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Global burden of irritable bowel syndrome: trends, predictions and risk factors

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Abstract | Irritable bowel syndrome (IBS) is one of the most common disorders of gut–brain interaction worldwide and is defined according to patterns of gastrointestinal symptoms, as described by the Rome diagnostic criteria. However, these criteria, developed with reference to research conducted largely in Western populations, might be limited in their applicability to other countries and cultures. Epidemiological data show a wide variation in the prevalence of IBS globally and more rigorous studies are needed to accurately determine any differences that might exist between countries and potential explanations. The effect of IBS on the individual, in terms of their quality of life, and on healthcare delivery and society, in terms of economic costs, is considerable. Although the magnitude of these effects seems to be comparable between nations, their precise nature can vary based on the existence of societal and cultural differences. The pathophysiology of IBS is complex and incompletely understood; genetics, diet and the gut microbiome are all recognised risk factors, but the part they play might be influenced by geography and culture, and hence their relative importance might vary between countries. This Review aims to provide an overview of the burden of IBS in a global context, to discuss future implications for the care of people with IBS worldwide, and to identify key areas for further research.

Key points

- Irritable bowel syndrome (IBS) is one of the most common disorders of gut–brain interaction and is estimated to affect around 1 in 10 people globally.
- Prevalence rates appear to differ between countries, but the magnitude of the effect of IBS, in terms of cost and quality of life, seems comparable around the world.
- The pathophysiology of IBS is complex, and the role of risk factors such as genetics, diet and the microbiome might operate differently, dependent on geography.
- As developing countries increasingly adopt a Western diet and lifestyle, we might see a corresponding increase in IBS prevalence rates, a trend that might also reflect increasing awareness of the condition.
- Even if prevalence rates remain unchanged, projections of global population growth alone indicate that there will be many more people living with IBS worldwide.
- Well-designed and adequately funded research, which is multi-cultural in design and encourages global collaboration, is needed to further advance our understanding of IBS and promote optimised patient care.

[H1] INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common disorders of gut–brain interactions (previously called functional gastrointestinal disorders) and is estimated to affect around 1 in 10 people globally. [1] Typically, research in IBS has focused on North American, European and, to a lesser extent, Asian populations. However, studies have shown that IBS affects people living across the world, although the reported prevalence varies considerably and there are some countries where, unfortunately, no data are available. Prevalence varies from ~7.0% in Southeast Asian and Middle Eastern studies, to between 11.8–14.0% in North American, North European and Australasian studies, and to between 15.0–21.0% in South

European, African, and South American studies[1]. The variation in prevalence might reflect methodological differences between studies. However, it might also, in part, reflect the diverse pathophysiology of the condition and potential risk factors for IBS, such as genetics, gastrointestinal infection, the role of diet and the gut microbiome, and the influence of psychological co-morbidity, which can contribute differently, depending on geographical context. Overall, IBS has a substantial effect on the individual and their quality of life (QoL), and incurs substantial costs, both in terms of healthcare delivery, but also with respect to society and the economy [2]. Notably, it has been suggested that IBS might become increasingly common due to a wider recognition of the condition, but also as a consequence of developing countries adopting a more Westernised diet and lifestyle; behaviours that might be associated with an increased risk of developing IBS. [3] For example, a cross-sectional survey from Thailand, published in 1988, reported a prevalence of IBS of <5%, [4] but studies published since 2000 have reported a prevalence of between 6–9%, [5,6] which is more in line with Western estimates.

The importance of considering the effect of IBS worldwide has been highlighted in a report from 2018, led by experts in the field of IBS and funded by the pharmaceutical industry. [7] This report highlights that it takes 4 years on average for people with IBS to be given a diagnosis, with many feeling that they are not taken seriously by their doctor, that people can be left feeling stigmatised by their diagnosis, and that they can experience problems accessing effective treatment and support. Although the report aims to provide a worldwide overview, much of the data relates to Europe and North America. This Review aims to provide an overview of the burden of IBS in a global context, to discuss implications for future IBS healthcare delivery worldwide and to identify key areas for further research.

[H1] DEFINING IBS

Over the past 30 years, the Rome Foundation, through a process of consultation among experts in the field, has developed and refined diagnostic criteria for all disorders of gut–brain interactions, including IBS, each of which is defined according to a particular complex of symptoms reported by the patient. IBS is characterised by the presence of abdominal pain in association with defecation or a change in bowel habit (Box 1). [8] However, this process has been guided mainly by Western research and clinical experience, which creates potential problems when applying these criteria to other countries and cultures. Moreover, in the majority of clinical trials of treatments in IBS, the Rome criteria are used to define eligibility. Although this approach helps both to reduce bias by recruiting a more homogenous trial population and to facilitate comparison between trials, it might limit the generalisability of any findings for non-Western populations.

In recognition of these issues and prior to the publication of Rome IV in 2016, [8] the latest iteration of the Rome diagnostic criteria, a Rome Foundation working group sought to improve understanding of multicultural aspects of disorders of gut–brain interaction and the conduct of research in this context. [9,10] This work led to a dedicated article on multicultural issues being published as part of the Rome criteria for the first time. [11] The working group concluded that although cross-cultural, multinational research is important, the development of necessary collaborations is in its infancy and barriers exist in terms of a lack of proficiency with the required study methodologies. [9] Furthermore, there are differences in how healthcare for disorders of gut–brain interactions is delivered between countries, and problems with both physician awareness and applicability of the Rome criteria in certain cultures (Table 1). [10]

This work, in part, led to the removal of the term ‘abdominal discomfort’ from the Rome IV definition of IBS, because it was felt to be ambiguous with no equivalent in some languages. [12] This decision means that a diagnosis of IBS now requires the reporting of

abdominal pain specifically. However, a study in India found that both abdominal pain and abdominal discomfort are absent in up to 30% of patients who are considered to have IBS by their physician. [13] Similarly, the term 'bloating', which can be interpreted as a sensation of increased pressure within the abdomen, has no equivalent in Spanish, in which the word 'distension' is frequently used instead, but which English-speakers might take to mean visible abdominal distension. [14] Furthermore, bloating is a common symptom among Asian patients with IBS, who also report upper abdominal pain frequently, and can therefore be misdiagnosed as having functional dyspepsia when, in fact, the relationship of this pain with defecation means they have IBS. [15] These examples serve to illustrate the inherent difficulties of defining universally applicable symptom-based diagnostic criteria for IBS with a reliance on Western research data, a difficulty that is further compounded by the technical complexities of translating the criteria into other languages, and validating them so they can be utilised worldwide.

Accordingly, although the Rome Foundation highlight the need to conduct such studies to facilitate use of the Rome criteria in different languages and countries, they caution that this process needs to be conducted rigorously, such that any translation is "conceptually equivalent", meaning that it simultaneously retains the meaning and intent of the original questionnaire, while also being culturally relevant and comprehensible to the target population rather than simply being a literal translation. [9] Despite this understanding, studies in Australian populations and in Asian patients with functional symptoms using a locally adapted and validated Rome questionnaire have observed symptom clusters that differ from, and are fewer in number than, the categories proposed in the Rome classification. [16] These findings illustrate the inherent difficulties in the universal application of rigid symptom-based criteria across different countries and cultures. The Rome Foundation recommend that a

programme of educational activities is required to disseminate knowledge regarding use of the Rome criteria. [10]

It is also relevant to consider that the Rome IV criteria for diagnosing IBS seem more restrictive than their predecessor, the Rome III criteria [17]. The term "abdominal discomfort" was removed from the revised definition and the required symptom frequency for the presence of abdominal pain increased from at least 3 days per month to at least 1 day per week. Consequently, many patients who would previously have been given a diagnosis of IBS will now, instead, be classified as having a different disorder of gut–brain interaction, such as functional constipation, functional diarrhoea or functional bloating. [18] Therefore, any overall increase in the burden of functional gastrointestinal symptoms might also translate into an increase in the prevalence of these other functional bowel disorders, not just IBS, which will have important implications for future clinical trials and treatment development.

[H1] EPIDEMIOLOGY OF IBS

[H2] Global prevalence of IBS

In 2012, a systematic review and meta-analysis involving 260,960 individuals across 81 countries worldwide calculated a pooled global prevalence of IBS of 11%. [1] However, the prevalence varied widely, dependent on both the criteria used to define IBS and also according to country, ranging from 1.1% in one Iranian study and another conducted in the USA, to 45% in Pakistan. The reasons for this variation are unclear. Although there might be genuine differences in the population prevalence of IBS between countries, possibly mediated by ethnicity or the differential effect of risk factors such as diet or genetics, any differences might equally be the result of methodological variation between studies. For example, prevalence was higher when participants were allowed to self-administer the study questionnaire, compared with when it was administered face-to-face or over the telephone by

an interviewer [1]. Indeed, heterogeneity between studies was substantial in many of the analyses, confirming that differences in either the methodology, the clinical characteristics of participants or a combination of these factors was probably relevant to understanding the variability in reported prevalence between studies. In addition, as alluded to earlier, the potential diversity of IBS symptoms between countries and the complexities of applying diagnostic criteria to non-Western populations might also be relevant. A Rome Foundation working group re-examined the literature in 2017. [19] Again, the reported prevalence of IBS varied widely, from 1.1% in France and Iran to 35.5% in Mexico, and the extent of methodological variance between studies was substantial with measures of heterogeneity approaching 100%. This finding led the authors to conclude that calculating a pooled global prevalence was unlikely to be meaningful.

Overall, the findings of these two studies serve to illustrate the problems inherent in characterising the prevalence of IBS around the world. Furthermore, in some countries, including the majority of African nations, the prevalence of IBS was unknown as there were no available data, and there was also a lack of data from many Eastern European, Middle Eastern and Central American countries. [1,19] Consequently, a Rome Foundation global survey is currently in progress, which aims to quantify the prevalence of several disorders of gut–brain interactions, including IBS, in 34 countries around the world using the Rome IV diagnostic criteria with symptom questionnaires translated into 21 different languages. [20] However, the study will also pose more specific questions to facilitate investigation of the role that variations in pathophysiological, psychological and sociocultural factors have in determining differences in IBS prevalence, both between nations and across cultures. The results of this study are yet to be published, but it will be the first to make direct comparisons between multiple countries simultaneously and, as such, is likely to be important in advancing our understanding of the epidemiology of IBS from a global perspective.

In the intervening years since these two systematic reviews, the majority of published population-based studies examining the prevalence of IBS have used the Rome III criteria. These 26 studies span 16 separate. [21-46] The prevalence of IBS in the community in these studies, according to the Rome III criteria, is provided in Figure 1. One study published in 2019 used an online population-based survey to estimate the prevalence of functional gastrointestinal disorders in the USA, Canada, and the UK using both the Rome III and Rome IV criteria. [46] The prevalence of IBS using the Rome IV criteria was very similar between the three countries, ranging between 4.4% and 4.8%. Rome IV-defined IBS was only around half as prevalent as Rome III-defined IBS, mainly because of the increased minimum frequency of abdominal pain required by the Rome IV criteria.

[H2] Prevalence according to sex and age

In an analysis of 56 studies worldwide, the prevalence of IBS was modestly, but significantly, higher in women than men (OR 1.67; 95% CI: 1.53–1.82). [47] However, when data were examined according to country, there were no differences between the prevalence of IBS in women compared with men in studies conducted in South Asian, South American, or African countries. Indeed, in contrast to findings in Western cohorts, epidemiological studies in India have consistently found no difference in prevalence between the sexes. [48] With respect to age, the prevalence of IBS decreased modestly with increasing age, although this trend did not reach statistical significance. [1] However, the odds of IBS were significantly lower in those aged ≥50 years compared with those <50 years (OR 0.75; 95% CI: 0.62–0.92), although heterogeneity was substantial.[1]

[H2] Prevalence according to ethnicity

Although variations exist in the prevalence of IBS according to geography, data relating to the role of ethnicity are very limited. One US study found that IBS occurs less frequently in African-Americans compared with white individuals, [49] which was also the finding of a systematic review on this topic. [50] This review also identified three community surveys from Singapore and Malaysia that showed no difference in prevalence between individuals of Chinese, Malay or Indian ethnicity. [5,51,52]

[H2] Prevalence in minority groups

Capturing the prevalence of IBS in certain minority groups, such as refugees, is challenging. A study of 1,352 Palestinians aged ≥50 years of age and living in a range of settings, including residents of refugee camps, found an overall prevalence of IBS of 30%. [53] Living in a refugee camp (OR 1.68; 95% CI: 1.14–2.40) or a rural village (OR 1.33; 95% CI: 1.02–1.72) was associated with increased odds of having IBS compared with living in an urban setting. Another study examined the prevalence of disorders of gut–brain interaction in the Israeli Bedouin population, a traditionally nomadic people, who had seen a substantial increase in settlement in permanent towns. [54] The authors reported a significantly higher prevalence of IBS among Bedouins living in towns compared with rural Bedouins (9.4% versus 5.8%; $P<0.01$), which they suggested might be due to the effects of the stressful social upheaval they had experienced.

Overall, data regarding the prevalence of IBS in minority groups such as these are very limited, and because they are difficult to reach, minority groups are unlikely to be captured in population-based studies. Nevertheless, the fact that IBS is a problem for these individuals at all highlights the relevance of conducting studies that include them, so that they

are not overlooked when planning healthcare policy. Indeed, one study indicated that exposure to severe wartime conditions in early childhood was associated with an increased risk of developing IBS later in life. [55] This finding suggests that IBS will continue to be an important and possibly more widely recognised health issue for those living through conflict around the world.

[H1] THE BURDEN OF IBS

The effect of IBS for the individual patient, their family and society is substantial, creating a driver for ongoing research in the field (Figure 2).

[H2] Quality of life

It has long been recognised that IBS has a substantial effect on QoL, [56,57] which might be greatest in those with predominant diarrhoea (IBS-D), [58] for whom the fear of incontinence in a social situation can be especially debilitating. [59] Indeed, patients with IBS-D report more avoidance of places without bathrooms and reluctance to leave home, whereas individuals with IBS with predominant constipation (IBS-C) are more likely to report avoiding sex, difficulty concentrating and feeling self-conscious. [60] The effects of IBS symptoms on work, including loss of earnings, socialising and the ability to travel also have a negative effect on QoL. [61] Overall, patients with IBS report feeling a loss of freedom and spontaneity, highlight the unpredictability of their symptoms, and can feel stigmatised by family, friends and physicians, who might struggle to understand the effects on their life. [62] Indeed, patients with severe symptoms appear more willing to accept substantial degrees of risk for resolution of their symptoms. For example, a questionnaire-based study showed they would accept a median 1% risk of sudden death from a hypothetical medication in return for a 99% chance of a cure. [63] In another questionnaire study, people with IBS were found to be willing to give up 25% of their remaining life expectancy, an average of 15 years, to be symptom-free. [64]

Consulting with a gastroenterologist regarding IBS symptoms has, unfortunately, been associated with only a small, non-statistically significant improvement in QoL, which was not maintained over time in one study. [65] This finding might reflect the fact that many patients with IBS report dissatisfaction with clinical management overall, and feel that a

patient-centred approach is lacking. Indeed, it has been suggested that long term QoL might be affected more by psychological well-being than by improvement in gastrointestinal symptom severity. [66,67] This understanding highlights the importance of adopting a holistic attitude to care, which can be sometimes overlooked in favour of a largely symptom-driven approach.

Studies examining health-related QoL in IBS conducted in North American and European populations show consistent mean reductions in QoL measures.[2] However, the extent to which QoL is impaired can differ between countries, as can the nature of any impairment, whether related to physical, emotional or social aspects of life, because QoL is a complex and subjective concept, determined by the perceptions of the individual in the context of their culture and society. [68] Japanese patients with IBS have been demonstrated to have significantly poorer QoL than healthy individuals as controls (P<0.001), [69] which was found to correlate significantly with symptom severity, [70] findings which were also observed in another study from South Korea. [71] However, although studies from other countries agree broadly with the negative effect of IBS on QoL overall, comparative data exploring the nature and relevance of any differences between countries are minimal. One study compared female patients with IBS from North Carolina and Mexico; the latter group had lower QoL scores, with a focus on body image and health worry, although reasons underpinning this difference were unclear. [72]

[H2] Healthcare costs

Overall, direct care costs of IBS — those costs that are entirely attributable to resource use for healthcare delivery, investigation and treatment of the condition — are substantial. Estimates range from £45.6–200 million per annum in the UK[2], $2 billion per annum in China[73] and €3–4 billion per annum in Germany. [74] An appraisal in 2013, based on an analysis of 35 studies, suggested direct cost estimates in the USA vary considerably, with

figures of between $1,562 and $7,547 per patient per year. [75] Estimates encompassing six European countries, although more conservative, were nevertheless considerable at between €1,183–3,358 per capita, [76] and similar values were seen in an evaluation of European patients with IBS-C, [77] for whom the biggest cost drivers were hospitalisation and visits to the emergency room. However, comparing costs between countries is difficult due to variations in methods used to calculate them, and the year in which the analyses were conducted. Indeed, many of the available cost analyses require updating in order to reflect current tariffs, and no study has sought to map the global health economic landscape of IBS.

[H2] Issues for society

Patients with IBS often find it difficult to work due to their symptoms. Accordingly, they might take time off, referred to as absenteeism, or instead report that, although at work, they struggle to perform at their best, referred to as so-called presenteeism. Studies relating to absenteeism in IBS are conflicting. It has been suggested that although people with IBS are more likely to take time off work, the total amount of time is no different to people without IBS. [78] However, one survey of 40,000 individuals across a number of European countries demonstrated that those with IBS took almost twice as many days off per year compared with those without IBS. [79] Overall, studies in Europe and Canada suggest that anywhere between 5–50% of people with IBS require some time off work due to symptoms. [2,59] A questionnaire study in 2018 of 525 patients with IBS reported that 24% of employed patients reported absenteeism. [80] Presenteeism is more difficult to quantify due its subjective nature, but was reported by 86% of patients with IBS in the same questionnaire study, for whom higher degrees of work impairment were linked to severity of symptoms and gastrointestinal-specific symptom anxiety. [80] Estimates of presenteeism are somewhat lower in other studies, ranging between 2–32%.[2]

Indirect costs of absenteeism and presenteeism, in terms of loss of work productivity, are considerable and similar to those for other chronic conditions such as asthma or migraine. [81] In an analysis of data from 13 European countries, an estimated mean per-capita indirect cost for IBS was €2,314 per year, [76] higher than in China (~ €670). [73] Although an updated analysis is needed, a study in 2003 found that absenteeism cost employers in the USA an average of $901 each year per employee with IBS, compared with $528 per employee without IBS. [82] Additional costs to society might be incurred if patients who are unable to work due to their IBS symptoms claim sickness or disability benefits. In a longitudinal population-based study in Denmark, the expected number of weeks on sickness benefits was 61% higher among those with IBS symptoms, which remained statistically significant following adjustment for age, sex, time in education, comorbidity and mental vulnerability (P=0.01)[83]. There was also a trend towards an increased number of weeks on disability benefits among those with IBS symptoms, compared with people without IBS symptoms, but this difference was not statistically significant following adjusted analysis[83].

Finally, the effect on families of those with IBS is relatively unknown. In one study, the partners of 152 patients with IBS were under significantly more strain, and bore a greater perceived burden, compared with the partners of 39 individuals as healthy controls (P=0.0002), and this effect increased in correlation with the severity of a patient's IBS (P<0.0001). [84] It is conceivable that these effects have implications for the health and economic contribution of partners, which are absent from previous assessments of the cost of IBS to society, but this situation requires further research.

[H1] IBS RISK FACTORS

The pathophysiology of IBS is complex and incompletely understood (Figure 3). Proposed potential risk factor include genetics, diet, disturbances in the gut microbiome, gastrointestinal infection and psychological factors, all of which can exert influence on the bi-directional brain–gut axis. However, post-infectious IBS (PI-IBS) is the only example where a clear causative factor has been identified.

[H2] Genetics

Many patients with IBS report having relatives who share their diagnosis, or who report similar symptoms, and indeed studies have observed familial aggregation of IBS, suggesting an underlying genetic component. [85,86] Nonetheless, such findings are confounded by the fact that, within families, individuals will often have shared childhood experiences or environmental exposures in common, which might equally explain clustering of IBS symptomatology. Moreover, findings from twin studies are conflicting. Some studies demonstrate increased concordance of an IBS diagnosis in monozygotic twins compared with dizygotic twins,[87,88] and others show no notable difference,[89] although in one study having a mother with IBS was equally as important as having a monozygotic twin with IBS. [87] Consequently, any genetic influence in IBS is likely to be polygenic, whereby common variants in a large number of genes and their interaction with environmental factors have a role in determining the clinical manifestations of IBS. As a result, efforts have focused on trying to identify possible genetic markers in IBS and how these might correlate with certain patient subgroups.

Owing to the role that serotonin has in the brain–gut axis as both a brain neurotransmitter related to mood and as an enteric neurotransmitter important in mediating gastrointestinal motility and physiology, the genetics of serotonergic pathways are amongst

the most widely studied, specifically genetic variations in the serotonin reuptake transporter (SERT). [90] It has been suggested that a genetic polymorphism in the promotor region of the *SLC6A4* gene encoding SERT might be associated with IBS. In a meta-analysis of 27 studies with 7,039 participants, the risk of IBS was significantly associated with the SERT insertion or deletion polymorphism in both Asian (dominant model: P=0.001; recessive model: P=0.0003; allele model: P=0.001) and white individuals (dominant model: P=0.04; additive model: P<0.0001), but only for those with IBS-C when patients were stratified by stool form (recessive model: P=0.04). [91] Other studies have identified rare pathogenic variants in genes encoding sucrase–isomaltase [92] or SCN5A, [93] a voltage gated sodium channel, suggesting that IBS symptoms in a small proportion of patients might relate to disaccharide intolerance or ion channelopathies. Indeed, a genome-wide association study (GWAS) meta-analysis of five European cohorts supports the hypothesis of ion-channel involvement in IBS pathophysiology. [94]

Another GWAS study comparing UK biobank data from 9,576 people with IBS and 336,449 healthy controls looked for significant genome-wide findings and investigated associations further in a multicentre population of tertiary care patients from Europe and the USA and a small Swedish population cohort. [95] This study identified variants at a locus on chromosome 9 that were associated with risk of IBS in women only, and additionally associated with constipation, which might support a rationale for investigating the role of sex hormones in the pathophysiology of IBS. In addition, familial dysautonomia has been linked to mutations of a gene residing at this locus. [96] This is a rare condition affecting the autonomic and sensory nervous systems, which leads to a variety of symptoms including labile blood pressure, altered pain sensation, speech difficulties, episodic vomiting and abnormal gastrointestinal motility. Consequently, this finding might support the role of autonomic dysfunction in IBS pathophysiology; however, these associations are tentative and

require further examination. Studies in Japanese individuals have identified associations between IBS symptoms and single nucleotide polymorphisms in genes encoding the corticotrophin-releasing hormone (CRH) receptor 1 and 2. [97,98] CRH is key to the body's stress response and studies have shown that administration of exogenous CRH can induce an increase in colonic motility, and that motility can be reduced using CRH-receptor antagonists. These findings, together with the fact that altered gastrointestinal motility is a component of IBS pathophysiology, have led some to conclude that the CRH pathway plays a part in IBS. [97,98]

Although our understanding of the part that genetics might play in the aetiology of IBS is expanding, many unanswered questions remain, particularly whether these gene mutation associations actually contribute to pathophysiological mechanisms.

[H2] Dietary factors

Patients frequently report dietary triggers for their IBS symptoms, [99] and a Western diet high in sugar and fat has been associated with IBS in a large (n=44,350) French cohort. [100] Some patients with IBS report symptomatic benefit from reducing the amounts of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) in their diet, [101] although estimates of response rates show considerable variation, between 50–86% [102]. Alternatively, non-coeliac gluten intolerance might play a part for some patients, although estimates of prevalence in the general population, ensuring coeliac disease is excluded, vary widely from 0.6% to 10.6%. [103] However, a systematic review and meta-analysis concluded there was currently insufficient evidence to recommend a gluten-free diet and found only low-quality evidence for the efficacy of a low FODMAP diet. [104] Data from a single placebo-controlled trial of 106 patients suggested that dietary glutamine supplements

might be beneficial in PI-IBS by reducing intestinal permeability, [105] although further adequately powered trials are needed to confirm these findings. Patients with IBS might have lactose malabsorption, although the relevance of this suggestion is questionable given the poor response of symptoms to a lactose-free diet, [106] and the similar prevalence of lactose malabsorption in people with no IBS symptoms. [107] Finally, one study suggests that patients with IBS might have food allergies that are not part of the classic IgE-mediated immune pathway, [108] but these findings and the clinical ramifications require further study. Although individual dietary components might be a factor in the pathogenesis of IBS, the interaction of diet with the gut microbiome and the composition of microorganisms living in the gut might also be important. [109]

[H2] The gut microbiome

Interest has been growing into the role that the gut microbiome, with a particular focus on bacteria, might play in health and gastrointestinal disease. It has previously been shown that the faecal microbiota of people with IBS differs significantly from that of healthy individuals (P<0.0253), [110] and might influence colonic transit, contributing to altered bowel habits. [111] The existence of a microbiome 'signature' specific to IBS has been proposed, with reduced microbial diversity and the presence of methanogenic or Clostridiales species associated with more severe symptoms. [112] Indeed, Clostridiales species might adversely affect gastrointestinal physiological activity via their possible role in serotonin synthesis, although this speculative link requires further investigation. [113] Inflammatory pathways, changes in intestinal permeability and the gut metabolome, which includes products of bacterial metabolism of intestinal contents, have also been suggested to play a part in a microbiome-related construct of gastrointestinal disease[114]. In addition, long-term FODMAP restriction can lead to alterations in the microbiome [115].

These findings have sparked interest in whether modifying the composition of the gut microbiota could be an effective treatment for IBS, although the clinical relevance of identifying either particular changes in an individual's gut microbiome or a reduced diversity of species is uncertain. A trial in patients with IBS conducted in the USA demonstrated improvements in constipation and straining with a combination of the minimally absorbed antibiotics rifaximin and neomycin, compared with neomycin alone. [116] The authors reported that breath methane levels after treatment predicted response to therapy. Faecal microbiota transplantation (FMT) might be beneficial but, in a meta-analysis, when data were pooled from five randomised-controlled trials there was no significant improvement in IBS symptoms with FMT versus placebo[117]. All of the studies were small, the largest containing 86 patients, and at high-risk of bias, so larger more rigorously conducted trials are needed. [117] Of note, a double-blind randomised-controlled trial in 165 patients with IBS, published subsequent to this meta-analysis, showed that FMT was associated with a significant improvement in IBS symptom severity compared with placebo (P <0.0001); however, there was no significant change in the degree of overall dysbiosis after FMT [118]. Similarly, some probiotics might be effective in IBS, but definitive conclusions are limited by the poor methodological quality of trials so far. [119,120] Moreover, the extent to which treatments might alter the composition of the gut microbiota, whether these changes are responsible for any clinical improvement and whether they persist requires clarification. The situation is further complicated by the fact that the gut microbiome can show considerable variation between people of different ethnicities living in the same country, [121] and can also vary substantially between residents of different countries, [122] even neighboring ones. [123] In addition, changes in an individual's native microbiome can occur following migration, [124] which could reflect dietary change or differing healthcare practices between countries, such as the prescription of antibiotics.

[H2] Post-infection IBS

Infective gastroenteritis is frequently identified as a risk factor for developing IBS, referred to as PI-IBS, [125] with such patients generally experiencing looser and more frequent stools rather than constipation. [126] Early studies determined that a quarter of individuals with infective gastroenteritis reported persistence of altered bowel habits 6 months after their infective episode, with one in 14 people developing IBS. [127] A range of bacterial pathogens have been implicated in PI-IBS, including *Campylobacter jejuni, Escherichia coli,* and *Salmonella enterica* serovar Typhimurium, [128] as well as *Clostridioides difficile* [129] and *Vibrio cholerae.* [130] Symptoms can persist for many years following the initial infection, [131] sometimes for more than a decade in some studies, [132] and the development of IBS in this context appears to be independent of other risk factors, such as age and sex. [133] Associations have also been demonstrated between viral infections such as norovirus, [134,135] and protozoal infections such as *Giardia lamblia*. [136,137] However, there are far fewer available studies than for bacterial pathogens, [138] and symptoms following viral infection might be relatively transient with a similar prevalence of IBS among exposed and non-exposed individuals by 6 months. [125,135]

A systematic review and meta-analysis of 45 cohort studies involving 21,421 individuals with infective enteritis who were followed for between 3 months and 10 years to identify the development of IBS, reported a pooled prevalence of IBS at 12 months following infection of 10%, rising to 15% beyond 12 months. [139] The risk of IBS in those with enteritis was four-fold higher than in individuals without, and this risk was significantly associated with female sex (OR 2.2; 95% CI: 1.6–3.1), psychological co-morbidity, such as anxiety (OR 2.0; 95% CI: 1.3–2.9) or somatisation (OR 4.1; 95% CI: 2.7–6.0), and antibiotic use (OR 1.7; 95% CI: 1.2–2.4). Individuals with protozoal enteritis were found to be at highest risk of IBS, with around 40% developing the condition compared with 13% of those with a bacterial

aetiology[139]. Although an increased risk was seen across different geographic regions, the majority of studies were in European and North American populations. One study of PI-IBS from Bangladesh in 345 patients with acute gastroenteritis demonstrated that, although patients with a history of acute gastroenteritis had a significantly higher prevalence of IBS than age-matched and sex-matched healthy controls, approximately one in 10 of those fulfilling criteria for PI-IBS actually had post-infection malabsorption or sprue following investigation. [140] A study in East Indian patients hospitalised with acute gastroenteritis found that a quarter developed IBS within 6 months of the infection, and this finding was associated with younger age and increased duration of the gastroenteritis. [141] Another prospective cohort study of individuals with shigellosis, following an outbreak in a Korean hospital, observed a significantly increased risk of developing IBS up to 3 years after the infection (OR 3.93; 95% CI: 1.20–12.86), but by 10 years the prevalence of IBS was similar between the Shigella cohort and healthy controls (23.3% versus 19.7%; P=0.703). [142]

Overall, the prognosis for PI-IBS and non-PI-IBS appears to be the same, with symptoms persisting beyond 12 months in ~75% of cases and few differences in clinical features between the subtypes. [126] However, given that the prevalence of gastrointestinal infections is high throughout the world and unlikely to diminish, with foodborne illness affecting 48 million people in the USA per annum, [143] and an estimated 2.4 billion cases of acute diarrhoea per annum worldwide, the majority of which will be infective, [144] it is important to improve our understanding of the pathophysiology of PI-IBS with the aim of developing more effective treatments for this subgroup of patients.

[H2] Psychological co-morbidity

Psychological co-morbidity, including stress, anxiety or depression is frequently associated with IBS and might exacerbate symptoms. One meta-analysis highlighted that the prevalence of both anxiety disorders and depressive disorders among patients with IBS is 23%, with anxiety and depressive symptoms being even more common, with a prevalence of 39% and 29%, respectively. [145] Psychological co-morbidity contributes to the aetiology of IBS as part of an integrated biopsychosocial model. It is important to consider that psychological symptoms might have developed as a consequence of the severity and effect of IBS on an individual, or might instead have been present prior to the onset of gastrointestinal symptoms. [146] Within this construct, the brain–gut axis — the interaction between the central (CNS) and enteric nervous system — is important in the pathophysiology of IBS and functions in a bi-directional manner. [147] The CNS can alter gut physiology, such as motility or visceral sensitivity, which in turn mediates IBS symptomatology, such as transit and bowel habit or the experience of pain. Similarly, changes in the gut can feed back to the brain, resulting in effects on psychological well-being and health. The microbiome might also be important in this mechanism. [148] Indeed, higher levels of anxiety and depression at baseline in people without IBS were significant predictors for the development of IBS after 1 year of follow-up. [149] When these findings were examined over the longer term, with follow-up at 12 years, the same association was seen for anxiety, but not for depression. [147] Both these studies also found that, among patients with IBS with no psychological co-morbidity at baseline, there was a significant increase in the reporting of anxiety and depression at follow-up. [147,149]

Overall, anxiety and depression are common and disabling mental health disorders worldwide. [150] In the past 20 years, it has been suggested that they are becoming more common; however, it is perhaps more likely that this idea reflects greater awareness, coupled with increasing numbers of affected patients driven by an expanding population size. [151] The

global prevalence of anxiety is substantial, with one meta-analysis reporting a pooled lifetime prevalence of 12.9% based on the results of 70 studies from 39 countries, [152] but it has been seen to vary between countries, ranging from 5% in African cultures, to 10% in European countries. [153] However, similar to the IBS field, these findings might reflect methodological differences between studies rather than true variation in prevalence rates. Nevertheless, psychological co-morbidities are likely to be an important factor in IBS throughout the world and need to be considered when planning approaches to management.

[H1] PREDICTIONS AND FUTURE IMPLICATIONS

It seems plausible that the prevalence of IBS could increase over time, partly as a consequence of a growing awareness among patients and increased recognition of the condition by physicians, but also due to the influence of Westernisation around the world and the accompanying changes in diet and lifestyle. [154] To accurately determine the true prevalence of IBS in different countries worldwide, higher quality epidemiological studies are needed that also attempt to quantify the effects of geographical and cultural differences. Epidemiological projections for the pharmaceutical industries forecast a rise in cases of IBS in the seven major markets from 24,414,879 in 2016 to 25,163,675 in 2026 — an increase of almost 750,000 cases over 10 years, with an annual growth rate of 0.31% per year. [155] Even if prevalence rates remain unchanged, the projected growth in the world's population means that a greater number of people will be affected by IBS. If we apply existing age-specific estimates of global prevalence of IBS [1] to projected figures for world population growth, [156,157] there would be an expected increase of close to 120 million people living with IBS between 2020 and 2040, as detailed in Supplementary information (Table 1). This increase occurs despite trends showing an ageing population globally, with a decrease in the proportion of younger individuals who are generally considered more likely to suffer from IBS. Indeed, it appears there will be more older people with IBS, which will present its own unique health resource challenges, as older individuals are much more likely to require investigations to exclude organic pathology, such as colorectal cancer, prior to making a diagnosis of IBS.

It is interesting to note that in UK government reports exploring the health of the post-war 'baby boomer' generation (those born between 1946–1964), [158] and also commercial reports relating to the Millennial generation (those born between the early 1980s and the mid 1990s), [159] discussion of medically unexplained symptoms such as IBS is conspicuously

absent. However, psychological health and mental health feature prominently, with Millennials and also Generation X (those born between 1960 and 1980) reporting increasing levels of stress, [159-161] which might conceivably translate into a concurrent increase in the prevalence of disorders of brain-gut interaction.

The burden of IBS is substantial and costs associated with managing the condition, as well as the indirect economic effects, are considerable and can only increase if more people are affected by the condition over time. It is therefore vital that management is evidence-based to minimise costs and to limit unnecessary use of healthcare resources, such as restricting the use of extensive clinical investigations that are rarely indicated. [162] However, current evidence has a Western bias and there is consequently a need for further studies that address gaps in our understanding of how IBS pathophysiology and treatment responses might differ between countries. Some of the key research priorities in IBS are detailed in Table 2.

In addition, there have been calls to improve the management of patients with IBS with a focus on early diagnosis, rational investigation and timely treatment, aiming to improve the overall quality and value of care in IBS. [163] Unfortunately, patients with IBS often perceive a lack of a patient-centred approach to their care, and management strategies can vary between physicians dependent on expertise, a situation that a more focused approach could help to address. Seven pillars of quality-of-care have been suggested, covering diagnosis and management, and the aim should be to incorporate these into the care of any patient, although differences in healthcare behaviour and infrastructure worldwide, which are discussed in Table 3, might result in some barriers to implementation.

[H1] CONCLUSIONS

IBS is a common condition globally, although more rigorous epidemiological studies are needed to quantify any differences in prevalence that might exist between countries, as well as the potential explanations for these differences. The influence of ethnicity has also been under-studied. Nevertheless, the magnitude of the effect of IBS, in terms of costs and effects on QoL, appears to be comparable the world over, although differences might exist in the precise nature of this effect, based on variability both in healthcare delivery, and in societal and cultural norms between nations. The pathophysiology of IBS is complex, and a number of risk factors have been identified; however, gaps remain in our knowledge of the disorder, and it is unclear whether certain risk factors, such as genetics, diet or the microbiome, might operate differently according to geography. As developing countries become increasingly Westernised in terms of their diet and lifestyle, we might see a corresponding increase in the prevalence of IBS, a trend that might also correlate with increasing awareness of the condition among physicians and patients, especially given the ready access to relevant health information in the digital age. In addition, expected expansion of the global population will, in itself, result in more people with IBS even if prevalence rates remain unchanged. Moreover, there is evidence that the burden of mental health disorders, such as anxiety and depression, which are associated with the development of IBS, is increasing. This understanding, together with the increasing prevalence of stress-related illness in younger generations, might mean that IBS and functional disorders in general become a much greater health problem for Millennials than for the post-war generations that came before.

Well-designed and adequately funded research in IBS is key to improving our understanding and management of this condition, and it is now increasingly recognised that research needs to be multi-cultural in design, encouraging global collaboration. In this way,

we can look to optimise the management of patients with IBS, taking into account an individual's geographical and cultural context, in order to provide high-quality and high-value care to people living with IBS around the world.

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Box 1: Rome IV diagnostic criteria for IBS.

Rome IV IBS Diagnostic Criteria
1. Recurrent abdominal pain, on average, at least **1 day per week** in the last 3 months and associated with two or more or the following:
a. **Related** to defaecation
b. Associated with a change in frequency of stool
c. Associated with a change in form of stool
2. Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Adapted from Mearin *et al.* [8]

Figure 1: Global prevalence of irritable bowel syndrome. a | Map shows the prevalence of irritable bowel syndrome (IBS) by country based on a combination of studies using either the Manning, Rome I or Rome II criteria. The data are taken from Ref.[1]. **b |** Map shows the prevalence of IBS by country based on the updated definition of IBS in the Rome III criteria. The data are taken from population prevalence studies (REFs. [21-46]).

Figure 2: The effects of irritable bowel syndrome. Irritable bowel syndrome (IBS) affects the individual and their family, and also has implications for society. This figure summarises these effects based on current knowledge. It also highlights the broad aims of IBS research, which is driven by the fact that IBS is a common and costly disorder.

Figure 3: Proposed pathophysiological mechanisms in irritable bowel syndrome. The pathophysiology of irritable bowel syndrome (IBS) is complex and multifactorial. The onset of the condition is probably due to a triggering event in a genetically susceptible individual. The gut–brain axis — the bi-directional interaction between the central and enteric nervous systems — is pivotal to our understanding of IBS pathophysiology. Changes in the gut, for example, those relating to diet or enteric illness, can feedback to the brain with consequences for psychological well-being. The gut microbiome might be important in mediating these effects with higher degrees of dysbiosis observed among patients with IBS. Equally, the central nervous system can affect gastrointestinal physiology, altering motility or visceral sensitivity. These changes can result in symptoms, such as altered bowel habit due, in part, to changes in intestinal transit or the experience of pain. Moreover, an individual's perception of their symptoms can be influenced by altered central processing that, in turn, might be affected by psychological co-morbidity or stress. At the gut level, alterations in intestinal

permeability, gastrointestinal immune function, and inflammatory pathways might also be important.

Table 1: Knowledge and use of the Rome criteria for irritable bowel syndrome in four different countries.

Characteristics		**Italy**	**South Korea**	**India**	**Mexico**
GPs	**Knowledge**	Yes	Yes	No	Yes
	Use	No	Limited	No	Limited
Gastroenterologists	**Knowledge**	Yes	Yes	Yes	Yes
	Use	Limited	Yes	No	Yes
Limitations of Rome criteria		None	Some patients consider BSFS type 3 as hard stools, and type 5 as loose stools	Absence of abdominal pain or discomfort in 30% of patients with IBS No differences in stool frequency between IBS-C and IBS-D, thus stool frequency criteria cannot be used for subgrouping	None
Criteria best suited*		Rome III	Rome III	Manning Asian Criteria	Rome II

BSFS, Bristol stool form scale
*This analysis was published prior to the publication of the Rome IV criteria
Adapted from Schmulson *et al.* [10]

Table 2 | Future research priorities in irritable bowel syndrome.

Area of research	Current knowledge gaps	Strategies to address knowledge gaps
Gut neuromuscular dysfunction and the microbiome	• What are the persistent changes in the enteric nervous system following intestinal inflammation? • What are the physiological and neurochemical changes within the gut in response to stress? • How do gut bacterial products interact with gut function? • What are the mechanisms underlying differences between the IBS subtypes?	• Use advances in cell and stem cell engineering to create better *in vitro* models • Use molecular and cellular approaches to understand specific alterations in the enteric nervous system • Determine how best to use animal models to reflect IBS in humans, and how to use these in translational studies
Brain–gut pathways in models of IBS	• What is the role of the vagus nerve in IBS pathophysiology? • What do interactions between sensory afferent nerves, immune cells and enterochromaffin cells imply about visceral hypersensitivity? • What are the underlying brain–gut–neuroendocrine mechanisms involved in chronic stress or early life adverse events that affect development of IBS?	• Histologically localise classes of colorectal afferent nerve endings • Characterise the role of specific brain loci in the bidirectional brain–gut axis
Genetic mechanisms and environmental factors	• What are the protective influences and risk factors for development of IBS early and later in life? • Which genes or gene combinations contribute to variations in IBS phenotypes? • How do interactions between genes and the environment affect risk of IBS and disease pathophysiology?	• Conduct longitudinal studies of children and adults with IBS, encompassing key time points through life • Replicate and confirm genetic studies in larger samples and encourage multidisciplinary collaborations in gene discovery • Examine the interaction of genes and the environment, and investigate epigenetic mechanisms
Role of dietary triggers in IBS	• What measures (clinical,	• Conduct large-scale

	phenotypic, and biological) can predict response to dietary interventions? • What are the mechanisms by which a low FODMAP diet may work in IBS? • How do wheat and other FODMAPs interact with gut bacteria and the mucosal barrier in IBS pathophysiology?	multicentre studies of a low FODMAP diet across diverse populations, and increase study durations to understand longer term effects • Conduct studies to understand how a low FODMAP diet may work • Examine the re-introduction phase of a low FODMAP diet • Study the prevalence of wheat sensitivity in patients with IBS, and the roles of microbiota and intestinal permeability in gluten sensitivity
Management of IBS	• Can specific biomarkers be identified that are useful for diagnosis and management? • What is a normal microbiome and can microbiome and metabolomic profiling help identify patients who are more likely to respond to dietary interventions and probiotics? • What is the natural history of IBS, and how do phenotypes change in transition from children to adults? • How do psychological co-morbidities and somatic disorders affect response to treatments?	• Investigate the role of biomarkers for diagnosing IBS, targeting and monitoring treatments, and predicting outcomes • Better understand how modifications of the gut microbiome affect the gastrointestinal tract and emotional components of IBS symptoms, and whether this approach can help identify patients more likely to respond to dietary and probiotic treatments • Perform longitudinal studies to determine the natural history of IBS and establish the predictive value of endophenotypes in symptom severity and treatment response • Identify aspects of the physician–patient relationship that can improve patient satisfaction, adherence to treatment and efficacy of treatment • Explore the role of apps or wearable/implantable devices to gather real-time data from individuals with

		IBS

IBS, irritable bowel syndrome; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols. Adapted from Chang *et al.* [164]

Table 3: Suggested seven pillars of standardised care in irritable bowel syndrome and potential pitfalls of global implementation.

Pillar of Standardised Care [163]		Potential Pitfalls of Global Implementation [10]
1	Make a positive diagnosis as soon as possible. The Rome IV criteria should be used internationally to accurately characterise patients based on bowel symptoms, enabling the effect of culture and country to be examined more precisely.	Making an early diagnosis, in general, should be achievable, however: Knowledge and use of the Rome criteria is limited, especially amongst GPs, and might not be equally applicable in every culture Patients with IBS receive healthcare at different levels (primary, secondary or tertiary care) across countries. Thus, patients in primary care in one country might have similar disease severity to those receiving tertiary care in another country.
2	Perform limited diagnostic testing at the first visit.	Diagnostic investigations vary between countries based on availability and costs. The most likely pathology to account for a patient presenting with abdominal pain and bowel symptoms will vary dependent on country. Epidemiological differences in disease prevalence will therefore influence practice with respect to investigation. Patients with IBS receive healthcare at different levels (primary, secondary or tertiary care) across countries. Thus, patients in primary care in one country may have similar disease severity to those receiving tertiary care in another country. This will affect availability and choice of investigations.
3	A colonoscopy is not required in all patients with IBS symptoms (colonoscopy should be reserved for those with suspected IBD, persistent diarrhoeal symptoms despite standard therapies, and age-appropriate patients with a change in bowel habit, or other alarm symptoms suggestive of colorectal cancer).	See comments about investigation in general in (2), above.
4	Patients should be counselled on the diagnosis of IBS and treatment options, their expectations should be reviewed and their fears and concerns should addressed.	No key difficulties anticipated, however: Discussions should take an individual's cultural context into account, which might influence their expectations and perceptions. Some healthcare systems might have a more paternalistic approach, which might limit discussion of a patient's ideas, concerns and expectations.
5	Early treatment, initiated at the first visit	The aim of initiating early treatment should be

	or first follow-up visit, after limited diagnostic testing. Treatment should focus on the predominant symptom.	achievable, however: Available and approved medications for IBS vary around the world and according to healthcare systems. Some cultures use complementary and alternative medicine (for example, acupuncture and herbal treatments) more than others, and practices vary. Well-designed controlled trials of such treatments are lacking. Patients with IBS receive healthcare at different levels (primary, secondary, or tertiary care) across countries. Thus, patients in primary care in one country may have similar disease severity to those receiving tertiary care in another country. This will affect knowledge and practice relating to treatment.
6	Dietary consultation should be requested in those with persistent symptoms thought to be related, in part, to diet.	Variability in availability and training of dieticians worldwide[165].
7	Patients with persistent psychological distress, affecting quality of life, should be referred for appropriate assessment and treatment.	Perceptions of psychological aspects of illness can vary between countries and there is the potential for fear of stigmatisation[166]. Access to psychological treatments can vary between countries[167].

Adapted from Lacy *et al.* [163] and Schmulson *et al.* [10]