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TITLE PAGE

Title: Symptom Stability in Rome IV vs. Rome III Irritable Bowel Syndrome.

Short title: Stability of Rome IV vs Rome III IBS.

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Abbreviations:

BSFS	Bristol stool form scale
CI	confidence interval
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
OR	odds ratio
PHQ-12	patient health questionnaire-12

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ABSTRACT

Objectives: Irritable bowel syndrome (IBS) is a chronic functional bowel disorder, which follows a relapsing and remitting course. Little is known about how evolving definitions of IBS, or treatment for the condition, affect symptom stability. We conducted a 12-month longitudinal follow-up study of individuals who self-identify as having IBS to examine these issues.

Methods: We collected complete demographic, symptom, mood, and psychological health data at baseline, and symptom data at 12 months, from adults who self-identified as having IBS, registered with three organizations providing services to people with IBS. We applied the Rome III and Rome IV criteria simultaneously at baseline and 12 months, and subtyped participants according to predominant stool form or frequency. We examined stability of a diagnosis of IBS, and stability of IBS subtype, for the Rome IV and III criteria separately, and examined the effect of commencing new therapy on fluctuation of symptoms.

Results: Of 1375 individuals recruited at baseline, 784 (57.0%) provided data at 12 months. Of these, 452 met the Rome IV criteria for IBS at baseline, of whom 133 (29.4%) fluctuated to another functional bowel disorder at 12 months. In the remaining 319 (70.6%) who still met Rome IV criteria for IBS, IBS subtype changed in 101 (31.7%) subjects, with IBS with mixed stool pattern (IBS-M) the least stable. Commencing a new treatment for IBS did not affect symptom stability. Among 631 who met Rome III criteria at baseline responding at 12 months, 104 (16.5%) fluctuated to another functional bowel disorder. In the 527 (83.5%) who still met Rome III criteria for IBS, IBS subtype fluctuated in 129 (24.5%), with IBS-M the most stable subtype. Again, commencing a new treatment for IBS did not affect symptom stability.

Conclusions: Fluctuation between functional bowel disorders, and predominant stool subtype, is common in people with IBS, and does not appear to be influenced solely by treatment. Rome IV IBS appears less stable than Rome III IBS.

Key words: irritable bowel syndrome; Rome III criteria; Rome IV criteria; therapy; stability

What is known

Functional bowel disorders, such as irritable bowel syndrome (IBS), are chronic, relapsing and remitting conditions.

IBS stool subtype also appears to lack stability, particularly if assessed at repeated intervals.

It is unclear how much of this fluctuation between IBS and other functional bowel disorders, and IBS subtypes, is due to natural variability of the condition, how much due to treatment for it, and whether the degree of variability is affected by diagnostic criteria.

What is new here

Between one-in-three and one-in-six people with IBS fluctuate between this diagnosis and another functional bowel disorder, and the degree of fluctuation appeared higher with the Rome IV criteria.

IBS stool subtype instability occurred in as many as one-in-three people, and again this was higher when the Rome IV criteria were used to define IBS.

Movement between IBS and another functional bowel disorder, or between IBS subtypes, did not relate solely to the commencement of a new treatment.

Fluctuation of symptoms in IBS is to be expected, and is not an indication for further diagnostic work-up, unless alarm symptoms develop.

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common disorders of gut-brain interaction (previously called functional gastrointestinal disorders), characterized by altered stool form or frequency in association with abdominal discomfort or pain. (1, 2) The condition is diagnosed using the Rome criteria, which have evolved over the years from the Rome I criteria, (3) to the latest iteration, Rome IV. (2) As these definitions have been refined, and in an effort to give more realistic estimates of the prevalence of IBS globally, (4) as well as to recruit more homogeneous groups of patients into clinical trials, they have become more restrictive.

In moving from the Rome III to the latest Rome IV definition of IBS, the term abdominal discomfort was removed from the nomenclature, and the symptom frequency at which abdominal pain needed to be experienced to meet criteria for IBS was increased to a minimum of 1 day per week, from 3 days per month. (2) The effects of these latest changes appear to be that fewer patients who believe they have IBS now meet the Rome IV criteria for the condition, while those that do meet these criteria have more severe bowel symptoms and higher levels of psychological comorbidity. (5-8) Another consequence of this is that patients who would previously have been diagnosed as having IBS are now classified by current diagnostic criteria as having another functional bowel disorder, such as functional constipation, functional diarrhea, or functional bloating or abdominal distention. (5)

Conventionally, IBS is categorized into four subtypes based on the predominant stool form or frequency reported by the individual: IBS with constipation (IBS-C); IBS with diarrhea (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. (2) Assigning patients with IBS to the appropriate subtype is the mainstay of management, as treatment is symptom-based, and according to the patient's predominant

stool pattern. (9-12) As most drugs used to treat IBS are designed to address either constipation or diarrhea, their use in an incorrect subtype could lead to a worsening of bowel symptoms. It is, therefore, important to know whether these subtypes, and indeed IBS itself, remain stable over time.

Previous longitudinal follow-up studies suggest that functional bowel disorders are not stable and fluctuate considerably during extended follow-up. (13-16) IBS subtype, as defined by predominant stool form or frequency, also appears to lack stability, (17-20) particularly if assessed at repeated intervals. (17) However, it is unclear how much of this fluctuation between IBS and other functional bowel disorders, and IBS subtypes, is due to natural variability of the condition, how much due to treatment for it, and whether the degree of variability is affected by diagnostic criteria used. We examined these issues in a longitudinal follow-up study conducted over 12 months, which recruited people with IBS who met the Rome III and Rome IV criteria.

METHODS

Participants and Setting

We recruited individuals who self-identified as having IBS registered with three organizations in the UK. 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. We have reported data from this cohort previously. (5, 21) There were no exclusion criteria, other than an inability to understand written English. We contacted all individuals registered with these organizations, via a postal and electronic mailshot, between December 2017 and December 2018. This correspondence directed them to a website, where they were able to access further information about the study. Those who wanted to participate could complete a web-based questionnaire, with their responses stored in an online database. Follow-up questionnaires were sent 12 months later, using the same methods, between December 2018 and December 2019. The University of Leeds research ethics committee approved the study in November 2017.

Data Collection and Synthesis

Demographic Data

We collected demographic data at baseline, and asked respondents to state whether they had seen a primary care physician or gastroenterologist about their symptoms. We asked participants to keep a record of any new treatments (dietary, drugs, and/or psychological) that

they commenced after the baseline questionnaire, using a checklist. The questionnaires were otherwise identical at baseline and 12-month follow-up.

Lower Gastrointestinal Symptom Data

We captured lower gastrointestinal symptom data at baseline and follow-up using both the Rome IV and Rome III questionnaires. (22, 23) 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, 2) We categorized IBS subtype according to criteria recommended in the Rome III and IV questionnaires. We used the proportion of time stools looked abnormal according to the Bristol stool form scale (BSFS) for individuals meeting Rome IV criteria for IBS, (2) and the proportion of time that stools were hard or lumpy, or loose or watery, for Rome III. (1) We examined stability of Rome IV and Rome III IBS, by using 12-month symptom data to classify individuals who no longer met either set of criteria for IBS at 12 months in to one of the other functional bowel disorders, including functional constipation, functional diarrhea, functional abdominal bloating or distension, and unspecified functional bowel disorder. The latter is where lower gastrointestinal symptoms are present, but they do not meet criteria for any of the other four functional bowel disorders.

We assessed IBS symptom severity using the IBS severity scoring system (IBS-SSS), (24) which measures presence, severity, and frequency of abdominal pain, presence and severity of abdominal distension, satisfaction with bowel habit, and degree to which IBS symptoms are affecting, or interfering with, the person's life. The maximum score is 500 points: <75 points indicates remission of symptoms; 75-174 points mild symptoms; 175-299 points moderate symptoms; and 300-500 points severe symptoms.

Psychological Health Data

We collected anxiety and depression data at baseline using the hospital anxiety and depression scale (HADS). (25) The total HADS score ranges from a minimum of 0 to a maximum of 21 for either anxiety or depression. We collected somatization data at baseline using the patient health questionnaire-12 (PHQ-12), (26) which is derived from the validated patient health questionnaire-15. (27) The total PHQ-12 score ranges from a minimum of 0 to a maximum of 24.

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 also compared proportions of patients with Rome IV or III IBS at baseline who fluctuated to another functional bowel disorder at 12 months, and proportions who met Rome IV or III IBS at both baseline and 12-month follow-up who fluctuated to another IBS subtype, according to whether or not a new treatment was commenced for their IBS, using a χ^2 test. Due to multiple comparisons a 2-tailed P value of <0.01 was considered statistically significant for all analyses. We used a logistic regression model, controlling for all baseline data to examine predictors of fluctuation of IBS subtype at 12 months among those meeting Rome IV or III criteria for IBS at both baseline and 12 months, and reported the results with odds ratios (ORs) with 95% confidence intervals (CIs). We also classified appropriateness of new treatments commenced in those individuals with IBS-D or IBS-C at baseline and examined fluctuation to another IBS subtype according to whether this new treatment appeared appropriate or not. We deemed laxatives, suppositories or enemas, secretagogues, prucalopride, or selective serotonin re-uptake inhibitors as appropriate treatments for IBS-C, and antispasmodics, anti-diarrheals, ondansetron, or

tricyclic antidepressants as inappropriate treatments. For IBS-D we assumed the reverse. We performed all analyses using SPSS for Windows (version 26.0 SPSS Inc., Chicago, IL, USA). Given this was a longitudinal follow-up study, we did not perform a power calculation *a priori*; instead our analyses should be viewed as hypothesis generating.

RESULTS

There were 1375 individuals who self-identified as having IBS recruited into the study between December 2017 and December 2018. Mean age of respondents was 49.2 years (range 18 to 86 years), 1157 (84.1%) were female, and 1293 (94.0%) were White Caucasian. In total, 180 (13.1%) individuals stated that their IBS symptoms commenced after an acute enteric infection, 1302 (94.7%) stated that they had previously seen their primary care physician about their IBS, and 789 (57.4%) had seen a gastroenterologist.

Of these, 784 (57.0%) were followed up successfully at 12 months and provided complete data. The majority of differences between responders and non-responders were relatively modest and related to demographic data (Table 1). Those who responded were older (50.7 years versus 47.1 years), 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. There were no differences in the proportion who met either the Rome IV or Rome III criteria at baseline, symptom severity, or psychological comorbidity between those successfully followed up, and those who were not.

Stability of a Diagnosis of IBS in Those with Rome IV versus Rome III IBS

Among 811 participants meeting Rome IV criteria for IBS at baseline, 452 (55.7%) responded to the 12-month questionnaire. Of these individuals, 319 (70.6%) met Rome IV criteria for IBS at both baseline and follow-up. Among the other 133 (29.4%) individuals with Rome IV IBS at baseline, 48 (10.6%) met Rome IV criteria for functional diarrhea at 12 months, 39 (8.6%) functional abdominal bloating or distension, 32 (7.1%) unspecified functional bowel disorder, and 14 (3.1%) functional constipation (Figure 1). A change in Rome IV functional bowel disorder at 12 months occurred in 87 (26.4%) of 330 individuals

with Rome IV IBS at baseline who commenced a new treatment during follow-up, compared with 46 (37.7%) of 122 who did not (Figure 1) (P = 0.03).

There were 631 (58.4%) of 1080 participants meeting Rome III criteria for IBS at baseline who responded to the questionnaire. Of these 631 subjects, 527 (83.5%) still met the Rome III criteria for IBS at 12 months (Figure 2). Among the remaining 104 (16.5%), 34 (5.4%) met criteria for an unspecified functional bowel disorder at 12 months, 31 (4.9%) functional abdominal bloating or distension, 28 (4.4%) functional diarrhea, and 11 (1.7%) functional constipation. There was a change in Rome III functional bowel disorder in 66 (15.1%) of 438 subjects with Rome III IBS at baseline who commenced a new treatment, compared with 38 (19.7%) of the 193 who did not (Figure 2) (P = 0.19).

Findings were similar when only individuals with IBS after acute enteric infection were considered in the analyses (see Supplementary Table 1).

Stability of IBS Subtype in Those with Rome IV versus Rome III IBS

Of the 319 subjects meeting Rome IV criteria for IBS at both baseline and follow-up, 46 (14.4%) had IBS-C, 135 (42.3%) IBS-D, 130 (40.8%) IBS-M, and eight (2.5%) IBS-U at baseline. Overall, 218 (68.3%) individuals remained in the same IBS subtype at 12 months as at baseline. Due to small numbers, those with IBS-U were removed from further analyses. IBS-M was the least stable subtype, with 61.7% of subjects still meeting criteria for IBS-M at 12 months (Figure 3a), compared with 78.3% of those with IBS-C, and 76.7% of those with IBS-D (P<0.001). Subjects with IBS-M fluctuated to both IBS-C and IBS-D, whereas no individuals with IBS-C fluctuated to IBS-D, and only 1.5% of participants with IBS-D fluctuated to IBS-C.

Among these 319 individuals, 243 (76.2%) had commenced at least one new treatment during the 12 months of the study (Table 2). When IBS subtype stability was

examined according to whether a new treatment had been commenced in those with IBS-C, IBS-D, or IBS-M, there was still fluctuation of IBS subtype in similar proportions of participants (Figures 3b and 3c). In total, 166 (68.3%) of 243 individuals who commenced a new treatment remained in the same subtype at 12 months, compared with 52 (68.4%) of 76 who did not (P = 0.99). After logistic regression controlling for all baseline demographic data, symptom severity, mood, and subtype, a stable subtype at 12 months was less likely only in those with IBS-M at baseline (OR 0.41; 95% CI 0.18 to 0.94). Analysis according to appropriateness of therapy for those with IBS-D or IBS-C did not provide any evidence that likelihood of fluctuation was increased by selection of an appropriate therapy (Supplementary Table 2).

Among 527 individuals still meeting the Rome III criteria for IBS at 12 months, 49 (9.3%) had IBS-C, 160 (30.4%) IBS-D, 315 (59.8%) IBS-M, and three (0.6%) IBS-U at baseline. In total, 398 (75.5%) individuals' stool subtype remained stable during follow-up. When those with IBS-U were removed from the analysis, 81.9% of subjects still met criteria for IBS-M at 12 months (Figure 4a), compared with 68.8% of those with IBS-C, and 66.9% of those with IBS-D (P<0.001). Fluctuation between all three subtypes occurred, although only 3.2% of those with IBS-D fluctuated to IBS-C.

Among these 527 individuals, 372 (70.6%) commenced at least one new treatment during the 12 months of the study (Table 2). When stool subtype stability was examined according to whether a new treatment had been commenced in those with IBS-C, IBS-D, or IBS-M, degree of fluctuation in IBS subtypes remained similar (Figures 4b and 4c). In total, 285 (76.6%) of 372 individuals who commenced a new treatment remained in the same subtype at 12 months, compared with 113 (72.9%) of 155 who did not (P = 0.37). Logistic regression controlling for all baseline demographic data, symptom severity, mood, and subtype, did not reveal any predictors of stable subtype at 12 months. Again, analysis

according to appropriateness of therapy for those with IBS-D or IBS-C did not suggest that fluctuation was more likely if an appropriate therapy was selected (Supplementary Table 2).

Stability of IBS subtype, overall, was similar when only individuals with IBS after acute enteric infection were considered in the analyses (see Supplementary Table 3).

Stability of IBS Symptom Severity in Those with Rome IV versus Rome III IBS

Of the 319 subjects meeting Rome IV criteria for IBS at both baseline and follow-up, 33 (10.3%) had symptoms considered to be in remission or mild at baseline according to the IBS-SSS, 120 (37.6%) had moderate symptoms, and 166 (52.0%) severe symptoms. In total, 197 (61.8%) individuals' symptom severity category remained stable during follow-up. Among the 527 individuals still meeting the Rome III criteria for IBS at 12 months, 120 (22.8%) had symptoms considered to be in remission or mild at baseline, 217 (41.2%) had moderate symptoms, and 190 (36.1%) severe symptoms. In total, 312 (59.2%) individuals' symptom severity category remained stable during follow-up. Fluctuation was greatest amongst those with moderate symptoms for both Rome IV and Rome III IBS (Table 3).

DISCUSSION

This longitudinal follow-up study demonstrates that IBS fluctuates over time, both in terms of overall symptoms, and also stool form or frequency, and that this does not appear to relate solely to treatment, whether this is deemed as appropriate based on subtype, or not. Among individuals meeting the Rome IV criteria at baseline, almost 30% fluctuated to another functional bowel disorder at 12 months, the majority of whom met criteria for functional diarrhea. Fluctuation was slightly more likely in those who did not commence a new treatment for their IBS. This compares with less than 20% fluctuation at 12 months according to Rome III, most of whom instead met criteria for functional abdominal bloating or distension, or functional diarrhea. In terms of IBS subtype, among those meeting the Rome IV criteria at both baseline and follow-up, more than 30% fluctuated to another subtype; IBS-M was significantly less stable than IBS-C or IBS-D. Among participants meeting the Rome III criteria at baseline and follow-up, one-in-four fluctuated to another IBS subtype, with IBS-M being significantly more stable than IBS-D or IBS-C. Results were broadly similar when only those with IBS after acute enteric infection were considered in the analysis. Fluctuation among IBS subtypes did not appear to occur only as a consequence of treatment and, following logistic regression controlling for all baseline data, no predictors of stability of IBS subtype were identified other than having Rome IV IBS-M. Severity of symptoms also varied from baseline to 12-month follow-up, and the degree of fluctuation was similar with Rome IV and III criteria.

We recruited a large number of individuals into this study, all of whom were in the community and self-identified as having IBS. Some had consulted a primary care physician, some a gastroenterologist, and some had never consulted a physician. This implies the participants will be generalizable to many individuals living with IBS. Our use of a web-based questionnaire, meant that data collection at baseline and 12-months was near complete

for many of the variables of interest. In addition, we used the Rome III and Rome IV questionnaires side-by-side in the same study, (5) rather than trying to approximate a definition of Rome III or Rome IV IBS from a single questionnaire, as previous investigators have done. (6, 7)

Weaknesses include the fact that we did not confirm the diagnosis of IBS in all individuals in this study using medical records. As the people who took part believed that they had IBS, and met diagnostic criteria, we assumed they had the condition, but there is overlap between symptoms of IBS and some organic gastrointestinal disorders. (28-31) However, the prevalence of these in the community is much lower than IBS. In addition, given that over 95% of study subjects had seen a primary care physician with IBS, and almost 60% had consulted a gastroenterologist in secondary care, they are likely to have had at least some investigations to excluded coeliac disease or inflammatory bowel disease, such as coeliac serology or fecal calprotectin. We therefore believe the majority of participants truly had IBS. The response rate to the 12-month questionnaire was 57%. 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, suggesting that the population we studied may not be representative of the original cohort of people we recruited. This response rate is similar to other longitudinal follow-up studies of gastrointestinal disorders conducted over a similar time frame. (16, 32-35) There were no differences between responders and the original study participants in terms of symptoms, symptom severity, or psychological comorbidity, and absolute differences in demographic data were relatively modest. As the majority of participants were White Caucasian, we cannot extrapolate our results to individuals of other ethnicities with IBS. Finally, we did not collect information on complementary or alternative medicines use by participants, which may also have influenced the stability of symptoms.

Previous studies have explored the stability of a diagnosis of IBS, and IBS subtype, (14, 17, 19, 20, 36-39) but many were population-based cross-sectional surveys, or were conducted in referral populations. Therefore, few have examined this issue in such a large number of subjects with IBS. Although other studies have compared stability of IBS subtypes according to different diagnostic criteria, (40, 41) we are not aware of any, to date, that have compared the Rome IV and III criteria simultaneously. One Icelandic study, with 10 years of follow-up demonstrated 39% of people meeting the Rome III criteria for IBS still met criteria 10 years later, and this was higher than for IBS defined either according to the Manning criteria or via self-report. (41) Another study, conducted in the US, demonstrated that the behavior of Rome II and Rome III IBS subtypes was similar during 15 months of follow-up. (40) However, neither of these studies collected information about new treatments commenced during follow-up.

Our study suggests that IBS is unstable, irrespective of the definition used, and that this instability is not explained entirely by treatment of the disorder, or whether it is viewed as appropriate based on initial subtype. Individuals commencing a new treatment for their IBS were no more likely to fluctuate to another functional bowel disorder, or another IBS subtype, than those who did not. Overall, the Rome IV criteria IBS appeared less stable than Rome III, both in terms of likelihood of fluctuating to another functional bowel disorder, and in terms of fluctuation of IBS subtype. The former may be due to the more restrictive definition, meaning that it is more difficult to meet criteria for IBS at two consecutive points of follow-up. The latter may be due to the use of the BSFS to define IBS subtype for Rome IV, (2) rather than the proportion of time that stools are hard or lumpy, or loose or watery, as is used in Rome III. (1) These areas require further study, but our results suggest that the Rome IV criteria may be less suitable for use in population-based epidemiological surveys examining the natural history of the disorder.

In summary, this 12-month longitudinal follow-up has made three key observations that have implications for future research and clinical practice, as definitions of IBS continue to evolve. Firstly, between one-in-three and one-in-six people with IBS fluctuate between this diagnosis and another functional bowel disorder, and the degree of fluctuation appears higher with Rome IV. This should, therefore, be expected in routine care, and is not an indication for a review of the diagnosis with requests for further diagnostic work-up, unless alarm symptoms develop. Secondly, IBS subtype instability occurred in one-in-three to one-in-four people, and again this was higher when the Rome IV criteria were used to define IBS. Finally, movement between IBS and another functional bowel disorder, or between IBS subtypes, did not relate solely to the commencement of a new treatment, or whether this appeared appropriate based on IBS subtype at baseline. Studies that use the Rome IV criteria, which are more restrictive, may observe less stability among both functional bowel disorder groups, and IBS subtypes. Using stool type to subgroup patients, in order to direct therapy is therefore problematic. Other approaches to subgrouping people with IBS, which take account of the complex and multi-faceted nature of the disorder may be preferable. We believe that criteria that incorporate measures of the psychological impact of IBS, as well as associated features, such as extra-intestinal symptom reporting, are more intuitive, and better reflect the fact that IBS is now considered to be a disorder of gut-brain interaction.

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FIGURE LEGENDS

Figure 1. Stability of a Diagnosis of IBS in Those with Rome IV IBS at Baseline.

Figure 2. Stability of a Diagnosis of IBS in Those with Rome III IBS at Baseline.

Figure 3a. Stability of IBS Subtype in Those with Rome IV IBS at Baseline.

Figure 3b. Stability of IBS Subtype in Those with Rome IV IBS at Baseline: New Treatment Commenced.

Figure 3c. Stability of IBS Subtype in Those with Rome IV IBS at Baseline: No New Treatment Commenced.

Figure 4a. Stability of IBS Subtype in Those with Rome III IBS at Baseline.

Figure 4b. Stability of IBS Subtype in Those with Rome III IBS at Baseline: New Treatment Commenced.

Figure 4c. Stability of IBS Subtype in Those with Rome III IBS at Baseline: No New Treatment Commenced.

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
Tobacco user (%)	49 (6.3)	71 (12.0)	<0.001
Alcohol user (%)	469 (59.8)	335 (56.8)	0.26
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
White Caucasian ethnicity (%)	754 (96.2)	539 (91.7)	<0.001
IBS after acute enteric infection (%)	102 (13.0)	78 (13.2)	0.90
Seen a primary care physician about IBS (%)	754 (96.2)	548 (92.9)	0.007
Seen a gastroenterologist about IBS (%)	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)	
Diarrhea	310 (39.5)	207 (35.1)	
Mixed stool pattern	296 (37.8)	220 (37.3)	
Unclassified	32 (4.1)	35 (5.9)	0.03

IBS-SSS symptom severity (%)			
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

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

Table 2. New Treatments Commenced According to Criteria Used to Define IBS and IBS Subtype.

	Rome IV IBS subtype at baseline (n = 319)				Rome III IBS subtype at baseline (n = 527)			
New treatment commenced (%)*	**IBS-D (n = 135)**	**IBS-C (n = 46)**	**IBS-M (n = 130)**	**IBS-U (n = 8)**	**IBS-D (n = 160)**	**IBS-C (n = 49)**	**IBS-M (n = 315)**	**IBS-U (n = 3)**
Laxative	13 (9.6)	16 (34.8)	29 (22.3)	2 (25.0)	14 (8.8)	15 (30.6)	65 (20.6)	0 (0)
Suppositories or enemas	6 (4.4)	7 (15.2)	10 (7.7)	2 (25.0)	7 (4.4)	5 (10.2)	24 (7.6)	0 (0)
Secretagogue	2 (1.5)	6 (13.0)	4 (3.1)	1 (12.5)	2 (1.3)	4 (8.2)	7 (2.2)	0 (0)
Prucalopride	2 (1.5)	4 (8.7)	8 (6.2)	0 (0)	2 (1.3)	4 (8.2)	11 (3.5)	0 (0)
Antispasmodic	50 (37.0)	22 (47.8)	47 (36.2)	3 (37.5)	51 (31.9)	19 (38.8)	105 (33.3)	0 (0)
Anti-diarrheal	64 (47.4)	1 (2.2)	37 (28.5)	1 (12.5)	70 (43.8)	2 (4.1)	93 (29.5)	0 (0)
Ondansetron	2 (1.5)	1 (2.2)	5 (3.8)	1 (12.5)	2 (1.3)	1 (2.0)	6 (1.9)	0 (0)
TCA	13 (9.6)	7 (15.2)	18 (13.8)	1 (12.5)	12 (7.5)	8 (16.3)	36 (11.4)	0 (0)
SSRI	19 (14.1)	9 (19.6)	25 (19.2)	2 (25.0)	14 (8.8)	5 (10.2)	54 (17.1)	0 (0)
SNRI	5 (3.7)	2 (4.3)	7 (5.4)	0 (0)	3 (1.9)	2 (4.1)	11 (3.5)	0 (0)
CBT	10 (7.4)	2 (4.3)	7 (5.4)	0 (0)	9 (5.6)	2 (4.1)	17 (5.4)	0 (0)
Hypnotherapy	1 (0.7)	0 (0)	5 (3.8)	1 (12.5)	3 (1.9)	0 (0)	5 (1.6)	0 (0)

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

CBT; cognitive behavioral therapy; SNRI; serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Table 3. Stability of Symptom Severity According to Criteria Used to Define IBS.

	Rome IV IBS at baseline (n = 319)			**Rome III IBS at baseline (n = 527)**		
	Remission or mild symptoms at baseline (n = 33)	**Moderate symptoms at baseline (n = 120)**	**Severe symptoms at baseline (n = 166)**	**Remission or mild symptoms at baseline (n = 120)**	**Moderate symptoms at baseline (n = 217)**	**Severe symptoms at baseline (n = 190)**
Remission or mild symptoms at follow-up (%)	19 (57.6)	23 (19.2)	8 (4.8)	77 (64.2)	61 (28.1)	16 (8.4)
Moderate symptoms at follow-up (%)	9 (27.3)	63 (52.5)	43 (25. 9)	36 (30.0)	119 (54.8)	58 (30.5)
Severe symptoms at follow-up (%)	5 (15.2)	34 (28.3)	115 (69.3)	7 (5.8)	37 (17.1)	116 (61.1)