

MATERIALS AND METHODS

Participants and Setting

We recruited individuals, registered with three organizations in the UK, who self-identified as having IBS and agreed to participate in a previous study published elsewhere.^{26,}
²⁷ 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 research register allowing individuals with IBS to participate in research. We have previously reported data from the individuals with confirmed irritable bowel syndrome (IBS), according to the Rome III or IV criteria, in this cohort.^{18, 28-31} People aged ≥ 18 years were eligible and there were no exclusions, other than an inability to understand written English. We invited individuals, via email and post, between December 2017 and December 2018. Potential participants were directed to a study information leaflet and those interested completed an online questionnaire. All fields were mandatory to minimize missing data, and responses were stored securely in an online database. There were no financial incentives to participate. We sent follow-up questionnaire to all participants 12 months later, using the same methods. The University of Leeds research ethics committee approved both the baseline and follow-up study in November 2017.

Data Collection and Synthesis

Demographic Data and Lower Gastrointestinal Symptom Data

We collected demographic data at baseline. We captured lower gastrointestinal data at baseline and 12-month follow-up using the Rome IV questionnaire.³² Among those individuals who did not meet the Rome IV criteria for IBS, we used the scoring algorithms

proposed for use with the Rome IV questionnaire to assign presence or absence of the four other Rome IV-defined functional bowel disorders: FC, FDr, FABD, or UFBD. We assessed the stability of all functional bowel disorders by examining the proportion of individuals who met the criteria for the same disorder or who transitioned to another disorder at 12 months, again according to the Rome IV questionnaire.³²

Disease Impact and Psychological Health Data at Baseline and Follow-up

We measured the impact of gastrointestinal symptoms at baseline and follow-up in each functional bowel disorder, in terms of the proportion of time that they limited normal daily activities, according to the Rome IV questionnaire,³² and dichotomized this at a threshold of interference with daily activities $\geq 50\%$ of the time. We examined psychological health at baseline and at 12 months in all individuals according to functional bowel disorder at baseline. We collected anxiety and depression data using the hospital anxiety and depression scale (HADS).³³ The total HADS score ranges from 0 to 21 for either anxiety or depression, with a score ≤ 7 being normal, 8-10 borderline abnormal, and ≥ 11 abnormal. We collected somatization data using the patient health questionnaire-12 (PHQ-12),³⁴ derived from the validated patient health questionnaire-15.³⁵ The total PHQ-12 score ranges from 0 to 24. We categorized severity into high (total PHQ-12 ≥ 13), medium (8-12), low (4-7), or minimal (≤ 3). We assessed stress using the 10-item version of Cohen Perceived Stress Scale (CPSS), which is derived from the original 14-item questionnaire,³⁶ and measures the degree to which an individual feels they have experienced stress in the previous month. It is considered reliable and comparable to the original questionnaire.³⁷ There are no validated cut offs to define low, medium, or high levels of perceived stress, so we divided these data into tertiles of equal size. Finally, we assessed gastrointestinal symptom-specific anxiety using the visceral sensitivity index, a validated 15-item instrument.³⁸ Replies to each of the questions

are provided on a six-point scale from “strongly disagree” (scored as 0) to “strongly agree” (scored as 5). Again, as there are no recommended cut offs to define low, medium, or high gastrointestinal symptom-specific anxiety scores, we divided these data into equally sized tertiles.

Consultation Behavior and Treatment Data During Follow-up

We asked participants to state whether they had seen a primary care physician or gastroenterologist about their gastrointestinal symptoms at baseline and in the 12 months since study entry, and whether they had commenced any new treatments (dietary, drugs, and/or psychological) for their symptoms since study entry.

Statistical analysis

We compared demographic characteristics of all participants according to their functional bowel disorder at baseline. We compared the proportions of individuals with each functional bowel disorder at baseline who fluctuated to another disorder at 12 months. We used a logistic regression model, controlling for all baseline data to examine predictors of fluctuation of functional bowel disorders at 12 months among those meeting Rome IV criteria for any of the functional bowel disorders at both baseline and 12 months, and reported results with odds ratios (ORs) with 95% confidence intervals (CIs).

We also examined whether baseline functional bowel disorder influenced subsequent disease behavior by comparing proportions of people who had seen a primary care physician, consulted a gastroenterologist, or commenced a new treatment for their gastrointestinal symptoms, as well as the number of new treatments commenced, during the 12-month follow-up period. We also compared the proportion of individuals with each functional bowel disorder who had abnormal anxiety, depression, or somatization scores at 12 months. We

used a χ^2 test for categorical data and a one-way analysis of variance for continuous data. Due to multiple comparisons, a 2-tailed p value of <0.01 was considered statistically significant for all analyses, which were performed using SPSS for Windows (version 26.0 SPSS Inc., Chicago, IL, USA).

RESULTS

Of 1375 participants providing complete baseline data, there were 1372 (99.8%) individuals providing data for this study, as three individuals did not meet criteria for any of the functional bowel disorders. Of these 1372, 811 (59.1%) met Rome IV criteria for IBS, 76 (5.5%) FC, 199 (14.5%) FDr, 130 (9.5%) FABD, and 156 (11.4%) UFBD. Of these, 782 (57.0%) were successfully followed up at 12 months. Characteristics of those responding to the 12-month questionnaire, compared with those who did not are provided in Table 1. There were 452 (55.7%) individuals with IBS, 41 (53.9%) with FC, 121 (60.8%) with FDr, 77 (59.2%) with FABD, and 91 (58.3%) with UFBD providing follow-up data at 12 months ($p=0.67$). Responders were significantly older ($p<0.001$), more likely to be married or cohabiting ($p=0.008$), to have attained a university or postgraduate level of education ($p<0.001$), and to be White Caucasian ($p<0.001$), and less likely to be smokers ($p<0.001$). They were also more likely to have seen a primary care physician or gastroenterologist about their symptoms ($p=0.007$ and $p=0.006$, respectively).

Characteristics of Individuals Meeting Rome IV Criteria for Functional Bowel

Disorders at Baseline

Baseline demographic, gastrointestinal symptom, and psychological health data for all 1372 individuals are presented in Table 2. Compared with those with IBS, individuals with the four other functional bowel disorders were significantly older ($p<0.001$), more likely to have achieved a university or postgraduate level of education ($p=0.009$), and more likely to drink alcohol ($p=0.002$). Other differences related to symptom profiles, enforced by the Rome IV criteria themselves, including higher rates of weekly abdominal pain and continuous abdominal pain among those with IBS ($p<0.001$ for both), higher rates of urgency and fecal incontinence among those with IBS or FDr ($p<0.001$ for both), and higher rates of

weekly abdominal bloating among those with IBS, FC, and FABD ($p < 0.001$).

Gastrointestinal symptoms were significantly more likely to be meal-related $\geq 50\%$ of the time among those with IBS, and to impact on activities of daily living $\geq 50\%$ of the time ($p < 0.001$ for both). In terms of psychological health, those with IBS were significantly more likely to report symptoms compatible with anxiety, depression, or somatoform-type symptom behavior, and reported significantly higher levels of perceived stress and gastrointestinal symptom-specific anxiety ($p < 0.001$ for all analyses).

When comparing characteristics of individuals with Rome IV functional bowel disorders, excluding those with IBS, there were fewer significant differences. Those with FDr were less likely to report weekly abdominal pain, but more likely to report urgency than the other three groups ($p < 0.001$ for both), and those with FC or FABD were more likely to report weekly abdominal bloating ($p < 0.001$). In terms of psychological health, those with UFBD had higher rates of somatoform symptom reporting, and there were higher levels of gastrointestinal symptom-specific anxiety among those with FABD or UFBD ($p = 0.001$ for both).

Stability and Natural History Among Individuals Meeting Rome IV Criteria for Functional Bowel Disorders

IBS was the most stable of the five functional bowel disorders during follow-up, with 319 (70.6%) of 452 participants still meeting criteria for IBS at 12 months, compared with 14 (34.1%) of 41, 43 (35.5%) of 121, 26 (33.8%) of 77, and 37 (40.7%) of 91 for FC, FDr, FABD, and UFBD respectively ($p < 0.001$) (Table 3). In all cases IBS was the likeliest disorder that the other four functional bowel disorders would fluctuate to, with around one-third of people in these groups meeting criteria for IBS at 12 months (Figure 1). Excluding individuals with IBS, UFBD was the most stable of the other four functional bowel disorders

during follow-up ($p < 0.001$). Following logistic regression controlling for all baseline data in all 782 individuals followed up successfully, those in the highest tertile of gastrointestinal symptom-specific anxiety and those reporting meal-related symptoms $\geq 50\%$ of the time at baseline were significantly more likely to remain in the same functional bowel disorder category at 12 months (OR = 1.86; 95% CI 1.20-2.86, $p = 0.005$ and OR = 1.56; 95% CI 1.14-2.13, $p = 0.005$). When individuals with IBS were excluded from the analysis, there was a trend towards those in the highest tertile of perceived stress at baseline being more likely to remain in the same functional bowel disorder category at 12 months (OR = 2.92; 95% CI 1.08-7.88, $p = 0.035$), but no significant predictors of stability.

There were no significant differences in likelihood of seeing a primary care physician or gastroenterologist during 12-month follow-up across the five functional bowel disorders, although rates were higher in those with IBS. Those with IBS were significantly more likely to report that symptoms interfered with activities of daily living at 12 months ($p < 0.001$), and those with IBS or FC were more likely to have commenced a new medication for their symptoms during follow-up ($p = 0.009$). Those with IBS were significantly more likely to report symptoms compatible with anxiety, depression, or somatoform-type symptom behavior, compared with individuals with one of the other four functional bowel disorders at 12 months ($P < 0.001$).

When excluding individuals with IBS, there were no significant differences in any analyses at 12 months. However, consultation rates with a primary care physician and impact on activities of daily living were highest in those with UFBD, whereas rates for seeing a gastroenterologist and commencing a new medication were highest in those with FC. Those with FC or UFBD had the highest rates of abnormal anxiety scores, whereas those with FABD reported the highest rate of symptoms compatible with depression. Rates of somatoform symptom reporting were lowest in those with FDr.

DISCUSSION

This longitudinal follow-up study has examined the characteristics of, and natural history among, individuals meeting criteria for the five Rome IV-defined functional bowel disorders. At baseline, by the nature of Rome IV criteria, individuals with IBS had higher rates of weekly abdominal pain, continuous abdominal pain, and meal-related symptoms than those with the other four functional bowel disorders. Participants with IBS or FDr experienced higher rates of urgency and fecal incontinence, and those with IBS, FC, or FABD had higher levels of weekly abdominal bloating. Those with IBS at baseline were more likely to report symptoms compatible with anxiety, depression, or somatoform-type symptom behavior both at baseline and 12-month follow-up, compared with those with the other four functional bowel disorders. They also reported a significantly greater impact of their symptoms on activities of daily living at both baseline and follow-up. Although there were few significant differences among the five functional bowel disorders in terms of healthcare usage at baseline or during follow-up, those with IBS or FC were more likely to have commenced a new medication. During 12-month follow-up, a diagnosis of IBS was significantly more stable than any of the other four functional bowel disorders. More than two-thirds of individuals with IBS at baseline still met criteria for IBS at follow-up, compared with only 30% to 40% of individuals with one of the other four functional bowel disorders. Moreover, IBS was the likeliest disorder that all of the other four functional bowel disorders would fluctuate to. Finally, the only predictors of stability at 12 months amongst individuals successfully followed up were meal-related symptoms $\geq 50\%$ of the time and higher gastrointestinal symptom-specific anxiety.

We recruited a large number of individuals into this study and obtained near complete data for the variables of interest because we used mandatory fields in our online questionnaire both at baseline and follow-up. As our participants were recruited from the

community and were not necessarily under the care of a treating clinician, our sample is likely to be representative of many individuals with functional bowel disorders. All questionnaires used were validated, are well-accepted, and have been used widely in studies with functional bowel disorders and other chronic gastrointestinal conditions. Although participants did not receive any financial incentive, our response rate of 57% is similar to other longitudinal follow-up studies conducted over a similar time frame.³⁹⁻⁴²

Weaknesses of this study include the fact that we recruited individuals who believed they had IBS, rather than one of the other four functional bowel disorders specifically. Even if most of them had consulted their primary care physician or a gastroenterologist about their symptoms, it can be difficult clinically to separate these disorders into different entities. Indeed, this suggests that, although patients and clinicians are identifying functional bowel symptoms, they are classifying them all as “IBS”, suggesting the Rome criteria are not being used, in favor of a pragmatic clinical approach. Fundamentally, this suggests that "real world" clinical practice differs from the narrower view of diagnoses made using Rome and, by extension, clinical trials. In fact, the Rome Foundation consider that these disorders exist as a continuum, rather than in isolation,⁵ and the lack of stability during follow-up, and high rates of fluctuation observed between them, supports this. When we applied the Rome IV criteria, only 59% of 1372 participants had IBS. We believe it is therefore likely that the other individuals recruited into this study had one of the other four functional bowel disorders, given they met Rome IV criteria for these, and only three individuals recruited did not meet criteria for any of the five functional bowel disorders. We did not check participants' medical records to rule out other organic diseases that may mimic functional bowel disorders, such as coeliac disease or inflammatory bowel disease.^{43, 44} However, functional bowel disorders are more prevalent than these conditions in the community, and a recent study confirms that the yield of colonoscopy in most patients with functional bowel

disorders, other than those with diarrhea, is extremely low.⁴⁵ The questionnaires were accessed online by the participants and hence, we were unable to assess how many individuals visited the website but chose not to complete the questionnaire or whether those who participated are representative of individuals from these three organizations. Despite an acceptable response rate, there were some significant differences between responders and non-responders at 12 months in terms of demographics, although not according to gastrointestinal or psychological symptoms. This means that those who provided longitudinal data may not be representative of the entire sample. We used validated questionnaires to assign the presence of abnormal scores for psychological comorbidities as proxy measures for the presence of common mental disorders.^{33, 34, 36, 38} The latter can only be established through psychiatric or psychological assessments, although our methodology in this regard is practical, well-accepted, and has been used widely in similar studies.^{26, 27, 41, 46-49} Finally, our use of the upper tertile to define abnormal levels of perceived stress or gastrointestinal symptom-specific anxiety is a compromise, but has been used in other similar studies due to the lack of validated cutoff levels.^{29, 48}

Our findings are in keeping with a recent cross-sectional study reporting that individuals with Rome IV IBS have significantly higher levels of anxiety, depression and somatoform-type symptom behavior than those with Rome IV FC or FDr.¹⁷ However, despite similar results, the authors recruited patients referred to a secondary care center and reported symptoms warranting colonoscopy. In addition, they did not conduct longitudinal follow up, so were only able to report associations at a single point in time, rather than examine the natural history of these conditions. Although there were differences in baseline demographics in terms of age, level of education, and alcohol use between individuals with Rome IV IBS and the other four functional bowel disorders in the present study, the crucial difference is the higher frequency of weekly abdominal pain, continuous abdominal pain, and meal-related

symptoms in those with IBS. This suggests that it is these factors in IBS that are the main driver for poor psychological health. Whether this relates to the pain itself or negative pain beliefs,⁵⁰ leading to catastrophizing,⁵¹ is unclear and could be the subject of further studies. Our findings are supported by the results of Shekhar *et al.*, who demonstrated increased symptoms after meal ingestion and lower sensory thresholds in patients with IBS-C compared with FC.⁵² In addition, Shiha *et al.* demonstrated that increasing abdominal pain frequency correlated with higher levels of anxiety, depression, and somatoform-type symptom reporting in IBS compared with FC or diarrhea.¹⁷ Comparison between IBS with diarrhea (IBS-D) and FDr, and IBS with constipation (IBS-C) and FC using the Rome III criteria in a previous cross-sectional study again showed that those with IBS-D and IBS-C reported higher levels of anxiety and somatoform-type symptom reporting, to those with FDr or constipation, but similar levels of depression.⁵³ The Rome III criteria for IBS are less restrictive, using a definition of abdominal discomfort or pain at a lower frequency of 3 days per month, and this may explain the slightly different results to our study.

Although other studies have investigated the stability of IBS and IBS sub-types,^{15, 18-25} or IBS, gastro-esophageal reflux, dyspepsia, FDr, and FC,^{13, 14, 54} to the best of our knowledge, this is the first study to examine the characteristics and natural history among individuals with all five functional bowel disorders simultaneously. IBS was the most stable functional bowel disorder in our study. The reasons for this are speculative, although given IBS itself consists of four separate subtypes this may allow more fluctuation within this single diagnostic category than among the four other functional bowel disorders we studied. In addition, those with IBS have abdominal pain which is relatively frequent and therefore likely to be persistent. Conversely, those with FDr or FC might also be experiencing abdominal pain, albeit less than weekly. However, if the frequency of abdominal pain

increases, they are then likely to meet criteria for IBS, even though the overall pattern of their gastrointestinal symptoms is actually little changed.

The results of our study have important clinical and research implications. Firstly, the high prevalence of symptoms compatible with common mental disorders in people with functional bowel disorders, particularly those with IBS, suggests that the presence of these disorders should be screened for routinely in these individuals. This is especially important given that the prognosis of individuals with Rome IV IBS appears to worsen with incremental increases in psychological comorbidity.²⁹ In fact, the Rome committee have recognized the importance of assessing psychological health in patients with DGBI by advocating the use of a multidimensional clinical profile approach.⁵⁵ Despite this recommendation 5 years ago, we are yet to see its implementation in routine clinical practice. Secondly, future treatment trials, including those investigating pharmacological and psychological therapies, in functional bowel disorders should include both gastrointestinal and psychological assessment at baseline and follow-up. Thirdly, gut-brain neuromodulators and psychological therapies are efficacious in IBS,^{7, 12, 56, 57} but given the degree of psychological comorbidity among individuals with all five functional bowel disorders in this study future trials should consider their use, irrespective of which of these conditions is met, particularly given the fluctuation between them. Finally, other than IBS, FC is the only other functional bowel disorder with evidence-based licensed therapies available.⁸ Individuals with the other three functional bowel disorders must rely on off-label therapies. Uncertainty as to how best to treat the other three conditions is perhaps reflected by the significantly lower prescription rates of drugs for symptoms we observed in the other three groups. In our study, 30% of individuals with IBS at baseline fluctuated to another functional bowel disorder at 12 months, and between 30% and 40% of those with one of the other four functional bowel disorders at baseline fluctuated to IBS. Future treatment trials should once again consider

including individuals with these other functional bowel disorders, for example patients with FDr in trials in IBS-D or FC in IBS-C, given that our study provides further evidence that these disorders exist on a continuum rather than as distinct entities. This approach has been used in some trials previously.^{58, 59}

In summary, in this study of individuals meeting criteria for Rome IV functional bowel disorders, those with IBS exhibited higher levels of anxiety, depression, or somatoform-type symptom reporting, and symptoms had a significantly greater impact on activities of daily living at both baseline and follow-up. IBS was the most stable diagnosis and was the likeliest disorder that the other four functional bowel disorders would fluctuate to. Our findings have implications for the design of future treatment trials in functional bowel disorders.

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Guarantor of the article: ACF is guarantor.

Specific author contributions: VCG, LAH, CJB, and ACF conceived and drafted the study.

CJB collected all data. ACF analyzed and interpreted the data. VCG and ACF drafted the manuscript. All authors have approved the final draft of the manuscript.

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Figure 1. Stability of Each Rome IV Functional Bowel Disorder According to Rome IV Functional Bowel Disorder at Baseline.

IBS; irritable bowel syndrome, FC; functional constipation, FDr; functional diarrhea, FABD; functional abdominal bloating or distension, UFBD; unspecified functional bowel disorder.

Table 1. Baseline Characteristics of Individuals Meeting Rome IV Criteria for Each Functional Bowel Disorder According to Response to the 12-month Questionnaire.

	Responded to Questionnaire at 12 Months (n=782)	Did not Respond to Questionnaire at 12 Months (n=590)	<i>p</i> value*
Rome IV functional bowel disorder (%)			
IBS	452 (57.8)	359 (60.8)	
FC	41 (5.2)	35 (5.9)	
FDr	121 (15.5)	78 (13.2)	
FABD	77 (9.8)	53 (9.0)	
UFBD	91 (11.6)	65 (11.0)	0.67
Mean age (SD)	50.7 (14.4)	47.1 (16.5)	<0.001
Female gender (%)	658 (84.1)	496 (84.1)	0.97
Married or co-habiting (%)	534 (68.3)	362 (61.4)	0.008
University or postgraduate level of education (%)	368 (47.1)	218 (37.3)	<0.001
White Caucasian ethnicity (%)	752 (96.2)	538 (91.7)	<0.001
Smoker (%)	49 (6.3)	71 (12.1)	<0.001
Alcohol use (%)	467 (59.7)	334 (56.7)	0.26
Lower abdominal pain more than once a week (%)	430 (55.0)	354 (60.0)	0.06
Meal-related symptoms \geq50% of the time (%)	501 (64.1)	394 (66.8)	0.30
Symptoms limited normal daily activities \geq50% of the time (%)	467 (59.7)	359 (61.3)	0.56
Continuous abdominal pain (%)	303 (38.7)	251 (42.8)	0.33
Urgency on at least most days (%)	182 (23.3)	145 (24.6)	0.58
Fecal incontinence once a week or more (%)	117 (15.0)	100 (16.9)	0.32
Abdominal bloating once a week or more (%)	620 (79.3)	457 (77.5)	0.42

Previously seen a primary care physician regarding symptoms (%)	752 (96.2)	547 (92.9)	0.007
Previously seen a gastroenterologist regarding symptoms (%)	474 (60.6)	313 (53.1)	0.006
HADS anxiety categories (%)			
Normal	251 (32.1)	177 (30.0)	
Borderline abnormal	166 (21.2)	118 (20.0)	
Abnormal	365 (46.7)	295 (50.0)	0.47
HADS depression categories (%)			
Normal	478 (61.1)	328 (55.6)	
Borderline abnormal	164 (21.0)	130 (22.0)	
Abnormal	140 (17.9)	132 (22.4)	0.07
PHQ-12 severity (%)			
Minimal	58 (7.4)	50 (8.5)	
Low	225 (28.8)	159 (26.9)	
Medium	333 (42.6)	239 (40.5)	
High	166 (21.2)	142 (24.1)	0.49
Perceived Stress (%)			
Low	336 (43.0)	211 (35.9)	
Medium	248 (31.7)	205 (34.9)	
High	198 (25.3)	172 (29.3)	0.03
Gastrointestinal symptom-specific anxiety (%)			
Low	362 (46.3)	251 (42.8)	
Medium	240 (30.7)	161 (27.5)	
High	180 (23.0)	174 (29.7)	0.02

IBS; irritable bowel syndrome, FC; functional constipation, FDr; functional diarrhea, FABD; functional abdominal bloating or distension, UFBD; unspecified functional bowel disorder.

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

Table 2. Baseline Characteristics of Individuals Meeting Rome IV Criteria for Each Functional Bowel Disorder.

	IBS (n=811)	FC (n=76)	FDr (n=199)	FABD (n=130)	UFBD (n=156)	<i>p</i> value*	<i>p</i> value**
Mean age (SD)	47.4 (15.2)	51.6 (15.5)	53.5 (15.0)	49.9 (15.5)	51.0 (15.8)	<0.001	0.19
Female gender (%)	697 (85.9)	67 (88.2)	158 (79.4)	108 (83.1)	124 (79.5)	0.06	0.33
Married or co-habiting (%)	526 (64.9)	50 (65.8)	127 (63.8)	86 (66.2)	107 (68.6)	0.90	0.83
University or postgraduate level of education (%)	315 (39.0)	33 (43.4)	101 (50.8)	64 (49.6)	73 (47.1)	0.009	0.71
White Caucasian ethnicity (%)	763 (94.3)	72 (94.7)	190 (95.5)	120 (93.0)	145 (92.9)	0.84	0.71
Smoker (%)	79 (9.8)	2 (2.6)	16 (8.0)	6 (4.6)	17 (10.9)	0.08	0.07
Alcohol user (%)	442 (54.6)	43 (56.6)	138 (69.3)	79 (60.8)	99 (63.5)	0.002	0.18
Lower abdominal pain more than once a week (%)	667 (82.2)	19 (25.0)	22 (11.1)	33 (25.4)	43 (27.6)	<0.001	<0.001
Continuous abdominal pain (%)	386 (47.7)	23 (30.3)	43 (21.6)	43 (33.3)	59 (38.1)	<0.001	0.03
Urgency on at least most days (%)	233 (28.7)	2 (2.6)	51 (25.6)	20 (15.4)	21 (13.5)	<0.001	<0.001
Fecal incontinence once a week or more (%)	157 (19.4)	2 (2.6)	27 (13.6)	14 (10.8)	17 (10.9)	<0.001	0.08
Abdominal bloating once a week or more (%)	712 (87.8)	56 (73.7)	94 (47.2)	130 (100)	85 (54.5)	<0.001	<0.001

Meal-related symptoms $\geq 50\%$ of the time (%)	601 (74.1)	34 (44.7)	103 (51.8)	75 (57.7)	82 (52.6)	<0.001	0.35
Symptoms limited normal daily activities $\geq 50\%$ of the time (%)	573 (70.8)	27 (35.5)	91 (45.7)	57 (44.2)	78 (50.3)	<0.001	0.21
Previously seen a primary care physician regarding symptoms at study entry (%)	778 (96.0)	70 (92.1)	185 (93.0)	124 (95.4)	142 (91.0)	0.049	0.55
Previously seen a gastroenterologist regarding symptoms at study entry (%)	492 (60.7)	40 (52.6)	104 (52.3)	73 (56.2)	78 (50.0)	0.038	0.78
HADS anxiety categories (%)							
Normal	202 (24.9)	27 (35.5)	87 (43.7)	52 (40.0)	60 (38.5)		
Borderline abnormal	167 (20.6)	15 (19.7)	47 (23.6)	28 (21.511)	27 (17.3)		
Abnormal	442 (54.5)	34 (44.7)	65 (32.7)	50 (38.5)	69 (44.2)	<0.001	0.35
HADS depression categories (%)							
Normal	434 (53.5)	51 (67.1)	144 (72.4)	82 (63.1)	95 (60.9)		
Borderline abnormal	191 (23.6)	17 (22.4)	30 (15.1)	28 (21.5)	28 (17.9)		
Abnormal	186 (22.9)	8 (10.5)	25 (12.6)	20 (15.4)	33 (21.2)	<0.001	0.12

PHQ-12 severity (%)							
Minimal	42 (5.2)	7 (9.2)	23 (11.6)	14 (10.8)	22 (14.1)		
Low	175 (21.6)	33 (43.4)	81 (40.7)	49 (37.7)	46 (29.5)		
Medium	356 (43.9)	30 (39.5)	82 (41.2)	52 (40.0)	52 (33.3)		
High	238 (29.3)	6 (7.9)	13 (6.5)	15 (11.5)	36 (23.1)	<0.001	0.001
Perceived Stress (%)							
Low	226 (27.9)	27 (35.5)	90 (45.5)	50 (38.5)	57 (36.5)		
Medium	294 (36.3)	27 (35.5)	71 (35.9)	41 (31.5)	64 (41.0)		
High	290 (35.8)	22 (28.9)	37 (18.7)	39 (30.0)	35 (22.4)	<0.001	0.15
Gastrointestinal symptom-specific anxiety (%)							
Low	196 (24.3)	44 (57.9)	98 (49.5)	47 (36.2)	79 (50.6)		
Medium	281 (34.8)	23 (30.3)	68 (34.3)	52 (40.0)	35 (22.4)		
High	331 (41.0)	9 (11.8)	32 (16.2)	31 (23.8)	42 (26.9)	<0.001	0.001

IBS; irritable bowel syndrome, FC; functional constipation, FDr; functional diarrhea, FABD; functional abdominal bloating or distension,

UFBD; unspecified functional bowel disorder.

**p* value for one-way analysis of variance for continuous data and Pearson χ^2 for comparison of categorical data across all five Rome IV functional bowel disorders.

***p* value for one-way analysis of variance for continuous data and Pearson χ^2 for comparison of categorical data across four Rome IV functional bowel disorders, excluding IBS.

Table 3. Stability, Consultation Behavior, Disease Impact, Commencement of New Treatment, and Psychological Health at 12-month Follow-up According to Functional Bowel Disorder at Baseline.

	IBS at baseline (n=452)	FC at baseline (n=41)	FDr at baseline (n=121)	FABD at baseline (n=77)	UFBD at baseline (n=91)	<i>p</i> value*	<i>p</i> value**
Rome IV functional bowel disorder at 12-month follow-up (%)							
IBS	319 (70.6)	15 (36.6)	39 (32.2)	31 (40.3)	32 (35.2)		
FC	14 (3.1)	14 (34.1)	0 (0.0)	2 (2.6)	7 (7.7)		
FDr	48 (10.6)	1 (2.4)	43 (35.5)	10 (13.0)	6 (6.6)		
FABD	39 (8.6)	6 (14.6)	13 (10.7)	26 (33.8)	9 (9.9)		
UFBD	32 (7.1)	5 (12.2)	26 (21.5)	8 (10.4)	37 (40.7)	<0.001	<0.001
Saw a primary care physician regarding symptoms during 12-month follow-up (%)	202 (44.7)	13 (31.7)	35 (28.9)	26 (33.8)	37 (40.7)	0.01	0.35
Saw a gastroenterologist regarding symptoms during 12-month follow-up (%)	119 (26.3)	9 (22.0)	18 (14.9)	15 (19.5)	14 (15.4)	0.03	0.66
Symptoms limited normal daily activities \geq50% of the time at 12-month follow-up (%)	280 (61.9)	14 (34.1)	49 (40.5)	33 (42.9)	44 (48.4)	<0.001	0.45

Commenced new treatment for symptoms during 12-month follow-up (%)	330 (73.0)	29 (70.7)	74 (61.2)	49 (63.6)	52 (57.1)	0.009	0.50
Number of new treatments commenced for symptoms during 12-month follow-up (%)							
0	122 (27.0)	12 (29.3)	47 (38.8)	28 (36.4)	39 (42.9)		
1	113 (25.0)	11 (26.8)	36 (29.8)	25 (32.5)	17 (18.7)		
2	110 (24.3)	9 (22.0)	24 (19.8)	14 (18.2)	12 (13.2)		
3	67 (14.8)	6 (14.6)	9 (7.4)	6 (7.8)	19 (20.9)		
4	28 (6.2)	2 (4.9)	5 (4.1)	4 (5.2)	3 (3.3)		
5	3 (0.7)	1 (2.4)	0 (0.0)	0 (0.0)	1 (1.1)		
6	9 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.02	0.16
HADS anxiety categories at 12-month follow-up (%)							
Normal	136 (30.1)	12 (29.3)	60 (49.6)	34 (44.2)	35 (38.5)		
Borderline abnormal	86 (19.0)	10 (24.4)	30 (24.8)	15 (19.5)	18 (19.8)		
Abnormal	230 (50.9)	19 (46.3)	31 (25.6)	28 (36.4)	38 (41.8)	<0.001	0.12

HADS depression categories at 12-month follow-up (%)							
Normal	232 (51.3)	32 (78.0)	91 (75.2)	54 (70.1)	62 (68.1)		
Borderline abnormal	108 (23.9)	7 (17.1)	14 (11.6)	8 (10.4)	16 (17.6)		
Abnormal	112 (24.8)	2 (4.9)	16 (13.2)	15 (19.5)	13 (14.3)	<0.001	0.31
PHQ-12 severity at 12-month follow-up (%)							
Minimal	22 (4.9)	0 (0.0)	16 (13.2)	9 (11.7)	13 (14.3)		
Low	129 (28.5)	19 (46.3)	46 (38.0)	31 (40.3)	25 (27.5)		
Medium	182 (40.3)	17 (41.5)	51 (42.1)	25 (32.5)	37 (40.7)		
High	119 (26.3)	5 (12.2)	8 (6.6)	12 (15.6)	16 (17.6)	<0.001	0.06

IBS; irritable bowel syndrome, FC; functional constipation, FDr; functional diarrhea, FABD; functional abdominal bloating or distension,

UFBD; unspecified functional bowel disorder.

**p* value for Pearson χ^2 for comparison of categorical data across all five Rome IV functional bowel disorders.

***p* value for Pearson χ^2 for comparison of categorical data across four Rome IV functional bowel disorders, excluding IBS.