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TITLE PAGE

Title: Overlap of Rome IV Irritable Bowel Syndrome and Functional Dyspepsia and Effect on Natural History: A Longitudinal Follow-up Study.

Short title: Overlap Between Rome IV IBS and FD.

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Abbreviations:

CPSS	Cohen perceived stress scale
DGBI	disorders of gut-brain interaction
EPS	epigastric pain syndrome
FD	functional dyspepsia
HADS	hospital anxiety and depression scale
IBS	irritable bowel syndrome

IBS-SSS	irritable bowel syndrome severity scoring system
PHQ-12	patient health questionnaire-12
PDS	postprandial distress syndrome
VSI	visceral sensitivity index

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ABSTRACT

Objectives: Disorders of gut-brain interaction, such as irritable bowel syndrome (IBS) and functional dyspepsia (FD) frequently overlap, but the impact of this on the natural history is unknown. We examined this issue in a longitudinal follow-up study conducted in a large cohort of individuals.

Methods: We collected complete demographic, symptom, mood, and psychological health data from 1374 adults who self-identified as having IBS. We applied the Rome IV criteria to examine what proportion met criteria for IBS and FD, as well as the degree of overlap between them. At 12 months, we collected data regarding IBS symptom severity and impact, consultation behavior, treatments commenced, and psychological health according to degree of overlap between IBS and FD.

Results: Overall, 807 individuals met the Rome IV criteria for IBS at baseline and provided complete data. At study entry, overlap of FD occurred in 446 (55.3%) people who met Rome IV criteria for IBS. At 12 months, 451 (55.9%) individuals were successfully followed up. The proportion of individuals consulting their primary care physician (p=0.001) or a gastroenterologist (p<0.001) because of their IBS was significantly higher in those with overlap of IBS and FD, and the number of new IBS treatments commenced was significantly higher (p=0.007). Those with overlap of IBS and FD reported significantly more severe IBS symptoms (p<0.001), continuous abdominal pain, and that their IBS symptoms limited normal daily activities ≥50% of the time. Finally, those with overlap were more likely to report abnormal anxiety and depression scores at 12 months compared with those with IBS alone, and to have higher levels of somatization (p<0.001 for all analyses).

Conclusions: The natural history of people with IBS with overlap FD defined according to Rome IV criteria is more severe than those with IBS alone. This has important implications for future treatment trials in IBS.

Key words: abdominal pain; bloating; early satiety; postprandial fullness; Rome IV criteria

INTRODUCTION

Functional gastrointestinal disorders, including irritable bowel syndrome (IBS) and functional dyspepsia (FD), redefined as disorders of gut–brain interaction (DGBI),[1] are common entities characterized by chronic or recurrent gastrointestinal symptoms, in the absence of structural abnormalities.[2][3][4] DGBI are diagnosed and classified using standardized symptom-based criteria, recommended by the Rome Foundation, the latest of which are Rome IV.[1][5] Over 40% of the general population meet these criteria for a DGBI at any given point in time,[6] and these conditions frequently overlap with each other.[7] This overlap may increase the detrimental effect of symptoms on quality of life and psychological health,[8] and increase probability of consultation, need for medical therapy, and potential for unnecessary surgery.[7]

According to the Rome IV criteria, IBS is defined by abdominal pain occurring at least once per week, in association with altered stool form or frequency,[9] and FD by bothersome epigastric pain or burning at least one day per week, or bothersome early satiety or postprandial fullness occurring at least three days per week.[10] These conditions affect approximately 4% and 7% of the general population, respectively,[11][12] and overlap is well-recognized.[13][14] A previous meta-analysis reported an eight-fold increase in odds of IBS in people with FD, compared with those without, and overlap between the two in up to 40% of individuals.[15] In fact, although overlap between DGBI is not specifically dealt with in the Rome classification system, it is represented by a genuine cohort of patients in daily clinical practice.[14]

Nevertheless, there are limited data exploring differences between patients with IBS alone and those with IBS and FD overlap. In addition, whether individuals with overlap of IBS and FD have a worse prognosis than individuals with IBS is unknown as, to our knowledge, there have been no studies conducting longitudinal follow-up to examine their

natural history. We hypothesized that, during follow-up, those with IBS with overlapping FD would have a worse disease prognosis than those with IBS alone. Specifically, over 12 months, we expected those with IBS and FD overlap to exhibit higher levels of health care usage, cycle through greater numbers of treatments, have more severe symptoms, which would have a greater impact on activities of daily living, and have higher levels of psychological co-morbidity. We examined these issues in a longitudinal follow-up study conducted over 12 months, recruiting people in the community who self-identified as having IBS, and who met the Rome IV criteria.

METHODS

Participants and Setting

Participants were registered with three organizations in the UK: The IBS network, TalkHealth, and ContactMe-IBS. We have described this cohort elsewhere.[16][17][18][19] Briefly, 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 an information leaflet about the study, and those interested completed an online questionnaire, collecting demographic and symptom data. 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 received University of Leeds research ethics committee approval to conduct the baseline and follow-up studies in November 2017.

Data Collection and Synthesis

Demographic, Gastrointestinal Symptom, and Psychological Co-morbidity Data

We collected all demographic, gastrointestinal symptom, and psychological co-morbidity data at baseline, as previously described,[16][17][18][19] using the Rome IV questionnaire, the hospital anxiety and depression scale (HADS), the patient health questionnaire-12, the 10-item version of the Cohen perceived stress scale, visceral sensitivity index, and the IBS severity scoring system (IBS-SSS). More information is provided in the Supplementary Methods.

Consultation Behavior and Treatment Data During Follow-up

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

Statistical Analysis

We compared demographic characteristics of all participants according to the presence or absence of FD at baseline, using a χ^2 test for categorical data and a one-way analysis of variance for continuous data. We examined the degree to which the presence or absence of FD 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 for their IBS, as well as the number of new treatments commenced for their IBS, impact of IBS on normal daily activities, and IBS symptom severity at 12-month follow-up, according to the presence of one or both FD subtypes at baseline, using a χ^2 test for categorical data and a one-way analysis of variance for continuous data. Due to multiple comparisons, a 2-tailed *p* value of <0.01 was considered statistically significant for all analyses. We conducted logistic regression analysis for all these endpoints, controlling for all baseline data. We performed all analyses using SPSS for Windows (version 26.0 SPSS Inc., Chicago, IL, USA).

RESULTS

In total, there were 1374 respondents, of whom 811 (59.0%) met the Rome IV criteria for IBS at baseline, and 807 (99.5%) provided complete data for these analyses. Among these, 361 (44.7%) individuals were classified as having IBS alone, 208 (25.8%) as having IBS and postprandial distress syndrome (PDS), 60 (7.4%) IBS and epigastric pain syndrome (EPS), and 178 (22.1%) as having IBS with overlapping PDS and EPS. Characteristics of individuals meeting Rome IV criteria for IBS according to presence or absence of FD at baseline are presented in the Supplementary Materials.

Symptom Fluctuation, Consultation Behavior, Commencement of New Treatment, and Disease Impact and Severity During Follow-up According to Presence or Absence of FD at Baseline

Overall, 451 (55.9%) of 807 individuals were followed-up successfully at 12 months. Differences between responders and non-responders are provided in Table 1. Responders were more likely to have attained a university or postgraduate level of education (44.1% versus 32.5%, p<0.001), were less likely to smoke (6.9% versus 13.5%, p=0.001), and were more likely to have seen a gastroenterologist about their IBS symptoms at baseline (65.0% vs. 55.2%, p=0.005) than non-responders. There was also a trend towards respondents being older.

IBS alone and IBS with overlapping PDS and EPS were the most stable groups at 12 months (46.3% and 51.5% remained in this subgroup at 12 months, versus 34.0% of those with IBS and PDS and 17.1% of those with IBS and EPS, p<0.001) (Table 2). IBS subtype remained relatively stable between baseline and 12 months in these four groups (Table 3). During the 12-month follow-up, the proportion of individuals consulting their primary care

physician (36.4% of those with IBS alone, versus 59.6% with IBS with overlapping PDS and EPS, p=0.001) or a gastroenterologist for their IBS (16.8% of those with IBS alone, versus 44.4% with IBS with overlapping PDS and EPS, p<0.001) increased with the degree of overlap between IBS and FD. There were no significant differences between the proportion of subjects commencing a new treatment for their IBS according to overlap between IBS and FD. However, the number of new treatments commenced for IBS was significantly higher in those with IBS with overlapping PDS and EPS (p=0.007 for trend).

In addition, the proportion of individuals who had continuous abdominal pain at 12-month follow-up was significantly higher among those with IBS and PDS, and IBS with overlapping PDS and EPS (22.4% of those with IBS alone, versus 42.7% of those with IBS and PDS, and 55.6% of those with IBS with overlapping PDS and EPS, p<0.001). Similarly, the proportion who reported that IBS symptoms impacted on daily activities ≥50% of the time was significantly higher in these two groups (50.5% with IBS alone, versus 73.8% of those with IBS and PDS, and 72.7% with IBS with overlapping PDS and EPS, p<0.001). Finally, there was a stepwise increase in severity of symptoms, according to the IBS-SSS, at 12 months according to degree of overlap between IBS and FD at baseline (19.2% with severe symptoms with IBS alone, versus 53.4% with IBS and PDS, 51.4% with IBS and EPS, and 63.6% with IBS with overlapping PDS and EPS, p<0.001). Mean IBS-SSS scores at 12 months also increased significantly with the degree of overlap between IBS and FD (217.6 in those with IBS alone, versus 296.4 in those with IBS and PDS, 299.2 in IBS and EPS, and 331.5 in those with IBS with overlapping PDS and EPS, p<0.001).

Data concerning psychological health at follow-up according to presence or absence of FD at baseline are provided in Table 3 but discussed in more detail in the Supplementary Materials. The results of multivariate logistic regression analysis are provided in Supplementary Table 2. Those with IBS with overlapping PDS and EPS remained more

likely to consult a gastroenterologist, report continuous abdominal pain, and have high levels of somatization at 12 months. Those with IBS and PDS were more likely to have abnormal HADS depression scores at 12 months.

DISCUSSION

This longitudinal 12-month follow-up study has examined the characteristics and natural history of Rome IV IBS according to the presence or absence of overlapping Rome IV FD at baseline. At study entry, among 807 individuals, overlap of FD occurred in 55% of people who met Rome IV criteria for IBS. During the follow-up period, among those who still met criteria for IBS, significantly higher proportions of those with IBS alone and those with IBS and overlapping PDS and EPS remained in these subgroups. The proportion of individuals consulting their primary care physician or a gastroenterologist for their IBS was significantly higher in those with overlap between IBS and FD, and number of new IBS treatments commenced significantly higher. Those with IBS and FD overlap reported significantly more severe symptoms, which had a significantly greater impact on normal activities of daily living, and were more likely to report continuous abdominal pain. Finally, those with IBS with overlapping PDS and EPS at baseline were more likely to report abnormal anxiety and depression scores at 12 months, compared with those with IBS alone, and to have higher levels of somatization, and there was a trend towards those with IBS and overlapping PDS and EPS being more likely to develop new onset abnormal depression scores.

We recruited a large community sample who self-identified as having IBS and who met Rome IV 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 the variables of interest at baseline and 12-month follow-up. We used the validated Rome IV questionnaires, rather than approximating definitions of IBS and FD using another

questionnaire. We also considered overlap not only between IBS and FD, but also between IBS and the different subgroups of FD.

Weaknesses include the fact that we did not check medical records to rule out organic gastrointestinal conditions that may masquerade as IBS, such as celiac disease or inflammatory bowel disease.[20],[21] However, IBS is more prevalent than these disorders in the community and, at baseline, 95% of participants reported having seen a primary care physician for their IBS, and almost 60% a gastroenterologist, we believe it is likely that they did have IBS. As the questionnaire was completed online, we cannot assess how many individuals chose not to complete it, or whether those who responded are broadly representative of all the people with IBS registered with these three organizations. It may also be the case that the people registered with these three organizations are more likely to report more severe symptoms, have higher levels of psychological co-morbidity, and seek healthcare, and that this could have affected our findings. In addition, because this study was conducted in a real-world community setting, a diagnosis of FD was assumed in this study, if participants met the Rome IV criteria; a normal endoscopy was not mandated. However, given that 80% of individuals with dyspepsia will have a normal endoscopy, and ultimately be labelled as having FD, this is not an unreasonable assumption.[22] There were relatively minor demographic differences between responders and non-responders at 12 months, but our response rate of 55.9% is comparable to that in other longitudinal follow-up studies of gastrointestinal disorders conducted over a similar time frame.[23][24][25][26] Finally, given that IBS and FD are chronic, 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 degree of overlap between FD and IBS.[14][27][28] However, these studies were all cross-sectional and restricted their analyses to comparing

characteristics between the two groups, rather than the prognostic implications of overlap between the two conditions according to the Rome criteria. This means that they are only able to report associations, rather than examining influence of the presence and extent of overlap on healthcare seeking behavior, prognosis, and disease impact. Our results suggest that overlap between IBS and FD occurs in more than 50% of people and these individuals are more likely to seek healthcare and have a worse disease prognosis, compared with those with IBS alone. There was a stepwise increase in severity of symptoms, according to the IBS-SSS, and impact of these symptoms at 12 months according to degree of overlap between IBS and FD at baseline, particularly for those with IBS, PDS, and EPS. Thus, the issue of overlap between different DGBI should not be underestimated, as our data suggest not only that overlap between IBS and FD is common, but also is associated with a worse clinical course.

The 12-month longitudinal follow-up is one of the novel aspects of this study. This allowed us to examine the stability of the degree of overlap between IBS and FD. In most cases, among those who remained symptomatic and still met criteria for both IBS and FD, the subgroups remained relatively stable. As this was a real-world study, with medications commenced by the participants' responsible physician it is difficult to untangle reasons for fluctuation of the degree of overlap. The observations that abnormal HADS scores and somatization scores were more likely in those with IBS with overlapping PDS and EPS may be an indicator that some individuals are more likely to report multiple symptoms, and therefore meet criteria for more than one DGBI. In turn, these higher levels of psychological co-morbidity may have driven the higher levels of reporting of severe symptoms and continuous pain, as well as the higher rates of healthcare seeking, but this is speculative.

As is well recognized, common mental disorders are frequent in patients with DGBI, with up to 40% and 30% of patients with IBS having measurable anxiety and depression symptoms, respectively.[29] Likewise, IBS and FD are constellations of symptoms, which

are likely not only limited to the gastrointestinal tract, but may also include sexual dysfunction, sleep disturbance, chronic fatigue, and mood disorders.[30][31] A cross-sectional study by Yao *et al.* demonstrated that patients with IBS with overlapping FD had statistically significantly higher levels of both anxiety and depression compared with those with IBS alone. [32] In our study, both at baseline and 12-month follow-up, patients with IBS with overlapping EPS and PDS were significantly more likely to report abnormal anxiety and depression scores at 12 months, compared with IBS alone.

Our findings have implications for future research. Most pivotal treatment trials in IBS, to date, have recruited homogenous groups of patients who do not fulfil criteria for other DGBI, or do not assess for overlap of DGBI. The fact that many patients with IBS have co-existent FD, and the fact that overlap of the two is associated with more severe symptoms, could have important implications for the design of future clinical trials and may explain why some treatments have failed to demonstrate only modest efficacy overall.[33][34][35][36] Therefore, assessing for co-existent FD and performing subgroup analysis according to presence or absence of overlap, may be beneficial in demonstrating specific patient groups who are more or less likely to respond to therapies in clinical trials, and also in "fixing" stool subtypes, to make them more stable during follow-up.

In terms of clinical practice, it is interesting to note that those with IBS with symptoms compatible with PDS were more likely to meet criteria for IBS with constipation and report frequent abdominal bloating, suggesting whole gut dysmotility, and those with IBS with EPS were more likely to report abdominal pain that was continuous, compatible with central sensitization, and meet criteria for IBS with diarrhea. This could provide clues as to how best to manage those with overlap, with drugs such as 5-hydroxytryptamine-4 receptor agonists being used to treat symptoms of constipation, bloating, and PDS, [35] and gut-brain neuromodulators, such as tricyclic antidepressants, being used to treat diarrhea and EPS.[37]

In summary, during 12 months of longitudinal follow-up, individuals with overlap of Rome IV IBS and FD, especially those with IBS with overlapping PDS and EPS, were more likely to consult a primary care physician or gastroenterologist about their IBS symptoms and required a greater number of IBS treatments than their counterparts with Rome IV-defined IBS alone. IBS symptoms were more severe, abdominal pain more likely to be continuous, normal daily activities were impacted significantly more, and psychological health significantly more impaired at both baseline and 12 months in those with overlap of IBS and FD. The implications of overlap of IBS and FD for the response to therapies, including the response rates in clinical trials, need to be further investigated.

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ETHICS COMMITTEE APPROVAL

University of Leeds research ethics committee approved the baseline and follow-up study in November 2017 (MREC17-018).

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

	Responders to Questionnaire at 12 Months (n=451)	**Non-Responders to Questionnaire at 12 Months (n=356)**	**P value***
Mean age (SD)	49.1 (14.4)	45.0 (15.7)	0.012
Female gender (%)	386 (86.1)	309 (86.8)	0.35
Married or co-habiting (%)	307 (68.1)	218 (61.2)	0.26
University or postgraduate level of education (%)	199 (44.1)	115 (32.5)	<0.001
White Caucasian ethnicity (%)	430 (95.3)	330 (93.0)	0.09
Smoker (%)	31 (6.9)	48 (13.5)	0.001
Alcohol use (%)	252 (55.9)	189 (53.2)	0.25
IBS after acute enteric infection (%)	62 (13.7)	44 (12.4)	0.33
Previously seen a primary care physician regarding IBS at study entry (%)	436 (96.7)	338 (95.2)	0.29
Previously seen a gastroenterologist regarding IBS at study entry (%)	293 (65.0)	196 (55.2)	0.005
Overlap of Rome IV IBS and FD at baseline (%)			
Rome IV IBS alone	214 (47.5)	147 (41.3)	
Rome IV IBS and PDS	103 (22.8)	105 (29.5)	
Rome IV IBS and EPS	35 (7.8)	25 (7.0)	
Rome IV IBS, PDS, and EPS	99 (22.0)	79 (22.2)	0.15
Severity on IBS-SSS at baseline (%)			
Remission (<75 points)	3 (0.7)	5 (1.4)	
Mild (75-174 points)	58 (12.9)	32 (9.0)	
Moderate (175-299 points)	180 (39.9)	150 (42.3)	
Severe (≥300 points)	210 (46.6)	168 (47.3)	0.26

Continuous abdominal pain at baseline (%)	176 (49.4)	209 (43.6)	0.32
Abnormal HADS anxiety score at baseline (score of ≥11) (%)	246 (54.5)	195 (54.8)	0.87
Abnormal HADS depression score at baseline (score of ≥11) (%)	97 (21.5)	88 (24.7)	0.52
Severity of somatization at baseline (%)			
Minimal (score of ≤3)	22 (4.9)	19 (5.3)	
Low (score of 4-7)	102 (22.6)	73 (20.5)	
Medium (score of 8-12)	198 (43.9)	156 (43.8)	
High (score of ≤13)	129 (28.6)	108 (30.3)	0.87
High levels of perceived stress at baseline (%)	145 (32.2)	118 (33.2)	0.89
High levels of gastrointestinal symptom-specific anxiety at baseline (%)	138 (30.6)	128 (36.3)	0.24

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

Table 2. Fluctuation of IBS and FD Among Individuals Still Meeting Rome IV Criteria for IBS at 12-month Follow-up According to Presence or Absence of FD at Baseline Among Individuals Meeting Rome IV Criteria for IBS.

	Rome IV IBS alone at baseline (n=214)	**Rome IV IBS and PDS at baseline (n=103)**	**Rome IV IBS and EPS at baseline (n=35)**	**Rome IV IBS, PDS, and EPS at baseline (n=99)**	***p* value***
Rome IV IBS alone at 12-month follow-up (%)	99 (46.3)	18 (17.5)	13 (37.1)	9 (9.1)	
Rome IV IBS and PDS at 12-month follow-up (%)	18 (8.4)	35 (34.0)	0 (0)	21 (21.2)	
Rome IV IBS and EPS at 12-month follow-up (%)	14 (6.5)	3 (2.9)	6 (17.1)	4 (4.0)	
Rome IV IBS, PDS, and EPS at 12-month follow-up (%)	2 (0.9)	19 (18.4)	7 (20.0)	51 (51.5)	<0.001
No longer met criteria for Rome IV IBS or FD at 12-month follow-up (%)	71 (33.2)	17 (16.5)	7 (20.0)	5 (5.1)	N/A*
Met criteria for Rome IV FD only at 12-month follow-up (%)					
Rome IV PDS only	8 (3.7)	10 (9.7)	0 (0)	2 (2.0)	
Rome IV EPS only	1 (0.05)	1 (1.0)	2 (5.7)	2 (2.0)	
Both Rome IV PDS and EPS	0 (0)	0 (0)	0 (0)	5 (5.1)	N/A†

* Not applicable, no comparator

†Not applicable, number of individuals too small for any meaningful comparison

Table 3. Consultation Behaviour, Commencement of New Treatment, and Disease Impact and Severity During Follow-up According to Presence or Absence of FD at Baseline Among Individuals Meeting Rome IV Criteria for IBS.

	Rome IV IBS alone at baseline (n=214)	**Rome IV IBS and PDS at baseline (n=103)**	**Rome IV IBS and EPS at baseline (n=35)**	**Rome IV IBS, PDS, and EPS at baseline (n=99)**	***p* value***
Saw a primary care physician regarding IBS during 12-month follow-up (%)	78 (36.4)	51 (49.5)	14 (40.0)	59 (59.6)	0.001
Saw a gastroenterologist regarding IBS during 12-month follow-up (%)	36 (16.8)	27 (26.2)	11 (31.4)	44 (44.4)	<0.001
Commenced new treatment for IBS during 12-month follow-up (%)	147 (68.7)	77 (74.8)	28 (80.0)	78 (78.8)	0.19
Number of new treatments for IBS commenced during 12-month follow-up (%)					
0	67 (31.3)	26 (25.2)	7 (20.0)	21 (21.2)	
1	61 (28.5)	27 (26.2)	8 (22.9)	17 (17.2)	
2	51 (23.8)	19 (18.4)	12 (34.3)	28 (28.3)	
3	25 (11.7)	21 (20.4)	5 (14.3)	16 (16.2)	
4	8 (3.7)	7 (6.8)	1 (2.9)	12 (12.1)	
5	2 (0.9)	0 (0)	1 (2.9)	0 (0)	
6	0 (0)	3 (2.9)	1 (2.9)	5 (5.1)	0.007
Continuous abdominal pain at 12-month follow-up (%)	48 (22.4)	44 (42.7)	11 (31.4)	55 (55.6)	<0.001

Symptoms limit normal daily activities ≥50% of the time at 12-month follow-up (%)	108 (50.5)	76 (73.8)	23 (65.7)	72 (72.7)	<0.001
IBS subtype at 12-month follow-up (%)					
Constipation	38 (17.8)	22 (21.4)	6 (17.1)	22 (22.2)	
Diarrhoea	96 (44.9)	37 (35.9)	16 (45.7)	24 (24.2)	
Mixed bowel habits	73 (34.1)	42 (40.8)	13 (37.1)	51 (51.5)	
Unclassified	7 (3.3)	2 (1.9)	0 (0)	2 (2.0)	0.07
Severity on IBS-SSS at 12-month follow-up (%)					
Remission (<75 points)	10 (4.7)	4 (3.9)	0 (0)	0 (0)	
Mild (75-174 points)	68 (31.8)	15 (14.6)	4 (11.4)	10 (10.1)	
Moderate (175-299 points)	95 (44.4)	29 (28.2)	13 (37.1)	26 (26.3)	
Severe (≥300 points)	41 (19.2)	55 (53.4)	18 (51.4)	63 (63.6)	<0.001
Mean IBS-SSS score at 12-month follow-up (SD)	217.6 (97.8)	296.4 (109.0)	299.2 (105.5)	331.5 (97.8)	<0.001
Abnormal HADS anxiety score at 12-month follow-up (score of ≥11) (%)	81 (37.9)	60 (58.3)	20 (57.1)	68 (68.7)	<0.001
New onset abnormal HADS anxiety score at 12-month follow-up (score of ≥11) (%)†	2 (2.8)	3 (14.3)	1 (16.7)	4 (25.0)	0.034
Abnormal HADS depression score at 12-month follow-up (score of ≥11) (%)	26 (12.1)	33 (32.0)	10 (28.6)	43 (43.4)	<0.001
New onset abnormal HADS depression score at 12-month follow-up (score of ≥11) (%)±	2 (1.4)	5 (9.3)	1 (6.7)	4 (11.8)	0.01
High levels of somatization at 12-month follow-up (score of ≥13) (%)	61 (28.5)	57 (55.3)	20 (57.1)	82 (82.8)	<0.001

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

†Denominators for normal anxiety score at baseline was 72 for those with Rome IV IBS alone, 21 for those with Rome IV IBS and PDS, 6 for those with Rome IV IBS and EPS, and 16 for those Rome IV IBS, PDS, and EPS.

±Denominators for normal depression score at baseline was 145 for those with Rome IV IBS alone, 54 for those with Rome IV IBS and PDS, 15 for those with Rome IV IBS and EPS, and 34 for those Rome IV IBS, PDS, and EPS.

REFERENCES

[1] Drossman DA, Hasler WL. Rome IV - Functional GI disorders: Disorders of gut-brain interaction. Gastroenterology 2016;150:1257–61.

[2] Black CJ, Drossman DA, Talley NJ, Ruddy J, Ford AC. Functional gastrointestinal disorders: advances in understanding and management. Lancet 2020;396.

[3] Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. Lancet 2020;396. https://doi.org/10.1016/S0140-6736(20)31548-8.

[4] Ford AC, Mahadeva S, Carbone MF, Lacy BE, Talley NJ. Functional dyspepsia. Lancet 2020;396. https://doi.org/10.1016/S0140-6736(20)30469-4.

[5] Drossman DA. Functional gastrointestinal disorders: History, pathophysiology, clinical features, and Rome IV. Gastroenterology 2016;150:1262-1279.e2.

[6] Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, imren M, Tack J, et al. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. Gastroenterology 2020;160.1:99-114.e3.

[7] Aziz I, Palsson OS, Törnblom H, Sperber AD, Whitehead WE, Simrén M. The prevalence and impact of overlapping Rome IV-diagnosed functional gastrointestinal disorders on somatization, quality of life, and healthcare utilization: A cross-sectional general population study in three countries. Am J Gastroenterol 2018;113:86–96.

[8] Pinto-Sanchez MI, Ford AC, Avila CA, Verdu EF, Collins SM, Morgan D, et al. Anxiety and depression increase in a stepwise manner in parallel with multiple FGIDs and symptom severity and frequency. Am J Gastroenterol 2015;110:1038–48.

[9] Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. Gastroenterology 2016;150:1393-1407.e5.

[10] Stanghellini V, Chan FKL, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. Gastroenterology 2016;150:1380–92.

[11] Barberio B, Mahadeva S, Black CJ, Savarino E V., Ford AC. Systematic review with meta-analysis: global prevalence of uninvestigated dyspepsia according to the Rome criteria. Aliment Pharmacol Ther 2020;52:762–73.

[12] Oka P, Parr H, Barberio B, Black CJ, Savarino E V., Ford AC. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:908–17.

[13] Koloski NA, Talley NJ, Boyce PM. Epidemiology and health care seeking in the functional GI disorders: a population-based study. Am J Gastroenterol 2002;97:2290–9.

[14] von Wulffen M, Talley NJ, Hammer J, McMaster J, Rich G, Shah A, et al. Overlap of Irritable Bowel Syndrome and Functional Dyspepsia in the Clinical Setting: Prevalence and Risk Factors. Dig Dis Sci 2019;64:480–6.

[15] Ford AC, Marwaha A, Lim A, Moayyedi P. Systematic Review and Meta-analysis of the Prevalence of Irritable Bowel Syndrome in Individuals With Dyspepsia. Clin Gastroenterol Hepatol 2010;8:401–9.

[16] Black CJ, Yiannakou Y, Houghton LA, Ford AC. Epidemiological, Clinical, and Psychological Characteristics of Individuals with Self-reported Irritable Bowel Syndrome Based on the Rome IV vs Rome III Criteria. Clin Gastroenterol Hepatol 2020;18:392-398.e2.

[17] Black CJ, Yiannakou Y, Houghton LA, Shuweihdi F, West R, Guthrie E, et al. Anxiety-related factors associated with symptom severity in irritable bowel syndrome. Neurogastroenterol Motil 2020;32. https://doi.org/10.1111/nmo.13872.

[18] Black C, Yiannakou Y, Guthrie E, West R, Houghton L, Ford A. A Novel Method to Classify and Subgroup Patients With IBS Based on Gastrointestinal Symptoms and Psychological Profiles. Am J Gastroenterol 2020:DOI:

10.14309/ajg.0000000000000975.

[19] Barberio B, Houghton L, Yiannakou Y, Savarino E, Black C, Ford A. Symptom Stability in Rome IV vs Rome III Irritable Bowel Syndrome. Am J Gastroenterol 2020;doi: 10.14309/ajg.0000000000000946

[20] Sainsbury A, Sanders DS, Ford AC. Prevalence of irritable bowel syndrome-type symptoms in patients with celiac disease: A meta-analysis. Clin Gastroenterol Hepatol 2013;11:359-365.e1.

[21] Fairbrass KM, Costantino SJ, Gracie DJ, Ford AC. Prevalence of irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease in remission: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:1053–62.

[22] Ford AC, Marwaha A, Lim A, Moayyedi P. What is the prevalence of clinically significant endoscopic findings in subjects with dyspepsia? Systematic review and meta-analysis. Clin Gastroenterol Hepatol 2010;8.10:830-837.

[23] Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of Brain–Gut Interactions in Patients With Inflammatory Bowel Disease. Gastroenterology 2018;154:1635-1646.e3.

[24] Gracie DJ, Hamlin PJ, Ford AC. Longitudinal impact of IBS-type symptoms on disease activity, healthcare utilization, psychological health, and quality of life in inflammatory bowel disease. Am J Gastroenterol 2018;113:702–12.

[25] Nicholl BI, Halder SL, Macfarlane GJ, Thompson DG, O'Brien S, Musleh M, et al. Psychosocial risk markers for new onset irritable bowel syndrome - Results of a large prospective population-based study. Pain 2008;137:147–55.

[26] Bolling-Sternevald E, Aro P, Ronkainen J, Storskrubb T, Talley NJ, Junghard O, et al. Do gastrointestinal symptoms fluctuate in the short-term perspective? The Kalixanda study. Dig Dis 2008;26:256–63.

[27] Choi YJ, Kim N, Yoon H, Shin CM, Park YS, Kim JW, et al. Overlap between irritable bowel syndrome and functional dyspepsia including subtype analyses. J Gastroenterol Hepatol 2017;32:1553–61.

[28] Steinsvik EK, Valeur J, Hausken T, Gilja OH. Postprandial symptoms in patients with functional dyspepsia and irritable bowel syndrome: Relations to ultrasound measurements and psychological factors. J Neurogastroenterol Motil 2020;26:96–105.

[29] Zamani M, Alizadeh-Tabari S, Zamani V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. Aliment Pharmacol Ther 2019;50:132–43.

[30] Wilhelmsen I. Somatization, sensitization, and functional dyspepsia. Scand J Psychol 2002;43:177–80.

[31] Fischler B, Tack J, De Gucht V, Shkedy Z, Persoons P, Broekaert D, et al. Heterogeneity of symptom pattern, psychosocial factors, and pathophysiological mechanisms in severe functional dyspepsia. Gastroenterology 2003;124:903–10.

[32] Yao X, Yang YS, Cui LH, Sun G, Peng LH, Wang WF, et al. The overlap of upper functional gastrointestinal disorders with irritable bowel syndrome in Chinese outpatients: A multicenter study. J Gastroenterol Hepatol 2016;31:1584–93.

[33] Black CJ, Yuan Y, Selinger CP, Camilleri M, Quigley EMM, Moayyedi P, et al. Efficacy of soluble fibre, antispasmodic drugs, and gut–brain neuromodulators in irritable bowel syndrome: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol 2020;5:117–31.

[34] Black CJ, Burr NE, Camilleri M, Earnest DL, Quigley EMM, Moayyedi P, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: systematic review and network meta-analysis. Gut 2020;69:74–82.

[35] Black CJ, Burr NE, Quigley EMM, Moayyedi P, Houghton LA, Ford AC. Efficacy of

Secretagogues in Patients With Irritable Bowel Syndrome With Constipation: Systematic Review and Network Meta-analysis. Gastroenterology 2018;155:1753–63.

[36] Black CJ, Thakur ER, Houghton LA, Quigley EMM, Moayyedi P, Ford AC. Efficacy of psychological therapies for irritable bowel syndrome: Systematic review and network meta-analysis. Gut 2020;69.8:1441-1451.

[37] Ford AC, Moayyedi P, Black CJ, Yuan Y, Veettil SK, Mahadeva S, et al. Systematic review and network meta-analysis: efficacy of drugs for functional dyspepsia. Aliment Pharmacol Ther 2021;53.1:8-21.