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TITLE PAGE

Title: Natural History and Disease Impact of Rome IV versus Rome III Irritable Bowel Syndrome: A Longitudinal Follow-up Study.

Short title: Longitudinal Follow-up of Rome IV Versus Rome III IBS.

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Abbreviations:

HADS	hospital anxiety and depression scale
IBS	irritable bowel syndrome
IBS-SSS	IBS severity scoring system
PHQ-12	patient health questionnaire-12
RCT	randomized controlled trial

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ABSTRACT

Objectives: Irritable bowel syndrome (IBS) is a chronic functional bowel disorder diagnosed using the Rome criteria, which have evolved since their original description 30 years ago. Little is known about the effects on the natural history of IBS of moving to the latest iteration, Rome IV, from the previous Rome III criteria. We conducted a 12-month longitudinal follow-up study examining this.

Methods: We collected complete demographic, symptom, mood, and psychological health data at baseline from 1097 adults who self-identified as having IBS and met either Rome IV or III criteria. At 12 months, we collected data regarding IBS symptom severity and impact, consultation behavior, treatments commenced, and psychological health. We examined whether subsequent disease behavior in Rome IV or Rome III-defined IBS differed.

Results: At 12 months, 638 (58.2%) of the 1097 participants were successfully followed up. Of these, 452 met Rome IV criteria and 186 met Rome III criteria at baseline. During the 12-month study period, individuals with Rome IV IBS were significantly more likely to have seen a primary care physician (44.7% vs 28.5%, $p<0.001$) or a gastroenterologist (26.3% vs 12.4%, $p<0.001$) for their IBS symptoms, were significantly more likely to have commenced a new treatment (73.0% vs 60.2%, $p=0.001$), and cycled through significantly more treatments ($p=0.007$), for their IBS compared with those with Rome III IBS. At follow-up, individuals with Rome IV IBS had more severe symptoms, which had a significantly greater impact on activities of daily living, were more likely to report continuous abdominal pain, and a higher proportion demonstrated poor psychological health, compared with those with Rome III IBS ($p<0.001$ for all analyses).

Conclusions: The natural history of IBS defined according to Rome IV criteria is more severe than that of Rome III-defined IBS. This has important implications for future treatment trials in IBS.

Key words: irritable bowel syndrome; diagnostic criteria; prognosis; natural history

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common functional bowel disorders, affecting between 5% and 10% of the population.[1-3] It is diagnosed using symptom-based criteria, proposed by the Rome Foundation in 1990,[4] consisting of abdominal pain associated with a change in stool form or frequency. The pathophysiology remains incompletely understood, although several mechanisms, including motility disturbances, visceral hypersensitivity, altered mucosal barrier and immune function, gut microbiota, and central nervous system processing, have been proposed.[5] However, it is well recognized that mood and psychological health play an important role in the development and persistence of IBS symptoms.[6-9] In recognition of this complex multifactorial interplay, the Rome Foundation redefined IBS as a disorder of gut-brain interaction.[10, 11]

The Rome criteria for IBS have changed over the last 30 years. The latest iteration, Rome IV,[12] published in 2016, were a modification of the previous Rome III criteria.[13] The three main changes were the removal of abdominal discomfort from the definition, an increase in the threshold for frequency of abdominal pain required to meet criteria for IBS from 3 days per month to 1 day per week, and the recognition that abdominal pain was related to, rather than just relieved by, defecation.[10] The aim of these changes was to increase specificity of the Rome IV criteria over prior iterations.[14]

As a result of these changes, the characteristics of individuals who meet Rome IV criteria for IBS differ from those meeting Rome III, and these differences appear consistent between studies.[15-18] Those with Rome IV IBS have more severe symptoms and higher levels of psychological co-morbidity. These differences may have a deleterious impact on the natural history of IBS but, to our knowledge, there have been no studies conducting longitudinal follow-up to examine whether this is the case.

Due to previous observations, from our own group and others,[15-18] that individuals with Rome IV IBS had more severe symptoms at baseline, and had higher levels of psychological co-morbidity,[18] we hypothesized that, due to their more restrictive nature, those with Rome IV IBS at baseline would have a worse disease prognosis than those with Rome III IBS. We examined these issues in a longitudinal follow-up study, which recruited individuals with IBS who met either the Rome IV or Rome III criteria. If the Rome IV criteria select a group of people with IBS with more refractory disease and a higher psychological burden, this will have implications for future randomized controlled trials (RCTs) testing both novel and existing therapies. We assessed consultation rates, commencement of new IBS-related medications, and disease severity and impact during 12 months of follow-up. We also assessed transition between Rome IV and Rome III IBS, and subsequent psychological health according to presence of Rome IV or Rome III IBS at baseline.

METHODS

We recruited individuals self-identifying 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 research register allowing individuals with IBS to participate in research. This cohort has been described elsewhere.[18-21] We invited individuals, via email and post, between December 2017 and December 2018, informing them we would re-contact them 12 months later. Individuals aged ≥18 years were eligible. There were no exclusions, other than an inability to understand written English. Potential participants were directed to a study information leaflet and those interested completed an online questionnaire. Responses were stored in a secure online database. There was no financial incentive. All participants gave their time freely to answer the questionnaires. We sent follow-up questionnaire to all participants 12 months later, using the same methods. The University of Leeds research ethics committee approved the baseline and follow-up study in November 2017. Data collected at baseline and 12 months and questionnaires used are provided in the Supplementary Methods.

Statistical Analysis

We compared baseline characteristics between individuals responding to the 12-month questionnaire, and those who did not, and responders according to whether they met Rome IV or Rome III criteria. We examined whether baseline Rome IV or Rome III-defined IBS influenced subsequent disease behavior by comparing proportions of people with either Rome IV or Rome III IBS who had seen a primary care physician, consulted a gastroenterologist, or commenced a new treatment, as well as the number of new treatments commenced, during the 12-month follow-up period. We compared the proportion of

individuals with either Rome IV or Rome III IBS who reported abnormal anxiety or depression scores, or high levels of somatization, at 12-month follow-up. Finally, we compared anxiety and depression scores, and somatization levels, at 12-month follow-up according to anxiety and depression scores, and somatization levels, at baseline. We used a χ^2 test for categorical data and an independent samples *t*-test for continuous data. We conducted logistic regression analysis to assess predictors of transition from Rome IV IBS to Rome III, and vice versa, controlling for all baseline data. Due to multiple comparisons, a 2-tailed *p* value of <0.01 was considered statistically significant for all analyses. We performed all analyses using SPSS for Windows (version 26.0 SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 1375 individuals (mean age 49.2 years (range 18-86 years), 1157 (84.1%) female) self-identifying as having IBS responded and completed the baseline questionnaire. Of these, 1097 (79.8%) met either the Rome IV or Rome III criteria for IBS. There were 811 participants meeting Rome IV criteria for IBS at baseline, 794 of whom also met the Rome III criteria due to the similarity between symptom items used in both sets of criteria (the Rome IV cohort), and 286 who met Rome III criteria, but who did not meet Rome IV criteria (the Rome III cohort). At 12 months, 638 (58.2%) of 1097 participants who met either Rome IV or Rome III criteria for IBS at baseline were successfully followed up and provided complete data. Most differences between responders and non-responders related to demographic characteristics (Table 1), although a higher proportion who were followed up had previously seen a gastroenterologist (P=0.005) and a higher proportion of the Rome III cohort responded at 12 months. Of the 811 in the Rome IV cohort at baseline, 452 (55.7%) were followed up, compared with 186 (65.0%) of 286 participants in the Rome III cohort (p=0.006). There were no differences between responders and non-responders in terms of IBS subtype, symptom severity, or psychological co-morbidity at baseline. Differences in baseline data among those with Rome IV versus Rome III IBS at baseline successfully followed up are provided in Table 2. Those with Rome IV IBS were younger (p=0.006), less likely to have attained university or postgraduate level of education (p=0.005), more likely to have seen a gastroenterologist at baseline (p=0.002), more likely to report continuous pain, had more severe symptoms, and exhibited higher levels of psychological co-morbidity, (p<0.001 for all analyses).

Consultation Behavior, Commencement of New Treatment, Disease Severity and Impact During Follow-up, and Transition Among those with Rome IV versus Rome III IBS at Baseline

Overall, 202 (44.7%) of the 452 individuals who met Rome IV criteria at baseline consulted their primary care physician during 12-month follow-up compared with 53 (28.5%) of 186 with Rome III IBS ($p<0.001$) (Table 3). Similarly, 119 (26.3%) with Rome IV IBS had seen a gastroenterologist, compared with 23 (12.4%) of those with Rome III IBS ($p<0.001$). In total, 330 (73.0%) of those with Rome IV IBS commenced at least one new treatment during the 12 months, compared with 112 (60.2%) of the Rome III cohort ($p=0.001$). The number of new treatments commenced was significantly higher in the Rome IV cohort ($p=0.007$). A greater number of individuals with Rome IV IBS had severe symptoms at follow-up according to the IBS-SSS (177 (39.2%) versus 11 (5.9%), $p<0.001$), and a greater proportion reported continuous abdominal pain at 12 months (209 (46.2%) versus 51 (27.4%), $p<0.001$). Those with Rome IV IBS were more likely to report that their symptoms impacted on normal daily activities ≥50% of the time (280 (61.9%) versus 76 (40.9%), $p<0.001$).

319 (70.6%) of those with Rome IV IBS at baseline still met Rome IV criteria at 12-month follow-up, and 88 (47.3%) of those with Rome III IBS at baseline still met Rome III criteria at 12 months ($p<0.001$). Among those with Rome IV IBS there was a trend towards those with abnormal depression scores continuing to meet Rome IV criteria at 12 months (odds ratio 3.62; 95% CI 1.24-10.6, $p=0.019$) after logistic regression, but no statistically significant predictors (see Supplementary Table 1). There were no significant predictors of transitioning from Rome III IBS to Rome IV (see Supplementary Table 2).

Psychological Health at Follow-up Among those with Rome IV versus Rome III IBS at Baseline

At 12-month follow-up those with Rome IV IBS at baseline were more likely to report abnormal anxiety scores at 12 months (230 (50.9%) of 452) compared with those with Rome III IBS (58 (31.2%) of 186) (p<0.001) (Table 4). Similarly, participants with Rome IV IBS were more likely to report abnormal depression scores at 12 months (112 (24.8%) of 452) than those with Rome III (19 (10.2%) of 186) (p<0.001). When we restricted the analysis to only the 199 individuals with normal anxiety scores at baseline, there was no difference between the proportion developing borderline abnormal or abnormal anxiety scores at 12 months between those with Rome IV and Rome-III defined IBS (30 (26.1%) of 115 versus 16 (19.1%) of 84, respectively, p=0.50). However, restricting the analysis to the 385 participants with normal depression scores at 12 months, those with Rome IV IBS were more likely to develop borderline abnormal or abnormal depression scores (54 (21.7%) of 248, versus 12 (8.8%) of 137, respectively, p=0.005). Although individuals with Rome IV IBS at baseline were more likely to exhibit high levels of somatoform symptom-reporting at 12 months (119 (26.3%) of 452 with Rome IV IBS versus 17 (9.1%) of 186 with Rome III, p<0.001), among those with low or mild levels of somatoform symptom-reporting at baseline there was no difference in the proportion of individuals developing moderate or high levels at follow-up (p=0.30).

DISCUSSION

This longitudinal 12-month follow-up study has examined the natural history of Rome IV, versus Rome III, IBS in more than 600 individuals. During follow-up, those with Rome IV IBS were significantly more likely to have seen a primary care physician or a gastroenterologist regarding their symptoms, were significantly more likely to have commenced a new treatment, and cycled through significantly more IBS treatments than those with Rome III-defined IBS. At 12-month follow-up, individuals with Rome IV IBS reported significantly more severe symptoms, which had a significantly greater impact on activities of daily living and were more likely to report continuous abdominal pain. In addition, there was a significantly greater proportion of individuals with Rome IV IBS exhibiting psychological co-morbidity, including abnormal anxiety or depression scores, and high levels of somatoform symptom-reporting, at 12 months. When we restricted the analysis to only individuals with normal depression scores at baseline, individuals with Rome IV IBS were significantly more likely to develop borderline abnormal or abnormal depression scores at 12 months.

We recruited individuals from the community who self-identified as having IBS meeting Rome IV or Rome III criteria. At the point of recruitment, some had consulted a primary care physician, some a gastroenterologist, and some had never seen a clinician for their symptoms; the results are likely to be generalizable to individuals with IBS in the UK. Because we used an online questionnaire with mandatory fields, we obtained near complete data for all variables of interest at baseline and 12-month follow-up. We also used the validated Rome IV and III questionnaires side-by-side, rather than approximating one or other definition of IBS.

Weaknesses of this study include the fact that we did not check medical records to rule out organic gastrointestinal conditions that mimic IBS, such as coeliac disease or

inflammatory bowel disease.[22, 23] However, given that IBS is more prevalent than these disorders in the community and the fact that, at baseline, 95% of participants reported having seen a primary care physician for their IBS symptoms, and almost 60% a gastroenterologist, we believe it is likely that these individuals had IBS. As the questionnaire was completed online, we cannot assess how many individuals chose not to complete it, or whether those who responded were representative of all the people with IBS registered with these three organizations. All participants had to be motivated to complete two questionnaires 12 months apart. Our response rate of 58% is similar to other longitudinal follow-up studies of gastrointestinal disorders conducted over a similar time frame.[24-27] Responders at 12 months were older, more likely to have attained a university or postgraduate level of education, and more likely to have seen a gastroenterologist for their IBS prior to study entry. Moreover, a higher proportion of the Rome III cohort responded at 12 months compared with Rome IV. However, there were no other significant differences, including according to IBS subtype, IBS symptom severity, or psychological co-morbidity at baseline. Because we did not check medical records of participants, we relied on their recall as to whether they had seen a primary care physician or a gastroenterologist, as well as whether new treatments were commenced, during the 12-month study period. Finally, given that IBS is a chronic illness, the 12-month follow-up period is relatively short. Further studies with longer follow-up would be valuable in confirming our findings.

Previous studies have explored the differences between individuals who meet Rome IV and III criteria for IBS.[15-18] However, these are all cross-sectional and restricted analysis to characteristics of individuals with Rome IV versus Rome III IBS, rather than prognosis of IBS according to one definition versus another. This design limitation means that, unlike the present longitudinal follow-up study, they can only report associations, rather than examine the influence of the changes made in moving from the Rome III to the Rome IV criteria on

the natural history of IBS, including healthcare-seeking behavior, prognosis, and disease impact. Other weaknesses of these studies include the fact that most recruited participants from referral populations, limiting generalizability, and did not apply the Rome IV and Rome III questionnaires simultaneously, but instead approximated one or other of the definitions.

Our study suggests that the Rome IV criteria select a population with IBS more likely to seek healthcare and with a worse disease prognosis, both in terms of future gastrointestinal symptoms and new onset of psychological co-morbidity, than Rome III. Although some of this probably relates to the fact that individuals with Rome IV IBS had more severe symptoms at baseline, higher levels of psychological co-morbidity, and were more likely to have consulted a doctor about their IBS,[18] it may also be explained by the more restrictive nature of these criteria. The Rome IV definition of IBS includes only individuals with abdominal pain, rather than just abdominal discomfort, and requires a higher pain frequency. Previous cross-sectional studies have shown that pain severity and duration are associated with healthcare seeking behavior.[28-30] Our observation that among individuals with normal depression scores at baseline those with Rome IV IBS were significantly more likely to develop borderline abnormal or abnormal depression scores at follow-up, although novel, is in keeping with population-based longitudinal follow-up studies demonstrating that those with gastrointestinal symptoms and normal mood have a higher likelihood of developing abnormal mood in the future.[7, 9] Finally, 70% of those with Rome IV IBS still met Rome IV criteria at 12 months, whereas Rome III IBS was less stable. No significant predictors of transition between the two were identified, although this may relate to the relatively small number of individuals included in these analyses, and there may be other factors not captured by our questionnaire that influence this.

These findings have implications for future research. Although the Rome IV criteria appear more specific than their predecessor,[14] and are likely to select a more homogenous

population of patients, most treatment trials to date have been conducted using Rome III.[31-34] Pivotal treatment trials in IBS, other than those run by the pharmaceutical industry, are scarce. Future RCTs that recruit participants with Rome IV IBS may find that many people who believe they have IBS are ineligible, based on these more restrictive criteria. In addition, because the Rome IV criteria identify a subgroup of patients who are more likely to seek healthcare, and who have more refractory disease, the therapeutic gain of active therapies over a placebo may be smaller, particularly as endpoints used to judge treatment response become more stringent. Such trials may need larger numbers of patients, requiring a greater number of sites, and therefore have higher running costs. This would put them beyond the financial scope of many grant-giving bodies. Thus, for RCTs seeking to confirm efficacy of more "traditional" or over-the-counter therapies with a well-established safety profile, particularly those in primary care, a more pragmatic real-world approach may be necessary, to limit running costs and make them feasible and deliverable. This could include using either a primary care physician's diagnosis of IBS or patient self-report, with limited confirmatory testing to exclude organic disease,[35, 36] as other investigators have utilized.[37]

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Table 1. Characteristics of Individuals Meeting Rome IV or Rome III IBS Responding to the 12-month Questionnaire Compared with Non-responders.

	Responded to Questionnaire at 12 Months (n=638)	**Did not Respond to Questionnaire at 12 Months (n=459)**	***p* value***
Mean age (SD)	50.1 (14.5)	46.1 (16.2)	<0.001
Female gender (%)	539 (84.5)	389 (84.7)	0.90
Married or co-habiting (%)	434 (68.0)	278 (60.6)	0.011
University or postgraduate level of education (%)	305 (47.8)	165 (36.2)	<0.001
White Caucasian ethnicity (%)	611 (95.8)	425 (93.0)	0.045
IBS after acute enteric infection (%)	88 (13.8)	62 (13.6)	0.91
Previously seen a primary care physician regarding IBS at study entry (%)	615 (96.4)	433 (94.5)	0.14
Previously seen a gastroenterologist regarding IBS at study entry (%)	391 (61.3)	242 (52.8)	0.005
IBS cohort at baseline (%)			
Rome IV	452 (70.8)	359 (78.2)	
Rome III	186 (29.2)	100 (21.8)	0.006
IBS subtype at baseline (%)			
Constipation	114 (17.9)	85 (18.6)	
Diarrhea	257 (40.3)	167 (36.5)	
Mixed stool pattern	248 (38.9)	184 (40.2)	
Unclassified	19 (3.0)	22 (4.8)	0.31

Severity on IBS-SSS at baseline (%)			
Remission	12 (1.9)	13 (2.8)	
Mild	139 (21.8)	68 (14.9)	
Moderate	263 (41.2)	196 (42.9)	
Severe	224 (35.1)	180 (39.4)	0.03
Continuous abdominal pain at baseline (%)	260 (40.8)	206 (45.0)	0.20
HADS anxiety categories at baseline (%)			
Normal	199 (31.2)	124 (27.0)	
Borderline abnormal	132 (20.7)	98 (21.4)	
Abnormal	307 (48.1)	237 (51.6)	0.32
HADS depression categories at baseline (%)			
Normal	385 (60.3)	252 (54.9)	
Borderline abnormal	138 (21.6)	105 (22.9)	
Abnormal	115 (18.0)	102 (22.2)	0.14
PHQ-12 severity at baseline (%)			
Minimal	39 (6.1)	33 (7.2)	
Low	178 (27.9)	115 (25.1)	
Medium	278 (43.6)	194 (42.3)	
High	143 (22.4)	117 (25.5)	0.48

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

Table 2. Characteristics of Individuals Meeting Rome IV IBS Compared with Rome III IBS Responding to the 12-month Questionnaire.

	Rome IV Cohort (n=452)	**Rome III Cohort (n=186)**	***p* value***
Mean age (SD)	49.1 (14.3)	52.6 (14.5)	0.006
Female gender (%)	386 (85.4)	153 (82.3)	0.32
Married or co-habiting (%)	308 (68.1)	126 (67.7)	0.92
University or postgraduate level of education (%)	200 (44.2)	105 (56.5)	0.005
White Caucasian ethnicity (%)	431 (95.4)	180 (96.8)	0.42
IBS after acute enteric infection (%)	62 (13.7)	26 (14.0)	0.93
Previously seen a primary care physician regarding IBS at study entry (%)	437 (96.7)	178 (95.7)	0.55
Previously seen a gastroenterologist regarding IBS at study entry (%)	294 (65.0)	97 (52.2)	0.002
IBS subtype at baseline (%)			
Constipation	75 (16.6)	39 (21.0)	
Diarrhea	181 (40.0)	76 (40.9)	
Mixed stool pattern	185 (40.9)	63 (33.9)	
Unclassified	11 (2.4)	8 (4.3)	0.20
Severity on IBS-SSS at baseline (%)			
Remission	3 (0.7)	9 (4.8)	
Mild	58 (12.8)	81 (43.5)	
Moderate	181 (40.0)	82 (44.1)	
Severe	210 (46.5)	14 (7.5)	<0.001
Continuous abdominal pain at baseline (%)	209 (46.2)	51 (27.4)	<0.001

HADS anxiety categories at baseline (%)			
Normal	115 (25.4)	84 (45.2)	
Borderline abnormal	91 (20.1)	41 (22.0)	
Abnormal	246 (54.4)	61 (32.8)	<0.001
HADS depression categories at baseline (%)			
Normal	248 (54.9)	137 (73.7)	
Borderline abnormal	107 (23.7)	31 (16.7)	
Abnormal	97 (21.5)	18 (9.7)	<0.001
PHQ-12 severity at baseline (%)			
Minimal	22 (4.9)	17 (9.1)	
Low	102 (22.6)	76 (40.9)	
Medium	199 (44.0)	79 (42.5)	
High	129 (28.5)	14 (7.5)	<0.001

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

Table 3. Consultation Behavior, Commencement of New Treatment, Disease Severity and Impact, and Transition During Follow-up Among those with Rome IV versus Rome III IBS at Baseline.

	Rome IV Cohort (n=452)	**Rome III Cohort (n=186)**	***p* value***
Saw a primary care physician regarding IBS during 12-month follow-up (%)	202 (44.7)	53 (28.5)	<0.001
Saw a gastroenterologist regarding IBS during 12-month follow-up (%)	119 (26.3)	23 (12.4)	<0.001
Commenced new treatment for IBS during 12-month follow-up (%)	330 (73.0)	112 (60.2)	0.001
Number of new treatments commenced for IBS during 12-month follow-up (%)			
0	122 (27.0)	74 (39.8)	
1	113 (25.0)	52 (28.0)	
2	110 (24.3)	35 (18.8)	
3	67 (14.8)	16 (8.6)	
4	28 (6.2)	8 (4.3)	
5	3 (0.7)	1 (0.5)	
6	9 (2.0)	0 (0)	0.007
Severity on IBS-SSS at 12-month follow-up (%)			
Remission	14 (3.1)	18 (9.7)	
Mild	97 (21.5)	76 (40.9)	
Moderate	164 (36.3)	81 (43.5)	
Severe	177 (39.2)	11 (5.9)	<0.001
Continuous abdominal pain at 12-month follow-up (%)	209 (46.2)	51 (27.4)	<0.001
Symptoms limited normal daily activities ≥50% of the time at 12-month follow-up (%)	280 (61.9)	76 (40.9)	<0.001

IBS subtype at 12-month follow-up (%)			
Constipation	88 (19.5)	43 (23.1)	
Diarrhea	173 (38.3)	73 (39.2)	
Mixed stool pattern	180 (39.8)	63 (33.9)	
Unclassified	11 (2.4)	7 (3.8)	0.40
Rome IV or Rome III IBS at 12-month follow-up (%)			
Rome IV	319 (70.6)	61 (32.8)	
Rome III	69 (15.3)	88 (47.3)	
Neither Rome IV or Rome III	64 (14.1)	37 (19.9)	<0.001

*p value for Pearson χ^2 for comparison of categorical data.

Table 4. Psychological Health at Follow-up Among those with Rome IV versus Rome III IBS at Baseline.

	Rome IV Cohort (n=452)	**Rome III Cohort (n=186)**	***p* value***
HADS anxiety categories at 12-month follow-up (%)			
Normal	136 (30.1)	85 (45.7)	
Borderline abnormal	86 (19.0)	43 (23.1)	
Abnormal	230 (50.9)	58 (31.2)	<0.001
HADS depression categories at 12-month follow-up (%)			
Normal	232 (51.3)	143 (76.9)	
Borderline abnormal	108 (23.9)	24 (12.9)	
Abnormal	112 (24.8)	19 (10.2)	<0.001
PHQ-12 severity at 12-month follow-up (%)			
Low	22 (4.9)	22 (11.8)	
Mild	129 (28.5)	71 (38.2)	
Moderate	182 (40.3)	76 (40.9)	
High	119 (26.3)	17 (9.1)	<0.001
HADS anxiety categories at 12-month follow-up among 199 individuals with normal anxiety scores at baseline (%)			
Normal	85 (73.9)	68 (81.0)	
Borderline abnormal	20 (17.4)	11 (13.1)	
Abnormal	10 (8.7)	5 (6.0)	0.50
HADS anxiety categories at 12-month follow-up among 307 individuals with abnormal anxiety scores at baseline (%)			
Normal	19 (7.7)	4 (6.6)	
Borderline abnormal	39 (15.9)	16 (26.2)	
Abnormal	188 (76.4)	41 (67.2)	0.17

HADS depression categories at 12-month follow-up among 385 individuals with normal depression scores at baseline (%)			
Normal	194 (78.2)	125 (91.2)	
Borderline abnormal	42 (16.9)	10 (7.3)	
Abnormal	12 (4.8)	2 (1.5)	0.005
HADS depression categories at 12-month follow-up among 115 individuals with abnormal depression scores at baseline (%)			
Normal	7 (7.2)	4 (22.2)	
Borderline abnormal	18 (18.6)	4 (22.2)	
Abnormal	72 (74.2)	10 (55.6)	0.11
PHQ-12 severity at 12-month follow-up among 217 individuals with low or mild severity at baseline (%)			
Low	21 (16.9)	22 (23.7)	
Mild	75 (60.5)	56 (60.2)	
Moderate	27 (21.8)	13 (14.0)	
High	1 (0.8)	2 (2.2)	0.30
PHQ-12 severity at 12-month follow-up among 421 individuals with moderate or high severity at baseline (%)			
Low	1 (0.3)	0 (0)	
Mild	54 (16.5)	15 (16.1)	
Moderate	155 (47.3)	63 (67.7)	
High	118 (36.0)	15 (16.1)	0.002

*p value for Pearson χ^2 for comparison of categorical data.