IBS GLOBAL IMPACT REPORT

A report investigating the human, societal, and healthcare burden imposed by irritable bowel syndrome (IBS) globally

Funded and facilitated by

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ABOUT THE GLOBAL IMPACT REPORT

This report presents key evidence outlining the human, societal and healthcare burden imposed by irritable bowel syndrome (IBS) globally, in order to stimulate discussion on how patients may receive better management and patient outcomes improved.

Using evidence gathered through a literature review of current and recent papers, this document represents a consensus view of the members of the Steering Committee. The report was funded and facilitated by Allergan, and coordinated by a secretariat service provided by HAVAS Just:: and Dr Sue Libretto.

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Executive summary

IBS is a chronic functional bowel disease characterised by symptoms of abdominal pain and/or discomfort associated with altered bowel habits, in the absence of any structural or organic cause. This burdensome disease has an estimated global prevalence of 11.2%, predominantly affecting adults of a working age. Patient experience of IBS varies according to symptoms and disease severity.

IBS creates a significant burden on society due to the impact on direct and indirect healthcare costs, as well as having a negative effect on a patient's quality of life, social functioning and productivity in the workplace.

Despite the high prevalence, IBS does not receive the attention it deserves. This report summarises current knowledge on the impact of IBS, drawing on information about the humanistic, societal and healthcare burden imposed by IBS globally.

Currently, it may take years for a patient with IBS to receive a positive diagnosis. There is no accepted standard of care for the disease and a lack of clarity in the management approach results in an unnecessary use of resources, particularly in more severe patients.

Studies cited in this report reveal the clinical challenge associated with the management of IBS and suggest a need for improved understanding of the disease and a greater uniformity of care.

Further research and discussion among healthcare professionals (HCPs), commissioners, payers and patient groups will help to address these inefficiencies and will bring IBS out of the shadows.

The Steering Committee

Call to action

Following a review of the documented studies on the impact of IBS in this report, the Steering Committee makes the following observations and recommendations:

IBS GUIDELINES

- There is a need for greater uniformity and efficiency in the care of patients with IBS and recognition that IBS should be managed as **one disease** with a collection of symptoms.
- There is a need for **simple guidelines that are applicable to everyday clinical practice**, which will help primary and secondary care HCPs diagnose IBS and manage the patients with more certainty.
- Existing guidelines provide an up-to-date assessment of treatment evidence which, if followed, may lead to an established standard of care for IBS.

FURTHER RESEARCH

- Initial evidence shows that the treatment of IBS relies on a limited source of evidence-based studies. **A greater understanding of inefficiencies in IBS management through state-of-the-art study methodologies**, including prospective studies, may lead to a standardised and evidence-based approach to IBS care in the future.

DOCUMENTING THE IMPACT

- There is a growing body of evidence that there are **significant hidden costs of IBS**. More studies are needed to provide an accurate picture of the hidden costs of IBS on society to enable a greater appreciation of the true impact vis-à-vis other chronic conditions.
- **Healthcare professionals (HCPs) should ask patients in the consultation about the impact of IBS symptoms** on their overall quality of life, including their productivity at work. An accurate assessment of impact can be a crucial indicator of their disease severity.

ALLOCATION OF RESOURCES

- HCPs and commissioners should **consider directing resources to those patients with more severe symptoms and therefore the highest need**. In some countries, this could be delivered through IBS-specific models of care.

* ***Scientific advice to:*** *Abide Therapeutics; AlfaWassermann; Allergan; AstraZeneca; Danone; Genfit; Ironwood; Janssen; Menarini; Mylan; Novartis; Nutricia; Ono Pharma; Rhythm; Shionogi; Shire; SK Life Sciences; Takeda; Theravance; Tsumura; Yuhan; Zeria*

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THE IBS LANDSCAPE

IBS – a definition

IBS is a chronic functional bowel disease characterised by symptoms of abdominal pain and/or discomfort associated with altered bowel habits, in the absence of a structural or organic cause.[1,2] In 1989, an international working group based in Rome developed the first guidelines for the classification of IBS (Rome criteria),[3] which have been updated over subsequent years.[4] To date, Rome III criteria have been the standard for IBS diagnosis[4,5] and are thus used in most recent scientific publications. They were superseded in May 2016 by the Rome IV criteria (Box 1).[6,7]

Rome III and Rome IV diagnostic criteria for IBS[1,7]

Rome III diagnostic criteria* for IBS

- Recurrent abdominal pain or discomfort† at least 3 days per month over the previous 3 months associated with two or more of the following:
  - Improvement with defecation
  - Onset associated with a change in frequency of stool
  - Onset associated with a change in form (appearance) of stool

* Criteria fulfilled for the past 3 months with symptom onset greater than 6 months prior to diagnosis

† "Discomfort" means an uncomfortable sensation not described as pain

Rome IV diagnostic criteria* for IBS

- Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with two or more of the following:
  - Related to defecation
  - Associated with a change in frequency of stool
  - Associated with a change in form (appearance) of stool

* Criteria fulfilled for the past 3 months with symptom onset at least 6 months prior to diagnosis

Box 1

Compared with the Rome III criteria, the term 'discomfort' has been removed from the Rome IV diagnostic criteria, because not all languages have a word for discomfort, it has different meanings in different languages, and it is ambiguous to patients.[7]

IBS – subtypes

Based upon bowel patterns at a particular point in time, the disorder may be categorised into four groups: constipation-predominant (IBS-C), diarrhoea-predominant (IBS-D), mixed (IBS-M), and unsubtyped (IBS-U) (Table 1).[1,2,7] Specific symptoms may also vary among the subgroups (Box 2).

Table 1. Characterisation of IBS by predominant stool pattern[1,2,7]

	Stool consistency (% of bowel movements)[c]	
	Hard or lumpy[a] Rome IV (Rome III) criteria	**Loose, mushy, or watery**[b] Rome IV (Rome III) criteria
IBS with constipation (IBS-C)	>25% (≥25%)	<25% (<25%)
IBS with diarrhoea (IBS-D)	<25% (<25%)	>25% (≥25%)
Mixed IBS (IBS-M)	>25% (≥25%)	>25% (≥25%)
Unsubtyped IBS	Insufficient abnormality to meet criteria for IBS-C, IBS-D, or IBS-M	

a Bristol Stool Scale (BSS) 1 or 2 ("separate hard lumps like nuts" or "sausage shaped but lumpy")
b BSS 6 or 7 ("fluffy pieces with ragged edges, a mushy stool" or "watery, no solid pieces, entirely liquid")
c IBS subtypes related to bowel habit abnormalities (IBS-C, IBS-D, and IBS-M) should be established in the absence of patients taking medications for such abnormalities

Symptom differences between IBS subtypes

- In a study conducted in 287 patients, nausea appeared to occur in more patients with IBS-M (43.1%) vs. those with IBS-D (24.6%) and IBS-C (26.2%; p=0.014).[8]
- A significantly greater proportion of patients with IBS-M (75.2%) and IBS-D (76.9%) report experiencing urgency vs. patients with IBS-C (34.7%; p<0.001).[8]
- In patients meeting the Rome III diagnostic criteria with a history of ≥3 pain attacks per month, median pain attack frequency per month was significantly higher in IBS-D patients (6.4) vs. IBS-C (4.4) and IBS-M (5.5) patients (p=0.019).[9] The majority of pain attacks resulted in defecation (78%).[9]
- Similarly, another study found that in patients meeting the Rome III diagnostic criteria with a history of ≥ 3 pain attacks per week, mean pain attack frequency per two weeks was greatest for IBS-D patients (10.7) than for IBS-C (8.4) and IBS-M (7.1) patients (p=nonsignificant).[10] IBS-D patients also had:
  - Significantly shorter episodes (9 h 23 min) compared with IBS-M (15 h 01 min) and IBS-C (15 h 25 min) patients (P<0.04).
  - Greater stool frequency and looser stool consistency than IBS-M and IBS-C patients, who were similar.

Box 2

IBS – a clear pathogenesis?

The precise cause of IBS remains unknown.[11,12,13] However, several factors have been implicated in the pathophysiology of IBS symptoms, including genetic disposition, diet, intestinal microbiota, and mucosal low-grade inflammation.[11] To date, no specific biomarker related to IBS has been found.[14]

IBS – symptom severity

The Rome Foundation Working Team Committee published a working model of factors that can differentiate severity into subgroups, with mild severity estimated at ~40% prevalence, moderate estimated at ~35% and severe estimated at ~25% (Table 2).[15] Severity in IBS, and functional gastrointestinal disorders (FGIDs), is determined by symptom reports and behaviours rather than by blood tests or histopathological markers in the bowel, and it has been defined as a *"biopsychosocial composite of patient reported gastrointestinal and extra-intestinal symptoms, degree of disability, and illness related perceptions and behaviours"*.[15] As such, the complexity of defining severity, combined with the subjectivity of patient reporting means it is difficult to measure and currently there is no universal consensus on what entails mild, moderate and severe symptoms.[15]

Table 2. Proposed clinical profile for patient-rated severity[15]

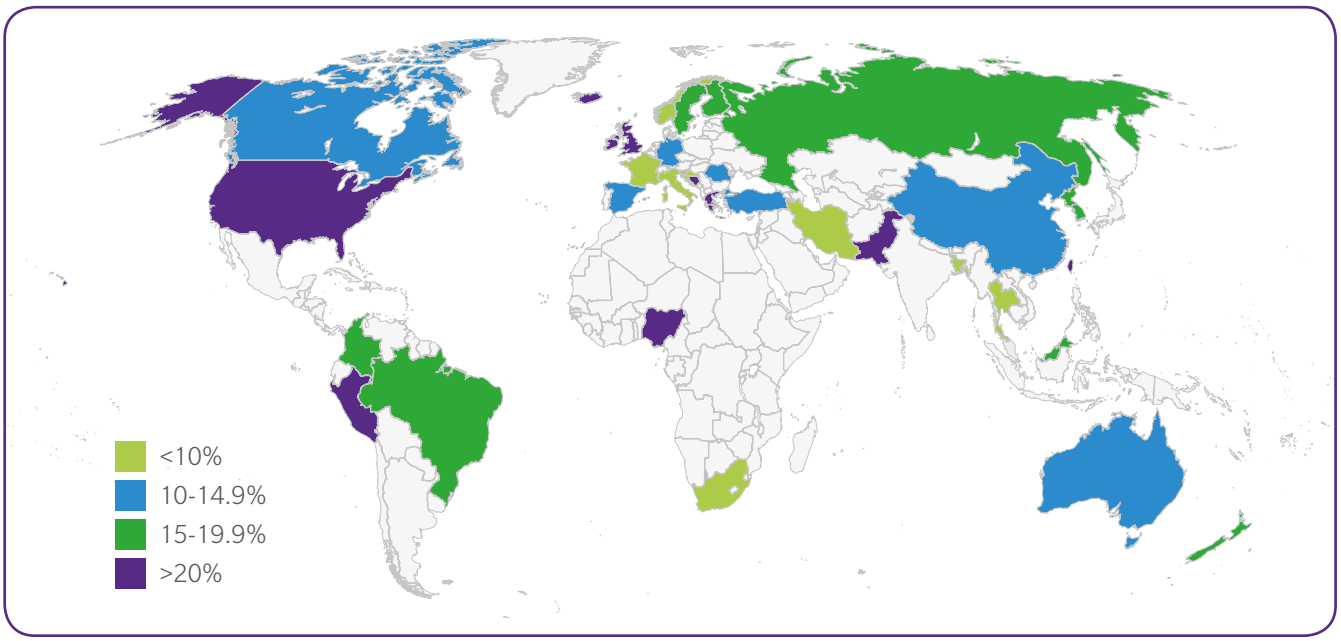
Clinical feature	Mild	Moderate	Severe
Estimated prevalence	40%	35%	25%
Psychometric correlate	FBDSI: <36 IBS-SSS: 75-175	FBDSI: 36-109 IBS-SSS: 175-300	FBDSI: >110 IBS-SSS: >300
Physiological factors	Primarily bowel dysfunction	Bowel dysfunction and CNS pain dysregulation	Primarily CNS pain dysregulation
Psychosocial difficulties	None or mild psychological distress	Moderate psychological distress	Severe – high psychological distress, catastrophising, abuse history
Gender	Men=women	Women>men	Women>>men
Age	Older>younger	Older=younger	Older<younger
Abdominal pain	Mild/intermittent	Moderate, frequent	Severe, very frequent or constant
No. of other symptoms	Low (1-3)	Medium (4-6)	High (>7)
Health-related quality of life	Good	Fair	Poor
Healthcare utilisation	0-1/Year	2-4/Year	>5/Year
Activity restriction	Occasional (0-15 days)	More often (15-50 days)	Frequent/constant (>50)
Work disability	<5%	6-10%	>11%

CNS= central nervous system; FBDSI= Functional Bowel Disorders Severity Index; IBS-SSS, IBS Severity Scoring System

IBS – prevalence and incidence

IBS is common worldwide, with an estimated global prevalence of 11.2% (Figure 1).[16,17] However, prevalence rates depend on the classification criteria and study methodologies used.[16,17,18] Considerable methodological variance between studies is reported.[18] As a result, prevalence rates vary not only between countries but for individual countries and within individual countries.

Figure 1. Prevalence of IBS – a global picture[16]



Source: *Adapted from Canavan et al 2014*

Globally, IBS is prevalent both in developed and developing countries.[19,20] Early studies suggested a low IBS prevalence in developing countries, with more recent studies indicating an increasing prevalence in newly developed and developing economies (i.e. Asia) as they become 'westernised'.[19] Prevalence estimates for IBS vary considerably between countries, from less than 5% in some to more than 20% in others.[16] Meta-analyses report:

- In a 2012 systematic review paper, estimated prevalence across countries varies from 1.1% to 45.0% and, when individual country data were pooled, the lowest prevalence of IBS occurred in Southeast Asia (7.0%) and the highest in South America (21.0%).[17]
- In a 2016 review paper, estimated mean prevalence among individual countries ranged from 1.1% in France and Iran to 35.5% in Mexico. Pooled regional prevalence rates were 17.5% in Latin America, 9.6% in Asia, 7.1% in North America/Europe/Australia/New Zealand and 5.8% in the Middle East and Africa.[18]

Following the publication of Rome IV Criteria in 2016, which provide increased sensitivity and specificity for diagnosing IBS, prevalence estimates are thought to reduce overall to around 5.0% (based on a population sample of 5,931).[21] For example, recent data suggest the prevalence in France may actually be nearer 5.0% (4.6% men, 5.6% women).[22]

Varying sub-type prevalence estimates

The prevalence of each IBS subtype also varies considerably depending on the criteria used for classification. Using predominant stool pattern, the prevalence of IBS across the four subtypes is relatively even, with IBS-M in 24.0%, IBS-D in 23.4%, IBS-C in 22.0% and IBS-U in 22.2% of patients.[17] However, **the World Gastroenterology Organisation reports that up to one-third of cases are IBS-C, up to one-third of cases are IBS-D, and that one-third to one-half of cases are IBS-M**.[23] Large individual studies using Rome III criteria indicate that IBS-M may be more prevalent than IBS-D and IBS-C worldwide.[22,24,25] For example, a community survey of 41,984 individuals, among 5 European countries (France, Germany, Italy, Spain and the UK) reported rates among IBS-diagnosed patients of 53% for IBS-M, 32% for IBS-D and 16% for IBS-C.[26] However, increased use of Rome IV criteria, which has increased specificity for IBS diagnoses, is likely to alter these subtype proportions.[21]

Prevalence rates and undiagnosed IBS

Due to the multi-symptomatic nature of IBS and lack of awareness of diagnostic criteria in clinical practice, a substantial proportion of patients may not receive a formal diagnosis of IBS.[27] In turn this will affect prevalence estimates of clinically diagnosed IBS. It is thought that only 30% of people with symptoms of IBS consult a physician with regards to their IBS symptoms,[16] and only a proportion of those who do consult and meet IBS criteria are given an IBS diagnosis.[28]

Where a diagnosis is given, studies show that this can take an average of four years[29] and patients are often diagnosed on the basis of the most prevalent, or severe, symptom.[21] The length of time to diagnosis also means there is potentially a substantial number of patients within the system who are not currently considered within current IBS prevalence estimates.

IBS affects all ages

IBS occurs in all age groups across the life span, generally appearing in late adolescence/early adulthood, with a peak in the third and fourth decade, and a decline in older years.[30,31,32] **This prevalence is reportedly higher in younger adults,**[16,32,33,34] **mostly affecting people of working age.**[16]

Women report more IBS symptoms than men

In most populations, women report more IBS symptoms than men, with rates in women approximately 1.5- to 3-fold higher than those seen in men.[16,31,35] Internationally, the absolute difference in prevalence between genders is just over 5%, with the prevalence in women at 14.0% vs. 8.9% in men. IBS-C and IBS-D are more common in women and men, respectively.[23,36]

The efficacy and effectiveness of treatments for IBS – no universal treatment pathway*

Owing to the complex, multimodal nature of IBS, there is no recognised standard treatment (Box 3).[37] All patients with IBS have symptoms of abdominal pain and disordered defecation, and treatment often focuses on single symptom management.[32,38] In general, therapy comprises dietary/lifestyle modifications and pharmacological therapy, tailored to an individual's symptoms.[39]

The challenge in treating IBS

There is no single treatment regarded as being universally applicable to the management of IBS and no clear treatment pathway.[23] This is in part due to a general lack of understanding about the cause of IBS[37] and is compounded by: poorly designed studies and ill-defined outcomes,[40] mixed and in many cases weak evidence,[41] inconsistent medical literature regarding IBS therapy, and a significant placebo response rate with short-term trials reporting a 30-80% response.[40] New guidelines, such as those produced by the American College of Gastroenterology,[41] are beginning to recognise the importance of robust evidence to support therapeutic decision-making. Studies providing robust evidence are needed to help guide appropriate prescribing.

Box 3

Dietary interventions – uncertain efficacy

Diet or lifestyle modifications are often advocated as the first step in the management of IBS, but the efficacy of standard dietary measures is uncertain.[39,40] There is some evidence to suggest that a diet low in poorly absorbed carbohydrates (fermentable oligo, di- and monosaccharaides, and polyols; FODMAPs) and a gluten-free diet may be efficacious.[24] However, dietary interventions present many challenges and those with demonstrable benefit can be limited by long-term adherence and risk of nutritional deficiencies.[24] Emerging evidence supports diets for IBS patients that are gluten free and low FODMAPs.[1] Probiotics are often used by patients.[42] They have been shown to improve global symptoms, bloating, and flatulence in IBS, however, recommendations regarding individual species, preparations, or strains cannot be made at this time because of insufficient, conflicting and overall low quality of data.[43]

*Some classes of drugs referred to in this report may not be licensed for use in IBS

Pharmacological treatments for the symptoms of IBS

Despite the many symptomatic treatments, a proportion of patients will have exhausted all options. There is frequently insufficient improvement of symptoms with classical treatments, emphasising the need for new and more targeted therapies.[37] Indeed, **less than one-third of IBS patients reported satisfaction with the therapies they currently use to treat their IBS symptoms, with less than half (45%) of patients describing their prescription drugs as "effective"**.[44] Moreover, in many countries, some treatments are not available[47] or do not have approval from local health authorities.[39] As a consequence, medications are often used without a clear indication in IBS but with some indication of efficacy.[39]

Until recently, there have been few treatments that target all key symptoms of IBS and the effectiveness of available treatments is widely variable.[41]

Conventionally available pharmacological treatments have only a short-term response rate[45] and few controlled studies have demonstrated efficacy for conventional therapies in IBS.[41,46] Therapies for IBS-C include soluble fibre and laxatives, and for IBS-D include antidiarrhoeals and bile acid sequestrants; both subtypes may be treated with antispasmodics and antidepressants.[46,47] Osmotic laxatives have been shown to be effective for relieving constipation associated with IBS, but no more effective than placebo for reducing abdominal pain, bloating, or other symptoms associated with IBS.[47] Meanwhile, antidiarrhoeals might reduce the frequency of stools, but do not affect the overall symptoms of IBS[40] and some studies have shown that use of antidiarrhoeals can in fact increase certain IBS symptoms such as pain.[47]

Selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs), not all with marketing authorisation for IBS,[39] have been shown to provide global relief of IBS gut symptoms compared with placebo.[37,41] However, long term-efficacy is uncertain.[37,41] Agents acting on 5-hydroxytryptamine (5-HT) receptors (5-HT3 antagonists, 5-HT4 agonists, and mixed -HT3 antagonists/5-HT4 agonists) have been developed, but the possibility of severe and/or serious adverse events (e.g. severe constipation, ischaemic colitis, and cardiovascular events) led to some of these agents being permanently withdrawn, or available only with restricted access and risk management programmes.[37]

Prosecretory agents[41] and agents acting on opioid receptors[48] may be better tolerated. The National Institute for Health and Care Excellence (NICE) 2008, IBS in adults: diagnosis and management clinical guideline, recommends particular treatments, assuming that the choice of single or combination medication is determined by the predominant symptom(s) (Box 4).[39]

Predominant symptom-based treatment of IBS[37,39]

- Consider antispasmodics alongside dietary and lifestyle advice
- Consider laxatives for treatment of constipation
- Consider prosecretory agents (if different classes of laxatives have not helped and the patient has had constipation for at least one year)
- Consider tricyclic antidepressants (if laxatives, prosecretory agents, and antispasmodics have not helped)
- Consider SSRIs if TCAs are ineffective

Box 4

Source: *National Institute for Health and Care Excellence 2008b*

Psychological therapies for IBS

Since many patients with IBS also suffer with anxiety and depression,[49] psychological therapies (particularly cognitive behavioural therapy, hypnotherapy, multicomponent psychological therapy, and dynamic psychotherapy) may be an effective management option in some patients.[37,43] However, lack of availability of skilled therapists limits the use of psychological therapies and such therapies are time consuming, difficult to organise, often not reimbursed, and may not be acceptable to all patients.[1,43,45]

A Low Standard of Care in IBS

The availability of a range of treatments with varying effectiveness means that the standard of care in IBS has remained low.[37] There is no gold standard for the treatment of IBS, meaning that when new therapies are tested, they are usually compared with placebo. At present, no drug has been shown to alter the clinical course of IBS, and most of the treatments available currently have only a modest effect on symptom improvement, with their efficacy in the longer term remaining unknown. There is therefore a clear need for further research into potential novel treatments for this condition.[37]

Box 5

IBS: BURDEN ON HEALTHCARE SYSTEMS

- It may take many years for a patient to be formally diagnosed with IBS.[29] During this time, many people with IBS will have repeated visits to healthcare services in primary and secondary care.
- IBS puts considerable strain on healthcare resources, incurring a significant financial burden – IBS accounts for up to 50% of gastroenterology consultations.[52]
- Greater severity of IBS symptoms results in higher use of more costly healthcare resources: the onset of severe symptoms is often associated with referral to a specialist, patients with symptoms of moderate severity consult a general practitioner (GP) and patients with mild symptoms generally do not seek healthcare support.
- Calculations of the level of healthcare resource utilisation and financial burden of IBS are likely to be under-estimated due to under-diagnosis.

This summary reflects the consensus opinion of the Steering Committee

DIRECT COSTS AND RESOURCE IMPACT

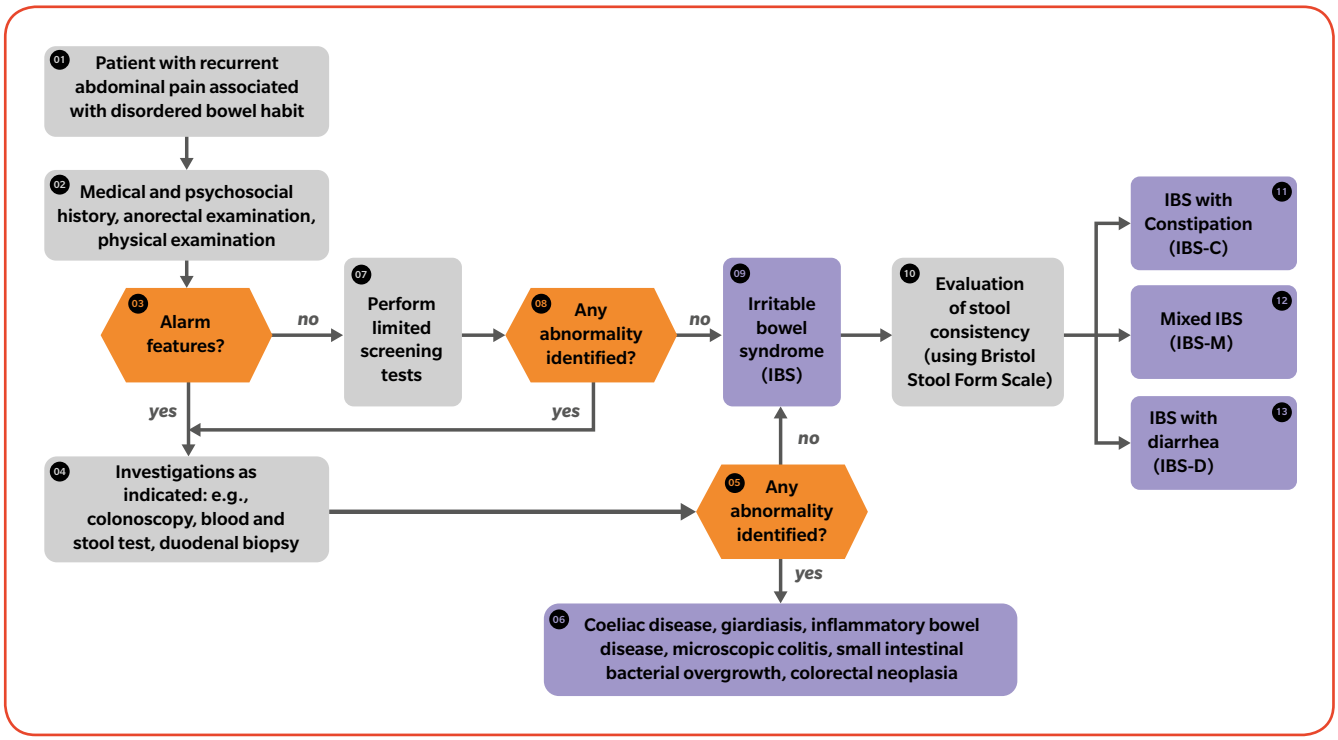
Healthcare resource utilisation: physician visits – primary and secondary care

Adult patients presenting to their GP with lower gastrointestinal tract disorders account for one in 20 of all general practice consultations, with functional disorders, such as IBS, being most prevalent.[28] **It is estimated that between 33-50% of people who have symptoms suggesting IBS will seek medical advice and those who do consult a physician tend to consult regularly.**[50] However, IBS patients do not always consult a physician and a substantial proportion meeting IBS criteria may not be diagnosed with IBS.[27]

Overall, primary care visits account for up to 30% of the total direct healthcare costs for patients with IBS.[50] In the UK, people with IBS will consult with their primary care physician at rates of 8.1 to 10.7 times per year during the three years prior to and after their first gastroenterology appointment.[51] This compares with a reported average of two to three visits per year in North America.[50] IBS is a common reason for consulting a gastroenterologist, accounting for up to 50% of such consultations.[52] In the UK specifically, 29% of IBS cases are referred to a secondary care specialist and the majority are returned to primary care for long-term management.[28]

In 2010, the Rome Foundation formulated a diagnostic algorithm for IBS (Figure 2).[53] The algorithm is used for patients who present with recurrent abdominal pain/discomfort with disordered bowel function. A diagnosis of IBS can be made if the patient's symptoms fulfil Rome IV criteria for IBS, there are no red flags, and the results of the screening investigations are negative.[7,53]

Figure 2. Diagnostic algorithm for IBS[7, 53]



Source: *adapted from Spiller & Thompson 2010*

Impact on health systems prior to diagnosis

There is a lack of information on healthcare resource utilisation before diagnosis. **A formal diagnosis of IBS is generally associated with increases in the number of consultations and home visits in primary and secondary care.**[54] However, a UK study found that in the year prior to or after their index episode of IBS, 3.8% of patients had a gastrointestinal secondary care referral.[55] In the European National Health and Wellness study, an Internet survey (n=41,984) of a population sample of adults aged ≥18 years (5EU: France, Germany, Italy, Spain and the UK), higher proportions of patients with IBS were found to seek consultations with GPs and HCPs than people without an IBS diagnosis.[26] Notably, the mean number of visits to a clinician, the proportion visiting an emergency room (ER), and the proportion hospitalised was approximately ≥1.5-fold higher among survey participants with a diagnosis for IBS than controls without a diagnosis (Table 3).[26]

Moreover, since visits to any healthcare provider have been shown to be significantly greater in patients with diagnosed IBS-D compared with undiagnosed controls,[56] this may be the case across all subtypes.

Table 3. Impact of IBS on consultations and hospitalisation in the 5EU population[26]

Resources over the past 6 months	Total 5EU adult population N = 62,000	Not diagnosed with IBS N = 59,155	Diagnosed with IBS-C N = 450	Diagnosed with IBS-D N = 859	Diagnosed with IBS-M N = 1,536
Visited GP, %	65	65	81	78	84
Visited any HCP, %	82	81	95	93	94
No. visits, mean	4.8	4.6	8.6	8.9	9.0
Visited ER, %	12	11	21	18	20
Hospitalised, %	8	8	15	11	13

Healthcare resource utilisation: diagnostic tests

In Europe, 63–84% of IBS patients receive a diagnostic procedure, with half having abdominal ultrasound scans and over a third undergoing colonoscopy.[50] In the UK, gastroscopy, flexible sigmoidoscopy, and colonoscopy are the most common diagnostic procedures reported (estimated rates of 55%, 55%, and 35%, respectively),[57] while in Italy, colonoscopy, ultrasound, and small bowel follow-through are the most common diagnostic procedures reported (50%, 90%, and 35%, respectively).[58] In France, 87% of patients have a colonoscopy.[59] Utilisation of diagnostic tests tends to depend on access to and expertise in the different tests. Reimbursement, which differs significantly between healthcare systems, is also a likely factor in usage.

Healthcare resource utilisation: hospital visits and admissions

Due to its high cost, **in-patient care accounts for 25–30% of total healthcare cost for IBS**.[50] The proportion of patients with IBS receiving emergency care appears to be similar in Europe and North America, ranging from 2% to 5%, while rates of admission to hospital for IBS (0.5–6.5%) are lower in North America than in Europe.[50] **Rates for abdominal surgery also appear to be higher in those with IBS than in those without, with IBS patients receiving twice as many appendectomies or hysterectomies, and two to three times as many cholecystectomies.** [27,60]

Healthcare resource utilisation: therapy for IBS

Patients use a variety of prescription, over-the-counter, and complementary therapies to treat their IBS. **In any one year, it is estimated that between 33% and 91% of patients with IBS receive a prescription for medication.**[50] Moreover, 31% of patients are prescribed NICE-guideline recommended medications for IBS in the year prior to their first episode of IBS.[55]

Cohorts from the Moderate-to-Severe Irritable Bowel Syndrome IBIS-C study[61,62] and from a survey by the French IBS patient organisation (Association pour les Patients Souffrant du Syndrome de l'Intestin Irritable, APSSII)[59] reveal high current medication usage across Europe (Appendix Table A). Among the 112 patients with IBS-C from Italy, 90% of patients took pharmacological medication, and 48% took prescription medicines, while 27% took more than one prescription medicine from two or more drug classes.[62]

Medication usage in the 5EU countries (France, Germany, Italy, Spain and the UK) was similar across the IBS subtypes, demonstrating that under half of patients had used treatment and that, of those who had never been treated, 80% or more had never been recommended any treatment (Table 4).[26]

Table 4. Prescription medication usage among IBS patients in the 5EU countries[26]

	Diagnosed with IBS-C N = 450	Diagnosed with IBS-D N = 859	Diagnosed with IBS-M N = 1,536
Used treatment, %	40	36	38
No treatment, %	60	64	62
Had prior treatment, %	49	44	47
Never treated, %	51	56	54
Doctor recommended treatment, %	18	20	16
Doctor did not recommend treatment, %	82	80	84

Direct costs on patients

Whilst the direct financial costs to patients will be explored in a separate report, it may be noted that these costs are likely to be substantial. In a European study, approximately one-quarter of patients reported using an OTC or herbal product, and 64% of patients with either IBS-C or IBS-D had 'out-of-pocket' expenses of up to £100 per month.[26] Use of complementary and alternative medicine is never reimbursed but in a study of 410 patients diagnosed with IBS, it was reported to be used by 38.4% of patients with IBS, at a median yearly cost of US $240.[63]

Box 6

Total resource allocation of direct costs in Europe

The IBIS-C study shows the resource utilisation across six European countries (France, Germany, Italy, Spain, Sweden, and the UK) in patients with IBS-C (Table 5).[64,65] The mean annual direct cost for moderate-to-severe IBS-C per patient was €1,363.[64] For the German national healthcare system it was €1,423[65] and in Italy it was €937.[66]

Table 5. Percentage of patients in Europe utilising healthcare services (over 6 months for the total, French, and German cohorts, and 12 months for the Italian cohort)[64,65,66]

	Total population N = 525 (%)	French cohort N = 59 (%)	German cohort N = 102 (%)	Italian cohort N = 112 (%)
GP consultation, %	73	76	78.4	58
No. visits, mean	4.9	4.2	nr	6.4
Gastroenterologist consultation, %	89.7	100	69.6	100
No. visits, mean	2.8	2.2	nr	4.0
ER visits/hospitalisation, %	18.1	16.9	18.6	13.4
Stay, mean days	13.8	5.7	nr	17.9
Diagnostic test, %	Nr	nr	66.7	74
Prescription drugs, %	65	51	54.9	41
Non-prescription drugs, %	67	61	69.6	82
Total mean annual cost, %	€4,639	€4,128	€4,581*	€1,761†

Nr, not reported; *Mean direct costs, €1423; mean indirect costs, €2619; mean costs per patient, €539; †Mean direct costs, €937; mean indirect costs, €339; mean costs per patient, €485.[66]

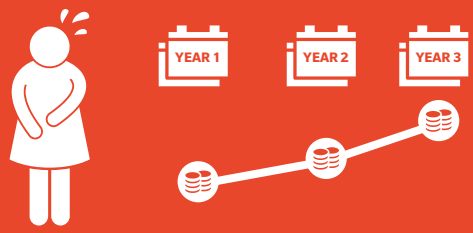
Impact of IBS on direct costs of healthcare

Variations in estimates of overall direct healthcare costs are considerable, with differences between studies.[50] This may be largely due to the different study methodologies and assumptions. Despite such variation making cost estimates difficult to compare, all studies indicate the substantial direct healthcare cost burden of IBS (Appendix Table B).

Box 7

Increased costs following diagnosis

A study from the Netherlands demonstrates how costs can increase following a diagnosis of IBS (Appendix Table C).[54] For the three years after diagnosis compared to the three years before diagnosis, mean total annual healthcare costs increased after the diagnosis by €486 for primary care IBS patients and by €2,328 for secondary care IBS patients. There was a substantial difference between the cost increase in primary and in secondary care patients, mainly explained by the increase in hospital specialists' costs and in medication costs that increased over each of the three years after diagnosis.

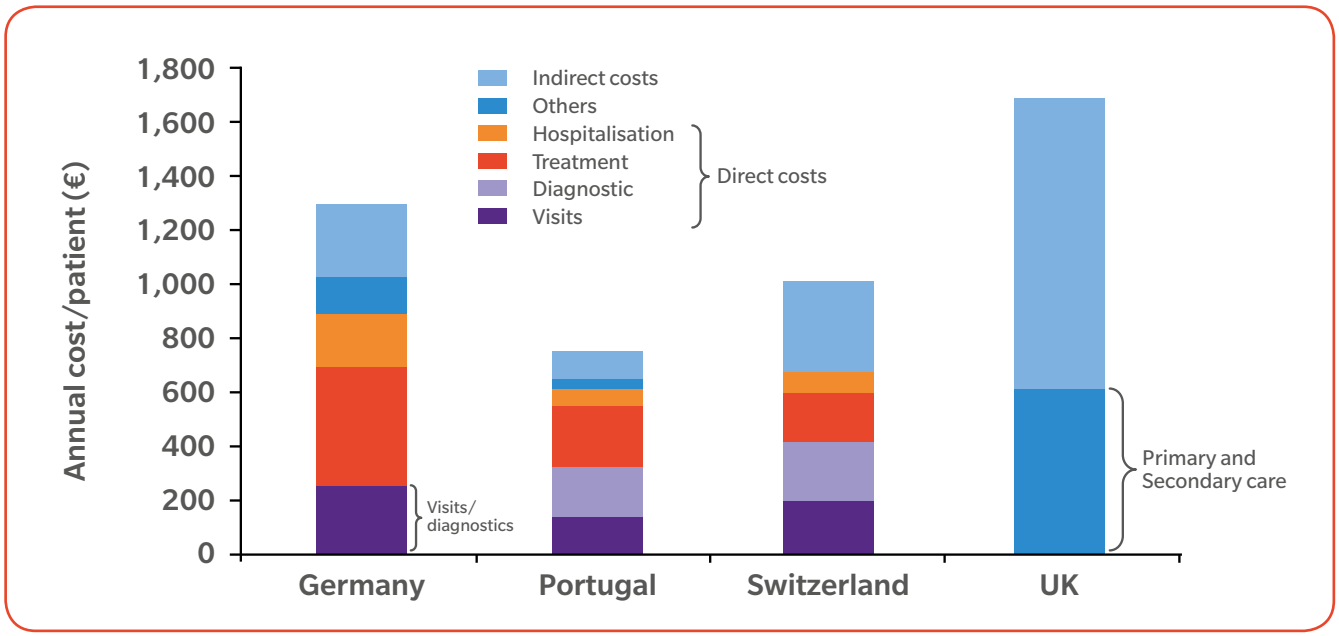


The cost of healthcare in patients with IBS is higher than in individuals without IBS, specifically in the year that they are diagnosed, and this increased cost persists up to three years after diagnosis.[50,54]

A literature review reported that annual cost estimates averaged between £90 and £316 in the UK, between €567 and €862 in France, $259 in Canada, €791 in Germany, and $92 in Iran. National annual projections for the cost to a country of treating patients with IBS ranged from £45.6 - £200 million in the UK, from €3.1 - €4.1 billion in Germany, and $2.94 billion in Iran. Mean cost for Norwegian IBS patients directly related to their IBS over 6 months was NOK 1,049.[50]

A study from 2006[57] indicates the substantial annual impact of medical resource use, and variations in the costs of IBS patient care (Figure 3) with direct costs estimated to be between €700-€1,600 per patient.[38] Similar results were reported in the recent IBS-C study, nearly ten years later, comprising of data from six European countries (France, Germany, Italy, Spain, Sweden and the UK), where an average direct cost of almost €1,363 was reported per patient (including cost of medication, diagnostic tests, hospitalisations, medical consultations with specialists and nurses, and medical consultations with general/family doctors).[64]

Figure 3. Costs per IBS patient per year in four European countries[38]



Source: *Quigley et al 2006*

Cost of individual factors associated with the diagnosis and management of IBS

The NICE 2008 costing report for IBS[31] robustly describes the cost to the UK of individual factors that have a role in the diagnosis and management of IBS (Appendix Table D).[31]

In the UK, outpatient attendances to gastroenterology and colorectal surgery specialties for patients with IBS or IBS-related symptoms have been shown to be increasing, accounting for approximately 7.5% of total outpatient attendances across all specialties, and there was an increase in 15.3% from 2010 to 2013, with a total attributable cost of almost £12 million for 2012–2013. These figures may still be an underestimate as patients coming from primary care and into secondary care are often not given a final diagnosis of IBS until a number of investigations are carried out.[67] The total in-patient cost of those with diagnosed IBS and those coded as having IBS-related symptoms (but without a formal IBS diagnosis), is estimated at around £96 million.[67] According to an analysis of NHS prescribing data (PACT) collected between 1 April 2012 and 31 March 2013, the total costs of laxatives and antispasmodics, treatments that are commonly prescribed by GPs to treat IBS, were around £45 million and £25.5 million, respectively.[67] These are treatments that are commonly used to treat IBS.[47]

The challenges of coding

It is difficult to measure absolute costs attributable to IBS in database type studies simply because IBS is not often clearly coded. This is in part due to poor diagnostic knowledge by healthcare practitioners, or, for example, there is no clinical code for IBS-C in the UK.[67] Therefore, the absolute costs of IBS can only be seen where a code is applied i.e. because the patient has received a formal diagnosis; but as IBS remains under-diagnosed, figures are likely to be underestimated. Whilst it is unclear whether patients suffering from IBS related symptoms are in actual fact suffering from IBS, these data imply a need for more work to be done to determine the true cost of IBS.[67]

Box 8

The cost of inefficient diagnosis

A Danish study suggested that adherence to current guidelines for diagnosing IBS confers a cost saving without detriment to the patient.[68] This primary care study compared a diagnosis of exclusion with a positive diagnosis following clinical guidelines.[68] The total cost of the minimum number of investigations undertaken for a diagnosis of exclusion was $913.59 compared with $50.11 for a positive diagnosis. During the following year, the median total cost of care per patient was similar at $127 and $112, respectively (n=302).[68]

Box 9

Specialty IBS services: a case study

Managing patients via specialty IBS services could drive health cost efficiencies. One example of how a specialty approach may potentially deliver efficiencies is the 'Innovating cost effective management for Irritable Bowel Syndrome (IBS) across Somerset: The Case for Change', run by the Somerset Gastroenterology Flexible Healthcare Team in the UK.[69,70] This multidisciplinary gastroenterology clinical team was created to establish effective IBS diagnosis and treatment pathways for GPs county-wide. Within the first year of operation, the initiative led to appreciable reductions in secondary care referrals. Specialist community dietetics services provide an individualised diet and lifestyle approach to symptom management, with 74% of patients reporting an increased QoL.[69,70]

Box 10

Disease severity

Consultations, diagnostic tests, medication, emergency department visits, and hospital admissions all impact on the direct cost of IBS healthcare. Foremost is the severity of IBS symptoms as a driver of healthcare resource use among patients with IBS. Patients with mild symptoms generally do not seek healthcare. Patients with moderate symptoms consult a GP, while the onset of severe symptoms is often associated with referral to a specialist.[15] Patients classified with severe symptoms visit healthcare services over five times per year when compared to those with mild symptoms who will attend up to once per year.[15]

Box 11

The impact of symptoms

The type of IBS symptom can also affect resource use. In a retrospective, cross-sectional study of patients with physician-diagnosed IBS in France,[71] physician consultations were frequent for pain (66%) and diarrhoea (61%), and abdominal pain was cited as the cause for 45% of IBS-related hospitalisations. Symptoms associated with the highest prescription use were abdominal pain/discomfort (72%), bloating (58%), and diarrhoea (32%). Moreover, the duration of an IBS episode may drive patients to seek medical attention, and these may last from a few days to six months (median three days).[72]

Box 12

Patient satisfaction

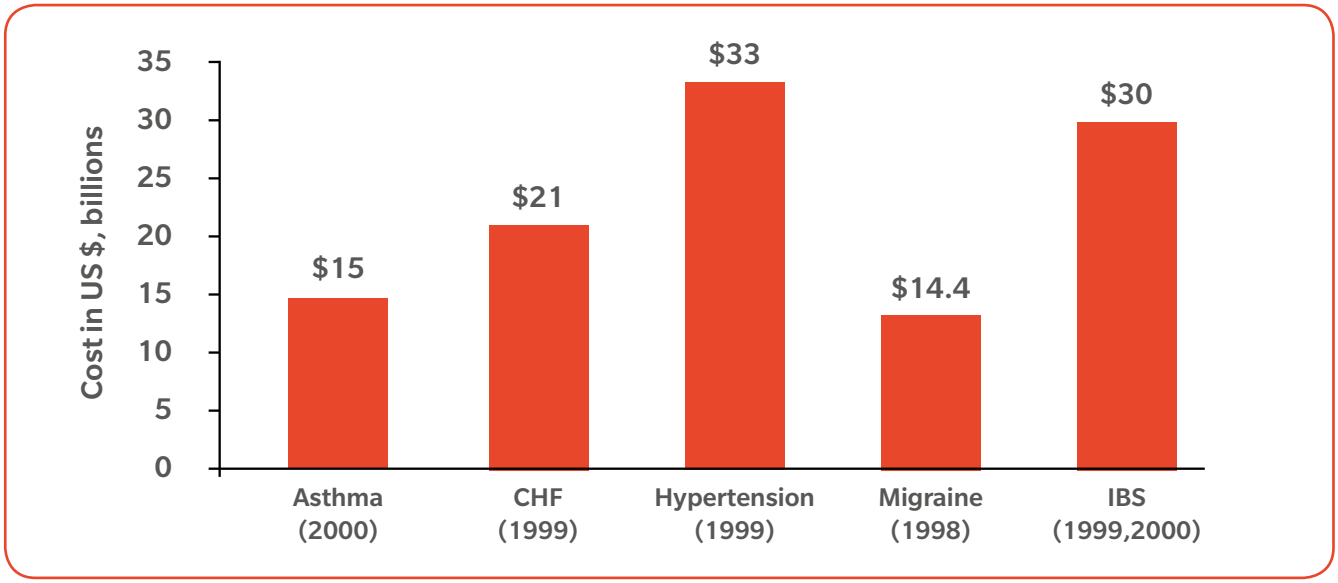
Importantly, for IBS the relationship between patient and HCP is central to a patient's experience and therefore, the patient pathway. Patient satisfaction with their disease management, facilitated by positive doctor-patient communications, may positively impact healthcare resource utilisation by enabling patients to be diagnosed and treated more effectively.[49]

Box 13

Direct costs of IBS compared to other medical conditions

Analyses comparing the cost of IBS with other long-term diseases are limited in number. However, putting the cost of IBS in perspective with other long-term diseases with a similar prevalence to IBS, **it is estimated that the total cost (direct and indirect) of IBS is comparable to that of asthma, migraine, hypertension and congestive heart failure** (Figure 4).[72]

Figure 4. Total costs of IBS compared to other long-term conditions in the US



Source: *Cash et al 2005b*

IBS: BURDEN ON SOCIETY

- The high prevalence of IBS among adults of working age can result in substantial indirect costs to society.
- The multiple symptoms experienced by patients with IBS can compromise their ability to work; this loss of productivity in the workplace can be categorised into absenteeism (missed days from work) and presenteeism (decreased work productivity).[96]
- The impact of IBS on absenteeism has been shown to be extensive, particularly in more severe cases, with people with IBS twice as likely to take time off work than those without IBS.[26] Studies show that greater IBS symptom severity leads to lower productivity. Presenteeism is difficult to capture and is considered to be under-represented.
- Improved understanding of the impact of IBS on a patient's working life could help clinicians and commissioners to appreciate the impact of IBS both on society and the wider economy.

This summary reflects the consensus opinion of the Steering Committee

Impact of IBS on work productivity

The effects on industry from absenteeism or presenteeism may be particularly important in disorders such as IBS that have a high burden of morbidity.[73] IBS patients generate significant indirect costs as a consequence of both missed work and impaired work performance while on the job.[74]

Individuals with IBS are twice as likely to take time off work as their colleagues without IBS,[26] with high rates of absenteeism, presenteeism and impairment in performing daily activity regardless of IBS subtype (Table 6).[26,75] [Addendum A2][75] Similarly, studies have shown work productivity may be reduced by 1.7-fold in patients with IBS vs. individuals without an IBS diagnosis.

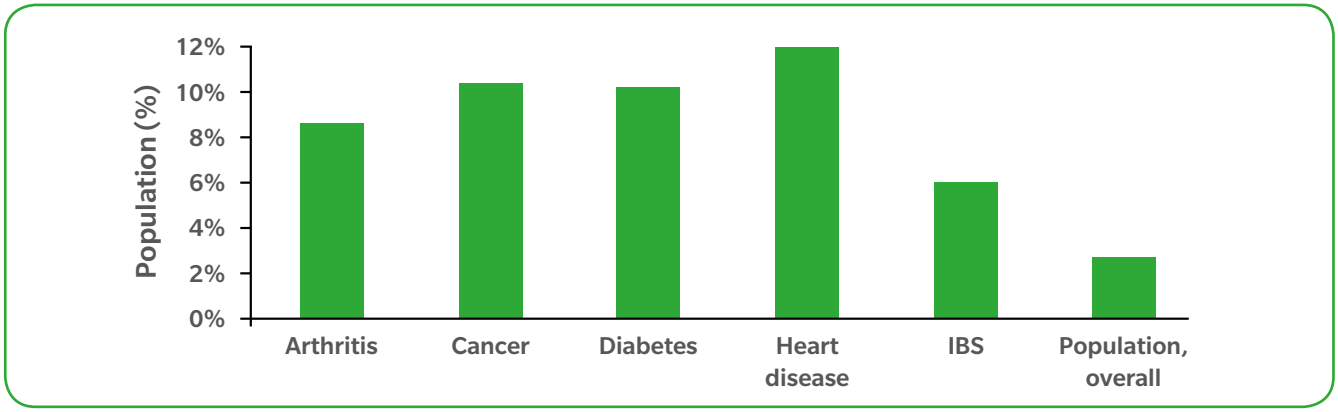
Table 6. Impact of IBS on work productivity and activity impairment in the 5EU population

WPAI	Total 5EU adult population N = 62,000	Not diagnosed with IBS N = 59,155	Diagnosed with IBS-C N = 450	Diagnosed with IBS-D N = 859	Diagnosed with IBS-M N = 1,536
Employed full time, %	39	39	29	33	30
Absenteeism*, mean %	5.5	5.3	11.8	10.1	8.8
Presenteeism*, mean %	16.5	16.2	26.9	25.7	25.4
Work productivity loss*, mean %	19.9	19.6	33.3	31.4	30.5
Activity impairment	25.2	24.5	40.1	37.8	43.7

WPAI, work productivity and activity impairment score; *differing base size.
Source: Data on File[26]

Despite the impact of IBS symptoms on the working population, **a survey of 1,597 IBS sufferers reported that in only 60% of cases employers accept these symptoms as a valid reason for absence**.[76] Indeed, a Canadian Community Health Survey found that IBS prevented twice as many people from working compared to the general population, although the impact of some other conditions such as arthritis and heart disease was greater (Figure 5).[32] However, as evaluated using Work Productivity and Activity Impairment (WPAI) scores, time off work and work impairment for IBS, particularly when severe, is greater than for asthma and social phobia.[72]

Figure 5. People in Canada permanently unable to work due to chronic illness

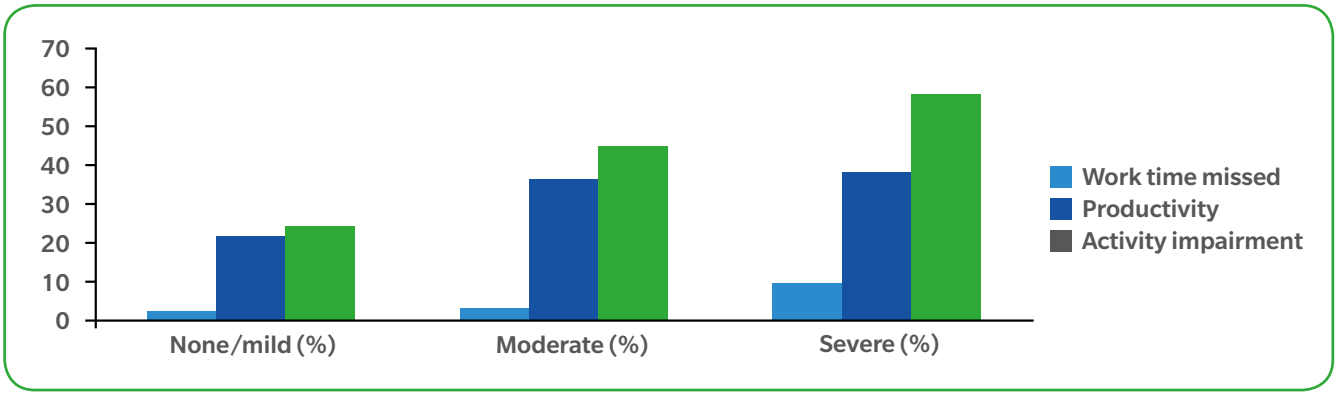


Source: *Fedorak et al 2012*

IBS severity and impact on productivity

In a validation study of the WPAI-IBS, **symptom severity level has been shown to be a significant predictor of the proportion of work and activity impairment**, and overall work impairment (p=0.04 to p<0.0001), with missed work time affected substantially (p=0.06; Figure 6).[77]

Figure 6. Relationship between symptom severity and work and activity impairment



Source: *Reilly et al 2004*

Impact of IBS at work – absenteeism

Across Europe, between 15% and 50% of people with IBS require time off work due to their IBS symptoms,[50] and in a community survey of 41,984 individuals, this amounted to almost twice as many days per year as non-sufferers (5.5 days vs. non-sufferers, 3.1 days).[27]

A systematic review of 24 publications from 1991-2003 for the UK and US concluded that the average number of days off work per year because of IBS was between 8.5 and 21.6.[78]

Studies indicate that approximately a quarter of patients each year are absent from work for more than three days due to their IBS symptoms and 7% take more than two weeks' time off work.[50] The number of missed work-days is associated with IBS symptom severity, with: patients experiencing very severe symptoms (n=25) taking an average of one day off per month (0.5 missed work-days a fortnight) compared to those with moderate symptoms taking less than half a day off work a month (0.2 missed work-days a fortnight), and those with mild symptoms (n=7) taking no days off a month (0.0 missed work-days a fortnight).[79]

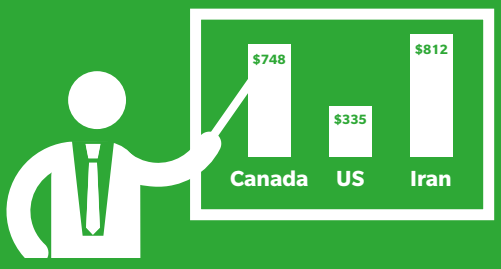
Impact of IBS at work – presenteeism

Presenteeism is a particularly subjective measure as it is assessed by the individual.[50] However, as IBS is thought to be under-diagnosed, where calculations have been made, presenteeism is likely to be under-estimated.

Studies using debriefing questionnaires, retrospective diaries, Work Limitations Questionnaires, and an activity impairment measure (Dimensions of Daily Activities) indicate that **patients with IBS estimate that between 2% and 32% of their working week is lost due to IBS symptoms, and those with mild symptoms lose 7% less time than those with moderate or severe symptoms**.[50] In the US, reported presenteeism was increased by more than 21% by gastrointestinal symptoms consistent with IBS, amounting to a 15% increase over employees without IBS.[80] Presenteeism is also shown to significantly increase with symptom severity.[77]

Cost impact of IBS on society

Differing study methodologies and assumptions have resulted in a wide range of estimates for the indirect costs of IBS (Appendix Table E). An all-country systematic review that evaluated eight studies with indirect cost data for IBS (including work productivity loss, absenteeism, and lost work time) found that from the US perspective, the indirect cost per patient of IBS ranged from US$791 per year for IBS-C (1998; extrapolated to US$1,356 per year in 2012) to US$7,737 for general IBS (study published in 2005; extrapolated to US$9,933 per year in 2012).[81]



Together, absenteeism and presenteeism due to IBS amount to an estimated annual loss per patient of $748 in Canada (1996),[82] US$335 (converted from UK£; prior to 2001),[83] and $812 in Iran (2005).[84]

In 2005, a US company (a banking institution) calculated their total productivity loss attributable to IBS to be $7,737 per patient annually.[80] This study noted that total productivity loss among employees with IBS-C (18.2%) and IBS-D (20.8%) were comparable. The average loss per year was $10,884 and $3,147 for employees with and without IBS, respectively.[80]

In Denmark, the median annual cost through absenteeism is $1,360 and $1,508 per patient for a guideline-recommended diagnosis and a diagnosis of exclusion, respectively.[68]

In a US study that compared adults with IBS-D and without IBS, patients with IBS-D had indirect costs US$2,486 higher per patient per year than for those without (US$7,008 vs. US$4,552).[85]

Impact of standard pharmacological treatment of IBS on workplace productivity

Few studies examine the effect of treatment on work productivity. However, there is evidence to suggest a relationship between pharmacological treatment response in patients with IBS and an associated improvement.[86,87,88,89,90]

IMPACT ON PATIENT QUALITY OF LIFE

- The impact on quality of life for patients with IBS is significant and far-reaching, and similar to other chronic conditions.[72]
- Quality of life (QoL) reductions can be explained by the chronic nature of IBS, the delays in diagnosis, the lack of effective treatment approaches and the stigma associated with IBS.

This summary reflects the consensus opinion of the Steering Committee

Impact of IBS on patient QoL

The spectrum, duration and severity of symptoms can range from inconvenient to incapacitating,[15] and can prevent individuals from participating in everyday activities.[91]

Unsurprisingly, **QoL of patients with IBS decreases with severity.**[59] Bowel/abdominal symptom severity and psychological symptom severity are estimated to have the most important effect on reducing QoL of IBS patients, and persisting together have an additive effect on reducing QoL.[92] Moreover, **patients with IBS report uncertainty and unpredictability, with loss of freedom, spontaneity, social contacts, feelings of fearfulness, shame, and embarrassment**.[93] IBS is also associated with stigma, which may arise from the lack of understanding by family, friends, and physicians of the effects of the disorder on the individual and the reality of their emotions and adaptive behaviours.[93]

While IBS is not known to be associated with the development of serious conditions or mortality, it is disruptive and can have a significant impact on QoL.[28]

European and North American IBS studies have shown relatively consistent reductions in overall mean patient-reported QoL scores (e.g. EQ-5D rating scale) vs. the general population.[50] European research shows patients with IBS also have a lower perception of their own health status than people without IBS.[94] However, the degree of IBS impact on QoL components may differ between IBS populations in different countries. Therefore, the full understanding of the impact of IBS on QoL is difficult to determine. For example, IBS patients from Mexico reported significantly lower scores on 'body image' and 'health worry', and a substantial 'interference with activities' in the overall score compared to patients from North Carolina.[95]

Impact on social functioning and daily activities

There is also a substantial negative impact on social functioning and activities of daily living, affecting personal relationships with family and friends, ability to travel, sleep, and sexual function.[96]

Over half of patients in the Truth in IBS Survey (2004) (n=318) reported that IBS symptoms had a substantial impact on social activities, such as going shopping and eating out, and that it negatively affected their sexual and physical relationships.[96]

A US survey (n=350) found that two-thirds of respondents reported missing an average of over 10 activities or social events over a three-month period due to IBS, equivalent to one activity per week.[96]

QoL and IBS subtypes

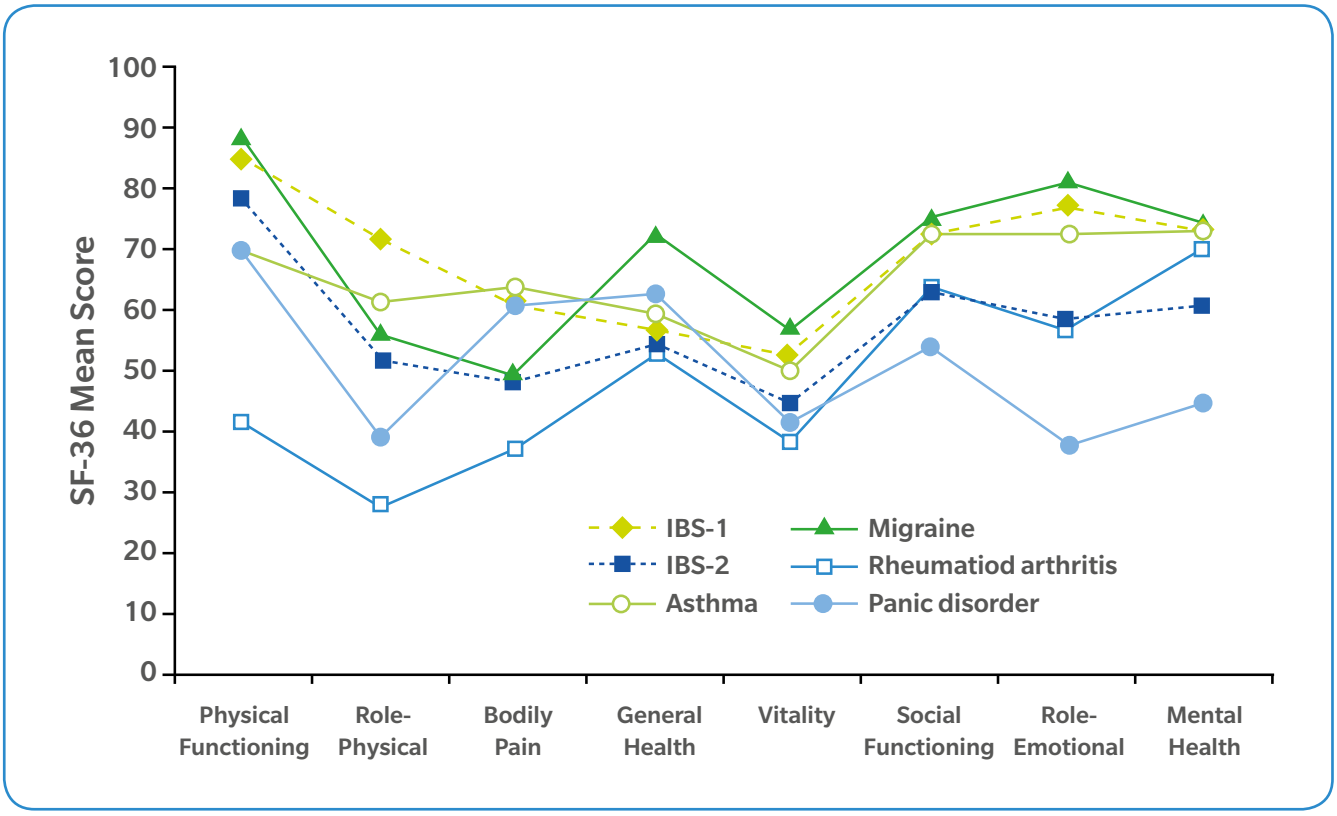
IBS-D patients have been shown to have significantly lower health-related quality of life (HRQoL) compared with controls[97] [Addendum A3] and this may also be true of IBS-C and IBS-M patients.[98] While differences in QoL have been reported between IBS subtypes in some studies, there has been little consistency. A review of QoL in patients with IBS concluded that there does not appear to be a major difference in QoL between IBS subtypes,[99] which may reflect the use of HRQoL questionnaires, such as the Short-Form Health Survey data (SF-36) rather than IBS-specific measures.[98]

The lack of comparative analyses of IBS-specific QoL among IBS subtypes has been addressed in a study of 243 Rome III diagnosed patients that evaluated IBS-specific QoL using the IBS-QoL questionnaire.[98] This study suggested that IBS-D and IBS-M patients have lower IBS-QoL than IBS-C patients (Appendix Table F). Specifically, patients with IBS-D reported more interference with daily activities and food avoidance than patients with IBS-C; while patients with IBS-M reported more interference in daily activities, a lower social reaction score, and a greater impact on relationships vs. IBS-C patients. Between-subtype differences in the remaining subscales – dysphoria, health worries, sexual health, and body image – were not significant. Meanwhile, however, a recent prospective study conducted in France found that whilst overall QoL was impaired for women (FDDQL score), no difference between subtypes was found, but QoL was correlated to severity.[59]

HRQoL in IBS is comparable to other chronic conditions

Patients with severe IBS symptoms are more likely to have poorer HRQoL and higher healthcare resource utilisation than the general population.[15] European and North American IBS studies demonstrate that reduction in overall mean EQ-5D* scores (0.62–0.75) is similar to utility values for other gastrointestinal disorders, such as for inflammatory bowel disease (0.77–0.92), coeliac disease (0.82–0.84), and potentially treatable colorectal cancer (0.76–0.85).[50] However, when comparing IBS with other chronic disorders (i.e. asthma, migraine, rheumatoid arthritis, panic disorder, gastroesophageal reflux disease (GERD), diabetes mellitus and end-stage renal disease) (Figure 7),[100,101] it is worth noting that such disorders will impact to varying extents on the different health domains.

Figure 7. Comparison of HRQoL (SF-36) in patients with IBS and with other gastrointestinal and non-gastrointestinal chronic disorders



IBS-1, a largely untreated community sample of health maintenance organisation members with irritable bowel syndrome (IBS); IBS-2, a sample of patients with IBS recruited through clinics and in the community with constipation predominant.[100]

Source: *Frank et al 2002*

* EQ-5D is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments: http://www.euroqol.org

Beyond the patient – impact of IBS on partners

As recognised in other chronic disorders, **the burden of IBS extends beyond patients to family members, friends and carers, and research shows HRQoL can be lower in these partners than the patients themselves**.[102] Partner burden may also increase indirect costs of IBS healthcare. Using the Zarit Burden Interview (a care-giver self-report measure), IBS partners reported higher burden scores than partners of healthy controls.[102]

When evaluating burden within IBS, **higher IBS illness severity is seen to be associated with higher partner burden**. When it comes to relationships, IBS partners scored their sexual relationship similar to healthy control partners, but about one-third of IBS partners believed that IBS interfered frequently with their sexual relationship. This correlated with the partners' perception that patients use IBS as an excuse to avoid sex.[102]

Effect of IBS treatment on HRQoL

Few clinical trials assess HRQoL, but it appears that patients who have a response to therapy for IBS have an associated improvement in HRQoL.[99] However, an assessment of the risk patients would take to receive an effective IBS treatment is one way to illustrate the impact of IBS on QoL; IBS patients would be willing to give up 15.1 years of their remaining life to achieve perfect health.[103] Moreover, **13.5% would accept at least a 1/1000 chance of death and 10.1% would accept at least a 1/1000 risk of serious or permanent side effects**, with the acceptable degree of risk greatest for patients with severe IBS.[103]

APPENDIX

APPENDIX

Table A. Medication usage in Europe

	France[a] N = 222 (%)		Germany[b] N = 102 (%)	Italy[c] N = 112 (%)
	Past or current	Current		
Prescription medicines		nr	54.9	48.2
Analgesics	nr	nr	11.0	NR
Antidepressants	24.8	17.0	nr	1.8
Antispasmotics	46.4	38.7	15.1	11.6
Laxatives	25.2	17.5	35.6	27.7
Prokinetics	nr		23.3	11.6
Non-prescription medicines	nr	nr	69.6	82.1
Fibre preparations	nr	nr	nr	43.8
Herbal medicines	nr	nr	19.6	19.6
Laxatives	nr	nr	32.4	48.2
Probiotics/prebiotics	38.3	28.1	nr	49.1
Psyllium, Metamucil, Guar gum	nr	nr	nr	21.4
Complementary therapies	nr	nr	27.5	36.6
Acupuncture	24.8	9.6	nr	Nr
Counselling	nr	nr	nr	0.9
Diet	0	46	nr	34.8
Homeopathy	33.8	13.4	nr	Nr
Hypnosis	14.9	1.8	nr	Nr
Osteopathy	27.9	11.0	nr	Nr
Relaxation	30.6	7.8	nr	0.9

Nr, not reported.

Source: a, Sabate et al 2014; b, Layer et al 2015a; c, Stanghellini et al 2015a.

Table B. Studies evaluating the direct costs of IBS

Author	Country	Setting / Population	Perspective Resources	Currency Cost year	Outcome (annual costs)
Talley 1995[I]	USA	*Community* 536 responders to a postal questionnaire sent to randomly selected people in a computerised healthcare database (utilisation and billing)	*Third-party payer* Primary and secondary care costs, out-patient costs, laboratory and radiology costs	US $ 1992	Overall median costs per patient: $742 Extrapolation to US white population cost: $8 billion
Wells 1997[II]	UK	*National Health Service* Aggregate utilisation and costs from general practice database and physician survey data	*National Health Service* Primary care consultations, prescriptions, out-patient attendance, in-patient care	UK £ 1995	Mean total cost per patient: £90 Extrapolated costs for hospital sector:£20 million Extrapolated UK population cost: £45.6 million (0.1% total NHS annual expenditure)
Ricci 2000[III]	USA	*Administrative claims database* 2770 patients from a medical and pharmacy claims database (first IBS diagnostic record of IBS 1 July 1996 to 30 September 1997)	*Third-party payer* Physician visits, in-patient care, out-patient care, hospitalisation, medication	US $ 1997	Mean cost per patient: $7547
Creed 2001[IV]	UK	*Secondary care* 257 patients with severe refractory IBS attending seven gastrointestinal out-patient clinics	*National Health Service* In-patient days, out-patient and day case attendance, A&E visits, GP visits, home visits, nurse consultations, domiciliary care, day rehabilitation centre attendance, alternative therapy use, prescriptions	Calculated in UK £, converted to US $ Date not reported	Mean direct annual healthcare costs: $1743
Akehurst 2002[V]	UK	*Primary care* 161 IBS patients (Rome I criteria)	*National Health Service* Primary care appointment, home visits; prescriptions, hospital out-patient, emergency attendances, in-patient episodes	UK £ 1997/1998	Mean cost per patient: £316.20 (£123/year more than controls) Scaled up population direct cost: £200 million
Muller-Lissner 2002[VI]	Germany	*Primary and secondary care* 200 randomly selected IBS patients with medical record data	*Third-party payer and Societal* Diagnostic procedures, out-patients, prescriptions, other therapy, hospitalisation	€ 2002	Total direct healthcare costs for 1 IBS patient: €791.48 Total direct and indirect cost for sick leave: €994.97 per year
Sandler 2002[VII]	USA	*US population* National survey data for healthcare utilisation	*Societal* In-patient care, out-patient visits, emergency care, procedures, prescriptions	US $ 1998	Total US population societal cost: $1353 million
Leong 2003[VIII]	USA	*Administrative claims database* Employees and retirees of a national company and their spouses and dependents with recorded IBS diagnoses (claims database reimbursements)	*Third-party payer* Physician visits, in-patient care, out-patient care	US $ 1998	Overall total cost per patient: $4527 ($1251 more than controls)
Martin 2003[IX]	USA	*Health Maintenance Organisation* 2,546 patients with IBS (Medicaid Insurance claims database health care utilisation and expenditure)	*Managed care* Prescriptions, physician visit, inpatient, outpatient, other costs	US$ Year not reported	Average Medicaid expenditures per IBS case: $2952 and $5908 in California and North Carolina, respectively
Brun-Strang 2007[X]	France	*Primary and secondary care* 452 patients with IBS (not all with Rome II criteria) in 2001	*National health service* Physician consultations, medical fees, hospitalisations, ambulatory examinations, medication	€ 2000	Mean total direct cost per patient: €756.14

Author	Country	Setting / Population	Perspective Resources	Currency Cost year	Outcome (annual costs)
Roshandel 2007[XI]	Iran	*Secondary care* Patients with IBS (Rome II criteria) in 2001	*Societal* Physician visit, hospitalisation, laboratory tests, imaging studies, and drugs, days off work and days with low functionality at work	US $ 2005	Mean gastrointestinal direct cost per patient: cost: $92.04 Extrapolated population societal cost: $2.94 billion
Nyrop 2007[XII]	USA	*Healthcare Maintenance Organisation* 588 patients with IBS (Rome II criteria) through questionnaire from health maintenance organisation database sampling (administrative claims)	*Managed care* In-patient costs, primary care office visit, GI clinic office visit, mental health office visit, pharmacy, radiology, emergency visits, laboratory costs, other medical costs	US $ 2002	Mean total direct costs per patient: $5049
Johansson 2010[XIII]	Norway	*Primary care* 208 patients identified with IBS through questionnaires using Rome II criteria	*National health service* Consultations (primary/ secondary/ alternative care), hospitalisation, prescribed medication, alternative medication	NOK 2001	Mean overall 6 months IBS related costs: NOK 1,049 Mean overall 6-monthly total costs (IBS and non-IBS care): NOK 15,905 (1,049 + 14,856) (addition of IBS-related and comorbidity-related costs) [median 6-monthly overall IBS-related costs = NOK 0 (0–60, 468)]
Begtrup 2013[XIV]	Denmark	*Primary care* 302 patients with IBS (Rome III criteria)	*National Health Service and societal analysis* GP consultations, specialist consultations, emergency visits, Investigations	US$ 2012	Mean total direct costs over 1 year following diagnosis: - Diagnosed by exclusion: $127/patient - Positive clinical diagnosis: $112 /patient Overall mean total annual societal cost per patient: - Diagnosed by exclusion: $1,614 - Positive diagnosis: $1,776

I Talley NJ, Gabriel SE, Harmsen WS, et al. Medical costs in community subjects with irritable bowel syndrome. Gastroenterology. 1995;109:1736–41.
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V Akehurst RL, Brazier JE, Mathers N, et al. Health-Related Quality of Life and Cost Impact of Irritable Bowel Syndrome in a UK Primary Care Setting. Pharmacoeconomics. 2002;20(7): 455-62.
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VII Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. Gastroenterology. 2002;122:1500-11.
VIII Leong SA, Barghout V, Birnbaum HG, et al. The economic consequences of irritable bowel syndrome: a US employer perspective. Arch Intern Med. 2003;28;163(8): 929-35.
IX Martin BC, Ganguly R, Pannicker S, et al. Utlization patterns and net direct medical cost to Medicaid of irritable bowel syndrome. Curr Med Res Opin. 2003;19:771-80.
X Brun-Strang C, Dapoigny M, Lafuma A, et al. Irritable bowel syndrome in France: quality of life, medical management, and costs: the Encoli study. Eur J Gastroenterol Hepatol. 2007;19:1097–103.
XI Roshandel D, Rezailashkajani M, Shafaee S, et al. A cost analysis of functional bowel disorders in Iran. Int J Colorectal Dis. 2007;22:791-9.
XII Nyrop KA, Palsson OS, Levy RL, et al. Costs of health care for irritable bowel syndrome, chronic constipation, functional diarrhoea and functional abdominal pain. Aliment Pharmacol Ther. 2007;26:237–48.
XIII Johansson PA, Farup PG, Bracco A, et al. How does comorbidity affect cost of health care in patients with irritable bowel syndrome: A cohort study in general practice. BMC Gastroenterol. 2010;10:31.
XIV Begtrup LM, Engsbro AL, Kjeldsen J, et al. A positive diagnostic strategy is noninferior to a strategy of exclusion for patients with irritable bowel syndrome. Clin Gastroenterol Hepatol. 2013;11(8):956-62.

Studies identified in two reviews employing literature searches of current appropriate databases: Nellesen et al 2013 and Canavan et al 2014a.

Table C. Mean healthcare costs per patient per year for primary and secondary care IBS patients and matched controls in the three years before and after the diagnosis of IBS

Mean annual costs (€)	IBS				Control			
	Primary care patients		Secondary care patients		Primary care patients		Secondary care patients	
	Before[a]	After[b]	Before[a]	After[b]	Before[a]	After[b]	Before[a]	After[b]
GP	102	127	122	154	72	70	77	80
Hospital specialists[c]	1111	1409	1303	3173*	792	955	1322	1337
Medication	434	598	579	1005*	457	466	552	560
Total	1648	2134	2003	4331*	1320	1492	1951	1976

a, Mean annual costs three years before diagnosis; b, mean annual costs three years after diagnosis; c, excludes psychiatric care; *p<0.01 for the difference in cost increase between primary and secondary care patients.

Source: *Flik CE, Laan W, Smout AJ, et al. Comparison of medical costs generated by IBS patients in primary and secondary care in the Netherlands. BMC Gastroenterol. 2015;15:168.*

Table D. Individual costs associated with the diagnosis and management of IBS (England 2008)

	Patients[a] (%)	Unit cost (UK £)	Annual number of tests	Annual recurrent cost (UK £000s)
Diagnostic test				
Full blood count	74	3.04	58,200	177
ESR or plasma viscosity	74	3.04	58,200	177
C-reactive protein	43	£1.60	33,800	54
EMA or TTG	18	1.60	14,100	23
Ultrasound	14	77.61	11,000	854
Rigid sigmoidoscopy	10	212.61	7,800	1,671
Flexible sigmoidoscopy	4	365.59	3,100	1,149
Colonoscopy	5	544.45	3,900	2,140
Barium enema	33	178.86	25,900	4,639
Thyroid function test	36	1.60	28,300	45
Faecal ova and parasite test	36	7.49	28,500	212
Faecal occult blood	5	1.60	3,900	6
Hydrogen breath test	6	48.23	4,700	227
Low-dose antidepressants				
TCA[b]	14	21.13	316,200	6,681
SSRI[c]	9	25.73	210,800	5,425
Other				
Referral to a dietician	11	72.88	8,600	630
Psychological interventions	5	290.86	3,900	1,143

EMA, endomysial antibodies; ESR, erythrocyte sedimentation rate; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; TTG, tissue transglutaminase.

a, Based on the proportion of incidence population receiving test/medication/service; b, TCAs based on amitriptyline hydrochloride; c, most commonly prescribed SSRIs for use as a co-analgesic are fluoxetine (60%), citalopram (30%) and sertraline (10%).

Source: *National Institute for Health and Clinical Excellence. National costing report: Irritable bowel syndrome. 2008.*

Table E. Studies evaluating the indirect costs of IBS

Author	Country	Setting / Population	Perspective Resources	Currency Cost year	Outcome (annual costs)
Bentkover 1999[I]	Canada	*Primary and secondary care* 120 medical records of IBS patients followed up for 5 and 2 years in primary and secondary care, respectively	*Societal* Presenteeism and absenteeism	Canadian $ 1996	Mean indirect (workplace) cost per patient: $748.16 Overall societal cost: $1,006.98
Creed 2001[II]	UK (Northern England)	*Secondary care* 257 patients with severe refractory IBS attending seven gastrointestinal out-patient clinics	*National Health Service* Productivity loss	Calculated in UK £, converted to US $ Date not reported	Cost per patient due to lost productivity: $334.50
Sandler 2002[III]	USA	*US population* National survey data for healthcare utilisation	*Societal* Work loss secondary to receiving health care	US $ 1998	Total US population societal cost: $205 million
Leong 2003[IV]	USA	*Administrative claims database* Employees and retirees of a national company and their spouses and dependents with recorded IBS diagnoses (claims database reimbursements)	*Third-party payer* Disability claims and time lost from sporadic sick days and time at medical appointments	US $ 1998	Cost of absenteeism $901 ($373 more than controls)
Dean 2005[V]	USA	*Community* 720 responders to a postal questionnaire sent to all employees (single employer-based sample	*Societal* Work productivity loss due to IBS-attributable symptoms. Productivity expressed as absenteeism, and presenteeism	US$ 2002	Work productivity loss per individual: $7737
Brun-Strang 2007[VI]	France	*Primary and secondary care* 452 patients with IBS (not all with Rome II criteria) in 2001	*National health service and societal* Sick leave days, restriction of activities	€ 2001	Mean days off work: 1.6 days Mean total indirect cost per patient:€37.89 (non-Rome II diagnosed patients incurred higher costs than Rome II diagnosed patients)
Roshandel 2007[VII]	Iran	*Secondary care* Patients with IBS (Rome II criteria) attending a gastroenterology out-patient clinic	*Societal* Days off work or with low functionality	US $ 2005	Productivity loss: $811.85 Extrapolated population societal cost: $2.94 billion

I Bentkover JD, Field C, Greene EM, et al. The economic burden of irritable bowel syndrome in Canada. Can J Gastroenterol. 1999;Suppl A: 89A-96A.

II Creed F, Ratcliffe J, Fernandez L, et al. Health-related quality of life and health care costs in severe, refractory irritable bowel syndrome. Ann Intern Med. 2001;134(9 Pt2): 860-8.

III Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. Gastroenterology. 2002;122(5):1500-11.

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VII Roshandel D, Rezailashkajani M, Shafaee S, D et al. A cost analysis of functional bowel disorders in Iran. Int J Colorectal Dis. 2007;22(9):791-9.

Studies identified in two reviews employing literature searches of current appropriate databases: Nellesen et al 2013 and Canavan et al 2014a.

Table F. IBS-specific quality of life subscale scores among IBS subtypes

IBS-QOL subscale	IBS-C (n = 54)	IBS-D (n = 56)	IBS-M (n = 121)	ANOVA *F*-test p value
Interference with activity	82.3	59.6	61.6	< 0.001[I]
Social reaction	80.0	70.7	66.1	0.008[II]
Food avoidance	61.1	45.0	47.2	0.020[III]
Relationships	84.7	75.4	73.3	0.030[IV]
Dysphoria	69.2	57.1	58.0	0.060
Health worry	64.3	60.9	57.3	0.280
Sexual	73.9	74.6	68.8	0.500
Body Image	69.2	66.0	64.9	0.631
Total	74.5	61.6	63.0	0.010[V]

ANOVA, analysis of variance (comparisons after controlling for age and gender); IBS-C, irritable bowel syndrome-constipation; IBS-D, irritable bowel syndrome-diarrhoea; IBS-M, irritable bowel syndrome-mixed; IBS-QOL: Irritable bowel syndrome specific quality of life.

I Interference with activity: IBS-D vs. IBS-C, p<0.001; IBS-M vs. IBS-C, p < 0.001.
II Social reaction: IBS-M vs. IBS-C, p=0.005.
III Food avoidance: IBS-D vs. IBS-C, p=0.04; IBS-M vs. IBS-C, p=0.04.
IV Relationships: IBS-M vs. IBS-C, p=0.02.
V Overall IBS-QOL scores were significantly different among various IBS-subtypes, p=0.01. IBS-D vs. IBS-C, p=0.03; IBS-M vs. IBS-C, p=0.02.

Source: *Singh P, Staller K, Barshop K, et al. Patients with irritable bowel syndrome have lower specific quality of life than irritable bowel syndrome-constipation. World J Gastroenterol. 2015;21(26):8103-9.*

ADDENDUM

Addendum 1

OP084 - HEALTHCARE RESOURCE UTILISATION AMONG PATIENTS WITH IRRITABLE BOWEL SYNDROME WITH DIARRHOEA IN THE EU5

Catherine Tucker (United Kingdom), Jessica L. Abel (United States of America), Robyn T. Carson (United States of America), Natalia M. Flores (United States of America), Ryan Liebert (United States of America)

- Healthcare resource utilisation associated with IBS-D among a sample of adults in the EU5 (Spain, France, Italy, Germany, UK). Respondents were identified from the 2013 National Health and Wellness Survey.

Table. Impact of IBS-D on healthcare resource utilisation in IBS-D patients from the EU5

Adjusted mean, number in past 6 months (SE)	Diagnosed IBS-D (n=859)	Undiagnosed IBS-D (n=370)	Controls (n=56,932)	p-value		
				Diagnosed vs. controls	Diagnosed vs. undiagnosed	Diagnosed vs. controls
Any provider visits	7.23 (0.31)	5.17 (0.35)	4.14 (0.02)	<0.001	<0.001	0.001
Gastroenterologist visits	0.19 (0.02)	0.01 (0.01)	0.03 (0)	<0.001	<0.001	0.146
GP visits	2.69 (0.12)	2.06 (0.15)	1.70 (0.01)	<0.001	0.001	0.007
Emergency room visits	0.27 (0.04)	0.12 (0.03)	0.17 (0)	0.002	0.012	0.264
Hospitalisations	0.14 (0.03)	0.08 (0.03)	0.11 (0)	0.099	0.148	0.430

All diagnosed vs. undiagnosed comparisons were not significant.

Addendum 2

PO382 - IMPACT OF IRRITABLE BOWEL SYNDROME WITH DIARRHOEA ON WORK PRODUCTIVITIY AND DAILY ACTIVITY AMONG PATIENTS IN THE EU5

Catherine Tucker (United Kingdom), Jessica L. Abel (United States of America), Robyn T. Carson (United States of America), Natalia M. Flores (United States of America), Ryan Liebert (United States of America)

- The impact of IBS-D on work productivity and daily activity impairment in adult IBS-D patients from the EU5 (Spain, France, Italy, Germany, United Kingdom), based on 2013 National Health and Wellness Survey data (859 diagnosed IBS-D; 370 undiagnosed IBS-D; 56,932 controls), demonstrated that patients with IBS-D have significantly greater presenteeism, overall work impairment, and activity impairment, particularly if they are severe cases.

Table. Impact of IBS-D on work productivity and daily activity impairment in IBS-D patients from the EU5

Adjusted mean (SE)	Diagnosed IBS-D (n=859)	Undiagnosed IBS-D (n=370)	Controls (n=56,932)
Absenteeism (%)	6.39 (1.13)^{NS}	6.01 (1.49)^{NS}	4.87 (0.10)
Presenteeism (%)	22.45 (1.63)**	20.31 (2.09)*	15.39 (0.13)
Overall work impairment (%)	26.22 (1.85)**	24.33 (2.41)*	18.57 (0.15)
Activity impairment (%)	31.98 (1.32)**	28.47 (1.80)**	22.38 (0.11)
Work missed annually (days)	15.59 (2.99)^{NS}	11.94 (3.26)^{NS}	11.25 (0.25)

*P=0.007 vs. controls; **P<0.001 vs. controls; NS not significant vs. controls.
All diagnosed vs. undiagnosed comparisons were not significant.

Addendum 3

PO383 - HEALTH-RELATED QUALITY OF LIFE AMONG PATIENTS WITH IRRITABLE BOWEL SYNDROME WITH DIARRHOEA

Catherine Tucker (United Kingdom), Jessica L. Abel (United States of America), Robyn T. Carson (United States of America), Natalia M. Flores (United States of America), Ryan Liebert (United States of America)

- The impact of IBS-D on HRQoL in patients with IBS-D identified from the 2013 National Health and Wellness Survey, conducted in Spain, France, Italy, Germany, and the United Kingdom (EU5), demonstrated that both diagnosed and undiagnosed IBS-D patients had significantly lower HRQoL compared with controls (Table). HRQoL scores were significantly worse for patients with moderate or severe IBS-D than for those with mild IBS-D.

Table. Impact of IBS-D on HRQoL in IBS-D patients from the EU5

Adjusted mean (SE)	Diagnosed IBS-D (n=859)	Undiagnosed IBS-D (n=370)	Controls (n=56,932)	p-value		
				Diagnosed vs. controls	Diagnosed vs. undiagnosed	Undiagnosed vs. controls
MCS	41.98 (0.34)	42.44 (0.52)	46.65 (0.04)	**<0.001**	0.454	**<0.001**
PCS	48.83 (0.27)	50.33 (0.41)	51.52 (0.03)	**<0.001**	**0.002**	**0.004**
SF-6D	0.66 (0.004)	0.67 (0.007)	0.72 (0.001)	**<0.001**	0.277	**<0.001**

MCS, Mental Component Scores; PCS, Physical Component Scores; SF-6D, Short Form Health Survey

A1 Tucker C, Abel JL, Carson RT, et al. OP084 Healthcare resource utilisation among patients with irritable bowel syndrome with diarrhoea in the EU5. Abstract accepted for presentation by congress organisers at the UEGW Congress. 2016;NA:1-3. Available at: https://cslide.ctimeetingtech.com/ueg2016/confcal/tucker [Last accessed October 2016].

A2 Tucker C, Abel JL, Carson RT, et al. PO382 Impact of irritable bowel syndrome with diarrhoea on work productivity and daily activity among patients in the EU5. Abstract accepted for presentation by congress organisers at the UEGW Congress. 2016;NA:1-3. Available at: https://cslide.ctimeetingtech.com/ueg2016/confcal/tucker [Last accessed October 2016].

A3 Tucker C, Abel JL, Carson RT, et al. PO83 Health-related quality of life among patients with irritable bowel syndrome with diarrhoea. Abstract accepted for presentation by congress organisers at the UEGW Congress. 2016;NA:1-3. Available at: https://cslide.ctimeetingtech.com/ueg2016/confcal/tucker [Last accessed October 2016].

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