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Black, CJ, Yiannakou, Y, Houghton, LA et al. (1 more author) (2020) Epidemiological, Clinical, and Psychological Characteristics of Individuals with Self-reported Irritable Bowel Syndrome Based on the Rome IV vs Rome III Criteria. Clinical Gastroenterology and Hepatology, 18 (2). pp. 392-398. ISSN 1542-3565

https://doi.org/10.1016/j.cgh.2019.05.037

Accepted 21st May 2019

TITLE PAGE

Title: Epidemiological, Clinical, and Psychological Characteristics of Individuals with Self-reported Irritable Bowel Syndrome Based on the Rome IV vs Rome III Criteria.

Short title: Using the Rome IV Criteria to Diagnose IBS.

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Grant support: None

Abbreviations:

BMI	body mass index
CPSS	Cohen perceived stress scale
HADS	hospital anxiety and depression scale
IBS	irritable bowel syndrome
IBS-SSS	irritable bowel syndrome severity scoring system
PHQ-15	patient health questionnaire-15
RCT	randomized controlled trial

VSI visceral sensitivity index

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Disclosures: CJB: none to declare. YY: none to declare. LAH: none to declare. ACF: none to declare.

Writing assistance: None.

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

Guarantor of the article: ACF is guarantor.

Word count: 3,837

ABSTRACT

Objectives: Few studies have examined the effects of applying the Rome IV criteria for irritable bowel syndrome (IBS) vs the previous standard, the Rome III criteria. We conducted a cross-sectional survey of individuals who self-identify as having IBS to examine this issue.

Methods: We collected complete demographic, symptom, mood, and psychological health data from 1375 adults who self-identified as having IBS, but were not recruited from a referral population. We applied the Rome III and the Rome IV criteria simultaneously to examine what proportion met each of these diagnostic criteria for IBS. We measured the level of agreement between the Rome III and Rome IV criteria, and assessed for presence of an alternative functional bowel disorder in individuals who no longer met diagnostic criteria for IBS with the more restrictive Rome IV criteria. Finally, we compared characteristics of individuals who met only Rome III criteria with those who met Rome IV criteria.

Results: In total, 1080 of 1368 individuals (78.9%) with IBS met the Rome III criteria. In contrast, 811 of 1373 individuals (59.1%) with IBS met the Rome IV criteria. Agreement between the criteria was only moderate (Kappa = 0.50). Among those who no longer had IBS according to the Rome IV criteria, 33 (11.5%) met Rome IV criteria for functional constipation, 118 (41.3%) for functional diarrhea, 68 (23.8%) for functional abdominal bloating or distension, and 67 (23.4%) for an unspecified functional bowel disorder. Individuals with Rome IV-defined IBS had more severe symptoms, and a higher proportion had a mood disorder and evidence of poor psychological health, compared with individuals who only met the Rome III criteria for IBS ($P < .001$).

Conclusions: The characteristics of people who believe they have IBS differ between those who meet criteria as defined by Rome IV vs Rome III, including the spectrum of disease severity. Studies are needed to determine how these changes will affect outcomes of clinical trials.

Key words: irritable bowel syndrome; Rome III criteria; Rome IV criteria; incontinence; urgency

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder, characterized by abdominal pain, in association with defecation or a change in bowel habit. [1] The prevalence in the community is around 10%, [2] and the condition is commoner in women and younger individuals. [2, 3] The diagnosis of IBS is made using symptom-based diagnostic criteria, developed by consensus among experts. The aim of these criteria is to reduce unnecessary and exhaustive investigation before a diagnosis of IBS is reached, as well as to facilitate the recruitment of homogenous groups of patients into research studies that examine either underlying pathophysiological mechanisms in IBS, or the efficacy of therapies.

The most recent diagnostic criteria, and the current gold standard for diagnosing IBS, are the Rome IV criteria. These were described in 2016, [1] and were modified from the previous Rome III criteria. [4] There were three main changes made from the Rome III criteria to Rome IV. Firstly, abdominal discomfort was removed from the definition of IBS, as this was felt to be an ambiguous term, with no equivalent in some languages. It was also hypothesized that, regardless of whether the term abdominal pain or abdominal discomfort was used, the same individuals would meet criteria for IBS. [5] Secondly, the threshold for the frequency of abdominal pain required to meet criteria for IBS was increased from 3 days per month, to one day per week, based on a survey of the frequency of the occurrence of abdominal pain in the general population. [5] Finally, there was an appreciation that abdominal pain in IBS is related to, rather than just relieved, by defecation.

The aim of these changes was to increase the specificity of the Rome IV criteria, over prior iterations, which have performed only modestly in diagnosing IBS in previous studies conducted among unselected patients with lower gastrointestinal symptoms. [6, 7] Due to their more restrictive nature, the prevalence of symptoms compatible with IBS among individuals in population-based surveys is likely to fall when using the Rome IV criteria. However, other

investigators have suggested that among patients with IBS in secondary or tertiary care, implementation of these criteria, in preference to Rome III, has few implications, other than an increase in the severity of symptoms among those with Rome IV IBS. Most patients with Rome III-defined IBS still meet the Rome IV criteria for IBS, [8, 9] and there are little in the way of demographic differences between individuals when the different criteria are used. [10]

Unfortunately, most of these studies did not actually apply the Rome III and Rome IV criteria simultaneously in their study design, but rather used a retrospective surrogate set of criteria approximating Rome IV. In addition, as the spectrum of patients in secondary and tertiary care is likely to be relatively narrow, there may be other differences in the characteristics of individuals with IBS in the community when using the Rome IV criteria, instead of Rome III, which were not uncovered by the design of these studies. We have therefore applied the Rome III and Rome IV criteria simultaneously to a large cohort of individuals who self-identify as having IBS, but who were not recruited from a referral population.

We had several hypotheses. First, despite believing they have IBS, many of these individuals would not meet Rome IV criteria for IBS. Second, the degree of agreement between Rome III and Rome IV would be only modest. Third, many of those with Rome III-defined IBS, but who did not meet the Rome IV criteria for IBS, would instead be classified as suffering from one of the other functional bowel disorders, and that this may have implications in terms of available treatment options. Fourth, there may be substantial implications for clinical trials of novel therapies for IBS, in terms of symptom severity, mood, and psychological health among individuals now defined as having IBS according to the Rome IV criteria.

METHODS

Participants and Setting

The study was conducted among individuals who self-identified as having IBS, and who were registered with three organizations in the UK. The first was the IBS network, the registered charity for people living with the condition. The second was TalkHealth, an online social health community providing information about various medical conditions. The third was ContactMe-IBS, a dedicated register allowing individuals with IBS not receiving specialist care currently to participate in research. There were no exclusion criteria, other than an inability to understand written English. We approached all individuals registered with these organizations, contacting them 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 questionnaire online, with their responses stored in an online database. The University of Leeds research ethics committee approved the study in November 2017.

Data Collection and Synthesis

Demographic Data

Basic demographic data included age, gender, ethnicity, marital status, educational level, lifestyle (tobacco and alcohol use), height (in meters), and weight (in kilograms), which were used to calculate body mass index (BMI), were collected using the questionnaire. We also asked respondents to state whether their IBS symptoms commenced after an acute enteric infection, and whether they had seen a primary care physician or a gastroenterologist with their symptoms.

Definitions of Functional Bowel Disorders and Assessment of Symptom Severity and Impact on Activities of Daily Living

Lower gastrointestinal symptom data were captured using the Rome III and Rome IV questionnaires, and severity of IBS symptoms was assessed using the IBS severity scoring system (IBS-SSS). Further details are provided in the Supplementary Methods.

Assessment of Mood and Somatoform-type Behavior, Perceived Stress, and Visceral Sensitivity

We used the hospital anxiety and depression scale (HADS), the patient health questionnaire-15 (PHQ-15), the 10-item version of the Cohen perceived stress scale (CPSS), and the visceral sensitivity index (VSI). Details are provided in the Supplementary Methods.

Statistical Analysis

We calculated the proportions of individuals who self-identified as having IBS who met either the Rome III or Rome IV criteria for IBS. We measured agreement between the Rome III and Rome IV criteria for the presence of IBS using the modified Kappa statistic, where a value <0.2 indicates poor agreement and a value >0.8 indicates excellent agreement beyond chance. We then examined whether individuals with Rome III-defined IBS were classified into another functional bowel disorder, based on the Rome IV criteria. Finally, we compared the characteristics of individuals meeting the Rome III and Rome IV criteria. Categorical variables, such as sex, ethnicity, impact on activities of daily living, presence of other lower gastrointestinal symptoms, and presence or absence of abnormal anxiety scores, abnormal depression scores, high somatization scores, high perceived stress scores, and high levels of visceral sensitivity were compared between individuals with Rome III and Rome IV IBS using a χ^2 test, and continuous data such as age, BMI, and scores for IBS-SSS, HADS,

PHQ-15, CPSS, and VSI were compared using an independent samples t-test. Due to multiple comparisons a 2-tailed P value of <0.01 was considered statistically significant for all analyses. All statistical analyses were performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

There were 1375 individuals who self-identified as having IBS recruited into the study between December 2017 and December 2018. The mean age of recruited subjects was 49.2 years (range 18 to 86 years) 1157 (84.1%) were female, and 1293 (94.0%) of the respondents were White Caucasian. There were 180 (13.1%) individuals who stated that their IBS symptoms commenced after an acute enteric infection. Overall, 1048 (95.5%) of participants stated that they had previously seen their primary care physician with their IBS, and 633 (57.7%) had seen a gastroenterologist.

Proportion of Individuals with IBS Meeting the Rome III and Rome IV Criteria and Level of Agreement

In total, 1368 individuals with IBS provided complete Rome III data, and 1080 (78.9%) of these met the Rome III criteria for IBS. Overall, 1373 individuals provided complete Rome IV data, of whom 811 (59.1%) met the Rome IV criteria for IBS (Supplementary Table 1). Of those 1080 individuals who met Rome III criteria for IBS, 794 (73.5%) also met Rome IV criteria. Among 811 individuals meeting the Rome IV criteria for IBS, only 17 (2.1%) did not also meet the Rome III criteria. The Kappa statistic for the level of agreement between the Rome III and Rome IV was 0.50, indicating only moderate agreement. When the analysis was restricted to only those who had seen a gastroenterologist, the Kappa statistic for agreement between Rome III and Rome IV was very similar at 0.54.

Other Functional Bowel Disorder Diagnoses Among Individuals not Meeting the Rome IV Criteria for IBS

We examined whether the 286 individuals who met the Rome III criteria for IBS, but who did not meet Rome IV, satisfied the Rome IV criteria for another functional bowel disorder. Overall, 33 (11.5%) subjects met the Rome IV criteria for functional constipation, 118 (41.3%) functional diarrhea, 68 (23.8%) functional abdominal bloating or distension, and 67 (23.4%) an unspecified functional bowel disorder. This meant that of those individuals with Rome III IBS who did not meet the Rome IV criteria for IBS, only 11.5% were reclassified into another functional bowel disorder where licensed and evidence-based therapies are available. Reasons for not meeting the Rome IV criteria among those with Rome III IBS overall, and according to other Rome IV-defined functional bowel disorders, are provided in Table 1. The commonest reason was not meeting the required symptom frequency threshold for abdominal pain.

Characteristics of Individuals with Rome III and Rome IV IBS

We examined the characteristics of the 286 individuals who met the Rome III criteria, but not the Rome IV criteria, for IBS and compared them with the 811 who met the Rome IV criteria (Table 2). Individuals with Rome IV IBS were significantly younger ($P < 0.001$) and more likely to use alcohol ($P = 0.005$), but there were no other differences in demographic characteristics. There was no difference in the proportion of people who had seen a primary care physician with their IBS symptoms, but significantly more of those with Rome IV IBS had seen a gastroenterologist ($P = 0.001$). Those with Rome III IBS were more likely to meet criteria for the mixed stool pattern subtype, and those with Rome IV IBS were more likely to have IBS with diarrhea or IBS with constipation ($P < 0.001$). Symptoms were significantly more severe among those with Rome IV IBS, and were more likely to interfere with activities

of daily living ($P < 0.001$). Debilitating urgency occurring on most days and fecal incontinence on at least a weekly basis were significantly more frequent, mood and psychological health were significantly worse, and perceived stress levels and visceral sensitivity were higher among those with Rome IV IBS ($P < 0.001$).

DISCUSSION

This study has examined the characteristics of people who believe they have IBS when using the Rome IV criteria, compared with Rome III, in a cohort of 1300 individuals who self-identify as having the condition in the UK. Almost 80% met the Rome III criteria, compared with 60% using Rome IV. Agreement between Rome III and Rome IV criteria for diagnosing IBS was moderate. Participants with Rome IV IBS were more likely to report either diarrhea or constipation than a mixed stool pattern, likely reflecting the fact that questions regarding stool consistency with Rome IV now only relate to days on which the stools are abnormal. Importantly, the change in terminology from abdominal pain or discomfort in Rome III to abdominal pain only in Rome IV did not appear to have any great impact on the proportion of people meeting criteria for IBS. Finally, when comparing the characteristics of the 811 individuals with Rome IV-defined IBS with the 286 subjects who met Rome III criteria, there were significantly more individuals with severe symptoms, which had a greater impact on activities of daily living, and higher proportions of participants with low mood, poor psychological health, and high levels of stress and visceral sensitivity among those meeting the Rome IV criteria for IBS.

A large number of individuals were recruited into this study, all of whom were in the community and self-identified as having IBS. Some individuals had consulted a primary care physician, some a gastroenterologist, and some had never consulted a physician, meaning the participants are likely to be generalizable to many individuals living with IBS in the UK. This is further supported by the proportion of individuals in our study who stated that their IBS symptoms commenced after an acute enteric infection, which at 13.1% is almost identical to that reported in another recent, large internet survey of subjects with IBS, [11] and the fact that the proportion with each IBS subtype is similar to other community based surveys. [2, 12] Due to our use of an online questionnaire, data collection was near complete for many of the

variables of interest. We believe this is the first study to examine differences in the characteristics of individuals living with IBS in the community when using the Rome IV criteria, instead of Rome III, that has actually used the validated Rome III and Rome IV questionnaires side by side in the same study.

Weaknesses of the study include the fact that we did not confirm the diagnosis of IBS in all individuals in this study by looking at their medical records. This means that we relied on the fact that the people who took part believed that they had IBS as a means of confirming a diagnosis. This may have led to a reduction in performance of both the Rome III and Rome IV criteria. However, given that almost 80% of those who responded did meet the Rome III criteria for IBS, more than 95% had previously seen a primary care physician with their IBS, and almost 60% had seen a gastroenterologist, we do not feel this is likely to have affected our results to any great degree. As the questionnaire was completed online, after visiting a website, we are unable to assess how many individuals chose not to complete the questionnaire, or whether those who responded are broadly representative of all the people with IBS registered with these three organizations. In addition, because of the setting in which this study was conducted, and the fact that participants had to have internet access and be motivated to participate, the individuals taking part may not be generalizable to patients consulting with a gastroenterologist in secondary or tertiary care. However, we feel this is unlikely, as 57.7% had previously consulted in this setting. Finally, there may have be an over representation of White Caucasians in this study, meaning that the results cannot be extrapolated to individuals with IBS of other ethnicities.

Previous studies have suggested there may be few differences in characteristics between people meeting Rome III versus Rome IV criteria for IBS. [8-10] In a study conducted in a tertiary referral population in Sweden, [8] 85% of patients with Rome III-defined IBS met the Rome IV criteria, but quality of life was impaired to a greater degree, and symptoms more

severe among those with Rome IV IBS. Another study, conducted in secondary and tertiary care in the Netherlands demonstrated similar findings. [9] More than 85% of individuals meeting Rome III criteria for IBS still met the Rome IV criteria, although symptoms were more severe, and quality of life worse, in those with Rome IV IBS. However, neither study applied the Rome III and IV criteria for IBS simultaneously, but instead used a surrogate for Rome IV, consisting of reporting abdominal pain on ≥2 days in the last 10 days in one study, [8] or reporting abdominal pain once a week in a diary in the other study. [9] In addition, the consequences, in terms of reclassification to another functional bowel disorder when using Rome IV, compared with Rome III, were only examined in one of these studies, with approximately one-third of patients meeting criteria for each of functional constipation, functional diarrhea, and functional abdominal bloating or distension. [9] A third tertiary care study showed less diagnostic agreement between Rome III and IV criteria, with a Kappa of 0.45, and only 46.5% of those with Rome III-defined IBS meeting the Rome IV criteria. [10] Symptom severity was greater among those with Rome IV IBS, but there were few other differences.

There are likely to be several implications of our study for research and clinical practice. Firstly, when using the Rome IV for IBS, approximately one-in-four individuals who believe that they have IBS will no longer meet strict criteria for the condition. Although all these individuals can be reclassified as suffering from another functional bowel disorder according to Rome IV, functional constipation is the only other condition with evidence-based licensed therapies available to treat it. [13, 14] The others rely on off-label therapies with only anecdotal evidence for their efficacy. Alternatively, these individuals could still be treated as if they have IBS. If use of the Rome IV criteria for IBS makes these conditions more prevalent, this highlights the need for rigorous randomized controlled trials (RCTs) of neuromodulators, probiotics, anti-diarrheals, and other agents in these disorders. Secondly,

the degree of agreement between Rome III and IV criteria for IBS was only modest; a previous study demonstrated Kappa values of between 0.74 to 0.95 for the Rome I, II, and III criteria for diagnosing IBS. [6] The main reason for the lack of agreement between Rome III and Rome IV was an increase in the frequency threshold for abdominal pain required to meet Rome IV criteria. Our study shows that applying this threshold leads to a substantial number of individuals who believe they have IBS no longer meeting diagnostic criteria for the condition. Finally, the increased severity of symptoms, and higher levels of mood disorder, poor psychological health, perceived stress, and visceral sensitivity seen among those with Rome IV IBS demonstrate that this is the more severe end of the disease spectrum.

Often, previous treatment trials using the Rome III criteria utilized a run-in period, where a minimum threshold of symptom severity was required for trial entry, so it is likely that many individuals in these RCTs would have also met the Rome IV criteria for IBS. Nevertheless, our findings may have implications for future trials. Placebo response rates in IBS are high, [15] and most drugs that have been tested in patients with Rome III IBS only have modest efficacy. [16-21] The changes made to the Rome IV criteria appear to lead to a more homogeneous population, who may therefore respond better to novel pharmacological therapies in future RCTs. However, due to the higher prevalence of severe symptoms and psychological co-morbidity seen when using the Rome IV criteria to diagnose IBS the opposite could also occur.

In summary, using the Rome IV criteria for IBS, compared with Rome III, led to a reclassification of one-in-four individuals who believe they have IBS to another functional bowel disorder. Most of this reclassification occurred due to the change in the frequency threshold for abdominal pain required by Rome IV. Agreement between Rome III and Rome IV was modest. Individuals meeting Rome IV criteria for IBS had more severe symptoms, which impacted more on activities of daily living, and had higher prevalence of abnormal

mood, psychological co-morbidity, perceived stress, and visceral sensitivity. Understanding the impact of these changes to the diagnostic classification system for IBS on the efficacy of novel therapies for the disorder in future RCTs will be important.

ACKNOWLEDGEMENTS

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

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Table 1. Reasons for not Meeting the Rome IV Criteria for IBS Among those Meeting the Rome III Criteria.

	Reported abdominal discomfort, rather than abdominal pain (%)	**Reported abdominal pain, but not at the required frequency (%)**	**Other reasons (%)**
Met Rome III criteria, but not Rome IV criteria, for IBS (n = 286)	26 (9.1)	253 (88.5)	7 (2.4)
Rome IV functional constipation (n = 33)	3 (9.1)	29 (87.9)	1 (3.3)
Rome IV functional diarrhea (n = 118)	9 (7.6)	108 (91.5)	1 (0.8)
Rome IV functional abdominal bloating (n = 68)	6 (8.8)	61 (89.7)	1 (1.5)
Rome IV unspecified functional bowel disorder (n = 67)	8 (11.9)	55 (82.1)	4 (6.0)

Table 2. Characteristics of Individuals Meeting Rome III Criteria, but not Rome IV Criteria for IBS, Compared with those Meeting Rome IV criteria for IBS.

	Met Rome III Criteria, but not Rome IV Criteria, for IBS (n = 286)	**Met Rome IV Criteria for IBS (n= 811)**	**P value***
Mean age (SD)	51.5 (15.5)	47.4 (15.2)	<0.001
Mean body mass index (SD)	26.9 (8.5)	28.4 (8.3)	0.03
Female gender (%)	231 (80.8)	697 (85.9)	0.04
Tobacco user (%)	12 (4.2)	79 (9.7)	0.01
Alcohol user (%)	187 (65.4)	442 (54.5)	0.005
Married or co-habiting (%)	186 (65.0)	526 (64.9)	1.00
University or postgraduate level of education (%)	72 (25.2)	164 (20.3)	0.10
White Caucasian ethnicity (%)	273 (95.5)	763 (94.3)	0.47
IBS after acute enteric infection (%)	44 (15.4)	106 (13.1)	0.38
Seen a primary care physician with IBS (%)	270 (94.4)	778 (95.9)	0.24
Seen a gastroenterologist with IBS (%)	141 (49.3)	492 (60.7)	0.001
IBS subtype (%)			
Constipation	33 (11.5)	142 (17.5)	
Diarrhea	89 (31.1)	311 (38.3)	
Mixed stool pattern	159 (55.6)	331 (40.8)	
Unclassified	5 (1.7)	26 (3.2)	<0.001

IBS-SSS symptom severity (%)			
Remission	17 (6.0)	8 (1.0)	
Mild	117 (41.1)	90 (11.1)	
Moderate	126 (44.2)	333 (41.1)	
Severe	25 (8.8)	379 (46.8)	<0.001
Mean IBS-SSS score (SD)	188.2 (79.2)	292.0 (95.8)	<0.001
IBS limits activities ≥50% of the time (%)	136 (47.6)	573 (70.7)	<0.001
Urgency at least most days (%)	44 (15.4)	233 (28.7)	<0.001
Fecal incontinence at least once a week (%)	26 (9.1)	157 (19.4)	<0.001
HADS-A categories (%)			
Normal	121 (42.3)	202 (24.9)	
Borderline	63 (22.0)	167 (20.6)	
Abnormal	102 (35.7)	442 (54.5)	<0.001
Mean HADS-A score (SD)	8.7 (4.4)	11.0 (4.7)	<0.001
HADS-D categories (%)			
Normal	203 (71.0)	434 (53.5)	
Borderline	52 (18.2)	191 (23.6)	
Abnormal	31 (10.8)	186 (22.9)	<0.001
Mean HADS-D score (SD)	5.6 (4.1)	7.7 (4.5)	<0.001
PHQ-15 categories (%)			
Mild somatization	8 (2.8)	6 (0.7)	
Low somatization	71 (24.8)	78 (9.6)	
Medium somatization	128 (44.8)	270 (33.3)	
High somatization	79 (27.6)	457 (56.4)	<0.001
Mean PHQ-15 score (SD)	11.8 (4.0)	15.4 (4.9)	<0.001

CPSS tertiles (%)			
Low	131 (45.8)	226 (27.9)	
Medium	98 (34.3)	294 (36.3)	
High	57 (19.9)	290 (35.8)	<0.001
Mean CPSS score (SD)	17.6 (7.8)	21.6 (8.2)	<0.001
VSI tertiles (%)			
Low	141 (49.3)	196 (24.3)	
Medium	94 (32.9)	281 (34.8)	
High	51 (17.8)	331 (41.0)	<0.001
Mean VSI score (SD)	39.5 (16.9)	50.7 (16.8)	<0.001

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