Assessing the Burden of Irritable Bowel Syndrome in the United Kingdom

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CHAPTER 1: Introduction

- **Goodoory VC**, Ng CE, Black CJ, Ford AC. Prevalence and impact of faecal incontinence among individuals with Rome IV irritable bowel syndrome. *Aliment Pharmacol Ther*. 2023;57(10):1083-92. The first author conducted the literature search, collected the data, undertook all analyses, and wrote the manuscript, following which it was critically reviewed by the remaining authors.
- **Goodoory VC**, Ng CE, Black CJ, Ford AC. Editorial: faecal incontinence is prevalent in IBS, as are effective treatment options! Authors' reply. *Aliment Pharmacol Ther*. 2023;57(10):1176-7. The first author wrote the manuscript following which it was critically reviewed by the remaining authors.
- **Goodoory VC**, Ng CE, Black CJ, Ford AC. Letter: determining priorities for patients with faecal incontinence and irritable bowel syndrome-authors' reply. *Aliment Pharmacol Ther*. 2023;58(1):139-40. The first author wrote the manuscript following which it was critically reviewed by the remaining authors.
- **Goodoory VC**, Ng CE, Black CJ, Ford AC. Prevalence and impact of faecal incontinence among individuals with Rome IV irritable bowel

syndrome. The first author presented the results as a poster presentation at *Digestive Disease Week*, 2023.

- **Goodoory VC**, Ford AC. Antibiotics and Probiotics for Irritable Bowel Syndrome. *Drugs*. 2023;83(8):687-99. The first author wrote the manuscript following which it was critically reviewed by the remaining author.
- **Goodoory VC**, Khasawneh M, Black CJ, Quigley EMM, Moayyedi P, Ford AC. Efficacy of Probiotics in Irritable Bowel Syndrome: Systematic Review and Meta-analysis. *Gastroenterology*. 2023;165(5):1206-18. The first author was jointly involved in the literature search, data collection, and analyses, and critically reviewed the final draft of the manuscript.
- Khasawneh M, Shaikh FA, Ng CE, Black CJ, **Goodoory VC**, Ford AC. Utility of irritable bowel syndrome subtypes and most troublesome symptom in predicting disease impact and burden. *Neurogastroenterol Motil.* 2024;36(4):e14756. The highlighted joint last author conducted the literature search, collected the data, undertook all analyses, and co-authored the manuscript following which it was critically reviewed by the remaining authors.
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- **Goodoory VC**, Khasawneh M, Thakur ER, Everitt HA, Gudleski GD, Lackner JM, et al. Effect of Brain-Gut Behavioural Treatments on Abdominal Pain in Irritable Bowel Syndrome: Systematic Review and

Network Meta-Analysis. Gastroenterology. 2024;167(5):934-43 e5. The first author was jointly involved in the literature search, data collection, and analyses, and critically reviewed the final draft of the manuscript.

CHAPTER 3: Assessing the impact of IBS on work and activities of daily living.

- **Goodoory VC**, Ng CE, Black CJ, Ford AC. Impact of Rome IV irritable bowel syndrome on work and activities of daily living. *Aliment Pharmacol Ther*. 2022;56(5):844-56. The first author conducted the literature search, collected the data, undertook all analyses, and wrote the manuscript, following which it was critically reviewed by the remaining authors.
- **Goodoory VC**, Ng CE, Black CJ, Ford AC. Editorial: work and activity impairment are important considerations to optimise treatment plans for irritable bowel syndrome. Authors' reply. *Aliment Pharmacol Ther*. 2022;56(5):894-5. The first author wrote the manuscript following which it was critically reviewed by the remaining authors.
- **Goodoory VC**, Ng CE, Black CJ, Ford AC. Impact of Rome IV irritable bowel syndrome on work and activities of daily living. The first author presented the results as a moderated poster presentation at *United European Gastroenterology Week*, 2022. The first author won the best abstract presentation in outcomes in functional gastrointestinal disease.

CHAPTER 4: Assessing the quality of life of individuals with IBS.

- **Goodoory VC**, Guthrie EA, Ng CE, Black CJ, Ford AC. Factors associated with lower disease-specific and generic health-related quality of life in Rome IV irritable bowel syndrome. *Aliment Pharmacol Ther.* 2023;57(3):323-34. The first author conducted the literature search,

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CHAPTER 5: Assessing the willingness to accept medication risks among individuals with IBS.

- **Goodoory VC,** Ng CE, Black CJ, Ford AC. Willingness to accept risk with medication in return for cure of symptoms among patients with Rome IV irritable bowel syndrome. *Aliment Pharmacol Ther*. 2022;55(10):1311-9. The first author conducted the literature search, collected the data, undertook all analyses, and wrote the manuscript, following which it was critically reviewed by the remaining authors.
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CHAPTER 6: Estimating the direct healthcare cost of IBS in the UK.

- **Goodoory VC**, Ng CE, Black CJ, Ford AC. Direct healthcare costs of Rome IV or Rome III-defined irritable bowel syndrome in the United Kingdom. *Aliment Pharmacol Ther*. 2022;56(1):110-20. The first author conducted the literature search, collected the data, undertook all analyses,

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- **Goodoory VC**, Ng CE, Black CJ, Ford AC. Direct healthcare costs of Rome IV or Rome III-defined irritable bowel syndrome in the United Kingdom. The first author presented the results as an oral presentation at *United European Gastroenterology Week*, 2022.

CHAPTER 7: Assessing whether individuals with Rome IV IBS have a different prognosis to those with Rome III IBS in terms of future gastrointestinal and psychological symptoms.

- **Goodoory VC**, Houghton LA, Yiannakou Y, Black CJ, Ford AC. Natural History and Disease Impact of Rome IV Vs Rome III Irritable Bowel Syndrome: A Longitudinal Follow-Up Study. *Clin Gastroenterol Hepatol*. 2022;20(3):569-77 e3. The first author conducted the literature search, was jointly involved in analyses, and wrote the manuscript, following which it was critically reviewed by the remaining authors.

CHAPTER 8: Assessing the impact of psychological comorbidity on the prognosis of IBS.

- **Goodoory VC**, Mikocka-Walus A, Yiannakou Y, Houghton LA, Black CJ, Ford AC. Impact of Psychological Comorbidity on the Prognosis of Irritable

Bowel Syndrome. *Am J Gastroenterol*. 2021;116(7):1485-94. The first author conducted the literature search, was jointly involved in analyses, and wrote the manuscript, following which it was critically reviewed by the remaining authors.

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My own contributions, fully and explicitly indicated in the thesis, have been:

- Design of all study protocols
- Conducting literature searches
- Data collection and database construction
- Statistical analysis of data
- Drafting of all manuscripts; first author of all published articles relating to results chapters
- Design and drafting of thesis

The other members of the group and their contributions have been as follows:

- Assistance in study protocol design (CJB, ACF, and LAH)
- Assistance in database construction (CJB, ACF, and LAH)
- Assistance in analysing data (CJB, ACF, and EAG)
- Critical review of drafted manuscripts for publication (CJB, ACF, EAG, LAH, AM-W, CEN, and YY)

Abstract

Introduction: Irritable bowel syndrome (IBS) does not seem to confer an increased mortality risk but the burden of the disorder on individuals, the health service, and society seems to be substantial. The aim of this thesis was to examine these issues.

Methods: In cross-sectional surveys recruiting individuals with IBS from the community, the impact of IBS on work and activities of daily living, the quality of life of individuals with IBS, the willingness to accept risk with medication in return for symptom cure, and the annual direct healthcare cost of IBS in the UK were examined. In two longitudinal follow-up studies in a separate cohort of individuals with IBS, the impact of a change from Rome III to Rome IV criteria for IBS, and the cumulative effect of psychological comorbidity on the prognosis of the disorder were assessed.

Results: In total, 752 participants with Rome IV-defined IBS were recruited from the community. Individuals with IBS reported a substantial impact of IBS on work leading to absenteeism and loss of work productivity, and reported interference of their symptoms with activities of daily living. Quality of life among those with Rome III or IV IBS was comparable with chronic organic conditions and was poorer amongst those with more severe gastrointestinal and psychological symptoms. A standard gamble demonstrated that individuals with Rome IV IBS were willing to accept a median 2% risk of death from a hypothetical medication in return for a 98% chance of permanent cure of their IBS. The mean annual direct healthcare cost of IBS was estimated to be between £1.2 billion and £2 billion. The two longitudinal follow-up studies demonstrated that those with Rome

IV IBS, compared with those with Rome III IBS, and those with more psychological comorbidities have a worse prognosis.

Conclusion: IBS causes substantial burden to the individual, the health service, and society. Quantifying this accurately provides a strong mandate for adequate funding into IBS research. Changes in clinical practice, such as making a positive diagnosis of IBS, routine psychological assessments, and earlier introduction of brain-gut behavioural therapy, may help reduce the burden of IBS.

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Glossary of Terms

5-HT	5-hydroxytryptamine
ACG	American College of Gastroenterology
ANOVA	one way analysis of variance
BAD	bile acid diarrhoea
BDA	British Dietetic Association
BGBT	brain-gut behavioural therapy
BSFS	Bristol stool form scale
BSG	British Society of Gastroenterology
CBT	cognitive behavioural therapy
CI	confidence interval
CPSS	Cohen perceived stress scale
CRP	C-reactive protein
DGBI	disorder of gut-brain interaction
DRE	digitial rectal examination
EPS	epigastric pain syndrome
ESR	erythrocyte sedimentation rate
FBC	full blood count
FDA	Food and Drug Administration
FODMAP	fermentable oligosaccharides, disaccharides, monosaccharides, and polyols

GDH	gut-directed hypnotherapy
GFD	gluten-free diet
GP	general practitioner
HADS	hospital anxiety and depression scale
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhoea
IBS-M	irritable bowel syndrome with mixed stool pattern
IBS-QOL	irritable bowel syndrome quality of life
IBS-SSS	irritable bowel syndrome severity scoring system
IBS-U	irritable bowel syndrome unclassified
IL	interleukin
IQR	interquartile range
LR	likelihood ratio
MDCP	multi-dimensional clinical profile
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
OTC	over the counter

PDS	postprandial distress syndrome
PEG	polyethylene glycol
PHQ-12	patient health questionnaire-12
PHQ-15	patient health questionnaire-15
PI-IBS	post-infection IBS
PPI	proton pump inhibitor
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SeHCAT	23-seleno-25-homotaurocholic acid
SIBO	small intestinal bacterial overgrowth
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TNF-α	tumour necrosing factor alpha
UK	United Kingdom
USA	United States of America
VSI	visceral sensitivity index
WPAI: IBS	work productivity and activity impairment questionnaire for irritable bowel syndrome
WSAS	work and social adjustment scale

Chapter 1 Introduction

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction (DGBI), affecting between 5% and 10% of the world's population. IBS is characterised by recurrent abdominal pain in association with a change in stool form and/or frequency. It disproportionately affects women and younger individuals and, for most people, is a chronic illness with a relapsing and remitting course. Although several mechanisms, including motility disturbances, visceral hypersensitivity, altered mucosal barrier and immune function, gut microbiota, and central nervous system processing may be involved in IBS, the underlying pathophysiological processes are complex and incompletely understood. It is also well recognised that mood and psychological health play an important role in the development and persistence of IBS symptoms, which has led the Rome Foundation to reclassify IBS from a functional gastrointestinal disorder to a DGBI.

A diagnosis of IBS is reached in individuals with typical symptoms in the absence of red flags and with limited investigations. Clinicians are aided by symptom-based criteria proposed by the Rome Foundation, the latest iteration being the Rome IV criteria for IBS, although they are only applied strictly in research. Because a diagnosis is made based on symptoms reported by patients, it is likely that individuals with IBS form a heterogenous group with different underlying pathophysiological abnormalities that cause similar symptoms of abdominal pain and altered bowel habit. Given that the cause(s) of IBS is yet to be elucidated, targeted treatment is not available and current strategies focus on alleviating the predominant symptom(s) reported by patients. A sensitive and empathetic approach with clear explanation of the condition is recommended to build a trusting doctor-patient relationship.

IBS does not seem to confer an increased mortality risk. However, it is reported to affect individuals' quality of life to a substantial degree, similar to

organic diseases such as Crohn's disease. Individuals with IBS report difficulties in carrying out activities of daily living and impairment at work. The embarrassing nature of their gastrointestinal symptoms often leave them fearful or ashamed, especially when they socialise with others outside their home environment. Some individuals also report fear of symptoms such as urgency or faecal incontinence, or of having intimate physical relationships. Patients also report the stigma associated with being diagnosed with a "functional" disease and their friends, relatives, or colleagues may struggle to understand their symptoms given the lack of structural features. In addition, many healthcare professionals attach negative attitudes or perceptions towards patients with IBS, considering them to have a psychiatric illness. These perceptions not only reduce resources allocated to provide healthcare services to these patients but also mean that research in IBS is not a funding priority. In addition, even though novel drugs continue to be developed, access to these is often restricted because of costs to the National Health Service (NHS) or perceived serious adverse events. The high prevalence, chronicity, lack of a cure or effective medications to alleviate symptoms of IBS, and associated physical and psychological comorbidities, mean that healthcare usage and hence, costs of IBS are high.

Previous studies have examined the impact of IBS but the results have been hampered by the use of referral populations, historical definitions of IBS, relatively small sample sizes, and limited assessment of psychological comorbidities. In addition, the only two studies that have attempted to estimate the cost of IBS in the United Kingdom (UK) in the last 20 years have substantial limitations. One of these reported total annual healthcare costs, rather than costs related to IBS specifically. The second included patients with symptoms suggestive, but not diagnostic of, IBS, such as constipation, change in bowel

habit, or abdominal pain in isolation. It is, therefore, important to conduct a contemporary assessment of the impact of IBS on patients, the healthcare system, and on society as a whole to highlight the importance of the condition. The results presented in this thesis regarding the impact of IBS may be helpful in clinical practice, healthcare resource planning, research funding allocation, and drug licensing decision making.

This chapter will provide an overview of IBS, describing the evolving definition, epidemiology, current hypotheses on possible cause(s) of IBS, and natural history of the disorder. The current diagnostic and treatment algorithm for IBS will also be discussed. The literature will be reviewed to examine current knowledge on the impact of IBS on patients, healthcare systems, and society as a whole. This will be the basis to identify gaps in our knowledge, which will provide the rationale for the work (section 1.7) described in this thesis.

1.1 Definition of IBS

IBS is complex and the underlying pathophysiological abnormalities have not yet been delineated clearly. Because of our limited knowledge concerning potential structural or biochemical abnormalities there is no available diagnostic test or biomarker to make a diagnosis of IBS. Nevertheless, these individuals needed to be grouped so that clinicians could identify those with IBS in their own practice and epidemiological, pathophysiological, and clinical research studies could reliably identify them to better understand the condition. Hence, throughout the history of IBS, the definitions used have been based purely on the symptoms experienced and reported by patients.

1.1.1 History of IBS

The first description of IBS-type symptoms appears to be by Dr Powell in 1820 when he reported a disorder characterised by the presence of abdominal pain and the passage of mucus per rectum.[1] Dr Powell later made the critical observation that these individuals experienced gastrointestinal symptoms in the absence of an inflammatory process, which was initially thought to be responsible for these symptoms.[2] Throughout the 19th century, several clinicians described clusters of patients with similar symptoms of abdominal pain and the passage of mucus,[3, 4] summarised by Sir William Osler in 1892 in his seminal book, *The Principles and Practice of Medicine.*[5] Osler described a disease called "mucous colitis" which is "an affection of the large bowel characterised by the production of a very tenacious adherent mucous." He explained that the condition "persists for years, varying extremely from time to time…". Although it was felt that the disorder was primarily triggered by a psychological distress, it was acknowledged that "occasionally errors in diet or dyspepsia precede an outbreak".

During the 1920s, the term colonic spasm was used to describe abdominal discomfort or pain in the absence of an organic pathology. Dr Ryle described a series of 50 patients with colonic spasm who reported lower abdominal pain which worsened with anxiety, smoking, menses, and defaecation.[6] Because of the similarities between mucus colitis and colonic spasm, Dr Ryle and Dr Barker, who were working independently of each other, concluded that they were part of the same entity.[6, 7] The term "irritable colon" also emerged in the 1920s when Jordan and Kiefer, using barium enema, discovered that 30% of the patients seen in gastroenterology outpatient clinics had "colonic musculoneural disturbance" explaining their gastrointestinal symptoms.[8] Despite using different nomenclatures, there were three shared beliefs about this disorder: symptoms originated from the colon, the symptoms were functional in nature with no

identifiable structural abnormality, and the nervous system was dysregulated.[9] Finally, in 1944, the term “irritable bowel syndrome” was first coined and has since replaced all previous terminologies.[10]

1.1.2 Historical definitions of IBS

IBS is characterised by numerous gastrointestinal symptoms including abdominal pain, diarrhoea, constipation, and occasionally bloating with a certain combination of symptoms taken to indicate the presence of IBS. However, some of these symptoms can be attributable to a number of other disorders including other DGBI, coeliac disease, inflammatory bowel disease (IBD), or colorectal cancer.[11] In addition, the individual symptoms alone are neither sensitive nor specific enough to diagnose IBS.[12] For these reasons, there have been several attempts to define IBS using different combinations of symptoms at a varying frequency that can facilitate a diagnosis of IBS.

Chaudhary and Truelove were the first to attempt to define and classify IBS.[13] They defined IBS as pain originating from the colon in association with either diarrhoea or constipation. Individuals were subgrouped into either a spastic colon group, consisting of those with abdominal pain and variable bowel habits, or a painless diarrhoea group, consisting of those with diarrhoea in the absence of abdominal pain. However, this definition was limited by its inability to differentiate between IBS and other organic pathologies.

Manning *et al*., in 1978, were the first to propose symptom-based criteria for the diagnosis of IBS in an attempt to make a positive diagnosis of IBS through careful history taking, instead of exhaustive investigations.[14] These were later known as the Manning criteria and consisted of six symptoms: looser stools at the onset of pain, more frequent bowel movements at the onset of pain, pain eased after bowel movement, visible abdominal distension, mucus *per rectum*,

and a feeling of incomplete bowel emptying. Although only the first four symptoms were statistically more likely to be present in those diagnosed with IBS after investigation compared with those with an organic disease, the more of these symptoms that were present, the more likely it was that patients' gastrointestinal symptoms were attributable to IBS. However, the Manning criteria, although specific, were not sensitive enough to identify those with IBS.[15]

1.1.3 The Rome criteria for IBS

In 1990, the Rome Foundation, a group of experts in functional bowel disorders, proposed symptom-based criteria established based on expert consensus, with reference to the available evidence. These were known as the Rome criteria (now called the Rome I criteria).[16] As further evidence became available and understanding of IBS improved, revisions of these criteria led to the publication of the Rome II (1999),[17] Rome III (2006),[18] and Rome IV (2016) criteria,[19] with the latter being the current gold standard for the diagnosis of IBS. These criteria are accepted widely and used in research, although they are not applied strictly in clinical practice.[20] Most IBS research studies in the last 15 years have used either the Rome III or Rome IV criteria for IBS.

The Rome III criteria define IBS as recurrent abdominal pain or discomfort for at least 3 days per month in association with at least two of the following: improvement of abdominal pain or discomfort with defaecation, onset of abdominal pain or discomfort associated with a change in frequency of stool, or onset of abdominal pain or discomfort associated with a change in form of stool.[18] In addition, these criteria should be fulfilled in the last 3 months, with symptom onset at least 6 months prior to diagnosis. In contrast, the Rome IV criteria removed abdominal discomfort from the definition, increased the threshold for frequency of abdominal pain required to meet criteria for IBS from 3 days per

month to 1 day per week, and recognised that abdominal pain was related to, rather than just relieved by, defaecation.[19] The details of the Rome III and Rome IV criteria for IBS are summarised in Table 1.1. Because of the changes, the characteristics of individuals meeting Rome IV criteria for IBS are different from those meeting Rome III criteria. Several studies have demonstrated that those with Rome IV IBS have more severe IBS symptoms and higher levels of psychological comorbidities.[21-24] The definition of IBS used in studies is, therefore, an important consideration when comparing treatment trials that have used different definitions of IBS. In addition, randomised controlled trials (RCTs) that recruit participants with Rome IV IBS are likely to find that many people who believe they have IBS are ineligible, based on these more restrictive criteria. This may have important implications for new RCT design when the Rome IV criteria are used.

Table 1.1. Rome III and IV criteria for IBS.

Criteria	Symptom-based Definition	Minimum Symptom Duration
Rome III[18]	Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following: 1. Improvement with defaecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form of stool	Symptom onset ≥6 months prior to diagnosis
Rome IV[19]	Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with two or more of the following criteria: 1. Related to defaecation 2. Associated with a change in frequency of stool 3. Associated with a change in form of stool	Symptom onset ≥6 months prior to diagnosis

The Rome foundation also classified IBS into subtypes based on abnormal stool form, not only to guide investigations and direct drug therapy towards predominant symptoms in clinical practice, but also to aid recruitment of individuals with IBS into research studies, especially those targeting a specific stool pattern.[17-19] Abnormal stool form is identified using the Bristol Stool Form Scale (BSFS) (Table 1.2).[25] The four subtypes of IBS are IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D), IBS with mixed bowel habits (IBS-M), and IBS unclassified (IBS-U). The Rome III criteria defined patients with IBS-C as those experiencing hard or lumpy stools for ≥25% of all bowel movements and loose or watery stools for <25% of all bowel movements and patients with IBS-D as those experiencing loose or watery stools ≥25% of all bowel movements and hard or lumpy stools for <25% of all bowel movements. If both stool forms occurred for ≥25% of all bowel movements, patients were classified as having IBS-M, whereas if there was insufficient abnormality of stool consistency to meet criteria for any of these three subgroups, patients were defined as having IBS-U. The subtypes defined by the Rome IV criteria are similar to the Rome III criteria but in recognition that many patients with IBS have periods of normal bowel movements, the subtyping in the latest iteration, the Rome IV criteria, are based only on days with at least one abnormal bowel movement rather than including all bowel movements. The IBS subtypes based on the Rome III and Rome IV criteria are shown in Table 1.3.

Table 1.2. The Bristol Stool Form Scale.[25]

Type	Description
1	Separate hard lumps like nuts (difficult to pass)
2	Sausage shaped but lumpy
3	Like a sausage but with cracks on its surface
4	Like a sausage or snake, smooth and soft
5	Soft blobs with clear-cut edges (passed easily)
6	Fluffy pieces with ragged edges, a mushy stool
7	Watery, no solid pieces, entirely liquid

Table 1.3. IBS Subtypes according to Rome III and Rome IV criteria.

Criteria	Description
Rome III[18]	• IBS-C: hard or lumpy stools [a] ≥25% and loose (mushy) or watery stools [b] <25% of bowel movements • IBS-D: loose (mushy) or watery stools [b] ≥25% and hard or lumpy stools [a] <25% of bowel movements • IBS-M: hard or lumpy stools [a] ≥25% and loose (mushy) or watery stools [b] ≥25% of bowel movements • IBS-U: insufficient abnormality of stool to meet criteria for IBS-C, IBS-D, or IBS-M [a] Bristol Stool Form Scale 1-2 [b] Bristol Stool Form Scale 6-7
Rome IV[19]	• IBS-C: Bristol stool form types 1 or 2 ≥25% and Bristol stool form types 6 or 7 <25% of bowel movements* • IBS-D: Bristol stool form types 6 or 7 ≥25% and Bristol stool form types 1 or 2 <25% of bowel movements* • IBS-M: Bristol stool form types 1 or 2 ≥25% and Bristol stool form types 6 or 7 ≥25% of bowel movements* • IBS-U: insufficient abnormality of stool to meet criteria for IBS-C, IBS-D, or IBS-M (i.e. Bristol stool form types 1 or 2 <25% and Bristol stool form types 6 or 7 <25% of bowel movements*) *Based only on days with abnormal bowel movements

1.2 Epidemiology of IBS

The recent definitions of IBS with alterations in terminology and varying thresholds for frequency of symptoms have been discussed. Any change in definition affects the prevalence of the condition as the number of people meeting criteria for IBS changes. In order to assess the burden of IBS and to improve outcomes in IBS, it is crucial to understand its epidemiology. For clinicians, it is important to understand how common IBS is and, hence, the probability of a diagnosis when faced with a patient with gastrointestinal symptoms. Healthcare systems should also appreciate the prevalence of the disorder for adequate resource allocation for clinical care and research funding, and a high prevalence should be an impetus for pharmaceutical companies to develop new medications that could potentially be used by many patients around the world.

1.2.1 Global prevalence of IBS

The most up-to-date systematic review and meta-analysis, published in 2020, reported a pooled global prevalence of IBS of 9.2% when the Rome III criteria were used in 53 studies, among 395,385 individuals from 38 countries, and 3.8% with the Rome IV criteria in six studies, among 82,476 individuals from 34 countries.[26] However, the range for IBS prevalence was wide with the lowest being 0.2% in India when the Rome IV criteria were used and the highest being 29.2% when the Rome III criteria were used in Croatia. There was significant heterogeneity between studies in all analyses illustrating the wide variations in methodology, characteristics of participants, or a combination of other factors in these population-based studies. Even when the results were pooled according to whether Rome criteria were strictly applied or approximated using another questionnaire, or whether the questionnaires were self-administered or completed via an interview, the variation in the prevalence of IBS in different

countries persisted. This suggests that there may be a true variation in the prevalence of IBS, an observation that still remains incompletely understood. This may be related to, but not limited to, factors including genetic susceptibility, dietary, environmental, or cultural differences, prevalence of psychological disorders, or differences in symptom reporting based on cultural beliefs.

Another systematic review and meta-analysis, performed by a Rome Foundation working team in 2017, estimated the global prevalence of IBS using the Manning, and the Rome I, II, and III criteria.[27] They reported a significant difference in the prevalence of IBS among countries. However, because of significant heterogeneity between studies, the authors concluded that calculating a global pooled prevalence would not be meaningful. Although both of the aforementioned systematic reviews and meta-analyses included studies from over 40 countries, they highlighted the lack of data from some geographical areas, such as Africa or the Middle East. Because prevalence estimates of IBS are very broad, for reasons discussed previously, it is important to discuss the results of two studies,[28, 29] which although included in the latest systematic review and meta-analysis in 2020,[26] have more meaningful results because of their use of standardised methodology in more than one country.

Palsson *et al.* conducted a population based survey, using an online questionnaire, of 6,300 individuals in the United States of America (USA), Canada, and the UK to estimate the prevalence of functional bowel disorders using both the Rome III and Rome IV criteria.[28] The authors used rigorous methodology to ensure good quality data collection. The overall prevalence of Rome III-defined IBS was 9.0%, ranging from 8.6% in the USA to 9.5% in Canada, with no significant differences between countries. Rome IV-defined IBS was almost half as prevalent as Rome III-defined IBS with an overall prevalence

of 4.6%, ranging from 4.5% in Canada to 4.7% in the USA, with again no significant differences between countries. When examining the cause for a reduction in prevalence of IBS when moving from Rome III to Rome IV, the authors reported that 81% of individuals who failed to meet the stricter Rome IV criteria for IBS did so because of the increase in the abdominal pain frequency threshold, 17% because of the removal of the term “abdominal discomfort”, and the remaining 2% because of the wording change from abdominal pain “related to”, rather than “relieved by”, defaecation. Importantly, although the majority of those who met the Rome III criteria, but not the Rome IV criteria, for IBS met criteria for another Rome IV-defined functional bowel disorder, such as functional diarrhoea, almost 30% did not meet criteria for any functional bowel disorder.

To determine the prevalence of all DGBI, the Rome Foundation conducted a global survey of over 73,000 individuals in 33 countries on six continents.[29] Standardised methodology was used although in a minority of countries where an online survey was not feasible, usually because of poor internet coverage, personal interviews were conducted. Amongst those who completed the online questionnaire, the pooled prevalence of Rome III and Rome IV-defined IBS was 10.1% and 4.1%, respectively. Despite differences in these studies, the key messages are that IBS is common and that there is a reduction in the prevalence of IBS with the use of the more stringent Rome IV criteria for IBS compared with their predecessor.

1.2.2 Prevalence according to IBS subtypes

Because IBS subtypes are used extensively in clinical practice and in research, it is important to understand their prevalence. Oka *et al.* reported, in their systematic review and meta-analysis,[26] the prevalence of IBS subtypes by pooling data from 23 studies which included over 100,000 individuals with Rome

III IBS and two studies which included nearly 7,000 individuals with Rome IV IBS. Among those with Rome III IBS, 20.0% had IBS-C, 27.8% IBS-D, 33.8% IBS-M, and 14.1% IBS-U, whereas among those with Rome IV IBS, 29.3% had IBS-C, 31.5% IBS-D, 26.4% IBS-M, and 11.9% IBS-U. When both Rome III and IV IBS questionnaires were applied simultaneously to the same population in the three-nation study previously discussed,[28] the distribution of IBS subtypes was significantly different between Rome III and IV IBS. When the Rome III criteria were used, 17.9% had IBS-C, 19.8% IBS-D, 59.7% IBS-M, and 2.6% IBS-U. In contrast, when the Rome IV criteria were applied, 28.5% had IBS-C, 35.0% IBS-D, 31.0% IBS-M, and 5.5% IBS-U. Similar subgrouping for IBS-C, IBS-D, and IBS-M using the Rome IV criteria for IBS was demonstrated in the Rome Foundation Global Study.[29]

1.2.3 Prevalence according to age, sex, and ethnicity

The two systematic reviews and meta-analyses discussed previously did not analyse prevalence of IBS according to age.[26, 27] A prior meta-analysis conducted in 2012 demonstrated that the prevalence of IBS, using the Manning, Rome I, II, or III criteria for IBS, decreased modestly with age but did not reach statistical significance.[30] However, the odds of IBS in those aged ≥50 years were significantly lower than those aged <50 years. Using both Rome III and IV criteria for IBS, the Rome Foundation Global Study reported conflicting results on the prevalence of IBS according to age with a decreasing prevalence of IBS with older age in internet-surveyed countries and an increasing prevalence in household-surveyed countries.[29]

Pooling the results from 30 studies reporting the prevalence of Rome III IBS according to sex, Oka *et al.* reported a higher prevalence of IBS in women compared with men (odds ratio (OR) 1.46; 95% confidence interval (CI) 1.33 to

1.59). This meta-analysis did not find any studies reporting prevalence according to sex using the Rome IV criteria. However, the subsequently published Rome Foundation Global Study reported a higher prevalence of Rome IV IBS in women compared with men (OR 1.7; 95% CI 1.5 to 1.9).[29]

The prevalence of IBS according to ethnicity has been less well examined and currently available evidence is based on historical definitions of IBS. One systematic review identified three community studies, using the Manning, Rome I, and II definitions of IBS in Singapore and Malaysia, which demonstrated no difference in IBS prevalence amongst individuals of Chinese, Malay, or Indian ethnicity.[31] A subsequent study recruiting 990 individuals in the USA demonstrated that white individuals were more likely to have IBS based on the Rome II criteria compared with African-Americans (OR 2.5; 95% CI 1.5 to 4.0).[32]

1.3 Pathophysiology of IBS

The pathophysiology of IBS is complex and poorly understood.[33] As discussed previously, individuals with IBS are a group of people with similar symptoms of abdominal pain and altered bowel habit. It is unlikely that there is a single unifying theory to explain the symptoms of all those affected by IBS, meaning that there are likely to be different underlying pathophysiological abnormalities that cause similar gastrointestinal symptoms. IBS is thought to have a biopsychosocial aetiology. Although genetic and epigenetic changes, infection, and childhood adverse life events may predispose an individual to develop IBS, commonly accepted abnormalities include disordered communication between the gut and the brain, altered gastrointestinal transit and motility, changes in the gut microbiome, mucosal inflammation, immune activation, and altered intestinal permeability.[33]

1.3.1 Gut-brain interaction

Regardless of the primary cause of IBS, the central nervous system is thought to receive interoceptive signals from the gut to create the subjective awareness of symptoms.[34] These signals are influenced by emotional factors, such as anxiety and depression, cognitive aspects, such as attention and expectation, and motivational factors. Advances in multimodal brain imaging have enhanced our understanding of gut-brain interactions in DGBI and identified similarities and differences to other chronic painful conditions and psychiatric disorders.[34] Individuals with IBS are known to have altered brain activation in regions involved in cognitive processing and emotional and autonomic responses to visceral and somatic stimuli.[34, 35] These observations align with the symptoms of somatisation and gastro-intestinal symptom-specific anxiety observed in those with IBS.[36]

The autonomic nervous system, which consists of the sympathetic and parasympathetic nervous system, appears to be involved in the pathophysiology of IBS. A reduction in parasympathetic, and an increase in sympathetic, nervous system activity have been described in individuals with IBS.[37] Reduced vagal tone, meaning a reduced parasympathetic nervous system activation, has been shown to increase gut motility, sensitivity, and peripheral inflammation and gut permeability.[38] The vagus nerve also plays a crucial role in interoceptive awareness, enabling it to detect metabolites from the gut microbiota and communicating this to the central nervous system.

1.3.2 Psychological factors

Evidence for the involvement of the gut-brain axis in IBS is further strengthened by clinical research investigating psychological comorbidities in IBS. A meta-analysis examining the prevalence of anxiety or depression in IBS

estimated the prevalence of both anxiety and depression disorders at 23%, whereas the prevalence of anxiety or depression symptoms were higher at 39% and 29%, respectively.[39] Compared with healthy individuals, patients with IBS have a three-fold increased odds of either anxiety or depression.[39] Psychological factors form an important part of the complex biopsychosocial model thought to be responsible for causing and perpetuating symptoms of IBS. In acknowledgement of this, the Rome Foundation developed the multi-dimensional clinical profile (MDCP), a framework allowing clinicians to build a unique profile for each patient based not only on their gastrointestinal symptoms but also taking into account the psychological symptoms and the impact of the illness.[40]

Psychological symptoms may develop as a result of the severity and impact of gastrointestinal symptoms, or may be a risk factor for developing, perpetuating, and exacerbating symptoms of IBS.[41] Two important longitudinal studies have provided the evidence for bi-directional influence of psychological and gastrointestinal symptoms.[42, 43] Amongst individuals without IBS, those with higher levels of anxiety or depression were significantly more likely to develop IBS after 1 year of follow-up.[43] The same observation was demonstrated in another longitudinal study following participants for 12 years strengthening the brain-gut hypothesis.[42] In addition, the gut-brain hypothesis is supported by these studies, which also demonstrate that those with a diagnosis of IBS, but no anxiety or depressive symptoms at baseline, were more likely to report anxiety or depressive symptoms at follow-up.[42, 43]

A recent cross-sectional survey, conducted in 106 patients with IBS, demonstrated a cumulative increase in IBS symptom severity with increasing number of psychological comorbidities.[44] However, there have been no large-

scale studies conducting longitudinal follow-up to examine the cumulative effects of number of psychological comorbidities on the prognosis of individuals with IBS.

1.3.3 Visceral hypersensitivity

Visceral organs, such as the gut, function in health without causing any conscious awareness or pain. Visceral hypersensitivity is an altered sensation in response to a physiological stimulus, usually experienced as pain or discomfort.[45] Using rectal and colonic balloon distension to determine pain or discomfort thresholds, studies have demonstrated that up to 60% of patients with IBS experience visceral hypersensitivity.[46, 47] Although there have been some suggestions that visceral hypersensitivity may be affected by cognitive and emotional factors,[48] this finding is not supported by other studies.[46, 49, 50] One of these studies, conducted in separate patient cohorts in Sweden, Belgium, and the USA demonstrated that there was a gradual increase in gastrointestinal symptom severity with increasing gastrointestinal sensitivity, using colonic and rectal balloon distension, even after adjusting for tendency to report symptoms or presence of comorbid anxiety or depression.[50]

1.3.4 Transit and motility

Gastrointestinal transit and motility abnormalities have been proposed as potential reasons for symptoms of IBS. Disturbances in gut motility in IBS are thought to be characterised by abnormal colonic myoelectric activity,[51] altered small bowel contractions associated with cramping abdominal pain,[52] and alterations in gastrointestinal or colonic transit.[53-55] Patients with IBS-D tend to have increased motility, increased high amplitude propagating contractions of the colon, and faster transit, whereas those with IBS-C tend to have reduced motility, fewer high amplitude propagating contractions of the colon, and delayed transit.[56] Both stool consistency and stool form on the BSFS correlate negatively with

colonic transit.[54] However, other symptoms experienced by patients with IBS, such as abdominal pain and bloating do not correlate with colonic transit time.[54, 55] Finally, gut motility may be influenced by changes in serotonin ((5-hydroxytryptamine (5-HT)) metabolism. Higher levels of postprandial serum 5-HT levels have been reported in those with IBS-D,[57] and lower levels in those with IBS-C.[58-60]

1.3.5 Gut microbiome

In the last two decades, the role of the gut microbiome in IBS has attracted considerable scientific interest. There are several indicators that the gut microbiota may be implicated in the pathophysiology of IBS.[61] The best known aetiological factor for IBS is the development of symptoms following an acute enteric infection,[62, 63] which is commonly referred to as post-infection IBS (PI-IBS). The faecal microbiota of those with PI-IBS is different from that of healthy controls but similar to those with IBS-D, suggesting that PI-IBS and IBS-D may share a common pathophysiology.[64] A large proportion of patients with IBS experience meal-related symptoms and IBS symptoms are often triggered by specific food items.[65, 66] As diet is known to modify the gut microbiome, even in the short term,[67] this raises the possibility of the microbiome being involved in IBS. A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) has been shown to reduce global IBS symptoms in RCTs.[68] This improvement in symptoms, as demonstrated in a recent study analysing the clinical response and changes in microbiota in patients with IBS and a household control, may be because a low FODMAP diet induces a shift of the profile of the faecal microbiota in some patients with IBS towards one similar to that of healthy individuals.[69]

Antibiotics and probiotics have also been used with varying success to improve symptoms of IBS by modifying the composition of the gut microbiota.[70-72] Although the use of broad spectrum antibiotics may also be associated with the development of IBS,[73] rifaximin, an antibiotic that remains largely unabsorbed by the gut, leads to improvement of IBS symptoms in some patients.[74, 75] Another indication that the gut microbiota may be involved is the potential association between small intestinal bacterial overgrowth (SIBO) and IBS,[76-78] with treatment for presumed SIBO leading to an improvement in IBS symptoms in some patients.[79] Finally, faecal microbiota transplantation may be beneficial in the treatment of IBS,[80] with symptom improvement sustained up to 3 years in one RCT,[81] further supporting involvement of the gut microbiota in IBS. Despite rapid advances made in the ability to examine the microbiota,[82] there is still no clear evidence of a specific, reproducible, microbial profile of individuals with IBS.[83, 84]

1.3.6 Mucosal inflammation, immune regulation, and epithelial permeability

Low grade mucosal inflammation and immune activation may also play a role in the pathogenesis of IBS. Histological analysis of the gut, particularly the descending and sigmoid colon, rectum, and small bowel, have demonstrated an increased number of mast cells.[85-87] In addition, some patients with IBS-D and PI-IBS have mast cell hyperplasia.[85, 88] Despite conflicting results from different studies,[89, 90] activated mast cells located close to nerve endings may play a role in causing visceral hypersensitivity and hence, abdominal pain in IBS.[91] Cytokines, which are known to be involved in inflammation and regulation of immune cells in IBD, may have a role in the pathophysiology of IBS. Individuals with IBS have higher levels of inflammatory cytokines interleukin (IL)-6 and IL-8 as well as tumour necrosing factor alpha (TNF-α).[85] Those with IBS-D and PI-IBS

also have lower levels of an anti-inflammatory cytokine IL-10, which apart from being an important regulator of TNF-α, is also associated with anxiety and depression.[92]

Low grade mucosal inflammation is also known to increase intestinal permeability, which may have a role in the pathophysiology of IBS.[93] Mast cell activation is associated with a reduction in tight junction proteins, which are essential to maintain adjacent mucosal cells together, in patients with IBS-D.[94] This defect in the physical integrity of the mucosa may increase intestinal permeability.[95] Amongst those with IBS-D and PI-IBS, increasing permeability has been associated with more severe IBS symptoms and worse visceral hypersensitivity.[96-99]

1.3.7 Genetic and epigenetic changes

Genetic mechanisms also appear to be important in IBS.[100, 101] Studies have observed familial aggregation of IBS, which may be due to genetic and shared environmental factors, including childhood experiences.[102, 103] Twin studies comparing monozygotic and dizygotic twins have demonstrated conflicting results suggesting that there is no single gene associated with the symptom phenotype of IBS.[104-106] Several studies have examined the role of single nucleotide polymorphisms in modulating the function of various components across the gut-brain axis, including ion channel function, neurotransmitter synthesis, receptor function, or inflammatory barrier function.[100, 101] For example, the *SLC6A4* gene encoding the 5-HT reuptake transporter,[107] the *CNR1* gene encoding the cannabinoid receptor,[108, 109] and the *TNFSF15* gene encoding TL1A, a member of the TNF ligands expressed primarily in macrophages and T cells,[110] have all been reported to be associated with IBS.

Although improving, our understanding of the role of genetics in IBS is somewhat limited and, hence, it has limited implications outside of research studies.

1.4 Natural history of IBS

For most individuals, IBS is a chronic illness with a relapsing and remitting course. It is important to consider the natural history, especially the chronicity, of IBS when examining the impact of the disease on individuals, the health service, and society. One population-based study showed that only 61.3% of people meeting the Rome III or IV criteria for IBS consulted a doctor for symptoms of IBS.[28] This is important, as most studies examining the impact of IBS recruit participants from referral population, meaning that the full impact of the disorder may not always be captured.

A 10-year longitudinal follow-up study recruited and successfully followed-up nearly 4,000 individuals with IBS, defined using the presence of a minimum of three Manning criteria, from primary care in the UK.[111] It demonstrated that amongst those with IBS at baseline, approximately two-thirds reported persistent symptoms at 10-year follow-up whereas amongst those without IBS at baseline, 15% had new onset IBS at 10 years with, therefore, a presumed incidence of 1.5% per year. IBS also fluctuates to other functional bowel disorders. One longitudinal study, recruiting individuals with IBS from the community, showed that amongst those with Rome IV-defined IBS at baseline, around 30% fluctuated to another functional bowel disorder at 12 months.[112] This observational study also reported that fluctuation to another functional bowel disorder was more likely in those who had commenced a new treatment for IBS during those 12 months. The authors also reported that, amongst those with Rome IV IBS at baseline, severity of IBS severity, measured using the IBS Severity Scoring System (IBS-SSS),[113] fluctuated in 42.4% of those in remission or with mild symptoms, 47.5%

of those with moderate symptoms, and 30.7% of those with severe symptoms at baseline during longitudinal follow-up. Finally, this study also demonstrated that in those with IBS at baseline and at follow-up, IBS subtypes fluctuated with IBS-M being the least stable subtype.[112]

Individuals with IBS are more likely to have other comorbidities. For example, IBS may co-exist with other DGBI,[114] with overlap and fluctuation of symptoms frequently observed.[115, 116] As previously discussed, IBS is also associated with poor psychological health,[117] although it is still unclear whether this is a cause or a sequelae of the gastrointestinal symptoms.[42, 43] Although anxiety and depression are more common in individuals with IBS, there are other psychological comorbidities, such as stress, somatic symptom disorder, and gastrointestinal symptom-specific anxiety, which not only co-exist with IBS,[118, 119] but are also associated with more severe gastrointestinal symptoms.[44, 120-122] IBS is associated with other conditions that are considered to be “medically unexplained”, such as chronic fatigue syndrome[123] and fibromyalgia.[124] Perhaps more worryingly, IBS is also associated with an increased likelihood of having undergone surgical procedures such as cholecystectomy, hysterectomy, or appendicectomy, likely due to misattribution of abdominal symptoms.[125] Despite this, two large population-based studies have demonstrated that IBS does not seem to confer any mortality risk.[126, 127]

Given the chronicity of IBS, lack of a cure, and the nature of IBS symptoms, individuals report impairments in quality of life, which has been the subject of multiple previous studies.[128-139] It is also reported to affect individuals’ quality of life to a substantial degree, similar to organic diseases such as Crohn’s disease.[128]

1.5 Diagnosing IBS

A diagnosis of IBS has traditionally been viewed as a diagnosis of exclusion, meaning that clinicians would exclude an extensive array of organic diseases before diagnosing IBS. Although there has been a slow shift towards making a positive diagnosis of IBS, some clinicians still adhere to this framework.[140] Several factors may contribute to the persistence of this approach, including fear of missing important organic pathologies, a lack of education about, and confidence in, managing patients with IBS,[141] or reluctance of some patients to accept a diagnosis of IBS because of the perceived stigma associated with it.[142] Current guidelines recommend making a positive diagnosis of IBS in patients with typical symptoms in the absence of red flag symptoms and after limited investigations.[143-145] It is, therefore, important to review the literature on the diagnosis of IBS as it is an important consideration when discussing the burden of managing patients with IBS.

1.5.1 Symptom criteria and clinical presentation

As discussed, the Rome IV criteria are the current gold standard criteria for diagnosing IBS. One study conducted in a single secondary care centre validated the Rome IV criteria in patients with IBS in routine clinical practice.[146] The sensitivity and specificity of the Rome IV criteria for IBS were 82.4% and 82.9% respectively. Perhaps more interestingly, the positive likelihood ratio (LR) of the Rome IV criteria for IBS was 4.82 (95% CI 3.30 to 7.28), meaning if a patient with suspected IBS meets the Rome IV criteria, they are nearly five times more likely to have IBS than to not have IBS. The likelihood ratio was the highest amongst patients with IBS-C (LR = 25.7; 95% CI 5.07 to 145), followed by those with IBS-M (LR = 10.6; 95% CI 3.39 to 38.2), and then those with IBS-D (LR = 2.07; 95% CI 1.48 to 3.12). This is because most of the false positives with

organic disease, such as bile acid diarrhoea (BAD) or microscopic colitis, were found in the IBS-D group. During a mean follow-up of 4 years in this same cohort of patients, 1 in 6 were re-referred for ongoing IBS or other gastrointestinal symptoms.[147] More than two-thirds of those referred were re-investigated, but only 1% were diagnosed subsequently with an organic gastrointestinal disease that may have been missed at their initial presentation. Hence, making a positive diagnosis of IBS in the presence of typical symptoms, limited investigations, and absence of red flags combined with diagnostic criteria is safe and the yield of further investigation for the same or similar symptoms is very low.

In order to meet the definition of Rome IV IBS, strict symptom-based criteria need to be met.[19] Although these are necessary for research purposes, they are often not used in clinical practice, especially in primary care. Applying these criteria in clinical practice would mean that a number of patients with troublesome IBS-type symptoms would be left without a clear diagnosis increasing the uncertainty about the cause of their symptoms and management. In the clinical setting, the more pragmatic definition of IBS, focusing on abdominal pain or discomfort associated with altered stool frequency or form for at least 6 months, in the absence of alarm symptoms or signs, endorsed by the National Institute for Health and Care Excellence (NICE) may be preferable.[145] In recognition of these pitfalls, the Rome Foundation have issued more recent guidance for the use of the Rome IV criteria in clinical practice.[20] As long as the nature of the symptoms corresponds to those of IBS, the symptoms are bothersome and interfering with activities of daily living, and other diagnoses have been ruled out based on the history and additional limited investigations as required, a shorter duration of symptoms of 8 weeks, rather than 6 months, can be used in clinical practice.

There are other individuals with IBS who may have had symptoms for a long time before seeking medical attention and some who may never see a clinician for their IBS symptoms. Although IBS is probably heterogenous in terms of the underlying pathophysiology, because symptom-based criteria are used to define IBS, there are some typical features that are commonly observed. In addition to the cardinal features of abdominal pain associated with a change in stool frequency and/or form, individuals often experience abdominal bloating and/or visible abdominal distension.[148, 149] In one cross-sectional survey recruiting over 800 individuals with Rome IV IBS, more than half of the participants had abnormal anxiety or somatisation scores, 40% had abnormal scores for gastrointestinal-specific anxiety, and one in four had abnormal depression scores, highlighting the high prevalence of psychological symptoms.[21] Because similar gastrointestinal symptoms can be present in colorectal cancer, IBD, coeliac disease, BAD, or microscopic colitis, a careful history is required to differentiate IBS from these other conditions.

Exclusion of red flag symptoms, such as unexplained rectal bleeding or weight loss, which raise concerns for possible colorectal cancer, is required in IBS. Patients with any of these symptoms should be referred for urgent lower gastrointestinal investigations as per NICE guidance.[150] It is important to enquire about other aspects of the history to identify risk factors for mimics of IBS.[151] An individual who has had cholecystectomy or right hemicolectomy may have BAD rather than, or in addition to, IBS. A family history of IBD, coeliac disease, or colorectal cancer may also be relevant. A careful medication history, including over the counter (OTC) medications, is important. For example, proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs (NSAIDs), or selective serotonin reuptake inhibitors (SSRIs) are known risk factors for microscopic

colitis. The use of opioids may suggest opioid-induced constipation, rather than IBS-C or IBS-M, whereas diarrhoea is often a side-effect of several medications, such as metformin.

Although there are no physical findings to support a diagnosis of IBS, a physical examination, including a digital rectal examination (DRE), is helpful in excluding other medical conditions. The presence of an abdominal or rectal mass, for instance, requires further investigation for a possible colorectal cancer.[150] A DRE is useful to diagnose anal fissures or haemorrhoids, as well as paradoxical anal contraction on straining, which is observed in those with dyssynergic defaecation.[152]

1.5.2 Investigations

As previously discussed, guidelines recommend making a positive diagnosis of IBS using limited investigations.[143-145] One RCT recruited 302 patients with Rome III-defined IBS to investigate the impact of making a positive diagnosis of IBS compared with a strategy of exclusion, in which patients underwent standardised investigation.[153] The strategy of exclusion had a low yield for organic pathology and was associated with increased costs, but had similar outcomes to the group randomised to a positive diagnostic strategy in terms of symptom severity and patient satisfaction at 4 weeks and 1 year after randomisation. In a follow-up study of these patients 5 years later,[154] there were no new cases of coeliac disease, or gastrointestinal or gynaecological malignancy. The proportion of those later diagnosed with IBD, upper gastrointestinal disorders, or benign gynaecological conditions were similar and negligible in both groups. From 1 to 5 years after randomisation, there was a significantly higher proportion of participants who underwent at least one lower gastrointestinal endoscopy in the positive strategy group compared with the

exclusion group (23 (16%) vs. 13 (11%), $p = 0.03$). However, the positive strategy group still had a lower number of unnecessary endoscopies over 5 years because all those in the exclusion group underwent lower gastrointestinal endoscopy before a diagnosis of IBS was made.

Other than full blood count (FBC), C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), and coeliac serology, there is little evidence to suggest that other blood tests, including thyroid function tests, are helpful.[151, 155] A systematic review and meta-analysis demonstrated that those with IBS were almost three times more likely to have abnormal coeliac serological tests compared with controls (OR 2.75; 95% CI 1.35 to 5.61).[156] Another meta-analysis showed that a CRP <0.5 mg/dL yielded a <1% risk of having IBD, with ESR being less useful.[157] A FBC is also important to identify those with anaemia and, although the yield of organic disease using a panel of routine bloods is low in those with IBS, it is a reasonable screening tool to exclude organic gastrointestinal disease.

In those with diarrhoea, it is important to differentiate between IBD and IBS-D. Although a colonoscopy is the gold standard investigation for IBD, it is invasive, time-consuming, expensive, not always desirable to some patients and, perhaps more importantly, has a low yield for organic disease in those with typical symptoms of IBS in the absence of alarm symptoms.[158] Faecal calprotectin, a cytosol protein released by neutrophils, can be detected in the stool and is a non-specific marker of inflammation. In a meta-analysis of six studies, including 670 adults, assessing diagnostic accuracy of faecal calprotectin in IBD, the pooled sensitivity and specificity were 93% and 96% respectively.[159] The authors estimated that even though screening patients using faecal calprotectin would lead to a delayed diagnosis of IBD in a minority of patients due to false negatives,

this strategy would lead to a 67% reduction in the number of colonoscopies required. A study conducted in primary care in the UK estimated that using a faecal calprotectin cut-off <100 mcg/g in patients with normal routine blood tests, and who were not suspected to have gastrointestinal cancer, identified IBS with 98% certainty.[160] Those with a faecal calprotectin of 100-249 mcg/g required repeated testing, with a subsequent referral to secondary care if persistently elevated, and those with a faecal calprotectin ≥250 mcg/g required a referral to secondary care to exclude IBD. This pathway has now been adopted by NICE and is estimated to save between £100,000 and £160,000 per 1000 faecal calprotectin tests requested.[161] However, faecal calprotectin is not specific to IBD, but can be elevated in a number of other scenarios, including NSAID or PPI use, age ≥45, gastrointestinal infections, and malignancy. Hence, it should be interpreted with caution and should only be performed in individuals aged <45 years with chronic diarrhoea to differentiate between IBS-D and IBD.

Although colonoscopy is often performed in patients with IBS,[162, 163] it imposes a substantial burden on both patients, due to bowel preparation, lost hours of work, and the invasive nature of the test, and the health service, because of the extensive resources required and cost implications. The recommendation for an urgent colonoscopy is reserved for patients with alarm symptoms.[143-145] However, over 70% of patients with IBS reported at least one alarm symptom and the positive predictive value of individual alarm symptoms for identifying organic gastrointestinal disease is low.[164, 165] Not surprisingly, therefore, the yield of colonoscopy in individuals with suspected IBS is low. A prospective case-control study, recruiting 466 patients with suspected non-constipated IBS without alarm symptoms, demonstrated similar prevalence of structural abnormalities to healthy individuals undergoing colonoscopy for colorectal cancer screening or polyp

surveillance.[166] Another study with over 4000 individuals with lower gastrointestinal symptoms undergoing colonoscopy demonstrated that those meeting the Rome III criteria for IBS had similar prevalence of organic disease compared with those who did not.[167] Apart from those with symptoms concerning for colorectal cancer and those with persistently raised faecal calprotectin, colonoscopy should be considered to exclude microscopic colitis in individuals with IBS-D. This is especially important for those with risk factors for microscopic colitis which include female sex, age ≥50 years, coexistent autoimmune disease, nocturnal or severe watery diarrhoea, duration of diarrhoea <12 months, weight loss, or use of potential precipitating drugs including NSAIDs, PPIs, SSRIs, or statins.[168, 169]

Other investigations that may be considered in those with IBS are a 23-seleno-25-homotaurocholic acid (SeHCAT) scan for those with IBS-D, and anorectal physiological tests for those with symptoms suggestive of a pelvic floor disorder. BAD can be diagnosed using a SeHCAT scan, although this is not universally available.[170] A systematic review and meta-analysis conducted in 2015 estimated the prevalence of BAD amongst patients with IBS-D to be almost 30%,[171] with the prevalence rate being similar in those with Rome IV defined IBS-D in a subsequent study.[172] It is important to make a diagnosis of BAD, as it can be treated effectively with bile acid sequestrants, especially in those with moderate or severe BAD.[173] Some clinicians advocate a trial of bile acid sequestrants in those with suspected BAD but this approach is not recommended.[174] This is because a therapeutic trial may miss a diagnosis of BAD, as one study demonstrated that up to 44% of patients with BAD, confirmed using a SeHCAT scan, failed to respond to colestyramine.[175] Clinicians should also consider anorectal physiological tests for those with symptoms of anorectal

dysfunction. The prevalence of anorectal dysfunction is estimated to be as high as 40% in those with IBS and affects individuals with all IBS subtypes.[176-178] Symptoms of anorectal dysfunction include straining on passing stools, the feeling of incomplete or blocked evacuation, or the need to use digital manoeuvres to aid defaecation. These symptoms can occur on their own, or co-exist with IBS or another functional bowel disorder. Symptoms alone cannot distinguish these entities and the underlying pathophysiology is complex and likely to be multifactorial.[176, 177, 179] A diagnosis of dyssynergic defaecation can be reached if abnormalities are detected in two of three tests, namely anorectal manometry, balloon expulsion test, and defaecating proctogram.[180] It is important to identify anorectal dysfunction in patients with IBS as pelvic floor biofeedback therapy may improve not only anorectal function, but also abdominal pain associated with IBS.[181-184]

1.6 Treatment of IBS

In order to assess the burden of IBS, it is important to consider the management of the disorder, in particular the limitations of current treatment strategies. As previously discussed, IBS is diagnosed based on patient-reported symptoms and it is likely that there are several underlying pathophysiological abnormalities. Because of an incomplete understanding of the aetiology, the current treatment approach is to alleviate patients' most troublesome symptom(s) instead of addressing the underlying cause. The efficacy of most therapies in IBS is modest when tested in RCTs.[68, 72, 185-188] Partly as a result of these issues, IBS is incurable and is a chronic illness with a relapsing and remitting course,[111] leading to high consultation rates,[111] multiple unnecessary investigations,[189] and trials of different therapies. In addition to these challenges, there is no biomarker through which clinicians can assess treatment response, leaving them to rely

solely on patient-reported outcome measures. Novel drugs in IBS can be expensive and may not be available to all whether through private funding, insurance policies, or public sector funding. When considering the treatment of IBS, particularly for those with severe or refractory symptoms, it is important to also consider the risks associated with medication that individuals with IBS are willing to accept. Previous studies have examined this issue but have important limitations, including the fact that none of them examined the predictors of a higher acceptance of medication-related risk among individuals with IBS.[190-193]

1.6.1 Communication

Over the last few decades, the doctor-patient relationship has been under strain for several reasons including the increasing demand on clinician time for documentation and other administrative tasks, the introduction of electronic healthcare records, the reduction in face-to-face appointments, and revalidation requirements for clinicians.[194] This means that clinicians have less time to undertake a comprehensive history and examine patients, potentially affecting the relationship between them and their patients. In several qualitative studies, individuals with IBS report that they feel unsupported, isolated, and even alienated from their care providers.[195-199] They also feel that they do not receive enough information about their condition leaving them frustrated about their inability to understand how to manage their symptoms and obtain medical validation of the condition.[196, 198] However, this frustration may also be because of the unrealistic expectations from some patients looking for a cure for their symptoms.[200] In addition, there are many misconceptions about IBS among both patients and doctors. For instance, one study demonstrated that one in seven patients with IBS believed that IBS could lead to cancer,[201] and other studies have demonstrated that many general practitioners (GPs) believe IBS to be

primarily a psychological disorder,[202] or occurring as a result of stress.[203] This disparity creates a further disruption in the doctor-patient relationship.

Good and effective communication is especially important in managing patients with DGBI, such as IBS, where there are no obvious structural causes for symptoms and which are often viewed to be less legitimate or to be psychiatric disorders.[142, 204] In acknowledgement of this, the Rome Foundation conducted a systematic review of 73 RCTs and controlled observational studies, and made recommendations to improve communication skills and the patient-provider relationship.[205] Ten recommendations for clinicians to optimise the patient-provider relationship were proposed: listen actively to patients, understand their agenda, empathise with their feelings, validate their stance, set realistic goals, educate them, provide reassurance, negotiate treatment options, encourage patient responsibility, and be there for them. The guidance also made recommendations for patients, healthcare systems, training programmes, and researchers to help enhance the patient-provider relationship. Such a holistic approach with a positive patient-provider relationship may help improve outcomes in IBS,[206] with similar recommendations on communication and doctor-patient relationship made by the latest UK guidelines for the management of IBS.[143]

1.6.2 Diet

When evaluating patients with IBS and discussing a treatment plan with them, it important to ask whether gastrointestinal symptoms are triggered or exacerbated by food intake. Adverse reactions to food are common and are reported in up to 20% of the general population.[207, 208] Patients with IBS are more likely to experience adverse reactions to food with up to 84% reporting meal-related symptoms.[65, 66, 201] There are several mechanisms by which food may

cause symptoms of IBS, such as direct osmotic effects of food in the gut lumen, changes in the gut microbiota, or immune activation.[209] It is unlikely that these adverse reactions are food allergies mediated by the development of specific immunoglobulin E antibodies, which usually occur reproducibly and rapidly when exposed and are absent during avoidance.[210] Although marketed to diagnose food intolerances, serum immunoglobulin G panels have not been validated,[211] and are, therefore, not recommended.[143, 144] Three diets for IBS, namely the use of traditional dietary advice, a low FODMAP diet, or a gluten-free diet (GFD), have become increasingly popular.

1.6.2.1 Traditional dietary advice

Traditional dietary advice is considered as first line therapy in IBS. NICE and the British Dietetic Association (BDA) advocate the use of a food fact sheet, which provides clear and concise information for patients without the need for formal dietetic input.[212, 213] This provides general healthy eating advice including eating regular meals, limiting alcohol, caffeine, and fizzy drink intake, maintaining adequate hydration, reducing processed foods, and adjusting fibre intake. It also includes specific advice for individuals with IBS with regards to individual symptoms. For example, it recommends limiting the intake of gas-producing foods such as beans and pulses for those with bloating, reducing the intake of artificial sweeteners such as sorbitol and mannitol for those with diarrhoea, and gradually increasing fibre, especially linseeds, for those with constipation. This dietary advice is largely based on clinical experience, rather than evidence from research studies. However, the use of fibre as a treatment has been studied in several trials. A systematic review and meta-analysis of 14 RCTs demonstrated a significant benefit of fibre on global symptoms ((relative risk (RR) of symptoms persisting = 0.86; 95% CI 0.80-0.94) with the effect limited to soluble fibre, such

as ispaghula (RR = 0.83; 95% CI 0.73-0.94), rather than insoluble fibre, such as bran (RR = 0.90; 95% CI 0.79-1.03).

1.6.2.2 A diet low in fermentable oligo, di, and monosaccharides and polyols

A low FODMAP diet is recommended as a second-line dietary therapy for IBS.[143, 145] FODMAPs are short-chain fermentable carbohydrates that are present in various fruits, vegetables, dairy products, and artificial sweeteners. Their exact mechanism of symptom generation is incompletely understood and although a high FODMAP diet increases colonic gas production, it may be the hypersensitivity to distension rather than the excessive gas production itself, that leads to gastrointestinal symptoms in patients with IBS.[214] A recent systematic review and network meta-analysis comparing a low FODMAP diet with various other diets, including BDA/NICE dietary advice, sham dietary advice, habitual diet, alternative dietary advice, or a high FODMAP diet, identified 13 RCTs involving 944 patients. A low FODMAP diet was ranked first, based on a failure to achieve an improvement in global IBS symptoms, compared with habitual diet (RR of symptoms not improving = 0.67; 95% CI 0.48 to 0.91), and was superior to all other dietary interventions.[68] Although no trials were at low risk of bias due to the difficulties of blinding participants in dietary trials, the fact that most of the trials were conducted in secondary or tertiary care, and that there was no evidence of funnel plot asymmetry for all analyses, these results are important to inform dietary treatment decisions in IBS. Despite its efficacy, a low FODMAP diet can be expensive for patients and requires dietetic supervision, meaning that it is resource intensive for healthcare systems. For instance, to implement a low FODMAP diet, three phases are required: a period of low FODMAP restriction usually lasting around 6 weeks, a period of FODMAP reintroduction, where

individual food items are introduced to determine tolerance to each, and a FODMAP personalisation period, where a modified FODMAP-containing diet is created based on individual tolerance to FODMAPs identified in the second phase.[215] Dietetic supervision is also important to screen for overly restrictive eating habits, which would preclude commencement of a low FODMAP diet, and to avoid the development of disordered eating habits or nutritional deficiencies.[216, 217]

1.6.2.3 A gluten-free diet

Patients with IBS often use a range of diets in an attempt to eliminate trigger foods. Even though they do not have coeliac disease, wheat appears to be a trigger for symptoms in some patients with IBS.[218, 219] This is described as non-coeliac gluten sensitivity. The current theory is that it is the reduction in fructans, which are fermentable oligosaccharides, in a GFD, rather than removal of gluten, which results in an improvement in symptoms of IBS.[220] A systematic review and meta-analysis of two RCTs of a GFD in IBS, involving 111 patients, demonstrated no significant benefit of a GFD in terms of an improvement in global IBS symptoms (RR of symptoms not improving = 0.42; 95% CI 0.11 to 1.55).[221] A GFD diet is, therefore, not recommended in IBS.

1.6.3 Probiotics

The potential role of the microbiome in the pathogenesis of IBS has been discussed earlier. This has led to a huge interest, in the last decade, in whether modulating the microbiome using probiotics can improve symptoms of IBS. A recent systematic review and meta-analysis identified 82 RCTs, which included 10,332 patients, comparing probiotics with placebo in adults with IBS.[72] When data from 32 RCTs were pooled, there was a significant benefit, in terms of persistence of global IBS symptoms, of combination probiotics over placebo (RR

= 0.78; 95% CI 0.71 to 0.87). Similarly, for global IBS symptoms, specific species and strains, including *Escherichia* strains, *Lactobacillus* strains, *Lactobacillus plantarum* 299V, LacClean Gold S, Duolac 7s, and *Bacillus* strains, showed a significant benefit over placebo. In addition, combination probiotics, *Lactobacillus*, *Saccharomyces*, *Bacillus* and *Bifidobacterium* strains as well as *Saccharomyces cerevisiae I-3856* led to a significant reduction in abdominal pain scores compared with placebo. Finally, combination probiotics and *Bacillus* strains led to a significant reduction in abdominal bloating or distension scores. Only 24 of the 82 studies were low risk of bias across all domains, there was significant heterogeneity between trials, and evidence of publication bias in some of the analyses. Nevertheless, these results suggest that some probiotics may be beneficial in IBS. Although no strong recommendation can be made, it is reasonable to advise patients wishing to try probiotics to take them for a period of 12 weeks, and to discontinue them if there is no improvement in symptoms.[143] Despite being recommended by UK IBS guidelines, probiotics are not able to prescribed in the NHS and are an out-of-pocket expense for patients with IBS.[143]

1.6.4 First-line pharmacological therapies

A number of first-line medications are available OTC or through a clinician's prescription. These are used to alleviate individual symptoms of IBS.

1.6.4.1 Antispasmodics and peppermint oil

The cardinal symptom of IBS is abdominal pain and there is no evidence that traditional analgesia used for musculoskeletal pain or headache such as paracetamol, NSAIDs, or opiates are effective in relieving pain in IBS. In fact, they can worsen gastrointestinal symptoms or be responsible for other gastrointestinal conditions, such as mucosal ulceration or opioid-induced constipation.

Instead, antispasmodics have been used for decades as an empirical treatment for IBS and are still the most frequently used OTC medications. Through their antimuscarinic and intestinal smooth muscle relaxant properties, they work by slowing intestinal motility and relaxing smooth muscle in the gut, which are thought to be mechanisms responsible for at least some of the symptoms of IBS.[222] Examples of antimuscarinics are dicycloverine and hyoscine butylbromide, whereas smooth muscle relaxants include alverine and mebeverine. A prior meta-analysis, as part of an American College of Gastroenterology (ACG) monograph on the management of IBS in 2018, identified 26 RCTs (including 2811 patients) which compared 13 different antispasmodics with placebo.[223] Fewer patients on antispasmodics had persistent global IBS symptoms or abdominal pain (RR = 0.65; 95% CI 0.56 to 0.76). However, there was significant heterogeneity and evidence of publication bias as well as many different antispasmodics studied, meaning that these results should be interpreted with caution. Hence, the latest ACG guidelines recommended against the use of antispasmodics available in the USA,[144] although the British Society of Gastroenterology (BSG) guidelines in the UK recommend that certain antispasmodics may be effective in treating global IBS symptoms or abdominal pain.[143] Overall, although adverse events were more common with antispasmodics compared with placebo,[223] they are generally safe medications that may be beneficial in some patients.

Peppermint oil is another widely used OTC medication for IBS. A meta-analysis of 10 RCTs, which included 1030 patients, demonstrated that peppermint oil was more efficacious than placebo (RR of symptoms not improving = 0.65; 95% CI 0.43 to 0.98) for global IBS symptoms or abdominal pain (RR of abdominal pain not improving = 0.76; 95% CI 0.62 to 0.93).[224] Adverse events

were significantly higher with peppermint oil (RR of any adverse event = 1.57; 95% CI 1.04 to 2.37).[224] It may, therefore, also be reasonable to recommend a trial of peppermint oil.[143, 144]

1.6.4.2 Antidiarrhoeal drugs

In an attempt to improve troublesome symptoms of diarrhoea, urgency, or faecal incontinence, many patients with IBS use loperamide. Loperamide is a μ-opioid agonist that reduces the activity of the myenteric plexus. This reduces smooth muscle tone in the colon, which increases intestinal transit time and water reabsorption. A pooled analysis of two RCTs involving 42 patients with IBS-D and IBS-M demonstrated that, although loperamide improved stool frequency and consistency, there was no statistically significant effect of loperamide compared with placebo on global IBS symptoms (RR of symptoms not improving = 0.44; 95% CI 0.14 to 1.42).[223] Rates of adverse events were similar in both the loperamide and placebo groups. Loperamide is only recommended for diarrhoea in IBS.[143] Despite the limited evidence as described, it is used widely, partly because of the limited efficacy of, and access to, other medications for diarrhoea. In clinical practice, loperamide may not be tolerated because of reported adverse effects including abdominal pain, bloating, nausea, and constipation. Nevertheless, some patients still continue to use it because of the fear of diarrhoeal symptoms, urgency, or faecal incontinence, which may affect quality of life to a greater degree than other gastrointestinal symptoms.[225, 226] Because loperamide is widely available, relatively cheap, and does not have any major adverse effects, it may be a good first-line antidiarrhoeal medication for some patients with IBS.

1.6.4.3 Laxatives

Laxatives are another group of readily available medications that can be used to help with constipation. Both osmotic and stimulant laxatives are efficacious in chronic idiopathic constipation.[227] Polyethylene glycol (PEG), a common osmotic laxative, is an inert substance that remains unabsorbed in the body and increases the luminal water content, thereby improving stool consistency and frequency in those with constipation. However, evidence for its use in IBS is limited. Two RCTs, recruiting patients with IBS-C, have investigated the efficacy of PEG.[228, 229] One RCT which recruited 42 patients with IBS-C did not demonstrate any benefit of PEG compared with placebo in improving spontaneous bowel movements or abdominal pain.[228] However, the second RCT which recruited 139 patients with IBS-C demonstrated a significant improvement in spontaneous bowel movements, although not abdominal pain, compared with placebo.[229] Abdominal pain was the most common adverse effect in those taking PEG. These trials only measured efficacy after 4 weeks of treatment, meaning that the long-term efficacy of PEG in IBS-C is unknown. Again, because PEG is readily available, cheap, and does not have any major adverse effects, it is often used in individuals with IBS in clinical practice to treat constipation.

1.6.5 Second-line pharmacological therapies

As discussed, either the efficacy of first-line medications is modest or there is limited evidence for their use in IBS. Not surprisingly, patients who do not experience adequate relief of their symptoms may seek further medical attention from their GP or may ask for a referral to a gastroenterologist. Second-line pharmacological therapies, which have mainly been developed in the last 20 years, may then be considered. They also target individual symptoms of abdominal pain, constipation, or diarrhoea.

1.6.5.1 Neuromodulators

As outlined earlier, IBS is a DGBI meaning the bidirectional dysfunction in the gut-brain axis is thought to be implicated in the pathophysiology. This, together with visceral hypersensitivity, is thought to be the cause of abdominal pain in IBS. Neuromodulators such as tricyclic antidepressants (TCAs) or SSRIs may act on these pathways to improve symptoms of IBS, especially abdominal pain.

A systematic review and meta-analysis in 2019 identified 12 RCTs, recruiting 787 patients, which compared TCAs with placebo in IBS.[230] TCAs were superior to placebo in improving global IBS symptoms or abdominal pain (RR of symptoms not improving = 0.65; 95% CI 0.55 to 0.77) and abdominal pain alone (RR of abdominal pain not improving = 0.59; 95% CI 0.42 to 0.83). Six different TCAs were studied, which included amitriptyline, desipramine, trimipramine, doxepin, imipramine, and nortriptyline. Seven RCTs, recruiting 356 patients, compared SSRIs with placebo in IBS. SSRIs were also superior to placebo in improving global IBS symptoms or abdominal pain (RR of symptoms not improving = 0.68; 95% CI 0.51 to 0.91) but not abdominal pain alone. Those randomised to a TCA or an SSRI, compared with those allocated to a placebo, were more likely to experience adverse events (RR of any adverse event = 1.56; 95% CI 1.23-1.98), with drowsiness and dry mouth being the most common.

Selective serotonin norepinephrine reuptake inhibitors are often used in other chronic painful disorders, such as fibromyalgia or low back pain.[231] Three RCTs have demonstrated an improvement in IBS symptoms and quality of life in patients taking duloxetine,[232, 233] or venlafaxine,[234] compared with those taking placebo, although the sample sizes of these RCTs are small.

It is, therefore, reasonable to consider using a TCA or SSRI as a second-line pharmacological therapy in IBS with the use of TCA to improve global

symptoms or abdominal pain and an SSRI to improve global symptoms or if there is co-existent anxiety. The BSG guidelines recommend that they can be started at a low dose in either primary or secondary care and titrated according to response and tolerability. This is supported by a recent trial published in 2023 of amitriptyline as a second-line treatment for IBS in primary care, which demonstrated that self-titration of low dose amitriptyline was superior to placebo across multiple outcomes, and was safe and well tolerated.[235] These results will hopefully improve access to a safe and efficacious drug to patients with IBS in primary care.

1.6.5.2 Drugs for diarrhoea

Several pharmacological therapies with different mechanisms of action can improve symptoms in patients with IBS-D. These include eluxadoline, rifaximin, and 5-HT_3 antagonists, such as alosetron, ramosetron, or ondansetron. One systematic review and network meta-analysis, which included 18 RCTs of these drugs, other than ondansetron, in 9844 patients, compared their relative efficacy in patients with IBS-D or IBS-M.[186] The Food and Drug Administration (FDA) composite endpoint for IBS-D, which consists of improvement in abdominal pain and diarrhoea, was used as the endpoint of interest.

Eluxadoline, a μ-opioid and κ-opioid agonist and a δ-opioid antagonist which reduces intestinal transit, was superior to placebo using the FDA composite endpoint for IBS-D (RR of symptoms not improving for 100mg eluxadoline twice daily = 0.87; 95% CI 0.83 to 0.91 and RR for 75mg eluxadoline twice daily = 0.89; 95% CI 0.84 to 0.94).[186] Adverse events included constipation, nausea, and headache, and serious adverse events (pancreatitis and sphincter of Oddi spasm), although low at 0.5%, were significantly more common in those treated with eluxadoline compared with placebo. [236] Rifaximin has also been investigated

in IBS based on the hypothesis that gut dysbiosis is at least partly responsible for symptoms of IBS. Using the same FDA composite endpoint for IBS-D, rifaximin 550mg twice daily for 14 days was superior to placebo (RR of symptoms not improving = 0.92; 95% CI 0.86 to 0.98).[186]

5-HT_3 antagonists that have been investigated in RCTs in patients with IBS are alosetron, ramosetron, and ondansetron. They reduce gut motility to improve symptoms of diarrhoea. Both alosetron 1mg twice daily (RR of symptoms not improving = 0.69; 95% CI 0.60 to 0.80) and ramosetron 2.5μg once daily (RR of symptoms not improving = 0.78; 95% CI 0.67 to 0.91) were superior to placebo using the FDA composite endpoint for IBS-D.[186] Alosetron was withdrawn due to a small risk of ischaemic colitis identified in post-marketing surveillance,[237] but was later reintroduced in the USA under more stringent regulations at a lower dose. Despite the efficacy of these second-line medications, none of them are available or licensed in the UK for patients with IBS, even for those with more severe, or refractory, symptoms. A subsequent meta-analysis of three RCTs of ondansetron versus placebo in patients with IBS-D included 327 patients.[238] Using the FDA composite endpoint for IBS-D, ondansetron was superior to placebo (RR of symptoms not improving = 0.86; 95% CI 0.75 to 0.98). Ondansetron is a safe, inexpensive, and commonly used drug but is currently not licensed for use in IBS-D. Given that alosetron and ramosetron are not available in the UK, ondansetron may be a suitable alternative, especially for those with diarrhoea and urgency.

As discussed in section 1.3.6, some patients with IBS demonstrate low-grade inflammation in the intestine. A recent systematic review and meta-analysis, which assessed the efficacy and safety of mesalamine in IBS, included 8 RCTs, containing 820 patients.[239] Mesalamine was more efficacious than

placebo for global IBS symptoms (RR of global symptoms not improving = 0.86; 95% CI, 0.79–0.95), but not for abdominal pain or bowel habit or stool frequency. Subgroup analyses demonstrated efficacy of mesalamine in IBS with diarrhoea for global IBS symptoms (RR, 0.88 = 95% CI, 0.79–0.99), but not patients with other predominant bowel habits or those with post-infection IBS. Adverse event rates were no higher with mesalamine (RR = 1.20; 95% CI, 0.89–1.63) but were reported in only 5 trials. The authors concluded that mesalamine could, therefore, a safe and efficacious treatment option for some patients but larger trials recruiting only patients with IBS with diarrhoea are warranted.

1.6.5.3 Drugs for constipation

As previously highlighted, the evidence for the use of laxatives in IBS is limited and, when they are not effective in relieving symptoms, second-line medications such as secretagogues or 5-HT_4 agonists could be considered.

Secretagogues such as linaclotide, plecanatide, lubiprostone, and tenapanor work through their action on different ion channels on the intraluminal surface of enterocytes to increase luminal electrolytes and, hence, water. This softens stools and accelerates luminal transit. Linaclotide and plecanatide are both guanylate cyclase-C agonists, whereas lubiprostone is a chloride channel activator, and tenapanor is sodium-hydrogen exchange inhibitor. A systematic review and network meta-analysis, which included 15 RCTs of these four secretagogues, in 8462 patients, compared their relative efficacy in patients with IBS-C.[185] The FDA composite endpoint, which consists of improvement in abdominal pain and an increase of ≥1 complete spontaneous bowel movements, was used as the endpoint. Linaclotide 290 μg once daily (RR of symptoms not improving = 0.82; 95% CI 0.78 to 0.87), plecanatide 3μg and 6 μg once daily (RR of symptoms not improving for 3μg once daily = 0.88; 95% CI 0.82 to 0.94 and

RR of symptoms not improving for 6 μg once daily = 0.87; 95% CI 0.81 to 0.93), lubiprostone 8 μg twice daily (RR of symptoms not improving = 0.87; 95% CI 0.78 to 0.96), and tenapanor 50 mg twice daily (RR of symptoms not improving = 0.85; 95% CI 0.79 to 0.92) were all superior to placebo for the FDA composite endpoint for IBS-C. When comparing these four secretagogues indirectly in this network meta-analysis, linaclotide 290 μg once daily ranked highest for the FDA composite endpoint and almost all other endpoints analysed. Adverse events were more common amongst those taking secretagogues compared with placebo, with diarrhoea being a common side effect for linaclotide, plecanatide, and tenapanor, whereas nausea was the commonest side effect for lubiprostone.

5-HT_4 agonists such as tegaserod and prucalopride have prokinetic effects, which increase luminal transit. One meta-analysis of 11 RCTs demonstrated that tegaserod was superior to placebo for the treatment of IBS-C in 9242 patients (RR of symptoms not improving = 0.85; 95% CI 0.80 to 0.90).[240] Again, diarrhoea was the most common adverse event and was significantly more likely than with placebo. Prucalopride is another 5-HT_4 agonist, which is effective in chronic idiopathic constipation,[227] but is not licensed in IBS-C because there have been no RCTs. Despite the efficacy of these second-line medications, only linaclotide is licensed and readily available for the treatment of IBS-C in the UK.

1.6.6 Brain-gut behavioural therapies

Given the increasing recognition that the gut-brain axis is involved in the development and persistence of IBS symptoms, brain-gut behavioural therapies (BGBTs) in IBS have been investigated. There are several BGBTs including cognitive behavioural therapy (CBT), acceptance and commitment therapy, and gut-directed hypnotherapy (GDH).

One systematic review and network meta-analysis of BGBTs in IBS identified 41 RCTs, containing 4072 participants.[187] There was evidence of publication bias and other small study effects affecting trials examining some BGBTs. The authors reported the psychological interventions with the largest number of trials and patients recruited that demonstrated efficacy for improving global IBS symptoms included self-administered or minimal contact CBT (RR of symptoms not improving = 0.61; 95% CI 0.45 to 0.83), face-to-face CBT (RR of symptoms not improving = 0.62; 95% CI 0.48 to 0.80), and GDH (RR of symptoms not improving = 0.67; 95% CI 0.49 to 0.91). A recent systematic review and network meta-analysis, which examined the effects of BGBTs on abdominal pain in IBS, identified 42 RCTs, containing 5220 participants.[241] The authors reported BGBTs with the largest number of trials and patients recruited demonstrating efficacy for abdominal pain, specifically, included self-guided/minimal contact CBT (RR of abdominal pain not improving, 0.71; 95% CI, 0.54–0.95; P score, 0.58), face-to-face multicomponent behavioural therapy (RR of abdominal pain not improving, 0.72; 95% CI, 0.54–0.97; P score, 0.56), and face-to-face GDH (RR of abdominal pain not improving, 0.77; 95% CI, 0.61–0.96; P score, 0.49).

Despite evidence that BGBTs are effective in IBS, they are only recommended for patients with persistent symptoms after 12 months of pharmacological treatment.[143, 145] BGBTs may also be expensive as they require multiple sessions with therapists and may not be widely available in all areas, although remote or self-administered options may improve this.

1.7 Burden of IBS

After the general overview of IBS provided, including the current knowledge and limitations in the diagnosis and treatment of the disorder, it is important to discuss the burden of IBS and explain the rationale for this thesis.

1.7.1 Burden to the individual

Individuals with IBS suffer from a chronic incurable disorder associated with troublesome and embarrassing gastrointestinal symptoms. Qualitative studies examining the impact of IBS on individuals have demonstrated that symptoms of IBS leave them fearful, embarrassed, or ashamed.[142, 199, 242, 243] Individuals with IBS report that the unpredictability of symptoms leads to loss of freedom or spontaneity.[142] They also report feeling embarrassed using toilets at work or in public, or having to pass flatus, due to their IBS symptoms.[199] Other individuals report the fear of symptoms of urgency or faecal incontinence, and the fact that bowel symptoms make it difficult to have physical relationships.[199] Although these qualitative studies are important to understand the themes concerning the burden of IBS in private and professional life, they lack the ability to determine the proportion of individuals affected by their IBS symptoms, and to what extent, as well as to identify predictors of impairment at work and at home. Previous studies examining these issues have important limitations because they recruited a small sample,[244] recruited individuals with prior definitions of IBS,[138, 245] recruited individuals with specific IBS subtype(s),[245, 246] or used non-validated questionnaires to examine the impact of IBS on work and activities of daily living.[245] The impact of IBS, defined according to the Rome IV criteria, on work and activity impairment among a wider population of individuals with IBS is, therefore, unknown.

The stigma attached to a diagnosis of IBS,[142] the unnecessary investigations or surgical procedures that some patients with IBS undergo,[125, 189] and the lack of effective medications have already been discussed.[68, 185-188] Assessment of quality of life in individuals with IBS is important to understand the burden of the disorder on individuals. Contemporaneous estimates are

particularly important, as the Rome IV criteria seem to select a more extreme spectrum of IBS than previous iterations, with more severe gastrointestinal symptoms and higher rates of psychological comorbidity.[21-24] Multiple studies have examined the quality of life of individuals with IBS,[128-139] but only one has used the Rome IV criteria.[139] The sample size in this study was relatively small and the results may have been hampered by selection bias as individuals recruited were taking part in two RCTs and none of them suffered from anxiety or depression. Because of the negative attitudes or perceptions towards patients with IBS,[202, 204, 247] it is important to be able to compare the quality of life of those with IBS to those with other chronic medical conditions. This may help legitimise the burden that IBS represents to individuals. In addition, none of the previous studies have examined features associated with lower quality of life. This means that a detailed assessment of the quality of life of individuals with IBS is needed and this will be addressed in this thesis.

It has already been discussed that IBS is associated with psychological comorbidities.[39, 41-43] Previous studies examining influence of psychological comorbidities 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. [44, 118-120, 122] A recent cross-sectional survey, conducted in 106 patients with IBS, demonstrated a cumulative increase in IBS symptom severity with increasing number of psychological comorbidities. [44] It is important, especially for individuals with IBS, to further understand the burden of these psychological comorbidities. There has been no study examining the cumulative impact of psychological comorbidities on the prognosis of IBS and this will be addressed in this thesis.

1.7.2 Burden to the health service

The healthcare costs of managing patients with IBS are considerable for several reasons. These include the relatively high prevalence of the condition,[26, 29] the chronicity of symptoms,[111] the non-fatal nature of the disorder,[126, 127] the inappropriate use of exhaustive investigations to make a diagnosis,[140, 189] and the lack of a cure. In addition, even though IBS is a prevalent disorder, it does not seem to be a research priority. For example, between 2007 and 2017, coeliac disease, which has a substantially lower prevalence, attracted 11% of European Union research funding compared with <1% for IBS.[248] Highlighting the impact of IBS on patients in the work presented in this thesis may, therefore, be a strong impetus for change. This is especially important because of the potentially enormous cost of IBS to healthcare systems. Annual IBS-related costs are estimated at €8 billion in Europe,[249] ¥123 billion in China,[250] and $10 billion in the USA.[251] Only two studies examining the cost of IBS have been conducted in the UK in the last 20 years, but both have major limitations as one examined total annual healthcare costs rather than IBS-specific costs,[252] and the other included patients with symptoms suggestive of IBS, rather than with a confirmed diagnosis.[253] There is, therefore, a lack of contemporaneous data on the costs of IBS to inform healthcare planning and research funding in the UK.

Over the last 20 years, several drugs have been withdrawn, or their use restricted, due to safety concerns. Examples include ischaemic colitis with alosetron,[254] an excess of cardiovascular and cerebrovascular events with tegaserod,[255] and episodes of acute pancreatitis with eluxadoline.[256] Although regulatory bodies with responsibility for the licensing of drugs and therapeutics often have lay representation on their committees, including from patients and carers, they do not generally require formal consideration, review, or quantification of the risks patients are willing to accept to relieve or cure their

symptoms when evaluating treatments. In a chronic, incurable, condition like IBS, in which most drugs have limited efficacy, it is important to determine these risks. This will allow a fairer assessment of drug licensing, particularly for those with more severe, or refractory, symptoms.

Patients with IBS appear willing to accept remarkable risks from medications in return for cure of their symptoms. In one survey, individuals with IBS were, on average, willing to relinquish 15.1 years of their life to achieve perfect health with a new medication.[190] Another study demonstrated that women with IBS-D were willing to accept a 2.65% risk of bowel impaction and a 1.34% risk of bowel perforation from alosetron.[191] Two other studies reported that patients with IBS were willing to accept a median 1% risk of sudden death for a 99% chance of cure of their symptoms,[192] and that patients with IBS with predominant severe diarrhoea would accept a mean 10.2% risk of sudden death for a 99% chance of cure,[193] but these studies were relatively small and patients were recruited from referral populations. These prior studies have other important limitations including the fact that none of them examined the predictors of a higher acceptance of medication-related risk among individuals with IBS. Because they were also all conducted in the USA, these results may not be applicable to people with IBS in the UK. This data will not only be important for regulatory agencies, but also for pharmaceutical companies, when deciding on continued drug development if serious adverse events arise.

As discussed in section 1.1.3, individuals with Rome IV IBS have more severe symptoms and higher levels of psychological comorbidities, compared with those with Rome III IBS.[21-24] Even though the Rome criteria are not necessarily strictly applied in clinical practice, the introduction of the latest criteria to diagnose IBS, the Rome IV criteria, has important implications for research

studies. The natural history of Rome IV-defined IBS in individuals is unknown. Because most current treatment trials have been conducted using the Rome III criteria, this thesis will also aim to examine the natural history and disease impact of Rome IV and Rome III IBS separately. These results may have important implications for future design of RCTs that recruit individuals with Rome IV IBS.

1.7.3 Burden to society

It has been discussed in section 1.2 that IBS is a common condition affecting between 5% and 10% of the population. When such a prevalent condition affects individuals, the impact of the disorder is not only felt at the level of the health service but also at societal level. When evaluating the burden of IBS to society, both cost of IBS to the health service and the impact of the disorder on work should be considered. A common condition that impairs individuals' ability to work means that any absenteeism or impairment in work productivity will represent a substantial burden to society. The burden of Rome IV-defined IBS in a working population and the number of hours lost due to the disorder in the UK are unknown and will be examined in this thesis. Similarly, a prevalent condition, which impairs individuals' ability to carry out their activities of daily living will have a considerable burden to society. Because of the limitations of previous studies as discussed in section 1.7.1, impairment in various home and social activities have not been clearly defined in individuals with Rome IV IBS and will be addressed in this thesis.

Chapter 2 Aims and Objectives

After discussing the burden of IBS, the limitations of previous studies, and the rationale of this thesis, this chapter describes the aims and objectives of this thesis. It will assess the burden of IBS in the UK and study the implications of this disorder on people with IBS, clinicians, pharmaceutical companies, regulatory agencies, the NHS, and society as a whole. This will be achieved by examining the characteristics of individuals with IBS in a cross-sectional survey to determine the impact of IBS on work and activities of daily living, the annual direct healthcare cost of IBS in the UK, the willingness to accept risk with medication in return for symptom cure, and the quality of life of individuals with IBS. A separate longitudinal follow-up study will also be conducted to determine whether individuals with Rome IV IBS have a different prognosis to those with Rome III IBS in terms of future gastrointestinal and psychological symptoms, and to examine the impact of incremental increases in psychological comorbidity on the prognosis of IBS. The following pieces of work have been conducted to achieve these aims:

2.1 Assessing the impact of IBS on work and activities of daily living.

As discussed in Chapter 1, the symptoms of IBS have a negative impact on individuals at work and in their private life. The aim of the study reported in Chapter 3 was to examine the impact of IBS on work and activities of daily living. In particular, the study examined the impact of IBS on absenteeism and work productivity, and assessed the interference of IBS symptoms with home management, social leisure activities, private leisure activities, and close relationships.

2.2 Assessing the quality of life of individuals with IBS.

Due to the nature of gastrointestinal symptoms in IBS, the chronicity of the condition, the other comorbidities associated with IBS, and the impact of the disorder on work and daily life, patients with IBS may report impaired quality of life. An analysis of quality of life is important to achieve the overarching aim of this thesis to assess the overall burden of IBS. The aim of the study reported in Chapter 4 was to assess the impact of IBS on quality of life, examine predictors of lower quality of life, and compare generic quality of life scores observed in IBS with other chronic conditions.

2.3 Assessing the willingness to accept medication risks among individuals with IBS.

Even though IBS is not known to reduce life expectancy, patients with IBS, as discussed in Chapter 1, appear willing to accept remarkable risks, in terms of the risk of death, from medications in return for cure of their symptoms. The aim of the study reported in Chapter 5 was to assess the willingness to accept risk with medication in return for symptom cure in people with IBS in the UK. In addition to being a surrogate marker of the impact of IBS on individuals with the condition, this study may be important to guide drug licensing.

2.4 Estimating the direct healthcare cost of IBS in the UK.

As previously discussed, the healthcare costs of managing patients with IBS are considerable. The aim of the study reported in Chapter 6 was to estimate contemporaneous mean annual healthcare costs of IBS per person with the condition and extrapolate these across the entire UK adult population using IBS prevalence data to provide a contemporaneous approximation of the economic burden of IBS on the UK healthcare system.

2.5 Assessing whether individuals with Rome IV IBS have a different prognosis to those with Rome III IBS in terms of future gastrointestinal and psychological symptoms.

The changes to the Rome criteria for IBS over the last 30 years have been discussed in Chapter 1. The aim of the study reported in Chapter 7 was to conduct a longitudinal follow-up study to assess the gastrointestinal and psychological symptoms at follow-up of individuals who met the Rome III or IV criteria for IBS at baseline. This will facilitate an understanding of the impact of the changes made in moving from the Rome III criteria to the Rome IV criteria on the natural history of IBS.

2.6 Assessing the impact of psychological comorbidity on the prognosis of IBS.

It has been discussed in Chapter 1 that people with IBS often exhibit psychological comorbidity. There have been no large-scale longitudinal follow-up studies to examine the cumulative effects of number of psychological comorbidities on the prognosis of individuals with IBS. The aim of the study reported in Chapter 8 was to conduct a longitudinal follow-up study to assess the impact of increasing psychological comorbidities on the prognosis of IBS.

Chapter 3 Assessing the Impact of Irritable Bowel Syndrome on Work and Activities of Daily Living.

3.1 Introduction

In qualitative studies examining the impact of IBS on work and activities of daily living, patients with IBS state that their symptoms leave them fearful, embarrassed, or ashamed.[142, 199, 242, 243] The unpredictability of symptoms leads to loss of freedom or spontaneity.[142] Individuals also report feeling embarrassed using toilets at work or in public, or having to pass flatus, due to their IBS symptoms.[199] Other themes include fear of symptoms of urgency or faecal incontinence, and the fact that bowel symptoms make it difficult to have physical relationships.[199] Finally, patients report stigma associated with a "functional" disease and the lack of a structural cause for their symptoms makes it difficult for colleagues, friends, or family to understand.[142] To gain control of various work and personal situations, patients often make adjustments some of which, such as activity avoidance, are maladaptive in nature.[199, 242, 243] Although qualitative studies facilitate understanding of themes underlying impairment at work or in activities of daily living, they lack the ability to determine the proportion of individuals affected by their IBS symptoms and to identify predictors of work and activity impairment.

A previous cross-sectional survey in secondary care demonstrated that one-quarter of participants with Rome III IBS reported absenteeism, more than 80% presenteeism, and that work impairment was associated with severity of IBS, quality of life, and gastrointestinal symptom-specific anxiety.[257] Two previous studies have attempted to quantify the impact of IBS on activities of daily living but they were either small, containing only 42 patients,[244] or recruited individuals with Rome III IBS.[138] A more recent large survey of individuals with Rome III IBS also had important limitations as this recruited individuals with only IBS-C and

IBS-D, and used non-validated questionnaires to examine the impact of IBS on work and activities of daily living.[245]

The impact of IBS, defined according to the Rome IV criteria, on work and activity impairment among a wider population of individuals with IBS is, therefore, unknown. These issues were examined in a cross-sectional survey recruiting a large cohort of people with IBS. It was hypothesised that IBS would affect a large proportion of individuals at work and in their activities of daily living, and that those with more severe symptoms of IBS, higher levels of psychological comorbidities, or poorer quality of life would experience more impairment at work and in their activities of daily living.

3.2 Methods

3.2.1 Participants and setting

Individuals registered with ContactME-IBS, a national UK registry of 4280 members with IBS who are interested in volunteering for research, were recruited.[258] They find out about the registry via numerous sources including their GP, specialist hospital clinics, posters in pharmacies, or social media. Individuals enrol by completing a short questionnaire about their bowel symptoms and providing contact details. The registry is run by County Durham and Darlington NHS Foundation Trust. Although all adults in the UK who self-identified as having IBS were able to register with ContactME-IBS, an opportunity that was formally promoted by GPs in the north and southwest of England, the registry did not collect data on the geographical location of its members. Amongst all registrants, 2268 (53%) have seen their GP with IBS, and another 1455 (34%) a gastroenterologist. There were no exclusion criteria apart from inability to understand written English. All registered individuals were contacted, via electronic mailshot, in July 2021, directing them to a website where they could

access study information (Appendix A – Patient Information Sheet). Those willing to participate completed an online questionnaire (Appendix B – Questionnaire), with responses stored in an online database. Non-responders received a reminder email in August 2021. Participants were given a chance to win one of three gift cards (worth £200, £100, or £50). The University of Leeds research ethics committee approved the study in March 2021 (MREC 20-051) (Appendix C – Research Ethics Committee Approval).

3.2.2 Data collection and synthesis

3.2.2.1 Demographic and symptom data

Basic demographic data, including age, gender, lifestyle (tobacco and alcohol consumption), ethnicity, marital status, educational level, and annual income were collected. Respondents were asked to state whether their IBS symptoms commenced after an acute enteric infection. Presence of IBS was defined according to the Rome IV questionnaire,[259] assigning this in all individuals according to the scoring algorithm proposed for its use.[19] IBS subtype was categorised according to the criteria recommended in the questionnaire, using the proportion of time stools were abnormal according to the BSFS. All participants were asked to provide time since their diagnosis of IBS, the number of IBS drugs used in the 12 months prior to study recruitment, and whether they used opiates for any reason, as well as their most troublesome symptom from a list of five possibilities, including abdominal pain, constipation, diarrhoea, bloating/distension, or urgency.

3.2.2.2 IBS symptom severity and impact

The severity of symptoms was assessed using the IBS-SSS,[113] which measures presence, severity, and frequency of abdominal pain, presence and severity of abdominal distension, satisfaction with bowel habit, and degree to

which IBS symptoms are affecting, or interfering with, the individual's life. The IBS-SSS is scored from 0 to 500 points, with <75 indicating remission of symptoms; 75-174 mild symptoms; 175-299 moderate symptoms; and 300-500 severe symptoms.

3.2.2.3 Mood and somatic symptoms

The hospital anxiety and depression scale (HADS) was used to collect anxiety and depression data. The total HADS score ranges from 0 to 21 for either anxiety or depression. Severity for each were categorised into normal (total HADS depression or anxiety score 0-7), borderline normal (8-10), or abnormal (≥11).[260] Somatic symptom data were collected using the patient health questionnaire-12 (PHQ-12),[119] derived from the validated patient health questionnaire-15 (PHQ-15).[261] The total PHQ-12 score ranges from 0 to 24. Severity was categorised into high (total PHQ-12 ≥13), medium (8-12), low (4-7), or minimal (≤3).

3.2.2.4 Gastrointestinal symptom-specific anxiety

The visceral sensitivity index (VSI),[262] which measures gastrointestinal symptom-specific anxiety, was used. Replies to each of the 15 items are provided on a 6-point scale from "strongly disagree" (score 0) to "strongly agree" (score 5). These data were divided into equally sized tertiles, as there are no validated cut offs to define low, medium, or high levels of gastrointestinal symptom-specific anxiety.

3.2.2.5 IBS-related quality of life

The irritable bowel syndrome quality of life (IBS-QOL), a validated IBS-specific questionnaire, was used to measure health-related quality of life in individuals with IBS.[263, 264] The IBS-QOL consists of 34 items, each ranked on a 5-point Likert scale ranging from 0 to 4, with a total possible score of 0 to 136 and

lower scores indicating better quality of life. The 34 items are based on the following eight variables: dysphoria, interference with activity, body image, health worry, food avoidance, social reactions, sexual activity, and relationships. Scores were transformed to a 0 to 100-point scale with zero indicating worst quality of life and 100 indicating best quality of life, according to the recommended approach from the development and validation study of the IBS-QOL.[263] These data were divided into equally sized tertiles, as there are no validated cut offs to define low, medium, or high levels of quality of life.

3.2.2.6 Impact of IBS on work and activities of daily living

The work productivity and activity impairment questionnaire for irritable bowel syndrome (WPAI:IBS),[265] which is validated to assess the level of work productivity loss in people with IBS who are employed, as well as impairment in activities of daily living was used. There are four domains: absenteeism (percentage of work hours missed because of IBS); presenteeism (percentage of impairment experienced whilst working because of IBS); overall work impairment (percentage of work productivity loss); and activity impairment (percentage impairment in activities of daily living). The work and social adjustment scale (WSAS) was also used in all participants, irrespective of employment status.[266] WSAS has previously been used to measure the impact of IBS on individuals' ability to work, manage at home, engage in social and private leisure activities, and maintain close relationships.[267-270] The five domains are scored on a 9-point scale from "not at all" (score 0), through "definitely" (score 4), to "very severely" (score 8).

3.2.3 Statistical analysis

Only participants who met Rome IV criteria for IBS were included in the analysis. The presence (≥1%) or absence (0%) of absenteeism, presenteeism,

overall work impairment, or activity impairment were dichotomised. Similarly, the presence (score ≥4 (“definitely” impacting)) or absence (score <4) of an impact of IBS on home management activities, social leisure activities, private leisure activities, or maintaining close relationships were dichotomised. The characteristics of participants in each of these groups were examined. Categorical variables were compared using a χ^2 test and continuous data using an independent samples *t*-test, with statistical significance defined as a *P* value <0.01. Logistic regression was performed, controlling for all baseline demographic data (including annual income), IBS subtype, duration, severity, and impact of IBS symptoms, most troublesome symptom, presence of meal-related symptoms, opiate use, number of IBS-related drugs in the last 12 months, mood and somatic symptom reporting, gastrointestinal symptom-specific anxiety, and IBS-related quality of life to examine factors associated with absenteeism, presenteeism, overall work impairment, or activity impairment, as well as impairment of home management activities, social leisure activities, private leisure activities, or maintaining close relationships. ORs with 95% CIs were reported.

A contemporaneous prevalence of Rome IV IBS in the UK of 4.6%, derived from the Rome Foundation three-nation prevalence study,[28] was used to extrapolate the total number of hours of work lost because of IBS per person from this study across the entire UK adult working population (aged 18 to 64), using published census data, [271-273] and the assumption that individuals worked an average of 46 weeks per year. In the current study, most participants had consulted with a doctor, which may skew the results. The authors of the three-nation Rome Foundation study were, therefore, contacted to obtain the prevalence of individuals with Rome IV IBS consulting a doctor for IBS in the UK,

which was 2.8% (data on file, personal communication: Dr. Olafur Palsson, University of North Carolina, Chapel Hill, NC, USA). These data were used to perform a more conservative sensitivity analysis of the number of hours of work lost because of IBS. All analyses were performed using SPSS for Windows (version 27.0 SPSS, Chicago, IL).

3.3 Results

In total, 1278 (29.9%) of 4280 registrants completed the questionnaire. Of these, 752 (58.8%) met Rome IV criteria for IBS (mean age 45.3 years (range 18-81 years), 655 (87.1%) female). In total, 136 (18.1%) had IBS-C, 306 (40.7%) IBS-D, 301 (40.0%) IBS-M, and 9 (1.2%) IBS-U. Of the 752 individuals who met Rome IV criteria for IBS, 484 (64.4%) were employed, 467 (96.5%) of whom provided complete data. Of the 268 individuals who were not currently in employment, 189 (70.5%) stated that they were either retired or not employed for reasons other than their IBS, implying that 79 (10.5%) of the 752 people with Rome IV IBS were unemployed partly as a result of their condition. The median level of absenteeism in all 467 employed individuals with Rome IV IBS was 0.0% ((interquartile range (IQR) 0.0% - 2.9%), presenteeism 35.0% (IQR 20.0% - 60.0%), and overall work impairment 30.0% (IQR 10.0% - 60.0%). Among all 752 individuals, median activity impairment was 40.0% (IQR 20.0% - 70.0%).

Among working age (18 to 64 inclusive) employed individuals with Rome IV IBS, the mean number of hours of work lost because of IBS was 1.97 hours per week and, therefore, 90.5 hours per year. According to UK census data, there are 39,361,324 adults aged 18 to 64 in the UK. With a prevalence of 4.6% of Rome IV-defined IBS in the UK,[28] and an employment rate of 72.2% (479 of 663 individuals of working age with Rome IV IBS) in the current study, there are likely to be 1,307,268 employed individuals of working age with Rome IV IBS. This

implies the total amount of work lost to IBS is 118,213,657 hours. In a sensitivity analysis, assuming 2.8% of the UK adult population have Rome IV IBS and will consult a physician (data on file, personal communication: Dr. Olafur Palsson, University of North Carolina, Chapel Hill, NC, USA),[28] there are likely to be 795,729 employed individuals of working age with Rome IV IBS who have consulted a physician in the UK. Applying this data to these figures yielded an estimated total of 71,956,139 hours of work lost due to IBS.

3.3.1 Characteristics of patients with impairment at work and in activities of daily living because of IBS

The characteristics of 133 (28.5%) individuals who reported any absenteeism, 373 (85.6%) any presenteeism, 382 (81.8%) any overall work impairment, and 684 (91.0%) any activity impairment were compared with those who did not (Figure 3.1). Participants with any absenteeism were significantly less likely to be married (56.4%, vs. 70.7%, P =0.003), and significantly more likely to have severe IBS (61.7%, vs. 39.5%, $P < 0.001$), higher levels of anxiety (60.9%, vs. 44.9%, $P = 0.006$), depression (25.6%, vs. 16.8%, $P < 0.001$), somatisation (37.6%, vs. 25.1%, $P = 0.009$), and gastrointestinal symptom-specific anxiety (47.4%, vs. 28.4%, $P < 0.001$), and lower quality of life (44.4%, vs. 21.3%, $P < 0.001$) (Table 3.1). Those with any presenteeism were significantly more likely to be younger (mean age, 40.1, vs. 45.6, $P < 0.001$), have more severe IBS (47.2%, vs. 31.7%, $P < 0.001$), higher levels of somatisation (28.4%, vs. 19.0%, $P = 0.008$) and gastrointestinal symptom-specific anxiety (35.9%, vs. 19.0%, $P < 0.001$), and have lower quality of life (30.8%, vs. 9.5%, $P < 0.001$). Participants with overall work impairment were significantly more likely to be younger (mean age, 40.1, vs. 44.7, $P < 0.001$), to have higher levels of gastrointestinal symptom-specific anxiety (36.4%, vs. 22.4%, $P < 0.001$), and

lower quality of life (31.2%, vs. 12.9%, *P* < 0.001). Finally, those with any activity impairment were significantly more likely to have severe IBS (49.9%, vs. 26.5%, *P* <0.001), higher levels of anxiety (51.9%, vs. 33.8%, *P* = 0.004), depression (26.2%, vs. 5.9%, *P* <0.001), somatization (32.5%, vs. 16.2%, *P* < 0.001), and gastrointestinal symptom-specific anxiety (36.7%, vs. 10.3%, *P* < 0.001), and lower quality of life (34.4%, vs. 5.9%, *P* < 0.001).

There were no predictors of absenteeism on logistic regression. Younger participants (OR per year = 0.95; 95% CI 0.92 to 0.98), those with abdominal bloating or distension as their most troublesome symptom (OR = 0.19; 95% CI 0.06 to 0.64), compared with abdominal pain, or with higher IBS-related quality of life (OR = 0.13; 95% CI 0.03 to 0.54) were less likely to report presenteeism. Younger participants (OR per year = 0.96; 95% CI 0.94 to 0.99), those with bloating or distension (OR = 0.25; 95% CI 0.10 to 0.62) or urgency as their most troublesome symptom (OR = 0.22; 95% CI 0.08 to 0.59), compared with abdominal pain, or with higher IBS-related quality of life (OR = 0.16; 95% CI 0.05 to 0.49) were less likely to report overall work impairment. Finally, smokers (OR = 0.24; 95% CI 0.09 to 0.65) were less likely to report any activity impairment, and those with moderate IBS (OR = 3.10; 95% CI 1.37 to 7.02), compared with those with mild IBS, or moderate levels of somatisation (OR = 5.84; 95% CI 1.71 to 19.87), compared with those with low levels of somatisation, more likely.

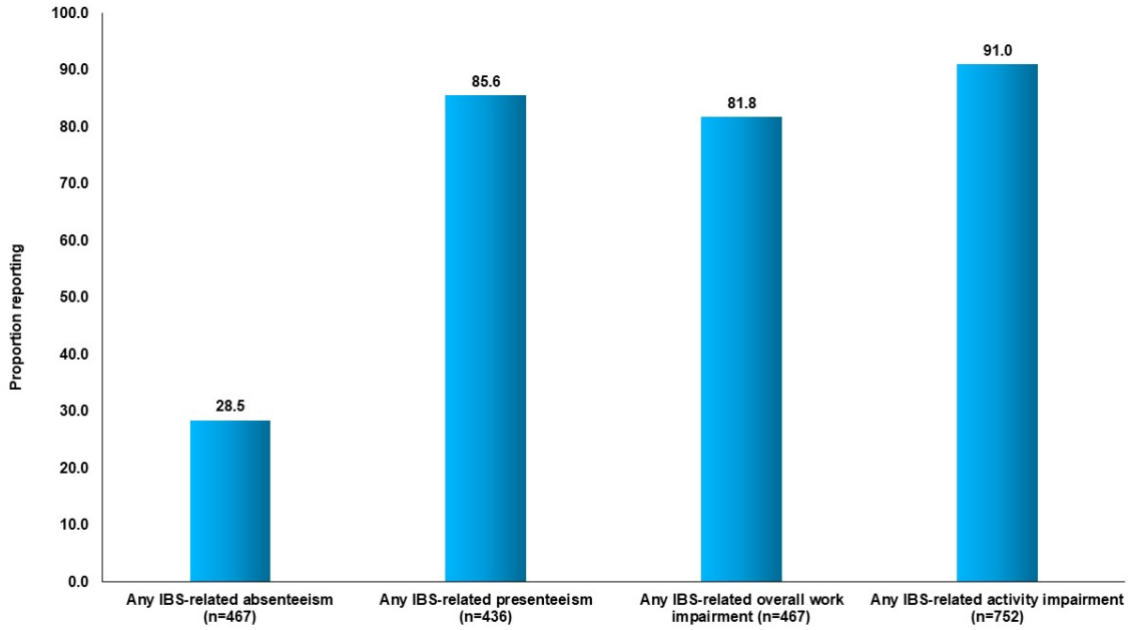

Figure 3.1. Impairment at work or in activities of daily living because of IBS.

Table 3.1. Characteristics of individuals with Rome IV IBS who reported absenteeism, presenteeism, overall work impairment, and activity impairment compared with those who did not.

	Absenteeism (n=467)			Presenteeism (n=436)			Overall work impairment (n=467)			Activity impairment (n=752)		
	Yes (n=133)	No (n=334)	P value	Yes (n=373)	No (n=63)	P value	Yes (n=382)	No (n=85)	P value	Yes (n=684)	No (n=68)	P value
Female (%)	116 (87.2)	297 (88.9)	0.60	327 (87.7)	55 (87.3)	0.94	336 (88.0)	77 (90.6)	0.49	597 (87.3)	58 (85.3)	0.64
Mean age (Standard deviation)	39.5 (11.6)	41.5 (11.5)	0.096	40.1 (11.4)	45.6 (11.5)	<0.001	40.1 (11.4)	44.7 (11.5)	<0.001	45.0 (14.9)	48.6 (13.3)	0.057
White ethnicity (%)	127 (95.5)	322 (96.4)	0.64	357 (95.7)	61 (96.8)	0.68	366 (95.8)	83 (97.6)	0.43	662 (96.8)	67 (98.5)	0.43
Married (%)	75 (56.4)	236 (70.7)	0.003	248 (66.5)	45 (71.4)	0.44	251 (65.7)	60 (70.6)	0.39	441 (64.5)	46 (67.6)	0.60
Smoker (%)	19 (14.3)	32 (9.6)	0.14	42 (11.3)	5 (7.9)	0.43	44 (11.5)	7 (8.2)	0.38	71 (10.4)	11 (16.2)	0.14
Alcohol user (%)	77 (57.9)	210 (62.9)	0.32	232 (62.2)	39 (61.9)	0.97	237 (62.0)	50 (58.8)	0.58	390 (57.0)	49 (72.1)	0.016
University or postgraduate level of education (%)	60 (45.1)	166 (49.7)	0.37	178 (47.7)	30 (47.6)	0.99	184 (48.2)	42 (49.4)	0.84	288 (42.1)	26 (38.2)	0.54
Annual income of £30,000 or more (%)	47 (37.0)	123 (38.4)	0.78	131 (36.6)	29 (50.0)	0.05	134 (36.5)	36 (45.0)	0.16	173 (27.9)	24 (40.0)	0.049
IBS after acute enteric infection (%)	22 (16.5)	37 (11.1)	0.11	51 (13.7)	6 (9.5)	0.37	52 (13.6)	7 (8.2)	0.18	85 (12.4)	6 (8.8)	0.39
Meal-related symptoms ≥50% of the time (%)	101 (75.9)	258 (77.2)	0.76	292 (78.3)	44 (69.8)	0.14	299 (78.3)	60 (70.6)	0.13	512 (74.9)	49 (72.1)	0.61

IBS subtype (%)												
IBS-C	18 (13.5)	74 (22.2)		72 (19.3)	15 (23.8)		73 (19.1)	19 (22.4)		126 (18.4)	10 (14.7)	
IBS-D	64 (48.1)	126 (37.7)		155 (41.6)	20 (31.7)		158 (41.4)	32 (37.6)		281 (41.1)	25 (36.8)	
IBS-M	51 (38.3)	132 (39.5)		144 (38.6)	28 (44.4)		149 (39.0)	34 (40.0)		269 (39.3)	32 (47.1)	
IBS-U	0 (0.0)	2 (0.6)	0.074	2 (0.5)	0 (0.0)	0.45	2 (0.5)	0 (0.0)	0.78	8 (1.2)	1 (1.5)	0.63
Most troublesome symptom (%)												
Abdominal pain	31 (23.3)	68 (20.4)		86 (23.1)	7 (11.1)		88 (23.0)	11 (12.9)		156 (22.8)	13 (19.1)	
Constipation	8 (6.0)	21 (6.3)		24 (6.4)	5 (7.9)		24 (6.3)	5 (5.9)		50 (7.3)	3 (4.4)	
Diarrhoea	27 (20.3)	44 (13.2)		60 (16.1)	7 (11.1)		62 (16.2)	9 (10.6)		109 (15.9)	8 (11.8)	
Bloating/distension	32 (24.1)	121 (36.2)		117 (31.4)	28 (44.4)		119 (31.2)	34 (40.0)		190 (27.8)	28 (41.2)	
Urgency	35 (26.3)	80 (24.0)	0.09	86 (23.1)	16 (25.4)	0.11	89 (23.3)	26 (30.6)	0.09	179 (26.2)	16 (23.5)	0.22
Opiate use (%)	27 (20.3)	43 (12.9)	0.042	51 (13.7)	6 (9.5)	0.37	54 (14.1)	16 (18.8)	0.27	135 (19.7)	13 (19.1)	0.90
Duration of IBS diagnosis, year(s) (%)												
1	5 (3.8)	11 (3.3)		11 (2.9)	3 (4.8)		11 (2.9)	5 (5.9)		24 (3.5)	1 (1.5)	
2	9 (6.8)	17 (5.1)		22 (5.9)	3 (4.8)		22 (5.8)	4 (4.7)		39 (5.7)	2 (2.9)	
3	10 (7.5)	27(8.1)		31 (8.3)	5 (7.9)		32 (8.4)	5 (5.9)		50 (7.3)	4 (5.9)	
4	4 (3.0)	17 (5.1)		16 (4.3)	5 (7.9)		16 (4.2)	5 (5.9)		28 (4.1)	5 (7.4)	
5	9 (6.8)	16 (4.8)		22 (5.9)	0 (0.0)		23 (6.0)	2 (2.4)		38 (5.6)	0 (0.0)	
>5	96 (72.2)	246 (73.7)	0.82	271 (72.7)	47 (74.6)	0.32	278 (72.8)	64 (75.3)	0.45	505 (73.8)	56 (82.4)	0.17

Number of IBS drugs in the last 12 months (%)												
0	8 (6.0)	59 (17.7)		48 (12.9)	16 (25.4)		48 (12.6)	19 (22.4)		78 (11.4)	18 (26.5)	
1	35 (26.3)	85 (25.4)		93 (24.9)	21 (33.3)		97 (25.4)	23 (27.1)		174 (25.4)	15 (22.1)	
2	42 (31.6)	84 (25.1)		105 (28.2)	11 (17.5)		106 (27.7)	20 (23.5)		184 (26.9)	12 (17.6)	
3	20 (15.0)	52 (15.6)		60 (16.1)	7 (11.1)		61 (16.0)	11 (12.9)		118 (17.3)	11 (16.2)	
4	16 (12.0)	36 (10.8)		43 (11.5)	7 (11.1)		44 (11.5)	8 (9.4)		69 (10.1)	7 (10.3)	
≥5	12 (9.0)	18 (5.4)	0.028	24 (6.4)	1 (1.6)	0.027	26 (6.8)	4 (4.7)	0.27	61 (8.9)	5 (7.4)	0.019
IBS-SSS severity (%)												
Remission	1 (0.8)	5 (1.5)		2 (0.5)	4 (6.3)		3 (0.8)	3 (3.5)		4 (0.6)	3 (4.4)	
Mild	7 (5.3)	51 (15.3)		43 (11.5)	13 (20.6)		44 (11.5)	14 (16.5)		65 (9.5)	21 (30.9)	
Moderate	43 (32.3)	146 (43.7)		152 (40.8)	26 (41.3)		154 (40.3)	35 (41.2)		274 (40.1)	26 (38.2)	
Severe	82 (61.7)	132 (39.5)	<0.001	176 (47.2)	20 (31.7)	<0.001	181 (47.4)	33 (38.8)	0.087	341 (49.9)	18 (26.5)	<0.001
HADS anxiety categories (%)												
Normal	25 (18.8)	98 (29.3)		96 (25.7)	22 (34.9)		96 (25.1)	27 (31.8)		171 (25.0)	29 (42.6)	
Borderline abnormal	27 (20.3)	86 (25.7)		91 (24.4)	16 (25.4)		93 (24.3)	20 (23.5)		158 (23.1)	16 (23.5)	
Abnormal	81 (60.9)	150 (44.9)	0.006	186 (49.9)	25 (39.7)	0.24	193 (50.5)	38 (44.7)	0.44	355 (51.9)	23 (33.8)	0.004
HADS depression categories (%)												
Normal	56 (42.1)	213 (63.8)		210 (56.3)	44 (69.8)		213 (55.8)	56 (65.9)		349 (51.0)	55 (80.9)	
Borderline abnormal	43 (32.3)	65 (19.5)		88 (23.6)	12 (19.0)		89 (23.3)	19 (22.4)		156 (22.8)	9 (13.2)	
Abnormal	34 (25.6)	56 (16.8)	<0.001	75 (20.1)	7 (11.1)	0.11	80 (20.9)	10 (11.8)	0.12	179 (26.2)	4 (5.9)	<0.001

PHQ-12 severity (%)												
Low	2 (1.5)	21 (6.3)		17 (4.6)	5 (7.9)		17 (4.5)	6 (7.1)		25 (3.7)	11 (16.2)	
Mild	25 (18.8)	86 (25.7)		81 (21.7)	25 (39.7)		84 (22.0)	27 (31.8)		153 (22.4)	23 (33.8)	
Moderate	56 (42.1)	143 (42.8)		169 (45.3)	21 (33.3)		170 (44.5)	29 (34.1)		284 (41.5)	23 (33.8)	
Severe	50 (37.6)	84 (25.1)	0.009	106 (28.4)	12 (19.0)	0.008	111 (29.1)	23 (27.1)	0.13	222 (32.5)	11 (16.2)	<0.001
VSI scores (%)												
Low	24 (18.0)	129 (38.6)		109 (29.2)	34 (54.0)		111 (29.1)	42 (49.4)		203 (29.7)	44 (64.7)	
Medium	46 (34.6)	110 (32.9)		130 (34.9)	17 (27.0)		132 (34.6)	24 (28.2)		230 (33.6)	17 (25.0)	
High	63 (47.4)	95 (28.4)	<0.001	134 (35.9)	12 (19.0)	<0.001	139 (36.4)	19 (22.4)	0.001	251 (36.7)	7 (10.3)	<0.001
IBS-QOL score (%)												
Low	59 (44.4)	71 (21.3)		115 (30.8)	6 (9.5)		119 (31.2)	11 (12.9)		235 (34.4)	4 (5.9)	
Medium	50 (37.6)	116 (34.7)		136 (36.5)	17 (27.0)		139 (36.4)	27 (31.8)		239 (34.9)	13 (19.1)	
High	24 (18.0)	147 (44.0)	<0.001	122 (32.7)	40 (63.5)	<0.001	124 (32.5)	47 (55.3)	<0.001	210 (30.7)	51 (75.0)	<0.001

*P value for a χ^2 test for categorical variables and independent samples *t*-test for continuous variable.

3.3.2 Characteristics of patients with impairment in home management, social leisure activities, private leisure activities, and maintaining close relationships because of IBS

Of all 752 individuals with Rome IV IBS, the characteristics of those who reported that IBS affected their home management (220 (29.3%)), social leisure activities (423 (56.3%)), private leisure activities (207 (27.5%)), and close relationships (203 (27.0%)) above a threshold score of ≥4 were examined (Figure 3.2). There was a significantly lower proportion of individuals with alcohol use ($P < 0.001$ for trend for all analyses) amongst those who reported that IBS affected any of the four areas of activities of daily living (Table 3.2). A smaller proportion of individuals with an annual income of £30,000 or more amongst those with impairment in activities of daily living was observed but this was only statistically significant in those with impairment in social leisure activities (24.3%, vs 34.8%, $P = 0.002$). There were significantly higher proportions of individuals with more severe IBS, higher levels of anxiety, depression, somatization, and gastrointestinal specific anxiety scores, and lower IBS-related quality of life in those who reported an impact of IBS on any of the four areas of activity of daily living ($P < 0.001$ for trend for all analyses).

Following logistic regression, those who reported constipation (OR = 0.15; 95% CI 0.05 to 0.46) or urgency (OR = 0.40; 95% CI 0.20 to 0.78) as their most troublesome symptom, compared with those reporting abdominal pain, those with borderline abnormal anxiety scores (OR = 0.22; 95% CI 0.10 to 0.49), compared with those with normal scores, and those with higher IBS-related quality of life (OR = 0.05; 95% CI 0.02 to 0.13) were less likely to report impairment in home management, and those with higher levels of depression (OR = 3.30; 95% CI 1.73 to 6.31) more likely. Those who drank alcohol (OR = 0.42; 95% CI 0.27 to

0.65), those with borderline abnormal anxiety scores (OR = 0.41; 95% CI 0.22 to 0.76), compared with those with normal scores, or with higher IBS-related quality of life (OR = 0.08; 95% CI 0.04 to 0.16) were less likely to report impairment of social leisure activities, and those who had attended university or gained a postgraduate level of education (OR = 2.46; 95% CI 1.54 to 3.93) or those who had severe IBS (OR = 3.61; 95% CI 1.77 to 7.36) more likely. Individuals with higher levels of depression (OR = 4.35; 95% CI 2.33 to 8.14) were more likely to report impairment in private leisure activities, and those with higher IBS-related quality of life (OR = 0.12; 95% CI 0.05 to 0.28) less likely. Finally, those with higher levels of depression (OR = 2.82; 95% CI 1.47 to 5.41) were more likely to report impairment in close relationships, and those who were married (OR = 0.35; 95% CI 0.21 to 0.57) or with higher IBS-related quality of life (OR = 0.04; 0.01 to 0.10) less likely.

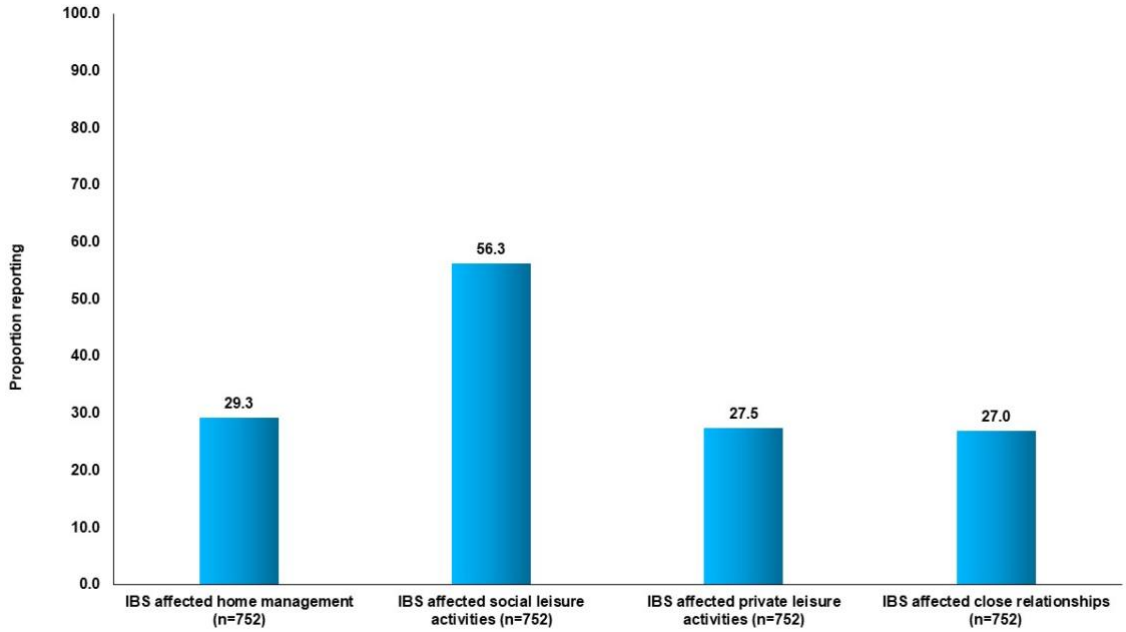

Figure 3.2. Impairment in home management, social leisure activities, private leisure activities, or maintaining close relationships because of IBS.

Table 3.2. Characteristics of individuals with Rome IV IBS who reported that IBS affected their home management, social leisure activities, private leisure activities, or close relationships compared with those who did not.

	IBS affects Home Management (n= 752)			IBS affects Social Leisure Activities (n= 752)			IBS affects Private Leisure Activities (n= 752)			IBS affects Close Relationships (n= 752)		
	Yes (n=220)	No (n=532)	P value	Yes (n=423)	No (n=329)	P value	Yes (n=207)	No (n=545)	P value	Yes (n=203)	No (n=549)	P value
Female (%)	192 (87.3)	463 (87.0)	0.93	370 (87.5)	285 (86.6)	0.73	179 (86.5)	476 (87.3)	0.75	172 (84.7)	483 (88.0)	0.24
Mean age (SD)	45.4 (13.7)	45.3 (15.2)	0.98	45.1 (14.6)	45.6 (15.1)	0.61	45.3 (14.0)	45.3 (15.1)	0.98	44.8 (13.9)	45.5 (15.1)	0.54
White ethnicity (%)	208 (94.5)	521 (97.9)	0.014	410 (96.9)	319 (97.0)	0.98	197 (95.2)	532 (97.6)	0.082	195 (96.1)	534 (97.3)	0.39
Married (%)	128 (58.2)	359 (67.5)	0.015	253 (59.8)	234 (71.1)	0.001	122 (58.9)	365 (67.0)	0.039	99 (48.8)	388 (70.7)	<0.001
Smoker (%)	33 (15.0)	49 (9.2)	0.02	50 (11.8)	32 (9.7)	0.36	31 (15.0)	51 (9.4)	0.027	30 (14.8)	52 (9.5)	0.038
Alcohol user (%)	94 (42.7)	345 (64.8)	<0.001	201 (47.5)	238 (72.3)	<0.001	94 (45.4)	345 (63.3)	<0.001	95 (46.8)	344 (62.7)	<0.001
University or postgraduate level of education (%)	82 (37.3)	232 (43.6)	0.11	167 (39.5)	147 (44.7)	0.15	71 (34.3)	243 (44.6)	0.011	70 (34.5)	244 (44.4)	0.014
Annual income of £30,000 or more (%)	42 (21.9)	155 (31.8)	0.011	91 (24.3)	106 (34.8)	0.002	41 (22.4)	156 (31.4)	0.022	41 (23.2)	156 (31.0)	0.048
IBS after acute enteric infection (%)	30 (13.6)	61 (11.5)	0.41	62 (14.7)	29 (8.8)	0.015	31 (15.0)	60 (11.0)	0.14	22 (10.8)	69 (12.6)	0.52

Meal-related symptoms ≥50% of the time (%)	0 (0.0)	391 (73.5)	0.28	327 (77.3)	234 (71.1)	0.053	162 (78.3)	399 (73.2)	0.16	160 (78.8)	401 (73.0)	0.11
IBS subtype (%)												
IBS-C	33 (15.0)	103 (19.4)		70 (16.5)	66 (20.1)		27 (13.0)	109 (20.0)		32 (15.8)	104 (18.9)	
IBS-D	96 (43.6)	210 (39.5)		193 (45.6)	113 (34.3)		99 (47.8)	207 (38.0)		93 (45.8)	213 (38.8)	
IBS-M	88 (40.0)	213 (40.0)		155 (36.6)	146 (44.4)		79 (38.2)	222 (40.7)		76 (37.4)	225 (41.0)	
IBS-U	3 (1.4)	6 (1.1)	0.50	5 (1.2)	4 (1.2)	0.02	2 (1.0)	7 (1.3)	0.047	2 (1.0)	7 (1.3)	0.36
Most troublesome symptom (%)												
Abdominal pain	66 (30.0)	103 (19.4)		89 (21.0)	80 (24.3)		52 (25.1)	117 (21.5)		52 (25.6)	117 (21.3)	
Constipation	7 (3.2)	46 (8.6)		23 (5.4)	30 (9.1)		6 (2.9)	42 (8.6)		11 (5.4)	42 (7.7)	
Diarrhoea	34 (15.5)	83 (15.6)		67 (15.8)	50 (15.2)		33 (15.9)	84 (15.4)		30 (14.8)	87 (15.8)	
Bloating/distension	56 (25.5)	162 (30.5)		111 (26.2)	107 (32.5)		52 (25.1)	166 (30.5)		49 (24.1)	169 (30.8)	
Urgency	57 (25.9)	138 (25.9)	0.003	133 (31.4)	62 (18.8)	0.001	64 (30.9)	131 (24.0)	0.017	61 (30.0)	134 (24.4)	0.17
Opiate use (%)	72 (32.7)	76 (14.3)	<0.001	107 (25.3)	41 (12.5)	<0.001	70 (33.8)	78 (14.3)	<0.001	59 (29.1)	89 (16.2)	<0.001
Duration of IBS diagnosis, year(s) (%)												
1	5 (2.3)	20 (3.8)		14 (3.3)	11 (3.3)		7 (3.4)	18 (3.3)		5 (2.5)	20 (3.6)	
2	10 (4.5)	31 (5.8)		21 (5.0)	20 (6.1)		14 (6.8)	27 (5.0)		12 (5.9)	29 (5.3)	
3	13 (5.9)	41 (7.7)		32 (7.6)	22 (6.7)		15 (7.2)	39 (7.2)		17 (8.4)	37 (6.7)	
4	7 (3.2)	26 (4.9)		16 (3.8)	17 (5.2)		5 (2.4)	28 (5.1)		5 (2.5)	28 (5.1)	
5	16 (7.3)	22 (4.1)		24 (5.7)	14 (4.3)		9 (4.3)	29 (5.3)		14 (6.9)	24 (4.4)	
>5	169 (76.8)	392 (73.7)	0.26	316 (74.7)	245 (74.5)	0.83	157 (75.8)	404 (74.1)	0.58	150 (73.9)	411 (74.9)	0.36

Number of IBS drugs in the last 12 months (%)												
0	19 (8.6)	77 (14.5)		42 (9.9)	54 (16.4)		17 (8.2)	79 (14.5)		14 (6.9)	82 (14.9)	
1	54 (24.5)	135 (25.4)		101 (23.9)	88 (26.7)		52 (25.1)	137 (25.1)		52 (25.6)	137 (25.0)	
2	51 (23.2)	145 (27.3)		110 (26.0)	86 (26.1)		47 (22.7)	149 (27.3)		41 (20.2)	155 (28.2)	
3	41 (18.6)	88 (16.5)		79 (18.7)	50 (15.2)		35 (16.9)	94 (17.2)		37 (18.2)	92 (16.8)	
4	23 (10.5)	53 (10.0)		43 (10.2)	33 (10.0)		26 (12.6)	50 (9.2)		25 (12.3)	51 (9.3)	
≥5	32 (14.5)	34 (6.4)	0.004	48 (11.3)	18 (5.5)	0.009	30 (14.5)	36 (6.6)	0.003	34 (16.7)	32 (5.8)	<0.001
IBS-SSS severity (%)												
Remission	0 (0.0)	7 (1.3)		0 (0.0)	7 (2.1)		0 (0.0)	7 (1.3)		0 (0.0)	7 (1.3)	
Mild	12 (5.5)	74 (13.9)		22 (5.2)	64 (19.5)		7 (3.4)	79 (14.5)		6 (3.0)	80 (14.6)	
Moderate	43 (19.5)	257 (48.3)		131 (31.0)	169 (51.4)		45 (21.7)	255 (46.8)		48 (23.6)	252 (45.9)	
Severe	165 (75.0)	194 (36.5)	<0.001	270 (63.8)	89 (27.1)	<0.001	155 (74.9)	204 (37.4)	<0.001	149 (73.4)	210 (39.3)	<0.001
HADS anxiety categories (%)												
Normal	39 (17.7)	161 (30.3)		85 (20.1)	115 (35.0)		30 (14.5)	170 (31.2)		23 (11.3)	177 (32.2)	
Borderline abnormal	33 (15.0)	141 (26.5)		81 (19.1)	93 (28.3)		34 (16.4)	140 (25.7)		41 (20.2)	133 (24.2)	
Abnormal	148 (67.3)	230 (43.2)	<0.001	257 (60.8)	121 (36.8)	<0.001	143 (69.1)	235 (43.1)	<0.001	139 (68.5)	239 (43.5)	<0.001
HADS depression categories (%)												
Normal	61 (27.7)	343 (64.5)		161 (38.1)	243 (73.9)		55 (26.6)	349 (64.0)		56 (27.6)	348 (63.4)	
Borderline abnormal	56 (25.5)	109 (20.5)		114 (27.0)	51 (15.5)		47 (22.7)	118 (21.7)		47 (23.2)	118 (21.5)	
Abnormal	103 (46.8)	80 (15.0)	<0.001	148 (35.0)	35 (10.6)	<0.001	105 (50.7)	78 (14.3)	<0.001	100 (49.3)	83 (15.1)	<0.001

PHQ-12 severity (%)												
Low	4 (1.8)	32 (6.0)		13 (3.1)	23 (7.0)		4 (1.9)	32 (5.9)		5 (2.5)	31 (5.6)	
Mild	24 (10.9)	152 (28.6)		71 (16.8)	105 (31.9)		30 (14.5)	146 (26.8)		27 (13.3)	149 (27.1)	
Moderate	74 (33.6)	233 (43.8)		170 (40.2)	137 (41.6)		68 (32.9)	239 (43.9)		72 (35.5)	235 (42.8)	
Severe	118 (53.6)	115 (21.6)	<0.001	169 (40.0)	64 (19.5)	<0.001	105 (50.7)	128 (23.5)	<0.001	99 (48.8)	134 (24.4)	<0.001
VSI scores (%)												
Low	42 (19.1)	205 (38.5)		74 (17.5)	173 (52.6)		28 (13.5)	219 (40.2)		31 (15.3)	216 (39.3)	
Medium	59 (26.8)	188 (35.3)		138 (32.6)	109 (33.1)		61 (29.5)	186 (34.1)		56 (27.6)	191 (34.8)	
High	119 (54.1)	139 (26.1)	<0.001	211 (49.9)	47 (14.3)	<0.001	118 (57.0)	140 (25.7)	<0.001	116 (57.1)	142 (25.9)	<0.001
IBS-QOL score (%)												
Low	139 (63.2)	100 (18.8)		215 (50.8)	24 (7.3)		134 (64.7)	105 (19.3)		142 (70.0)	97 (17.7)	
Medium	60 (27.3)	192 (36.1)		149 (35.2)	103 (31.3)		57 (27.5)	195 (35.8)		47 (23.2)	205 (37.3)	
High	21 (9.5)	240 (45.1)	<0.001	59 (13.9)	202 (61.4)	<0.001	16 (7.7)	245 (45.0)	<0.001	14 (6.9)	247 (45.0)	<0.001

*P value for a χ^2 test for categorical variables and independent samples *t*-test for continuous variables.

3.4 Discussion

In this study, 752 individuals with Rome IV-defined IBS were recruited to examine impact of IBS on work and activities of daily living. The results suggest that approximately 10% of individuals were unemployed partly as a result of their condition. Of those who were employed, nearly 30% reported absenteeism, and over 80% reported presenteeism or overall work impairment because of their IBS. 90% of participants reported that their IBS symptoms interfered with activities of daily living, with over 50% reporting interference with social leisure activities and over 25% reporting interference with home management, private leisure activities, or close relationships. Those with any absenteeism were significantly more likely to report more severe IBS, higher anxiety, depression, somatisation, and gastrointestinal specific anxiety scores, and lower IBS-related quality of life, whereas those with any presenteeism were significantly more likely to report more severe IBS, higher somatisation and gastrointestinal specific anxiety scores, and lower IBS-related quality of life. In terms of activities of daily living, individuals with impairment in home management, social leisure activities, personal leisure activities, or close relationships were significantly more likely to have more severe IBS, higher anxiety, depression, somatization, and gastrointestinal specific anxiety scores, and lower IBS-related quality of life. The results also showed that there were several independent predictors of work or activity impairment, including younger age, presence of abdominal pain, severity of IBS symptoms, anxiety, depression, and lower IBS-related quality of life.

The study recruited individuals who self-identified as having IBS and who also met the Rome IV criteria for IBS. They are, therefore, likely to represent individuals with IBS in the UK because some had never seen a doctor for their IBS, some had seen a primary care physician, and some had seen a

gastroenterologist. Although data on the type of work performed by participants were not collected, the sample also included participants from different age groups, levels of education, and income brackets, suggesting that individuals at different career stages have been included in this study. Validated questionnaires, including the WPAI:IBS, which has been validated for use in patients with IBS,[265] and has been used widely,[134, 246, 257, 274] were used. Because of the use of mandatory fields in the online questionnaire, near complete data for variables of interest were obtained.

Although a national UK registry to obtain a sample of individuals with IBS was used, participants' medical records were not checked to rule out other organic gastrointestinal diseases that present with similar symptoms such as coeliac disease or IBD.[275, 276] Given that IBS is more prevalent than these conditions, UK national guidance recommends these conditions are ruled out prior to a diagnosis of IBS.[143, 145] However, because almost 90% of the ContactME-IBS registrants have seen a GP or a gastroenterologist for IBS, and nearly 80% of the participants had had IBS for ≥5 years, suggesting that the diagnosis was stable, it is reasonable to assume that participants genuinely had IBS. All involved individuals were UK residents, 97% were White, 87% were female, and most had IBS-D or IBS-M. Although the WSAS is a validated questionnaire, has been widely used in studies in IBS, and is sensitive to change in IBS treatment trials,[267-270] it has not been validated formally in IBS.[277] Previous studies attempting to quantify the impact of IBS on activities of daily living have also resorted to generic, rather than disease-specific, questionnaires.[138, 244] Although the WPAI:IBS and WSAS examine the extent to which IBS impacts on work and activities of daily living, they are unable to capture the complex feelings and emotions, such as fear of uncertainty, loss of freedom, and shame, as well

as the reasons for behavioural adaptations, such as activity avoidance, which can be examined in qualitative studies.[142, 199, 242, 243] As this was a cross-sectional survey, some of the associations, or the lack of associations observed that may otherwise be expected, could be due to individuals having already altered their working patterns, employment status, home, or social activities as a result of their symptoms prior to this study. Similarly, findings such as a reduced likelihood of smokers reporting activity impairment may also relate to reverse causation, with smokers being more likely to have a pre-existing sedentary lifestyle unrelated to IBS. Finally, given the study was conducted during the COVID-19 pandemic, with the resultant shift towards home working and reduced social interactions, the possibility that the true effect of IBS on work and activities of daily living has been underestimated cannot be excluded.

Prior studies have demonstrated that a substantial proportion of individuals with IBS report absenteeism, presenteeism, overall work impairment, and activity impairment.[134, 246, 257, 274] Frandemark *et al.* reported absenteeism among almost 25% of participants and presenteeism in over 80%,[257] whereas other studies have only reported mean levels of absenteeism or presenteeism. In contrast to the current study, these studies were more selective, recruiting only people who had consulted a doctor for their IBS in primary or secondary care,[134, 257] only those with specific IBS subtypes,[245, 246] or only employees of a single institution.[274] Although Frandemark *et al.* examined the associations between work impairment and psychological comorbidities,[257] data on anxiety, depression, and somatic symptoms were only available in a subset of 155 participants. There are limited studies attempting to quantify the impact of IBS on activities of daily living.[138, 244, 245] One study, which recruited 42 patients from secondary care, found that 21% of participants reported impairment at work.[244] Another study,

recruiting 179 participants with Rome III-defined IBS from the community, reported that impairment of activities of daily living was associated with severe IBS, anxiety, depression, and gastrointestinal symptom-specific anxiety.[138] A large cross-sectional survey, conducted in almost 2000 people with IBS-C and IBS-D defined using the Rome III criteria, reported that symptoms affected productivity on average 8 days per month and led to approximately 1.5 days of absence from work per month.[245]

This study has demonstrated that a large proportion of individuals with IBS experience impairment in their personal and professional lives because of their disorder. The use of the WPAI:IBS allowed it to be established that the impairment to work and activities of daily living seen are likely to be a direct consequence of IBS. It is, perhaps, not surprising that those with more severe symptoms and lower IBS-related quality of life report the greatest impact on work and activities of daily living. The findings related to the association of psychological comorbidities with work and activity impairment are interesting. Although these psychological comorbidities may themselves impact on work and activities of daily living, participants attributed their impairment to IBS symptoms, not to these psychological comorbidities. However, psychological comorbidity is also associated with more severe IBS symptoms,[112, 146] which may be a confounding factor. Individuals with IBS may also lack the resilience to deal with the impact of symptoms of IBS and develop maladaptive behaviours, such as activity avoidance, further compounding the impact of IBS on their quality of life.[278, 279] The observation that the time since diagnosis was not associated with a reduction in impairment at work or in activities of daily living is also noteworthy, suggesting that those with a longer duration of disease may not have found

constructive adaptations to their personal or professional lives to reduce the impact of IBS.

The results from this study have important implications. First, people of working age with IBS should be aware that impairment at work because of their disorder is, perhaps, more common than readily acknowledged, likely due to the embarrassing nature of symptoms or the feeling that a “functional” disease without an identifiable structural cause is not a legitimate one. Instead, they should feel empowered to discuss their illness with their employer and occupational health physician so that reasonable adjustments can be made to balance work requirements with living with IBS.[243] Second, employers should appreciate that IBS is prevalent and is likely to impact on absenteeism and productivity and, ultimately, have cost implications. Creating a more supportive work environment may help reduce the impact of IBS on work.[280] Third, clinicians should be mindful that IBS impacts on a range of activities. Asking patients about the impact of IBS, together with active listening and an empathetic approach, may help establish a trusting patient-doctor relationship, which is essential for the acceptance of the diagnosis and may aid adherence to a shared management plan.[194, 205] Fourth, IBS-specific CBT, which uses repeated exposure to activities like physical exertion, food, or stressful situations that elicit symptoms, with management of elicited emotions and responses, has been shown to be an effective treatment.[187] Although one RCT reported that individuals randomised to therapist-delivered telephone CBT or web-based CBT with minimal therapist support, compared with those on standard treatment, had a significantly greater reduction in mean WSAS,[270] future studies should further examine whether CBT can improve work productivity. Fifth, compared with other symptoms of IBS, predominant abdominal pain appeared to be an independent predictor of

presenteeism and overall work impairment. This is, perhaps, not surprising given that painful DGBI, compared with non-painful DGBI, are more likely to be associated with work impairment,[281] and that abdominal pain severity appears to drive healthcare-seeking behaviour.[282, 283] Finally, the results of studies such as the current one can be used to inform cost-effectiveness analyses,[284, 285] to facilitate value-based care in IBS.

In summary, these results show that IBS has a substantial impact on work and activities of daily living. This study has estimated that, in the UK, between 72 and 188 million hours of work are lost per year due to the condition. The impairment at work because of IBS represents a substantial burden to society. Another source of societal burden is the impact of IBS on the healthcare system and the cost of IBS will be explored in Chapter 6. Impairments at work and in private life may also have important implications for quality of life and this will be explored in the next chapter.

Chapter 4 Assessing the Quality of Life of Individuals with Irritable Bowel Syndrome

4.1 Introduction

In Chapter 3, it has been demonstrated that IBS has a substantial impact on work and activities of daily living. This, in combination with the bothersome GI symptoms, psychological comorbidities, and the chronicity and incurable nature of the disorder, means that individuals with IBS experience significant morbidity as a result of their condition. Quality of life may be affected to the same degree as organic gastrointestinal disorders, such as Crohn's disease.[128] It is, therefore, important to understand how the quality of life of individuals with IBS is affected and compare that with individuals with other chronic conditions. Contemporaneous estimates of quality of life are particularly important as definitions of IBS evolve.

Multiple studies have examined quality of life of individuals with IBS.[128-139] However, only one of these recruited individuals with Rome IV-defined IBS,[139] who have been shown to exhibit more severe gastrointestinal symptoms and higher rates of psychological comorbidity.[21] This study used a generic health-related quality of life questionnaire, the EQ-5D, and reported the mean EQ-5D among these individuals. However, the study was relatively small, utilised data from patients taking part in two RCTs, and excluded those with anxiety or depression, which may have affected the results. In addition, it made no comparison with EQ-5D scores in other chronic conditions. Finally, none of the previous studies have examined features associated with lower quality of life amongst individuals with IBS.

Both disease-specific and generic health-related quality of life of individuals with Rome IV IBS were, therefore, assessed in a cross-sectional survey to identify factors associated with lower quality of life, and compare generic quality of life scores observed in IBS with other chronic conditions. It was hypothesised that

those with Rome IV IBS would have a poor quality of life, comparable to those with other chronic organic diseases, and that those with more severe symptoms of IBS, or higher levels of psychological comorbidities, would have lower quality of life.

4.2 Methods

4.2.1 Participants and setting

This study recruited individuals registered with ContactME-IBS, a national UK registry of people with IBS who are interested in research.[258] Full details of the recruitment methodology have already been discussed in Chapter 3.

4.2.2 Data collection and synthesis

4.2.2.1 Demographic and symptom data

Full details of the demographic and symptom data have already been discussed in Chapter 3. In addition, respondents were asked to state whether they had seen a GP or a gastroenterologist about their IBS symptoms. Data on presence of co-existing functional dyspepsia according to Rome IV criteria were collected,[286] assigning presence or absence of epigastric pain syndrome (EPS) or postprandial distress syndrome (PDS).

4.2.2.2 Quality of life

The IBS-QOL, a validated IBS-specific questionnaire, was used to measure health-related quality of life.[263, 264] Full details of the IBS-QOL and transformation of the IBS-QOL scores have already been provided in Chapter 3. In addition, the EQ-5D,[287] a generic health-related quality of life questionnaire from EuroQOL widely used in healthcare, was used. The EQ-5D-5L instrument,[288] one of the three versions of EQ-5D, consisting of five items capturing different aspects of health, including mobility, self-care, ability to carry

out usual activities, pain/discomfort, and anxiety/depression, was used. Each item has five levels of responses, giving a total of 3125 possible health states. Each health state was mapped to obtain a utility score for a UK population using a crosswalk calculator,[289] a mapping function recommended by NICE.[290]

4.2.2.3 IBS symptom severity, mood, somatic symptoms, and gastrointestinal symptom-specific anxiety

Symptom severity was assessed using the IBS-SSS.[113] Anxiety and depression data were collected using the HADS,[260] somatic symptom-reporting data using the PHQ-12,[119] and gastrointestinal symptom-specific anxiety using the VSI.[262] Full details of the assessment of gastrointestinal symptom severity and these psychological data have already been provided in Chapter 3.

4.2.2.4 IBS-related resource use

Data on healthcare usage related to a person's IBS over the 12 months prior to recruitment were collected. Participants were asked to report number of appointments (primary care physicians, gastroenterologists, specialist nurses, dietitians, or psychologists), number of investigations (blood or stool tests, endoscopies, radiological investigations, or breath tests), number of unplanned emergency department attendances or inpatient admissions (including length of stay in days), and OTC or prescribed drug usage (in months). Costs for primary care physician appointments from Unit Costs of Health and Social Care 2020,[291] and other appointments, investigations, or unplanned inpatient days in secondary care using 2019/20 NHS National Cost Collection Data were applied.[292] All appointments were assumed to be follow-up appointments, which cost less than a new patient appointment. The lowest price for a 1-month supply of each drug, using the British National Formulary (BNF) online, were applied.[293]

4.2.2.5 Impact of IBS on work and activities of daily living

The WPAI:IBS[265] and WSAS[266] were used to assess level of work productivity loss in employed people with IBS and impairment in activities of daily living in all people with IBS, respectively. Full details have already been provided in Chapter 3.

4.2.3 Statistical analysis

The mean IBS-QOL and EQ-5D scores were calculated for individuals with Rome IV IBS, those with Rome III IBS, and all individuals with a self-reported diagnosis of IBS. The mean EQ-5D score in this study was compared with those for other chronic illnesses. For only those with Rome IV IBS, presence or absence of severe impairment in health-related quality of life were dichotomised, with an IBS-QOL $\leq$50.86 corresponding to a severe score on the functional bowel disorder severity index in the original IBS-QOL validation study.[263] Because there are no validated cut-offs to define low, medium, or high generic health-related quality of life according to the EQ-5D, these data were divided into tertiles of equal size. The characteristics of individuals with Rome IV IBS in the lowest EQ-5D tertile were compared with the remaining individuals with Rome IV IBS in this cohort. Categorical variables were compared using a χ^2 test and continuous data using an independent samples *t*-test, with statistical significance defined as a *P* value <0.01. Logistic regression was performed, controlling for baseline data to examine factors associated with severe IBS-related quality of life or the lowest EQ-5D tertile, and results were reported with ORs with 95% CIs. The variance in the data explained by the logistical regression model was assessed using the Nagelkerke R^2 statistic. All analyses were performed using SPSS for Windows (version 27.0 SPSS, Chicago, IL).

4.3 Results

In total, 1278 (29.9%) of 4280 registrants (mean age 47.2 years (range 18-89 years), 1086 (85.0%) female) responded and completed the questionnaire. Mean IBS-QOL and EQ-5D scores in all individuals with self-reported IBS were 55.0 (Standard deviation (SD) 23.3) and 0.633 (SD 0.269), respectively. In total, 995 individuals met Rome III criteria for IBS (mean age 46.5 years (range 18-85 years), 852 (85.6%) female, and 961 (96.6%) White), in whom mean IBS-QOL scores were 52.3 (SD 22.6) and mean EQ-5D scores 0.615 (SD 0.274). There were 752 (58.8%) individuals meeting Rome IV criteria for IBS (mean age 45.3 years (range 18-81 years), 655 (87.1%) female, and 729 (96.9%) White). The mean IBS-QOL was 48.4 (SD 22.3) and the mean EQ-5D score was 0.570 (SD 0.283). The latter is on a par with people living with a stroke, leg ulcers, or chronic obstructive pulmonary disease (Table 4.1).[294-298] Mean IBS-QOL scores were significantly lower among those with IBS-D, versus other subtypes (IBS-C 52.3 (SD 19.9), IBS-D 45.4 (SD 23.0), IBS-M 49.4 (SD 22.0), $P = 0.005$) but there was no difference in the mean EQ-5D score according to IBS subtype (IBS-C 0.595 (SD 0.268), IBS-D 0.569 (SD 0.280), IBS-M 0.558 (SD 0.294), $P = 0.45$).

Table 4.1. EQ-5D Score among individuals with other chronic conditions compared with those with IBS in the present study.[294-298]

Chronic Condition	Mean EQ-5D Score (SD)
Asthma	0.840 (0.200)
Menopause	0.729 (0.262)
Diabetes mellitus	0.673 (0.283)
Rheumatoid arthritis	0.660 (0.270)
Heart failure	0.640 (0.270)
Low back pain	0.636 (0.266)
Self-reported IBS (from the present study)	0.633 (0.269)
Rome III IBS (from the present study)	0.615 (0.274)
Elderly (age >75)	0.614 (0.299)
Stroke	0.612 (0.318)
Rome IV IBS (from the present study)	0.570 (0.283)
Leg ulcers	0.552 (0.307)
Chronic obstructive pulmonary disease	0.540 (0.309)
Osteoarthritis	0.442 (0.336)

4.3.1 Characteristics of individuals with, compared with those without, severely impaired IBS-related quality of life.

Individuals with, compared with those without, severely impaired IBS-related quality of life were significantly younger (mean age, 44.0 years vs. 46.9 years, $P = 0.006$), less likely to use alcohol (49.0% vs. 69.5%, $P < 0.001$), to have a higher level of education (34.1% vs. 50.9%, $P < 0.001$), or to have an income of £30,000 or more (24.0% vs. 34.6%, $P = 0.002$), and more likely to use opiates for any reason (24.3% vs. 14.2%, $P < 0.001$) (Table 4.2). There was a higher proportion of individuals with co-existing EPS or PDS ($P < 0.001$ for both) among those with severely impaired IBS-related quality of life. A greater proportion of those with severely impaired IBS-related quality of life had severe IBS symptom scores, abnormal HADS-anxiety scores or HADS-depression scores, higher somatic symptom-reporting scores, or higher VSI scores ($P < 0.001$ for trend for all analyses). Proportion of individuals having seen a primary care physician or gastroenterologist in the previous 12 months with IBS symptoms was significantly higher ($P < 0.001$ for both) amongst those with severely impaired IBS-related quality of life. Mean cost of appointments, investigations, unplanned attendances, and total direct healthcare costs were all significantly higher with severely impaired IBS-related quality of life ($P < 0.001$ for all analyses). Finally, a higher proportion of those with severely impaired IBS-related quality of life reported any IBS-related absenteeism, presenteeism, or overall work or activity impairment, or reported that IBS affected home management, social or private leisure activities, or close relationships ($P < 0.001$ for all analyses).

Following logistic regression controlling for all other data, only those who reported medium (OR = 10.8; 95% CI 5.41 to 21.5) or high levels of gastrointestinal symptom-specific anxiety (OR = 44.0; 95% CI 19.0 to 102.1),

those with borderline abnormal HADS-depression scores (OR = 2.65; 95% CI 1.34 to 5.26), those with impairment in their social leisure activities because of IBS (OR = 3.62; 95% CI 2.01 to 6.53), and those with impairment in their close relationships because of IBS (OR = 5.67; 95% CI 2.60 to 12.4) were more likely to report severely impaired IBS-related quality of life. The logistic regression model explained 69.3% of the variance of the data.

Table 4.2. Characteristics of individuals with, compared with those without, severely impaired IBS-related quality of life amongst those with Rome IV IBS.

	Severely Impaired IBS-related quality of life		*p* value*
	Yes (n = 408)	No (n = 344)	
Mean age (SD)	44.0 (14.4)	46.9 (15.1)	0.006
Female (%)	364 (89.2)	291 (84.6)	0.06
Smoker (%)	48 (11.8)	34 (9.9)	0.41
Alcohol use (%)	200 (49.0)	239 (69.5)	<0.001
White ethnicity (%)	394 (96.6)	335 (97.4)	0.52
Married (%)	249 (61.0)	238 (69.2)	0.02
University or postgraduate level of education (%)	139 (34.1)	175 (50.9)	<0.001
Annual income of £30,000 or more (%)	87 (24.0)	110 (34.6)	0.002
IBS subtype (%)			
IBS-C	70 (17.3)	66 (19.5)	
IBS-D	180 (44.6)	126 (37.2)	
IBS-M	154 (38.1)	147 (43.4)	0.13
Duration of IBS diagnosis, year(s) (%)			
1	14 (3.4)	11 (3.2)	
2	24 (5.9)	17 (4.9)	
3	31 (7.6)	23 (6.7)	
4	13 (3.2)	20 (5.8)	
5	25 (6.1)	13 (3.8)	
>5	301 (73.8)	260 (75.6)	0.35
IBS after acute enteric infection (%)	52 (12.7)	39 (11.3)	0.56
Opiate use (%)	99 (24.3)	49 (14.2)	<0.001
Most troublesome symptom (%)			
Abdominal pain	85 (20.8)	84 (24.4)	
Constipation	27 (6.6)	26 (7.6)	
Diarrhoea	70 (17.2)	47 (13.7)	
Bloating/distension	108 (26.5)	110 (32.0)	
Urgency	118 (28.9)	77 (22.4)	0.10
Co-existent EPS (%)	162 (39.7)	72 (21.0)	<0.001
Co-existent PDS (%)	235 (57.9)	96 (28.2)	<0.001
IBS-SSS severity (%)			
Mild	20 (4.9)	66 (19.6)	
Moderate	124 (30.4)	176 (52.2)	
Severe	264 (64.7)	95 (28.2)	<0.001
HADS-anxiety categories (%)			
Normal	52 (12.7)	148 (43.0)	
Borderline abnormal	88 (21.6)	86 (25.0)	
Abnormal	268 (65.7)	110 (32.0)	<0.001

HADS-depression categories (%)				
Normal			141 (34.6)	263 (76.5)	
Borderline abnormal			118 (28.9)	47 (13.7)	
Abnormal			149 (36.5)	34 (9.9)	<0.001
PHQ-12 severity (%)				
Low			8 (2.0)	28 (8.1)	
Mild			59 (14.5)	117 (34.0)	
Moderate			175 (42.9)	132 (38.4)	
Severe			166 (40.7)	67 (19.5)	<0.001
VSI scores (%)				
Low			35 (8.6)	212 (61.6)	
Medium			144 (35.3)	103 (29.9)	
High			229 (56.1)	29 (8.4)	<0.001
Seen a primary care physician regarding IBS in the last 12 months (%)			189 (46.3)	105 (30.5)	<0.001
Seen a gastroenterologist regarding IBS in the last 12 months (%)			107 (26.2)	40 (11.6)	<0.001
Number of IBS-related drugs in the last 12 months (%)				
0			40 (9.8)	56 (16.3)	
1			98 (24.0)	91 (26.5)	
2			106 (26.0)	90 (26.2)	
3			72 (17.6)	57 (16.6)	
4			46 (11.3)	30 (8.7)	
≥5			46 (11.3)	20 (5.8)	0.014
Mean direct healthcare costs of IBS (SD)	**Appointments**		303.28 (644.32)	131.02 (464.73)	<0.001
	Investigations		215.30 (410.07)	89.37 (252.26)	<0.001
	IBS-related drugs		81.73 (105.78)	61.82 (82.50)	0.011
	Unplanned attendances		150.84 (538.18)	43.76 (253.29)	<0.001
	Total direct healthcare costs		751.14 (1201.36)	325.96 (696.11)	<0.001
WPAI:IBS (%)	**Any IBS-related absenteeism**		95 (38.3)	38 (17.4)	<0.001
	Any IBS-related presenteeism		212 (92.6)	161 (77.8)	<0.001
	Any IBS-related overall work impairment		218 (87.9)	164 (74.9)	<0.001
	Any IBS-related activity impairment		395 (96.8)	289 (84.0)	<0.001
WSAS (%)	**IBS affected home management**		183 (44.9)	37 (10.8)	<0.001
	IBS affected social leisure activities		328 (80.4)	95 (27.6)	<0.001
	IBS affected private leisure activities		172 (42.2)	35 (10.2)	<0.001
	IBS affected close relationships		181 (44.4)	22 (6.4)	<0.001

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

4.3.2 Overlap between visceral sensitivity index and irritable bowel syndrome quality of life.

Because of the highly significant association between gastrointestinal symptom-specific anxiety and severely impaired IBS-related quality of life, the VSI and IBS-QOL questionnaires were compared side-by-side (Table 4.3). Of the 15 items of the VSI questionnaire, eight assessed almost identical issues to items on the IBS-QOL, and a further six shared similar themes. The model was, therefore, run again excluding the VSI. In this analysis, those with a university or postgraduate level of education (OR = 0.43; 95% CI 0.26 to 0.70) were less likely to report severely impaired IBS-related quality of life whilst those with borderline abnormal (OR = 3.19; 95% CI 1.65 to 6.17) or abnormal (OR = 4.49; 95% CI 2.46 to 8.19) HADS-anxiety scores, those with borderline abnormal HADS-depression scores (OR = 2.43; 95% CI 1.37 to 4.33), those with impairment in their social leisure activities because of IBS (OR = 5.54; 95% CI 3.29 to 9.35), and those with impairment in their close relationships because of IBS (OR = 4.13; 95% CI 2.14 to 7.96) were more likely to report severely impaired IBS-related quality of life. The logistic regression model explained 57.5% of the variance of the data.

Table 4.3. Overlap between Visceral Sensitivity Index (VSI) and Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaires.

Visceral Sensitivity Index (VSI) items	Irritable Bowel Syndrome Quality of Life (IBS-QOL) items	
	Match	**Similar themes**
1. I worry that whenever I eat during the day, bloating and distension in my belly will get worse.	23. I have to watch the kind of food I eat because of my bowel problems.	11. I have to watch the amount of food I eat because of my bowel problems. 28. I feel frustrated that I cannot eat when I want because of my bowel problems.
2. I get anxious when I go to a new restaurant.		11. I have to watch the amount of food I eat because of my bowel problems. 23. I have to watch the kind of food I eat because of my bowel problems. 28. I feel frustrated that I cannot eat when I want because of my bowel problems.
3. I often worry about problems in my belly.	15. I worry that my bowel problems will get worse.	31. I worry about losing control of my bowels 32. I fear that I won't be able to have a bowel movement.
4. I have a difficult time enjoying myself because I cannot get my mind off of discomfort in my belly.	7. I feel my life is less enjoyable because of my bowel problems.	30. My life revolves around my bowel problems.
5. I often fear that I won't be able to have a normal bowel movement.	32. I fear that I won't be able to have a bowel movement.	
6. Because of fear of developing abdominal discomfort, I seldom try new foods.	23. I have to watch the kind of food I eat because of my bowel problems.	

7. No matter what I eat, I will probably feel uncomfortable.	23. I have to watch the kind of food I eat because of my bowel problems.	28. I feel frustrated that I cannot eat when I want because of my bowel problems.
8. As soon as I feel abdominal discomfort I begin to worry and feel anxious.		
9. When I enter a place I haven't been before, one of the first things I do is to look for a bathroom.	29. It is important to be near a toilet because of my bowel problems.	31. I worry about losing control of my bowels.
10. I am constantly aware of the feelings I have in my belly.		30. My life revolves around my bowel problems.
11. I often feel discomfort in my belly could be a sign of a serious illness.		15. I worry that my bowel problems will get worse.
12. As soon as I awake, I worry that I will have discomfort in my belly during the day.		5. I feel like I'm losing control of my life because of my bowel problems. 30. My life revolves around my bowel problems.
13. When I feel discomfort in my belly, it frightens me.		15. I worry that my bowel problems will get worse.
14. In stressful situations, my belly bothers me a lot.	19. I have to avoid stressful situations because of my bowel problems.	
15. I constantly think about what is happening inside my belly.		1. I feel helpless because of my bowel problems. 5. I feel like I'm losing control of my life because of my bowel problems. 30. My life revolves around my bowel problems.

4.3.3 Characteristics of individuals in the lowest, compared with the middle and highest, tertiles of generic health-related quality of life.

Those in the lowest EQ-5D tertile were significantly more likely to smoke (17.2% vs 7.8%, $P < 0.001$) or use opiates for any reason (37.2% vs 11.1%, $P < 0.001$) and significantly less likely to use alcohol (38.8% vs 68.1%, $P < 0.001$), to be married (55.6% vs 69.3%, $P < 0.001$), to have a university or postgraduate level of education (29.2% vs 48.0%, $P < 0.001$), or to have an income of £30,000 or more (15.9% vs 35.5%, $P < 0.001$) (Table 4.4). We observed a significantly higher proportion with co-existing EPS or PDS ($P < 0.001$ for both) among those in the lowest EQ-5D tertile. Again, a significantly greater proportion of those in the lowest EQ-5D tertile had severe IBS symptom scores, abnormal HADS-anxiety or HADS-depression scores, higher somatic symptom-reporting scores, or higher VSI scores ($P < 0.001$ for trend for all analyses). A significantly greater proportion of those in the lowest tertile had seen a primary care physician or gastroenterologist in the previous 12 months with IBS symptoms, and the number of drugs used for IBS in the last 12 months was significantly higher ($P < 0.001$ for all). All mean costs for IBS were significantly higher in those in the lowest EQ-5D tertile ($P < 0.01$ for all analyses). Finally, a higher proportion of those in the lowest EQ-5D tertile reported any IBS-related absenteeism, presenteeism, or activity impairment, or reported that IBS affected home management, social or private leisure activities, or close relationships ($P < 0.01$ for all analyses).

Following logistic regression controlling for all data, those who used alcohol (OR = 0.52; 95% CI 0.32 to 0.85) were less likely to be in the lowest EQ-5D tertile whilst those with abnormal HADS-depression scores (OR = 5.27; 95% CI 2.73 to 10.2), those with moderate (OR = 5.04; 95% 2.24 to 11.3) or higher

levels of somatisation (OR = 9.11; 95% CI 3.90 to 21.3), or those with impairment in home management (OR = 2.89; 95% CI 1.49 to 5.60) were more likely to report lower EQ-5D scores for quality of life. The logistic regression model explained 59.0% of the variance of the data.

Table 4.4. Characteristics of individuals with Rome IV IBS in the lowest, compared with the middle and highest, tertiles of generic health-related quality of life.

	Lowest tertile for EQ-5D		*p* value*
	Yes (n = 250)	No (n = 502)	
Mean age (SD)	43.4 (14.1)	46.3 (15.1)	0.013
Female (%)	214 (85.6)	441 (87.8)	0.39
Smoker (%)	43 (17.2)	39 (7.8)	<0.001
Alcohol use (%)	97 (38.8)	342 (68.1)	<0.001
Married (%)	139 (55.6)	348 (69.3)	<0.001
White ethnicity (%)	239 (95.6)	490 (97.6)	0.13
University or postgraduate level of education (%)	73 (29.2)	241 (48.0)	<0.001
Annual income of £30,000 or more (%)	36 (15.9)	161 (35.5)	<0.001
IBS subtype (%)			
IBS-C	36 (14.6)	100 (20.2)	
IBS-D	107 (43.3)	199 (40.1)	
IBS-M	104 (42.1)	197 (39.7)	0.18
Duration of IBS diagnosis, year(s) (%)			
1	8 (3.2)	17 (3.4)	
2	17 (6.8)	24 (4.8)	
3	15 (6.0)	39 (7.8)	
4	11 (4.4)	22 (4.4)	
5	14 (5.6)	24 (4.8)	
>5	185 (74.0)	376 (74.9)	0.82
IBS after acute enteric infection (%)	29 (11.6)	62 (12.4)	0.77
Opiate use (%)	93 (37.2)	55 (11.0)	<0.001
Most troublesome symptom (%)			
Abdominal pain	64 (25.6)	105 (20.9)	
Constipation	15 (6.0)	38 (7.6)	
Diarrhoea	41 (16.4)	76 (15.1)	
Bloating/distension	65 (26.0)	153 (30.5)	
Urgency	65 (26.0)	130 (25.9)	0.47
Co-existent EPS (%)	124 (49.6)	110 (22.0)	<0.001
Co-existent PDS (%)	154 (62.3)	177 (35.4)	<0.001
IBS-SSS severity (%)			
Mild	12 (4.8)	74 (14.9)	
Moderate	63 (25.2)	237 (47.9)	
Severe	175 (70.0)	184 (37.2)	<0.001
HADS anxiety categories (%)			
Normal	31 (12.4)	169 (33.7)	
Borderline abnormal	33 (13.2)	141 (28.1)	
Abnormal	186 (74.4)	192 (38.2)	<0.001

HADS depression categories (%)				
Normal			56 (22.4)	348 (69.3)	
Borderline abnormal			61 (24.4)	104 (20.7)	
Abnormal			133 (53.2)	50 (10.0)	<0.001
PHQ-12 severity (%)				
Low			0 (0.0)	36 (7.2)	
Mild			16 (6.4)	160 (31.9)	
Moderate			91 (36.4)	216 (43.0)	
Severe			143 (57.2)	90 (17.9)	<0.001
VSI scores (%)				
Low			45 (18.0)	202 (40.2)	
Medium			71 (28.4)	176 (35.1)	
High			134 (53.6)	124 (24.7)	<0.001
Seen a primary care physician regarding IBS in the last 12 months (%)			122 (48.8)	172 (34.3)	<0.001
Seen a gastroenterologist regarding IBS in the last 12 months (%)			78 (31.2)	69 (13.7)	<0.001
Number of IBS drugs in the last 12 months (%)				
0			23 (9.2)	73 (14.5)	
1			53 (21.2)	136 (27.1)	
2			61 (24.4)	135 (26.9)	
3			44 (17.6)	85 (16.9)	
4			30 (12.0)	46 (9.2)	
≥5			39 (15.6)	27 (5.4)	<0.001
Mean direct healthcare costs of IBS (SD)	**Appointments**		391.23 (693.37)	141.44 (486.25)	<0.001
	Investigations		260.33 (475.19)	106.58 (256.86)	<0.001
	IBS-related drugs		86.01 (97.25)	65.95 (95.20)	0.007
	Unplanned attendances		208.95 (641.29)	48.52 (265.55)	<0.001
	Total direct healthcare costs		946.52 (1393.31)	362.48 (702.21)	<0.001
WPAI:IBS (%)	**Any IBS-related absenteeism**		44 (38.3)	89 (25.3)	0.007
	Any IBS-related presenteeism		98 (93.3)	275 (83.1)	0.009
	Any IBS-related overall work impairment		103 (89.6)	279 (79.3)	0.013
	Any IBS-related activity impairment		244 (97.6)	440 (87.6)	<0.001
WSAS (%)	**IBS affected home management**		148 (59.2)	72 (14.3)	<0.001
	IBS affected social leisure activities		203 (81.2)	220 (43.8)	<0.001
	IBS affected private leisure activities		141 (56.4)	66 (13.1)	<0.001
	IBS affected close relationships		125 (50.0)	78 (15.5)	<0.001

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

4.4 Discussion

This study recruited 752 individuals with Rome IV-defined IBS, assessing both disease-specific and generic health-related quality of life, using the IBS-QOL and the EQ-5D, and comparing scores for the latter with other chronic organic conditions. IBS-QOL and EQ-5D scores were examined in all individuals with self-reported IBS and those with Rome III IBS, as well as characteristics associated with poorer quality of life in Rome IV IBS. Disease-specific quality of life was significantly lower among those with Rome IV IBS-D, but there were no significant differences in generic quality of life according to Rome IV IBS subtype. Generic health-related quality of life among those with IBS, irrespective of the definition used, was comparable with chronic conditions like stroke, leg ulcers, or chronic obstructive pulmonary disease, although it was lowest in Rome IV IBS. Lower levels of both disease-specific and generic quality of life in Rome IV IBS were associated with severe IBS-SSS scores, abnormal HADS-anxiety or HADS-depression scores, and higher somatization and gastrointestinal symptom-specific anxiety scores. Not surprisingly, those with lower quality of life had significantly higher healthcare usage and direct healthcare costs, as well as significantly greater impairment in work and activities of daily living. A highly significant association between gastrointestinal symptom-specific anxiety and severely impaired IBS-related quality of life was demonstrated, which probably relates to the substantial overlap between the individual items of the instruments (VSI and IBS-QOL) that were used to measure these factors. Finally, these results showed that there were several factors independently associated with lower quality of life. These included avoidance of alcohol, lower educational level, abnormal anxiety, depression, and somatization scores, and impairment in social leisure activities, home management, or maintaining close relationships.

In addition to the strengths of the overall study design that have already been discussed in Chapter 3, the IBS-QOL and the EQ-5D, two validated questionnaires to examine disease-specific and generic health-related quality of life respectively, were administered simultaneously.[263, 287, 288] The IBS-QOL has been used widely in patients with IBS, and the EQ-5D allows comparison of quality of life across different chronic conditions and is often used for health economic evaluation.[290] In addition, the latter has been shown to be a valid and responsive measure of quality of life in patients with IBS.[129, 299] An online questionnaire, a validated method to administer both the IBS-QOL and EQ-5D questionnaires,[300] was used.

Several weaknesses that should be taken into consideration when interpreting the study results have been discussed in Chapter 3. The Rome IV criteria were used to define IBS, which are the current gold standard. These criteria select individuals with more severe gastrointestinal symptoms and higher levels of psychological comorbidities,[21-24] so it is, perhaps, not surprising that quality of life was lowest in these individuals compared with those meeting Rome III criteria for IBS. As this was a cross-sectional survey, with associations examined at one point in time, the direction of the effects observed cannot be determined. Lastly, participants were not asked to report other chronic medical conditions, which could also have affected quality of life.

Although previous studies have assessed quality of life in individuals with IBS,[128-139] only one study has examined this issue in Rome IV IBS.[139] As in the present study, the authors used the IBS-QOL and the EQ-5D simultaneously, but the main objective of their study was to develop a mapping algorithm for the EQ-5D-5L to enable the IBS-QOL to be transformed for economic evaluations. Associations with lower quality of life were not examined as only data on IBS

subtype, IBS severity, anxiety, and depression were collected. Another limitation of this study is that patients were those participating in two RCTs of peppermint oil and hypnotherapy. The authors also excluded those with clinically significant anxiety or depression, which together with the strict inclusion criteria of the RCTs, means the participants are unlikely to be generalisable to the wider population with Rome IV IBS. Perhaps because of the exclusion of those with significant anxiety or depression, both of which were independently associated with lower quality of life in the present study, the reported mean IBS-QOL and EQ-5D, 71.1 and 0.73, respectively, were higher than observed in this study. Other studies using prior iterations of the Rome criteria, or even the Manning criteria, have estimated the mean IBS-QOL to be between 61.4 and 83.6,[129, 131, 133-135, 137] and the mean EQ-5D to be between 0.64 and 0.76.[129, 131, 134, 136] It was anticipated that the mean IBS-QOL and EQ-5D scores observed would be lower among those meeting Rome IV criteria in the present study compared with that reported in these prior studies because these criteria, as previously discussed, select a more severely affected group of individuals with IBS with a worse prognosis.[21-24] The results of this study are also consistent with previous studies demonstrating that individuals with IBS experience substantial reduction in their quality of life, which is on a par with, or worse than, those with chronic organic conditions.[128, 130, 132, 133] The finding that more severe IBS or higher levels of psychological comorbidities were significantly associated with lower quality of life are similar to one previous study.[138]

This study has demonstrated that individuals with Rome IV IBS have a reduced quality of life using both disease-specific and generic health-related quality of life questionnaires. Mean IBS-QOL scores were significantly lower among those with IBS-D, but generic quality of life did not seem to differ by

subtype. It is, perhaps, not surprising that more severe IBS symptoms, psychological symptoms, increased healthcare costs, and higher levels of impairment in work and activities of daily living were associated with lower quality of life. Interestingly, after logistic regression IBS severity was not independently associated with lower quality of life. This suggests it may not be the gastrointestinal symptoms *per se* driving lower quality of life. The results demonstrated that the quality of life of those with Rome IV IBS was comparable with, or worse than, many other chronic organic conditions, even though IBS is not associated with increased mortality. Possible explanations are the higher levels of coexisting psychological comorbidities associated with IBS,[39, 117] and the nature of IBS symptoms, such as the embarrassment of having to use the toilet frequently in public or passing flatus, the unpredictability of symptoms, or the stigma associated with a “functional” disorder,[142, 195, 199, 243] compared with other chronic conditions.

Although alcohol abstinence was associated with better quality of life in one population-based study,[301] this study found that alcohol abstinence was associated with lower quality of life, and this may be because alcohol exacerbates symptoms of IBS. Binge drinking, but not light or moderate consumption, was associated with gastrointestinal symptoms of abdominal pain, diarrhoea, nausea, and indigestion the next day in one study.[302] Alcohol has been associated with self-reported dyspepsia, but not IBS.[303] However, given the overlap between IBS and functional dyspepsia,[304] this may explain the association observed in this study, as it is likely that patients who suffer from both these conditions will have greater impairment of their quality of life. The strong correlation between VSI and IBS-QOL was also observed in a recent study recruiting individuals with Rome II or III IBS, with the VSI being the most important factor in explaining overall IBS-

QOL[305] The analysis of these two questionnaires side-by-side in the present study demonstrated that the most likely reason is because of overlap between items on the IBS-QOL and the VSI, suggesting other investigators should be vigilant when analysing data from these two questionnaires together.

The results from this study have important implications. The substantial impairment of quality of life seen in Rome IV IBS highlights the impact of a prevalent disorder, still viewed as “functional” by many physicians, on individuals. These results should encourage those with IBS to feel less ashamed of, or embarrassed by, their illness and reduce the stigma associated with a diagnosis. The latter is especially important, given this study has demonstrated that impairment in generic health-related quality of life in IBS is comparable with many chronic organic conditions. The findings that anxiety, depression, and somatic symptom-reporting were independently associated with lower quality of life is further evidence that routine psychological assessment is crucial in those with IBS. Effective multidisciplinary management of IBS should be encouraged to improve patients’ quality of life.[306, 307] Funding bodies should more seriously consider commissioning further research to identify the causes of IBS, as well as effective management strategies for it, given it is so prevalent and affects quality of life to a degree similar to other chronic conditions.[248] Finally, clinical trials should consider using the EQ-5D as it allows quality-adjusted life year calculations and cost-effectiveness analyses, both of which are important for making decisions about ability to access novel treatments.[290] The results discussed in Chapters 3 and 4 have demonstrated that IBS is not a “benign” condition, due to its impact on various aspects of personal and work life as well as quality of life. It is, therefore, important to consider how this might influence

risk perception with regards to treatment of IBS, which will be the subject of Chapter 5.

Chapter 5 Assessing the Willingness to Accept Medication Risks among Individuals with Irritable Bowel Syndrome

5.1 Introduction

In Chapter 1, it has been discussed that several novel drugs for IBS have been withdrawn, or their use restricted, due to safety concerns. Examples include ischaemic colitis with alosetron,[254] an excess of cardiovascular and cerebrovascular events with tegaserod,[255] and episodes of acute pancreatitis with eluxadoline.[256] Although regulatory bodies with responsibility for the licensing of drugs and therapeutics often have lay representation on their committees, including patients and carers, they do not generally require formal consideration, review, or quantification of the risks patients are willing to accept to relieve or cure their symptoms when evaluating treatments. In a chronic, incurable, condition like IBS, which has a huge impact on quality of life as discussed in Chapter 4, and where most drugs have limited efficacy,[68, 185-188, 308] it is important to determine these risks.

In one study patients were willing to accept a 2.65% risk of bowel impaction and a 1.34% risk of bowel perforation from medication, although the use of a discrete choice experiment only allowed the authors to examine a specific set of trade-offs for alosetron for use in women with IBS-D.[191] A previous survey established that individuals with IBS were, on average, willing to relinquish 15.1 years of their life to achieve perfect health with a new medication.[190] Using a standard gamble, two other studies reported that patients with IBS were willing to accept substantial risks of sudden death for a chance of cure of their symptoms.[192, 193] However, these studies were relatively small and patients were recruited from referral populations. In addition, three of these previous studies used the Rome III criteria for IBS, but symptom severity appears worse with the current Rome IV criteria,[21] so their findings may no longer be applicable. Finally,

none of these examined predictors of a higher acceptance of medication-related risk amongst individuals with IBS.

This study, therefore, aimed to examine the willingness to accept risks with medications in return for cure of symptoms in a cohort of individuals with IBS defined according to the Rome IV criteria. It was hypothesised that individuals with IBS would be willing to accept substantial medication risks and that those more severe symptoms of IBS, higher levels of psychological comorbidities, or poorer QoL would be willing to accept greater risks.

5.2 Methods

5.2.1 Participants and setting

This study recruited individuals registered with ContactME-IBS, a national UK registry of people with IBS who are interested in research.[258] Full details of the recruitment methodology have already been discussed in Chapter 3.

5.2.2 Data collection and synthesis

5.2.2.1 Demographic and symptom data

Full details of the demographic and symptom data have already been discussed in Chapter 3. In addition, respondents were asked about their willingness to take risks in their daily life.

5.2.2.2 IBS symptom severity, mood, somatic symptoms, and gastrointestinal symptom-specific anxiety

Symptom severity was assessed using the IBS-SSS.[113] The HADS questionnaire was used to collect anxiety and depression data,[260] the PHQ-12 was used to collect somatic symptom-reporting data,[119] and the VSI was used to measure gastrointestinal symptom-specific anxiety.[262] Full details of the

assessment of gastrointestinal symptom severity and these psychological data have already been provided in Chapter 3.

5.2.2.3 IBS-specific quality of life

The IBS-QOL was used to measure health-related quality of life in individuals with IBS.[263, 264] Full details of the health-related quality of life data have been provided in Chapter 3.

5.2.2.4 Impact of IBS on productivity and ability to work

The WPAI:IBS questionnaire was used to assess level of work productivity loss in people with IBS who are employed.[265] Full details of the assessment of productivity and ability to work have already been provided in Chapter 3.

5.2.2.5 Willingness to accept risk of death in return for cure of IBS symptoms

A standard gamble was used to evaluate the risk of death that participants were willing to accept in return for a permanent cure of their IBS symptoms.[309] Each question offered participants a choice of a chance of permanent cure of their IBS symptoms with a hypothetical pill or a risk of a painless death in their sleep from the same pill (Figure 5.1). As the participants move from one question to the next, the chance of cure is titrated down from 100% whilst the risk of death is titrated up from 0%. In doing so, the maximum risk of death that participants are willing to accept for the corresponding minimum chance of cure can be estimated.

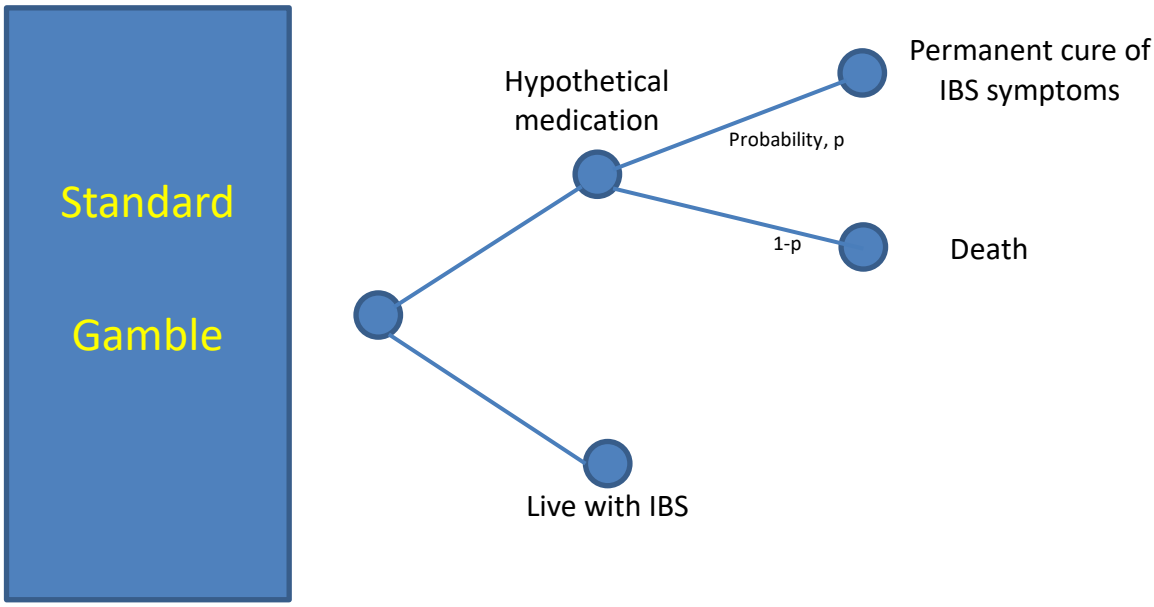

Figure 5.1. Evaluate risk of death participants were willing to accept in return for permanent cure of IBS symptoms.

5.2.3 Statistical analysis

All participants who met Rome IV criteria for IBS were included in the statistical analysis. The normality of data was assessed using histogram and normality plots and used the Kolmogorov-Smirnov statistic to test normality. The frequency distributions for all categorical variables were calculated, and the Mann-Whitney *U* test and Kruskal-Wallis H test were used to assess differences between groups. The characteristics of patients willing to accept above the median risk of death, compared with those willing to accept the median or below median risk of death, in return for cure of their IBS in the standard gamble were examined. Categorical variables such as sex, ethnicity, self-rated risk-taking behaviour, IBS subtype, IBS-SSS severity, presence or absence of abnormal anxiety or depression scores, levels of somatic symptom reporting, levels of gastrointestinal symptom-specific anxiety, and levels of QoL were compared between individuals willing to accept above the median risk of death compared with the median or below median risk of death using a χ^2 test. Data such as age, and scores for absenteeism, presenteeism, overall work impairment, or activity impairment were compared between these two groups using an independent samples *t* test or Mann-Whitney *U* test. Statistical significance was defined as a *P* value <0.01. A logistic regression model, controlling for all baseline data, was used to examine predictors of willingness to accept above the median risk of death, and the results were reported with ORs with 95% CIs. All analyses were performed using SPSS for Windows (version 27.0 SPSS, Chicago, IL).

5.3 Results

As previously stated, of the 1278 respondents, 752 (58.8%) met Rome IV criteria for IBS. The mean age of these 752 individuals was 45.3 years (range 18-81 years), 655 (87.1%) were female, and 729 (96.9%) were White. The mean

IBS-SSS score was 293.1 (SD 95.1). When asked to rate their risk-taking behaviour in their daily life, 66 (8.8%) reported never taking risk, 343 (45.6%) rarely, 323 (43.0%) occasionally, and 20 (2.7%) routinely.

5.3.1 Willingness to accept risk of death in return for cure of IBS symptoms from a hypothetical medication

Using a standard gamble, participants reported that they would accept a median 2.0% (IQR, 0.0% - 9.0%) risk of death from a hypothetical medication in return for a 98.0% (IQR, 91.0% - 100.0%) chance of permanent cure of their IBS symptoms. Men with IBS were willing to accept a higher risk of death compared with women (median 5.0% vs. 2.0%, $P < 0.001$) (Table 5.1). Willingness to accept risk was not associated with marital status, tobacco or alcohol use, level of education, annual income, IBS subtype, duration of IBS, or most troublesome symptom, but increasing degree of risk taken in daily life was associated with willingness to accept a higher risk of death in return for cure ($P < 0.001$ for trend). Willingness to accept death also increased significantly with the number of medications taken for IBS in the 12 months prior to the study ($P = 0.005$ for trend) and with the presence of continuous abdominal pain (median 4.0% vs. 1.0%, $P < 0.001$). A significantly higher median accepted risk of death was also observed in those with severe IBS (severe, 3.0% vs. moderate, 1.0% vs. mild, 2.0%, $P = 0.005$ for trend), those with abnormal HADS depression scores (abnormal, 5.0% vs. borderline, 2.0% vs. normal, 2.0%, $P < 0.001$ for trend) and higher VSI scores (high, 3.0% vs. medium, 2.0% vs. low, 1.0%, $P < 0.001$ for trend), but not abnormal HADS anxiety scores or high somatization scores. Median accepted risk of death was also significantly higher with lower IBS-related quality of life (low, 4.0% vs. medium, 2.0% vs. high, 1.0%, $P < 0.001$ for trend).

Table 5.1. Median willingness to accept risk of death in return for cure of IBS symptoms from a hypothetical medication according to demographics, symptom characteristics and level of psychological comorbidity among 752 individuals with Rome IV IBS.

	Median risk of death, % (IQR)	P value*
Sex		
Male (n = 97)	5.00 (1.00 – 10.00)	
Female (n = 655)	2.00 (0.00 – 8.00)	<0.001
Smoker		
Yes (n = 82)	3.5 (0.0 -10.0)	
No (n = 670)	2.0 (0.0 – 9.0)	0.15
Alcohol use		
Yes (n = 439)	2.0 (0.0 – 8.0)	
No (n = 313)	2.0 (0.0 – 10.0)	0.48
Married		
Yes (n = 487)	2.0 (0.0 – 7.0)	
No (n = 265)	3.0 (0.0 – 10.0)	0.02
University or postgraduate level of education		
Yes (n = 314)	2.0 (0.0 – 6.0)	
No (n = 438)	2.0 (0.0 -10.0)	0.15
Annual income of £30,000 or more		
Yes (n = 197)	3.0 (0.0 – 9.0)	
No (n = 483)	2.0 (0.0 - 9.0)	0.34
IBS subtype		
IBS-C (n = 136)	1.0 (0.0 – 5.0)	
IBS-D (n = 306)	2.0 (0.0 – 8.25)	
IBS-M (n = 301)	3.0 (0.0 – 10.0)	0.14
Most troublesome symptom		
Abdominal pain (n = 169)	3.0 (0.0 - 10.0)	
Constipation (n = 53)	2.0 (0.0 – 9.0)	
Diarrhoea (n = 117)	4.0 (0.0 – 10.0)	
Bloating/distension (n = 218)	2.0 (0.0 – 5.0)	
Urgency (n = 195)	2.0 (0.0 – 9.0)	0.11
Continuous abdominal pain		
Yes (n = 345)	4.0 (0.0 – 10.0)	
No (n = 407)	1.0 (0.0 – 5.0)	<0.001
Self-rated risk-taking behaviour		
Never (n = 66)	0.0 (0.0 – 4.0)	
Rarely (n = 343)	2.0 (0.0 – 6.0)	
Occasionally (n = 323)	3.0 (0.0 – 10.0)	
Routinely (n = 20)	3.5 (0.0 – 31.25)	<0.001

Duration of IBS diagnosis, year(s)		
1 (n = 25)	2.0 (0.0 - 5.0)	
2 (n = 41)	2.0 (0.0 – 6.5)	
3 (n = 54)	3.0 (0.0 – 11.25)	
4 (n = 33)	1.0 (0.0 – 9.0)	
5 (n = 38)	3.0 (0.0 – 9.25)	
>5 (n = 561)	2.0 (0.0 – 9.0)	0.56
Number of IBS drugs in the last 12 months		
0 (n = 96)	1.0 (0.0 – 5.0)	
1 (n = 189)	1.0 (0.0 – 7.0)	
2 (n = 196)	2.0 (0.0 – 9.0)	
3 (n = 129)	4.0 (0.0 – 10.0)	
4 (n = 76)	3.0 (0.0 – 10.0)	
≥5 (n = 66)	4.0 (0.0 – 10.0)	0.005
IBS-SSS severity		
Mild (n = 86)	2.0 (0.0 – 5.0)	
Moderate (n = 300)	1.0 (0.0 – 7.0)	
Severe (n = 359)	3.0 (0.0 – 10.0)	0.005
HADS anxiety categories		
Normal (n = 200)	2.0 (0.0 – 5.0)	
Borderline abnormal (n = 174)	2.0 (0.0 – 8.25)	
Abnormal (n = 378)	2.5 (0.0 – 10.0)	0.20
HADS depression categories		
Normal (n = 404)	2.0 (0.0 – 5.0)	
Borderline abnormal (n = 165)	2.0 (0.0 – 8.5)	
Abnormal (n = 183)	5.0 (0.0 – 15.0)	<0.001
PHQ-12 severity		
Low (n = 36)	2.0 (0.0 – 5.0)	
Mild (n = 176)	2.0 (0.0 – 9.0)	
Moderate (n = 307)	2.0 (0.0 – 6.0)	
Severe (n = 233)	4.0 (0.0 – 10.0)	0.14
VSI scores		
Low (n = 247)	1.0 (0.0 – 5.0)	
Medium (n = 247)	2.0 (0.0 – 9.0)	
High (n = 258)	3.0 (0.0 – 10.0)	<0.001
IBS-QOL scores		
Low (n = 239)	4.0 (0.0 – 10.0)	
Medium (n = 252)	2.0 (0.0 – 9.0)	
High (n = 261)	1.0 (1.0 – 5.0)	<0.001

*P value for Mann-Whitney U test for 2 groups and for Kruskal-Wallis test for 3 groups or more.

5.3.2 Characteristics of patients willing to accept above median risk of death in return for cure of IBS symptoms from a hypothetical medication

The characteristics of individuals willing to accept above median risk of death compared with those willing to accept median or below risk of death in return for a cure of their IBS were also examined (Table 5.2). There was a significantly lower proportion of female individuals (82.9% vs. 90.9%, $P < 0.001$) and a higher proportion of individuals willing to take a higher degree of risk in their daily life ($P = 0.008$ for trend). There was also a significantly higher proportion of individuals with continuous abdominal pain (53.1% vs. 39.4%, $P < 0.001$) in the above median risk of death group. A greater proportion of individuals willing to accept above median risk of death had more severe IBS, although this did not reach statistical significance ($P = 0.02$ for trend). There was a significantly higher proportion of individuals with abnormal depression scores ($P = 0.004$ for trend) in the group willing to accept above median risk of death, but not abnormal anxiety scores or high somatization scores. VSI scores were generally higher, although this did not reach statistical significance ($P = 0.02$ for trend), but IBS-related quality of life was significantly lower ($P < 0.001$ for trend). Finally, the association between work productivity and activity impairment and willingness to accept risk of death was investigated. Levels of presenteeism, overall work impairment (40.0% vs. 30.0% for both, $P = 0.002$ and $P = 0.004$, respectively), and activity impairment (50.0% vs. 40.0%, $P < 0.001$) were significantly higher among those willing to accept above median risk of death. Following logistic regression, those willing to accept above median risk of death were more likely to take higher risks in their daily life (OR = 3.64; 95% CI 1.19 to 11.2), to report continuous abdominal pain (OR = 1.50; 95% CI 1.03 to 2.18), to have IBS-M (OR

= 1.75; 95% CI 1.05 to 2.91), and less likely to be female (OR = 0.52; 95% CI 0.30 to 0.89) or married (OR = 0.68; 95% CI 0.48 to 0.98).

Table 5.2. Characteristics of individuals with Rome IV IBS willing to accept above median risk of death in return for cure of IBS symptoms from a hypothetical medication compared with median or below median risk of death.

	Above median risk of death (n = 356)	Median or below median risk of death (n = 396)	P value*
Female (%)	295 (82.9)	360 (90.9)	0.001
Mean age (SD)	45.7 (14.7)	45.0 (14.9)	0.54
White ethnicity (%)	346 (97.2)	383 (96.7)	0.71
Married (%)	216 (60.7)	270 (68.4)	0.03
Smoker (%)	45 (12.6)	37 (9.3)	0.15
Alcohol user (%)	200 (56.2)	239 (60.4)	0.25
University or postgraduate level of education (%)	140 (39.3)	174 (43.9)	0.20
Annual income of £30,000 or more (%)	102 (31.1)	95 (27.0)	0.24
IBS subtype (%)			
IBS-C	55 (15.5)	81 (20.8)	
IBS-D	146 (41.2)	160 (41.1)	
IBS-M	153(43.2)	148 (38.0)	0.13
Most troublesome symptom (%)			
Abdominal pain	87 (24.4)	82 (20.7)	
Constipation	26 (7.3)	27 (6.8)	
Diarrhoea	62 (17.4)	55 (13.9)	
Bloating/distension	92 (25.8)	126 (31.8)	
Urgency	89 (25.0)	106 (26.8)	0.26
Continuous abdominal pain (%)	189 (53.1)	156 (39.4)	<0.001
Self-rated risk-taking behaviour (%)			
Never	21 (5.9)	45 (11.4)	
Rarely	153 (43.0)	190 (48.0)	
Occasionally	171 (48.0)	152 (38.4)	
Routinely	11 (3.1)	9 (2.3)	0.008
Duration of IBS diagnosis, year(s) (%)			
1	9 (2.5)	16 (4.0)	
2	16 (4.5)	25 (6.3)	
3	28 (7.9)	26 (6.6)	
4	13 (3.7)	20 (5.1)	
5	20 (5.6)	18 (4.5)	
>5	270 (75.8)	291 (73.5)	0.51

Number of IBS drugs in the last 12 months (%)			
0	40 (11.2)	56 (14.1)	
1	80 (22.5)	109 (27.5)	
2	90 (25.3)	106 (26.8)	
3	69 (19.4)	60 (15.2)	
4	41 (11.5)	35 (8.8)	
≥5	36 (10.1)	30 (7.6)	0.16
IBS-SSS severity (%)			
Mild	33 (9.3)	53 (13.4)	
Moderate	132 (37.1)	168 (42.4)	
Severe	189 (53.1)	170 (42.9)	0.02
HADS anxiety categories (%)			
Normal	84 (23.6)	116 (29.3)	
Borderline abnormal	83 (23.3)	91 (23.0)	
Abnormal	189 (53.1)	189 (47.7)	0.19
HADS depression categories (%)			
Normal	171 (48.0)	233 (58.8)	
Borderline abnormal	81 (22.8)	84 (21.2)	
Abnormal	104 (29.2)	79 (19.9)	0.004
PHQ-12 severity (%)			
Low	16 (4.5)	20 (5.1)	
Mild	81 (22.8)	95 (24.0)	
Moderate	132 (37.1)	175 (44.2)	
Severe	127 (35.7)	106 (26.8)	0.06
VSI scores (%)			
Low	101 (28.4)	146 (36.9)	
Medium	118 (33.1)	129 (32.6)	
High	137 (38.5)	121 (30.6)	0.02
IBS-QOL score (%)			
Low	133 (37.4)	106 (26.8)	
Medium	124 (34.8)	128 (32.3)	
High	99 (27.8)	162 (40.9)	<0.001
WPAI: IBS, median % (IQR)			
Absenteeism	0.0 (0.0 – 5.1)	0.0 (0.0 – 1.3)	0.10
Presenteeism	40.0 (20.0 - 60.0)	30.0 (10.0 – 60.0)	0.002
Overall work impairment	40.0 (15.9 – 65.3)	30.0 (10.0 – 57.1)	0.004
Activity impairment	50.0 (30.0 – 70.0)	40.0 (20.0 – 60.0)	<0.001

*P value for Pearson $\chi 2$ for comparison of categorical data, independent samples t-test for age, and Mann-Whitney U test for all four dimensions of Work Productivity and Activity Impairment: Irritable Bowel Syndrome.

5.4 Discussion

This cross-sectional survey has recruited 752 individuals with Rome IV-defined IBS who, when presented with a standard gamble, were willing to accept a median 2% risk of death from a hypothetical medication in return for a 98% chance of permanent cure of their IBS. However, this increased to 5% in some of the analyses. Men, individuals with continuous abdominal pain, those who took increased risks in their daily life, and who had taken more IBS medications in the last 12 months were willing to accept a significantly higher risk of death. Not surprisingly, those with more severe IBS symptoms and those with poorer quality of life were also willing to accept significantly higher risks. In terms of psychological comorbidities, higher depression and gastrointestinal symptom-specific anxiety scores were associated with significantly higher willingness to accept risk. When the characteristics of those willing to accept above median risk of death were analysed, a significantly higher proportion of these individuals were male, they were more likely to report continuous abdominal pain, took higher levels of risks in their daily life, had higher depression scores, and lower quality of life. Finally, those who were more likely to accept above median risk from a medication reported greater impairment at work and in their daily life.

In addition to the strengths and weaknesses considered in Chapter 3, a discussion on the use of a standard gamble is required. Although it is a validated and well-established tool used widely in health economics to examine health utilities,[310] including studies in DGBI,[192, 193, 311] it has limitations. The choices given to the participants are hypothetical, given that there are currently no medications that can cure IBS. The choices that individuals were asked to make, although intended to simulate a clinical scenario, are unlikely to have captured the complex decision-making process involving health, emotional, or financial

consequences on both individuals and their relatives. Moreover, adverse effects for licensed medications used in IBS, when experienced by patients, are most likely to be mild rather can causing death. However, the term “painless death”, used in the standard gamble, may suggest to some people a pleasant death, which could have influenced the results. Previously, Johnson *et al.* attempted to minimise this hypothetical bias by using a discrete choice experiment, offering alternatives that mimicked the real-world.[191] The limitation of such a design is that one can only investigate a specific set of trade-offs for a specific medication in a defined subset of patients, such as constipation or risk of perforated ischaemic bowel requiring surgery with alosetron in women with IBS-D.[191] On the other hand, using standard gamble methodology allows for direct comparisons among subgroups of patients to identify those who are willing to accept higher levels of medication-related risks. This is important to inform drug development and approval processes for novel medications.

As discussed, there have been previous studies examining willingness to accept medication-related risks among IBS patients. One study using Rome III-defined IBS, recruiting 186 patients from a referral population, concluded that participants were willing to accept a median risk of 1% death in return for a 99% chance of cure.[192] However, there were no significant differences in willingness to accept risks according to various patient characteristics, other than self-reported symptom severity. In another study, recruiting 215 patients with Rome IV-defined IBS from a referral population, severity of IBS did not appear to affect willingness to accept risk with medication significantly, other than among those reporting intensity or unpredictability of constipation as their most bothersome symptom.[193] Both studies had relatively small sample sizes, which may have hampered their ability to detect significant differences. In an international survey

of almost 2000 individuals meeting Rome III criteria for IBS, participants were willing, on average, to forgo 15.1 years of their life expectancy to achieve perfect health.[190] Despite having a large sample size, the authors did not examine the associations between willingness to accept risk from medication and participants' demographics, IBS severity, anxiety, or depression. Finally, none of these studies have examined the relationship between willingness to accept risk and other psychological comorbidities such as gastrointestinal symptom-specific anxiety or somatisation and did not examine characteristics of individuals with IBS who were willing to accept higher levels of risk. Although the finding that men and those who take more risk in their daily lives were willing to accept higher levels of risk is unsurprising, other potential predictors were identified.

This study has demonstrated that individuals with IBS are willing to accept remarkable risks to achieve cure of their symptoms, even though IBS is not known to reduce life expectancy.[126, 312] This serves to highlight the substantial impact that IBS has on individuals, as reinforced by the results of Chapters 3 and 4. It is, perhaps, not surprising that those with more severe symptoms and lower IBS-related quality of life are willing to accept greater risks to cure their symptoms. Interestingly, individuals with higher levels of depression, but not anxiety, were also willing to accept greater risks from medications. One possible explanation is that those with higher levels of anxiety may be equally worried about adverse events from medications. In fact, the HADS anxiety score measures generalised, rather than health-related, anxiety. This hypothesis is further supported by the fact that those with higher levels of gastrointestinal symptom-specific anxiety were willing to accept significantly higher levels of risk.

This study has important implications. Clinicians should be mindful of the impact of IBS on patients' lives and the levels of risks they are willing to accept

to relieve their symptoms. Careful discussion about various treatment options, and their relative risks and benefits, should take place to allow patients to make informed decisions about therapies. These results are also important for pharmaceutical companies to aid decisions regarding continued drug development or marketing when serious adverse events arise, as well as the regulatory agencies responsible for assessing the risk-benefit profile of new drugs prior to approval. As IBS is considered a benign condition, drugs with serious side effects are often withdrawn or their use restricted. The results from this study suggest this debate needs to be recalibrated, particularly in those with more severe, or refractory, symptoms. Of course, it will be crucial to develop treatment algorithms and tools to help clinicians and patients to make such complex decisions. The results presented so far in Chapters 3, 4, and 5 have highlighted the substantial impact of IBS on individuals in terms of work productivity, activities of daily living, quality of life, and risk perception. However, it is also important to consider how this translates into impact on the health service. The cost of IBS will be the focus of the next chapter.

Chapter 6 Estimating the Direct Healthcare Cost of Irritable Bowel Syndrome in the UK

6.1 Introduction

Having examined the implications of IBS for quality of life, work and activities of daily living, and individuals' willingness to accept medication risks, it is important to estimate contemporaneous healthcare costs of IBS so that its impact on the healthcare system and the economy can be assessed. It has been discussed that most treatments for IBS are of limited efficacy.[68, 185-188] As a consequence, IBS may be difficult to treat and this contributes to it being a chronic problem, with a relapsing and remitting course for most patients, leading to high consultation rates.[111] Because the symptoms of IBS can be confused with certain organic gastrointestinal diseases, it is often perceived to be a diagnosis of exclusion amongst some clinicians, leading to unnecessary investigations and, therefore, additional costs may be associated with making a diagnosis.[140] Furthermore, novel drugs are often expensive. For these reasons, IBS represents a substantial burden to both healthcare systems and society.

Previous studies have estimated the costs to the health service of IBS in various countries.[249, 250, 313, 314] However, most have used a top-down approach, relying on coding of a diagnosis of IBS in existing databases. This also means that gold standard criteria for the diagnosis of IBS, such as the Rome criteria, have not been applied in many of these studies. In addition, most studies recruit patients from secondary care settings and are, therefore, not representative of all patients with IBS, many of whom either never consult a doctor or are managed solely in primary care.[315] Although previous studies have attempted to estimate direct healthcare costs of IBS in the UK,[131, 252, 253, 316] only two have been conducted in the last 20 years and have important limitations. Finally, few studies have examined patient factors that predict higher direct costs.[317, 318]

Assessing the burden of IBS to the healthcare system is important, not only to plan healthcare resource allocation, but also to provide a rationale for adequate funding for IBS research from grant-giving bodies. A cross-sectional survey was, therefore, conducted to estimate mean annual direct costs of IBS to the health service per person, extrapolating these across the entire UK adult population, to provide a contemporaneous approximation of the burden of IBS to the UK healthcare system, as well as examining predictors of higher costs.

6.2 Methods

6.2.1 Participants and setting

This study recruited individuals registered with ContactME-IBS, a national UK registry of people with IBS who are interested in research.[258] Full details of the recruitment methodology have already been provided in Chapter 3.

6.2.2 Data collection and synthesis

6.2.2.1 Demographic and symptom data

Full details of the demographic and symptom data have already been provided in Chapter 3. In this study, the presence of IBS was defined utilising both the Rome III and Rome IV questionnaires,[259, 319] via the scoring algorithms proposed for their use.[18, 19]

6.2.2.2 IBS symptom severity, mood, somatic symptoms, and gastrointestinal symptom-specific anxiety

Symptom severity was assessed using the IBS-SSS.[113] Anxiety and depression data were collected using the HADS,[260] somatic symptom data using the PHQ-12,[119] and gastrointestinal symptom-specific anxiety using the VSI.[262] Full details of the assessment of gastrointestinal symptom severity and these psychological data have already been provided in Chapter 3.

6.2.2.3 IBS-specific quality of life

The IBS-QOL was used to measure the health-related quality of life.[263, 264] Full details of the assessment of IBS-specific quality of life have already been provided in Chapter 3.

6.2.2.4 Annual direct costs

As briefly discussed in Chapter 4, data on healthcare usage related to IBS only over the 12 months prior to recruitment to the study were collected. Participants were instructed to report number of appointments with healthcare professionals (GPs, gastroenterologists, specialist nurses, dietitians, or psychologists), number of investigations (blood tests, stool tests, endoscopies, abdominal ultrasounds, computed tomography scans, magnetic resonance imaging scans, hydrogen breath tests, or SeHCAT), number of unplanned emergency department attendances or inpatient admissions (including length of stay), and OTC and prescribed medication usage (in months) only in relation to their IBS. Costs for GP appointments using Unit Costs of Health and Social Care 2020,[291] and all other appointments, investigations, emergency department attendances, and unplanned inpatient days in secondary care were applied using NHS 2019/20 National Cost Collection Data.[292] It was assumed that all the appointments for IBS were follow-up appointments, which cost less than a new patient appointment. Unit costs for appointments, investigations, and hospital attendances are provided in Table 6.1. The lowest price for a 1-month supply of each IBS-related medication were applied using the online version of the BNF.[293] These are provided in Table 6.2.

Table 6.1. Unit costs (in UK pounds) for IBS-related appointments, investigations, and unplanned hospital attendances or admissions.[291, 292]

	Cost (£)
Follow-up appointment with a GP	33.00
Follow-up appointment with a gastroenterologist	148.12
Follow-up appointment with a specialist nurse	127.91
Follow-up appointment with a dietician	83.03
Follow-up appointment with a psychologist	179.84
Blood test	1.81
Stool test	8.09
Gastroscopy	482.23
Colonoscopy	559.35
Hydrogen breath test	57.96
Abdominal ultrasound	62.39
Abdominal computed tomography	114.36
Abdominal magnetic resonance imaging	144.29
23-seleno-25-homo-tauro-cholic acid scan	367.73
Emergency department attendance	220.53
Inpatient admission under gastroenterology	1551.77

Table 6.2. Unit costs (in UK pounds) for a 1-month supply of IBS-related medications.[293]

	Cost (£)
Loperamide	1.68
Sodium picosulfate	4.62
Bisacodyl	1.67
Polyethylene glycol	2.99
Hyoscine	9.63
Alverine	7.64
Mebeverine	4.39
Dicycloverine	30.00
Ispaghula	3.24
Peppermint oil	4.95
Amitriptyline	1.08
Nortriptyline	1.00
Imipramine	2.15
Fluoxetine	0.50
Paroxetine	1.26
Sertraline	0.80
Citalopram	1.02
Escitalopram	1.55
Lubiprostone	53.48
Linaclotide	37.56
Prucalopride	47.62
Eluxadoline	88.20

6.2.3 Statistical analysis

Contemporaneous prevalence data for Rome IV and Rome III IBS in the UK, derived from the Rome Foundation three-nation prevalence study,[28] were used to extrapolate total annual direct costs per person from this study across the entire UK adult population, using published census data.[271-273] In the current study, the majority of participants had consulted with a doctor, which may skew the costs. The authors of the three-nation Rome Foundation study were, therefore, contacted to obtain consultation rates with a doctor for IBS among those meeting either the Rome IV or Rome III criteria only for the UK population recruited into that study (data on file, personal communication: Dr. Olafur Palsson, University of North Carolina, Chapel Hill, NC, USA) to perform a more conservative sensitivity analysis of annual direct costs.[28] Finally, among those with Rome IV IBS the mean annual direct costs per individual were examined according to demographic characteristics, gastrointestinal symptoms, psychological comorbidity, and quality of life. Mean annual direct costs were compared using an independent samples *t*-test or one way analysis of variance (ANOVA), depending on the number of groups being compared. A logistic regression model was used, controlling for all baseline data, to examine predictors of above mean annual direct costs in those with Rome IV IBS, and the results were reported with ORs with 95% CIs. A *P* value <0.01 was used to define statistical significance with all analyses performed using SPSS for Windows (version 27.0 SPSS, Chicago, IL).

6.3 Results

In total, and as reported in Chapter 3, 1278 individuals who had IBS by self-report responded and completed the questionnaire. Of these, 995 (77.9%) and 752 (58.8%) met Rome III and IV criteria for IBS respectively, and only their data were considered in all further analyses. Among those meeting Rome IV criteria for IBS, the mean age was 45.3 years (range 18-81 years) and 655 (87.1%) were female. In total, 136 (18.1%) had IBS-C, 306 (40.7%) IBS-D, and 301 (40.0%) IBS-M. The mean IBS-SSS score was 293.1 (SD 95.1). Amongst those meeting Rome III criteria, mean age was 46.5 years (range 18-85 years) and 852 (85.6%) were female. There were 185 (18.6%) with IBS-C, 414 (41.6%) with IBS-D, and 382 (38.4%) with IBS-M. The mean IBS-SSS score was 266.1 (SD 102.8).

6.3.1 Mean annual direct costs from IBS

The mean annual direct costs of IBS among individuals with Rome IV IBS was £556.65 per person (SD £1023.92) with appointments with healthcare professionals accounting for £224.48 (40.3%) of total costs, investigations £157.69 (28.3%), unplanned hospital attendances £101.85 (18.3%), and IBS-related medications £72.60 (13.1%), (Figure 6.1). The prevalence of Rome IV-defined IBS in the UK is 4.6%,[28] and there are 49,711,000 adults aged 18 years and over, meaning there are likely to be 2,286,706 individuals with Rome IV IBS in the UK. Applying these cost data resulted in an estimate of total annual direct costs of IBS to the health service of £1,272,894,895. In a sensitivity analysis, assuming 2.8% of the UK adult population have Rome IV IBS and will consult a physician, as per the UK population recruited into the three-nation Rome Foundation study (data on file, personal communication: Dr. Olafur Palsson, University of North Carolina, Chapel Hill, NC, USA),[28] there are likely to be

1,391,908 individuals with Rome IV IBS who have consulted a physician in the UK. Applying the costs data to these figures yielded estimated total annual direct costs of IBS to the health service of £774,805,588.

The annual mean direct costs of IBS among individuals with Rome III IBS was lower at £474.16 per person (SD £897.86), with appointments with healthcare professionals costing £184.61 (38.9% of costs), investigations £138.92 (29.3%), unplanned hospital attendances £87.21 (18.4%) and IBS-related medications £63.42 (13.4%) (Figure 6.1). Prevalence rates of Rome III-defined IBS in the UK are 8.8%,[28] meaning there are likely to be 4,374,568 adults with Rome III IBS. Applying the cost data to these figures yielded estimated total annual direct costs to the health service for IBS of £2,074,245,163. Even when a sensitivity analysis was performed, assuming 4.7% of the UK adult population have Rome III IBS and will consult a physician (data on file, personal communication: Dr. Olafur Palsson, University of North Carolina, Chapel Hill, NC, USA),[28] there are likely to be 2,336,417 individuals with Rome III IBS who have consulted a physician in the UK. Total annual direct costs were, therefore, estimated at £1,107,835,485.

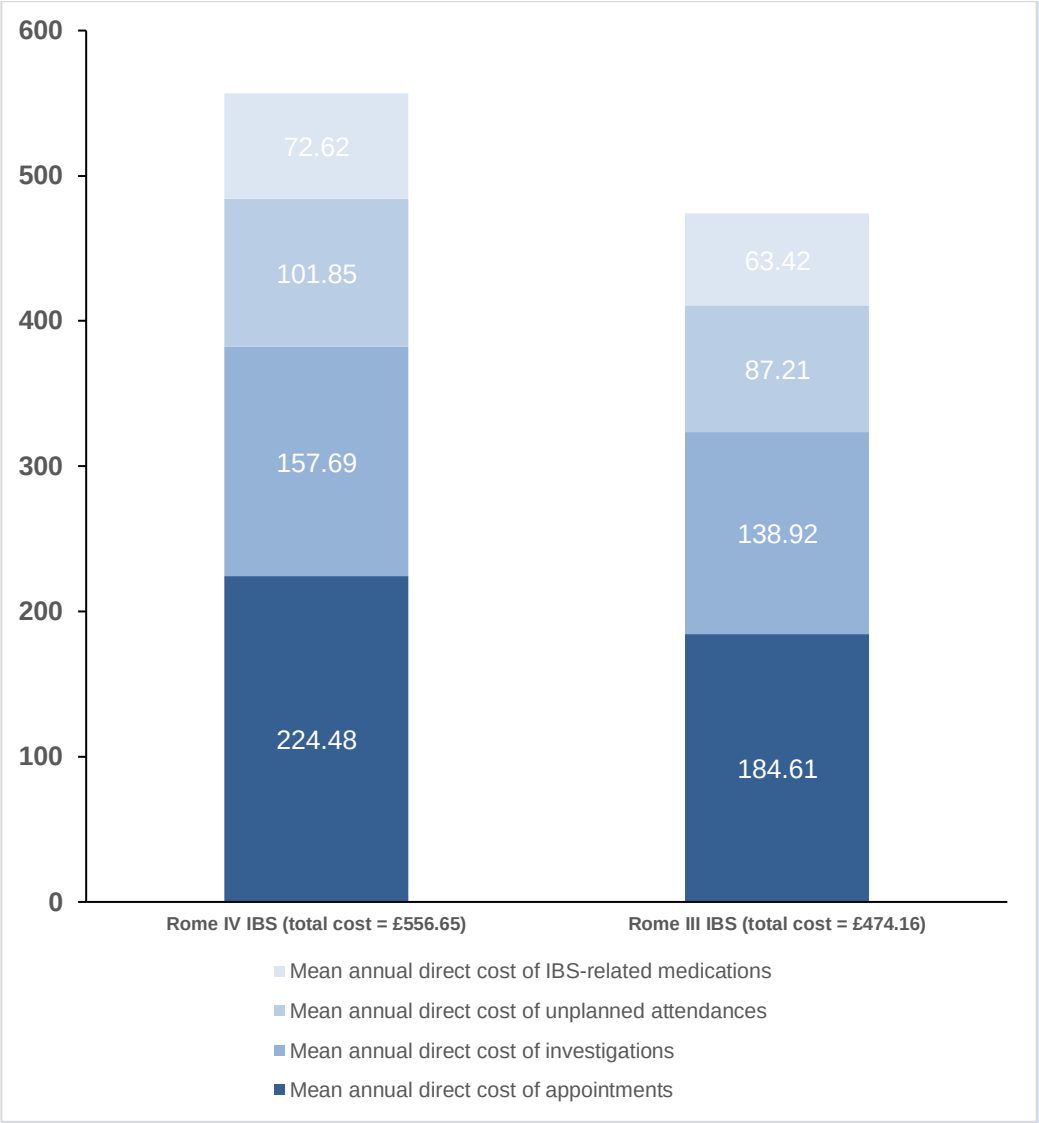

Figure 6.1. Mean annual direct costs of IBS among 752 individuals with Rome IV IBS and 995 individuals with Rome III IBS.

6.3.2 Mean annual direct costs in individuals with Rome IV-defined IBS according to demographics, gastrointestinal symptoms, and psychological comorbidities.

Annual mean direct healthcare costs for individuals with Rome IV IBS were not associated with sex, or level of education but were significantly higher in smokers (£845.13 vs. £521.34, P = 0.007), those who did not drink alcohol (£747.79 vs. £420.36, P < 0.001), and those who were not married (£702.19 vs. £477.45, P = 0.004) (Table 6.3). There was no association between costs and IBS subtype, most troublesome symptom, or whether IBS had been triggered after an acute enteric infection. However, mean costs were higher in those who used opiates (£907.90 vs. £470.58, P < 0.001), and those with more severe symptoms (severe, £724.03 vs. moderate, £448.76 vs. mild, £277.96 vs. remission, £19.38, P < 0.001 for trend). Costs of IBS reduced significantly as duration of a diagnosis of IBS increased, although even among those who were diagnosed >5 years ago mean annual direct costs were estimated at over £500 per year. A higher mean cost in those with abnormal HADS depression scores (abnormal, £953.69 vs. borderline, £609.77 vs. normal, £355.10, P < 0.001 for trend), higher somatisation scores (severe, £799.47 vs. moderate, £508.80 vs. mild, £365.91 vs. low, £325.52, P < 0.001 for trend), and higher VSI scores (high, £765.86 vs. medium, £459.86 vs. low, £434.89, P < 0.001 for trend), but not abnormal HADS anxiety scores, were observed. Finally, costs increased significantly with reductions in IBS-related quality of life (low, £858.61 vs. medium, £585.97 vs. high, £251.82, P < 0.001 for trend). Following logistic regression, older participants (OR per year = 1.02; 95% CI 1.01 to 1.04) were more likely to have above mean costs and those with higher IBS-related quality of life (OR = 0.29; 95% CI 0.14 to 0.61) less likely.

Table 6.3. Direct healthcare costs of IBS (in UK pounds), as defined by Rome IV criteria, according to demographics, symptom characteristics, psychological comorbidity, and quality of life.

	Annual mean cost per person, SD (£UK)	P value
Sex		
Male (n = 97)	517.79 (879.01)	
Female (n = 655)	562.40 (1044.14)	0.69
Smoker		
Yes (n = 82)	845.13 (1330.12)	
No (n = 670)	521.34 (975.33)	0.007
Alcohol use		
Yes (n = 439)	420.36 (797.18)	
No (n = 313)	747.79 (1252.46)	<0.001
Married		
Yes (n = 487)	477.45 (859.26)	
No (n = 265)	702.19 (1261.11)	0.004
University or postgraduate level of education		
Yes (n = 314)	489.17 (973.18)	
No (n = 438)	605.02 (1057.25)	0.13
Annual income of £30,000 or more		
Yes (n = 197)	404.14 (823.55)	
No (n = 483)	609.49 (1046.89)	0.014
IBS subtype		
IBS-C (n = 136)	558.86 (1159.35)	
IBS-D (n = 306)	522.75 (941.01)	
IBS-M (n = 301)	586.22 (1043.37)	0.75
IBS after acute enteric infection		
Yes (n = 91)	665.27 (942.49)	
No (n = 465)	547.87 (1065.70)	0.33
Most troublesome symptom		
Abdominal pain (n = 169)	686.02 (1191.23)	
Constipation (n = 53)	518.47 (810.23)	
Diarrhoea (n = 117)	566.34 (1055.48)	
Bloating/distension (n = 218)	457.65 (885.32)	
Urgency (n = 195)	559.74 (1041.55)	0.31
Opiate use		
Yes (n=148)	907.90 (1391.88)	
No (n=604)	470.58 (892.05)	<0.001

Duration of IBS diagnosis, year(s)		
1 (n = 25)	1227.14 (1954.19)	
2 (n = 41)	919.39 (1508.42)	
3 (n = 54)	449.03 (740.93)	
4 (n = 33)	701.18 (1420.32)	
5 (n = 38)	564.24 (854.99)	
>5 (n = 561)	501.60 (910.60)	0.002
IBS-SSS severity		
Remission (n = 7)	19.38 (21.88)	
Mild (n = 86)	277.96 (639.10)	
Moderate (n = 300)	448.76 (859.30)	
Severe (n = 359)	724.03 (1193.10)	<0.001
HADS anxiety categories		
Normal (n = 200)	438.63 (1072.39)	
Borderline abnormal (n = 174)	521.50 (839.28)	
Abnormal (n = 378)	635.26 (1069.61)	0.08
HADS depression categories		
Normal (n = 404)	355.10 (836.24)	
Borderline abnormal (n = 165)	609.77 (877.43)	
Abnormal (n = 183)	953.69 (1353.78)	<0.001
PHQ-12 severity		
Low (n = 36)	325.52 (671.59)	
Mild (n = 176)	365.91 (785.65)	
Moderate (n = 307)	508.80 (898.70)	
Severe (n = 233)	799.47 (1302.59)	<0.001
VSI scores		
Low (n = 247)	434.89 (983.63)	
Medium (n = 247)	459.86 (924.15)	
High (n = 258)	765.86 (1119.30)	<0.001
IBS-QOL scores		
Low (n = 239)	858.61 (1210.79)	
Medium (n = 252)	585.97 (1152.04)	
High (n = 261)	251.82 (476.60)	<0.001

*P value for independent samples t-test or one way ANOVA.

6.4 Discussion

Individuals with IBS, defined according to validated criteria,[146, 320] were recruited to estimate contemporaneous mean annual direct costs of IBS to the health service per person and extrapolate these results across the entire UK adult population using current IBS prevalence data, as well as published UK census data. The mean annual direct cost among individuals meeting Rome IV criteria for IBS was over £500 per person and almost £475 per person for those with Rome III IBS. For Rome IV IBS, 40.3% of direct costs were made up of appointments with healthcare professionals, 28.3% investigations, 18.3% unplanned hospital attendances, and 13.1% medications. Using these data, the total annual direct healthcare cost of IBS in the UK is estimated to be more than £1.2 billion if the Rome IV criteria are used to define IBS, and more than £2 billion using the Rome III criteria, due to the higher prevalence of IBS when these are applied. Even when a sensitivity analysis was performed, using prevalence data for only those who are likely to consult a doctor with IBS, total annual direct costs were estimated at £0.75 billion with Rome IV and £1.1 billion with Rome III. Mean direct costs were significantly higher in smokers, those who did not drink alcohol, those who were unmarried, those who used opiates, and those with a shorter duration of IBS. In terms of psychological comorbidity, higher depression, somatisation, and gastrointestinal symptom-specific anxiety scores were associated with higher mean direct costs. Finally, those with more severe IBS symptoms and lower quality of life had significantly higher direct costs.

The strengths of this study have already been discussed in Chapter 3. In addition, a bottom-up approach was used, where data concerning each individual appointment, investigation, or medication used were collected and the relevant unit cost for these items was applied to estimate the direct healthcare costs of

IBS across the UK, rather than a top-down approach, in which participants with IBS are identified via diagnostic coding and the average cost assigned to such a diagnosis is applied. This bottom-up approach to estimate costs meant that analysis did not have to rely on national databases, which are prone to coding errors,[321] and enabled the study to capture all IBS-related healthcare resource use, as well as OTC medications, which are used commonly by individuals with IBS.[322] This approach has been utilised previously in a study examining the economic impact of functional dyspepsia.[323]

Weaknesses of the study have been discussed in Chapter 3. Additionally, individuals joining ContactME-IBS, compared with the wider population of IBS patients, and those who responded to the study survey, compared with non-respondents, may be more proactive in managing their IBS and may have higher healthcare use. Although validated questionnaires were used to examine the presence and severity of IBS and psychological comorbidities, and to assess IBS-related quality of life, the study relied on self-report to collect IBS-related resource use retrospectively. Although it is impossible to eliminate errors in recall, this methodology sought to minimise them by limiting the recall period to the 12 months immediately prior to questionnaire completion, as accuracy generally decreases the longer the recall period.[324] Moreover, to limit variations in understanding that might affect recall, questions were designed to capture healthcare resource use were clear and precise. Importantly, self-reported healthcare utilisation has been shown to be accurate and reliable for hospital and specialist visits, although GP visits may be at risk of under reporting.[325] Minority ethnic groups were underrepresented in this study population, and this could have affected the results because of racial disparity in healthcare utilisation among patients with IBS.[326] The cost data were positively skewed, meaning that

the mean cost per individual will have been affected by a small proportion of participants with higher costs. Despite this, the mean cost was used, as using a median would involve applying the cost data from a single individual from the study sample to estimate the cost of IBS across the UK. The mean cost, although affected by outliers with higher costs, better reflects a real-life situation with a large proportion of patients with low levels of healthcare usage and a small number of individuals with higher costs. As a result of some of this, the total annual direct costs reported may be an overestimate. However, various steps were taken to reduce this. First, all appointments were assumed to be follow-ups, which are cheaper than new patient appointments, the cheapest drug price available from the BNF was used, including for OTC medications, and out of pocket expenses, complementary or alternative medicines, or other indirect costs were not considered. Second, the UK census data from 2011 were used because the latest 2021 census results were unpublished at the time the analysis was conducted. The population of individuals aged 18 years or over is likely to have increased further in the last decade. Third, a more conservative sensitivity analysis was performed using prevalence data for Rome IV or Rome III IBS only for those who are likely to have consulted a doctor in the UK,[28] because the costs may have been skewed by the fact that most responders in this study had consulted their GP or a gastroenterologist. Even in this analysis, costs were estimated at between £0.75 and £1.1 billion per year. Finally, 75% of participants were diagnosed more than 5 years prior to study recruitment, reflecting the chronicity of IBS, and costs were significantly lower in this group.

Several studies have attempted to estimate direct healthcare costs of IBS in the UK.[131, 252, 253, 316] Importantly, only two of these have been carried out in the last 20 years, and one reported a total annual healthcare cost 3 years before and

3 years after a patient's first appointment with a gastroenterologist with IBS,[252] rather than costs related to IBS *per se*. The second study reported a mean annual cost of IBS per patient of £383.20, but the authors also included patients with symptoms that were only suggestive of IBS, including constipation, change in bowel habit, or abdominal pain in isolation.[253] Both studies used a top-down approach, meaning that the Rome criteria for IBS were not applied and the authors relied on the accuracy of coding in existing databases, even though this approach is prone to error.[321] In addition, both used data from patients who had seen a gastroenterologist in secondary care for their IBS, which is not representative of all patients with IBS, because many either do not see a doctor at all or are managed solely in primary care.[315]

Although it is difficult to compare costs across countries using different currencies and healthcare systems over different periods of time, all prior studies conducted elsewhere have shown, consistently, that there are substantial costs associated with the care of individuals with IBS.[249, 313, 314] Annual direct healthcare costs estimates per patient in the most contemporaneous review, including studies conducted elsewhere, were between $742 and $7547 in the USA, £90 to £316 in the UK, €567 to €862 in France, $259 in Canada, €791 in Germany, and $92 in Iran.[313] No previous study has used the Rome IV criteria to estimate the annual direct cost of IBS. Only one study used the Rome III criteria, which reported annual direct costs for IBS of ¥12761.14 (approximately £1450) in 105 patients with IBS recruited from a university hospital in China.[250] The mean annual direct healthcare costs of IBS per patient observed in the present study is of a similar magnitude to that estimated for patients with functional dyspepsia in the USA, which was $699 (approximately £525) per patient.[323] Finally, to put these findings in context with other chronic diseases, the estimate for the annual

direct cost of IBS per patient in this study, irrespective of the criteria used to define its presence, is lower than that for asthma and chronic obstructive pulmonary disease (£808),[327] type 1 diabetes mellitus (£1323), or type 2 diabetes mellitus (£1080) in the UK.[328]

Few studies have examined associations between patient demographics, symptom characteristics, and costs.[317, 318] These were published some time ago, and therefore used the Manning, Rome I, or Rome II criteria to diagnose IBS, but their results are similar. Johansson *et al.* reported a positive correlation between both severity of IBS and the presence of somatic symptoms and costs, [317] whereas Lepen *et al.* demonstrated a negative correlation between quality of life, based on the IBS-QOL, and costs, [318] and no association between sex or IBS subtype and costs. The results from the present study demonstrate that those using opiates, those with more severe symptoms, and those with lower quality of life had higher annual mean costs. This probably reflects higher levels of consultations, investigations, and medication usage in this group of patients. Mean annual costs correlated negatively with duration of IBS, likely because of more frequent consultations and investigations at the onset of symptoms. The fact that those with higher depression, somatisation, and gastrointestinal symptom-specific anxiety scores had higher mean annual direct healthcare costs related to IBS may relate to confounding factors, such as severity of IBS symptoms, which is known to be associated with both costs and psychological comorbidities.[119, 120, 329]

Mean annual direct costs among individuals with Rome IV IBS were higher than in those with Rome III IBS, probably because the stricter Rome IV criteria select patients with more severe symptoms.[21] Despite this, the annual direct cost to the UK health service estimated in this study was higher using the Rome III

criteria because of the higher prevalence of Rome III IBS.[28] Overall costs of IBS are substantial, likely as a result of the chronicity of symptoms,[111] the non-fatal nature of IBS,[127, 330] the relatively high prevalence of the condition, the inappropriate use of exhaustive investigation to reach a diagnosis,[140, 151] and the lack of a cure. Money spent on medications was lowest compared with other costs. This may reflect the continued use of older medications, due to their familiarity, as well as the lack of availability of newer effective drugs, due to a perceived lack of demand for these in the UK by pharmaceutical companies, meaning that they are no longer marketed.

This study has important implications. The costs of IBS estimated would represent 0.7% or 1.2%, for those with Rome IV IBS or Rome III IBS respectively, of the total budget for Health and Social Care spending across all four nations in the UK for 2019 to 2020.[331-334] This represents an enormous burden to the health service and to society, especially when the results from Chapter 3, where the impact of IBS on work was presented, are also taken into account. Clinicians should, therefore, be encouraged to make a positive diagnosis of IBS in the absence of alarm symptoms or signs, rather than regarding IBS as a diagnosis of exclusion that requires numerous investigations, which may drive management costs.[153] Careful explanation of symptoms, active listening, being empathetic, educating patients, offering reassurance, and managing expectations are key to reducing multiple healthcare episodes, as previously discussed.[205, 335] The high level of spending in IBS highlights the need for optimised management of the condition, including a multidisciplinary approach and improved access to evidence-based treatments, such as eluxadoline, ramosetron, plecanatide, and tenapanor, which are not licensed in the UK. Compared with seeing a gastroenterologist alone, multidisciplinary care may not only reduce treatment

costs for IBS,[306, 307] but also unplanned hospital attendances. Finally, the high cost of IBS should be an impetus for funding bodies to commission more research into both the causes and management of IBS, especially considering that research monies for IBS in both Europe and the USA are considerably lower than those for less prevalent gastrointestinal conditions, such as coeliac disease.[248]

IBS is a chronic disorder which is costly to the health service and to society. It is, therefore, important to evaluate the prognosis of the disorder which will be the focus of the next chapter. The potential reasons for higher costs of Rome IV IBS, compared with Rome III IBS, discussed in this chapter will be further explored in Chapter 7, where the prognosis of Rome IV and Rome III IBS, in terms of healthcare usage, will be investigated.

Chapter 7 Assessing whether Individuals with Rome IV IBS have a Different Prognosis to those with Rome III IBS in terms of Future Gastrointestinal and Psychological Symptoms.

7.1 Introduction

The impact of IBS, defined using the Rome IV criteria, has been considered in Chapters 3, 4, 5, and 6. Because most studies in IBS have been conducted using the Rome III or IV criteria, it is important to investigate if there are any differences between the natural history of those meeting the Rome III and IV criteria that may alter the burden of IBS. As discussed in Chapter 1, the latest iteration, Rome IV,[19] published in 2016, were a modification of the previous Rome III criteria.[18] 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, defaecation.[336] The aim of these changes was to increase specificity of the Rome IV criteria over prior iterations.[146]

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.[21-24] Those with Rome IV IBS have more severe symptoms and higher levels of psychological comorbidity. These differences may have a deleterious impact on the natural history of IBS but there have been no studies conducting longitudinal follow-up to examine whether this is the case.

Due to previous observations that individuals with Rome IV IBS had more severe symptoms at baseline,[21-24] and had higher levels of psychological comorbidity,[21] it was hypothesised 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. These issues were examined 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 RCTs testing both novel and existing therapies.

7.2 Methods

7.2.1 Participants and setting

Individuals self-identifying as having IBS registered with three organizations in the UK were recruited. 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. Individuals were invited, via email and post, between December 2017 and December 2018, informing them that they would be re-contacted 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. A follow-up questionnaire was sent 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 (MREC17-018). This is a separate cohort of individuals with IBS to those used in Chapters 3, 4, 5, and 6.

7.2.2 Data collection and synthesis

7.2.2.1 Demographic and lower gastrointestinal symptom data

Demographic data were collected at baseline. Lower gastrointestinal data at baseline and 12-month follow-up were captured using both the Rome IV and Rome III questionnaires.[259, 319] The presence or absence of either Rome IV or Rome III-defined IBS were assigned among all individuals at baseline and 12-month follow-up according to the scoring algorithms proposed for these questionnaires.[18, 19] IBS subtypes were categorised according to the criteria used in the questionnaires. The proportion of individuals with Rome IV IBS transitioning to Rome III IBS, or no longer meeting either set of criteria for IBS, at 12 months was examined. The proportion of individuals with Rome III IBS transitioning to Rome IV IBS, or no longer meeting either set of criteria for IBS, at 12 months was also examined.

7.2.2.2 Consultation behaviour and treatment data during follow-up

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

7.2.2.3 Disease severity and impact, and psychological health data at baseline and during follow-up

IBS symptom severity, at both baseline and follow-up, was assessed using the IBS-SSS.[113] The impact of IBS symptoms at 12 months was measured, in terms of the proportion of time that they limited normal daily activities, as per the Rome IV questionnaire, [259] and was dichotomised at a threshold of interference with daily activities ≥50% of the time. Psychological health and symptom severity were examined at baseline and at 12 months in individuals with Rome IV or Rome III-defined IBS at baseline. Anxiety and depression data were collected using the

HADS,[260] and somatisation data the PHQ-12.[119] Full details of the IBS-SSS, HADS, and PHQ-12 have already been provided in Chapter 3.

7.2.3 Statistical analysis

The 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 were examined. An analysis of whether baseline Rome IV or Rome III-defined IBS influenced subsequent disease behaviour 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 was conducted. The proportion of individuals with either Rome IV or Rome III IBS who reported abnormal anxiety or depression scores, or high levels of somatisation, were compared at 12-month follow-up. Finally, anxiety and depression scores, and somatisation levels, were compared at 12-month follow-up according to anxiety and depression scores, and somatisation levels, at baseline. A χ^2 test was used for categorical data and an independent samples *t*-test for continuous data. Logistic regression analysis was conducted 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. All analyses were performed using SPSS for Windows (version 26.0 SPSS Inc., Chicago, IL, USA).

7.3 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 7.1), 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 comorbidity at baseline. Differences in baseline data among those with Rome IV versus Rome III IBS at baseline successfully followed up are provided in Table 7.2. 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 comorbidity, (p<0.001 for all analyses).

Table 7.1 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)	
Diarrhoea	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 7.2 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)	
Diarrhoea	181 (40.0)	76 (40.9)	
Mixed stool pattern	185 (40.9)	63 (33.9)	
Unclassified	11 (2.4)	8 (4.3)	0.20
IBS-SSS severity 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.

7.3.1 Consultation behaviour, 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 7.3). 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).

A total of 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 (OR = 3.62; 95% CI 1.24-10.6, p=0.019) after logistic regression, but no statistically significant predictors (Table 7.4). There were no significant predictors of transitioning from Rome III IBS to Rome IV (Table 7.5).

Table 7.3 Consultation behaviour, 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
IBS-SSS severity 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)	
Diarrhoea	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 IBS	319 (70.6)	61 (32.8)	
Rome III IBS	69 (15.3)	88 (47.3)	
No longer met either Rome IV or Rome III criteria for IBS	64 (14.1)	37 (19.9)	<0.001

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

Table 7.4 Results of logistic regression to assess predictors of transition from Rome IV IBS to Rome III IBS.

	Odds ratio	95% confidence interval	*P* value
Female sex	1.30	0.61 – 2.79	0.50
Age (per year)	1.00	0.98 – 1.02	0.69
Married or co-habiting	1.06	0.56 – 2.01	0.86
White Caucasian ethnicity	0.51	0.10 – 2.79	0.44
University or postgraduate level of education	0.48	0.26 – 0.87	0.016
IBS after acute enteric infection	1.29	0.56 – 3.00	0.55
Previously seen a primary care physician regarding IBS at study entry	1.68	0.29 – 9.58	0.56
Previously seen a gastroenterologist regarding IBS at study entry	1.20	0.65 – 2.24	0.56
IBS subtype at baseline			
Constipation	1.00		
Diarrhea	1.85	0.82 – 4.19	0.14
Mixed stool pattern	1.31	0.57 – 3.02	0.52
Unclassified	1.15	0.17 – 7.86	0.89
Severity on IBS-SSS at baseline			
Remission	1.00		
Mild	1.27	0.05 – 30.4	0.88
Moderate	1.57	0.07 – 36.9	0.78
Severe	3.26	0.14 – 76.9	0.46
Continuous abdominal pain at baseline	1.54	0.79 – 2.98	0.20
HADS anxiety categories at baseline			
Normal	1.00		
Borderline abnormal	1.23	0.55 – 2.77	0.62
Abnormal	0.64	0.30 – 1.34	0.24
HADS depression categories at baseline			
Normal	1.00		
Borderline abnormal	1.59	0.71 – 3.60	0.26
Abnormal	3.62	1.24 – 10.6	0.019
PHQ-12 severity at baseline			
Minimal	1.00		
Low	0.84	0.27 – 2.68	0.77
Medium	1.28	0.40 – 4.11	0.68
High	2.16	0.53 – 8.74	0.28

Table 7.5 Results of logistic regression to assess predictors of transition from Rome III IBS to Rome IV IBS.

	Odds ratio	95% confidence interval	*P* value
Female sex	0.80	0.25 – 2.49	0.69
Age (per year)	0.98	0.95 – 1.01	0.11
Married or co-habiting	0.91	0.36 – 2.26	0.84
White Caucasian ethnicity	Not estimable	Not estimable	1.00
University or postgraduate level of education	0.91	0.39 – 2.13	0.83
IBS after acute enteric infection	0.41	0.10 – 1.62	0.20
Previously seen a primary care physician regarding IBS at study entry	Not estimable	Not estimable	1.00
Previously seen a gastroenterologist regarding IBS at study entry	2.08	0.89- 4.86	0.09
IBS subtype at baseline			
Constipation	1.00		
Diarrhea	0.54	0.17 – 1.71	0.29
Mixed stool pattern	0.93	0.29 – 3.01	0.90
Unclassified	3.54	0.26 – 48.5	0.34
Severity on IBS-SSS at baseline			
Remission	1.00		
Mild	Not estimable	Not estimable	1.00
Moderate	Not estimable	Not estimable	1.00
Severe	Not estimable	Not estimable	1.00
Continuous abdominal pain at baseline	0.83	0.33 – 2.14	0.71
HADS anxiety categories at baseline			
Normal	1.00		
Borderline abnormal	1.01	0.34 – 3.04	0.99
Abnormal	0.50	0.17 – 1.44	0.20
HADS depression categories at baseline			
Normal	1.00		
Borderline abnormal	3.60	1.11 – 11.6	0.033
Abnormal	6.39	1.32 – 30.9	0.021
PHQ-12 severity at baseline			
Minimal	1.00		
Low	0.97	0.16 – 6.09	0.98
Medium	1.02	0.17 – 6.03	0.98
High	14.75	0.87 – 249	0.062

7.3.2 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 7.6). 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 the analysis was restricted 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 somatisation 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 somatisation at baseline there was no difference in the proportion of individuals developing moderate or high levels at follow-up (p=0.30).

Table 7.6 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.

7.4 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 comorbidity, including abnormal anxiety or depression scores, and high levels of somatisation, at 12 months. When the analysis was restricted 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.

Individuals were recruited 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. Therefore, the results are likely to be generalisable to individuals with IBS in the UK. Because of the use an online questionnaire with mandatory fields, near complete data were obtained for all variables of interest at baseline and 12-month follow-up. The validated Rome IV and III questionnaires were also used side-by-side, rather than approximating one or other definition of IBS, as other investigators have done.[22, 23]

Weaknesses of this study include the fact that medical records were not checked to rule out organic gastrointestinal conditions that mimic IBS, such as coeliac disease or IBD.[275, 276] 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, it is likely that these individuals had IBS. As the questionnaire was completed online, the proportion of individuals who chose not to complete it, or whether those who responded were representative of all the people with IBS registered with these three organisations could not be assessed. All participants had to be motivated to complete two questionnaires 12 months apart. A response rate of 58% in this study is similar to other longitudinal follow-up studies of gastrointestinal disorders conducted over a similar time frame.[337-340] 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 comorbidity at baseline. Because the medical records were not checked, participants' recall was relied upon regarding 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 the findings of this study.

Previous studies have explored the differences between individuals who meet Rome IV and III criteria for IBS.[21-24] However, these are all cross-sectional

and restricted their 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 behaviour, prognosis, and disease impact. Other weaknesses of these studies include the fact that most recruited participants from referral populations, limiting generalisability, and did not apply the Rome IV and Rome III questionnaires simultaneously, but instead approximated one or other of the definitions.[22, 23]

This study suggests that the Rome IV criteria select a population with IBS who are 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,[21] it may also be explained by the more restrictive nature of these criteria. As previously discussed, 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 surveys have shown that pain severity and duration are associated with healthcare-seeking behaviour.[283, 341, 342] The 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.[42, 43] 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 the questionnaire administered that influence this.

The burden of IBS on individuals, the health service, and society has, so far, been examined in terms of its impact on activities of daily living, professional life, healthcare cost, and risk perception. This chapter has demonstrated that the latest iteration of the Rome criteria for IBS, Rome IV, selects individuals with a worse prognosis of IBS and who have higher levels of healthcare usage, further increasing the burden of the disorder. Although the impact of psychological comorbidities has been examined in relation to the previous issues discussed in this thesis, the cumulative impact of psychological comorbidities on the prognosis of IBS has not been fully investigated and will be discussed in the next chapter.

Chapter 8 Assessing the Impact of Psychological Comorbidity on the Prognosis of IBS.

8.1 Introduction

In the previous chapter, individuals with Rome IV IBS, compared with those with Rome III IBS, exhibited higher levels of psychological comorbidity in terms of anxiety, depression, and somatisation at 12 months follow-up. There are other psychological comorbidities that not only co-exist with IBS,[44, 118] but are also associated with more severe gastrointestinal symptoms.[119-121] These include, but are not limited to, perceived stress, and gastrointestinal symptom-specific anxiety.[21, 122, 343] The additional cumulative burden of these psychological comorbidities is unclear.

Previous cross-sectional surveys and case-control studies examining influence of psychological comorbidity in IBS have demonstrated that there is an association between severity of IBS and anxiety, depression, perceived stress, somatisation, and gastro-intestinal symptom-specific anxiety.[44, 118-120, 122] A recent cross-sectional survey, conducted in 106 patients with IBS, demonstrated a cumulative increase in IBS symptom severity with increasing number of psychological comorbidities.[44] However, there have been no large-scale studies conducting longitudinal follow-up to examine the cumulative effects of number of psychological comorbidities on the prognosis of individuals with IBS.

A 12-month longitudinal follow-up study was, therefore, conducted to examine this issue in a cohort of individuals with IBS defined according to the Rome IV criteria. It was hypothesised that those with a higher number of psychological comorbidities at baseline would have a worse prognosis than those with fewer psychological comorbidities. It was expected that, over 12 months, those with higher number of psychological comorbidities would have more severe symptoms, which would have a greater impact on activities of daily living, cycle

through a greater number of treatments, and exhibit higher levels of healthcare usage.

8.2 Methods

8.2.1 Participants and setting

This study recruited individuals who self-identified as having IBS registered with three organizations in the UK: The IBS network, TalkHealth, and ContactMe-IBS. Full details of the recruitment methodology have already been provided in Chapter 7.

8.2.2 Data collection and synthesis

8.2.2.1 Demographic and lower gastrointestinal symptom data

Full details of the demographic and symptom data collected have already been provided in Chapter 7.

8.2.2.2 Assessment of psychological comorbidity

The collection of anxiety and depression data using the HADS,[260] somatisation data using the PHQ-12,[119] and gastrointestinal symptom-specific anxiety using the VSI.[262] Full details of the HADS, PHQ-12, and VSI have already been provided in Chapter 3.

The 10-item version of the Cohen perceived stress scale (CPSS) was used to assess perceived stress. This is derived from the original 14-item instrument,[344] has been used widely, and is psychometrically reliable and comparable with its predecessor.[345] 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 IBD.[346] As there are no validated cut offs to define low,

medium, or high perceived stress scores, these data were divided into tertiles of equal size.

Individuals were classified according to the total number of psychological comorbidities they exhibited, from a possible total of five, including one or more of abnormal anxiety scores, abnormal depression scores, high somatisation scores, high perceived stress scores, and high gastrointestinal symptom-specific anxiety scores. The degree of overlap between them was examined.

8.2.2.3 Consultation behaviour and treatment data during follow-up

Methods of data collection for consultation behaviour and treatment during follow-up have already been provided in Chapter 7.

8.2.2.4 Assessment of IBS symptom severity and impact at baseline and follow-up

IBS symptom severity was assessed at baseline and 12 months using the IBS-SSS,[113] which has already been described in full in Chapter 3. The impact of IBS symptoms was measured, in terms of the proportion of time that they limited normal daily activities at 12 months, as per the Rome IV questionnaire,[259] and this was dichotomised at a threshold of interference with daily activities ≥50% of the time, as described in Chapter 7.

8.2.3 Statistical analysis

The demographic characteristics of all participants were compared according to the number of psychological comorbidities at baseline, using a χ^2 test for categorical data and a one-way ANOVA for continuous data. These characteristics were compared for responders, versus non-responders, to the follow-up questionnaire at 12 months, using a χ^2 test for categorical data and an independent samples *t*-test for continuous data. The degree to which

psychological comorbidity at baseline influenced subsequent disease behaviour was examined. Specifically, 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, the impact on normal daily activities, and symptom severity at 12-month follow-up, were compared according to the number of psychological comorbidities 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. All analyses were performed using SPSS for Windows (version 26.0 SPSS Inc., Chicago, IL, USA).

8.3 Results

In total, and as detailed in Chapter 7, there were 1375 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 somatisation 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 comorbidities, and 562 (69.6%) had at least one psychological comorbidity. 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 comorbidities. The degree of overlap among the 562 individuals with one or more psychological comorbidity is provided in Figure 8.1.

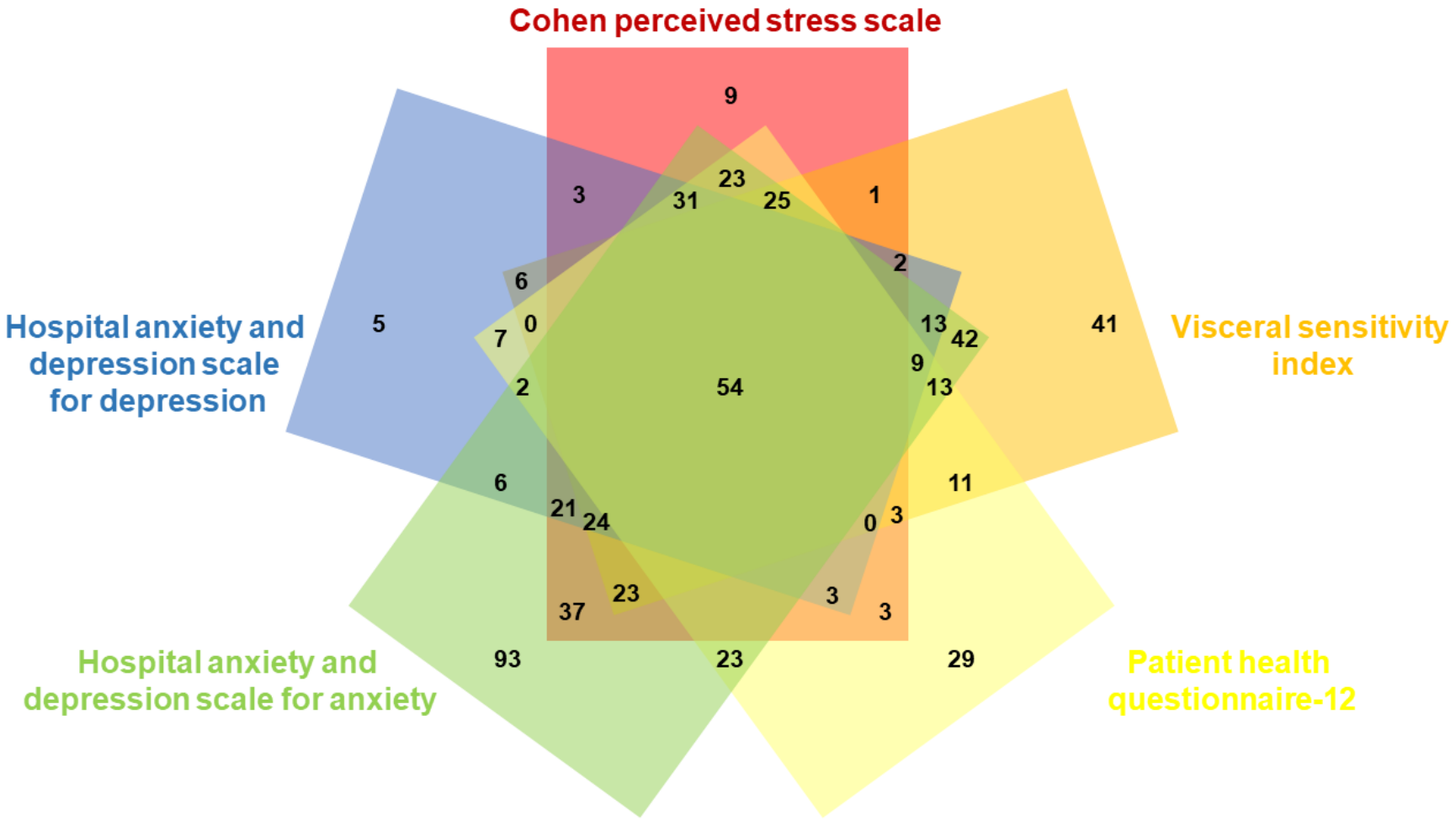

Figure 8.1. Overlap of psychological comorbidity amongst 562 individuals with Rome IV IBS and at least one psychological comorbidity.

8.3.1 Characteristics of individuals meeting Rome IV criteria for IBS according to number of psychological comorbidities at baseline

Demographic characteristics of all 807 participants with Rome IV IBS, according to number of psychological comorbidities, are provided in Table 8.1. Those with more psychological comorbidities 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 comorbidities 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 the number of psychological comorbidities (72.2% of those with five psychological comorbidities 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 8.1 and Figure 8.2), and median IBS-SSS scores increased significantly with each incremental increase in number of psychological comorbidities (381.5 in those with five psychological comorbidities, 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 8.1). The proportion of individuals with continuous abdominal pain also increased with increasing number of psychological comorbidities (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 8.1).

Table 8.1. Characteristics of 807 individuals meeting Rome IV criteria for IBS according to number of psychological comorbidities 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)	
Diarrhoea	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
IBS-SSS severity 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 PHQ-12 scores at baseline (%)	0 (0)	29 (16.4)	44 (31.7)	44 (42.7)	65 (73.0)	54 (100)	<0.001
High CPSS scores at baseline (%)	0 (0)	9 (5.1)	44 (31.7)	75 (72.8)	80 (89.9)	54 (100)	<0.001
High VSI scores at baseline (%)	0 (0)	41 (23.2)	60 (43.2)	54 (52.4)	58 (65.2)	54 (100)	<0.001

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

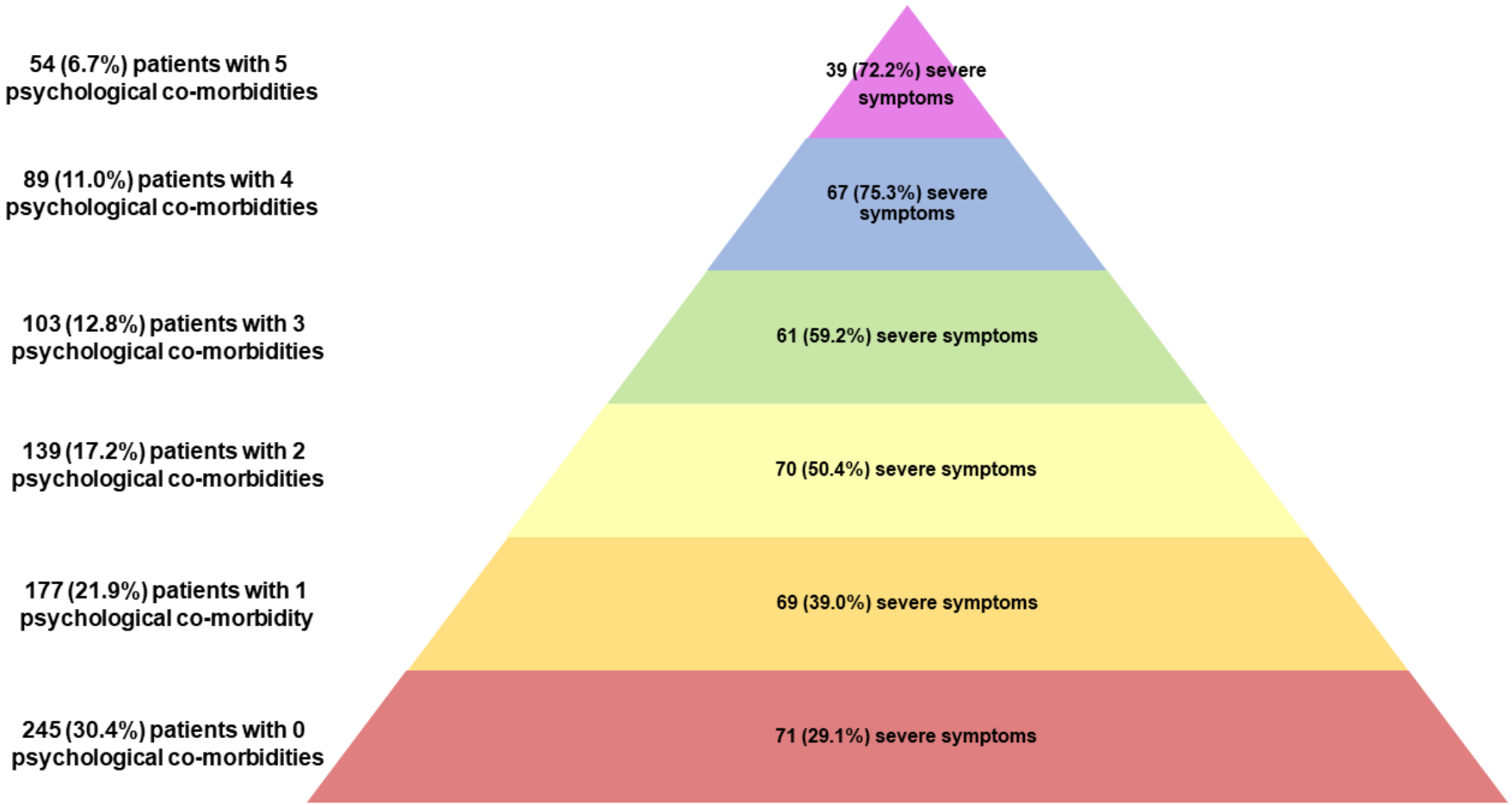

Figure 8.2. Number of individuals with Rome IV IBS with 0, 1, 2, 3, 4, or 5 psychological comorbidities and the proportion reporting severe symptoms on the IBS-SSS among them.

8.3.2 Consultation behaviour, commencement of new treatment, and disease impact and severity during follow-up according to number of psychological comorbidities 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 8.2). There were no other significant differences, including IBS subtype, IBS symptom severity at baseline, presence of continuous abdominal pain at baseline, or degree of psychological comorbidities.

The proportion of individuals consulting their primary care physician (32.8% with no psychological comorbidities, versus 52.4% with five psychological comorbidities, p=0.017) or commencing a new treatment for their IBS (70.2% with no psychological comorbidities, versus 76.2% with five, p=0.02) increased generally with increasing number of psychological comorbidities, although these differences were not statistically significant (Table 8.3). However, the number of new treatments commenced for IBS increased significantly according to psychological comorbidities at baseline (p<0.001 for trend). In addition, the proportion of individuals who had seen a gastroenterologist (21.4% with no psychological comorbidities, 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 comorbidities, 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 comorbidities. The proportion of individuals with continuous abdominal pain at 12 months increased with each increase in psychological comorbidity (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 comorbidities 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 comorbidities (median score 220.0 in those with no psychological comorbidity, 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 comorbidities 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 comorbidities at baseline predicted the number of psychological comorbidities at follow-up; more than 50% of individuals with five psychological comorbidities at baseline still had five at follow-up ($p<0.001$ for trend).

Table 8.2. 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)	
Diarrhoea	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 somatisation 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 comorbidities 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.

Table 8.3. Consultation behaviour, commencement of new treatment, and disease impact and severity during follow-up according to number of psychological comorbidities 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
IBS-SSS severity 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 comorbidities 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.

8.4 Discussion

This 12-month longitudinal follow-up study has examined the prevalence of psychological comorbidity, including anxiety, depression, somatisation, 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 comorbidity, and almost 50% had at least two. Those with a higher number of psychological comorbidities 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 comorbidities on IBS symptom severity at baseline. During follow-up, those with higher levels of psychological comorbidity 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 comorbidity at baseline, and levels of psychological comorbidity at baseline also predicted degree of psychological comorbidity at follow-up.

The strengths and weaknesses of the design of this study have been discussed in Chapter 7. In addition, although validated questionnaires were used to determine the proportion of individuals with abnormal scores for each psychological comorbidity,[119, 260, 262, 344] 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 well accepted in studies like this.[21, 43, 44, 118, 339, 343] The 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. [44] Finally, this study was limited to five psychological comorbidities, which have been extensively studied in IBS, but there may be other important psychological factors affecting outcomes in individuals with IBS that were not examined as part of this study, some of which are discussed below.

Although two recent cross-sectional surveys have examined the relationship between increasing levels of psychological comorbidity and IBS symptom severity, [44, 347] one of which included physiological test results within the analysis, [347] 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 comorbidities on the prognosis of IBS, including healthcare-seeking behaviour, symptom severity, 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 comorbidity. Prior to examining cumulative effects of psychological comorbidities in IBS, Midenfjord *et al.* assessed nine different psychological comorbidities individually, but only included five that were significantly associated with IBS symptoms in their analysis. [44] These included physical fatigue, gastrointestinal symptom-specific anxiety, perceived stress, pain catastrophizing, and trait anxiety. In contrast, somatisation and depression, whose association with IBS is well-recognised,[343,

[348, 349] were not significant associations, which could perhaps be explained by the small sample size of the study. [44]

In the present study, the focus was on common psychological comorbidities 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.[350, 351] 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,[352] or experiential avoidance, which consists of 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.[353] Preliminary studies suggest that acceptance and commitment therapy might decrease experiential avoidance and is useful in reducing psychological distress in people with gastrointestinal disorders.[354, 355] 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.[356, 357] Mindfulness is proposed to reduce stress via emotion regulation, such as positive reappraisal attention regulation, body awareness, and change in self-perspective.[358]

The results from this study demonstrate that, with increasing levels of psychological comorbidity, 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 comorbidities, suggesting central sensitization, which is in keeping with previous literature demonstrating that anxiety and hypervigilance lead to amplification of central pain processing.[359] 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,[185, 186, 188] which focus mainly on the physical symptoms of either intermittent and episodic abdominal pain or abnormal 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, BGBTs are only recommended as a last resort after the failure of pharmacological therapies.[145] Although recent trials assessing the effectiveness of BGBTs, such as CBT or GDH, in the treatment of patients with IBS with refractory symptoms have produced encouraging long term results,[187, 269, 270, 360] many RCTs of BGBTs 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,[361-364] as well as other patients within gastrointestinal symptoms.[365, 366]

The findings from this study 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. Therefore, psychological assessment should be part of the routine evaluation of patients with

IBS. In addition, access to formal psychological assessment and BGBTs 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.[307] 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.[367] These findings also have implications for future research. Although there is an association between psychological comorbidity and severity of IBS symptoms, as well as prognosis, it remains unclear which psychological comorbidity has the greatest effect on the prognosis of IBS, although anxiety was the most prevalent psychological comorbidity in this study, and whether one of these psychological comorbidities is driving one or more of the others. In addition, although the cumulative effects of psychological comorbidities on the prognosis of IBS were assessed during 12 months of follow-up, the longer-term effects are unknown.

In summary, individuals with Rome IV-defined IBS with higher levels of psychological comorbidities had worse prognosis of their disease, in terms of more severe IBS symptoms and worse psychological health at follow-up. They were more likely to seek healthcare and cycle through more treatments for their symptoms during follow-up. These results, taken together with the findings of the previous chapters, where the impact of psychological comorbidities have been described, demonstrate the burden of IBS not only on individuals but also on the health service and society.

Chapter 9 Conclusions

The diagnosis and management of IBS have evolved over the last few decades but, despite these recent advances, our understanding of IBS remains incomplete. The definition of IBS, the latest one being the Rome IV criteria, is still based on symptoms reported by patients as there are no available biomarkers to make a diagnosis. IBS, reassuringly, does not increase mortality but does increase morbidity for a number of reasons. It is a prevalent condition, affecting 5% to 10% of the world's population, is a chronic and incurable disorder, partly because of the modest efficacy of currently available treatments, is often poorly understood by healthcare professionals, and is associated with other DGBI and psychological comorbidities. The burden of IBS to individuals affected, the healthcare service, and society needed further rigorous examination.

Previous researchers had examined some of these issues. It has been discussed that previous studies had several methodological weaknesses, which meant that their results may have been inaccurate or that they were not applicable to the UK population. Some studies have been criticised because of the small sample of individuals meeting historical definitions of IBS recruited from referral populations. Others only examined individuals with specific IBS subtypes, used non-validated questionnaires, or did not examine the range of psychological disorders commonly reported in individuals with IBS.

This thesis has, therefore, attempted to address these shortcomings to estimate the burden of IBS on the individual, the health service, and society. One cross-sectional survey with four analyses, using the same cohort of over 750 participants with Rome IV-defined IBS recruited from the community, were conducted to examine the impact of IBS on work and activities of daily living, the quality of life of individuals with IBS, the willingness to accept medication risks, and the direct healthcare costs of IBS. In addition, two longitudinal studies

recruiting and successfully following more than 600 individuals, from a separate cohort, with Rome III or IV IBS for 12 months were conducted. The first study examined the impact of the changes made in moving from the Rome III to the Rome IV criteria on prognosis and healthcare usage, and the second investigated the cumulative effect of psychological comorbidities on the prognosis of Rome IV-defined IBS.

The study on work and activities of daily living, reported in this thesis, showed that approximately 10% of individuals were unemployed partly as a result of their IBS. Among those who were employed, almost one-in-three individuals with IBS reported absenteeism, and over 80% presenteeism and overall work impairment because of their IBS. This study estimated that, in the UK, between 72 and 188 million hours of work are lost per year due to the condition. In addition, more than 90% of participants reported that IBS symptoms interfered with their activities of daily living. These findings highlight the impact of the disorder on individuals with IBS. The burden is also likely to be felt by family members and friends, as individuals with IBS reported difficulties in home management and leisure activities. The results have several implications. Perhaps, the most important one to consider is whether IBS-specific CBT, which has been shown to be effective in managing emotions and responses resulting from an activity that elicit or perpetuate IBS symptoms, can be effective in reducing the burden of IBS in terms of its impact on work productivity. Finally, because of the high prevalence of IBS and the extent to which it affects people at work, the burden of the disorder to society, in addition to the direct healthcare cost, is likely to be substantial.

Subsequently, this thesis examined the impact of IBS on disease-specific and generic health-related quality of life of individuals affected using the IBS-QOL and the EQ-5D side-by-side. Disease-specific quality of life was significantly

lower among those with Rome IV IBS-D, and lower levels of both disease-specific and generic quality of life in Rome IV IBS were associated with severe IBS, anxiety, depression, somatisation, and gastrointestinal symptom-specific anxiety. An important finding was that generic health-related quality of life among those with Rome III or IV IBS was comparable with chronic organic conditions like stroke, leg ulcers, or chronic obstructive pulmonary disease. Because of the stigma associated with a disease that is viewed as “functional”, the latter observation should encourage those with IBS to feel less ashamed of, or embarrassed about, their illness. The fact that anxiety, depression, and somatic symptom-reporting were independently associated with lower quality of life is further evidence that routine psychological assessment is crucial in those with IBS and effective multidisciplinary management of IBS should be encouraged to improve patients’ quality of life.[306, 307] Clinical trials of IBS treatment should consider using the EQ-5D, as it allows quality-adjusted life year calculations and cost-effectiveness analyses, both of which are important for making decisions about ability to access novel therapy in publicly funded healthcare systems like the NHS.

Because of the impact of IBS on individuals, in terms of interference of gastrointestinal symptoms at work and in daily life, as well as the low levels of quality of life associated with IBS, the next study examined the risks associated with a hypothetical medication that these individuals were willing to accept in return for a cure of their symptoms. The results demonstrated that individuals with Rome IV IBS were willing to accept a median 2% risk of death from a hypothetical medication in return for a 98% chance of permanent cure of their IBS. This increased to 5% in some subgroups of patients, including men and individuals with depression. The fact that participants were willing to accept these risks to

achieve cure of their symptoms, even though IBS is not known to reduce life expectancy,[126, 312] is further evidence of the burden of the disorder felt by some individuals. These results are particularly important for pharmaceutical companies to aid decisions regarding continued drug development when serious adverse events arise, as well as the regulatory agencies responsible for assessing the risk-benefit profile of new drugs prior to approval or when adverse events arise during post-marketing surveillance. Because IBS is perceived as a benign condition, drugs with serious side effects are often withdrawn or their use restricted and the results from this study suggest this debate needs to be recalibrated, particularly in those with more severe, or refractory, symptoms.

The fourth cross-sectional survey demonstrated that the mean annual direct healthcare cost among individuals meeting Rome IV criteria for IBS was over £500 per person and almost £475 per person for those with Rome III IBS. Using these data, the costs of IBS was estimated to be between £1.2 billion or £2 billion, for those with Rome IV IBS or Rome III IBS, respectively, representing 0.7% or 1.2% of the total budget for Health and Social Care spending across all four nations in the UK for 2019 to 2020.[331-334] This represents a substantial burden to a publicly funded health service, such as the NHS, and to society. Because over a quarter of the money spent is on investigations, making a positive diagnosis of IBS may help reduce this cost. The high levels of spending in IBS also highlight the need for optimised management of the condition, including a multidisciplinary approach and improved access to some evidence-based treatments, such as ramosetron, plecanatide, and tenapanor, which are yet to be licensed in the UK. These findings should also provide a strong mandate for funding bodies to commission more research into IBS. Although the direct healthcare cost of IBS and the impact on work productivity was examined in this thesis, the indirect cost

of IBS was not investigated. Future research should address this so that the full economic burden of IBS on society can be calculated accurately.

To further investigate the burden of IBS, two longitudinal follow-up studies from a separate cohort of individuals, over a 1000 of whom met either the Rome III or IV criteria for IBS, were conducted. The first study evaluated the natural history of Rome IV IBS, compared with Rome III IBS, to determine the impact of a change in definition on prognosis and healthcare usage. During follow-up, those with Rome IV IBS, compared with those Rome III-defined IBS, had significantly higher levels of healthcare usage. Despite this, at 12-month follow-up, individuals with Rome IV IBS reported significantly more severe gastrointestinal and psychological symptoms, which had a significantly greater impact on activities of daily living. The burden of the disorder using the latest definition of IBS is, therefore, even higher. Despite the relatively long follow-up compared with most studies in IBS, a 12-month follow-up period for a chronic incurable disorder, such as IBS, may be considered inadequate to fully understand the natural history of the disorder and its impact. Future studies with longer follow-up are, therefore, required. In terms of implications for research, using the Rome IV criteria to recruit participants for RCTs may results in a smaller therapeutic gain of active therapies over a placebo or control treatment, particularly as endpoints used to judge treatment response have become more stringent. This means that RCTs using the Rome IV criteria may need larger numbers of patients, requiring a greater number of sites and, therefore, have higher running costs.

The second longitudinal follow-up study examined the prevalence of five psychological comorbidities and their effect on the prognosis of Rome IV IBS. The majority of individuals had at least one psychological comorbidity at baseline. The results from this study demonstrated that, with increasing levels of

psychological comorbidity, individuals with Rome IV IBS have worse IBS symptoms at baseline, higher healthcare usage, and a worse prognosis at follow-up. These results highlight the burden of psychological comorbidities on individuals with IBS and on the health service. An integrated approach to treatment of gastrointestinal and psychological symptoms, which has been demonstrated to lead to an improvement in biopsychosocial outcomes in those with IBS,[361-364] should be considered rather than the current approach of using BGBTs as a last resort after the failure of pharmacological therapies.[145] This study did not investigate which psychological comorbidity has the greatest effect on the prognosis of IBS and whether one of these psychological comorbidities is driving others. Future investigators should consider this to target psychological interventions.

In summary, this thesis has investigated several aspects related to the burden of IBS. It has demonstrated that the disorder causes substantial interference in the life of people with the disorder, leading to impairments in quality of life, comparable with other chronic organic disorders, to the extent that some are willing to accept substantial risks with medications in an attempt to cure their symptoms. The burden of IBS to the healthcare system and society has been assessed by estimating the direct healthcare costs of the disorder with the total cost to society, because of the loss in work productivity demonstrated in this thesis, likely to be much higher. It has also shown that the latest definition of IBS, the Rome IV criteria, select individuals with a worse prognosis compared with those who meet the Rome III criteria for IBS during longitudinal follow-up and that cumulative psychological comorbidities cause additional impact to the prognosis of IBS. These findings should provide a strong mandate for appropriate funding for future research into IBS.

Chapter 10 Bibliography

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Appendices

Appendix A – Patient Information Sheet

PARTICIPANT INFORMATION SHEET

A Study to Assess the Impact of Irritable Bowel Syndrome in the United Kingdom.

We would like to invite you to take part in our research study. Before you decide if you would like to participate, we want you to understand why the research is being done, and what it would involve for you.

Please take time to read the following information carefully, and talk to others about the study if you wish. Please ask us if there is anything that is unclear, or if you need further information.

PART 1

What is the purpose of the study?

Irritable bowel syndrome (IBS) is a common tummy condition. Even though it affects up to 1 in 10 people, we do not understand the cause. This means there is no cure. IBS seriously affects quality of life. The symptoms (tummy pain, diarrhoea, and constipation) are similar to other bowel conditions. This means expensive tests are often carried out to rule these out before IBS can be diagnosed. Although IBS costs the National Health Service (NHS) millions of pounds per year, the impact of symptoms on peoples' lives can be underestimated. Partly because of this, if a new effective drug is developed, costs and side effects are considered carefully before people can use it.

Our research will find out how much IBS costs the NHS currently. We will also find out how IBS affects people's personal, family, social, and work life. Finally, we will ask what cost and level of risk people would accept to feel better with a new drug. At the moment, we do not know this information.

Our research will highlight the impact of IBS on individuals and the NHS. This will raise awareness of the condition. Hopefully, this will lead to better funding for research into IBS. This is not only important for individuals with IBS, but also for healthcare systems and society.

Why have I been invited to take part?

You have been invited to take part because you are a member of the ContactME-IBS register, and we believe you have IBS.

We would only like you to fill in the questionnaire if you are 18 years of age or older and a UK resident, as this is a study of UK adults only.

Do I have to take part?

No. It is up to you to decide if you want to participate in this study. The information contained in this leaflet is designed to help you make your decision.

What will happen to me if I take part?

If you decide to take part simply fill out the questionnaire online. The questionnaire should take no more than 45 minutes to complete.

If you choose to take part and return the questionnaire, then your data will be included in this study but your identity will remain anonymous.

What are the possible disadvantages and risks of taking part?

Filling out the questionnaire may make some people worry about their bowel symptoms. If you find this to be the case, we would suggest you discuss it further with your GP in the first instance.

What are the possible benefits of taking part?

This study will not benefit your health directly, but the information we get from this study may help to increase our understanding of IBS, how it affects people and how much it costs to the NHS. It will also assess what risks people with IBS are willing to take in return for cure of symptoms, and how much they are willing to pay for new drugs.

In return for your time to complete the questionnaire, you will have the chance to win 1 of 3 Amazon gift cards (worth £200, £100 and £50).

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information on this is provided in Part 2 of this leaflet.

Will my taking part in this study be kept confidential?

Yes. We will follow appropriate ethical and legal practice. All information about you will be handled in the strictest confidence. Detailed information on this is provided in Part 2 of this leaflet.

If the information in Part 1 has interested you and you are considering participating in this study, please read the additional information provided in Part 2 before making your final decision.

PART 2

What will happen if I don't want to carry on with the study?

Once you have returned the questionnaire, your data will be included in our analyses. It will not be possible for you to withdraw your data.

What if there is a problem?

If you have a concern or complaint about any aspect of the study, then you should ask to speak to the study doctors who will do their best to answer your questions. Contact details are provided below.

You can also contact Clare Skinner, the Head of Research Integrity and Governance, Secretariat at the University of Leeds who is independent from the research team on c.e.skinner@leeds.ac.uk. They will be able to assist you if you are unhappy about the conduct of the study and wish to make a formal complaint.

Will my taking part in this study be kept confidential?

All information which is collected about you during this research study will be kept strictly confidential. It will only be used for this study. Only the researchers involved in this study will have access to the data. It will be kept securely for 3 years. Following this it will be destroyed.

Further information about how we will handle your data can be found by clicking on the following link: https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2020/11/Research-Participant-Privacy-Notice.docx

What will happen to the results of this study?

The results of this study may be published in a medical journal, but your identity will not be revealed. This study will form part of a Doctorate of Medicine (MD) degree being undertaken by a student at the University of Leeds.

Who is organising this study?

The study is being organised by The Leeds Teaching Hospitals NHS Trust. The research supervisor is Professor Alexander Ford.

Who has reviewed the study?

To protect your interests, all research in the NHS is scrutinised by an independent group of people called a Research Ethics Committee. This study has been reviewed and granted ethical approval by the Medical Research Ethics Committee at the University of Leeds (MREC 20-051)

FURTHER INFORMATION AND CONTACT DETAILS

If you have any questions about the study, you can get in touch with us by email (leedsth-tr.ibs@nhs.net) or by calling us on 0113 2068774 (Monday to Friday 9am to 5pm).

Lead Investigator:

Dr Vivek Goodoory
Clinical Research Fellow & Registrar in Gastroenterology St. James's University Hospital, Leeds, UK, LS9 7TF Tel: 0113 2068774

Research Supervisors:

Dr Christopher Black
Registrar in Gastroenterology, Yorkshire Deanery. Tel: 0113 2068774

Professor Alexander Ford
Professor of Gastroenterology & Honorary Consultant Gastroenterologist St. James's University Hospital, Leeds, UK, LS9 7TF
Tel: 0113 2068774

If you have any questions about your rights as a research volunteer you may either contact the study doctors above, or look for further information via the National Institute for Health Research (NIHR) website:

https://bepartofresearch.nihr.ac.uk

This website also provides links to other useful websites and resources.

Appendix B – Questionnaire

PATIENT QUESTIONNAIRE

A Study to Assess the Impact of Irritable Bowel Syndrome in the United Kingdom.

Thank you for your interest in our research study. You have been invited to participate in this study via ContactMe-IBS because you said that you have irritable bowel syndrome (IBS).

The study involves completing a questionnaire. The questionnaire will take **approximately 45 minutes to complete. You can save your progress to return to later if you wish.**

In return for taking your time to complete the questionnaire, you will have the chance to win 1 of 3 Amazon gift cards (worth £200, £100 and £50).

Please remember that your answers will be treated in the strictest confidence, and there will be nothing that identifies you individually in the results of the study.

To help you decide if you would like to participate or not, please read the information available via the link below. The link provides full information about the study and what is involved.

Please answer all questions.

Once again, thank you for your interest in this research study.

Kind regards,

Professor Alexander Ford

MBChB, MD, FRCP, RFF

Professor of Gastroenterology and Honorary Consultant Gastroenterologist

Leeds Institute of Medical Research at St. James's, University of Leeds and Leeds Teaching Hospitals NHS Trust.

Consent

Below is a consent form for this study. To participate in this study, please read each statement carefully and, if you are in agreement, please tick the box “I agree”.

You will then be able to participate in the study.

1. I can confirm that I have read and understood the Information Leaflet dated 29th March 2021 (version 1.1) for the above study. This document should be provided with this questionnaire. I have had the opportunity to consider the information, ask questions if desired (using the contact details provided in the Information Leaflet) and have had these answered satisfactorily.

   I agree •

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason.

   I agree •

3. I give consent for the research team to include the data I provide in other ethically approved research studies, and for it to be shared with other researchers for the purpose of ethically approved research. I understand that any data which is shared with other researchers will be anonymised so that I cannot be identified.

   I agree •

4. I agree to take part in the above study.

   I agree •

Personal details

1. Please enter your initials followed by your date of birth in box below. Please use the format given in the following example: If your name is Joe Frederick Bloggs, and your date of birth is 4th May 1979, you would enter JFB040579
   ……..

2. What is your gender?
   - ☐ Male
   - ☐ Female

3. What is your age?
   …….

4. What is your current marital status? *(Please tick one option)*
   - ☐ Married or cohabiting
   - ☐ Civil partnership
   - ☐ Divorced or separated
   - ☐ Widowed
   - ☐ Never married
   - ☐ Prefer not to say

5. What is your ethnic group? *(Please tick one option)*
   a) White Caucasian
   b) African
   c) South Asian
   d) South East Asian
   e) Middle-eastern
   f) Latin American
   g) Prefer not to say
   h) Other. Please specify: ……

6. Do you smoke tobacco? *(Please tick one option)*
   a) Yes
   b) No

   If yes, how many cigarettes do you smoke per

   day?.....

7. Do you drink alcohol? *(Please tick one option)*
    a) Yes
    b) No

    If yes, for how many units do you drink per

    week?.....

8. Do you take any of the following medications regularly, used for pain, called opiates? *(Please tick one or more options)*
    a) Codeine
    b) Dihydrocodeine
    c) Oxycodone
    d) Tramadol
    e) Oramorph
    f) Morphine
    g) Fentanyl
    h) Buprenorphine
    i) None of the above

9. What is your level of education? *(Please tick one option)*
    a) Some secondary school
    b) Completed secondary school
    c) Some technical school/college
    d) Technical school/college graduate
    e) Some university
    f) University graduate
    g) Post-graduate degree/professional

10. What is your annual (yearly) income? This includes money from employment and all benefits added together.
    a. Less than £10,000 per year
    b. £10,000 to £19,999
    c. £20,000 to £29,999
    d. £30,000 to £39,999
    e. £40,000 to £49,999
    f. £50,000 to £99,999
    g. £100,000 or more
    h. Prefer not to say

11. Thinking about your daily life, which of the following statements best describes you?
    a) I never take risk.
    b) I rarely take risks.
    c) I occasionally take risks.
    d) I routinely take risks.

Your symptoms

12. Did your IBS symptoms first start following an episode of gastroenteritis/food poisoning? *(Please tick one option)*
    - ☐ Yes
    - ☐ No
    - ☐ Can't remember

13. How long ago were you diagnosed with IBS?
    a. Within the last 1 year
    b. 2 years ago
    c. 3 years ago
    d. 4 years ago
    e. 5 years ago
    f. More than 5 years ago

14. In the last 3 months how often did you have ***discomfort*** (an uncomfortable sensation that you would not describe as pain) anywhere in your abdomen (tummy)? *(Please tick one option)*
    - ☐ Never
    - ☐ Less than one day per month
    - ☐ One day per month
    - ☐ Two to three days per month
    - ☐ Once a week
    - ☐ Two to three days per week
    - ☐ Most days
    - ☐ Every day
    - ☐ Multiple times per day or all the time

15. In the last 3 months how often did you have ***pain*** anywhere in your abdomen (tummy)? *(Please tick one option)*
    - ☐ Never
    - ☐ Less than one day per month
    - ☐ One day per month
    - ☐ Two to three days per month
    - ☐ Once a week
    - ☐ Two to three days per week
    - ☐ Most days
    - ☐ Every day
    - ☐ Multiple times per day or all the time

16. How often did this discomfort or pain in your abdomen (tummy) happen close in time to a bowel movement - just before, during, or soon after? (Percentage of times with discomfort or pain) *(Please select one option)*

0% (Never)	10 %	20 %	30 %	40 %	50 %	60 %	70 %	80 %	90 %	100% (Always)

17. When you had the discomfort or pain, how often did it get better or stop after a bowel movement? (Percentage of times with discomfort or pain) *(Please select one option)*

0% (Never)	10 %	20 %	30 %	40 %	50 %	60 %	70 %	80 %	90 %	100% (Always)

18. How often did your stools become either softer than usual or harder than usual when you had this discomfort or pain? (Percentage of times with discomfort or pain) *(Please select one option)*

0% (Never)	10 %	20 %	30 %	40 %	50 %	60 %	70 %	80 %	90 %	100% (Always)

19. How often did your stools become either more frequent than usual or less frequent than usual when you had this discomfort or pain? (Percentage of times with discomfort or pain) *(Please select one option)*

0% (Never)	10 %	20 %	30 %	40 %	50 %	60 %	70 %	80 %	90 %	100% (Always)

***20. For women*:** how often did your discomfort or pain get worse with menstrual bleeding? (Percentage of times with discomfort or pain) NB: If you are male, please select 0%. *(Please select one option)*

0% (Never)	10 %	20 %	30 %	40 %	50 %	60 %	70 %	80 %	90 %	100% (Always)

21. How often did your discomfort or pain start or get worse after a meal? (Percentage of times with discomfort or pain) *(Please select one option)*

0% (Never)	10 %	20 %	30 %	40 %	50 %	60 %	70 %	80 %	90 %	100% (Always)

22. When you had this discomfort or pain, how often did it limit or restrict your usual activities - for example, work, household activities, or social events? (Percentage of times with discomfort or pain) *(Please select one option)*

0% (Never)	10 %	20 %	30 %	40 %	50 %	60 %	70 %	80 %	90 %	100% (Always)

23. Has this discomfort or pain in your abdomen (tummy) been continuous or almost continuous - this means it never goes away during waking hours?
    - ☐ Yes
    - ☐ No

24. Has it been 6 months or longer since you started having this discomfort or pain?
    - ☐ Yes
    - ☐ No

25. In the last 3 months, how often did you have hard or lumpy stools? *(Please tick one option)*

- ☐ Never or rarely
- ☐ About 25% of the time
- ☐ About 50% of the time
- ☐ About 75% of the time
- ☐ Always, 100% of the time

26. In the last 3 months, how often did you have loose, mushy, or watery stools? *(Please tick one option)*
    - ☐ Never or rarely
    - ☐ About 25% of the time
    - ☐ About 50% of the time
    - ☐ About 75% of the time
    - ☐ Always, 100% of the time

27. Bowel movements of type 1 or 2 and also type 6 or 7 in the picture below can be considered to be abnormal. Type 1 or 2 means you are constipated, and type 6 or 7 means you have diarrhoea. People might also have times when their bowel movements are normal.

    In the last 3 months, ***when you had abnormal stools,*** what were they usually like? *(Please tick one option)*

    - ☐ Usually constipated (like type 1 or 2 in the picture)
    - ☐ Usually diarrhoea (like type 6 or 7 in the picture)
    - ☐ Both diarrhoea and constipation - that is: more than ¼ (25%) of all bowel movements were diarrhoea, and more than ¼ (25%) were constipation
    - ☐ Not applicable, because I never or rarely had abnormal bowel movements

Bristol stool chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces, **Entirely liquid**

28. In the last 3 months, how often did you have to rush to the toilet to have a bowel movement?
    - ☐ Never
    - ☐ Less than one day per month
    - ☐ One day per month
    - ☐ Two to three days per month
    - ☐ Once a week
    - ☐ Two to three days per week
    - ☐ Most days
    - ☐ Every day
    - ☐ Multiple times per day or all the time

29. In the last 3 months, how often have you accidentally leaked liquid or solid stool?
    - ☐ Never
    - ☐ Less than one day per month
    - ☐ One day per month
    - ☐ Two to three days per month
    - ☐ Once a week
    - ☐ Two to three days per week
    - ☐ Most days
    - ☐ Every day
    - ☐ Multiple times per day or all the time

30. In the last 3 months, how often did you have bloating or distension?
    - ☐ Never
    - ☐ Less than one day per month
    - ☐ One day per month
    - ☐ Two to three days per month
    - ☐ Once a week
    - ☐ Two to three days per week
    - ☐ Most days
    - ☐ Every day
    - ☐ Multiple times per day or all the time

31. What is your most troublesome symptom?
    - ☐ Abdominal (tummy) pain
    - ☐ Constipation (hard or infrequent stools)
    - ☐ Diarrhoea (loose or frequent stools)
    - ☐ Bloating or a swollen tummy
    - ☐ Urgency (having to rush to the toilet)

32. In the last 3 months, how often did you feel so full after a regular-sized meal (the amount you normally eat) that it interfered with your usual activities?
    a) Never
    b) Less than one day per month
    c) One day per month
    d) Two to three days per month
    e) Once a week
    f) Two to three days per week
    g) Most days
    h) Every day
    i) Multiple times per day or all the time

33. Has it been 6 months or longer since you started having these episodes of fullness after meals that were severe enough to interfere with your usual activities?
    a) Yes
    b) No
    c) Not applicable – I never get these episodes of fullness after meals.

34. In the last 3 months, how often were you unable to finish a regular-sized meal because you felt too full?
    a) Never
    b) Less than one day per month
    c) One day per month
    d) Two to three days per month
    e) Once a week
    f) Two to three days per week
    g) Most days
    h) Every day
    i) Multiple times per day or all the time

35. Has it been 6 months or longer since you started having these episodes of feeling too full to finish regular-sized meals?
    a) Yes
    b) No
    c) Not applicable – I never have these episodes.

36. In the last 3 months, how often did you have pain or burning in the middle part of your upper abdomen (above your belly button but not in your chest) that was so severe that interfered with your usual activities?
    a) Never

b) Less than one day per month
c) One day per month
d) Two to three days per month
e) Once a week
f) Two to three days per week
g) Most days
h) Every day
i) Multiple times per day or all the time

37. Has it been 6 months or longer since you started having this pain or burning in the middle part of your abdomen?
    a) Yes
    b) No
    c) Not applicable – I never have these episodes.

38. a. Do you currently suffer from abdominal (tummy) pain?
    ☐ Yes
    ☐ No

    b. ***If yes***, how severe is your abdominal (tummy) pain on a scale of 0 to 100 where 0 is no pain, and 100 is very severe pain? *(Write the score in the box)*:

    

    c. Please enter the number of days that you get the pain in every 10 days. For example, if you enter 4 it means that you get pain 4 out of 10 days. If you get pain every day enter 10. (*Write the number of days in the box):*

    

39. a. Do you currently suffer from abdominal distension (bloating, swollen or tight tummy)? For women, please ignore distension related to your periods.
    ☐ Yes
    ☐ No

b. ***If yes,*** how severe is your abdominal distension/tightness on a scale of 0 to 100, where 0 is no distension and 100 is very severe distension? *(Write the score in the box):*

40. How satisfied are you with your bowel habit on a scale of 0 to 100, where ***0 is very happy*** and 100 is very unhappy? *(Write the score in the box):*

41. Please indicate how much your irritable bowel syndrome is affecting or interfering with your life in general on a scale of 0 to 100, where 0 is not at all and 100 is completely. *(Write the score in the box):*

42. Please answer all the questions below.

During the past 4 weeks, how much have you been bothered by any of the following problems? *(Please tick)*

		Never	A Little	A lot
a.	Stomach pain	☐	☐	☐
b.	Back pain	☐	☐	☐
c.	Arm, leg, joint (hip, knee etc) pain	☐	☐	☐
d.	**For women:** period pain/period problems	☐	☐	☐
e.	Headaches	☐	☐	☐
f.	Chest pain	☐	☐	☐
g.	Dizziness	☐	☐	☐
h.	Fainting spells	☐	☐	☐
i.	Heart pounding/racing	☐	☐	☐
j.	Shortness of breath	☐	☐	☐
k.	Pain/problems during sex	☐	☐	☐
l.	Constipation/diarrhoea	☐	☐	☐
m.	Nausea/gas/indigestion	☐	☐	☐
n.	Feeling tired or low in energy	☐	☐	☐
o.	Trouble sleeping	☐	☐	☐

43. Please answer all the following questions. For each question, please choose one response only.

    Try to give an immediate response rather than thinking for too long about your answers. Answer each question as closely as possible to how it currently describes your feelings.

a. I feel tense or “wound up”:
    - ☐ Most of the time
    - ☐ A lot of the time
    - ☐ From time to time, occasionally
    - ☐ Not at all

b. I still enjoy the things I used to enjoy:
    - ☐ Definitely as much
    - ☐ Not quite so much
    - ☐ Only a little
    - ☐ Hardly at all

c. I get a sort of frightened feeling as if something awful is about to happen:
    - ☐ Very definitely and quite badly
    - ☐ Yes, but not too badly
    - ☐ A little, but it doesn’t worry me
    - ☐ Not at all

d. I can laugh and see the funny side of things:
    - ☐ As much as I always could
    - ☐ Not quite so much now
    - ☐ Definitely not so much now
    - ☐ Not at all

e. Worrying thoughts go through my mind:
    - ☐ A great deal of the time
    - ☐ A lot of the time
    - ☐ From time to time, but not too often
    - ☐ Only occasionally

f. I feel cheerful:

- ☐ Not at all
- ☐ Not often
- ☐ Sometimes
- ☐ Most of the time

g. I can sit at ease and feel relaxed:
   - ☐ Definitely
   - ☐ Usually
   - ☐ Not often
   - ☐ Not at all

h. I feel as if I am slowed down:
   - ☐ Nearly all the time
   - ☐ Very often
   - ☐ Sometimes
   - ☐ Not at all

i. I get a sort of frightened feeling like “butterflies in the stomach”:
   - ☐ Not at all
   - ☐ Occasionally
   - ☐ Quite often
   - ☐ Very often

j. I have lost interest in my appearance:
   - ☐ Definitely
   - ☐ I don’t take as much care as I should
   - ☐ I may not take quite as much care
   - ☐ I take just as much care as ever

k. I feel restless as if I have to be on the move:
   - ☐ Very much indeed
   - ☐ Quite a lot
   - ☐ Not very much
   - ☐ Not at all

l. I look forward with enjoyment to things:
   - ☐ As much as I ever did
   - ☐ Rather less than I used to
   - ☐ Definitely less than I used to
   - ☐ Hardly at all

m. I get sudden feelings of panic:
- ☐ Very often indeed
- ☐ Quite often
- ☐ Not very often
- ☐ Not at all

n. I can enjoy a good book, or radio or TV programme:
- ☐ Often
- ☐ Sometimes
- ☐ Not often
- ☐ Seldom

44. Below are statements that describe how some people respond to symptoms or discomfort in their belly or lower abdomen. These may include pain, diarrhoea, constipation, bloating or sense of urgency. Please answer "how you strongly agree or disagree" with each of these statements, as they relate to you.
Answer all the statements as honestly and thoughtfully as you can.

		Strongly agree	Moderately agree	Mildly agree	Mildly disagree	Moderately disagree	Strongly disagree
a.	I worry that whenever I eat during the day, bloating and distension in my belly will get worse	☐	☐	☐	☐	☐	☐
b.	I get anxious when I go to a new restaurant	☐	☐	☐	☐	☐	☐
c.	I often worry about problems in my belly	☐	☐	☐	☐	☐	☐
d.	I have a difficult time enjoying myself because I cannot get my mind off of discomfort in my belly	☐	☐	☐	☐	☐	☐
e.	I often fear that I won't be able to have a normal bowel movement	☐	☐	☐	☐	☐	☐
f.	Because of fear of developing abdominal discomfort, I seldom try new foods	☐	☐	☐	☐	☐	☐
g.	No matter what I eat, I will probably feel uncomfortable	☐	☐	☐	☐	☐	☐
h.	As soon as I feel abdominal discomfort I begin to worry and feel anxious	☐	☐	☐	☐	☐	☐
i.	When I enter a place I haven't been before, one of the first things I do is to look for a bathroom	☐	☐	☐	☐	☐	☐
j.	I am constantly aware of the feelings I have in my belly	☐	☐	☐	☐	☐	☐
k.	I often feel discomfort in my belly could be a sign of a serious illness	☐	☐	☐	☐	☐	☐

l.	As soon as I awake, I worry that I will have discomfort in my belly during the day	☐	☐	☐	☐	☐	☐
m.	When I feel discomfort in my belly, it frightens me	☐	☐	☐	☐	☐	☐
n.	In stressful situations, my belly bothers me a lot	☐	☐	☐	☐	☐	☐
o.	I constantly think about what is happening inside my belly.	☐	☐	☐	☐	☐	☐

45. Please think about your life over the past month (last 30 days) and look at the statements below. Each statement has five different responses. For each statement, please tick the response that best describes your feelings.

a. I feel helpless because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

b. I am embarrassed by the smell caused by my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

c. I am bothered by how much time I spend on the toilet. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

d. I feel vulnerable to other illnesses because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly

- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

e. I feel fat/bloated because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

f. I feel like I'm losing control of my life because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

g. I feel my life is less enjoyable because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

h. I feel uncomfortable when I talk about my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

i. I feel depressed about my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit

- ☐ Extremely

j. I feel isolated from others because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

k. I have to watch the amount of food I eat because of by bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

l. Because of my bowel problems, sexual activity is difficult for me. If not applicable, please tick “Not at all”. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

m. I feel angry that I have bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

n. I feel like I irritate others because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

o. I worry that my bowel problems will get worse. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

p. I feel irritable because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

q. I worry that people think I exaggerate my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

r. I feel I get less done because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

s. I have to avoid stressful situations because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

t. My bowel problems reduce my sexual desire. *(Please tick one option)*

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

u. My bowel problems limit what I can wear. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

v. I have to avoid strenuous activity because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

w. I have to watch the kind of food I eat because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

x. Because of my bowel problems, I have difficulty being around people I do not know well. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

y. I feel sluggish because of my bowel problems. *(Please tick one option)*
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately

- ☐ Quite a bit
- ☐ Extremely

z. I feel unclean because of my bowel problems. *(Please tick one option)*
- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

aa. Long trips are difficult for me because of my bowel problems. *(Please tick one option)*
- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

bb. I feel frustrated that I cannot eat when I want because of my bowel problems. *(Please tick one option)*
- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

cc. It is important to be near a toilet because of my bowel problems. *(Please tick one option)*
- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

dd. My life revolves around my bowel problems. *(Please tick one option)*
- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

ee. I worry about losing control of my bowels. *(Please tick one option)*

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

ff. I fear that I won't be able to have a bowel movement. *(Please tick one option)*

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

gg. My bowel problems are affecting my closest relationships. *(Please tick one option)*

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

hh. I feel that no one understands my bowel problems. *(Please tick one option)*

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

46. Under each heading, please tick the ONE box that best describes your health TODAY.

a) Mobility

a. I have no problems in walking about
b. I have slight problems in walking about
c. I have moderate problems in walking about
d. I have severe problems in walking about
e. I am unable to walk about

b) Self-care
   a. I have no problems washing or dressing myself
   b. I have slight problems washing or dressing myself
   c. I have moderate problems washing or dressing myself
   d. I have severe problems washing or dressing myself
   e. I am unable to wash or dress myself

c) Usual activities (*e.g., work, study, housework, family or leisure activities)*
   a. I have no problems in doing my usual activities
   b. I have slight problems in doing my usual activities
   c. I have moderate problems in doing my usual activities
   d. I have severe problems in doing my usual activities
   e. I am unable to do my usual activities

d) Pain/discomfort
   a. I have no pain or discomfort
   b. I have slight pain or discomfort
   c. I have moderate pain or discomfort
   d. I have severe pain or discomfort
   e. I have extreme pain or discomfort

e) Anxiety/Depression
   a. I am not anxious or depressed
   b. I am slightly anxious or depressed
   c. I am moderately anxious or depressed
   d. I am severely anxious or depressed
   e. I am extremely anxious or depressed

47. In the last 12 months, **in relation to your IBS**, have you had any of the following:

	No	Yes	If yes, how many?
A GP appointment			
An appointment with a gastroenterologist			
An appointment with a specialist nurse			

An appointment with a dietitian			
An appointment with a psychologist			
A blood test			
A stool test			
A gastroscopy (camera test to look at your stomach)			
A colonoscopy (camera test to look at your colon)			
A breath test			
An ultrasound scan			
A CT scan			
An MRI scan			
A SeHCAT scan			
A review in the Accident & Emergency (A&E) department			
An admission to hospital			Please state total number of days in hospital: ……

48. Have you had to take any of the following **drugs for your IBS** in the last 12 months?

	Yes	No	Number of months
Loperamide (Imodium)			
Sodium picosulfate (Picolax)			
Bisacodyl (Dulcolax)			
Polyethylene glycol (Macrogol)			
Hyoscine (Buscopan)			
Alverine (Spasmonal)			
Mebeverine (Colofac)			

Dicycloverine (Merbentyl)			
Ispaghula (Fybogel)			
Peppermint oil (Colpermin)			
Amitriptyline (Elavil, Domical, Tryptizol or Lentizol)			
Nortriptyline (Aventyl or Pamelor)			
Imipramine (Tofranil)			
Fluoxetine (Prozac)			
Paroxetine (Seroxat)			
Sertraline (Lustril)			
Citalopram (Celexa)			
Escitalopram (Lexapro)			
Lubiprostone (Amitiza)			
Linaclotide (Constella)			
Prucalopride (Resolor)			
Eluxadoline (Viberzi or Truberzi)			

49. The following questions ask you the effect of your IBS symptoms on your ability to work and perform regular activities. *Please tick the boxes, fill in the blanks or select a number, as indicated.*

a) Are you currently employed (working for pay)?

a. Yes

b. No

If No, please skip to question 48f.

b) During the past seven days, how many hours did you miss from work because of the problems associated with your IBS? *Include hours you missed on sick days, times you went in late, left early, etc. because of you IBS. Do not include time you missed to participate in this study.*

…… hours

c) During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

…… hours

d) During the past seven days, how many hours did you actually work?

…….hours *(If "0", skip to question 48f.)*

e) During the past seven days, how much did your IBS affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If IBS affected your work only a little, choose a low number. Choose a high number if IBS affected your work a great deal.

Consider only how much IBS affected

productivity while you were working.

IBS had no effect on my work — 0 1 2 3 4 5 6 7 8 9 10 — IBS completely prevented me from working

SELECT A NUMBER

f) During the past seven days, how much did your IBS affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If IBS affected your activities only a little, choose a low number. Choose a high number if IBS affected your activities a great deal.

Consider only how much IBS affected your ability

to do your regular daily activities, other than work at a job.

IBS had no effect on my daily activities — 0 1 2 3 4 5 6 7 8 9 10 — IBS completely prevented me from doing my daily activities

SELECT A NUMBER

50. People's IBS sometimes affect their ability to do certain day-to-day tasks in their lives. To rate your IBS look at each section and determine on the scale provided how much your IBS impairs your ability to carry out the activity. This assessment is not intended to be a diagnosis. If you care concerned about your results in any way, please speak with a qualified health professional.

If you're retired or choose not to have a job for reasons unrelated to your IBS,

tick here ☐

A. Because of my IBS my **ability to work** is impaired

0 (Not at all)	1	2 (Slightly)	3	4 (Definitely)	5	6 (Markedly)	7	8 (Very severely)

B. Because of my IBS my **home management** (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired

0 (Not at all)	1	2 (Slightly)	3	4 (Definitely)	5	6 (Markedly)	7	8 (Very severely)

C. Because of my IBS my **social leisure activities** (with other people e.g. parties, bars, clubs, outings, visits, dating, home entertaining) are impaired

0 (Not at all)	1	2 (Slightly)	3	4 (Definitely)	5	6 (Markedly)	7	8 (Very severely)

D. Because of my IBS my **private leisure activities** (done alone such as reading, gardening, collecting, sewing, walking alone) are impaired

0 (Not at all)	1	2 (Slightly)	3	4 (Definitely)	5	6 (Markedly)	7	8 (Very severely)

E. Because of my IBS, my ability to form and maintain **close relationships** with others, including those I live with, is impaired

0 (Not at all)	1	2 (Slightly)	3	4 (Definitely)	5	6 (Markedly)	7	8 (Very severely)

51. Suppose there is a pill available for IBS that gives a **30%** chance of **improving** your symptoms. This pill will not be provided by your GP or gastroenterologist. You have to go and buy this pill at your pharmacy. How much would you be willing to pay out of your own pocket per month for this pill?

Not willing to pay anything	£1-£50	£51-£100	£101-£150	£151-£200	£201-£250	£251-£300	£301-£350	£351-£400	£401-£450	£451-£500	More than £500

52. Suppose there is a pill available for IBS that gives a **50%** chance of **improving** your symptoms. This pill will not be provided by your GP or gastroenterologist. You have to go and buy this pill at your pharmacy. How much would you be willing to pay out of your own pocket per month for this pill?

Not willing to pay anything	£1-£50	£51-£100	£101-£150	£151-£200	£201-£250	£251-£300	£301-£350	£351-£400	£401-£450	£451-£500	More than £500

53. Suppose there is a pill available for IBS that gives a **100%** chance of **improving** your symptoms. This pill will not be provided by your GP or gastroenterologist. You have to go and buy this pill at your pharmacy. How much would you be willing to pay out of your own pocket per month for this pill?

Not willing to pay anything	£1-£50	£51-£100	£101-£150	£151-£200	£201-£250	£251-£300	£301-£350	£351-£400	£401-£450	£451-£500	More than £500

54. Suppose there is a pill available for IBS that gives a **30%** chance of **curing** your symptoms. This pill will not be provided by your GP or gastroenterologist. You have to go and buy this pill at your pharmacy. How much would you be willing to pay out of your own pocket per month for this pill?

Not willing to pay anything	£1-£50	£51-£100	£101-£150	£151-£200	£201-£250	£251-£300	£301-£350	£351-£400	£401-£450	£451-£500	More than £500

55. Suppose there is a pill available for IBS that gives a **50%** chance of **curing** your symptoms. This pill will not be provided by your GP or gastroenterologist. You have to go and buy this pill at your pharmacy. How much would you be willing to pay out of your own pocket per month for this pill?

Not willing to pay anything	£1-£50	£51-£100	£101-£150	£151-£200	£201-£250	£251-£300	£301-£350	£351-£400	£401-£450	£451-£500	More than £500

56. Suppose there is a pill available for IBS that gives a **100%** chance of **curing** your symptoms. This pill will not be provided by your GP or gastroenterologist. You have to go and buy this pill at your pharmacy. How much would you be willing to pay out of your own pocket per month for this pill?

Not willing to pay anything	£1-£50	£51-£100	£101-£150	£151-£200	£201-£250	£251-£300	£301-£350	£351-£400	£401-£450	£451-£500	More than £500

57. Unfortunately, a pill that completely cures all your IBS symptoms does not exist. Suppose we can offer you one of the following pills for free. You do not have to pay for it. Which pill would you choose to help with your IBS symptoms?

Pill A: Relieves pain **almost completely**; **hardly** relieves bloating, diarrhoea, or constipation

Pill B: Relieves bloating **almost completely**; **hardly** relieves pain, diarrhoea, or constipation

Pill C: Relieves diarrhoea **almost completely**; **hardly** relieves pain, bloating, or constipation

Pill D: Relieves constipation **almost completely**; **hardly** relieves pain, bloating, or diarrhoea

Pill E: Relieves pain **well;** relieves bloating, diarrhoea, or constipation **a little**

Pill F: Relieves bloating **well**; relieves pain, diarrhoea, or constipation **a little**

Pill G: Relieves diarrhoea **well**; relieves pain, bloating, or constipation **a little**

Pill H: Relieves constipation **well**; relieves pain, bloating, or diarrhoea **a little**

58. Imagine a new (make-believe) pill is now available for your ***IBS***. Your doctor advises you that if you take the pill today and it works, it cures every ***IBS*** symptom you ***currently*** have for the rest of your life. However, if you take the pill today and it ***does not*** work, it causes a sudden and painless death in your sleep tonight. Your doctor has no way of predicting which patients will be cured by this new (make-believe) pill, and will support whatever decision you make. We want to know what you think about this pill.

→***Would you take this pill right now if you knew***. . . (Please select "Yes" or "No" for **every** question.)

		Yes	No
a.	... it had a **100%** chance of cure and a **0%** risk of causing death in your sleep tonight?	☐	☐
b.	... it had a **99%** chance of cure and a **1%** risk of causing death in your sleep tonight?	☐	☐
c.	... it had a **98%** chance of cure and a **2%** risk of causing death in your sleep tonight?	☐	☐
d.	... it had a **97%** chance of cure and a **3%** risk of causing death in your sleep tonight?	☐	☐
e.	... it had a **96%** chance of cure and a **4%** risk of causing death in your sleep tonight?	☐	☐
f.	... it had a **95%** chance of cure and a **5%** risk of causing death in your sleep tonight?	☐	☐
g.	... it had a **94%** chance of cure and a **6%** risk of causing death in your sleep tonight?	☐	☐
h.	... it had a **93%** chance of cure and a **7%** risk of causing death in your sleep tonight?	☐	☐
i.	... it had a **92%** chance of cure and an **8%** risk of causing death in your sleep tonight?	☐	☐
j.	... it had a **91%** chance of cure and a **9%** risk of causing death in your sleep tonight?	☐	☐
k.	... it had a **90%** chance of cure and a **10%** risk of causing death in your sleep tonight?	☐	☐
l.	... it had an **85%** chance of cure and a **15%** risk of causing death in your sleep tonight?	☐	☐
m.	... it had an **80%** chance of cure and a **20%** risk of causing death in your sleep tonight?	☐	☐
n.	... it had a **75%** chance of cure and a **25%** risk of causing death in your sleep tonight?	☐	☐
o.	... it had a **70%** chance of cure and a **30%** risk of causing death in your sleep tonight?	☐	☐
p.	... it had a **65%** chance of cure and a **35%** risk of causing death in your sleep tonight?	☐	☐
q.	... it had a **60%** chance of cure and a **40%** risk of causing death in your sleep tonight?	☐	☐
r.	... it had a **50%** chance of cure and a **50%** risk of causing death in your sleep tonight?	☐	☐
s.	... it had a **40%** chance of cure and a **60%** risk of causing death in your sleep tonight?	☐	☐
t.	... it had a **30%** chance of cure and a **70%** risk of causing death in your sleep tonight?	☐	☐
u.	... it had a **20%** chance of cure and a **80%** risk of causing death in your sleep tonight?	☐	☐
v.	... it had a **10%** chance of cure and a **90%** risk of causing death in your sleep tonight?	☐	☐

59. Imagine a new (make-believe) pill is now available for your ***IBS***. Your doctor advises you that if you take the pill today and it works, there is a 99% chance of curing the ***IBS*** symptoms you ***currently*** have for the rest of your life. However, if you take the pill today and it ***does not*** work, it causes a sudden and painless death in your sleep tonight. Your doctor has no way of predicting which patients will be cured by this new (make-believe) pill, and will support whatever decision you make. We want to know what you think about this pill.

    If the pill has a **99% chance of curing all your IBS symptoms** for the rest of your life, would you take it if you knew:

		Yes	No
a.	… it had a **0%** risk of causing death in your sleep tonight?	☐	☐
b.	… it had a **1%** risk of causing death in your sleep tonight?	☐	☐
c.	… it had a **2%** of causing death in your sleep tonight?	☐	☐
d.	… it had a **3%** risk of causing death in your sleep tonight?	☐	☐
e.	… it had a **4%** risk of causing death in your sleep tonight?	☐	☐
f.	… it had a **5%** risk of causing death in your sleep tonight?	☐	☐
g.	… it had a **6%** risk of causing death in your sleep tonight?	☐	☐
h.	… it had a **7%** risk of causing death in your sleep tonight?	☐	☐
i.	… it had an **8%** risk of causing death in your sleep tonight?	☐	☐
j.	… it had a **9%** risk of causing death in your sleep tonight?	☐	☐
k.	… it had a **10%** risk of causing death in your sleep tonight?	☐	☐
l.	… it had a **15%** risk of causing death in your sleep tonight?	☐	☐
m.	… it had **20%** risk of causing death in your sleep tonight?	☐	☐
n.	… it had **25%** risk of causing death in your sleep tonight?	☐	☐
o.	… it had **more than 25%** risk of causing death in your sleep tonight?	☐	☐

Many thanks for taking the time to complete this questionnaire.

Please enter your email address to **have the chance to win one of three Amazon gift cards (worth £200, £100 and £50).**

……

Professor Alex Ford.

Professor of Gastroenterology and Honorary Consultant Gastroenterologist.

Leeds Teaching Hospitals NHS Trust, Leeds, UK.

Appendix C – Research Ethics Committee Approval

Compliance & Governance
Directorate
University of Leeds
Leeds, LS2 9JT
Email: fmhuniethics@leeds.ac.uk

UNIVERSITY OF LEEDS

Vivek Goodoory
School of Medicine
Faculty of Medicine & Health
University of Leeds
Leeds, LS2 9JT
30 March 2021

Dear Vivek
MREC 20-051 - Assessing the current burden of irritable bowel syndrome in the United Kingdom to guide future research priorities

NB: All approvals/comments are subject to compliance with current University of Leeds and UK Government advice regarding the Covid-19 pandemic.

I am pleased to inform you that the above research ethics application has been reviewed by School of Medicine Research Ethics Committee and I can confirm a conditional favourable ethical opinion based on the documentation received at date of this email. I can confirm that the conditions of the approval have all been met.
Please retain this email as evidence of approval in your study file.
Please notify the committee if you intend to make any amendments to the original research as submitted and approved to date. This includes recruitment methodology; all changes must receive ethical approval prior to implementation. Please see http://ris.leeds.ac.uk/downloads/download/179/amendment_form or contact the Research Ethics Team for further information (fmhuniethics@leeds.ac.uk) if required.
Ethics approval does not infer you have the right of access to any member of staff or student or documents and the premises of the University of Leeds. Nor does it imply any right of access to the premises of any other organisation, including clinical areas. The committee takes no responsibility for you gaining access to staff, students and/or premises prior to, during or following your research activities.
Please note: You are expected to keep a record of all your approved documentation, as well as documents such as sample consent forms, risk assessments and other documents relating to the study. This should be kept in your study file, which should be readily available for audit purposes. You will be given a two week notice period if your project is to be audited.
If you require this confirmation in letter form, for example to show to external funders, then please do email me. I am happy to provide this if required.
It is our policy to remind everyone that it is your responsibility to comply with Health and Safety, Data Protection and any other legal and/or professional guidelines there may be.

I hope the study goes well.
Yours sincerely
Sou Sit Chung, Compliance & Governance Directorate

On behalf of Dr Anthony Howard and Dr Naomi Quinton, co-Chairs, SoMREC