Published in final edited form as:

J Med Econ. 2017 March ; 20(3): 273–279. doi:10.1080/13696998.2016.1253584.

A case-control comparison of direct healthcare-provider medical costs of chronic idiopathic constipation and irritable bowel syndrome with constipation in a community-based cohort

Linda M. Herrick^{1,2}, William M. Spalding³, Yuri A. Saito¹, James Moriarty⁴, and Cathy Schleck⁵

¹Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN

²South Dakota State University, Brookings, SD

³Ironwood Pharmaceuticals, Cambridge, MA, United States

⁴Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN

⁵Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN

Abstract

Objective—Patients with constipation account for 3.1 million United States physician visits a year, but care costs for patients with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC) compared to the general public have received little study. The study aim was to describe healthcare utilization and compare medical costs for patients with IBS-C or CIC versus matched controls from a community-based sample.

Methods—A nested case-control sample (IBS-C and CIC cases) and matched controls (1:2) for each case group were selected from Olmsted County, MN individuals responding to a community-based survey of gastrointestinal symptoms (2008) who received healthcare from a participating Rochester Epidemiology Project (REP) provider. Using REP healthcare utilization data, unadjusted and adjusted standardized costs were compared for the 2- and 10-year periods prior to the survey for 115 IBS-C patients and 230 controls and 365 CIC patients and 730 controls. Two time periods were chosen as these conditions are episodic but long-term.

Results—Outpatient costs for IBS-C (\$6,800) and CIC (\$6,284) patients over a 2-year period prior to the survey were significantly higher than controls (\$4,242 and \$5,254 respectively) after adjusting for co-morbidities, age, and sex. IBS-C outpatient costs (\$25,448) and emergency room costs (\$6,892) were significantly higher than controls (\$21,024 and \$3,962 respectively) for the 10-year period prior. Unadjusted data analyses of cases compared to controls demonstrated significantly higher imaging costs for IBS-C cases and procedure costs for CIC cases over the 10-year period.

Corresponding author: Linda M. Herrick, South Dakota State University, Box 2275, SWG 255, Brookings, SD 57007, Linda.Herrick@sdstate.edu.

Transparency: Declaration of financial / other relationships: LH has stock ownership in Hormel, Corp; YS serves as a consultant/advisor for Commonwealth Labs, and participated in advisory boards for Synergy and Salix; WS was an employee with stock ownership of Ironwood Pharmaceuticals, Inc. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Limitations—Data were collected from a random community sample primarily receiving care from a limited number of providers in that area.

Conclusions—Patients with IBS-C and CIC had significantly higher outpatient costs for the 2-year period compared with controls. IBS-C patients also had higher ER costs than the general population.

Keywords

costs; irritable bowel syndrome with constipation; chronic idiopathic constipation; economic burden; healthcare resource utilization

Introduction

Constipation is a common ambulatory digestive disease diagnosis in the United States characterized by reduced stool frequency, difficulty passing stool, or both¹ and accounts for up to 3.1 million outpatient visits per year.² An earlier study found constipation was a diagnosis or reason for seeking care in approximately 5.7 million ambulatory visits with an estimated total annual cost of \$235 million.³ Mild intermittent episodes of constipation or irregularity that resolves with dietary or therapeutic measures is clinically insignificant however, constipation symptoms that persist despite treatment and having no identifiable organic or extrinsic cause (Chronic Idiopathic Constipation) may be a debilitating disorder⁴ that significantly impacts quality of life⁵. Chronic idiopathic constipation (CIC) is a common functional gastrointestinal disorder (FGID) affecting up to 10 to 15 % of adults in the general population.^{1, 2} Constipation also affects those with irritable bowel syndrome. Prevalence estimates indicate that approximately 10 to 15% of adults have irritable bowel syndrome, with approximately 30% of those having the constipation-predominant subtype (IBS-C).^{6, 7} Despite the high prevalence of IBS-C and CIC and high numbers of related ambulatory visits, little is known about the burden of these chronic constipation illnesses in terms of medical visits, diagnostic procedures, and costs for individuals with IBS-C or CIC over a prolonged period of time compared to the general population.

Studies have assessed costs in constipation demonstrating higher costs for those with constipation. However, a limited number of studies have assessed healthcare resource utilization (HCRU) and costs in patients with types of chronic constipation as studies have generally included both mild intermittent and chronic severe patients. Three separate studies compared costs of care related to IBS or constipation in relatively small samples. In a small nested case-control study of medical costs for constipated women (168) and matched controls (84) selected from a group of mothers of a birth cohort of children from a community setting, total direct medical costs and overall outpatient costs over a 15-year time period were significantly higher, more than double, for those with constipation than for controls.⁸ Similar findings were noted in a study in which costs extracted from administrative claims and through patient surveys demonstrated mean annual direct health care costs were \$5049 for people with IBS (all forms) and \$7522 for those with constipation.⁹ Annual patient out of pocket costs were found to be higher for IBS and constipation as well.⁹ Another study assessed use of health care resources and costs of care for adults with constipation (based on at least one physician visit with ICD-9-CM 564.0x)

utilizing a single state Medicaid claims database and demonstrated an average cost of physician visits for constipation at \$39/patient while costs for gastrointestinal procedures and laboratory testing were estimated at \$183/patient.¹⁰

Two recent studies using retrospective medical and pharmacy claims data from the HealthCore Integrated Research Database concentrating specifically on IBS-C and CIC demonstrated that both IBS-C and CIC imposed a substantial economic burden relative to matched controls.^{11,12} From this database, HCRU for over 22,000 patients were analyzed (n=7427 CIC, n=3826 IBS-C, n=11253 controls). Total all-cause health care costs associated with CIC were significantly higher after adjusting for demographic and co-morbidity factors.¹¹ Similarly, findings confirmed significantly higher all-cause health care costs for cases with IBS-C relative to matched controls, with the majority of the costs attributed to outpatient services.¹² Doshi et al. found with 3,826 patients in each of the IBS-C and control cohorts, mean annual all-cause health care costs for the IBS-C patients were \$11,182 with over half of those costs attributable to outpatient services. They found that after adjusting for demographics and co-morbidities, the incremental annual all-cause health care costs associated with IBS-C patients were significantly higher than costs for the control patients.¹²

Evidence suggests that many patients have constipation-associated symptoms on a long term basis.^{5,13} Johanson and Kralstein⁵ found that about 70% of patients with constipation had constipation for more than 2 years. Talley *et al.* reported that 89% of adults surveyed reported no change in gastrointestinal symptoms over a 12-20 month period.¹³ These findings suggest that adults with forms of constipation such as IBS-C and CIC may present repeatedly for constipation symptoms over prolonged periods of time, potentially leading to increased numbers of out-patient visits, diagnostic evaluations, and in-patient admissions.

The purpose of this study was to describe healthcare resource utilization and to estimate and compare medical costs for outpatient visits, diagnostic evaluations, and inpatient admissions for IBS-C and CIC cases and matched controls over the 2-year and 10-year periods prior to a community-based survey of gastrointestinal (GI) symptoms. Direct medical costs of IBS-C and CIC cases and matched control groups who did not report symptoms of IBS-C or CIC over a 10-year and 2-year periods were also compared.

Patients and Methods

This study utilized electronic medical record (EMR) data and results of a 2008 GI symptoms survey conducted among individuals residing in Olmsted County, MN who had previously registered as patients with a participating Rochester Epidemiology Project (REP) healthcare provider. The REP is a collaboration of nearly all medical care providers and both hospital systems within Olmsted County; one common database contains the EMR history and administrative data for over 92 percent of Olmsted County residents.¹⁴ Hence, this database provides an infrastructure for population-based case-control studies such as this one.

A nested case-control sample was used for this retrospective study. A survey of GI symptoms was sent to 8,006 randomly selected Olmsted county residents who participated in the REP in 2008. The study cohort was comprised of survey respondents 18 years of age

or older who had given prior research authorization. The response rate was 49.7% yielding 3,831 usable surveys for this study. The original survey study (2008) and this study were approved by the institutional review boards of the medical institutions whose data were used.

Cases consisted of 495 adults who were identified as having IBS-C (118) or CIC (377) based on a symptom survey using modified Rome II questions. Current research authorization and medical records were available for 115 of the IBS-C cases and 365 of the CIC cases. Reasons for the lack of records for the remaining sample included transient residence in Olmsted County at the time of the survey, no use of health care during the ten years prior to the survey, or accessing health care outside the REP.

The survey used to classify cases and controls was the validated Bowel Disease Questionnaire.^{15,16} Respondents were asked to identify the frequency of GI symptoms over the past year (“never or rarely”, “sometimes” [“about 25% of the time”] “often” [“about 50% of the time”], most of the time [about 75%], always [100% of the time in the last year]), as our group demonstrated lack of superiority of 3 month period over a 1 year period.¹⁵ Definitions of sometimes, often, etc. were further defined to provide greater consistency in responses. IBS-C cases were identified as those who reported abdominal pain or discomfort at least 2 or 3 days per month associated with two or more of the following at a level of “sometimes” or more often: relieved with a bowel movement (BM), change in stool frequency (fewer than 3 BMs per week), and/or change in stool consistency (hard stools at least sometimes).¹⁵

Cases classified as CIC reported two or more of the following on the survey: fewer than 3 BMs per week, straining (at least sometimes), lumpy or hard stools (at least sometimes), a sensation of incomplete evacuation (at least sometimes), a sensation of blockage (at least sometimes), or digital extraction (at least sometimes). In addition, they reported no loose or watery stools except if loose stools were due to laxative use, and did not meet the IBS criteria listed above.

Controls were classified as survey respondents who were not classified as having IBS-C or CIC and who did not have either diagnosis identified in their medical records at the time of the survey (2008). Controls may have had positive responses for GI symptoms but did not meet criteria for IBS-C or CIC and thus represented the community rather than an “ultra-healthy” group of individuals with no GI symptoms. Each case was randomly matched to controls in a 1:2 ratio based on gender, age (± 5 years) at the time of the survey, and first registration date in the REP (± 5 years) to assure balance between the two groups. Use of the REP registration date served as a proxy for entry time in the county.

This study utilized the resources of the Olmsted County Healthcare Expenditure and Utilization Database (OCHEUD) through the REP. The OCHEUD contains information on medical resource utilization, associated charges, and estimated, inflation-adjusted economic costs for patients included in the REP. The OCHEUD provides an estimated economic cost by use of widely accepted valuation techniques for each line item in the billing record. The line item costs were aggregated into relevant categories for comparison.¹⁴ OCHEUD data were grouped by resource utilization into the Medicare Part A and B classification system;

Part A billed charges were adjusted by using hospital cost-to-charge ratios and wage indexes, and Part B physician services were valued using Medicare reimbursement rates. Outpatient prescription or over-the-counter drugs dispensed by any institution and nursing home care costs are not included in the database. Limited services delivered to non-hospitalized patients that may have been delivered by providers other than health care institutions were not included in the analysis. Examples of such services include dental procedures, ambulance services, and durable medical equipment (e.g., wheel chairs). No actual costs were used since costs are difficult to determine as charges differ depending on insurance contract bundling and estimated, standardized costs were used where applicable. More than 80% of the residents of Olmsted County are seen at least once annually at 1 of the 2 health care organizations included in the OCHEUD.¹⁷

Cost and utilization data spanning the 10-year period 1999 to 2008 were collected for all subjects from the OCHUD database. Data included the numbers of events and assigned costs for inpatient hospitalization, outpatient physician visits, diagnostics tests, and inpatient and outpatient treatments. Primary outcome variables included: total costs, hospitalization costs, inpatient costs, outpatient costs, and emergency room (ER) costs. Utilization variables included number of hospitalizations, hospital days, emergency room visits, inpatient admissions (e.g. overnight observation or procedures in inpatient areas), outpatient services. Total costs included all costs as previously specified. Hospital costs were defined as the Medicare Part A costs that included hospital charges incurred due to inpatient or outpatient costs. For example, a number of endoscopy areas are assigned as hospital space due to the administration of anesthetics for procedures but patients are not inpatient. Inpatient costs include both Part A hospital charges and Part B physician costs that occur during inpatient stays in the hospital. A standardized cost was assigned to services as charges differ by payer. All costs were inflated to 2011 U.S. dollars.

Presence of complete data for the analysis time frame was investigated for each analysis group (cases and controls).

Complete versus incomplete status was determined by residency status taking into account each case and its respective matched controls. To be considered complete, the case and both of its matched controls needed to have no reported gaps in Olmsted residency over the time frame. Since the majority of the subjects met residency criteria and had health care costs, there was no adjustment for incomplete data. For the 10-year time period (1999-2008), 71% of IBS-C cases and controls and 76% of CIC cases and control had complete data. For the 2-year time period (2007-2008) 93% of IBS-C cases and controls and 86% of CIC cases and controls had complete data.

Subject comorbidities were assessed using the available Medical Index coding of diagnoses.¹⁴ Comorbidities were assessed using an electronic adaptation of the Charlson Comorbidity Index.¹⁸ In addition, selected diagnoses with a potential for impact on IBS-C or CIC and medical costs based on a priori expectations were identified based on the literature^{8, 19} and clinical experience. These diagnostic covariates included diagnoses with IBS of mixed- or diarrhea-predominant type, GI malignancy (150.xx-159.xx, 197.8x, 199.xx, 234.9x), Crohn's disease (555.xx), ulcerative colitis (556.xx), celiac disease and

other intestinal malabsorption (579.xx), diverticulitis (562.0x, 562.1x), vascular insufficiency of intestine (557.xx), multiple sclerosis (340.xx), Parkinson's Disease (332.xx), diabetic neuropathy (250.6x), pancreatitis (577.xx), depression (296.xx, 298.xx, 300.4, 311), and anxiety (300.xx, 309.xx).

The analysis included a 10-year (1999-2008) and a 2-year period (2007-2008) just prior to the time of the survey. The 10-year time period was chosen as there was little information available related to long-term costs for these chronic conditions. The 2-year time period prior to the report of symptoms was chosen, as additional costs may be seen at the time of active symptoms as reported on the survey with possible physician visits, diagnostic tests, and exams for purpose of diagnosis. An analysis was conducted among respondents younger than 65 years of age comparing mean predicted costs, as co-morbidities and medications may affect symptoms of IBS-C and CIC in older persons.

Statistical Methods

Descriptive costs were calculated for each analysis group. Mean, median and standard deviation were reported on unadjusted observed costs. Simple comparisons of cases to controls were performed using the nonparametric Wilcoxon Rank Sum test because samples were not normally distributed. All *p* values were considered significant at <0.05.

A descriptive unadjusted cost comparison of the IBS-C and CIC cases to control groups was completed; however, each outcome variable was restricted to those subjects with positive costs (costs above \$0.00). Costs were analyzed for hospital costs, inpatient costs, outpatient costs, ER costs, and total cost (addition of all costs).

Analyses used a two-part costing approach to account for zero costs in the time frame. The first part consisted of a logistic regression that modeled the presence of positive or non-zero costs in the time frame. The second part used a generalized linear model (GLM) with a gamma distribution and log link for those with positive costs. Predicted costs were calculated based on those in each cohort who had positive costs with predicted mean costs and bootstrapped 95% confidence intervals (CI) as well as the 95% CI of the mean difference. Predicted costs were then adjusted for by the predicted probability of having positive costs determined in part one. Part one of the two-part analysis was not performed for any outcome variable having less than 10% of individuals with zero costs; instead, only a one-part analysis consisting of the GLM model was performed.²⁰ The percentage of all subjects with zero costs was calculated (Table 1).

Predicted mean costs and bootstrapped 95% confidence intervals (CI) are reported as well as the 95% CI of the mean difference. Significant cost differences were identified by 95% CI in mean differences that do not contain zero. For these analyses, confidence intervals have been used instead of *p* values as it enables a direct statement about the size and direction of the difference between groups.²¹ Adjusted prediction cost models were controlled for case/control status, age, gender, patient-reported symptoms (heartburn, acid regurgitation, nausea, vomiting, bloating, functional dyspepsia, and GERD), GI-related comorbidities (IBS with mixed or diarrhea subtypes, GI malignancy, Crohn's disease, ulcerative colitis, celiac or

other malabsorption, diverticulitis, vascular insufficiency of the intestine, multiple sclerosis, Parkinson's disease, pancreatitis, depression, anxiety), and Charlson Comorbidities.

Results

Mean age for the IBS-C cases and controls was 60 (SD 14.7) years; mean age of CIC cases and controls was 66 (SD 14.8) years. Both IBS-C and CIC cases and controls were primarily female (76.3% and 63.9%, respectively). IBS-C cases reported significantly more bloating (<0.0001) and functional dyspepsia symptoms (<0.0001) than controls on the survey. IBS-C cases had a higher prevalence of pancreatitis (4.4% v. 0.4%, $p=0.02$) than controls. In contrast, there were significantly more multiple sclerosis cases in the CIC cases (1.6% v. 0.4%, $p=0.01$) than controls. There were no significant differences between IBS-C and CIC cases and controls in the Charlson co-morbidities.

No significant differences were noted between IBS-C cases and controls or CIC cases and controls in healthcare utilization related to hospital days, ER visits, or GI diagnostic tests and procedures for either the 10- or 2-year time periods. The numbers of individuals with hospital stays (58-60%) and ER visits (either as a single visit or with multiple visits over a short period of time resulting in a single charge) (average of less than 2.5 for each cohort) may have contributed to the lack of any statistically significant differences.

The analysis of unadjusted costs over the 10-year period demonstrated significantly higher mean imaging costs in the IBS-C cases (\$4,667) compared with their matched controls (\$3,714) ($p = 0.02$) while there were significantly higher procedure costs in the CIC cases than controls (\$6,662 vs \$4,993, respectively) ($p = 0.04$) with diagnostic tests and all costs approaching significance with 0.06 and 0.08 p values respectively. While significance was not achieved, costs for inpatient admissions, outpatient services, emergency-room visits, evaluation and management were higher for IBS-C and CIC cases than for their respective matched controls.

Based on a descriptive unadjusted cost comparison of IBS-C and CIC cases and controls, costs for the 10-year period prior to the survey were higher for IBS-C and CIC cases than controls with the exception of hospital costs; however, these results were not statistically significant. For the 10-year analyses, the sample sizes were small, especially in the areas of inpatient costs and ER costs.

IBS-C cases had significantly higher mean predicted adjusted outpatient and emergency room costs over the 10-year period compared with controls (Table 2). Though sample sizes are relatively small and there are wide confidence intervals, significant differences were noted. While the CIC cases had higher predicted adjusted mean costs than controls, they did not reach statistical significance (Table 3). The variances were very large and though sample sizes were larger than the IBS-C cases and controls, significant differences were not detected.

Mean predicted adjusted costs demonstrated significantly higher outpatient costs for the IBS-C cases compared to controls (Table 4) for the 2-year analysis. While other costs were numerically higher for those with IBS-C, statistical significance was not achieved; sample

sizes became very small for some of the outcomes. In the analysis of CIC, observed, outpatient costs for the 2-year period were significantly higher for CIC cases than controls (Table 5).

Results of the analysis of those patients under 65 years of age, demonstrated outpatient costs were significantly higher for the IBS-C cases than controls for the 2-year time period. No other areas were significantly different for the IBS-C cohorts, though costs trended higher for the IBS-C cases in all categories (Table 6). Again, there are small sample sizes and large variances in the cost variables. For the CIC cases under age 65 for the 2-year time period, emergency room costs were significantly higher for CIC controls than cases (Table 7).

Discussion

Epidemiological studies have demonstrated that irritable bowel syndrome with constipation and chronic idiopathic constipation are highly prevalent functional disorders, however despite their high prevalence, few studies have attempted to assess the economic burden of these disorders. Those studies that have assessed the economic burden of these disorders have generally relied upon large administrative medical claims datasets where precision in the identification of cases is hampered by a lack of disorder-specific diagnostic codes and dependence upon algorithms that may result in substantial misclassification of subjects. Additionally, few studies have attempted to assess the economic burden at the community rather than national level. Our study utilized data on participants in the Rochester Epidemiology Project which has captured the medical history of nearly all residents in the Olmsted County, MN community for over 40 years, and which has periodically sampled subjects regarding their GI symptoms allowing for identification of cases based on symptom-based criteria. Consistent with analyses of large administrative datasets, our study demonstrated that patients with IBS-C and CIC use significantly more outpatient resources than do others in the general population resulting in higher costs.

Utilization and cost of care

Significantly higher costs were found in selected categories for patients with IBS-C and CIC compared to the general public within a community setting. These were found over 2- and 10-year periods demonstrating the chronicity of the diseases. Significantly higher costs were primarily in the areas of imaging, diagnostic tests, and outpatient services as expected; however, costs in most areas were higher but did not reach statistical significance.

There were significant differences when analyzing mean adjusted costs for the 2-year period prior to the survey. IBS-C and CIC case costs were significantly higher in outpatient costs than respective controls. This is consistent with practice as these patients are often not hospitalized but present frequently in the clinic with chronic complaints, especially while having symptoms as indicated by the survey.

Costs were significantly higher for those patients with IBS-C with respect to outpatient costs and some procedure costs in the 10-year and the 2-year periods prior to the survey in which symptoms were identified and patients classified. Other costs trended higher for IBS-C cases than controls though statistical significance was not achieved. While the mean adjusted

predicted total cost for the two-year period for IBS-C patients was \$11,406, the mean adjusted predicted outpatient cost was \$6,800. Though fewer IBS-C patients were hospitalized than the matched controls, their mean adjusted predicted cost was nearly double, \$19,974 versus \$9,977 respectively. Costs related to outpatient costs were consistently higher for those cases with IBS-C over 2- and 10-year periods for all patients and those under 65 years of age. These higher costs demonstrate the economic burden of outpatient care and the chronicity of IBS-C and care.

Utilization and associated costs were found to be less in this study than in other recent studies.^{11, 12} A primary difference in this study was that only community-based patients and providers were included while those patients in a study using an insurance database may have sought medical care outside the community. This study would not have captured those additional costs.

The primary provider for this community setting is a large, multi-specialty clinic in close proximity to a highly managed care area in the U.S. There are primarily two major providers in the community, both of whom employ numbers of nurses who provide care management in the clinical settings. The physicians and nurses are known to manage chronic conditions through phone contact between annual appointments unless the condition warrants a visit. Ability to manage resource utilization of patients with chronic non-serious health conditions within this integrated delivery system framework may have resulted in some cost savings that are not available to other non-integrated systems.

Strengths and limitations

Strengths of this study are that it is community-based, the medical resource database allows for capture of resource utilization for county residents, and subjects were chosen based on self-reported symptoms that provide a clinically-based rather than medical claims algorithm-based classification of subjects. Use of the community-based sample reduced the possibility of regional variations in practice patterns and provided comprehensive coding of inpatient and outpatient visits and procedures. Classification by report of symptoms on a validated GI symptom survey¹⁵ captured those patients who may not have received a medical diagnosis of IBS-C or CIC but who have symptoms and have used medical resources.

The sample for the survey of GI symptoms was randomly selected, however an older population responded to the surveys. An analysis of response bias in this sample indicated that odds for response increased with those with higher body mass index, health-care seeking behaviors for non-GI related conditions, and completing a survey in the past however results related to GI symptoms or diagnosis were not associated with non-response.²² While this sample may differ from a general population, it reflects those who completed the survey from the community and were identified by symptoms of IBS-C and CIC.

Though the overall sample was older significant differences in costs in selected areas were identified. Co-morbidities and greater use of medications can contribute to constipation in those over 65 years of age, we still observed significantly higher outpatient costs for those with IBS-C and greater use of emergency room services for those with CIC. Given the age

and gender match, these results that the increased costs in select areas of health care utilization continue.

There were small sample sizes using the two-step analysis methods in some categories, resulting in the inability to detect significant differences though case costs were higher.²⁰ Overall costs did not include prescription and over the counter medications in these patient populations that are known to self-medicate with over the counter medications. Results may not be generalizable due to use of a single community with known low utilization of healthcare resources, and non-representative patient demographics (primarily Caucasian). The results do provide insight to utilization patterns that appear to exist throughout the lifespan. Findings indicate areas in which healthcare cost reduction strategies may be investigated.

Conclusions

This study supported the findings of Doshi and Cai that patients with IBS-C and CIC consume more healthcare resources than matched control patients, but these findings were primarily found in the 2-year pre-survey period with some trends observed over the 10-year window. Further exploration of costs and utilization patterns with larger sample sizes is needed to better understand the cost burden of IBS-C and CIC over time. The addition of cost of medications would be beneficial in understanding the full burden of these conditions. While there is some understanding of the increased utilization and financial burden of IBS-C and CIC, further research is warranted.

Acknowledgments

The investigators would like to thank Nilay Shah, Ph.D. Health Care Policy and Research, Mayo Clinic, Rochester, MN for his input and guidance on the statistical analysis. The investigators would also like to thank G. Richard Locke, III, M.D., Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN for his input and guidance on the data and interpretation of results.

Declaration of Funding: Study data were obtained from the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health (grant R01 AG034676). Ironwood Pharmaceuticals funded the data abstraction and analysis of costs.

References

1. Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. The American Journal Of Gastroenterology. 2014; 109(Suppl 1):S2. [PubMed: 25091148]
2. Prevention CfDCa. National Ambulatory Medical Care Survey. 2010
3. Martin BC, Barghout V, Cerulli A. Direct medical costs of constipation in the United States. Managed Care Interface. 2006; 19:43–9.
4. Lembo A, Camilleri M. Chronic constipation. The New England Journal Of Medicine. 2003; 349:1360–1368. [PubMed: 14523145]
5. Johanson JF, Kralstein J. Chronic constipation: a survey of the patient perspective. Alimentary Pharmacology & Therapeutics. 2007; 25:599–608. [PubMed: 17305761]
6. Rey E, Talley NJ. Irritable bowel syndrome: novel views on the epidemiology and potential risk factors. Digestive & Liver Disease. 2009; 41:772–80. [PubMed: 19665952]
7. Cremonini F, Talley NJ. Irritable bowel syndrome: epidemiology, natural history, health-care seeking and emerging risk factors. Gastroenterol Clin North Am. 2005; 34:189–204. [PubMed: 15862929]

8. Choung RS, Branda ME, Chitkara D, et al. Longitudinal direct medical costs associated with constipation in women. *Alimentary Pharmacology and Therapeutics*. 2011; 33:251–60. [PubMed: 21091523]
9. 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.
10. Singh G, Lingala V, Wang H, et al. Use of health care resources and cost of care for adults with constipation. *Clinical Gastroenterology & Hepatology*. 2007; 5:1053–8. [PubMed: 17625982]
11. Cai Q, Buono J, Spalding W, et al. Healthcare costs among patients with chronic constipation: a retrospective claims analysis in a commercially insured population. *Journal of Medical Economics*. 2014; 17:148–58. [PubMed: 24168640]
12. Doshi JA, Cai Q, Buono JL, et al. Economic burden of irritable bowel syndrome with constipation: a retrospective analysis of health care costs in a commercially insured population. *J Manag Care Pharm*. 2014; 20:382–90.
13. Talley N, Weaver A, Zinsmeister A, et al. Onset and disappearance of gastrointestinal symptoms and functional gastrointestinal disorders. *Am J Epidemiol*. 1992; 136:165–77. [PubMed: 1415139]
14. St Sauver JL, Grossardt BR, Yawn BP, et al. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. *American Journal of Epidemiology*. 2011; 173:1059–68. [PubMed: 21430193]
15. Rey E, Locke GR 3rd, Jung HK, et al. Measurement of abdominal symptoms by validated questionnaire: a 3-month recall timeframe as recommended by Rome III is not superior to a 1-year recall timeframe. *Alimentary Pharmacology & Therapeutics*. 2010; 31:1237–47. [PubMed: 20222912]
16. Rey E, Locke GR, Jung HK, et al. Measurement of abdominal symptoms by validated questionnaire: a 3-month recall timeframe as recommended by Rome III is not superior to a 1-year recall timeframe.
17. St Sauver JL, Grossardt BR, Leibson CL, et al. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. *Mayo Clinic Proceedings*. 2012; 87:151–60. [PubMed: 22305027]
18. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40:373–83. [PubMed: 3558716]
20. Choung RS, Locke GR 3rd, Rey E, et al. Factors associated with persistent and nonpersistent chronic constipation, over 20 years. *Clinical Gastroenterology & Hepatology*. 2012; 10:494–500. [PubMed: 22289877]
20. Duan N, Manning WG, Morris CN, et al. A comparison of alternative models for the demand for medical care. *Journal of Business and Economic Statistics*. 1983; 1:115–126.
21. Sedgwick P. P values of confidence intervals. *BMJ*. 2013; 20:346–347.
22. Choung RS, Locke GR, Schleck CD, Ziegenfuss JY, Beebe TJ, Zinsmeister AR, Talley NJ. A low response rate does not necessarily indicate non-response bias in gastroenterology survey research: a population-based study. *Journal of Public Health*. 2012

Table 1
Percentage of IBS-C and CIC cases and controls with zero costs and analysis approach for 10-year analysis

	IBS-C Cases and Controls		CIC Cases and Controls	
Outcome variable	%	Analysis approach	%	Analysis approach
Total costs	0.0	One-part analysis	0.0	One-part analysis
Hospital costs	3.7	One-part analysis	4.1	One-part analysis
Inpatient costs	40.7	Two-part analysis	42.3	Two-part analysis
Outpatient costs	0.0	One-part analysis	0.0	One-part analysis
ER costs	30.1	Two-part analysis	30.6	Two-part analysis

Table 2
Mean adjusted^{*} predicted costs of IBS-C and matched controls for 10-year analysis^{}**

Outcome Variable	IBS-C Case (N=115)				Control (N=230)				Difference	
	n (%)	Mean	95% CI		n (%)	Mean	95% CI		Mean	95% CI
Total costs	82 71%	\$45,952	\$36,022 - \$59,493		164 71%	\$37,142	\$31,287 - \$44,474		\$8,810	-\$3,702 to \$23,890
Hospital costs	79 69%	\$25,436	\$16,079 - \$38,366		158 69%	\$20,437	\$14,911 - \$28,049		\$4,999	-\$6,944 to \$19,975
Inpatient costs	57 50%	\$23,753	\$16,036 - \$33,271		89 39%	\$19,784	\$15,328 - \$25,428		\$3,969	-\$5,822 to \$14, 819
Outpatient costs	82 71%	\$25,448	\$22,285 - \$29,077		164 71%	\$21,024	\$19,150 - \$23,065		\$4,424	\$734 to \$8,437
ER costs	56 49%	\$6,892	\$4,381 - \$9,878		116 50%	\$3,962	\$3,101 - \$4,985		\$2,930	\$240 to \$6,205

* adjusted for age, gender, patient reported GI symptoms, and co-morbidities

** Bold indicates statistical significance at 0.05

Table 3
Mean adjusted* predicted costs of CIC and matched controls for 10-year analysis

Outcome Variable	CIC Case (N=365)			Control (N=730)			Difference		
	n (%)	Mean	95% CI	n (%)	Mean	95% CI	Mean	95% CI	
Total costs	278 76%	\$45,801	\$40,322 - \$51,934	556 76%	\$39,883	\$36,759 - \$43,341	5,918	-\$765 to \$12,725	
Hospital costs	267 73%	\$25,436	\$20,988 - \$30,160	533 73%	\$20,780	\$18,376 - \$23,354	\$4,656	-\$310 to \$10,079	
Inpatient costs	172 47%	\$24,692	\$20,455 - \$29,276	309 42%	\$21,650	\$18,911 - \$24,519	\$3,042	-\$2,038 to \$8,415	
Outpatient costs	278 76%	\$25,125	\$23,527 - \$26,843	556 76%	\$23,240	\$22,246 - \$24,351	\$1,885	-\$216 to \$3,923	
ER costs	195 53%	\$5,268	\$4,181 - \$6,565	384 53%	\$4,372	\$3,808 - \$4,941	\$896	-\$342 to \$2,230	

* Adjusted for age, gender, patient reported GI symptoms, and co-morbidities

Table 4
Mean adjusted* predicted costs of IBS-C and matched controls for 2-year analysis (2007-2008)**

Outcome Variable	IBS-C Case (N=115)			Control (N=230)			Difference		
	n (%)	Mean	95% CI	n (%)	Mean	95% CI	Mean	95% CI	
Total costs	107 93%	\$11,406	\$6,807-\$17,941	213 93%	\$7,410	\$6,115-\$8,948	\$3,996	-\$838 to \$10,840	
Hospital costs	69 60%	\$9,622	\$3,626-\$18,710	146 63%	\$5,240	\$3,402-\$7,722	\$4,382	-\$2,293 to \$13,740	
Inpatient costs	20 17%	\$19,974	\$4,399-\$40,397	42 18%	\$9,977	\$4,708-\$17,750	\$9,997	-\$7,605 to \$31,058	
Outpatient costs	107 93%	\$6,800	\$4,808-\$9,221	212 92%	\$4,242	\$3,840-\$4,627	\$2,558	\$428 to \$5,012	
ER costs	25 22%	\$2,430	\$959-\$4,482	69 30%	\$1,973	\$1,151-\$2,944	\$457	-\$1,301 to \$2,688	

* adjusted for age, gender, patient reported GI symptoms, and co-morbidities

** Bold indicates statistical significance at 0.05

Table 5
Mean adjusted^{*} predicted costs of CIC and matched controls for 2-year analysis (2007-2008)^{}**

Outcome Variable	CIC Case (N=365)				Control (N=730)				Difference		
	n (%)	Mean	95% CI	n (%)	Mean	95% CI	Mean	95% CI	Mean	95% CI	95% CI
Total costs	314 86%	\$11,162	\$9,604-\$12,756	629 86%	\$9,374	\$8,261-\$10,598	\$1,788	-\$232 to \$3,763	\$1,788	-\$232 to \$3,763	
Hospital costs	241 66%	\$6,742	\$5,577-\$8,117	422 58%	\$6,423	\$5,272-\$8,044	\$319	-\$1,634 to \$2,027	\$319	-\$1,634 to \$2,027	
Inpatient costs	77 21%	\$10,723	\$7,828-\$14,255	135 18%	\$8,439	\$6,444-\$10,821	\$2,284	-\$1,515 to \$6,488	\$2,284	-\$1,515 to \$6,488	
Outpatient costs	314 86%	\$6,284	\$5,808-\$6,714	629 86%	\$5,254	\$4,967-\$5,563	\$1,030	\$486 to \$1,563	\$1,030	\$486 to \$1,563	
ER costs	106 29%	\$2,231	\$1,223-\$3,628	193 26%	\$1,646	\$1,283-\$2,045	\$585	-\$474 to \$2,003	\$585	-\$474 to \$2,003	

* Adjusted for age, gender, patient reported GI symptoms, and co-morbidities

** Bold indicates statistical significance at 0.05

Table 6
Mean adjusted^{*} predicted costs of IBS-C and matched controls under 65 years of age for 2-year analysis (2007-2008)^{}**

Outcome Variable	IBS-C Case (N=65)			Control (N=130)			Difference		
	n (%)	Mean	95% CI	n (%)	Mean	95% CI	Mean	95% CI	
Total costs	65 100%	\$11,981	\$5,502-\$23,811	129 99%	\$6,197	\$4,767-\$7,963	\$5,784	-\$1,114 to \$18,249	
Hospital costs	40 62%	\$11,128	\$2,904-\$25,203	85 65%	\$3,802	\$2,515-\$5,595	\$7,326	-\$1,251 to \$21,413	
Inpatient costs	12 18%	\$27,563	\$5,072-\$67,258	19 15%	\$8,567	\$2,992-\$16,927	\$18,996	-\$6,329 to \$60,088	
Outpatient costs	65 100%	\$6,292	\$3,828-\$10,419	128 98%	\$3,716	\$3,209-\$4,230	\$2,576	\$47 to \$6,845	
ER costs	12 18%	\$3,774	\$1,031-\$7,528	34 26%	\$1,319	\$716-\$2,032	\$2,455	-\$461 to \$6,301	

* Adjusted for age, gender, patient reported GI symptoms, and co-morbidities

** Bold indicates statistical significance at 0.05

Table 7
Mean adjusted^{*} predicted costs of CIC and matched controls under 65 years of age for 2-year analysis (2007-2008)^{}**

Outcome Variable	CIC Case (N=115)				Control (N=230)				Difference		
	N (%)	Mean	95% CI		N (%)	Mean	95% CI		Mean	95% CI	
Total costs	115 100%	\$5,673	\$4,775-\$6,709		229 100%	\$5,940	\$4,934-\$7,214		-\$267	-\$1,792 to \$1,181	
Hospital costs	77 67%	\$2,638	\$2,018-\$3,406		127 55%	\$3,680	\$2,520-\$5,148		\$1,042	-\$2,760 to \$3,64	
Inpatient costs	12 10%	\$4,373	\$1,838-\$8,172		27 12%	\$5,250	\$3,598-\$8,592		-\$877	-\$5,085 to \$3,689	
Outpatient costs	115 100%	\$4,406	\$3,731-\$5,270		229 100%	\$4,237	\$3,709-\$4,893		\$169	-\$740 to \$1,132	
ER costs	27 23%	\$358	\$228-\$521		49 21%	\$675	\$447-\$938		-\$317	-\$609 to -\$27	

* Adjusted for age, gender, patient reported GI symptoms, and co-morbidities

** Bold indicates statistical significance at 0.05