Disease-Associated Costs in Children With Inflammatory Bowel Disease: A Systematic Review

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Background: As a chronic noncurable disorder often diagnosed in childhood or adolescence, inflammatory bowel disease (IBD) confers a significant financial lifetime burden. The objective of this systematic review was to determine the disease-associated costs (both direct and indirect) associated with IBD in children and young adults.

Methods: We conducted a systematic review of the literature and included any study reporting direct health services–related costs or the indirect economic burden of IBD in persons aged ≤19 years (PROSPERO protocol number CRD2016036128). A technical panel of experts in pediatric gastroenterology and research methodology formulated the review questions, reviewed the search strategies and review methods, and provided input throughout the review process.

Results: Nine studies met criteria for inclusion, 6 of which examined direct costs, 1 of which examined both direct and indirect costs, 1 of which assessed indirect costs, and 1 of which assessed out-of-pocket (OOP) costs. Inflammatory bowel disease–associated costs were significantly higher compared with costs in non-IBD populations, with wide variations in cost estimates, which prevented us from conducting a meta-analysis. Costs in Crohn's disease were higher than in ulcerative colitis. Overall, direct costs shifted from inpatient hospitalization as a major source of direct costs to medications, mainly driven by anti–tumor necrosis factor agents, as the leading cause of direct costs. Predictors of high costs included uncontrolled disease, corticosteroid treatment in the previous year, and comorbidity burden.

Conclusions: The pediatric literature examining IBD-attributable costs is limited, with widely variable cost estimates. There is a significant knowledge gap in the research surrounding indirect costs and OOP expenses.

Key Words: colitis, costs, Crohn, IBD

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic noncurable disorders characterized by inflammation of the gastrointestinal tract with a typical course of remissions and relapses. The 2 most common subtypes are Crohn's disease (CD) and ulcerative colitis (UC). The incidence of IBD has risen over the last few decades, especially in the pediatric population.[1–4] Inflammatory bowel disease is often diagnosed in the second or third decades of life, and therefore it can impact both patients' and their family members' social functioning and well-being. Costs associated with IBD could be direct, indirect, and out-of-pocket (OOP) expenses. Direct medical costs include disease-attributed expenses incurred during the administration of health care (eg, hospitalization, physician services, medications, nursing and allied health care workers care, laboratory and diagnostic procedures, and other health care services). Indirect costs are costs that are borne by people and society due to lost earnings or productivity (eg, work/school

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absenteeism, presenteeism [decreased productivity of workers], early retirement, disability payments, paid assistance, and transportation). OOP costs are those paid for by the patients or their families in cash or credit for health care–related expenses that are not covered by public health or insurance systems (eg, pharmacy dispensing fees, parking costs and travel expenses for medical appointments, special diets, alternative or natural therapies, and educational books).[5–7]

In a report from Crohn's and Colitis Canada entitled "The Impact of IBD in Canada 2018," direct medical costs for IBD in Canada were estimated to be C$1.28 billion, and indirect costs were C$1.29 billion in 2018.[7–9] According to the Crohn's and Colitis Foundation, the total annual financial burden of IBD in the United States was estimated to be between $14.6 billion and $31.6 billion.[10]

It is therefore well-recognized that IBD places a significant financial burden on patients and the health system, and this burden is likely rising over time due to the rising prevalence of the disease[4] and the increasing use of high-cost biological medications. However, the cost of caring for children with IBD was identified as a gap in knowledge in the recent Canadian report,[9] despite this being the fastest-growing group of incident cases.[11] The objective of this systematic review was to determine the extent of the literature on health care costs associated with IBD in persons age 19 years and younger.

METHODS

The protocol for this review was registered in PROSPERO (registration number CRD2016036128). We conducted a systematic review using methodological approaches outlined in the Cochrane Handbook for Systematic Reviewers[12] and reported our results according to the modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[13] A technical panel of experts in pediatric gastroenterology and research methodology formulated the questions, reviewed the search strategies and methods, and provided input throughout the review process.

Eligibility Criteria

We included all studies examining any type of health care–related costs in IBD population aged ≤19 years, irrespective of the study design or language of publication. The following studies were excluded:

1. cost-effectiveness, cost–utility, cost–benefit, and other economic models or Markov analyses;
2. studies addressing the economic burden of IBD without giving a currency value of the costs;
3. studies that compared costs of 1 specific intervention, investigation, or specific medication with another investigation or medication (ie, comparative effectiveness research);
4. studies with nonextractable data, including studies that did not separate the pediatric population from the adult population.

Literature Search Strategy

An experienced research librarian (M.L.) developed and tested the search strategy in consultation with the review team. The Medline strategy was peer-reviewed by another experienced librarian following the Peer Review of Electronic Search Strategies (PRESS) checklist[14] before the search was run on December 31, 2018. The following databases were searched from inception: Medline (Ovid; Medline 1946–2018), Embase (Ovid; 1974–2018), Global Health (Ovid; 1973–2018), CINAHL (EBSCOhost; 1981–2018), and the Cochrane Library (Wiley; CENTRAL and Cochrane Database of Systematic Reviews). The original search strategy was translated for each database and used a combination of controlled vocabulary and key word searching. The strategy for Ovid MEDLINE and Embase is shown in Appendix Table 1. All other strategies are available upon request.

Using guidance from the Canadian Agency for Drugs and Technologies in Health's (CADTH's) Grey Matters tool (focusing on health economics)[15] for searching the gray literature, the following sources were searched: the Turning Research Into Practice (TRIP) Database, Crohn's and Colitis Canada, Health Quality Ontario publications, CADTH, Pediatric Economic Database Evaluation, Institute of Health Economics, Centre for Health Economics and Policy Analysis, Economic Burden of Illness in Canada, the Toronto Health Economics and Technology Assessment Collaborative, National Quality Measures Clearinghouse (AHRQ; discontinued July 2018), Database from the Federal Reserve Bank of St. Louis (IDEAS), and the Health Economics Research Unit (Aberdeen). The searches for these sources were simplified from the journal database searches and used variations of ((Crohn* OR colitis OR inflammatory bowel disease OR IBD) AND (cost* or economic*)).

All references were uploaded into EndNote (version X7; Clarivate Analytics, Philadelphia, PA, USA), and duplicates were removed.

Study Selection

A 2-stage process for study screening and selection was used. Three reviewers (W.E., E.I.B., & H.S.) independently screened the titles and abstracts of identified studies to determine if a citation met the inclusion criteria, and the full texts of relevant citations were also assessed independently by the same 3 reviewers applying the eligibility criteria. Discrepancies between the reviewers were resolved by consensus.

Data Extraction and Management

We developed standardized data extraction forms in the Microsoft Excel 2013 database (Microsoft Corporation, Redmond, WA, USA) and piloted them on 5 studies. Four reviewers (M.E.K., G.O., M.M. & H.K.) independently extracted data from each study using the forms. Discrepancies

between the reviewers were resolved by consensus. Extracted data were stored and managed using Excel. We extracted the following data:

- Study details: first author, country, setting, number of centers involved, study period, funding information, publication year and language of publication, and the currency used for costing.
- Study population details: IBD patient population demographics and illness severity and phenotype, if reported, type of controls (for studies that had a control group), recruitment method, study population size, and participant inclusion and exclusion criteria.
- Outcome and results details: for direct health care costs (medical, surgical, out- and in-patient medications and investigation costs, total costs, and reported predictors of high costs); for indirect health care costs (methods used for costing, costs of hours lost, and costs lost as a result of sickness leave, unemployment, and disability, costs to family, total costs, and reported predictors of high costs); for OOP costs (travel, parking, meals, medicine, books and other costs, total costs, and data source and predictors of high costs, if reported).

Assessment of Study Quality

As there is currently no standardized or validated quality assessment tool for studies of costs, we assessed the quality of evidence using the Evers Checklist.[16] This checklist covered 19 quality assessment questions, 13 of which we have determined to be relevant to this review. Those relevant questions included whether study population and research questions were clearly described, the appropriateness of the study design, timing of costs, study perspective, cost measure, valued cost, sensitivity analysis, reported results and conclusions, discounting of future cost, declaration of conflicts of interest, and ethical considerations. Each of these 13 questions required a yes/no answer. Two of 3 reviewers (G.O., M.M., & H.K.) independently assessed the quality of each study. Any difference was resolved through consensus.

Data Analysis

We had a priori planned to conduct a metal analysis to calculate the estimated annual per-patient costs (with 95% confidence intervals) and total economic burden for persons with CD and UC for individual countries/regions. However, due to heterogeneity in study methodology, reported end points, and population, we were unable to justify a meta-analysis and data are summarized qualitatively.

RESULTS

The details of the literature search are summarized in Figure 1. Nine studies[17–25] met our inclusion criteria. The characteristics and findings of those studies are summarized in Table 1, and results of quality assessment are summarized in Appenidx Table 2. Seven studies examined direct costs, 1 of which also examined indirect costs.[21] One study exclusively examined indirect costs,[22] and 1 study assessed OOP costs.[23] Seven studies were published as full papers[17–23] and 2 as abstracts.[24, 25]

Direct Costs

In the 3 included studies that compared IBD cases with controls, direct costs were significantly higher in children with IBD compared with controls. Studies included examined various aspects of direct costs (Table 2). Two studies included children and adults with IBD, but costs were presented separately by age group.[17, 20]

Bernstein et al.[17] reported the mean and median costs among IBD patients to be more than double those of non-IBD controls ($3896 [US$3246] vs $1826 [US$1521] for mean and $1562 [US$1301] vs $448 [US$373] for median), with higher mean costs in those with CD than in those with UC. The largest components of costs were for inpatient hospital costs and prescription drugs (42% in IBD vs 37% in non-IBD). Costs were highest in the first year of diagnosis for both CD and UC, with a greater decrement between the first year of diagnosis and year 3 in UC than for CD.[17]

deBruyn et al.[18] reported the total hospital charges for CD to have significantly climbed from $81 million in 1997 to $194 million in 2009. The median charge per hospitalization for CD also rose from $14,598 in 1997 to $23,472 in 2009. The total hospital charges for UC climbed from $53 million in 1997 to $143 million in 2009. The median charge per hospitalization for UC rose from $14,841 in 1997 to $25,681 in 2009.[18]

In their IBD cohort, Karve et al.[19] reported the mean total medical costs during the 1-year postdiagnosis period to be 9 times the mean costs for its comparator cohort ($18,302 vs $2063). The overall IBD cohort had a higher prevalence of 1 or more comorbid conditions than its comparator group.

A study by Kappelman et al.[20] reported that for patients with CD, the mean total costs were $10,952 per year, compared with $2898 for controls. The mean (SD) and median (interquartile range) annual CD-associated treatment costs were $8265 ($21,342) and $3203 ($530–$9935) per patient-year. For UC, the mean total costs for patients were $7948 per year, compared with $2715 for controls. The mean (SD) annual treatment costs associated with UC were $5066 ($17,928) per patient-year.[20] Outpatient medications, mainly driven by infliximab (the only biologic therapy available in children at the time), ranked highest among direct costs for persons (pediatric and adults) with CD. Medication costs constituted 35%, followed by outpatient services (33%) and hospitalization (31%). In the same study, however, hospitalization in persons with UC constituted 37% of direct costs, followed by outpatient services and outpatient medications. The study also showed that disease-attributed costs were significantly higher in

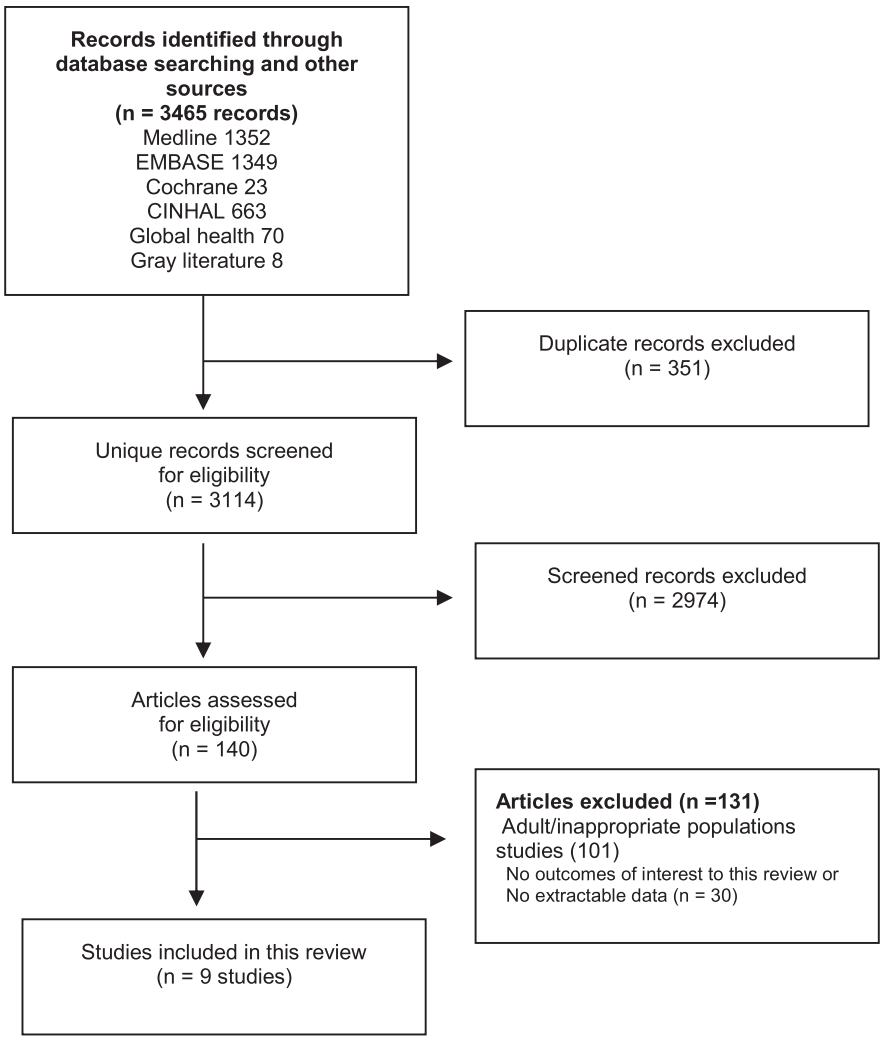

FIGURE 1. Modified PRISMA flowchart for literature search.

those aged 0–19 years compared with the older age groups, especially in persons with UC. On other hand, in the study by Bernstein et al.,[17] the mean cost in those with IBD aged 0–18 years was $3842, which was higher than that of adults aged 18–55 years but lower than that of those aged >55 years.

Indirect Costs

Two studies reported indirect costs in children with IBD.[21, 22] In a retrospective uncontrolled cross-sectional analysis from Canterbury, New Zealand (NZ), the annual total cost per patient with pediatric CD was NZ$14,375 (US$10,267), with indirect costs comprising NZ$1792 (US$1280). Based on these data, the investigators estimated the annual total direct and indirect costs of CD across NZ to be approximately NZ$25.9 million (US$18.5 million).[21] Another study from the United States exclusively assessed work hours and productivity losses for parents of children with CD and reported annual hours of work loss after initial diagnosis to be significantly higher in caregivers of children with CD (214 hours) compared with controls (169 hours; $P = 0.007$).[22]

No studies have reported indirect costs in children with UC.

Out-of-Pocket Costs

Only 1 multicenter study from the United States examined OOP through a series of surveys of parents of 150 children with IBD.[23] Travel expenses for the previous year were ≤$200.00 USD in 42% and ranged between US$200.01 and US$500 in 33% of participants. Families with a household income between $50,000 and $100,000 per year had a statistically significant probability of having higher annual OOP costs than families with a lower income of <$50,000

TABLE 1. Characteristics of the Included Studies

Study	Country	Cost Years	Data Source	Participants	Costs Assessed	Details of the Costs	Currency	Conclusion
Bernstein[17] [Full paper]	Canada	2005–2006	Provincial health administrative data (Manitoba)	89 CD, 62 UC, 1283 non-IBD controls: age-, sex-, and geography-matched to IBD patients	Direct	Mean direct cost of patients (0–18 y) (SE): CD = $3478 ($762), UC = $2803 ($565), non-IBD = $277 ($26)	Canadian dollar	Inpatient hospital care costs are 47% of total direct costs, and they are significantly higher in IBD compared with those without
deBruyn[18] [Full paper]	US	1997–2009	Hospitalization data (Kids' Inpatient Database)	12,649 and 7724 unweighted hospitalizations for CD and UC, respectively; no controls	Direct: hospital care	Total hospital charges for CD climbed from $81 million in 1997 to $194 million in 2009. Total hospital charges for UC climbed from $53 million in 1997 to $143 million in 2009	US dollar	Costs are increasing over the study period
Karve[19] [Full paper]	US	2000–2006	LifeLink insurance claims database	425 with IBD, 850 controls	Direct	Mean total medical costs during the 1-year postdiagnosis period in patients (0–15 y) (SD) was $24,074 ($60,201) for IBD vs $1336 ($10,292) for controls	US dollar	Health care utilization is higher in children with IBD compared with controls and increasing over time
Kappelman[20] [Full paper]	US	2003–2004	Health administrative data derived from insurance claims (Pharmetrics Patient-Centric Database)	737 CD, 488 UC, 3460 controls	Direct	Mean costs for CD and UC in patients (0–19 y) were $9555 and $10,063, respectively (SD was not stated)	US dollar	Health care utilization is higher in children with IBD compared with adults with IBD and with controls
Lion[21] [Full paper]	NZ	2009–2010	Provincial (Canterbury) health administrative data	24 CD, 0 controls	Direct and indirect	The average direct and indirect costs per patient were $8987 and $1280, respectively	NZ dollar	Inpatient hospital care costs were the largest source of direct costs. Loss of productivity was the largest source of indirect costs
Kahn[22] [Full paper]	US	2000–2012	Health administrative data derived from insurance claims (Truven MarketScan databases)	200 CD (caregivers), 200 age-matched controls	Indirect	Accumulated productivity losses over disease course were $24,118 for CD caregivers and $18,957 for controls	US dollar	Annual productivity losses were 27.2% ($1122) higher for caregivers of CD patients than controls
Sin[23] [Full paper]	US	2013–2014	Survey of patients	67 CD, 83 UC, 0 controls	OOP	Annually, 63.6%, 28.6%, and 5.3% of families had an OOP cost burden of <$500, $500– <$1000, and $1000–<$5000, respectively	US dollar	A high proportion of pediatric IBD families incur substantial OOP cost burden, especially in those who had prednisone in previous year
De Giacomo[24] [Abstract]	Italy	2010–2014	Hospital Discharge Database	1280 IBD-related ospitalizations, 0 controls	Direct	The total costs of hospitalizations were $1,281,575 for CD and $1,533,465 for UC	US dollar	Increase in IBD hospitalization and anti-TNF prescriptions over the study period
Quiros[25] [Abstract]	US	2014–2016	All-payer UB04 billing records	404 children with IBD, 0 controls	Direct	A total of $49,226,331 for inpatient and emergency room visit	US dollar	*C. difficile* infection was a predictor of higher costs

TABLE 2. Details of Direct Costs (if Stated) in Children With IBD in the Included Studies[a]

Study	Mean Costs (SD)	Inpatient Hospitalization	Outpatient	Medications	Physician Office Visits	Others
Bernstein[17] (IBD)	$3201 (SE $505) (over study period)	47%	6%	35%	12%	
Karve[18] (IBD)	24,074 (60,201) (>1 y postdiagnosis)	15,170 (63%)	4804 (20%)	2636 (11%)	1185 (5%)	Emergency room visits 280 (1%)
Kappelman[b20] (CD)	$8265 (21,342) (per patient-year)	31.4%	33.3%	35.3%	NS	
Kappelman[b20] (UC)	$5066 (17,928) (per patient-year)	37.6%	34.9%	27.5%	NS	
Sin[21] (CD)	$8987 (NS)	6071 (68%)	2916 (32%)	Included (45%) in outpatient costs	Included (38%) in outpatient costs	

All costs are in US dollars.
[a]Other included studies did not state the details of direct costs.
[b]Costs are for all included patients (pediatric and adults), as details of pediatric direct costs were not stated.

(P = 0.0001) or a higher income of >$100,000 ($P$ = 0.05) per year. High OOP costs were associated with uncontrolled IBD, prednisone course required during the previous year, at least 1 emergency department visit for IBD symptoms, at least 4 outpatient primary medical doctor visits for IBD symptoms, and a history of 4 or more lifetime hospitalizations for acute IBD care. Total OOP costs were similar between those with CD and those with UC.[23]

DISCUSSION

In this systematic review, we identified 9 studies that fulfilled our inclusion criteria. Except for 2 studies from New Zealand and Italy,[21, 24] all studies came from North America, mainly the United States. Overall, IBD-related direct costs are high compared with the non-IBD population and are rising over time. Predictors of high costs described in 1 study included uncontrolled disease, corticosteroid requirement, perianal disease, comorbid conditions such as *Clostridium difficile* infection, psychiatric disease such as depression and anxiety, and inpatient IBD-related hospitalization in the prior year.[19, 21, 23, 25] Some studies, as that of Krave et al.,[19] may be confounded by comorbid conditions. Several adult studies showed the same predictors of higher health care costs and utilization in persons with IBD.[26, 27] Additional predictors of higher costs in the adult IBD population included tobacco smoking, penetrating CD, pancolitis, and obesity.[28, 29]

Over time, there was a shift of the main driving factor of the majority of direct costs from inpatient hospitalization to medication expenses, mainly biological medications, as reflected in the study by Kappelman et al.[20] The discrepancy between this study and the other included studies from the United States in defining the major factor in driving direct costs is perhaps due to the reporting of actual reimbursements instead of charges to the insurer. A recent study that examined temporal patterns of hospitalization for IBD over 5 years in 34 countries across the globe showed that hospitalization rates for IBD are higher in Western countries but are typically stabilizing or decreasing.[30] This change may be due to several factors, including the recent introduction of biologics.[7, 31, 32]

Members of our group investigated the direct hospital costs from the payer perspective for a cohort of 187 CD and 115 UC adult patients at a tertiary care hospital in Manitoba in 1994–1995.[33] The mean cost of hospital admission per medical case was C$2571 (95% confidence interval [CI], C$1801–C$3340) for CD and C$2186 (95% CI, C$1449–C$2922) for UC. The mean cost per hospitalized surgical case was higher, at C$3427 (95% CI, C$2728–C$4126) for CD and C$4635 (95% CI, C$3549–C$5726) for UC. Surgery accounted for 50% of all hospital admissions, 58% of all hospital days, and 61% of all costs. Although surgery accounted for significant direct costs in the included study by deBruyn et al.,[18] inpatient surgical costs accounted for 12% and 16% for persons with CD and UC, respectively, in the study by Kappelman et al.[20] This is likely to be related to the difference in study design. Both Bernstein et al.[17] and Kappelman et al.[20] included children and adults with IBD. Pediatric IBD–related costs were higher than the cost of caring for adults in both cases. Several factors might explain this difference, including the more extensive and aggressive nature of pediatric IBD, with potential negative effects on growth and development.[34] In addition, there may be some differences in practice patterns between pediatric and adult gastroenterologists, including the frequency of scheduled office visits and the threshold for hospital admission. Finally, recent evidence suggested earlier introduction of anti–tumor necrosis factor (anti-TNF) agents,

especially in children with CD, with higher utilization rates of infliximab in pediatric IBD.[35] After introduction of anti-TNF agents, the COIN adult study from the Netherlands reported that surgery and hospitalization accounted for only 19% and <1% of the health care costs in adults with CD and 23% and 1% in UC.[7] Similar to our findings, they reported higher direct costs in CD compared with UC. This also seemed to be the case for indirect costs, as a recent systematic review that included 11 adult studies that examined indirect costs in both CD and UC concluded that indirect costs of UC seemed to be lower than those in CD.[36] As in our review, the authors could not perform a meta-analysis due to the heterogeneity of the study end points and methodologies. The COIN study reported that productivity losses accounted for 16% of the total costs in CD and 39% of the total costs in UC.[7] We included 2 pediatric studies that indicated high indirect costs related to caregiver work loss, which was significantly higher than in those without IBD.[21, 22] A recent pediatric study found that children with IBD are more frequently absent from school than a non-IBD group.[37] The main cause of school absenteeism was reported to be events related to the disease itself, such as scheduled clinic visits and endoscopies. Interestingly, by excluding the absences for scheduled care, the rate of school absenteeism of IBD patients was significantly lower than that of the non-IBD group. The study, however, did not report absenteeism-associated costs. The only study included in our systematic review that determined OOP costs was that of Sin et al.,[23] who reported a substantial OOP cost burden to families with children with IBD. No other pediatric studies have examined OOP costs, an area that is obviously a major knowledge gap. Out-of-pocket costs were also reported in the COIN adult study to be €75 in CD and €57 in UC per adult person over the 3 months preceding administration of the study questionnaire.[7]

Our review has several points of strength, including its systematic and extensive literature review and a search strategy that underwent peer review. We also attempted to reduce bias by including multiple reviewers of abstracts and data, with disagreements discussed and resolved by consensus with methodological and clinical experts. However, we were limited by the scarcity of studies to answer our research question and the small sample sizes of the included studies examining indirect and OOP costs. We could not obtain pediatric data of some published abstracts despite contacting the authors.[38, 39] We could not provide overall estimates of costs, as meta-analysis was precluded by included studies' heterogeneous methodologies, end points, and populations. The majority of the included studies were from the United States, and therefore the generalizability of our findings to other regions is questionable.

In summary, we found a paucity of studies that examined IBD-associated costs in children with IBD. Although the majority of studies evaluated direct costs, the methodology used was too heterogeneous and studies could not be pooled. Further, the vast majority of studies were conducted in North America. Hence, there is a great need for additional studies assessing costs of pediatric IBD using robust methodology and from an international perspective.

REFERENCES

1. Crohn's & Colitis Canada (CCC). http://crohnsandcolitis.ca/Crohns_and_Colitis/documents/reports/2018-Impact-Report-LR.pdf. Accessed February 15, 2019.
2. Benchimol EI, Fortinsky KJ, Gozdyra P, et al. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis.* 2011;17:423–439.
3. Benchimol EI, Guttmann A, Griffiths AM, et al. Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: evidence from health administrative data. *Gut.* 2009;58:1490–1497.
4. El-Matary W, Moroz SP, Bernstein CN. Inflammatory bowel disease in children of Manitoba: 30 years' experience of a tertiary center. *J Pediatr Gastroenterol Nutr.* 2014;59:763–766.
5. Bernstein CN, Papineau N, Zajaczkowski J, et al. Direct hospital costs for patients with inflammatory bowel disease in a Canadian tertiary care university hospital. *Am J Gastroenterol.* 2000;95:677–683.
6. Longobardi T, Jacobs P, Wu L, Bernstein CN. Work losses related to inflammatory bowel disease in Canada: results from a national population health survey. *Am J Gastroenterol.* 2003;98:844–849.
7. van der Valk ME, Mangen MJ, Leenders M, et al; COIN Study Group and the Dutch Initiative on Crohn and Colitis. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFα therapy: results from the COIN study. *Gut.* 2014;63:72–79.
8. Kuenzig ME, Lee L, El-Matary W, et al. The impact of inflammatory bowel disease in Canada 2018: indirect costs of IBD care. *J Can Assoc Gastroenterol.* 2019;2:S34–S41.
9. Benchimol EI, Bernstein CB, Bitton A, et al. The impact of inflammatory bowel disease in Canada 2018: a scientific report from the Canadian Gastro-Intestinal Epidemiology Consortium to Crohn's and Colitis Canada. *J Can Assoc Gastroenterol.* 2019;2:S1–S5.
10. Crohn's & Colitis Foundation (CCFA). www.crohnscolitisfoundation.org/assets/pdfs/updatedibdfactbook.pdf. Accessed February 25, 2019.
11. Benchimol EI, Bernstein CN, Bitton A, et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: distributed network analysis of multiple population-based provincial health administrative databases. *Am J Gastroenterol.* 2017;112:1120–1134.
12. Higgins JPT, Altman DG. Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1 (updated 2011)*. The Cochrane Collaboration; 2008. www.cochrane-handbook.org.
13. Moher D, Shamseer, Clarke M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015. *Syst Rev.* 2015;4:1–9.
14. McGowan J, Sampson M, Salzwedel DM, et al. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40–46.
15. Canadian Agency for Drugs and Technologies in Health. *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature*. Ottawa, ON: CADTH; 2015.
16. Evers S, Goossens M, de Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: consensus on health economic criteria. *Int J Technol Assess Health Care.* 2005;21:240–245.
17. Bernstein CN, Longobardi T, Finlayson G, Blanchard JF. Direct medical cost of managing IBD patients: a Canadian population-based study. *Inflamm Bowel Dis.* 2012;18:1498–1508.
18. Debruyn JC, Soon IS, Hubbard J, et al. Nationwide temporal trends in incidence of hospitalization and surgical intestinal resection in pediatric inflammatory bowel diseases in the United States from 1997 to 2009. *Inflamm Bowel Dis.* 2013;19:2423–2432.
19. Karve S, Candrilli S, Kappelman MD, et al. Healthcare utilization and comorbidity burden among children and young adults in the United States with systemic lupus erythematosus or inflammatory bowel disease. *J Pediatr.* 2012;161:662–670. e2.
20. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology.* 2008;135:1907–1913.
21. Lion M, Gearry RB, Day AS, Eglinton T. The cost of paediatric and perianal Crohn's disease in Canterbury, New Zealand. *N Z Med J.* 2012;125:11–20.

22. Kahn S, Lin CW, Ozbay B, et al. Indirect costs and family burden of pediatric Crohn's disease in the United States. *Inflamm Bowel Dis.* 2017;23:2089–2096.
23. Sin AT, Damman JL, Ziring DA, et al. Out-of-pocket cost burden in pediatric inflammatory bowel disease: a cross-sectional cohort analysis. *Inflamm Bowel Dis.* 2015;21:1368–1377.
24. De Giacomo C, Moretti C, Stacul EF, et al. A 5-year study on hospital discharges for pediatric inflammatory bowel diseases in Lombardia. *Dig Liv Dis.* 2015;47:e257.
25. Quiros JA, Andrews A, Jump C, et al. Cost of care analysis for children with inflammatory bowel disease in South Carolina. *J Pediatr Gastroenterol Nutr.* 2018;67:S73.
26. Limsrivilai J, Stidham RW, Govani SM, et al. Factors that predict high health care utilization and costs for patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2017;15:385–392.e2.
27. Click B, Ramos Rivers C, Koutroubakis IE, et al. Demographic and clinical predictors of high healthcare use in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2016;22:1442–1449.
28. Tan MC, El-Serag HB, Hou JK. Determinants of healthcare utilization among veterans with inflammatory bowel disease. *Dig Dis Sci.* 2017;62:607–614.
29. Nguyen NH, Ohno-Machado L, Sandborn WJ, Singh S. Obesity is independently associated with higher annual burden and costs of hospitalization in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2019;17:709–718.e7.
30. King JA, Underwood FE, Panaccione N, et al. Trends in hospitalisation rates for inflammatory bowel disease in Western versus newly industrialised countries: a population-based study of countries in the Organisation for Economic Co-operation and Development. *Lancet Gastroenterol Hepatol.* 2019;4:287–295.
31. Park KT, Colletti RB, Rubin DT, et al. Health insurance paid costs and drivers of costs for patients with Crohn's disease in the United States. *Am J Gastroenterol.* 2016;111:15–23.
32. Lachaine J, Feagan B, Martel MJ, et al. The impact of TNF inhibitors for Crohn's disease on health care resource utilization: an analysis using the RAMQ database. *Value Health.* 2012;15:A137.
33. Bernstein CN, Papineau N, Zajaczkowski J, et al. Direct hospital costs for patients with inflammatory bowel disease in a Canadian tertiary care university hospital. *Am J Gastroenterol.* 2000;95:677–683.
34. Carroll MW, Kuenzig E, Mack D, et al. The impact of inflammatory bowel disease in Canada 2018: children and adolescents with IB. *J Can Assoc Gastroenterol.* 2019;2:S49–S67.
35. El-Matary W, Leung S, Tennakoon A, et al. Trends of utilization of tumor necrosis factor antagonists in children with inflammatory bowel disease: a Canadian population-based study. *Gastroenterology.* 2019;156:S–614.
36. Kawalec P. Indirect costs of inflammatory bowel diseases: Crohn's disease and ulcerative colitis. A systematic review. *Arch Med Sci.* 2016;12:295–302.
37. Eloi C, Foulon G, Bridoux-Henno L, et al. Inflammatory bowel diseases and school absenteeism. *J Pediatr Gastroenterol Nutr.* 2019;68:541–546.
38. Baldassano RN, Shahabi A, Seabury SA, et al. Average annual healthcare costs for pediatric and adult patients with Crohn's disease or ulcerative colitis. *Gastroenterology.* 2018;154:S8.
39. Lichtenstein GR, Shahabi A, Seabury SA, et al. The total direct cost of healthcare in the United States in patients with Crohn's disease and ulcerative colitis: an age specific analysis. *Gastroenterology.* 2017;152:S448.

APPENDIX

Appendix Table 1. Literature Search Strategy for Ovid MEDLINE and Embase

1. exp Inflammatory Bowel Diseases/
2. (inflamm* bowel disease* or IBD).tw,kw.
3. crohn*.tw,kw.
4. ((regional or terminal or granulomatous or gravis or ulcerative) adj2 (ileiti* or enteriti* or colitis*)).tw,kw.
5. exp Colitis/
6. colitis*.tw,kw.
7. (Colon adj2 inflamm*).tw,kw.
8. exp Enterocolitis/
9. (enterocoliti* or entero-colit*).tw,kw.
10. exp Proctitis/
11. (proctiti* or proctocoliti* or procto-coliti*).tw,kw.
12. exp Ileitis/
13. (ileiti* or ileocolitis).tw,kw.
14. Jejunoileitis.tw,kw.
15. or/1–14
16. Value of Life/
17. exp Economics/
18. exp Health Care Costs/
19. exp "Costs and Cost Analysis"/
20. exp "Fees and Charges"/
21. exp economics, hospital/
22. exp economics, medical/
23. exp economics, nursing/
24. exp economics, pharmaceutical/
25. cost benefit analys*.tw,kw.
26. ((disease* or illness* or patient*) adj3 (cost* or burden* or econom*)).tw,kw.
27. (econom* adj2 (cost* or burden* or impact*)).tw,kw.

Appendix Table 1. (Continued)

28. (health care cost* or healthcare cost*).tw,kw.
29. (cost* adj2 illness*).tw,kw.
30. ((direct or indirect or in-direct) adj3 cost*).tw,kw.
31. Absenteeism/
32. ((work* or job* or employ*) adj3 (absent* or missed or missing or miss)).tw,kw.
33. exp Health Resources/ut
34. (healthcare utiliz* or health care utiliz* or resource utiliz* or health services utiliz*).tw,kw.
35. or/16–34
36. 15 and 35
37. exp Animals/ not (exp Animals/ and Humans/)
38. 36 not 37
39. exp inflammatory bowel disease/
40. (inflamm* bowel disease* or IBD).tw,kw.
41. crohn*.tw,kw.
42. ((regional or terminal or granulomatous or gravis or ulcerative) adj2 (ileiti* or enteriti* or colitis*)).tw,kw.
43. exp colitis/
44. colitis*.tw,kw.
45. (Colon adj2 inflamm*).tw,kw.
46. enterocolitis/
47. (enterocoliti* or entero-colit*).tw,kw.
48. (proctiti* or proctocoliti* or procto-coliti*).tw,kw.
49. ileitis/
50. (ileiti* or ileocolitis).tw,kw.
51. Jejunoileitis.tw,kw.
52. or/39–51
53. socioeconomics/
54. exp economics/
55. exp *health economics/

Appendix Table 1. (Continued)

56. cost benefit analys*.tw,kw.
57. ((disease* or illness* or patient*) adj2 (cost* or burden* or econom*)).tw,kw.
58. (econom* adj2 (cost* or burden* or impact*)).tw,kw.
59. (health care cost* or healthcare cost*).tw,kw.
60. (cost* adj2 illness*).tw,kw.
61. ((direct or indirect or in-direct) adj3 cost*).tw,kw.
62. absenteeism/
63. ((work* or job* or employ*) adj3 (absent* or missed or missing or miss)).tw,kw.
64. *health care utilization/
65. (healthcare utiliz* or health care utiliz* or resource utiliz* or health services utiliz*).tw,kw.
66. or/53–65
67. 52 and 66

Appendix Table 1. (Continued)

68. exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
69. exp human/ or exp human experimentation/ or exp human experiment/
70. 68 not 69
71. 67 not 70
72. editorial.pt.
73. letter.pt. not (letter.pt. and randomized controlled trial/)
74. 72 or 73
75. 71 not 74
76. 38 use prmz
77. 71 use oemezd
78. 76 or 77
79. remove duplicates from 78
80. 79 use prmz
81. 75 use oemezd

Appendix Table 2. Quality of Included Studies

First Author	Industry Funded	Population Description	Defined Question	Approved Study Design	Study Timing	Clear Perspective
Bernstein[17]	No	Yes	Yes	Yes	Yes	Yes
deBruyn[18]	No	Yes	Yes	Yes	Yes	Yes
Karve[19]	No	Yes	Yes	Yes	Yes	Yes
Kappelman[20]	No	Yes	Yes	Yes	Yes	Yes
Lion[21]	No	Yes	Yes	Yes	Yes	Yes
Kahn[22]	No	Yes	Yes	Yes	Yes	Yes
Sin[23]	No	Yes	Yes	Yes	Yes	Yes
De Giacomo[24]	No	Yes	Yes	Yes	Yes	Yes
Quiros[25]	No	Yes	Yes	Yes	Yes	Yes
First Author		Costs Discounting	Approved Analysis	Study Conclusions	Generalizability	COI Declaration
Bernstein[17]		No	No	Yes	No	Yes
deBruyn[18]		No	No	Yes	No	No
Karve[19]		No	No	Yes	No	Yes
Kappelman[20]		No	No	Yes	Yes	Yes
Lion[21]		No	No	Yes	No	No
Kahn[22]		No	No	Yes	No	No
Sin[23]		No	No	Yes	No	Yes
De Giacomo[24]		No	Yes	Yes	No	Yes
Quiros[25]		No	Yes	Yes	No	Yes

Approved Cost Measure	Cost Discounting	Appro Analysis	Study Conclusions	Generalizability	COI Declaration	Ethical Considerations
Yes	FALSE	FALSE	TRUE	TRUE	TRUE	FALSE
Yes	FALSE	FALSE	TRUE	FALSE	TRUE	TRUE
Yes						
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes						
Yes	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE
No	FALSE	FALSE	TRUE	FALSE	TRUE	TRUE
Yes						
Yes						
Ethical Considerations						
Yes						
No						
Yes						
No						
Yes						
No						
Yes						
No						
No						