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TITLE PAGE

Title: Impact of Psychological Co-morbidity on the Prognosis of Irritable Bowel Syndrome.

Short running head: Psychological Co-morbidity in IBS.

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Abbreviations:

CBT	cognitive behavioral therapy
CPSS	Cohen perceived stress scale
HADS	hospital anxiety and depression scale
IBS	irritable bowel syndrome
IBS-SSS	irritable bowel syndrome severity scoring system
PHQ-12	patient health questionnaire-12
VSI	visceral sensitivity index

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ABSTRACT

Introduction: Psychological co-morbidities are associated with irritable bowel syndrome (IBS), but little is known about their cumulative effect on its prognosis. We examined this issue in a longitudinal 12-month follow-up study.

Methods: We collected complete demographic, symptom, and psychological co-morbidity data (anxiety, depression, somatic symptom disorder, perceived stress, and gastro-intestinal symptom-specific anxiety) at baseline from 807 adults who met Rome IV criteria for IBS. At 12 months, we collected data regarding IBS symptom severity and impact, consultation behavior, and treatments commenced from 452 individuals successfully followed up. We examined the cumulative effects of psychological co-morbidities at baseline on subsequent IBS disease behavior.

Results: At baseline, among the 807 participants, 177 (21.9%) had one, 139 (17.2%) two, 103 (12.8%) three, 89 (11.0%) four, and 54 (6.7%) five psychological co-morbidities. IBS symptom severity at baseline increased significantly with the number of psychological co-morbidities (72.2% of those with five psychological co-morbidities reported severe symptoms, versus 29.1% of those with none, $p<0.001$). Among 452 (56.0%) participants followed up at 12 months, those with a higher number of psychological co-morbidities at baseline were significantly more likely to have seen a gastroenterologist (33.3% of those with five psychological co-morbidities, versus 21.4% of those with none, $p=0.001$), cycle through more treatments ($p<0.0001$), to report more severe IBS symptoms (66.7% with five, versus 24.4% with none, $p<0.001$) and continuous abdominal pain (22.1% with none, versus 61.9% with five, $p<0.001$), and to report that symptoms impacted on daily activities ≥50% of the time (90.5% with five, versus 41.2% with none, $p<0.001$).

Discussion: The prognosis of individuals with Rome IV-defined IBS worsens according to incremental increases in psychological co-morbidity. This has important clinical and research implications.

What is known

- Psychological co-morbidities are associated with irritable bowel syndrome (IBS), and may influence symptoms.
- A small cross-sectional study showed a cumulative increase in IBS severity with an increasing number of psychological co-morbidities.
- However, it remains unclear as to whether individuals who exhibit higher levels of psychological co-morbidities have a worse prognosis, in terms of levels of healthcare usage, treatments required, severity of symptoms, and impact on activities of daily living.

What is new here

- At baseline, almost 70% of participants with Rome IV-defined IBS exhibited at least one psychological co-morbidity, and IBS symptom severity increased significantly with a higher number of psychological co-morbidities.
- During follow-up, those with higher levels of psychological co-morbidity were significantly more likely to have seen a gastroenterologist, cycle through more treatments, and to report severe IBS symptoms, which had a significantly greater impact on their activities of daily living.
- They were also more likely to have seen their primary care physician or commenced a new treatment for their IBS, although these latter differences were not statistically significant.
- Access to formal psychological assessment and psychological therapies for those patients with a high psychological burden should be improved, as this may alter the prognosis of IBS for this subgroup.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, characterized by recurrent abdominal pain associated with a change in stool form or frequency. (1, 2) IBS affects between 5% and 10% of the world's population, (3, 4) and the annual estimated direct and indirect healthcare costs of IBS are up to €8 billion in Europe, (5) ¥123 billion in China, (6) and at least US$10 billion in the USA. (7) The pathophysiology of IBS remains incompletely understood and, hence, current treatment strategies are aimed at relieving predominant symptom(s). However, there is evidence that disordered communication between the gut and the brain, including visceral hypersensitivity and altered central nervous system pain processing are involved, which may provide potential treatment targets in IBS. (8) In view of this complex interplay, IBS is now regarded as a disorder of gut-brain interaction. (9)

Patients with IBS often exhibit psychological co-morbidity, (10) although it remains unclear whether this is a cause or a consequence of the gastrointestinal symptoms experienced. (11, 12) Anxiety and depression are more common in individuals with IBS than among healthy individuals. (13) However, although most studies have focused on anxiety and depression, there are other psychological co-morbidities that not only co-exist with IBS, (14, 15) but are also associated with more severe gastrointestinal symptoms. (16-18) These include, but are not limited to, stress, somatic symptom disorder, which is the experience of symptoms affecting different organ systems that cannot be explained medically, and gastrointestinal symptom-specific anxiety, which is fear of the potential adverse consequences of gastrointestinal symptoms. (19-21)

Studies demonstrate that psychological treatments, such as cognitive behavioral therapy (CBT) where one is taught to recognize and modify unhelpful thinking patterns and behaviors, are efficacious for symptoms of IBS, with encouraging long-term results. (22)

Central neuromodulators, such as tricyclic antidepressants, are also effective in reducing symptoms in patients with IBS. (23) It remains unclear whether the beneficial effects of these treatments are due to direct effects on the gut, or treatment of co-existing psychological disorders, which in turn improve gastrointestinal symptoms. However, doses used are generally lower than those used for depression, highlighting the importance of the interplay between the gut and the brain in IBS.

Previous cross-sectional surveys and case-control studies examining influence of psychological co-morbidity in IBS have demonstrated that there is an association between severity of IBS and anxiety, depression, perceived stress, somatic symptom disorder, and gastro-intestinal symptom-specific anxiety. (14-17, 19) A recent cross-sectional survey, conducted in 106 patients with IBS, demonstrated a cumulative increase in IBS symptom severity with increasing number of psychological co-morbidities. (15) However, to our knowledge, there have been no large-scale studies conducting longitudinal follow-up to examine the cumulative effects of number of psychological co-morbidities on the prognosis of individuals with IBS. We therefore examined this issue in a 12-month longitudinal follow-up study conducted in a cohort of individuals with IBS defined according to the Rome IV criteria. We hypothesized that those with a higher number of psychological co-morbidities at baseline would have a worse prognosis than those with fewer psychological co-morbidities. We expected that, over 12 months, those with higher number of psychological co-morbidities would have more severe symptoms that had greater impact on activities of daily living, cycle through greater numbers of treatments, and exhibit higher levels of healthcare usage.

METHODS

Participants and Setting

We recruited individuals who self-identified as having IBS registered with three organizations in the UK: The IBS network, TalkHealth, and ContactMe-IBS. We have described this cohort elsewhere. (20, 24-26) We invited individuals aged ≥18 years to participate, via email and post, between December 2017 and December 2018. There were no exclusion criteria, other than an inability to understand written English. We provided potential participants with an information leaflet about the study, which explained that we would re-contact them in 12 months' time. Those interested completed an online questionnaire, which took approximately 30 minutes, collecting demographic and symptom data. There was no financial remuneration. All participants gave their time freely to answer the questionnaires. We stored responses in a secure online database. We sent out invitations to complete a follow-up questionnaire to all participants after 12 months, using the same methods. We sent out up to two reminders to non-responders. We received University of Leeds research ethics committee approval to conduct the baseline and follow-up study in November 2017. The primary aim of the original study was to characterize subgroups of individuals with IBS using factors beyond stool form. (26) The current study is therefore a secondary analysis of data, and the relationship between psychological health and prognosis of IBS was not mentioned to the participants.

Data Collection and Synthesis

Demographic and Lower Gastrointestinal Symptom Data

We collected demographic data at baseline. We captured lower gastrointestinal symptom data at baseline using the relevant part of the Rome IV questionnaire, (27) assigning presence of Rome IV-defined IBS among all individuals according to the proposed criteria. We categorized IBS subtype according to the criteria recommended in the questionnaire.

Assessment of Psychological Co-morbidity

We collected anxiety and depression data using the hospital anxiety and depression scale (HADS). (28) The total HADS score ranges from a minimum of 0 to a maximum of 21 for either anxiety or depression. We categorized severity for each into normal (total HADS depression or anxiety score 0-7), borderline abnormal (8-10), or abnormal (≥11). (28) We collected somatic symptom disorder data using the patient health questionnaire-12 (PHQ-12), (16) which is derived from the validated PHQ-15. (29) The total PHQ-12 score ranges from a minimum of 0 to a maximum of 24. We categorized severity into high (total PHQ-12 ≥13), medium (8-12), low (4-7), or minimal (≤3) somatic symptom disorder scores.

We used the 10-item version of the Cohen perceived stress scale (CPSS) to assess perceived stress. This is derived from the original 14-item instrument, (30) has been used widely, and is psychometrically reliable and comparable with its predecessor. (31) It measures the degree to which the individual feels he or she has experienced stress in the previous month. High CPSS scores appear to be associated with poor quality of life and poor coping in other gastrointestinal diseases, including inflammatory bowel disease. (32) As there

are no validated cut offs to define low, medium, or high perceived stress scores, we divided these data into tertiles of equal size.

We assessed gastrointestinal symptom-specific anxiety using the visceral sensitivity index, (33) a 15-item instrument. 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 validated cut offs to define low, medium, or high gastrointestinal symptom-specific anxiety scores, we divided these data into tertiles of equal size.

We classified individuals according to the total number of psychological co-morbidities they exhibited, from a possible total of five, including one or more of abnormal anxiety scores, abnormal depression scores, high somatic symptom disorder scores, high perceived stress scores, and high gastrointestinal symptom-specific anxiety scores, and examined the degree of overlap between them.

Consultation Behavior and Treatment Data During Follow-up

In the follow-up questionnaire, we asked participants to state whether they had seen a primary care physician or gastroenterologist about their IBS symptoms in the 12 months since study entry, and whether they had commenced any new treatments for these (dietary, drugs, and/or psychological) since study entry. The questionnaires were otherwise identical.

Assessment of IBS Symptom Severity and Impact at Baseline and Follow-up

We assessed IBS symptom severity at baseline and 12 months using the IBS severity scoring system (IBS-SSS), (34) which measures the presence, severity, and frequency of both abdominal pain and distension, as well as satisfaction with bowel habit, and degree to which IBS symptoms are interfering with the individual's life. The IBS-SSS carries a maximum score of 500 points with <75 points indicating remission, 75-174 points mild symptoms, 175-

299 points moderate symptoms, and ≥300 points severe symptoms. We measured the impact of IBS symptoms, in terms of the proportion of time that they limited normal daily activities at 12 months, as per the Rome IV questionnaire,(27) and dichotomized this at a threshold of interference with daily activities ≥50% of the time.

Statistical Analysis

We compared demographic characteristics of all participants according to the number of psychological co-morbidities at baseline, using a χ^2 test for categorical data and a one-way analysis of variance for continuous data. We compared these characteristics for responders, versus non-responders, at 12 months, using a χ^2 test for categorical data and an independent samples *t*-test for continuous data. We examined the degree to which psychological co-morbidity at baseline influenced subsequent disease behavior. Specifically, we compared the proportion of people who had seen a primary care physician, consulted a gastroenterologist, or commenced a new treatment, as well as the number of new treatments commenced, impact on normal daily activities, and symptom severity at 12-month follow-up, according to the number of psychological co-morbidities at baseline, using a χ^2 test for categorical data and a Kruskal-Wallis one-way analysis of variance for IBS-SSS 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, there were 1374 participants who self-identified as having IBS, of whom 811 (59.0%) met the Rome IV criteria at baseline, and 807 (99.5%) provided complete data for these analyses. There were 439 (54.4%) subjects with abnormal HADS anxiety scores, 186 (23.0%) with abnormal HADS depression scores, 236 (29.2%) with high somatic symptom disorder scores, 262 (32.5%) with high perceived stress scores, and 267 (33.1%) with high gastrointestinal symptom-specific anxiety scores. In total, 245 (30.4%) had no psychological co-morbidities, and 562 (69.6%) had at least one. Overall, 177 (21.9%) individuals had one, 139 (17.2%) two, 103 (12.8%) three, 89 (11.0%) four, and 54 (6.7%) five psychological co-morbidities. The degree of overlap among the 562 individuals with one or more psychological co-morbidity is provided in Figure 1.

Characteristics of Individuals Meeting Rome IV Criteria for IBS According to Number of Psychological Co-morbidities at Baseline

Demographic characteristics of all 807 participants with Rome IV IBS, according to number of psychological co-morbidities, are provided in Table 1. Those with more psychological co-morbidities were significantly younger (52.3 years in those with none, versus 42.6 years in those with five, $p<0.001$). In addition, a greater proportion of those with no psychological co-morbidities had achieved a university or postgraduate level of education (50.6% in those with none, versus 20.8% in those with five, $p<0.001$), a lower proportion smoked (4.1%, versus 14.8%, $p<0.001$), and a higher proportion drank alcohol (62.4%, versus 37.0%, $p<0.001$). IBS symptom severity, according to the IBS-SSS, increased significantly with number of psychological co-morbidities (72.2% of those with five psychological co-morbidities reported severe symptoms, versus 75.3% with four, 59.2% with

three, 50.4% with two, 39.0% with one, and 29.1% with none, $p<0.001$ for trend) (Table 1 and Figure 2), and median IBS-SSS scores increased significantly with each incremental increase in number of psychological co-morbidities (381.5 in those with five psychological co-morbidities, versus 365.0 with four, 330.0 with three, 305.0 with two, 270.0 with one, 247.5, and 247.5 with none, $p<0.001$ for trend) (Table 1). The proportion of individuals with continuous abdominal pain also increased with increasing number of psychological co-morbidities (77.8% with five, versus 65.2% with four, 59.2% with three, 46.8% with two, 42.4% with one, and 33.6% with none, $p<0.001$ for trend) (Table 1).

Consultation Behavior, Commencement of New Treatment, and Disease Impact and Severity During Follow-up According to Number of Psychological Co-morbidities at Baseline

Overall, 452 (56.0%) of 807 individuals were followed-up successfully at 12 months. Smokers (13.6% of non-responders, versus 6.9% of responders, $p=0.001$) and younger individuals (mean age of non-responders 44.9 years, versus 49.1 years in non-responders, $p<0.001$) were less likely to be followed up, whereas those with a university or postgraduate level of education were more likely to be followed up (44.2% of responders, versus 32.4% of non-responders, $p=0.001$) (Table 2). There were no other significant differences, including in terms of IBS subtype, IBS symptom severity at baseline, presence of continuous abdominal pain at baseline, or degree of psychological co-morbidities.

The proportion of individuals consulting their primary care physician (32.8% with no psychological co-morbidities, versus 52.4% with five psychological co-morbidities, $p=0.017$) or commencing a new treatment for their IBS (70.2% with no psychological co-morbidities, versus 76.2% with five, $p=0.02$) increased generally with increasing number of psychological co-morbidities, although these differences were not statistically significant (Table 3).

However, the number of new treatments commenced for IBS increased significantly according to psychological co-morbidities at baseline ($p<0.001$ for trend). In addition, the proportion of individuals who had seen a gastroenterologist (21.4% with no psychological co-morbidities, versus 24.3% with one, 29.5% with two, 14.8% with three, 50.0% with four, and 33.3% with five, $p=0.001$ for trend), and who reported that symptoms impacted on daily activities ≥50% of the time (41.2% with no psychological co-morbidities, versus 58.6% with one, 67.9% with two, 72.1% with three, 90.0% with four, and 90.5% with five, $p<0.001$ for trend) increased according to number of psychological co-morbidities. The proportion of individuals with continuous abdominal pain at 12 months increased with each increase in psychological co-morbidity (22.1% with none, versus 27.9% with one, 37.2% with two, 45.9% with three, 56.0% with four, and 61.9% with five, $p<0.001$ for trend). A greater proportion of those with higher numbers of psychological co-morbidities at baseline reported severe symptoms at 12-month follow-up, according to the IBS-SSS (24.4% with none, versus 25.2% with one, 50.0% with two, 52.5% with three, 64.0% with four, and 66.7% with five, $p<0.001$), and median IBS-SSS scores at 12 months increased significantly with increasing number of psychological co-morbidities (median score 220.0 in those with no psychological co-morbidity, versus 250.0 with one, 302.5 with two, 305.0 with three, 350.0 with four, and 360.0 with five, $p<0.001$ for trend). There was a non-significant trend for those with a higher number of psychological co-morbidities at baseline, but without severe IBS symptoms at baseline, to have developed severe IBS symptoms at follow-up ($p=0.021$). Finally, the number of psychological co-morbidities at baseline predicted the number of psychological co-morbidities at follow-up; more than 50% of individuals with five psychological co-morbidities at baseline still had five at follow-up ($p<0.001$ for trend).

DISCUSSION

This 12-month longitudinal follow-up study has examined the prevalence of psychological co-morbidity, including anxiety, depression, somatic symptom disorder, perceived stress, and gastrointestinal symptom-specific anxiety, and its effect on the prognosis of Rome IV-defined IBS. Almost 70% of participants had at least one psychological co-morbidity, and almost 50% had at least two. Those with a higher number of psychological co-morbidities were younger, more likely to smoke, less likely to drink alcohol, and less likely to have achieved a university level of education. In addition, there was a cumulative effect of number of psychological co-morbidities on IBS symptom severity at baseline. During follow-up, those with higher levels of psychological co-morbidity were significantly more likely to have seen a gastroenterologist, cycle through more treatments, and to report severe IBS symptoms, which had a significantly greater impact on their activities of daily living, as well as continuous abdominal pain. They were also more likely to have seen their primary care physician or commenced a new treatment for their IBS, although these latter differences were not statistically significant. Those without severe IBS symptoms at baseline were also more likely to develop severe symptoms at follow-up if they had higher levels of psychological co-morbidity at baseline, and levels of psychological co-morbidity at baseline also predicted degree of psychological co-morbidity at follow-up.

We recruited a large number of individuals who self-identified as having IBS and who also met the Rome IV criteria for IBS. Because some had never seen a doctor for their IBS symptoms, some had seen their primary care physician and some had seen a gastroenterologist, it is likely that this sample is an accurate representation of individuals with IBS in the UK, which underlines the magnitude of the association between IBS and poor psychological health. However, these individuals may not be generalizable to a US population with IBS. We obtained near complete data for the variables of interest because of

the use of mandatory fields in our online questionnaire both at baseline and follow-up. All the questionnaires we used were validated, are well-accepted instruments, and have been used widely in studies in IBS and other chronic gastrointestinal diseases.

Because we recruited individuals directly from the community, to better represent individuals with IBS, we did not check their medical records to rule out other organic diseases that may lead to similar symptoms, such as coeliac disease or inflammatory bowel disease. (35, 36) However, given that IBS is more prevalent than these conditions in the community, the fact that national UK guidance recommends ruling out coeliac disease and inflammatory bowel disease in people with suspected IBS, via coeliac serology and fecal calprotectin, (37, 38) and given that 95% of individuals had consulted their primary care physician about their IBS symptoms prior to recruitment in this study, we believe that it is likely that these individuals had IBS. The questionnaire was completed online, so 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. We relied on the motivation of individuals to complete two questionnaires 12 months apart; our response rate of 56% is similar to other follow-up studies conducted in gastrointestinal diseases. (39-42) However, there were some significant differences between responders at 12 months and non-responders, meaning that the individuals who provided longitudinal follow-up data may not be representative of the entire sample. We asked participants to state whether they had seen a primary care physician or gastroenterologist over the 12-month follow-up period of the study, which may be prone to recall bias. Although we used validated questionnaires to determine the proportion of individuals with abnormal scores for each psychological co-morbidity, (16, 28, 30, 33) these are proxy measures for their presence or absence, as the questionnaires measure symptoms rather than actual disorders. The latter are only able to be established via a psychiatric or

psychological interview. However, these proxies are practical, often used and widely accepted in studies like this. (12, 14, 15, 20, 21, 40) Our approach of using the upper tertile to define abnormal levels of perceived stress or gastrointestinal symptom-specific anxiety is a compromise related to a lack of validated cut-off levels, although parallels the methodology in other studies. (15) Finally, we limited our study to five psychological co-morbidities, which have been extensively studied in IBS, but there may be other important psychological factors affecting outcomes in individuals with IBS.

Although two recent cross-sectional surveys have examined the relationship between increasing levels of psychological co-morbidity and IBS symptom severity, (15, 43) one of which included physiological test results within the analysis, (43) both were relatively small. Crucially, neither conducted longitudinal follow-up, so were only able to report associations between the two, rather than examine cumulative effects of psychological co-morbidities on the prognosis of IBS, including healthcare seeking behavior, prognosis, and disease impact. Other weaknesses include the fact that patients were recruited from referral populations in both studies, implying that they are likely to have more severe IBS symptoms and higher levels of psychological co-morbidity. Prior to examining cumulative effects of psychological co-morbidities in IBS, Midenfjord *et al.* assessed nine different psychological co-morbidities individually, but only included five that were significantly associated with IBS symptoms in their analysis. (15) These included physical fatigue, gastrointestinal symptom-specific anxiety, perceived stress, pain catastrophizing, and trait anxiety. In contrast, somatic symptom disorder and depression, whose association with IBS is well-recognized, (21, 44, 45) were not significant, which could perhaps be explained by the small sample size of the study. (15)

In the present study, we focused on common psychological co-morbidities in IBS. There are a variety of other psychological constructs, or measures, worth exploring in future

studies. For example, there is some research indicating that personality traits might contribute to the development of IBS. (46, 47) Other concepts, more amenable to change than personality traits, such as psychological flexibility, which is the extent to which a person can cope with changes in circumstances, and absent in many forms of psychopathology, (48) or experiential avoidance, which is attempts by the individual to change internal experiences, such as thoughts or emotions, might be of interest to future researchers. The latter is often considered to have a moderating effect on the relationship between psychological experiences, such as health anxiety, and other psychological constructs, including depression and stress. (49) Preliminary studies suggest that acceptance and commitment therapy might decrease experiential avoidance and is useful in reducing psychological distress in people with gastrointestinal disorders. (50, 51) Similarly, mindfulness-based therapies, which are derived from Buddhist contemplative practice, may reduce psychopathology, and improve bowel symptoms in IBS, although again the evidence, to date, is limited. (52, 53) Mindfulness is proposed to reduce stress via emotion regulation, such as positive reappraisal attention regulation, body awareness, and change in self-perspective. (54)

Our results demonstrate that, with increasing levels of psychological co-morbidity, individuals with Rome IV IBS have worse IBS symptoms at baseline, seek more healthcare consultations, cycle through more treatments, and have a worse prognosis, in terms of severity and impact of symptoms, and psychological health, at follow-up. Rates of reporting of continuous pain increased, with number of psychological co-morbidities, suggesting central sensitization, which is in keeping with previous literature demonstrating that anxiety and hypervigilance lead to amplification of central pain processing. (55) This reflects the fact that there are a subgroup of individuals with IBS with a high psychological burden, whose symptoms are likely to be refractory to current conventional medical therapies, (56-58) which focus mainly on the physical symptoms of either intermittent abdominal pain or stool form

and frequency, rather than addressing continuous abdominal pain or psychological factors. In fact, psychological assessment of individuals with IBS is not part of routine clinical practice and, in the UK, psychological therapies are only recommended as a last resort after the failure of pharmacological therapies. (37) Although recent trials assessing the effectiveness of psychological therapies, such as CBT or gut-directed hypnotherapy, in the treatment of patients with IBS with refractory symptoms have produced encouraging long term results, (22, 59-61) many RCTs of psychological therapies in IBS are not restricted to this particular patient group, suggesting they are likely to be beneficial at an earlier stage in the disease, and before symptoms become refractory. Further, an integrated approach to treatment, which targets psychosocial functioning as well as bowel symptoms, has been increasingly demonstrated as likely to improve biopsychosocial outcomes in those with IBS,(62-65) as well as other populations within gastroenterology.(66, 67)

In summary, individuals with Rome IV-defined IBS with higher levels of psychological co-morbidities had more severe IBS symptoms at baseline and were more likely to seek healthcare and cycle through more treatments for their symptoms during follow-up. In addition, the prognosis of their disease, in terms of IBS symptoms and their impact on routine daily activities, as well as psychological health, was worse. Our findings have important clinical implications. Unless psychological health is assessed formally in clinical practice, this subgroup of patients with IBS with a high psychological burden, and whose prognosis is worse, will not be identified, and their problems addressed. We believe, therefore, that this should be part of the routine evaluation of patients with IBS. In addition, access to formal psychological assessment and psychological therapies for those patients with a high psychological burden should be improved, as there is evidence that this may alter the natural history of IBS for this subgroup of patients.(68) Specialist clinics should consider embedding these within the framework of their outpatient service, including evidence-based

telehealth services to improve access for those based outside metropolitan areas.(69) Our findings also have implications for future research. Although there is an association between psychological co-morbidity and severity of IBS symptoms, as well as prognosis, it remains unclear which psychological co-morbidity has the greatest effect on the prognosis of IBS, although anxiety was the most common in this study, and whether one of these psychological co-morbidities is driving others. In addition, although we have assessed the cumulative effects of psychological co-morbidities on the prognosis of IBS during 12 months of follow-up, the longer-term effects are unknown. Future studies should address these issues.

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CONFLICTS OF INTEREST/STUDY SUPPORT

Guarantor of the article: ACF is guarantor.

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

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Table 1. Characteristics of 807 Individuals Meeting Rome IV Criteria for IBS According to Number of Psychological Co-morbidities at Baseline.

	0 (n=245)	**1 (n=177)**	**2 (n=139)**	**3 (n=103)**	**4 (n=89)**	**5 (n=54)**	***p* value***
Mean age (SD)	52.3 (15.2)	45.5 (15.6)	46.1 (14.3)	44.8 (15.0)	44.0 (12.5)	42.6 (13.5)	<0.001
Female gender (%)	199 (81.2)	150 (84.7)	125 (89.9)	94 (91.3)	79 (88.8)	46 (85.2)	0.09
Married or co-habiting (%)	176 (71.8)	118 (66.7)	86 (61.9)	61 (59.2)	54 (60.7)	29 (53.7)	0.049
University or postgraduate level of education (%)	124 (50.6)	77 (43.5)	49 (35.3)	32 (31.7)	21 (23.6)	11 (20.8)	<0.001
White Caucasian ethnicity (%)	240 (98.0)	165 (93.2)	130 (93.5)	94 (92.2)	84 (94.4)	46 (86.8)	0.023
Smoker (%)	10 (4.1)	12 (6.8)	17 (12.2)	14 (13.7)	18 (20.2)	8 (14.8)	<0.001
Alcohol use (%)	153 (62.4)	112 (63.3)	80 (57.6)	46 (45.1)	31 (34.8)	20 (37.0)	<0.001
IBS after acute enteric infection (%)	32 (13.1)	20 (11.3)	21 (15.1)	12 (11.8)	12 (13.5)	9 (16.7)	0.88
IBS subtype at baseline (%)							
Constipation	46 (18.8)	23 (13.0)	29 (20.9)	17 (16.7)	15 (16.9)	12 (22.2)	
Diarrhea	100 (40.8)	77 (43.5)	53 (38.1)	29 (28.4)	38 (42.7)	13 (24.1)	
Mixed stool pattern	88 (35.9)	72 (40.7)	55 (39.6)	52 (51.0)	34 (38.2)	28 (51.9)	
Unclassified	11 (4.5)	5 (2.8)	2 (1.4)	4 (3.9)	2 (2.2)	1 (1.9)	0.15

Severity on IBS-SSS at baseline (%)							
Remission	5 (2.0)	1 (0.6)	2 (1.4)	0 (0)	0 (0)	(0)	
Mild	52 (21.3)	18 (10.2)	10 (7.2)	6 (5.8)	1 (1.1)	3 (5.6)	
Moderate	116 (47.5)	89 (50.3)	57 (41.0)	36 (35.0)	21 (23.6)	12 (22.2)	
Severe	71 (29.1)	69 (39.0)	70 (50.4)	61 (59.2)	67 (75.3)	39 (72.2)	<0.001
Median IBS-SSS score at baseline	247.5	270.0	305.0	330.0	365.0	381.5	<0.001
Continuous abdominal pain at baseline (%)	82 (33.6)	75 (42.4)	65 (46.8)	61 (59.2)	58 (65.2)	42 (77.8)	<0.001
Abnormal HADS anxiety scores at baseline (%)	0 (0)	93 (52.5)	108 (77.7)	95 (92.2)	89 (100)	54 (100)	<0.001
Abnormal HADS depression scores at baseline (%)	0 (0)	5 (2.8)	22 (15.8)	41 (39.8)	64 (71.9)	54 (100)	<0.001
High somatic symptom disorder scores at baseline (%)	0 (0)	29 (16.4)	44 (31.7)	44 (42.7)	65 (73.0)	54 (100)	<0.001
High perceived stress scores at baseline (%)	0 (0)	9 (5.1)	44 (31.7)	75 (72.8)	80 (89.9)	54 (100)	<0.001
High gastrointestinal symptom-specific anxiety scores at baseline (%)	0 (0)	41 (23.2)	60 (43.2)	54 (52.4)	58 (65.2)	54 (100)	<0.001

*p value for one-way analysis of variance for continuous data and Pearson χ^2 for comparison of categorical data.

HADS; hospital anxiety and depression scale, IBS; irritable bowel syndrome, IBS-SSS; IBS symptom severity scoring system

Table 2. Characteristics of Individuals Meeting Rome IV Criteria for IBS Responding to the 12-month Questionnaire Compared with Non-responders.

	Responded to Questionnaire at 12 Months (n=452)	**Did not Respond to Questionnaire at 12 Months (n=355)**	***p* value***
Mean age (SD)	49.1 (14.3)	44.9 (15.7)	<0.001
Female gender (%)	386 (85.4)	307 (86.5)	0.66
Married or co-habiting (%)	308 (68.1)	216 (60.8)	0.031
University or postgraduate level of education (%)	200 (44.2)	114 (32.4)	0.001
White Caucasian ethnicity (%)	431 (95.4)	328 (92.9)	0.14
Smoker (%)	31 (6.9)	48 (13.6)	0.001
Alcohol use (%)	252 (55.8)	190 (53.7)	0.56
IBS after acute enteric infection (%)	62 (13.7)	44 (12.4)	0.59
IBS subtype at baseline (%)			
Constipation	75 (16.6)	67 (18.9)	
Diarrhea	181 (40.0)	129 (36.4)	
Mixed stool pattern	185 (40.9)	144 (40.7)	
Unclassified	11 (2.4)	24 (4.0)	0.43
Severity on IBS-SSS at baseline (%)			
Remission	3 (0.7)	5 (1.4)	
Mild	58 (12.8)	32 (9.0)	
Moderate	181 (40.0)	150 (42.4)	
Severe	210 (46.5)	167 (47.2)	0.27
Continuous abdominal pain at baseline (%)	209 (46.2)	177 (49.4)	0.32
Abnormal HADS anxiety scores at baseline (%)	246 (54.4)	193 (54.4)	0.99

Abnormal HADS depression scores at baseline (%)	97 (21.5)	89 (25.1)	0.23
High somatic symptom disorder scores at baseline (%)	129 (28.5)	107 (30.1)	0.62
High perceived stress scores at baseline (%)	145 (32.1)	117 (33.0)	0.79
High gastrointestinal symptom-specific anxiety scores at baseline (%)	138 (30.5)	129 (36.34)	0.082
Number of psychological co-morbidities at baseline (%)			
0	131 (29.0)	114 (32.1)	
1	111 (24.6)	66 (18.6)	
2	78 (17.3)	61 (17.2)	
3	61 (13.5)	42 (11.8)	
4	50 (11.1)	39 (11.0)	
5	21 (4.6)	33 (9.3)	0.057

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

HADS; hospital anxiety and depression scale, IBS; irritable bowel syndrome, IBS-SSS; IBS symptom severity scoring system

Table 3. Consultation Behavior, Commencement of New Treatment, and Disease Impact and Severity During Follow-up According to Number of Psychological Co-morbidities at Baseline Among 452 Individuals Meeting Rome IV Criteria for IBS.

	0 (n=131)	**1 (n=111)**	**2 (n=78)**	**3 (n=61)**	**4 (n=50)**	**5 (n=21)**	***p* value***
Saw a primary care physician regarding IBS during 12-month follow-up (%)	43 (32.8)	51 (45.9)	36 (46.2)	31 (50.8)	30 (60.0)	11 (52.4)	0.017
Saw a gastroenterologist regarding IBS during 12-month follow-up (%)	28 (21.4)	27 (24.3)	23 (29.5)	9 (14.8)	25 (50.0)	7 (33.3)	0.001
Commenced new treatment for IBS during 12-month follow-up (%)	92 (70.2)	72 (64.9)	65 (83.3)	42 (68.9)	43 (68.0)	16 (76.2)	0.02
Number of new treatments commenced during 12-month follow-up (%)							
0	39 (29.8)	39 (35.1)	13 (16.7)	19 (31.1)	7 (14.0)	5 (23.8)	
1	41 (31.3)	24 (21.6)	22 (28.2)	16 (26.2)	7 (14.0)	3 (14.3)	
2	36 (27.5)	18 (16.2)	20 (25.6)	14 (23.0)	17 (34.0)	5 (23.8)	
3	11 (8.4)	23 (20.7)	11 (14.1)	9 (14.8)	10 (20.0)	3 (14.3)	
4	4 (3.1)	5 (4.5)	6 (7.7)	3 (4.9)	5 (10.0)	5 (23.8)	
5	0 (0)	0 (0)	1 (1.3)	0 (0)	2 (4.0)	0 (0)	
6	0 (0)	2 (1.8)	5 (6.4)	0 (0)	2 (4.0)	0 (0)	<0.001
Continuous abdominal pain at 12-month follow-up (%)	29 (22.1)	31 (27.9)	29 (37.2)	28 (45.9)	28 (56.0)	13 (61.9)	<0.001
Symptoms limit normal daily activities ≥50% of the time at 12-month follow-up (%)	54 (41.2)	65 (58.6)	53 (67.9)	44 (72.1)	45 (90.0)	19 (90.5)	<0.001

Severity on IBS-SSS at 12-month follow-up (%)							
Remission	9 (6.9)	2 (1.8)	2 (2.6)	1 (1.6)	0 (0)	0 (0)	
Mild	37 (28.2)	30 (27.0)	15 (19.2)	9 (14.8)	4 (8.0)	2 (9.5)	
Moderate	53 (40.5)	51 (45.9)	22 (28.2)	19 (31.1)	14 (28.0)	5 (23.8)	
Severe	32 (24.4)	28 (25.2)	39 (50.0)	32 (52.5)	32 (64.0)	14 (66.7)	<0.001
Severe symptoms on IBS-SSS score at 12-month follow-up among 242 individuals without severe symptoms at baseline (%)	18 (18.6)	5 (7.6)	10 (29.4)	8 (32.0)	3 (23.1)	3 (42.9)	0.021
Median IBS-SSS score at 12-month follow-up	220.0	250.0	302.5	305.0	350.0	360.0	<0.001
Number of psychological co-morbidities at 12-month follow-up (%)							
0	96 (73.3)	35 (31.5)	7 (9.0)	9 (14.8)	1 (2.0)	0 (0)	
1	19 (14.5)	48 (43.2)	27 (34.6)	7 (11.5)	1 (12.0)	1 (4.8)	
2	12 (9.2)	14 (12.6)	21 (26.9)	13 (21.3)	6 (12.0)	0 (0)	
3	3 (2.3)	12 (10.8)	14 (17.9)	20 (32.8)	12 (24.0)	1 (4.8)	
4	1 (0.8)	1 (0.9)	7 (9.0)	8 (13.1)	18 (36.0)	7 (33.3)	
5	0 (0)	1 (0.9)	2 (2.6)	4 (6.6)	12 (24.0)	12 (57.1)	<0.001

*p value for one-way analysis of variance for continuous data and Pearson χ^2 for comparison of categorical data.

IBS; irritable bowel syndrome, IBS-SSS; IBS symptom severity scoring system

FIGURE LEGENDS.

Figure 1. Overlap of Psychological Co-morbidity Amongst 562 Individuals with Rome IV IBS and at Least One Psychological Co-morbidity.

Figure 2. Number of Individuals with Rome IV IBS with 0, 1, 2, 3, 4, or 5 Psychological Co-morbidities and the Proportion Reporting Severe Symptoms on the IBS-SSS Among Them.