

A Systematic Review of the Economic and Humanistic Burden of Illness in Irritable Bowel Syndrome and Chronic Constipation

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ABSTRACT

BACKGROUND: Irritable bowel syndrome (IBS) and chronic constipation (CC) are common functional gastrointestinal disorders affecting 14% and 20% of the U.S. population, respectively. Reviews of the evidence on the burden of illness associated with IBS and CC have not been comprehensive in scope and have not provided an assessment of the distribution of health care costs across categories of resource use.

OBJECTIVES: To (a) identify studies from any geographic region or country perspective that measure the economic burden of the disease; (b) analyze the direct (medical, drug, and other components) and indirect costs of illness; and (c) assess published evidence of the humanistic burden as measured by quality of life (QOL).

METHODS: An electronic literature search was conducted using journal databases, including MEDLINE, *The Cochrane Library*, *EconLit*, *CINAHL*, and Digestive Disease Week meeting abstracts. Specific search terms used were “irritable bowel syndrome” and “chronic constipation.” In databases that accommodated Boolean searches, terms related to economic and quality of life outcomes were incorporated. Studies were included if they evaluated patients with an IBS or CC diagnosis and quantitatively measured the economic or humanistic burden of disease. Results were descriptively analyzed.

RESULTS: The search identified a total of 882 unique publications. Thirty-five articles and abstracts met the inclusion criteria. Studies included 1,706 IBS-C, 2,264 IBS-D, 2,892 IBS-A, 15,830 IBS unclassified, and 1,278 CC patients. Nineteen of 35 studies assessed cost-of-illness endpoints, and from the U.S. perspective, the direct cost per-patient for IBS ranged from \$1,562 to \$7,547 per year, while direct costs of CC ranged from \$1,912 to \$7,522 per year. From the U.S. perspective, the indirect costs of IBS ranged from \$791 to \$7,737 per year, and no study assessed the indirect costs of CC. For IBS, data on the distribution of costs attributable to categories of resource use varied widely, particularly outpatient costs (12.7% to >50% of total costs), inpatient costs (6.2% to 40.8%), and pharmacy or drug costs (5.9% to 46.6%). Comparable data on CC were not identified. Nineteen studies of IBS patients measured the humanistic burden of disease; 14 studies utilized SF-36; and within-study domain scores were significantly lower in IBS patients compared with non-IBS controls. Only 1 study of CC patients reported humanistic burden of disease.

CONCLUSIONS: The studies identified in the systematic review varied in the method used to identify patients with IBS and CC. Results were not typically reported by IBS subtype. We observed a large variation in attributable direct and indirect costs and drivers of these costs. Future research should refine burden of illness estimates to subtypes so that estimates associated with IBS-C and CC are differentiated.

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What is already known about this subject

- Irritable bowel syndrome (IBS) and chronic constipation (CC) are 2 of the most common functional gastrointestinal disorders estimated to affect nearly 1 in 5 North Americans.
- It has been estimated that the annual cost of IBS in the United States is between \$1.7 and \$10 billion in direct medical costs, excluding prescription and over-the-counter drugs, and up to \$20 billion in indirect costs.
- Diagnostic criteria for IBS and CC have changed over time and have been applied inconsistently, making the investigation of the burden of illness challenging.

What this study adds

- This systematic assessment of the economic and humanistic burden of illness identified numerous studies documenting burden of illness measured in economic and humanistic terms.
- Direct costs of IBS ranged from \$1,562 to \$7,547 per year, and the indirect costs ranged from \$791 to \$7,737 per year, while the direct costs of CC ranged from \$1,912 to \$7,522 per year. Indirect costs for CC were not identified in this systematic review.
- The distribution health care cost of IBS varied widely, particularly outpatient costs (12.7% to >50% of total costs), inpatient costs (6.2% to 40.8%), and pharmacy or drug costs (5.9% to 46.6%). Only 2 studies reported health care cost of patients with CC. Neither study reported cost by standard categories of service.
- In studies that compared IBS with a non-IBS control population, quality of life (as measured by SF-36) was significantly lower in IBS patients than in controls. Only 1 study of CC patients reported humanistic burden.
- Published estimates have yet to address burden of illness according to disease subtypes.

Irritable bowel syndrome (IBS) and chronic constipation (CC) are common functional gastrointestinal disorders (FGIDs) characterized by abnormalities in motility and visceral hypersensitivity.¹ IBS is defined by the presence of symptoms of abdominal pain or discomfort associated with disturbed defecation,² while chronic or functional constipation is characterized by infrequent bowel movements (BM), hard or lumpy stools, straining, and a sensation of incomplete rectal evacuation.³ IBS is one of the most common FGIDs,⁴ with an

estimated prevalence of 14.1% in a survey of U.S. patients.⁵ IBS affects both men and women, but approximately 60% to 75% of sufferers are women.^{6,7} CC is estimated to affect up to 20% of the North American population.⁸ Although women report CC approximately twice as often as men,⁹ in U.S.-based surveys, CC occurred only moderately more frequently in women, at rates of 56%¹⁰ and 62%.¹¹ In both men and women, the incidence of CC increases with age.¹¹

IBS includes several clinically distinct different subtypes. The Rome III criteria¹ distinguish IBS subtypes by predominant bowel habit disturbance: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), and mixed or alternating bowel pattern with both diarrhea and constipation (IBS-M or IBS-A). Reports on the relative proportions of IBS subtypes range from 5.2% to 66% for IBS-C, 0.8% to 33.9% for IBS-D, and 5.2% to 33.1% for IBS-A.¹² The chronic, episodic nature of IBS and CC and the limited sensitivity and specificity in diagnosis, as well as changes in diagnostic criteria over time, present substantial challenges for clinicians and researchers in characterizing the spectrum of patients' experiences.

A number of studies have sought to measure economic and humanistic burden of illness attributable to IBS and CC. One systematic review published in 2002 assessed the health-related quality of life (HRQOL) burden of IBS,¹³ and a review published in 2003 documented the costs of IBS symptom management, direct costs, and productivity costs.¹⁴ Another review published in 2004 highlighted the considerable economic burden imposed by IBS, with direct medical costs (excluding prescription and over-the-counter drug costs) ranging between \$1.7 billion and \$10 billion and indirect costs reaching \$20 billion.¹⁵ There have been some studies comparing CC treatments, but no systematic reviews or meta-analyses of the burden of CC have been published. Together, these reviews demonstrate the limited scope of recent research undertaken to understand these conditions, in particular studies that have investigated the burden of illness in specific IBS subtypes.

Objectives

The main objectives of this systematic review are as follows: to (a) identify studies from any geographic region or country perspective that measure the economic burden of IBS and CC; (b) analyze the direct (medical, drug, and other components) and indirect costs of illness; and (c) assess published evidence of the humanistic burden of disease as measured by effects on HRQOL in IBS and CC. In particular, the goals were to identify studies that specifically assess the burden of disease in patients with CC or the IBS subtypes IBS-C, IBS-D, and IBS-M or IBS-A, and to describe aspects of the economic or humanistic burden of disease in patients with CC or an IBS subtype that could provide a better understanding of the disorders, their manifestations, and potential implications in managed care settings.

Methods

Literature Search

An electronic literature search was conducted in MEDLINE, MEDLINE In-Process, *The Cochrane Library*, *EconLit*, the *Cumulative Index to Nursing and Allied Health Literature (CINAHL)*, and Digestive Disease Week (DDW) meeting abstracts. There were no date restrictions; however, DDW abstracts were only available for the years 2008-2010. Across all databases searched, common keywords included "irritable bowel syndrome" and "chronic constipation." In addition, other terms may have been used to supplement these keywords, depending on the search capabilities and interface of the database. In databases that accommodated Boolean searches, terms specifically related to economic and quality of life outcomes were added. The MEDLINE search limited results to English language articles. All searches were performed in November 2010.

Study Selection Criteria

Inclusion criteria were (a) patients were specifically described as having an IBS or CC diagnosis, and (b) study quantifiably measured the economic or quality of life (QOL) burden attributable to IBS or CC. Studies were excluded if they assessed the economic or QOL impact of a particular treatment for IBS or CC (studies where impact may be attributable to an intervention rather than to the disease). Case studies and meta-analyses were excluded to minimize the chances of double-counting patients.

Data Abstraction

Studies were classified according to outcomes (i.e., burden of illness related to economics or QOL or both) and condition of interest (IBS, CC, or both). Where information was available, patient counts were further disaggregated by IBS subtype into IBS-C, IBS-D, and IBS-M or IBS-A. For economic outcomes, quantitative values for direct and indirect costs and narrative information on categories of resource use were collected. For QOL outcomes, overall and domain scores from available QOL scales were collected. Information was also collected regarding study design and patient characteristics. Studies were not evaluated for quality.

Statistical Analyses

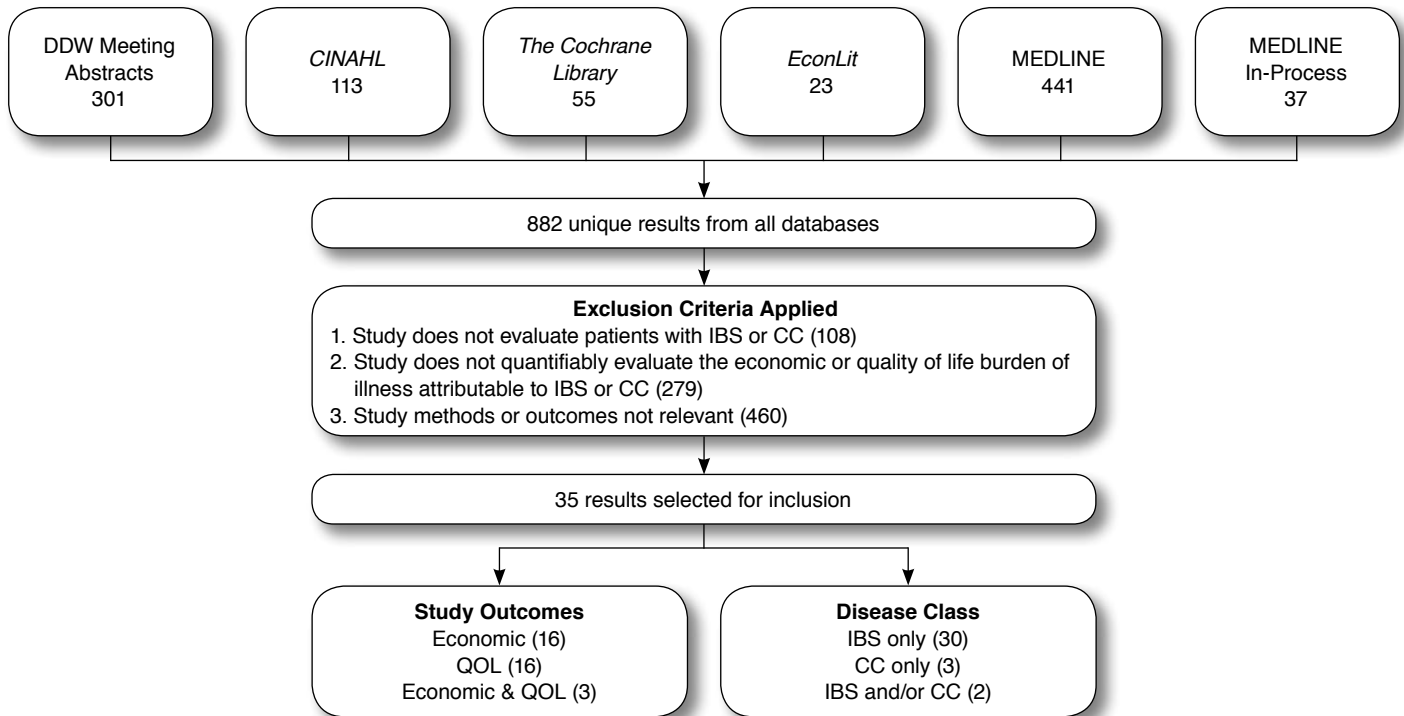
Descriptive analysis was performed for the included studies. Meta-analysis was not performed, since the inclusion criteria were not specific enough to control for variability in study design and patient characteristics.

Results

Characteristics of the Selected Studies

The search identified a total of 882 unique publications from all the databases; 35 articles and abstracts met the selection criteria and were included in the data-abstraction step (Figure 1).

FIGURE 1 Study Selection Schema



CC = chronic constipation; CINAHL = Cumulative Index to Nursing and Allied Health Literature; DDW = Digestive Disease Week; IBS = irritable bowel syndrome; QOL = quality of life.

The studies were classified according to study outcomes (economic, humanistic or both) and disease of interest (IBS, CC, or both). Of the 35 studies, 16 evaluated economic burden of disease or humanistic burden of disease only, and 3 assessed economic and humanistic burden of disease. By disease of interest, 30 studies investigated IBS only, 3 studied CC only, and 2 included patients with either IBS or CC. The criteria used for diagnosis of IBS, IBS-C, and CC varied widely (Figure 1). These 35 studies included a total of 63,816 patients with various digestive diseases and related conditions. The IBS and CC population included the following: 1,706 IBS-C, 2,264 IBS-D, 2,892 IBS-A, 15,830 IBS unclassified, and 1,278 CC patients.

The majority of the studies were conducted in the United States (n=17); the remaining studies were conducted in France (n=5); the United Kingdom (n=3); Canada, Korea, the Netherlands (n=2 each); and China, Germany, and Norway or Sweden (n=1 each). Selected characteristics of the 35 studies are presented in Table 1.

Studies Assessing Cost-of-Illness Endpoints

Nineteen of the 35 studies identified reported cost-of-illness outcomes. Eleven studies investigated the direct costs of IBS and/or CC, 1 investigated only the indirect costs, and 7 inves-

tigated both the direct and indirect costs. The majority of the cost studies were from the U.S. perspective (n=12); other countries studied were France and United Kingdom (n=2 each), Canada, Germany, and Norway (n=1 each). Fifteen of the economic studies were of patients with IBS only; 2 studies were of patients with CC only; and 2 studies included both IBS and CC patients. Only 2 studies specifically examined costs of patients with IBS-C.^{16,17}

Categories of resource use and associated direct and indirect costs from these studies are presented in Table 2. From the U.S. perspective, the direct cost per-patient of IBS ranged from \$1,562 per year (2002 U.S. dollars [USD]; \$2,269 per year in 2012 USD) to \$7,547 per year (year not reported [NR], published in 2000; \$12,007 per year in 2012 USD). The direct costs of CC ranged from \$1,912 per year (2002 USD; \$2,778 per year in 2012 USD) to \$7,522 per year (2002-2003 USD; \$11,967 per year in 2012 USD). Direct costs for IBS included those associated with medications, hospitalizations, outpatient services, emergency department visits, and laboratory tests. For IBS, the reported share of costs across categories of health care resource use varied widely, particularly outpatient costs (12.7% to >50% of total costs), inpatient costs (6.2% to 40.8%), and pharmacy or drug costs (5.9% to 46.6%).

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TABLE 1 Overview of Selected Studies

Reference	Population	Comparison Population	Country, Perspective	Number of Patients				
				IBS Total	IBS-C	IBS-D	IBS-A	CC
Prospective cohort study (IBS only)								
Johansson 2010 ³⁰	Sample of patients with IBS in Norwegian general practice	None	Norway	164				
Case-control study (IBS only)								
Park 2009 ³³	Patients aged 18-75, symptoms consistent with Rome II criteria, absence of abnormal colonoscopic exam results	Controls from the general population	Korea	664	168	368	128	
Faresjö 2007 ³⁴	Aged 18-65 with first diagnosis of IBS between 1997-2001	None	Sweden	347				
Martin 2003 ²⁶	Patients > 18 years with ICD-9-CM code of irritable colon	Control subjects with no claims for irritable colon, abdominal pain, or constipation	United States, Medicaid	2,546				
Akehurst 2002 ²³	Patients meeting Rome I criteria for IBS from 6 GP practices in the United Kingdom	Controls matched for age, sex, social characteristics	United Kingdom	161				
Patel 2002 ²⁸	Patients with IBS; Medicare and Medicaid HMO patients excluded [ACS]	Controls matched for gender, age, and number of comorbidities	United States	501				
Retrospective study (IBS only)								
Brun-Strang 2007 ³²	Patients meeting or not meeting Rome II criteria	None	France	452	121	120		
ten Berg 2006 ³⁵	Patients using mebeverine, a drug indicated for IBS [ACS]	Sample of the Dutch population, U.S. population of IBS patients	Netherlands	136				
Leong 2003 ¹⁷	Patients with IBS and a predominance of constipation [ACS]	Matched controls based on age, sex, employment, job classification, health plan, and ZIP code	United States	1,509				
Müller-Lissner 2002 ³⁶	Convenience sample of IBS patients	None	Germany	200				
Levy 2001 ²⁴	Patients > 18 years with a diagnosis of IBS or irritable colon [ACS]	Matched controls based on birth year and sex, who did not have IBD, GERD, or IBS	United States	3,153				
Ricci 2000 ²⁰	Patients presenting with a primary diagnosis of irritable colon (ICD-9-CM 564.1) [ACS]	Cohort of asthma patients matched by age and gender	United States	2,770				
Bentkover 1999 ³⁷	Patients >20 years with IBS	None	Canada	118				
Cross-sectional survey (IBS only)								
Graham 2010 ³⁸	Women veterans with IBS seeking care at a VA clinic	Female veterans without IBS	United States	113				
Thijssen 2010 ³⁹	Patients aged 18-65 with IBS according to Rome II criteria	None	Netherlands	268				
Drossman 2009 ⁴⁰	Patients >18 years, diagnosed with IBS by a physician	None	United States	1,966	191	576	1,199	
Jeong 2008 ⁴¹	Patients with chronic GI symptoms according to Rome II	General Korean population	Korea	31	12	13	6	
Lee 2008 ⁴²	Patients aged > 18 with lower functional abdominal symptoms	None	United Kingdom	420				
Amouretti 2006 ⁴³	Adults > 18 years with IBS based on Manning criteria, Rome I, or Rome II; France	Controls representative of French population	France	253	65	72	116	
Pare 2006 ⁴⁴	Patients with abdominal pain and at least 1 symptom of bloating, constipation, or alternating constipation and diarrhea	None	Canada	1,555	457	196	433	
Dean 2005 ²²	Single employer-based sample, IBS based on Rome II criteria	None	United States	720				
Coffin 2004 ⁴⁵	Adults > 18 years with IBS, attending metropolitan outpatient clinic	None	France	858	319	320	218	
Le Pen 2004 ⁴⁶	Patients aged > 18 with IBS according to Manning or Rome I or II criteria	None	France	253	65	72	116	

TABLE 1 Overview of Selected Studies (continued)

Reference	Population	Comparison Population	Country, Perspective	Number of Patients				
				IBS Total	IBS-C	IBS-D	IBS-A	CC
Si 2004 ⁴⁷	Consecutively enrolled IBS patients meeting Rome II criteria	None	China	662	108	258	174	
Longstreth 2003 ²⁵	Patients > 18 years who had undergone flexible sigmoidoscopy in the year 2000	Patients without IBS	United States	578				
Pace 2003 ⁴⁸	Patients > 18 years with ulcerative colitis, Crohn's disease, or IBS	Controls matched on sex and age	United States	85				
Sandler 2002 ⁴⁹	Patients with selected digestive diseases drawn from national databases	None	United States	15,396,000 (prevalence 1998)				
Creed 2001 ⁵⁰	Adults 18-65 years, meeting Rome criteria, symptom duration > 6 months, failure to respond to usual medical treatment, VAS > 59	None	United Kingdom	257	59	74	124	
Lee 2001 ⁵¹	Consecutively screened IBS patients	None	United States	714	141	195	378	
Gralnek 2000 ⁵²	Aged > 18, ambulatory, seen at UCLA clinic	U.S. general population, published data	United States	877				
Retrospective study (IBS or CC)								
Ahn 2008 ¹⁶	Sample of Medi-Cal population with IBS+C using combination of ICD-9-CM codes for constipation and IBS and claims for constipation-related prescriptions from 1995 to 2003 [ACS]	None	United States		NR			NR
Nyrop 2007 ²¹	Patients aged 18-75 years, enrolled in HMO for at least 1 year, no diagnosis of ulcerative colitis or Crohn's disease [ACS]	None	United States, HMO	558				203
Prospective study (CC only)								
Pekmezaris 2002 ³¹	CC patients in a large metropolitan skilled nursing facility	None	United States					31
Case-control study (CC only)								
Nguyen 2008 ²⁷	Patients with a clinical diagnosis of constipation (ICD-9-CM 564.0X) in the last year [ACS]	Patients without a clinical diagnosis of constipation for the previous 5 years	United States, HMO					936
Cross-sectional survey (CC only)								
Damon 2004 ¹⁸	Patients with chronic constipation or fecal incontinence referred to a hospital for anorectal manometry	None	France					78

ACS = administrative claims study; CC = chronic constipation; GERD = gastroesophageal reflux disease; GI = gastrointestinal; GP = general practitioner; HMO = health maintenance organization; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; IBS-A = irritable bowel syndrome with alternating constipation and diarrhea; IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; NR = not reported; UCLA = University of California, Los Angeles; VA = Veterans Administration; VAS = visual analog scale.

Nine studies were retrospective analyses of administrative claims databases, and in the remaining 7 studies, none analyzed cost outcomes by IBS subtypes. In 1 study using administrative claims data, 17 patients with IBS with constipation were identified using an algorithm that combined primary and secondary diagnosis codes (using *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM]) for irritable colon, abdominal pain, and constipation. This study estimated the annual direct cost of IBS to be \$3,736 (1998 USD). In a second study, 16 patients with constipation (C) or IBS co-occurring with constipation (termed IBS+C) were identified from the California Medicaid population using a

combination of ICD-9-CM codes for constipation and IBS and claims for constipation-related prescriptions. Per-patient total costs were \$1,912 for C and \$1,562 for IBS+C (2002 USD). All costs for all categories studied were similar between the C and IBS+C groups over the 6-year study period ($P > 0.05$).

From the U.S. perspective, the indirect cost per patient of IBS ranged from \$791 per year for IBS-C (1998 USD; \$1,356 per year in 2012 USD) to \$7,737 for general IBS (year NR, study published in 2005; \$9,933 per year in 2012 USD). Indirect cost was estimated as lost productivity due to IBS symptoms or health care-seeking behaviors. No studies assessed the indirect costs of CC (Table 2).

A Systematic Review of the Economic and Humanistic Burden of Illness in Irritable Bowel Syndrome and Chronic Constipation

TABLE 2 Economic Burden of Disease in Irritable Bowel Syndrome or Chronic Constipation

Reference	Condition	Country, Perspective	Distribution of Costs (% of Total) ^a		Total Costs		Units
			Direct	Indirect	Direct	Indirect	
Johansson 2010 ³⁰	IBS	Norway	Consultations (16.1%), hospitalizations (67.7%), medications (4.5%), and alternative products (2.5%)		1,049 NOK		2001; €1 = NOK 8
Brun-Strang 2007 ³²	IBS	France	Physician consultations, medical fees, hospitalizations, ambulatory examinations, examinations, medications, drug costs (% NR)	Mean number of sick leave days, restriction of activities (% NR)	€756.14	€37.89	2001 €
Dean 2005 ²²	IBS	United States		Work productivity loss due to IBS-attributable symptoms (100%)		\$7,737 [\$9,933]	NR, published in 2005 [2012 USD]
Le Pen 2004 ⁴⁶	IBS	France	Consultations (18.6%), tests and investigations (40.6%), hospitalizations (26.4%), and medications (14.4%)	Cost of absences from work (100%)	€47.3/month	€3.3/month	1999-2000 €
Leong 2003 ¹⁷	IBS	United States	Hospital outpatient (33.7%), hospital inpatient (21.7%), physician's office (14%), other medical (2.2%), and pharmacy (28.4%)	Disability (61.9%) and absenteeism (38.1%)	\$3,736 ^b [\$6,403]	\$791 [\$1,356]	1998 USD [2012 USD]
Longstreth 2003 ²⁵	IBS	United States	Outpatient (52.6%), inpatient (9.8%), pharmacy (28.3%), radiology (5.1%), and laboratory (4.2%)		\$3,729.04 ^b [\$5,932.78]		2000 USD [2012 USD]
Martin 2003 ²⁶	IBS	United States (CA or NC), Medicaid	(CA, NC) Prescriptions (46.6%, 23.3%), physician visit (19.2%, 13.9%), inpatient (6.2%, 23.9%), outpatient (7%, 20.3%), and other costs (21%, 18.6%)		PMPY CA: \$2,952 ^b [\$4,123] PMPY NC: \$5,906 ^b [\$8,248]		NR, published in 2003 [2012 USD]
Akehurst 2002 ²³	IBS	United Kingdom	Outpatient (25.3%), inpatient (38.1%), accident and emergency visits (2.1%), prescription medications (20.3%), home visits (0.5%), GP surgery attendances (13.8%)		£316.2 ^b		1997/1998 £
Müller-Lissner 2002 ³⁶	IBS	Germany	Physician costs (25%), drug costs (46%), psychotherapy (2%), other procedures (<1%), hospital (25%), and rehabilitation (2%)	Sick leave (100%)	€791.48	€398	1998 €
Patel 2002 ²⁸	IBS	United States	Laboratory, procedures, drug, emergency department, outpatient, and inpatient costs (% NR)		\$2,504 ^b [\$4,429]		1997-1999 USD [2012 USD]
Sandler 2002 ⁴⁹	IBS	United States	Hospital facility (62.7%), inpatient physician services (11%), hospital outpatient department (2.6%), hospital emergency room (1%), office visits (16.9%), and drugs (5.9%)	Work loss secondary to receiving health care (100%)	Total U.S.: \$1,353M [\$2,319M]	Total U.S.: \$205M [\$351M]	1998 USD [2012 USD]
Creed 2001 ⁵⁰	IBS	England	Hospital care (76.8%), primary care costs (23.5%), alternative therapies (0.2%), patient costs (3.6%), and community costs (0.9%)	Lost time from work (100%)	\$1,743 [\$2,651]	\$334.50 [\$508.77]	NR, published in 2003 [2012 USD]
Levy 2001 ²⁴	IBS	United States	Inpatient care (24.7%), primary care visits (19.6%), specialty care (15.9%), prescription medicines (12.3%), radiology (7.8%), mental health care (2.9%), laboratory tests (2.9%), emergency visits (2.8%), and other costs (9.6%)		\$4,044 ^b [\$7,610]		1995 USD [2012 USD]
Ricci 2000 ²⁰	IBS	United States	Outpatient charges (27.3%), pharmacy charges (8.0%), inpatient charges (40.8%), ancillary charges (23.9%)		\$7,547 [\$12,007]		NR, published in 2000 [2012 USD]
Bentkover 1999 ³⁷	IBS	Canada	Doctors' fees (18%-29%), diagnostic tests (45%-46%), drugs (5%-19%), medical professional referrals (10%), emergency room visits (7%-11%)	Lost time at work due to IBS (100%)	\$258.82	\$748.16	1996 CAD
Ahn 2008 ¹⁶	IBS+C, CC	United States	(C/IBS+C:) outpatient (53.8%, 62.3%), inpatient (18.3%, 13.4%), drugs (22.3%, 22.6%), and long-term care (5.8%, 1.7%)		C \$1,912, [\$2,778] IBS+C \$1,562, [\$2,269]		2002 USD [2012 USD]
Nyrop 2007 ²¹	IBS, CC	United States, HMO	(IBS/C) inpatient (14.2%, 22.9%), primary care office visit (19.8%, 17.1%), GI clinic office visit (12.8%, 12.6%), mental health office visit (3.5%, 1.5%), pharmacy (17.7%, 13.9%), radiology (7.6%, 5.8%), emergency (2.6%, 3.5%), lab		C \$7,522, [\$11,967] IBS \$5,049 [\$8,033]		2000-2003 USD [2012 USD]

TABLE 2 Economic Burden of Disease in Irritable Bowel Syndrome or Chronic Constipation (continued)

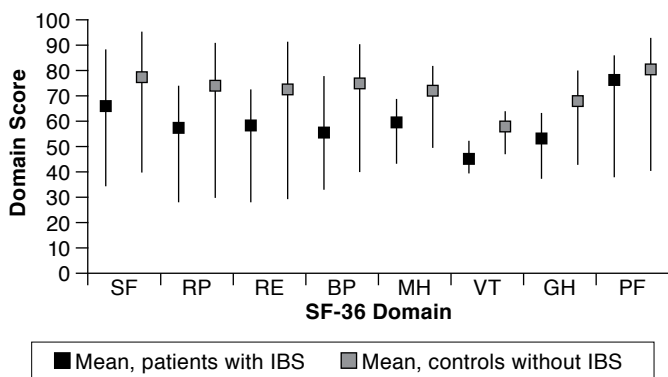
Reference	Condition	Country, Perspective	Distribution of Costs (% of Total) ^a		Total Costs		Units
			Direct	Indirect	Direct	Indirect	
Nguyen 2008 ²⁷	CC	United States, HMO	Outpatient visits, GI outpatient visits, non-GI outpatient visits (% NR)		\$7,510 ^b		NR
Pekmezaris 2002 ³¹	CC	United States	Constipation medication, medications not related to care of constipation, constipation work-up, time required to deliver constipation care, labor rates for constipation care, medication costs (% NR; staff time accounted for more than the cost of all drugs administered)		\$61.18/day [\$101.30/day]		1999 USD [2012 USD]

^aAll costs are annual costs, unless otherwise specified. Values in brackets are costs inflated to 2012 USD using the U.S. city average, medical care Consumer Price Index, and 1984 as the base year (<http://www.bls.gov/data>). Costs for countries other than the United States were not converted to USD or inflated.

^bCosts significantly higher in IBS or CC patients compared with matched non-IBS or non-CC controls.

CA = California; CAD = Canadian dollar; CC = chronic constipation; GI = gastrointestinal; GP = general practitioner; HMO = health maintenance organization; IBS = irritable bowel syndrome; M = million; NC = North Carolina; NOK = Norwegian kroner; NR = not reported; PMPY = per member per year; USD = U.S. dollar.

FIGURE 2 Range of SF-36 Domain Scores for IBS Patients Compared with Non-IBS Controls (14 Studies)



BP = bodily pain; GH = general health; IBS = irritable bowel syndrome; MH = mental health; PF = physical functioning; RE = role emotional; RP = role physical; SF = social functioning; VT = vitality.

Studies Assessing Humanistic Burden of Disease

Nineteen studies meeting the inclusion criteria measured humanistic burden of disease using the following instruments: Short Form (36) Health Survey (SF-36; n=14), EuroQol 5D health questionnaire (EQ-5D; n=1), Irritable Bowel Syndrome Quality of Life (IBS-QOL; n=6) or Gastrointestinal Quality of Life Index (GIQLI; n=1). Several studies used multiple instruments. Six studies investigated patients in the United States; 4 studied patients in France; 2 each studied patients in the United Kingdom, Korea, and the Netherlands; and 1 each studied patients in Sweden, Canada, and China.

Instruments used to study QOL may be generic or disease specific, and SF-36 is a widely used generic measure of health

status. All of the studies that measured SF-36 domain scores were in patients with IBS. In the studies that compared IBS with a non-IBS control population, SF-36 domain scores were significantly lower in IBS patients than in controls (Figure 2). The difference in minimum and maximum domain scores was smallest in the domain of vitality (16.7 points) and largest in the domain of role-emotional (62.2 points). None of these studies reported SF-36 scores by IBS subtype.

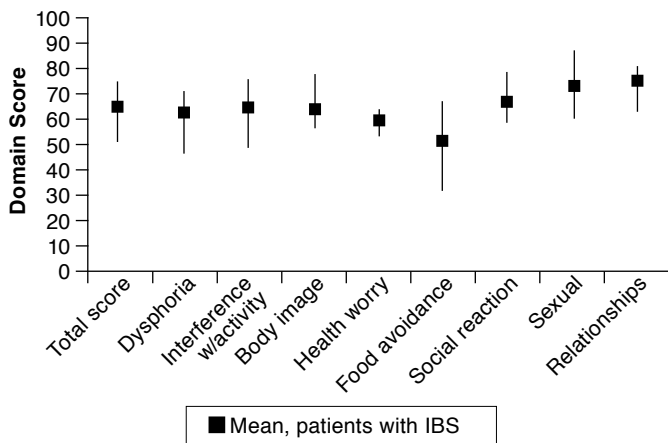
IBS-QOL is a condition-specific measure for assessing HRQOL among persons with IBS. A total of 6 studies in IBS patients measured QOL using the IBS-QOL. Variation in IBS-QOL domain scores across studies was less than SF-36 domain scores: the smallest score range was in the health worry domain (10.5 points), while the largest range was seen in the food avoidance (35.9 points) domain (Figure 3).

Only 1 study of CC patients that reported humanistic burden of disease met the inclusion criteria.¹⁸ This study included a total of 78 patients with CC and measured QOL using the GIQLI, an instrument developed for gastrointestinal and digestive disorders. The mean total GIQLI score for CC patients was 92.3 ± 24.8, which was lower than the mean total score for healthy subjects (126 ± 18).¹⁹

Discussion

This systematic review identified studies assessing the economic and humanistic burden of IBS and/or CC. A total of 35 studies met the inclusion criteria and were analyzed. The main findings were as follows: (a) estimates of the economic burden of disease vary widely by about a factor of 5 for direct costs and nearly a factor of 10 for indirect costs; (b) there is an overall lack of uniformity in methods used for patient identification and measurement of costs; (c) few studies have attempted to distinguish among IBS subtypes or between CC and IBS-C; and (d) few recent studies have been published.

FIGURE 3 Range of IBS-QOL Total and Domain Scores for IBS Patients (6 Studies)



IBS = irritable bowel syndrome.

This systematic review found a wide range of cost estimates for both IBS and CC. From the U.S. perspective, the direct costs of IBS and CC ranged nearly 5-fold from the lower estimates (\$1,562 per year¹⁶ for IBS and \$1,912 per year¹⁶ for CC; both 2002 USD) to the upper estimates (\$7,547 per year²⁰ [year NR] for IBS and \$7,522 per year²¹ for CC [2002-2003 USD]). Indirect per-patient costs of IBS from the U.S. perspective ranged from \$791 per year¹⁷ to \$7,737 per year.²² Notably, in studies comparing IBS or CC patients with controls without these FGIDs, costs were significantly higher in IBS or CC patients (Table 2).^{17,23-28} There are a number of possible reasons for this wide variation. Methodological differences such as definitions of IBS or CC, methods for identifying patients with these conditions, valuation years, regional cost differences, and different categories of service studied are likely factors.

In studies assessing humanistic burden of disease, identification of patients was still highly variable, but standard approaches were used to measure the QOL burden of disease. A total of 14 studies collected SF-36 scores in patients with IBS, 8 of which included non-IBS controls. In these 8 studies, SF-36 domain scores were consistently and significantly poorer in patients with IBS compared with matched non-IBS controls (Figure 2). Overall, SF-36 domain scores in patients with IBS varied widely, but scores for the domain of vitality appeared to be particular low and tightly grouped, with a mean score of 57.9 points and intra-domain range of 16.7 points (Figure 2). In the 6 studies that measured IBS-QOL scores, domain scores were more tightly grouped, but the average range between minimum and maximum domain scores was still approximately 25 points (Figure 3). No study reported QOL scores within specific IBS subtypes. Only 1 study included evaluated QOL in patients with CC and found diminished QOL as measured by

the GIQLI compared with healthy controls.

The difficulty in differentially identifying patients with IBS subtypes or CC has meaningful consequences for clinical practices and optimal treatment selection in a managed care setting. Decrements in functioning and pain for patients with IBS subtypes may differ, which could inform treatment selection. Findings from this systematic review suggest that patients with IBS suffer from decreased vitality, but differences in symptom burden and the impact on patients among IBS subtypes have apparently not yet been published outside the context of particular interventions. Results also reveal significant QOL burdens in IBS patients and highlight the need for future studies to investigate the QOL burdens specific to IBS subtypes and CC. A better understanding of patients' clinical experience within FGID subtypes is essential for selecting appropriate therapy.

A lack of diagnostic consensus for IBS or CC was also observed, which prevented rigorous comparisons of results across studies. In the claims database studies, no consistent set of ICD-9-CM codes was used to identify patients with IBS or CC, and the 2 studies that focused on patients with co-occurrence of constipation and IBS used markedly different technical approaches. In general, studies did not differentiate among IBS subtypes.

This analysis revealed considerable gaps in the literature measuring the burden of disease for IBS and CC. The aim of this systematic literature review was to estimate the burden of disease in 2 common gastrointestinal disorders, with particular focus on IBS subtypes, but few studies that attempted to parse findings by specific FGID were found. Only 2 studies examined the costs of patients with IBS-C.^{16,17} There were no studies that examined the humanistic burden associated with any IBS subtype, and only 3 of the included studies investigated cost or QOL burdens in patients with CC. There were no studies estimating the economic burden of these gastrointestinal disorders in recent (<5 years) values, and the only study¹⁸ that estimated the humanistic burden of CC used a comparison cohort of patients assessed in 1999. Finally, current treatment patterns for these FGIDs have not been documented extensively.

Previous systematic reviews assessing burden of disease have focused on the effect of IBS on HRQOL^{13,29} and direct resource utilization and productivity losses,¹⁴ whereas no systematic reviews documenting the burden of disease for CC have been recently published. This systematic review aimed to identify burden-of-illness studies for IBS and CC and focus on their subtypes. Findings suggest that there is a lack of information regarding the economic and humanistic burden of CC and IBS subtypes. This variation can be attributed to the difficulty in identifying patients with IBS subtypes and CC in retrospective studies and, particularly for economic studies, to the lack of consistency in methods used to measure direct or indirect health care costs.

Limitations

This systematic review has several important limitations. First, differences in disease definitions according to studies' ICD-9-CM criteria and lack of similarities in patient populations precluded meta-analysis of the results, which would have allowed us to estimate disease costs and humanistic burden. Second, the design of studies included in the systematic review varied considerably. Of the 35 included studies, only 2^{30,31} were prospectively conducted, while the remainder were case control (6), retrospective (9), or cross-sectional (18) in design. It was appropriate to include these study designs in the systematic review, since the stated criteria excluded studies that reported economic or humanistic outcomes attributable to a particular intervention (which eliminated many interventional studies). Third, the cost estimates used in the economic analyses were often dated: the most recent valuation period for direct costs was for 2000-2003,²¹ while for indirect costs the most recent values were for 2001.³² This hindered the ability to provide a precise estimate of the current economic burden of disease for IBS, IBS subtypes, and CC. Furthermore, studies used a range of international currencies and evaluated costs using different index years, which made it difficult to compare the cost estimates observed in the systematic review. This review included studies of varying rigor, including both abstracts and full publications, and the studies were not evaluated for quality. These limitations do not alter the main findings already described.

Conclusions

This systematic review included a total of 35 studies evaluating the economic or humanistic burden of disease of IBS or CC. In the 19 studies that assessed the costs of these FGIDs, 15 included patients with IBS only, 2 included patients with CC only, and 2 included patients with either IBS or CC. From the U.S. perspective, the direct costs of IBS ranged from \$1,562 to \$7,547 per year, and the indirect costs ranged from \$791 to \$7,737 per year, while the direct costs of CC ranged from \$1,912 to \$7,522 per year (indirect costs for CC were not observed in this systematic review). The humanistic burden of illness of IBS patients compared with matched controls was demonstrated in multiple studies using SF-36 and IBS-QOL scores; however, only 1 study that met our inclusion criteria assessed the burden of illness in CC patients, observing a diminished QOL compared with non-CC controls. Our review did not identify any studies that used standard diagnostic criteria to assess the economic or humanistic burden of IBS subtypes or CC. Given the limited information regarding economic and humanistic burden in these 2 common FGID conditions, future research should focus on characterizing the burden of illness associated with IBS subtypes and CC.

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DISCLOSURES

This study was conducted by Analysis Group, Inc., which received consultancy fees from Forest Laboratories, Inc., and Ironwood Pharmaceuticals, Inc. Forest Laboratories, Inc.; Ironwood Pharmaceuticals, Inc.; and Analysis Group, Inc., were involved in the study design, literature review and interpretation, and the decision to submit these data for publication. Funds for preparation of this manuscript were provided by Ironwood Pharmaceuticals, Inc., and Forest Laboratories, Inc.

At the time of the study, Lewis was an employee of Ironwood Pharmaceuticals, Inc. Carson is an employee of Forest Research Institute and owns stock/stock options in Forest Laboratories. Nellesen and Chawla are employees of Analysis Group, Inc., and Yee was an employee of Analysis Group at the time of the study.

Nellesen, Yee, Chawla, Carson, and Lewis conceived and designed the research; Yee performed the analysis; and Nellesen, Yee, Chawla, Lewis, and Carson prepared the manuscript.

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