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ORIGINAL ARTICLE

Perianal Fistulas Are Associated with Persistently Higher Direct Health Care Costs in Crohn's Disease: A Population-Based Study

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Abstract

Background The economic impact of perianal fistulas in Crohn's disease (CD) has not been formally assessed in population-based studies in the biologic era.

Aim To compare direct health care costs in persons with and without perianal fistulas.

Methods We performed a longitudinal population-based study using administrative data from Ontario, Canada. Adults (> 17 years) with CD were identified between 2007 and 2013 using validated algorithms. Perianal fistula positive "cases" were matched to up to 4 "controls" with CD without perianal fistulas based on age, sex, geographic region, year of CD diagnosis and duration of follow-up. Direct health care costs, excluding drug costs from private payers, were estimated annually beginning 5 years before (lookback) and up to 9 years after perianal fistula diagnosis (study completion) for cases and a standardized date for matched controls.

Results A total of 581 cases were matched to 1902 controls. The annual per capita direct cost for cases was similar at lookback compared to controls ($2458 ± 6770 vs $2502 ± 10,752; p = 0.952), maximally greater in the first year after perianal fistulas diagnosis ($16,032 ± 21,101 vs $6646 ± 13,021; p < 0.001) and remained greater at study completion ($11,358 ± 17,151 vs $5178 ± 9792; p < 0.001). At perianal fistula diagnosis, the cost difference was driven primarily by home care cost (tenfold greater), publicly-covered prescription drugs (threefold greater) and hospitalizations (twofold greater), whereas at study completion, prescription drugs were the dominant driver (threefold greater).

Conclusion In our population-based cohort, perianal fistulas were associated with significantly higher direct healthcare costs at the time of perianal fistulas diagnosis and sustained long-term.

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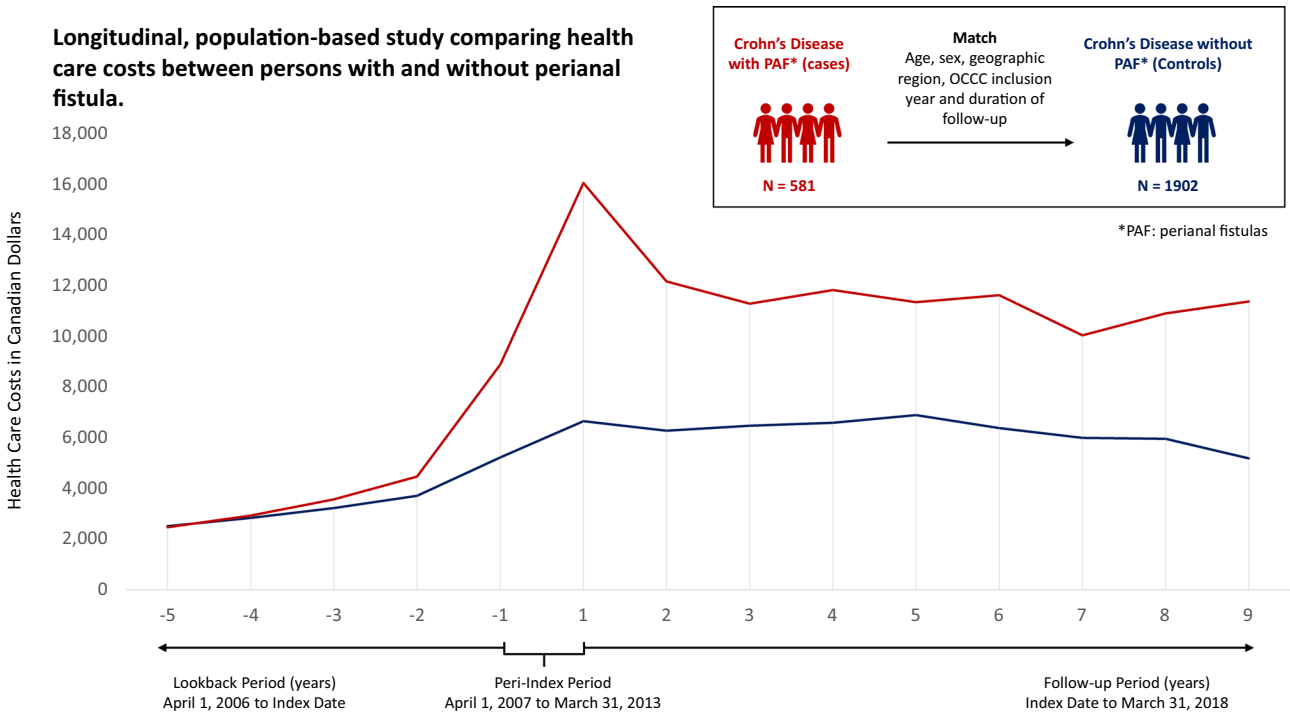
Graphical Abstract



Keywords Health care utilization · Health care economics · Inflammatory bowel disease · Perianal Crohn's disease

Introduction

Inflammatory bowel disease (IBD) has emerged as a global disease with rising prevalence world-wide [1, 2]. In newly industrialized countries the incidence is rising rapidly, while in Western countries the prevalence is projected to surpass 1% of the population by 2030 [1]. Canadians currently spend approximately $1.3B per year for direct health care related to the management of IBD and its complications [3]. Given these epidemiological trends, the young age of disease onset, progressive nature of IBD, and costly long-term treatments, it can be expected that IBD will increasingly place a tremendous economic strain on resource-constrained health care systems.

Accurate estimates of health care cost and the distribution of cost per health care dimension are essential for policy makers to allocate resources appropriately. Several systematic reviews and recent population-based studies from Denmark, Europe/Israel, and Canada have estimated the cost of care in IBD [4–7]. These studies found substantial differences between disease types (Crohn's disease [CD] vs. ulcerative colitis [UC]) and increased health care costs over time, driven largely by the expanding use of high-price biologic therapies [5, 7, 8]. An important limitation of these studies is that the impact of different disease phenotypes on health care cost has not been well established.

Perianal Crohn's disease is one of the most common disease phenotypes, occurring in roughly 30% of persons with CD [9, 10]. The presence of perianal fistulas (PAF) is associated with substantial morbidity and medical interventions are less effective for fistulizing disease than they are for inflammation confined to the intestinal lumen [11–13]. To date, few studies have assessed the direct health care cost specifically in persons with PAF [14–19]. These studies are limited by small sample sizes, lack of longitudinal follow-up, an absence of matched controls, and/or were performed prior to the era of biological therapies. Furthermore, no studies have assessed the impact of PAF on the long-term cost of care. Therefore, we performed a longitudinal, population-based study with an aim to compare the direct health care costs and resource utilization in persons with and without PAF. We hypothesized that persons with PAF impose greater direct health care costs at the time of diagnosis and that this is sustained over the long-term.

Methods

Study Design and Data Sources

We conducted a longitudinal retrospective population-based comparative cohort study between April 1, 2002 and March 31, 2017 using health administrative data from Ontario, Canada. Multiple databases, managed by ICES, were linked deterministically using unique encrypted identification numbers to estimate direct health care costs. A description of each database is included in Supplementary Table 1. The databases are completely integrated and provide end-to-end patient-physician interactions within the Ontario public healthcare system, for all residents who qualify for universal health care coverage (> 99% of the 14.6 million population). They capture complete health services utilization information and select demographic and clinical information pertaining to health care visits. Medication costs are available for persons covered under the Ontario Drug Benefit (ODB) program but not those with private insurance coverage. ODB applies to Ontario residents 65 years of age or older, and those living in a Long-Term Care Home or a Home for Special Care, and those who qualify through other governmental programs (e.g., income, disability).

Derivation of Cohorts

We identified all adults (≥ 18 years) with incident Crohn's disease from the Ontario Crohn's and Colitis Cohort (OCCC) using validated algorithms [20, 21]. The definition has a sensitivity of 77% and specificity of specificity of 96% for identifying adults with IBD aged 18–64 and can discriminate between persons with CD and UC with an accuracy of 91%.

Persons were included if they met the following criteria: member of the OCCC with a diagnosis of Crohn's at both incident date and latest contact; incident diagnosis of Crohn's on April 1, 2002 or later in the OCCC. A selection period from April 1, 2007 to March 31, 2013 was chosen to maximize follow-up time (up to 9 years post-study index date). Persons with perianal fistulizing disease were identified using a case definition that required at least two ICD-10 codes for fistula diagnosis or a Canadian Classification of Health Intervention (CCI) procedural code associated with perianal fistulas or a radiologic imaging code of the pelvis, all within 2 years (Supplementary Table 2). This case definition has been shown to have a sensitivity of 81% (73%–87%) and specificity of 90% (87%–93%) for discriminating between persons with PAF and without PAF [22].

Persons with CD with PAF (cases) were matched to a maximum of 4 persons with luminal CD without PAF (controls) based on age at index (± 2 years), sex, geographic region (using Local Health Integration Network), year of inclusion in the OCCC (exact match), and duration of follow-up. Persons were excluded for the following reasons: gap in public health care coverage, age outside 18–105 years during the study period, when death occurred or became ineligible for public health care coverage during the first 5 years of follow-up period, missing demographics (sex, age, and geographical location), when a matched control could not be found, and when there was insufficient follow-up (minimum of 1 year before and 5 years after the index date).

The date of Crohn's disease diagnosis was the date of inclusion into OCCC. The study index date for cases was defined as the date when the criteria for PAF was satisfied. An index date for controls was assigned relative to the index date of their respective matched case. As cases and controls were matched on year of inclusion in OCCC and duration of follow-up, controls have the same of follow-up as cases. Similarly, cases and controls had the same time between CD diagnosis (OCCC inclusion) and index date to allowing baseline characteristics and follow-up time periods to be equal between groups. This controlled for differences in cost that occur around the time of CD diagnosis.

Outcomes and Definitions

Our primary outcome was the overall annual direct cost of care per person. This was enumerated by adding the total costs per health care dimension: (1) outpatient costs (including physician billings, laboratory testing, and diagnostic imaging.), (2) emergency department visits, (3) hospitalizations, (4) same-day surgery, (5) home care, (6) public drug cost (among those who qualified for ODB) and (7) other (dialysis, cancer clinics, radiation clinics). The cost of "other" was negligible and was not included in the analysis that compared cost by health care dimension. Hospitalization costs were estimated by the resource intensity weight (RIW) methodology from the Canadian MIS Database, which attributes a hospital specific cost to the resource intensity of each visit [23]. All costs were adjusted to the 2018 Canadian dollar. A pre-planned sensitivity analysis included the total direct cost of care without ODB costs.

Our secondary outcomes included individual costs of care per health care dimension and health care resource utilization (the number of ambulatory encounters, emergency department encounters and hospital admissions). We also stratified time intervals into the pre-index period (> 1 to 5 years prior to the study index date), the peri-index period (1 year prior to 1 year after the study index date) and the post-index period (> 1 to 9 years after the study index date).

Our primary and secondary outcomes were estimated annually beginning 5 years prior to the index date (look

back), and up to 9 years after the index date (study completion). This allowed us to establish baseline and ongoing costs of care.

Statistical Analysis

Descriptive statistics were used for patient demographics, and baseline characteristics. Categorical variables are presented as proportions and continuous variables as means with standard deviation (SD) and medians with interquartile range (IQR).

The mean cost per patient was calculated annually beginning 5 years prior to the index date and up to 9 years after the index date. The mean difference between cases and controls were calculated along with standard deviations. No adjustment was made to account for loss to follow-up within specific years, for 2 to 5 years prior to the index date, and 6 to 9 years after the index date. Differences in costs between cases and controls were compared by regression assuming a gamma distribution of costs. P values less than 0.05 were considered statistically significant.

Ethics

This study was conducted in accordance with the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE and GPP. The administrative data used in this study are maintained by ICES, an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Separate ethics approval for the study was obtained from Advarra Inc's Institutional Review Board (Pro00033879).

Results

Study Cohorts

A total of 581 persons with CD with PAF met our study criteria and were matched to 1902 persons with CD without PAF (controls). The reasons for exclusion are reported in Fig. 1. The timing of when the criteria for PAF was satisfied (index date) in relation to the diagnosis of CD (OCCC inclusion) are reported in Fig. 2. The baseline demographics were similar for cases and controls (Table 1). All persons had data available for a minimum of one year before and 5 years after the index date. The numbers of persons with lookback and follow-up beyond these timepoints (up to 5 years before and 9 years after the index date) are reported in Supplementary Table 3.

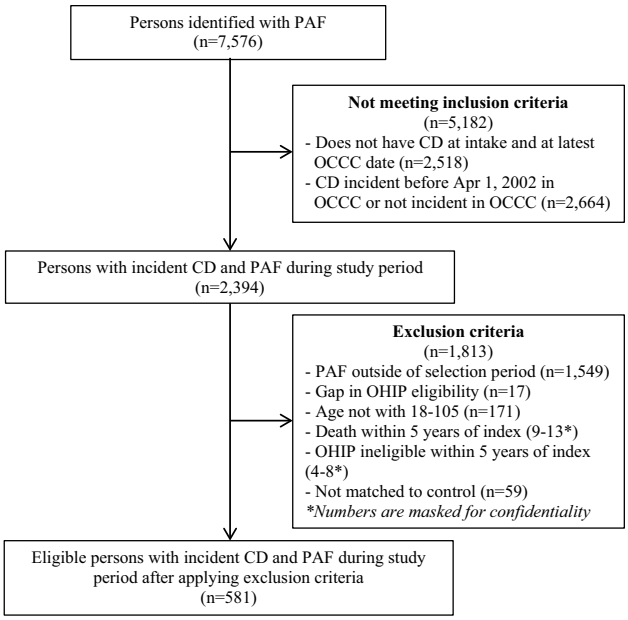


Fig. 1 Flow diagram of included persons with Crohn's disease with perianal fistulas

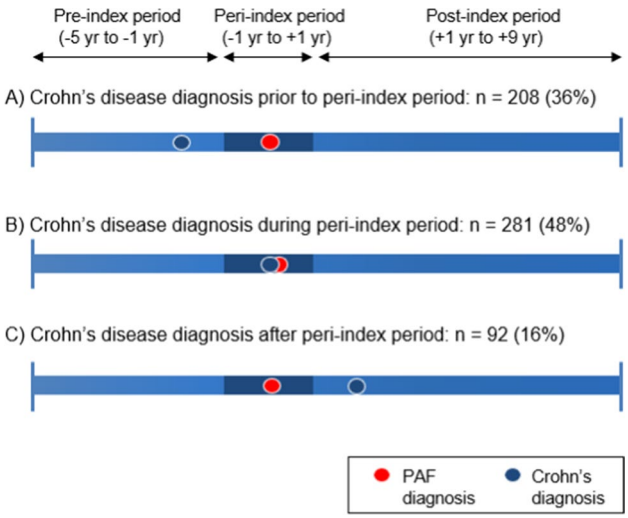


Fig. 2 The proportion of patients with perianal fistulas who were diagnosed with Crohn's disease prior to (pre-index period), during (peri-index period) or after (post-index period) the diagnosis of perianal fistulas (index date)

Overall Direct Cost of Care

The mean direct annual health care cost per person at lookback (5 years prior to the index date) was similar between persons with PAF and controls (mean dollars per person; $\$2503 \pm 10{,}752$ vs $\$2459 \pm 6771$; $p = 0.952$) (Fig. 3). The maximal annual cost per person for both cohorts occurred

Table 1 Demographics of included persons with Crohn's disease with (cases) and without (controls) perianal fistulas

Demographic	Controls (n = 1902)	Cases (n = 581)
Sex, n (%)		
Female	903 (47.5)	279 (48.0)
Age (years)		
18–44, n (%)	1581 (83.1)	468 (80.6)
45–64, n (%)	312 (16.4)	105 (18.1)
65–105, n (%)	9 (0.5)	8 (1.4)
Median (IQR)	29 (23–38)	29 (23–40)
Income quintile, n (%)		
Unknown	8 (0.4)	0 (0.0)
Lowest quintile	301 (15.8)	90 (15.5)
Medium–low quintile	404 (21.2)	106 (18.2)
Middle quintile	352 (18.5)	118 (20.3)
Medium–high quintile	410 (21.6)	151 (26.0)
Highest quintile	427 (22.5)	116 (20.0)
Local health integration network, n (%)		
Central	239 (12.6)	65 (11.2)
Central East	250 (13.1)	70 (12.0)
Central West	92 (4.8)	31 (5.3)
Champlain	322 (16.9)	97 (16.7)
Erie St. Clair	83 (4.4)	27 (4.6)
Hamilton Niagara Haldimand Brant	223 (11.7)	66 (11.4)
Mississauga Halton	111 (5.8)	34 (5.9)
North East	58 (3.0)	24 (4.1)
North Simcoe Muskoka	44 (2.3)	17 (2.9)
North West	21 (1.1)	9 (1.5)
South East	47 (2.5)	20 (3.4)
South West	157 (8.3)	45 (7.7)
Toronto Central	134 (7.0)	39 (6.7)
Waterloo Wellington	121 (6.4)	37 (6.4)

IQR, interquartile range

during the first year after the index date: $16,032 ± 21,102 dollars per persons with PAF and $6647 ± 13,021 dollars per person without PAF. The annual cost of care became significantly greater in persons with PAF in the year preceding the index date (mean difference per person, $3665; $p < 0.001$), was maximally greater in the first year after the index date (mean difference per person, $9385; $p < 0.001$) and remained greater for the remainder of the study period (mean difference $4033–$6180; all p-values < 0.01). Similar trends occurred when excluding ODB costs: mean difference per person was $3452 ($p < 0.001$) in the year prior to the index date, $7268 ($p < 0.001$) in the year after the index date, and $1069–$2372 for the remainder of the study follow-up (all p-values < 0.05) (Supplementary Table 4).

Direct Cost of Care Per Health Care Dimension

In the pre-index period, the cost of care between cohorts was similar for each health care dimension (Fig. 3 and Supplementary Table 5). In contrast, during the peri-index period (1 year preceding and 1 year after the index date), the cost of care was significantly greater for persons with PAF for all health care dimensions. The absolute per patient cost differences was greatest for drug costs ($2118 dollars; $p < 0.01$), home care services ($1920 dollars; $p < 0.01$), and hospitalizations ($1888 dollars; $p < 0.001$); whereas the relative per patient cost difference was greatest for home care services (tenfold greater), same day surgery (fourfold greater), and drug costs (twofold greater) (Supplementary Table 4). In the post-index period, the cost of each health care dimension in both cohorts declined, except for drug cost. During this period, drug cost was the major driver of cost difference between cohorts (absolute annual difference ranged from $2840–$4552), whereas the cost of outpatient care and same day surgery remained marginally greater in persons with PAF.

At least one ODB claim was made in 31% vs 18% of persons in the first year after the index date, 62% vs 45% of persons within 5 years after the index date and 67% vs 55% of persons within 9 years after the index date in persons with and without PAF respectively. Using data from years − 1 to + 5, where there was complete data for all persons, the proportion of the annual health care expenditures attributable to prescription drugs rose from 9 to 56%, and from 11 to 43% for persons with and without PAF respectively (Fig. 4). In contrast, the proportion of the annual care expenditures attributable to hospitalization costs decreased to a similar extent in both cohorts over the follow-up period. Changes in home care costs were most evident in persons with PAF, where the annual proportion of home care expenditure rose from 1% at lookback to a peak of 13% at the time of index date, and then declined to 1% by the end of study follow-up.

Health Care Utilization

Outpatient encounters, ED encounters, and hospitalizations increased gradually from baseline to the index date for both cohorts, after which they declined (Table 2). Peak differences in health care utilization occurred during the peri-index period: persons with PAF experienced 30% more outpatient visits ($p < 0.01$), 24% more hospitalizations ($p < 0.01$) and 110% more emergency department visits ($p < 0.01$) compared with controls. In the post-index period, there were only diminutive differences between cohorts in the annual rate of hospitalization and emergency department visits. In contrast, the annual rate of outpatient clinic encounters remained consistently higher in persons with PAF.

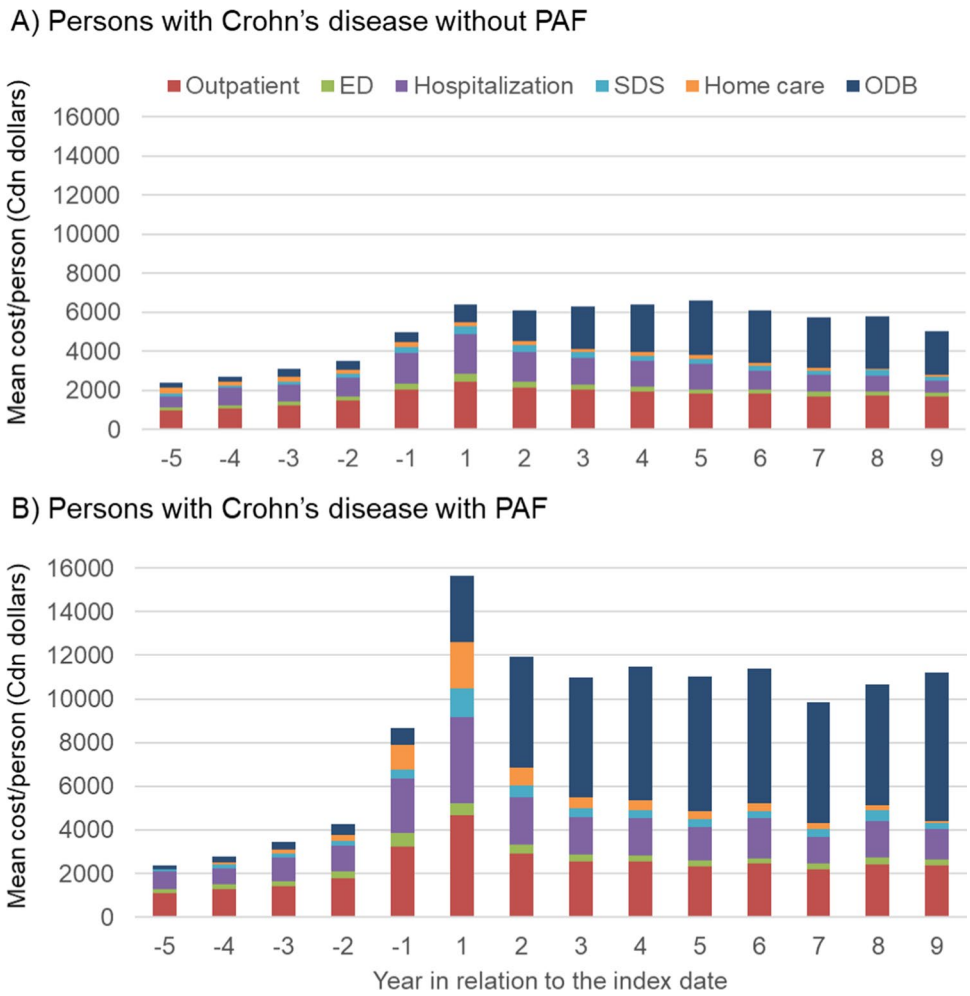


Fig. 3 Annual direct cost of care stratified by health care dimension in persons with Crohn's disease without and with perianal fistulas

Discussion

In this population-based cohort study, we found that persons with PAF incurred substantially higher direct health care costs. The difference in cost between cohorts became evident one year prior to the diagnosis of PAF and remained more than twice that of PAF-negative controls for up to 9 years after the diagnosis of PAF. At the time of PAF diagnosis, the cost difference was most pronounced for home care (tenfold greater), prescription drugs (fourfold greater) and hospitalizations (twofold greater), whereas during later years of follow-up, prescription drugs emerged as the dominant driver for increased direct health care spending for persons with PAF.

The estimated cost of CD varies considerably in published studies, owing to differences in study era, country of origin, patient population and access to biologic treatments [6]. In the most recent population-based studies, the overall cost of Crohn's disease was €3542 (SD, 7389) per patient-year in Europe/Israel and the attributable cost of Crohn's disease was $4630 and $10,747 per patient-year in 2005 and 2015 respectively in Manitoba, Canada [4, 7].

Studies assessing the cost of care associated with PAF in CD are scarce. An early administrative claims study in the USA, using the PharMetrics Patient-Centric Database, estimated an overall median cost of $10,863 (range, $0–$1,307,019) among persons with fistulizing CD [24]. However, this study did not stratify patients by luminal vs perianal CD separately. Several additional studies specific to PAF in CD, found highly variable mean annual costs (range, €3356 [SD, 5864] per person in Europe and Israel to $31,370 New Zealand dollars per person in New Zealand) [14–17, 19]. The majority of these studies contained small sample sizes and only one study was population-based. The study by Odes et al., consisted of 178 persons with PAF from countries across Europe and Israel and found a mean annual cost of care of €3356 (SD, 5864) per persons [17]. The lower cost compared to our study is not surprising, since it was conducted predominantly prior to the era of biologic therapies. The cost discrepancy is likely to be even greater than estimated given that we were not able to capture prescription

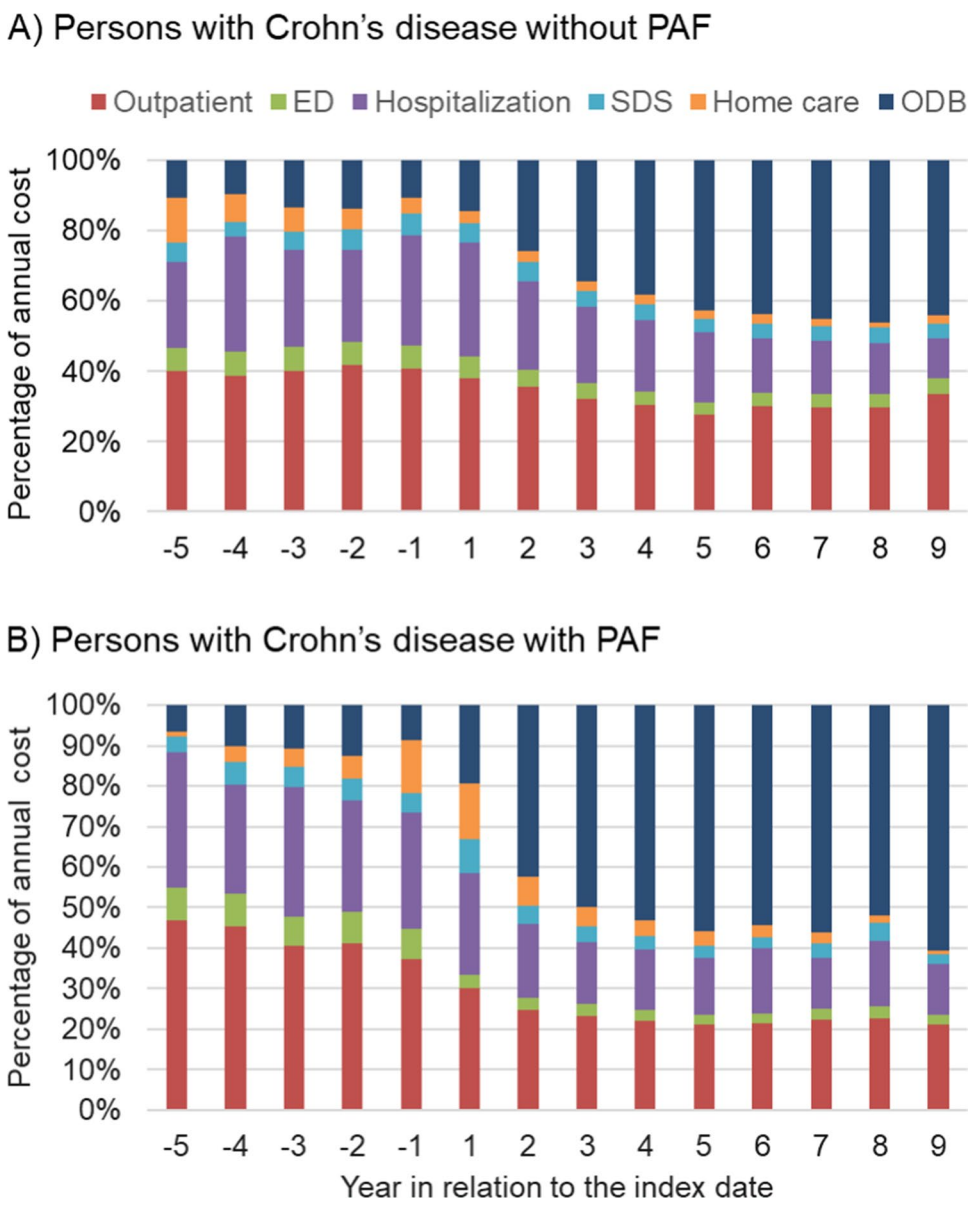


Fig. 4 Distribution of annual direct health care cost in persons with Crohn's disease without and with perianal fistulas

drug cost from private payers. In contrast to these studies, a recent study by Chen et al., using administrative data from IBM MarkScan demonstrated high annual per patient cost for persons with perianal CD $85,233 USD [18]. Similar to our study, they also found that persons with perianal CD had significantly greater health care costs than matched controls (CD without PAF) [18]. The increased costs of care for persons with perianal CD observed in our study and others is not surprising as it was recently demonstrated that patients with complications of CD incurred higher health care costs than persons with CD without intestinal complications [25].

The cost of care for CD nearly tripled from 2005 to 2015 in a population-based study from Manitoba, Canada [7], and most of this increase in costs is due to the increasing use of high-cost biologic therapies. Similar findings have been reported in other cohorts [4, 5, 8]. Given these trends, the cost of care for PAF will also undoubtably rise, and possibly at an even greater rate in persons with PAF, based on the results of our study. Moreover, costs of care may continue to rise due to the broader acceptance of modern treatment paradigms which promote more aggressive therapy with biologics. These include dose augmentation driven by biomarkers rather than symptoms alone [26], using biologic therapies earlier in the course of disease [27], and the recognition that higher dosing may promote higher fistula healing rates in persons with PAF [28–30], This anticipated increase in cost may be partially offset by a shift to biosimilars, which are approximately half the cost of their originator molecules in Canada [31].

Table 2 Health Care Utilization for persons with Crohn's disease with and without perianal fistulas

Year	Outpatient encounters			ED encounters			Hospitalizations		
	Controls, mean n ± SD	Case, mean n ± SD	Mean difference (p-value)	Controls, mean ± SD	Case, mean n ± SD	Mean difference (p-value)	Controls, mean n ± SD	Case, mean n ± SD	Mean difference (p-value)
-5	0.58 ± 1.68	0.75 ± 2.36	0.17 (0.2)	0.57 ± 1.33	0.58 ± 1.28	0.01 (0.962)	0.08 ± 0.43	0.12 ± 0.52	0.04 (0.277)
-4	0.64 ± 1.85	0.78 ± 1.97	0.14 (0.226)	0.67 ± 1.46	0.76 ± 1.45	0.09 (0.285)	0.12 ± 0.46	0.12 ± 0.52	0 (0.999)
-3	0.76 ± 2.06	1.06 ± 3.18	0.3 (0.019)	0.73 ± 1.73	0.80 ± 1.52	0.07 (0.451)	0.11 ± 0.42	0.14 ± 0.46	0.03 (0.279)
-2	0.99 ± 2.17	1.33 ± 2.60	0.34 (0.003)	0.77 ± 1.68	1.05 ± 1.93	0.28 (0.001)	0.13 ± 0.45	0.18 ± 0.54	0.05 (0.028)
-1	1.52 ± 3.25	2.86 ± 4.02	1.34 (< .001)	0.94 ± 1.92	2.04 ± 2.87	1.1 (< .001)	0.20 ± 0.63	0.40 ± 0.83	0.2 (< .001)
1	1.94 ± 3.16	4.71 ± 4.95	2.77 (< .001)	1.11 ± 2.04	1.55 ± 2.38	0.44 (< .001)	0.28 ± 0.75	0.52 ± 0.98	0.24 (< .001)
2	1.84 ± 3.01	3.01 ± 3.97	1.17 (< .001)	0.88 ± 1.99	1.16 ± 2.27	0.28 (0.004)	0.19 ± 0.59	0.25 ± 0.62	0.06 (0.026)
3	1.63 ± 2.65	2.52 ± 3.40	0.89 (< .001)	0.78 ± 1.52	1.08 ± 2.56	0.3 (< .001)	0.18 ± 0.54	0.21 ± 0.62	0.03 (0.199)
4	1.64 ± 2.76	2.51 ± 3.51	0.87 (< .001)	0.75 ± 1.65	0.99 ± 1.97	0.24 (0.004)	0.16 ± 0.57	0.22 ± 0.65	0.06 (0.031)
5	1.53 ± 2.72	2.42 ± 3.63	0.89 (< .001)	0.74 ± 1.63	0.80 ± 1.65	0.06 (0.473)	0.16 ± 0.54	0.19 ± 0.61	0.03 (0.277)
6	1.57 ± 2.94	2.43 ± 3.74	0.86 (< .001)	0.76 ± 1.74	0.83 ± 1.47	0.07 (0.426)	0.15 ± 0.48	0.21 ± 0.62	0.06 (0.028)
7	1.51 ± 2.70	2.20 ± 3.23	0.69 (< .001)	0.76 ± 2.39	0.95 ± 1.93	0.19 (0.168)	0.13 ± 0.50	0.18 ± 0.56	0.05 (0.108)
8	1.41 ± 2.50	2.46 ± 3.61	1.05 (< .001)	0.70 ± 2.58	1.01 ± 2.03	0.31 (0.09)	0.11 ± 0.42	0.21 ± 0.61	0.1 (0.005)
9	1.49 ± 2.53	2.42 ± 4.29	0.93 (0.003)	0.81 ± 2.10	0.81 ± 1.69	0 (0.994)	0.11 ± 0.44	0.26 ± 0.75	0.15 (0.005)

ED, emergency department; SD, standard deviation

Given these economic trends, a focus on developing and implementing cost-effective strategies to reduce PAF disease burden is required. Exams under anesthesia prior to initiating biologics, concomitant treatment with antibiotics, and targeting higher serum anti-TNF concentrations have all been shown to improve the rates of fistula healing [28–30, 32, 33]. A recent administrative study using the Truven Health MarketScan Database demonstrated that seton placement prior to the initiation of anti-TNF therapy also reduced health care utilization and cost associated with hospitalization, possibly by increasing the rate of fistula healing [34]. Furthermore, second generation biologics [35, 36] and mesenchymal stem cell therapy [37, 38] appear to be effective for refractory PAF. However, it should be recognized that although improving fistula healing will likely reduce hospitalizations, surgery, and ambulatory care physician encounters, it remains unclear if this would have a substantial impact on overall cost since long-term cost is driven primarily by prescription drugs. Formal cost effectiveness studies that consider both direct and indirect costs studies are required to answer these questions.

Disease prevention may be a better strategy to reduce costs associated with PAF. However, despite a growing body of research linking environmental factors and diet to IBD [39–41], it remains unclear if avoiding any of these triggers will prevent the development of CD, or of PAF in patients with established CD. A recent population-based study from Olmsted County, Minnesota demonstrated a reduction in the incidence of PAF since the introduction of biologics [42]. Similarly, treatment with steroid sparing medications reduced the risk of developing PAF by 51% which suggests that these treatments may reduce the incidence of PAF in patients with existing CD [43].

Our study is the largest study to date and the only population-based study conducted exclusively in the era of biologic therapies assessing the longitudinal cost of care associated with PAF. It consisted of a large sample of geographically and economically diverse persons, which ensured our data is generalizable at a population level. We used accurate case definitions for Crohn's disease (sensitivity = 0.77 and specificity = 0.96) and PAF (sensitivity = 0.81 and specificity = 0.90) to minimize cohort misclassification and matched cohorts on a wide range of factors including demographics, socioeconomic characteristics and follow-up duration. Finally, our selection of incident cases, matching of cohorts on year of entry into OCCC, standardization of index dates for controls and long follow-up period allowed us to accurately compare direct costs during different phases of care (pre-PAF diagnosis period, PAF diagnosis period, and post-PAF diagnosis period), and accounted for changes in practice that may have occurred over our study time period.

The most notable limitation of our study was that we were not able to capture drug costs from private payers, as well as drug costs from non-ODB sources such as over-the-counter drugs and alternative therapies. Although this leads to underestimated overall cost for both cohorts, it may also underestimate the cost difference between cohorts, since persons with PAF are more likely to be treated with biological therapies. We were also not able to control for the extent and phenotype of luminal disease, since health

administrative data is not able to accurately capture these variables. Prior studies have shown that PAF is associated with a more aggressive luminal disease course; therefore, this may have accounted for part of the differences in cost between our cohorts. Furthermore, administrative data does not accurately capture smoking status, which has also been associated with increased health care cost [4]. Finally, we were not able to assess indirect costs of care from lost wages and work productivity, which is not captured in this administrative database.

In conclusion, we demonstrate that in persons with Crohn's disease, PAF is associated with significantly greater health care costs that are sustained long-term. Future work is needed to determine the indirect cost of care associated with PAF and cost-effective strategies to adequately treat PAF.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-023-08096-9.

Author's contribution JM: Study design, interpretation of data, drafting manuscript. RW, AK, JC: Study design, interpretation of data and critical review of manuscript. JC: Interpretation of data, drafting and critical review of the manuscript. SG and GSP: Study design, data analysis, interpretation of data and critical review of manuscript. LT: Interpretation of data and critical review of manuscript.

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Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Competing interest JM: Consultancy fees and/or honoraria: Janssen, Abbvie, Takeda, Pfizer. LT: Consultancy fees and/or honoraria: Janssen, Abbvie, Takeda, Pfizer. RW and JC: employees of Takeda. AK, SG and GSP: employees of IQVIA who provided consulting services to Takeda.

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