Earlier Anti-TNF Initiation Leads to Long-term Lower Health Care Utilization in Crohn's Disease but Not in Ulcerative Colitis

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BACKGROUND & AIMS: **The timing of initiating biologic therapy in persons with Crohn's disease (CD) and ulcerative colitis (UC) is an area of ongoing controversy. In particular, there is concern that delaying the initiation of biologic therapy may lead to more treatment-resistant disease, which can result in more complications and hospitalizations.**

METHODS: **We used health administrative data from Manitoba, Canada to identify all persons with a new diagnosis of inflammatory bowel disease (IBD) between 2001 and 2018 who received tumor necrosis factor antagonists (anti-TNF) therapy and had at least 1 year of post anti-TNF initiation follow-up. We measured the rates of hospitalization, surgery, and outpatient visits, prior to and for up to 5 years following anti-TNF initiation. We compared the rates of these health care utilization outcomes between persons receiving anti-TNFs within 2 years following diagnosis and those receiving anti-TNFs more than 2 years following IBD diagnosis. We used inverse probability treatment weighting to adjust for baseline differences in risk between the 2 groups.**

RESULTS: **Among 742 persons with CD, early anti-TNF initiators had fewer IBD-specific and overall hospitalizations over the 5 years following the start of therapy. Incidence of resective surgery was also lower in earlier anti-TNF initiators with CD if the first year following initiation was excluded from the analysis. In 318 cases of UC, there was no impact of the timing of anti-TNF therapy on the rates of hospitalization and surgery.**

CONCLUSIONS: **Earlier administration of anti-TNF therapy is associated with reduced downstream health care resource utilization in CD, though these impacts are not evident in UC.**

Keywords: Anti-TNF; Biologics; Health Care Utilization; Inflammatory Bowel Disease; Timing of Therapy.

Biologic therapies are highly efficacious and effective in controlling inflammation, reducing symptoms, preventing long-term complications in persons with Crohn's disease (CD) and ulcerative colitis (UC).[1-4] The direct costs of having these agents available for use continue to escalate and now make up the largest fraction of health care expenditures among patients with inflammatory bowel disease (IBD).[4-6,7] However,

Abbreviations used in this paper: **Anti-TNF, tumor necrosis factor antagonists; CD, Crohn's disease; CI, confidence interval; HCU, health care utilization; IBD, inflammatory bowel disease; IPTW, inverse probability treatment weighting; IRD, incidence rate difference; UC, ulcerative colitis.**

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even when optimally dosed, biologic therapies are not universally effective in preventing complications or in controlling symptoms.[8-11] Moreover, there is equivocal evidence as to whether the introduction of tumor necrosis factor antagonists (anti-TNFs) as a treatment option has made a significant impact on hospitalization or surgery rates in the population, suggesting that these agents may not be optimally used in clinical practice.[12]

One potential explanation for the gap between the known efficacy of these medications and their equivocal impact on health care resource utilization is that biologics are being prescribed at a time when they may not be maximally effective. In CD, uncontrolled inflammation often will lead to the development of intestinal fibrosis and penetrating complications; these complications tend to be less responsive to medical therapies and often require surgical management. In UC, there is concern that a lack of early control of inflammation may lead to a higher incidence of colectomy.[3] Therefore, delaying the initiation of biologic therapy for persons with IBD may lead to lower effectiveness and a higher rate of complications and health care utilization (HCU). Data from REACT-CD and CALM suggest a more aggressive approach to initiating and optimizing biologic therapy leads to improved rates of clinical remission and prevention of hospitalizations over the short term.[13,14] However, the long-term impact on disease activity and complications is less clear.

We aimed to evaluate and compare the overall rate of HCU among persons with IBD after anti-TNF initiation, comparing those who received anti-TNFs within 2 years of diagnosis with those who initiated anti-TNF treatment more than 2 years post diagnosis.

What You Need to Know

Background

Tumor necrosis factor antagonists (anti-TNFs) are effective in reducing hospitalizations and surgery for Crohn's disease (CD) and ulcerative colitis (UC). Earlier administration of anti-TNF therapy may promote better long-term outcomes by preventing irreversible complications. There are limited data to evaluate the relative benefits of early vs later anti-TNF therapy over longer term follow-up.

Findings

Persons with CD who received anti-TNFs within 2 years following their inflammatory bowel disease diagnosis had lower health care utilization in the subsequent 5 years when compared with persons who did not start anti-TNFs within 2 years of diagnosis. We were not able to detect a similar effect of earlier anti-TNF initiation for persons with UC.

Implications for patient care

Our findings support the earlier use of biologic therapy in CD. The consequences of being more aggressive in the timing of anti-TNF therapy in persons with UC appear to be less clear.

Methods

Data Source

We used secondarily collected claims data from Manitoba Health, which contains HCU data for inpatient and outpatient physician-patient encounters and prescription dispensations for nearly all residents of the Canadian province of Manitoba (population in 2018: 1.37 million) from April 1984 until March 2018 (medications from April 1995 to March 2018). All adults and children with IBD were identified according to a validated administrative definition in the University of Manitoba IBD Epidemiology Database.[15] Data is collected from the time of IBD diagnosis until death, migration out of Manitoba, or March 31, 2018 (end of database follow-up).

Designation of Follow-up Cohorts

We created 5 overlapping cohorts, each containing all individuals with IBD who had continuous registration with Manitoba Health and complete follow-up for 1, 2, 3, 4, or 5 years following anti-TNF initiation. Separate cohorts were generated for CD and UC. For each of these cohorts, we enumerated all inpatient and outpatient health care contacts occurring from the time of anti-TNF initiation, until the end of cohort follow-up. As an example, for cohort 1, we counted all HCU for the first year following anti-TNF initiation, whereas for cohort 5, we specifically assessed the HCU in each of the 5 years following the start of anti-TNF therapy. We also assessed the cumulative HCU for each cohort, representing the total use of health care services from the time of anti-TNF initiation until the end of cohort follow-up (1 year for Cohort 1, 2 years for Cohort 2, etc). Inpatient health care contacts were considered to be IBD-specific if the most-responsible diagnosis was coded as IBD. Similarly, outpatient visits were counted as IBD-specific if the visit was associated with an International Classification of Diseases, ninth revision code for IBD. Gastroenterology-specific procedures included all colonoscopies, sigmoidoscopies, as well as computed tomography and magnetic resonance imaging scans of the abdomen. IBD-specific surgeries were tracked, using a previously validated list of Canadian Classification of Health Interventions surgical codes (Supplementary Table 1). Emergency department visits could not be determined because of they are not tracked in Manitoba Health administrative data.

A secondary post-hoc analysis was performed where the first year following initiation of anti-TNF therapy was excluded. Costs of care were calculated for overall,

inpatient, and outpatient costs using previously described methodology.[7] We excluded the direct costs of biologic therapy, as pricing policy in Canada as well as in much of the developed world renders opaque the cost of medications borne by private and governmental payers. The total count of HCU in each category was compared with the rate of use in the year prior to anti-TNF initiation.

Primary Analysis

Our primary comparisons were to assess the difference between the adjusted HCU in each category between persons who initiated anti-TNF therapy within the first 2 years following IBD diagnosis (early initiators) and those whose anti-TNF therapy occurred more than 2 years after the date of diagnosis (late initiators). We performed comparisons between early and late initiators using the final year of each cohort, as well as the cumulative HCU over 5 years. In order to adjust for potential channeling biases between early and late anti-TNF initiators and potential unmeasured confounding, we used inverse probability treatment weighting (IPTW), a statistical method used to alter the distribution of covariates in the 2 populations under comparison (in this case, early vs late initiators) so that the impact of potential confounders is brought close to equivalent in both groups. The result is expressed as the average treatment effect, representing the difference in the anticipated event rate in the early population vs the late population assuming a random distribution of all covariates included in the determination of the IPTW weights.[16] Standardized differences were calculated on each covariate before and after weighting to assess the effect of inverse probability weights on balancing the impact of the covariates, with standardized differences of <0.10 being considered to be balanced between the comparator pseudo-populations.[17] Covariates used in the construction of the inverse probability weights were age, sex, era of first anti-TNF use (2005–2008, 2009–2013, 2014–2018), history of resective surgery, IBD-specific hospitalization in the year prior to anti-TNF initiation, systemic corticosteroid use in the year prior to anti-TNF initiation, anti-TNF type (infliximab vs adalimumab) and use of concomitant immunomodulators, defined as there being a dispensation for azathioprine or methotrexate in the 60 days following biologic initiation. All results are expressed with 95% confidence intervals (CIs).

Results

Overall, we had 1060 (742 CD, 318 UC) anti-TNF users in our incident cohort who had at least 1 complete year of continuous follow-up, and 923, 797, 681, and 569 persons with 2 through 5 years of follow-up completely. Demographic and disease characteristics of these patients are described in Tables 1 and 2. The median duration from diagnosis until anti-TNF initiation was 4.43 years (interquartile range, 1.31–12.16 years).

Crohn's Disease

Of the 742 persons with CD, 247 received anti-TNF within 2 years of diagnosis. Results for IPTW-adjusted are shown in Figure 1 (HCU) and Supplementary Figure 1 (costs). Unadjusted incidence rates for HCU and costs are displayed in Supplementary Figures 2 and 3. Crude and IPTW-adjusted incidence rate differences (IRDs) between early and delayed anti-TNF initiators are shown in Table 3. Pre- and Post IPTW-adjusted standardized differences in the prevalence of covariates are shown in Supplementary Figure 4, *A*.

Hospitalizations. There was no difference in the rate of IBD-specific hospitalizations between early and late initiators in each of the first 2 years following the onset of anti-TNF therapy. However, early initiators had a significantly lower rate of IBD-specific hospitalizations than late initiators in the third through fifth year following anti-TNF initiation, and a lower rate of all hospitalization in years 4 and 5 following initiation of anti-TNFs. The cumulative rate of IBD-specific and all-cause hospitalization across all 5 years of follow-up was significantly lower among early anti-TNF initiators (IBD-specific hospitalization: 4.0 vs 8.6 per 100 person-years; IRD, −4.5 per 100 person years [95% CI, −7.0 to −2.1]; all-cause hospitalization, 23.1 vs 33.5 per 100 person-years; IRD, −10.4 [95% CI, −17.0 to −3.7]).

IBD-specific Surgical Resections. The IPTW-adjusted rate of IBD-specific surgery increased in the first year following anti-TNF follow-up, and gradually decreased each year across the 5 years of follow-up (Figure 1, *B*) The surgery rate was significantly lower among early initiators in the fourth and fifth years following anti-TNF initiation (0.5 vs 4.7 per 100 person-years for year 4; IRD, −4.2 events per 100 person-years [95% CI, −6.7 to −1.6]; 0.5 vs 6.0 per 100 person-years for year 5, IRD −5.5 events per 100 person-years [95% CI, −8.4 to −2.6]). The IPTW-adjusted cumulative surgery rate over the 5 years following anti-TNF initiation was not significantly different between early and late (5.7 vs 7.3 operations per 100 person-years; IRD, −1.6 [95% CI, −4.5 to 1.3]). However, when the first year of follow-up subsequent to anti-TNF initiation is excluded, the cumulate IBD-resective surgery rate is significantly lower among early anti-TNF initiators (IRD −3.6 per 100 person years [95% CI, −5.3 to −1.9]).

Outpatient Visits. The IPTW adjusted rate of IBD-specific outpatient visits were significantly lower among early anti-TNF initiators in years 2, 3, and 4 following the start of anti-TNF therapy. Overall, there was a significant reduction in the cumulative incidence of IBD-related outpatient visits over the 5 years following biologic initiation (5.9 vs 7.3 visits per person-year; IRD, −1.4 [95% CI, −2.0 to −0.9]). Similar findings were noted for overall outpatient visits, with a

Table 1. Baseline Characteristics of Study Population for Crohn's Disease

	Cohort 1		Cohort 2		Cohort 3		Cohort 4		Cohort 5	
	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late
Overall, n (%)	247 (33.3)	495 (66.7)	211 (32.2)	445 (67.8)	176 (30.8)	396 (69.2)	152 (30.1)	353 (69.9)	120 (28.0)	308 (72.0)
Age at anti-TNF initiation, *y*	31.0 (16.1)	41.3 (15.0)	30.5 (14.8)	40.8 (14.7)	30.2 (14.0)	40.6 (14.5)	30.1 (13.1)	40.4 (14.6)	30.5 (12.9)	40.0 (14.3)
Age <18.00	23.1	4.2	20.9	4.7	19.3	5.0	17.1	5.4	14.2	5.5
Age 18.00–39.99	51.0	46.1	55.5	46.7	58.0	46.5	61.8	46.7	64.1	47.1
Age ≥40.00	25.9	49.7	23.6	48.6	22.7	48.5	21.1	47.9	21.7	47.4
Female	55.5	53.3	55.0	51.9	56.8	52.3	55.3	52.4	59.2	54.2
Male	44.5	46.7	45.0	48.1	43.2	47.7	44.7	47.6	40.8	45.8
Era of first anti-TNF										
April 2004–March 2009	22.3	29.3	25.6	32.4	30.7	35.9	35.5	39.7	44.2	45.1
April 2009–March 2014	40.9	44.6	47.9	49.2	56.3	54.3	64.5	60.3	55.8	54.9
April 2014–March 2018	36.8	26.1	26.5	18.4	13.1	9.8	-	-	-	-
IBD-specific hospitalization in 1 year prior to anti-TNF initiation	31.6	22.8	32.7	23.1	31.8	23.5	31.6	24.1	30.8	24.7
Prior history of IBD-specific surgery	5.3	17.4	5.2	16.9	5.1	16.7	5.9	15.3	5.0	14.3
Corticosteroid use in 1 year prior to anti-TNF initiation	61.1	54.1	63.0	55.3	63.6	57.1	65.1	57.8	67.5	57.8
Intent to use Immunomodulators	58.7	47.9	57.3	49.7	56.3	49.2	59.2	47.6	60.0	50.0
Using infliximab	74.8	66.9	74.4	67.8	74.4	70.4	76.9	71.3	82.5	72.0

Note: Data are presented as percent or mean ± standard deviation.
Anti-TNF, Tumor necrosis factor antagonists; *IBD*, inflammatory bowel disease.

Table 2. Baseline Characteristics of Study Population for Ulcerative Colitis

	Cohort 1		Cohort 2		Cohort 3		Cohort 4		Cohort 5	
	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late
Overall, n (%)	123 (38.7)	195 (61.3)	104 (39.2)	161 (60.8)	85 (38.1)	138 (61.9)	60 (34.3)	115 (65.7)	47 (33.3)	94 (66.7)
Age at anti-TNF initiation, *y*	32.1 (16.2)	42.6 (16.0)	32.8 (16.8)	42.5 (15.6)	32.9 (16.7)	41.9 (15.5)	33.5 (17.7)	41.1 (15.4)	33.2 (17.6)	41.3 (15.0)
Age <18.00	19.5	5.1	19.2	5.6	17.7	5.8	16.7	7.0	17.0	5.3
Age 18.00–39.99	54.5	44.1	52.9	43.5	52.9	43.5	53.3	44.3	53.2	44.7
Age ≥40.00	26.0	50.8	27.9	50.9	29.4	50.7	30.0	48.7	29.8	50.0
Female	46.3	43.6	46.2	43.5	47.1	42	48.3	41.7	48.9	38.3
Male	53.7	56.4	53.8	56.5	52.9	58	51.7	58.3	51.1	61.7
Era of first anti-TNF										
April 2004–March 2009	9.7	14.8	11.5	18.0	14.1	21.0	20.0	24.3	25.5	29.8
April 2009–March 2014	42.3	46.7	48.1	55.3	58.8	63.8	80.0	75.7	74.5	70.2
April 2014–March 2018	48.0	38.5	40.4	26.7	27.1	15.2	-	-	-	-
IBD-specific hospitalization in 1 year prior to anti-TNF initiation	41.5	19.0	43.3	19.9	44.7	19.6	43.3	20.0	40.4	21.3
Prior history of IBD-specific surgery	1.6	3.1	1.9	2.5	2.4	2.9	1.7	2.6	2.1	3.2
Corticosteroid use in 1 year prior to anti-TNF initiation	91.1	80.5	94.2	80.7	94.1	81.2	96.7	81.7	95.7	83.0
Intent to use immunomodulators	47.2	44.6	44.2	44.1	40.0	44.2	41.7	45.2	40.4	45.7
Using infliximab	92.6	92.3	93.2	93.8	92.9	94.2	91.6	93.9	91.1	94.6

Note: Data are presented as percent or mean ± standard deviation.
Anti-TNF, Tumor necrosis factor antagonists; *IBD*, inflammatory bowel disease.

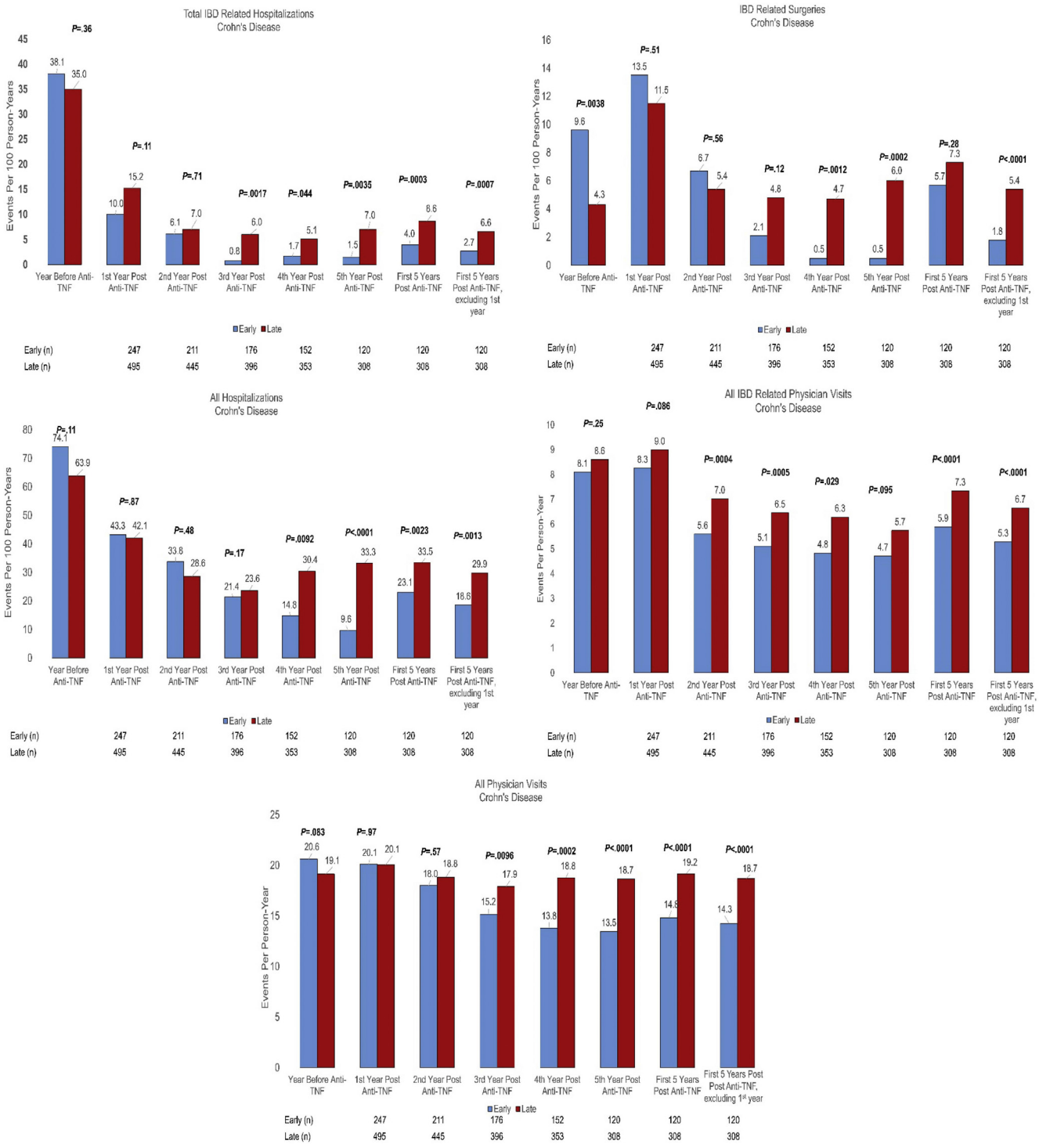

Figure 1. IPTW-adjusted incidence rates for IBD-specific outcomes pre and post anti-TNF initiation for CD.

cumulative reduction in the incidence rate over the 5 years following anti-TNF initiation significantly lower among early initiators (14.8 vs 19.1 visits per year; IRD, −4.3 [95% CI, −5.4 to −3.2]).

Costs. Total costs of care were significantly lower for years 3, 4, and 5 in follow-up for persons with CD, as were the cumulative costs of care over the 5 years following anti-TNF initiation. IPTW-adjusted costs showed similar effects. Most of the reduction in costs seen in early anti-TNF initiators can be ascribed to a reduction in inpatient associated costs. An analysis assessing for differential effects between strata did not show any significant effect modification. (Supplementary Figure 5).

Ulcerative Colitis

Of the 318 persons with UC, 123 received anti-TNF within 2 years of diagnosis. Results for IPTW-adjusted

Table 3. Difference in Unadjusted and Adjusted Incidence Rates of Events Between Early and Late Anti-TNF Initiators with Crohn's Disease (per 100 Person-years)

	Before anti−TNF initiation	Following anti−TNF initiation						
	Year −1	First year	Second year	Third year	Fourth year	Fifth year	First 5 years	Second to fifth year
IBD-specific hospitalizations								
Unadjusted IRD	**12.8 (2.6 to 23.0)**	−2.2 (−9.3 to 4.9)	−1.0 (−6.2 to 4.1)	**−4.2 (−8.2 to −0.1)**	−3.1 (−7.5 to 1.2)	−4.3 (−9.8 to 1.2)	**−3.0 (−6.0 to 0.0)**	−2.7 (−5.6 to 0.1)
IPTW-adjusted IRD	3.1 (−3.5 to 9.8)	−5.2 (−11.7 to 1.2)	−0.9 (−5.7 to 3.8)	**−5.2 (−8.4 to −1.9)**	**−3.5 (−6.8 to −0.1)**	**−5.5 (−9.1 to −1.8)**	**−4.5 (−7.0 to −2.1)**	**−3.9 (−6.2 to −1.6)**
All-cause hospitalizations								
Unadjusted IRD	14.9 (−0.4 to 30.2)	0.9 (−13.8 to 15.6)	2.1 (−10.6 to 14.7)	−7.5 (−18.1 to 3.0)	−11.3 (−26.1 to 3.5)	**−22.9 (−39.5 to −6.3)**	−7.3 (−14.9 to 0.2)	**−8.5 (−16.6 to −0.4)**
IPTW-adjusted IRD	10.2 (−2.2 to 22.7)	1.2 (−13.4 to 15.8)	5.1 (−9.0 to 19.3)	−7.0 (−16.9 to 3.0)	**−15.6 (−27.3 to −3.9)**	**−23.7 (−34.5 to −12.9)**	**−10.4 (−17.0 to −3.7)**	**−11.3 (−18.2 to −4.4)**
IBD-related surgery								
Unadjusted IRD	−1.0 (−4.5 to 2.5)	1.2 (−3.6 to 6.1)	0.1 (−3.7 to 3.9)	−2.6 (−5.9 to 0.7)	**−4.2 (−7.9 to −0.4)**	**−5.3 (−10.0 to −0.7)**	−1.8 (−4.2 to 0.6)	**−3.3 (−5.5 to −1.1)**
IPTW-adjusted IRD	**5.3 (1.7 to 8.9)**	2.0 (−4.1 to 8.2)	1.3 (−3.2 to 5.9)	−2.7 (−6.1 to 0.7)	**−4.2 (−6.7 to −1.7)**	**−5.5 (−8.4 to −2.6)**	−1.6 (−4.5 to 1.3)	**−3.6 (−5.3 to −1.9)**
IBD-related physician visits								
Unadjusted IRD	**−113.8 (−207.8 to −19.8)**	−4.4 (−96.7 to 87.8)	**−94.2 (−177.7 to −10.7)**	**−128.4 (−231.9 to −24.8)**	**−143.1 (−251.4 to −34.8)**	−88.2 (−200.0 to 23.7)	**−103.7 (−161.2 to −46.1)**	**−105.0 (−166.4 to −43.6)**
IPTW-adjusted IRD	−50.8 (−137.1 to 35.5)	−73.5 (−157.3 to 10.3)	**−142.0 (−221.2 to −62.7)**	**−153.3 (−239.0 to −67.5)**	**−144.9 (−240.2 to −49.7)**	−102.7 (−223.0 to 17.7)	**−145.6 (−198.2 to −92.9)**	**−136.5 (−193.0 to −80.0)**
All physician visits								
Unadjusted IRD	−0.1 (−162.5 to 162.4)	−53.9 (−241.2 to 133.3)	**−281.0 (−474.6 to −87.4)**	**−352.3 (−563.8 to −140.7)**	**−552.3 (−812.1 to −292.5)**	**−539.1 (−808.7 to −269.5)**	**−433.6 (−553.5 to −313.6)**	**−464.7 (−598.8 to −330.6)**
IPTW-adjusted IRD	147.8 (−19.5 to 315.1)	4.2 (−224.7 to 233.0)	−79.6 (−356.4 to 197.1)	**−273.0 (−479.7 to −66.4)**	**−497.0 (−754.2 to −239.7)**	**−519.0 (−756.6 to −281.3)**	**−433.1 (−544.9 to −321.3)**	**−444.0 (−571.6 to −316.5)**

Note: Negative differences → lower incidence in early anti-TNF initiators. All rates expressed as events per 100 person years of follow-up.
Note: Ninety-five confidence intervals in parentheses.
Note: Bolded values are statistically significant.
Anti-TNF, Tumor necrosis factor antagonists; *IBD*, inflammatory bowel disease; *IPTW*, inverse probability treatment weighting; *IRD*, incidence rate difference.

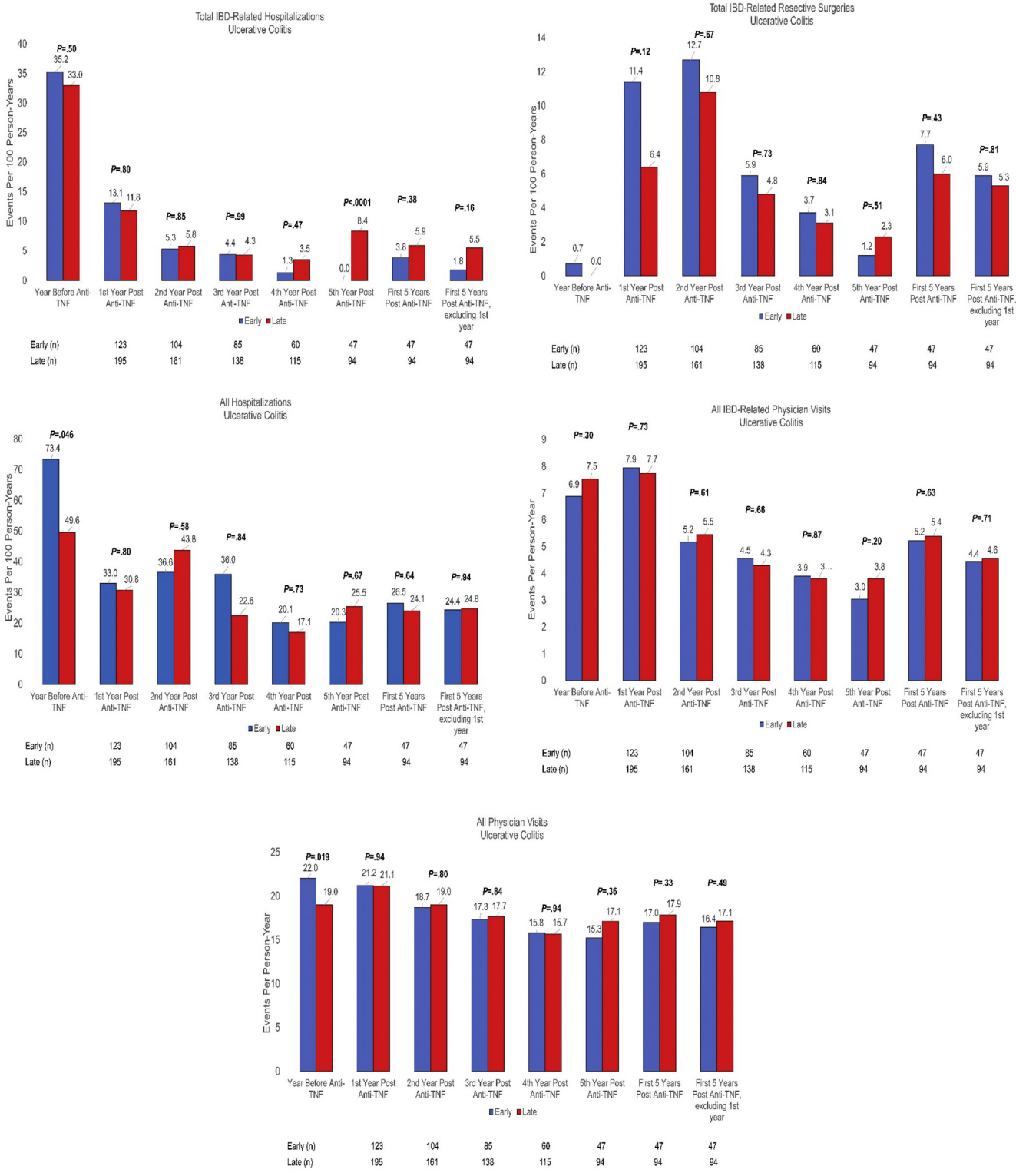

Figure 2. IPTW-adjusted incidence rates for IBD-specific outcomes pre and post anti-TNF initiation for UC.

are shown in Figure 2 (HCU) and Supplementary Figure 6 (costs). Unadjusted incidence rates are displayed in Supplementary Figures 7 and 8. Crude and IPTW adjusted IRDs between early and delayed anti-TNF initiators are shown in Table 4. Pre- and Post IPTW-adjusted standardized differences in the prevalence of covariates are shown in Supplementary Figure 4, *A*.

Hospitalizations. In contrast to persons with CD, there was no significant difference in the hospitalization rates between early and late initiators in any of the years following biologic initiation. After 5 years, there was also no significant difference in the adjusted cumulative rate of IBD hospitalizations (3.8 vs 5.9 IBD-specific hospitalizations per 100 person-years; 2.1 fewer IBD-specific

Table 4. Difference in Unadjusted and Adjusted Incidence Rates of Events Between Early and Late Anti-TNF Initiators with Ulcerative Colitis

	Before anti-TNF initiation	Following Anti-TNF initiation						
	Year −1	First year	Second year	Third year	Fourth year	Fifth year	First 5 years	Second to fifth year
IBD-specific hospitalizations								
Unadjusted IRD	**29.0 (15.3 to 42.6)**	7.0 (−1.7 to 15.8)	1.1 (−5.5 to 7.8)	−1.7 (−5.8 to 2.3)	−0.9 (−6.8 to 4.9)	–	0.6 (−4.1 to 5.4)	−1.9 (−6.8 to 3.1)
IPTW-adjusted IRD	2.3 (−4.4 to 8.9)	1.3 (−8.4 to 10.9)	−0.6 (−6.6 to 5.5)	0.0 (−8.6 to 8.7)	−2.2 (−8.2 to 3.8)	–	−2.1 (−6.9 to 2.6)	−3.7 (−8.8 to 1.4)
All-cause hospitalizations								
Unadjusted IRD	**49.1 (26.5 to 71.8)**	12.8 (−4.4 to 29.9)	3.7 (−17.0 to 24.5)	2.3 (−17.0 to 21.7)	8.5 (−10.5 to 27.5)	1.1 (−25.1 to 27.2)	8.5 (−2.0 to 19.0)	4.8 (−7.0 to 16.6)
IPTW-adjusted IRD	**23.9 (0.4 to 47.3)**	2.2 (−15.0 to 19.4)	−7.2 (−32.7 to 18.4)	1.9 (−16.2 to 19.9)	3.0 (−13.8 to 19.8)	−5.2 (−29.2 to 18.9)	2.4 (−7.6 to 12.4)	−0.4 (−11.6 to 10.8)
IBD-related surgery								
Unadjusted IRD	–	**8.0 (0.4 to 15.6)**	5.7 (−2.9 to 14.3)	0.8 (−5.4 to 7.0)	−0.1 (−6.8 to 6.5)	−1.1 (−7.0 to 4.8)	2.8 (−1.4 to 7.0)	1.1 (−3.1 to 5.3)
IPTW-adjusted IRD	–	5.0 (−2.1 to 12.1)	1.9 (−7.0 to 10.9)	1.1 (−5.1 to 7.2)	0.6 (−5.6 to 6.9)	−1.1 (−4.5 to 2.3)	1.7 (−2.5 to 5.9)	0.5 (−3.8 to 4.8)
IBD-related physician visits								
Unadjusted IRD	−113.4 (−240.0 to 13.2)	44.5 (−74.9 to 163.8)	−39.4 (−147.6 to 68.8)	16.2 (−87.4 to 119.7)	−0.1 (−118.3 to 118.2)	−91.5 (−227.6 to 44.7)	−22.3 (−96.1 to 51.4)	−29.0 (−100.3 to 42.3)
IPTW-adjusted IRD	−66.2 (−191.5 to 59.1)	21.2 (−98.8 to 141.2)	−28.4 (−138.7 to 82.0)	24.0 (−82.9 to 130.9)	9.0 (−103.4 to 121.4)	−78.3 (−197.9 to 41.3)	−18.1 (−91.4 to 55.2)	−13.4 (−85.4 to 58.5)
All physician visits								
Unadjusted IRD	184.5 (−61.9 to 431.0)	17.1 (−229.4 to 263.6)	−177.1 (−434.3 to 80.2)	−107.3 (−475.3 to 260.8)	47.5 (−296.8 to 391.8)	−144.7 (−567.8 to 278.5)	−97.7 (−279.9 to 84.6)	−103.5 (−310.4 to 103.5)
IPTW-adjusted IRD	**304.3 (51.3 to 557.3)**	8.2 (−247.5 to 264.0)	−36.5 (−318.1 to 245.2)	−33.6 (−366.0 to 298.9)	12.0 (−309.4 to 333.5)	−187.2 (−591.3 to 216.9)	−85.6 (−258.3 to 87.1)	−69.4 (−268.2 to 129.5)

Note: Negative differences → lower incidence in early anti-TNF initiators. All rates expressed as events per 100 person years of follow-up.
Note: Ninety-five confidence intervals in parentheses.
Note: Bolded values are statistically significant.
Anti-TNF, Tumor necrosis factor antagonists; *IBD*, inflammatory bowel disease; *IPTW*, inverse probability treatment weighting; *IRD*, incidence rate difference.

hospitalization per 100 person-years [95% CI, −6.9 to 2.6]). Similarly, there was no difference in the cumulative rate of all-cause hospitalizations (26.5 vs 24.1 per 100 person years; 2.3 greater hospitalizations [95% CI, −7.6 to 12.7]).

Surgeries. The rate of resective surgery was significantly higher in the first year following anti-TNF initiation in early initiators when compared with late initiators (11.4 vs 6.4 per 100 person-years; IRD, 5.0 surgeries per 100 person-years [95% CI, −2.1 to 12.1]). Surgery rates remained numerically higher among early initiators in all years of follow-up. Overall, the cumulate surgery rate for the 5 years following anti-TNF initiation remained non-significantly elevated among early anti-TNF initiators (7.7 vs 6.0 per 100 person-years; IRD, 1.7 per 100 person-years [95% CI, −2.5 to 5.9]). Removing the first year of follow-up after anti-TNF initiation did not significantly affect the impact of earlier anti-TNF initiation IRD (5.9 vs 5.3 surgeries per 100 person-years [95% CI, −3.7 to 4.8]).

Outpatient Visits. The IPTW-adjusted rate of IBD-specific or overall outpatient visits was no different between early and delayed anti-TNF initiators for persons in UC in any of the individual 5 years following the start of therapy, or cumulatively over the 5 years of follow-up. Full results are shown in Table 2.

Costs. As with rates of health care utilization, there was no significant reduction in overall, inpatient, or outpatient costs in any year of follow-up, or cumulatively in the 5 years following anti-TNF initiation, when comparing early vs late anti-TNF initiators. Similarly, no significant effect modification was seen with any of the covariates in stratified analysis (Supplementary Figure 9).

Discussion

In this intention-to-treat analysis, we demonstrated that persons with CD who were exposed to anti-TNF within 2 years of diagnosis had greater reductions in all-cause hospitalization, IBD-specific hospitalization, outpatient visits, and overall costs, compared with those whose anti-TNF therapy was delayed for more than 2 years following the date of IBD diagnosis. There was also a significant reduction in delayed intestinal resections among persons with CD who initiated therapy earlier, which was most pronounced in the later years of follow-up. However, we were not able to detect a similar effect of early anti-TNF initiation on hospitalizations, operations, or total direct costs among persons with UC among those who were treated within 2 years of diagnosis. These results suggest that the benefits of early initiation of biologic therapy are more striking among persons with CD.

Our reported findings lend further support to the emerging paradigm of adopting earlier use of biologic therapy, particularly in CD, where a timely intervention that reduces inflammation can decreased the burden of fibrotic disease, thereby potentially reducing the long-term impact of complications and the need for surgical interventions.[18] There is strong evidence from secondary analysis of previous randomized controlled trials that persons with CD who are relatively newly diagnosed are more likely to have a satisfactory clinical and endoscopic response to biologic therapy than those with more long-standing disease.[19] Evidence from the real-world setting has generally also shown that early therapy is associated with better outcomes when compared with later initiation of biologic therapy, including being less likely to require dose escalation, decreased likelihood of stricture formation, and lower rates of CD-related surgery.[20-24]

However, it is less clear in the established literature whether the timing of initiation of biologic therapy has any impact on the long-term course. Inflammation in UC is generally confined to the mucosa, and fibrotic disease rarely occurs. There are no pragmatic trials analogous to the CALM trial evaluating the impact of more aggressive therapy early in UC, and there is also limited evidence from observational trials. Han et al[25] recently showed, in a population-wide South Korean cohort, that persons receiving anti-TNFs within 2 years of disease onset were no less likely than late initiators to have emergency room visits or undergo colectomy, though there was a slight decrease in overall hospitalizations. Other studies have shown worse outcomes for persons with UC who start therapy early, though this could also be due to channeling bias (ie, patients with a more aggressive course of UC may be more likely to have early anti-TNF exposure). As there was a relatively small number of persons with UC with >2 years of follow-up post initiation of anti-TNFs, it is possible that the failure to see a benefit in favor of early anti-TNFs may represent a Type II error. Further studies on larger numbers of patients with UC may help address this issue.

The clinical implications of our study are significant. Most importantly, our studies confirm the benefits of early initiation of biologic therapy among persons with CD in a diverse population-based real-world setting. However, the use of biologic therapy is often delayed among persons with indications because of restrictions on reimbursement, which mandate trials of less effective medications prior to gaining access to biologic medication. Our study adds to the body of data demonstrating that delaying anti-TNF therapy may have long-term consequences and higher long-term costs among persons with CD. Given that the reduction in HCU and costs seen with earlier anti-TNF therapy is fairly modest, one could reasonably question whether the use of earlier anti-TNF therapy is cost-efficient, in light of the high price of biologic therapies. Although our analysis was limited by the available outcomes that can be assessed using health administrative data, it is conceivable that the beneficial impacts of early therapy in CD on hospitalizations, surgery, and outpatient visits can be extended to quality of life, symptom burden, and

disability.[26] The provision of anti-TNF therapy earlier in the course of disease provides the opportunity of breaking the cycle of disability that frequently plagues persons with Crohn's disease who develop treatment-resistant fibrosis if intestinal inflammation is allowed to continue unchecked, leading to a significant reduction in the indirect costs of care. In contrast for patients with UC, this study provides some level of reassurance to those who either wish to use step-up therapy with aminosalicylates or azathioprine, or who may struggle to access anti-TNF or other biologic medications early in the course of disease.

This study does have some notable limitations. It is reasonable to assume that, given the observational nature of our data, patients who receive early anti-TNF therapy have more aggressive disease and more complex disease phenotypes that those who receive therapy later, and as a result will be expected to have a higher incidence of subsequent HCU. Although we used a propensity score-based model to adjust for channeling bias, there may remain residual or unmeasured confounding that could have led to an underestimation of the benefits of the early initiation of biologic therapy. As an example, we were not able to assess the prevalence of smoking or the presence of a fistulizing/penetrating phenotype, which may be associated with greater health care resource utilization. Furthermore, as non-anti-TNF biologic therapies (vedolizumab and ustekinumab) were not available in Manitoba until 2017, we were not able to evaluate whether the early initiation of these therapies would lead to similar results. However, as we hypothesize that the benefits of early therapy in CD are driven by pre-empting the development of fibrosis but promoting mucosal healing, any agent that has a high likelihood of promoting mucosal healing and/or deep remission would be expected to have similar outcomes.[27] We also recognize that, as we have a smaller number of anti-TNF users with UC, we may not have had sufficient power to detect a similar magnitude of benefit to earlier anti-TNF therapy as was seen in the CD population.

Conclusion

In conclusion, we have demonstrated in a population-based setting that early anti-TNF therapy is associated with decreased use of health care services, lower downstream costs, and decreased need for surgical intervention for up to 5 years following treatment initiation (excluding the first year of follow-up). However, the impact of early intervention in UC is far less clear from our data. We support the performance of further pragmatic trials in UC to determine if protocols that favor the early adoption of biologic therapies and/or highly active small molecules will lead to sustained decreases in meaningful outcomes. In the interim, IBD experts and their patients should use this and similar data to continue to advocate for earlier and broader access to biologic therapies earlier in the course of disease for persons with CD, and to improve our understanding of which disease subpopulations may accrue the greatest benefits from early intervention with biologic therapy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.02.021.

References

1. Colombel JF, Reinisch W, Mantzaris GJ, et al. Randomised clinical trial: deep remission in biologic and immunomodulator naive patients with Crohn's disease - a SONIC post hoc analysis. Aliment Pharmacol Ther 2015;41:734–746.
2. Reinisch W, Sandborn WJ, Rutgeerts P, et al. Long-term infliximab maintenance therapy for ulcerative colitis: the ACT-1 and -2 extension studies. Inflamm Bowel Dis 2012;18:201–211.
3. Froslie KF, Jahnsen J, Moum BA, et al. , IBSEN Group. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology 2007;133:412–422.
4. 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-TNFalpha therapy: results from the COIN study. Gut 2014;63:72–79.
5. Kuenzig ME, Benchimol EI, Lee L, et al. The impact of inflammatory bowel disease in Canada 2018: direct costs and health services utilization. J Can Assoc Gastroenterol 2019;2:S17–S33.
6. Kuenzig E, 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.
7. Targownik LE, Benchimol EI, Witt J, et al. The effect of initiation of anti-TNF therapy on the subsequent direct health care costs of inflammatory bowel disease. Inflamm Bowel Dis 2019;25:1718–1728.
8. Chaparro M, Panes J, Garcia V, et al. Long-term durability of infliximab treatment in Crohn's disease and efficacy of dose "escalation" in patients losing response. J Clin Gastroenterol 2011;45:113–118.
9. Roda G, Jharap B, Neeraj N, et al. Loss of response to anti-TNFs: definition, epidemiology, and management. Clin Transl Gastroenterol 2016;7:e135.
10. Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. Aliment Pharmacol Ther 2011;33:987–995.
11. Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. Am J Gastroenterol 2011;106:674–684.
12. Murthy SK, Begum J, Benchimol EI, et al. Introduction of anti-TNF therapy has not yielded expected declines in hospitalisation and intestinal resection rates in inflammatory bowel diseases: a population-based interrupted time series study. Gut 2020;69:274–282.
13. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre,

randomised, controlled phase 3 trial. Lancet 2018; 390:2779–2789.
14. Khanna R, Bressler B, Levesque BG, et al. REACT Study Investigators. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. Lancet 2015;386:1825–1834.
15. Benchimol EI, Guttmann A, Mack DR, et al. Validation of international algorithms to identify adults with inflammatory bowel disease in health administrative data from Ontario, Canada. J Clin Epidemiol 2014;67:887–896.
16. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34:3661–3679.
17. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083–3107.
18. Ungaro RC, Yzet C, Bossuyt P, et al. Deep remission at 1 year prevents progression of early Crohn's disease. Gastroenterology 2020;159:139–147.
19. Hamdeh S, Aziz M, Altayar O, et al. Early vs late use of anti-TNFa therapy in adult patients with Crohn disease: a systematic review and meta-analysis. Inflamm Bowel Dis 2020; 26:1808–1818.
20. Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology 2013; 145:1230–1236.e1–2.
21. Lee WJ, Briars L, Lee TA, et al. Top-down versus step-up prescribing strategies for tumor necrosis factor alpha inhibitors in children and young adults with inflammatory bowel disease. Inflamm Bowel Dis 2016;22:2410–2417.
22. Frei R, Fournier N, Zeitz J, et al. Early initiation of anti-TNF is associated with favourable long-term outcome in Crohn's disease: 10-year-follow-up data from the Swiss IBD Cohort Study. J Crohns Colitis 2019;13:1292–1301.
23. Safroneeva E, Vavricka SR, Fournier N, et al. , Swiss IBD Cohort Study Group. Impact of the early use of immunomodulators or TNF antagonists on bowel damage and surgery in Crohn's disease. Aliment Pharmacol Ther 2015;42:977–989.
24. Ma C, Beilman CL, Huang VW, et al. Anti-TNF therapy within 2 years of Crohn's disease diagnosis improves patient outcomes: a retrospective cohort study. Inflamm Bowel Dis 2016; 22:870–879.
25. Han M, Jung YS, Cheon JH, et al. Similar clinical outcomes of early and late anti-TNF initiation for ulcerative colitis: a nationwide population-based study. Yonsei Med J 2020;61:382–390.
26. Shafer LA, Walker JR, Chhibba T, et al. Health care indicators of moderate to severe IBD and subsequent IBD-related disability: a longitudinal study. Inflamm Bowel Dis 2019;25:1996–2005.
27. Faleck DM, Shmidt E, Huang R, et al. Effect of concomitant therapy with steroids and tumor necrosis factor antagonists for induction of remission in patients with Crohn's disease: a systematic review and pooled meta-analysis. Clin Gastroenterol Hepatol 2021;19:238–245.e4.

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Charles N. Bernstein, MD (Conceptualization: Supporting; Funding acquisition: Supporting; Methodology: Supporting; Resources: Supporting; Writing – original draft: Supporting)

Eric I. Benchimol, MD, PhD (Conceptualization: Supporting; Funding acquisition: Supporting; Methodology: Supporting; Writing – original draft: Supporting)

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M. Ellen Kuenzig, PhD (Methodology: Supporting; Writing – original draft: Supporting)

Sanjay K. Murthy, MD, MSc (Conceptualization: Supporting; Funding acquisition: Supporting; Investigation: Supporting; Writing – original draft: Supporting)

Conflicts of interest
These authors disclose the following: Laura Targownik has received investigator initiated funding from Janssen Canada, and served on advisory boards for AbbVie Canada, Takeda Canada, Merck Canada, Pfizer Canada, Janssen Caenada, Roche Canada, and Sandoz Canada. Charles Bernstein has served on advisory boards for AbbVie Canada, Amgen Canada, Avir Pharmaceuticals, Bristol Myers Squibb Canada, Roche Canada, Janssen Canada, Sandoz Canada, Takeda Canada, and Pfizer Canada; has been a consultant for Mylan Pharmaceuticals and Takeda; has received educational grants from Abbvie Canada, Pfizer Canada, Takeda Canada, and Janssen Canada; has served on a speaker's panel for Abbvie Canada, Janssen Canada, Medtronic Canada, Pfizer Canada, and Takeda Canada; and has received research funding from Abbvie Canada, Sandoz Canada, and Pfizer Canada. Harminder Singh has been on the advisory board of Amgen Canada, Roche Canada, Sandoz Canada, Takeda Canada, Pendopharm, and Guardant Health, Inc. Gil Kaplan has received speaking or consultancy honoraria from AbbVie, Janssen, Pfizer, Takeda, and Shire; and has received a grant from Abbvie, Janssen, Merck, and Shire. Eric I. Benchimol has acted as a legal consultant for Hoffman La-Roche Limited and Peabody & Arnold LLP for matters unrelated to a medication used to treat inflammatory bowel disease, and received consulting fees from McKesson Canada. The remaining authors disclose no conflicts.

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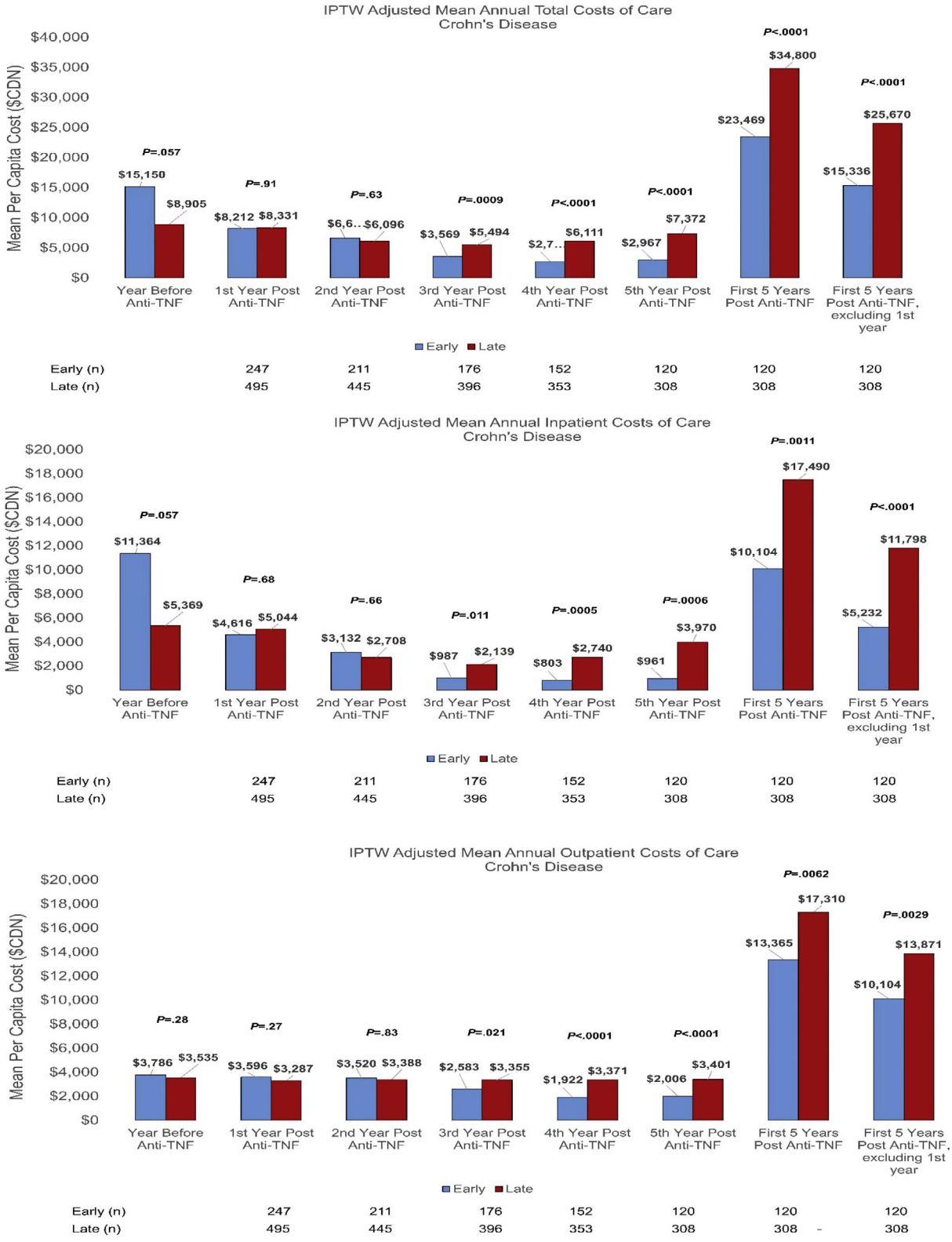
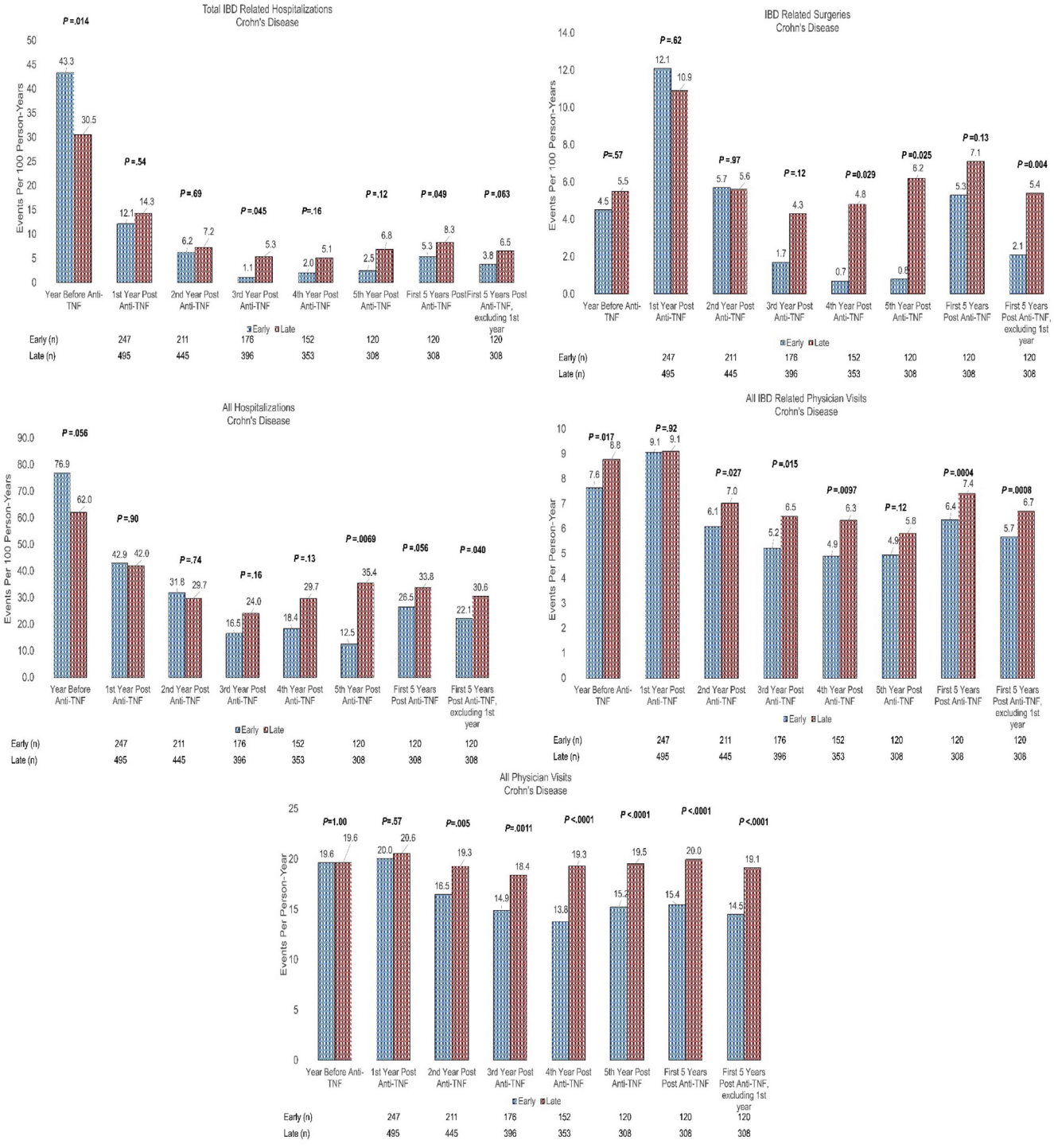
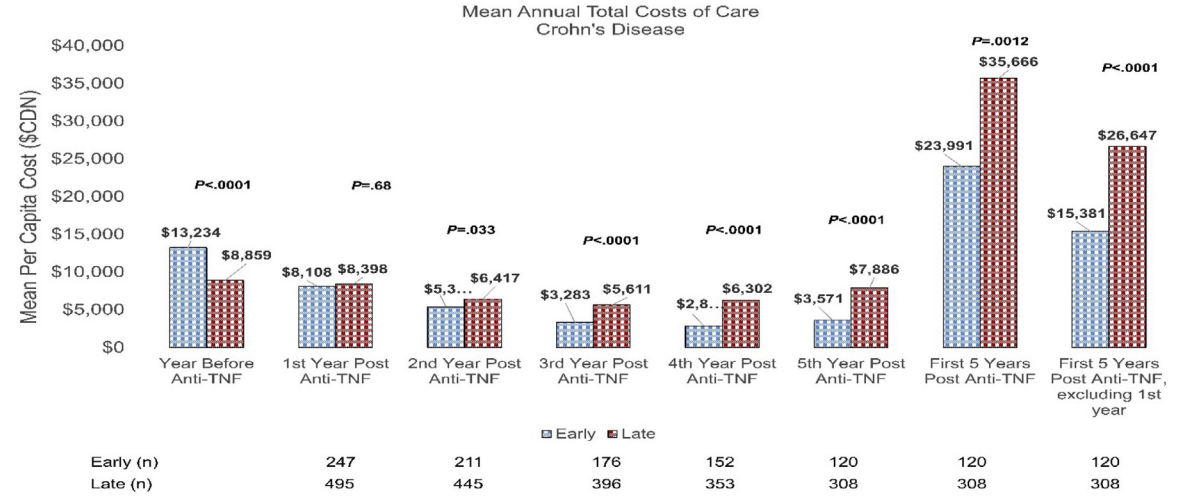
Disclaimer
This study is based in part on de-identified data Manitoba Health, obtained with the permission of the Manitoba Health Information Privacy Committee. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Manitoba.

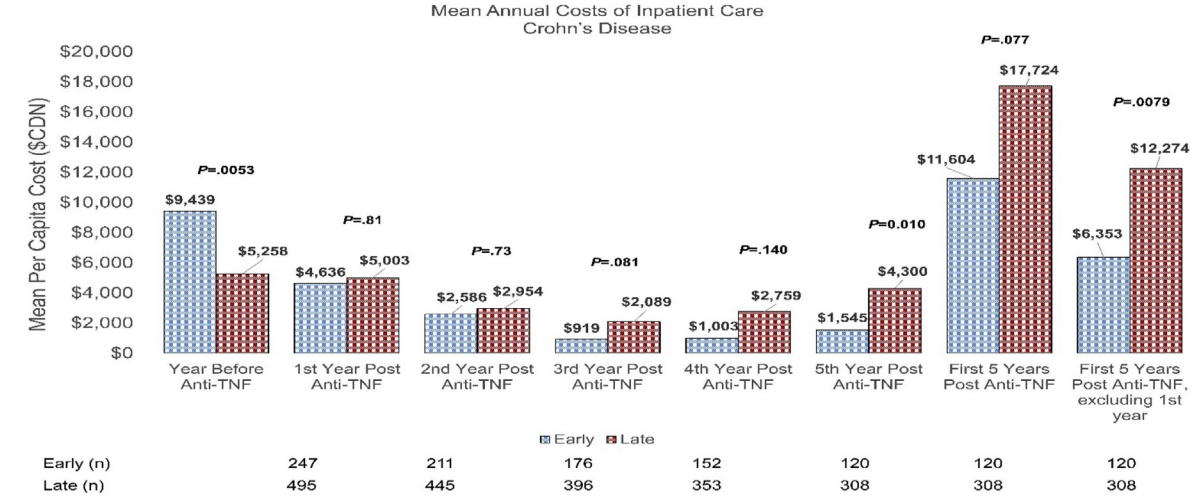


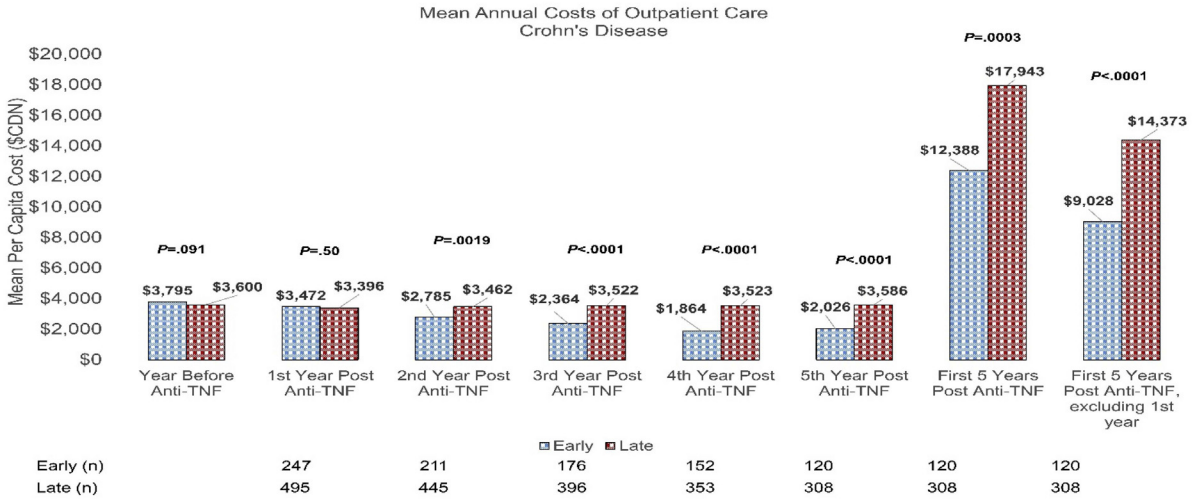
Supplementary Figure 1. IPTW-adjusted incidence rates for mean annual direct costs pre and post anti-TNF initiation for CD.



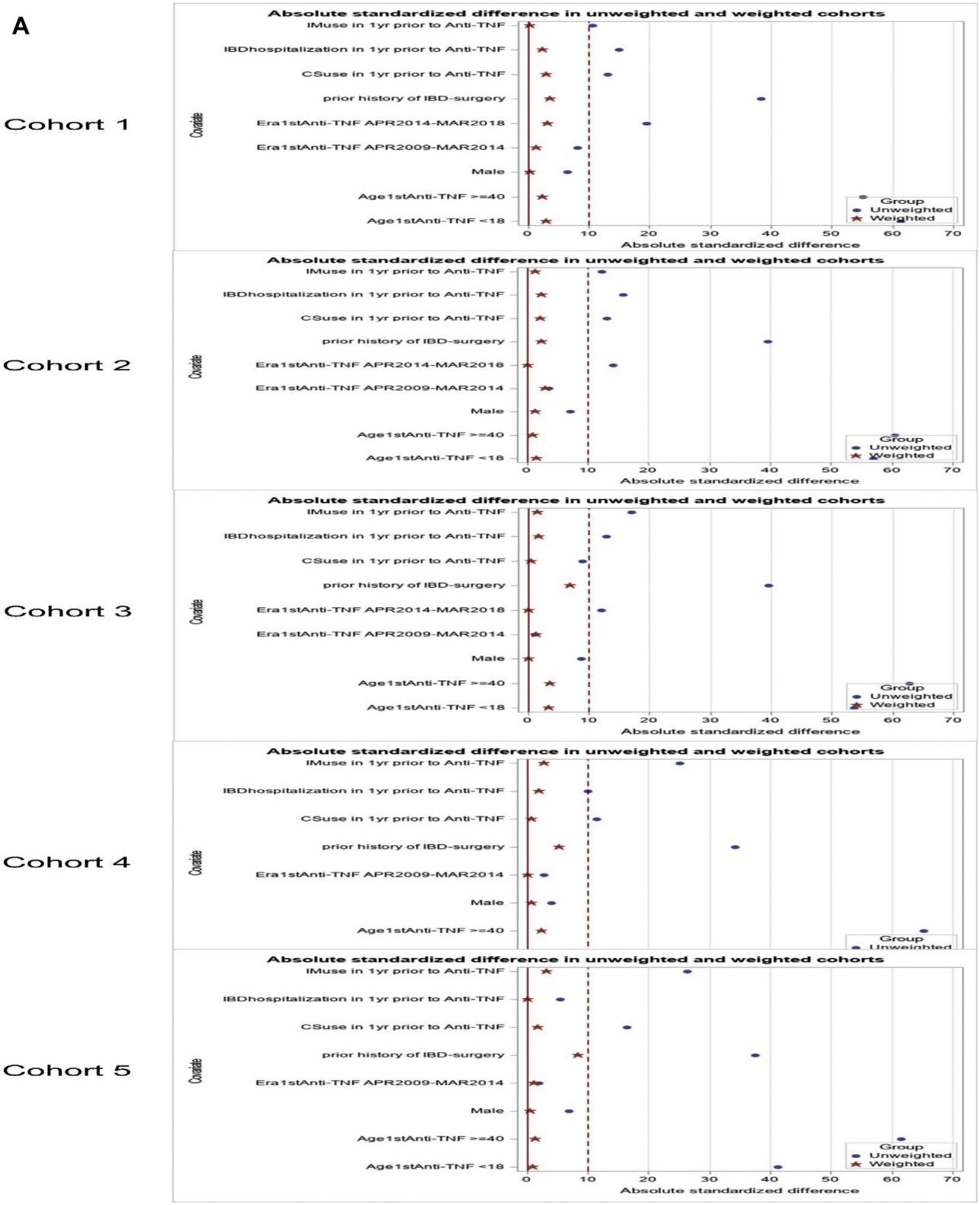
Supplementary Figure 2. Unadjusted incidence rates for IBD-specific outcomes pre and post anti-TNF initiation for CD.



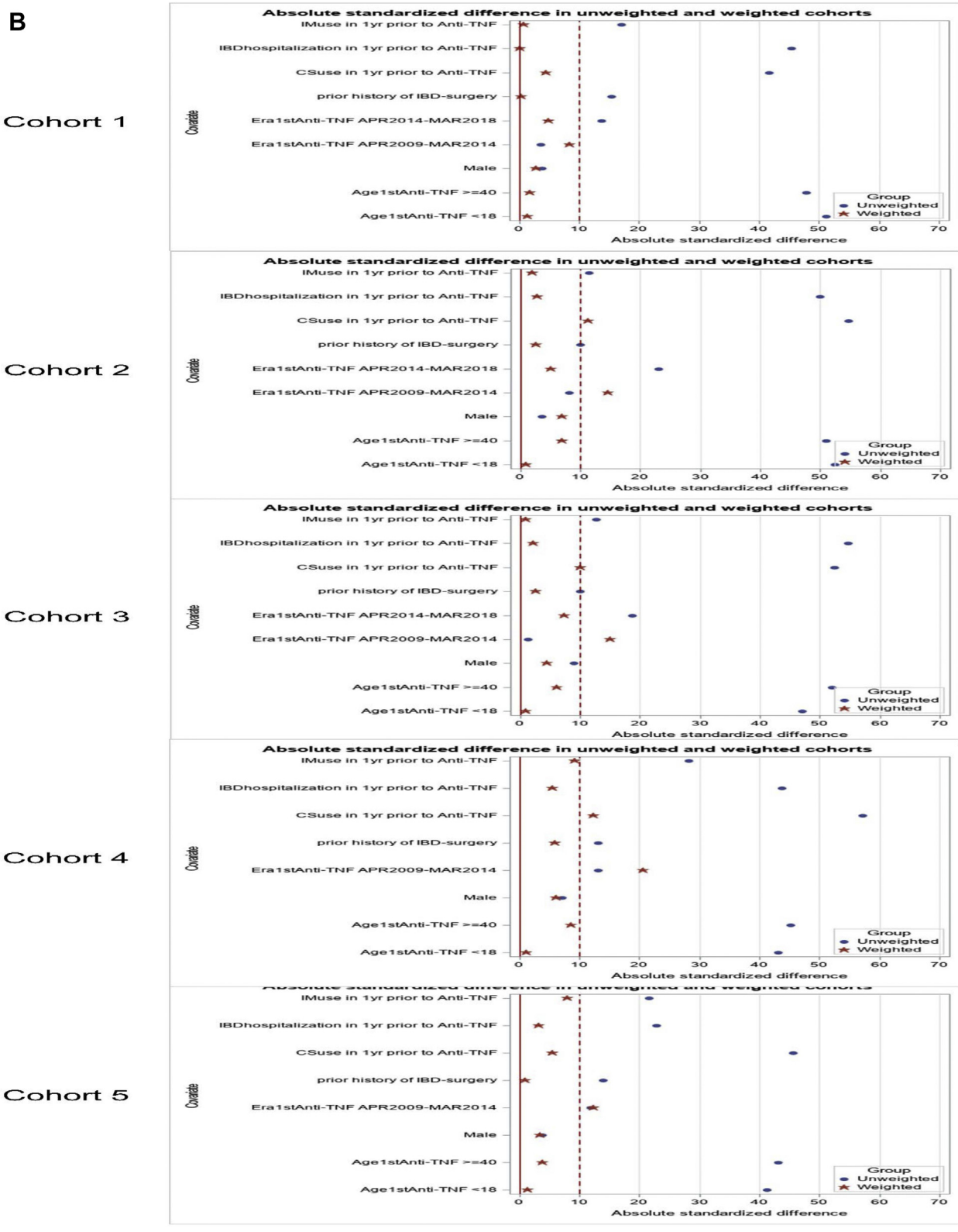




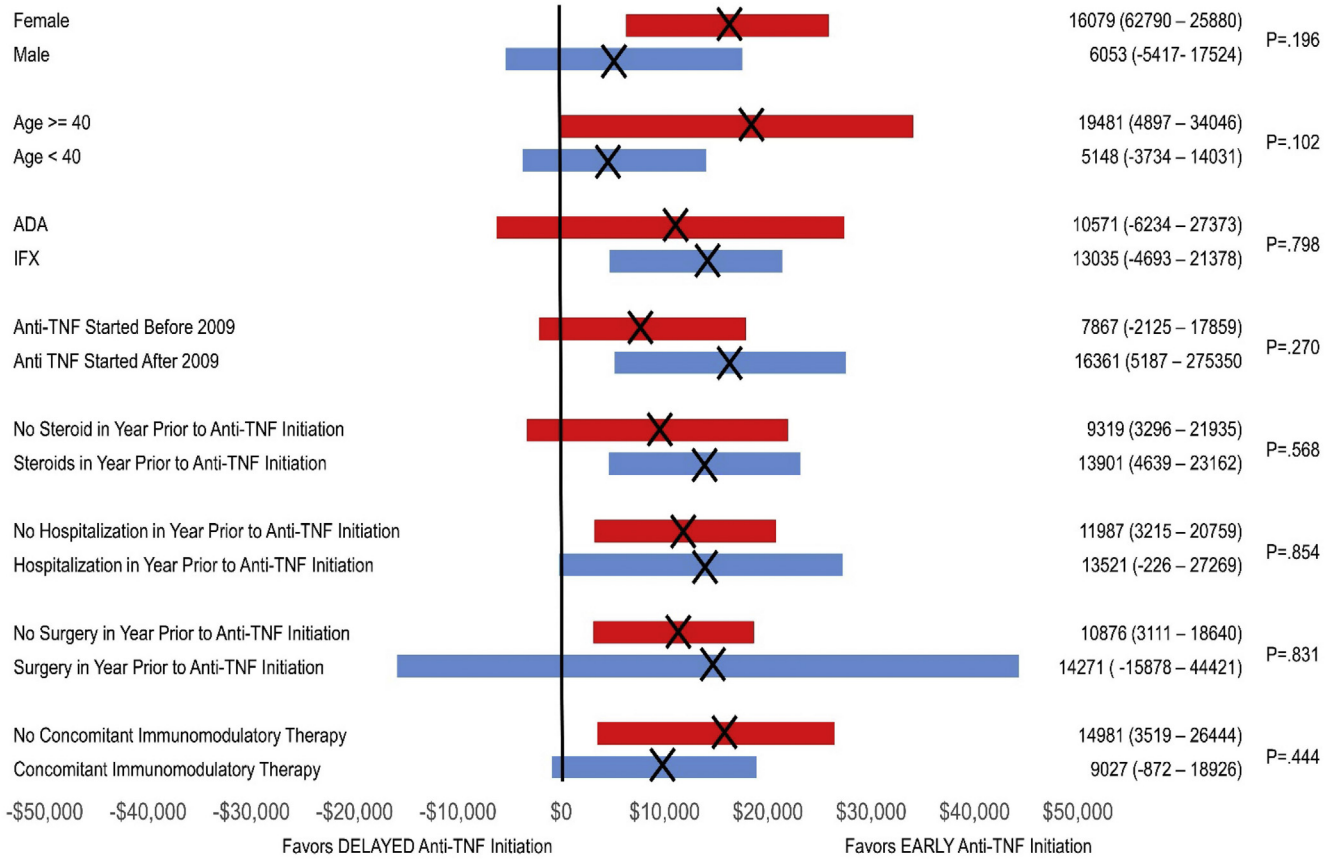
Supplementary Figure 3. Unadjusted incidence rates for mean annual direct costs pre and post anti-TNF initiation for CD.



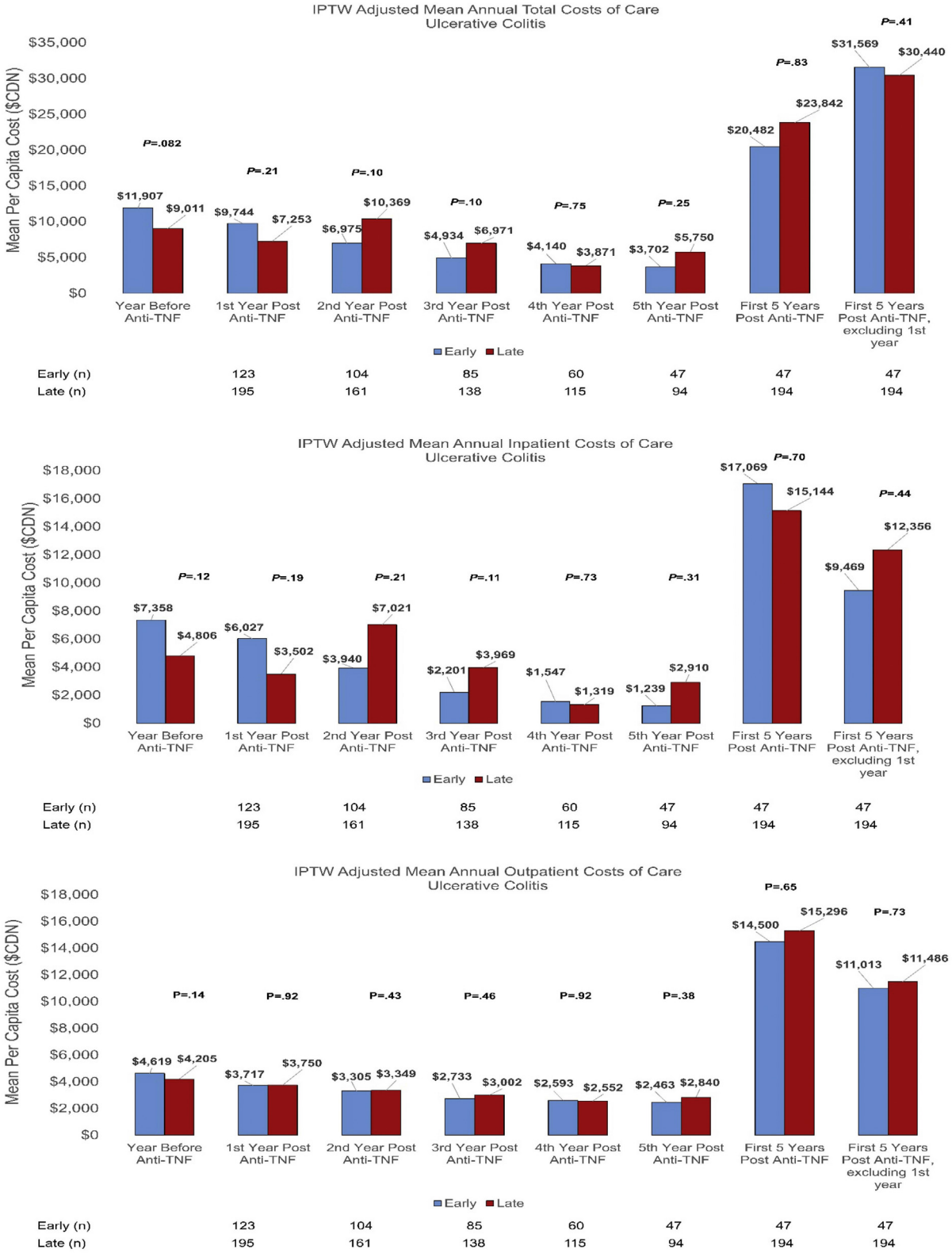
Supplementary Figure 4. *A*, Standardized differences pre and post IPTW adjustment for CD. *B*, Standardized differences pre and post IPTW adjustment for UC.



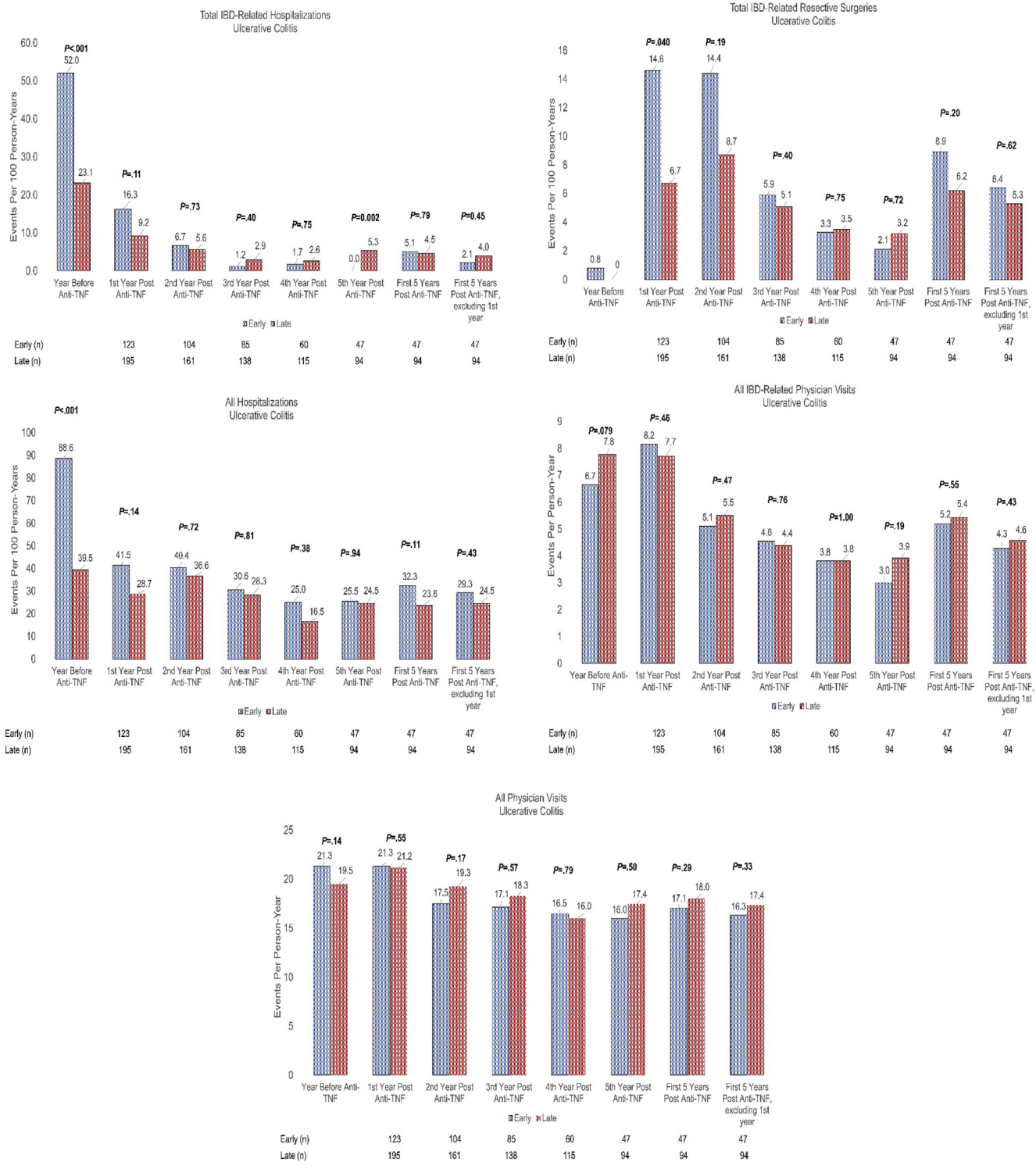
Supplementary Figure 4. *Continued.*



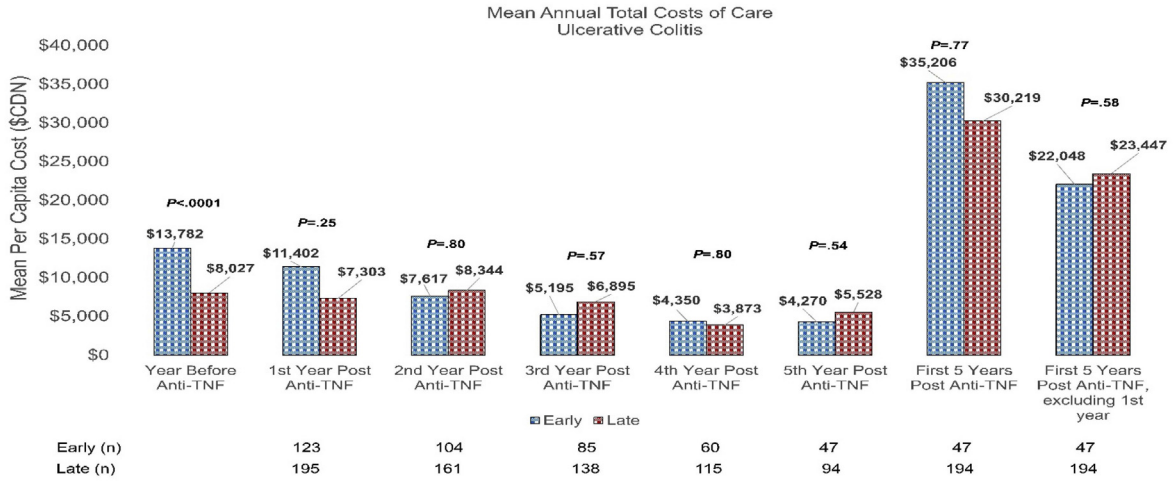
Supplementary Figure 5. Cumulative difference in IPTW-adjusted costs in first 5 years following anti-TNF initiation between early and late initiators with CD.

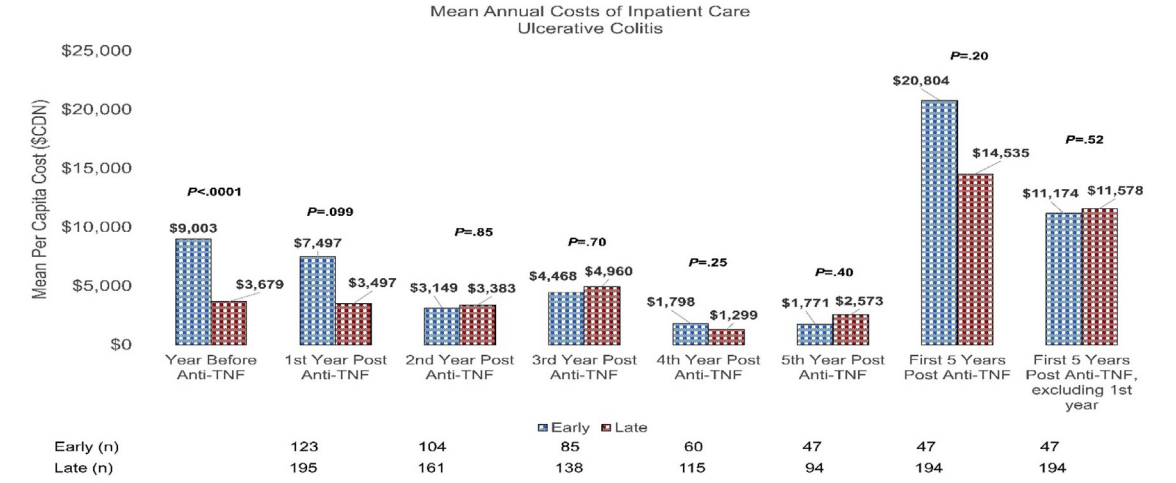


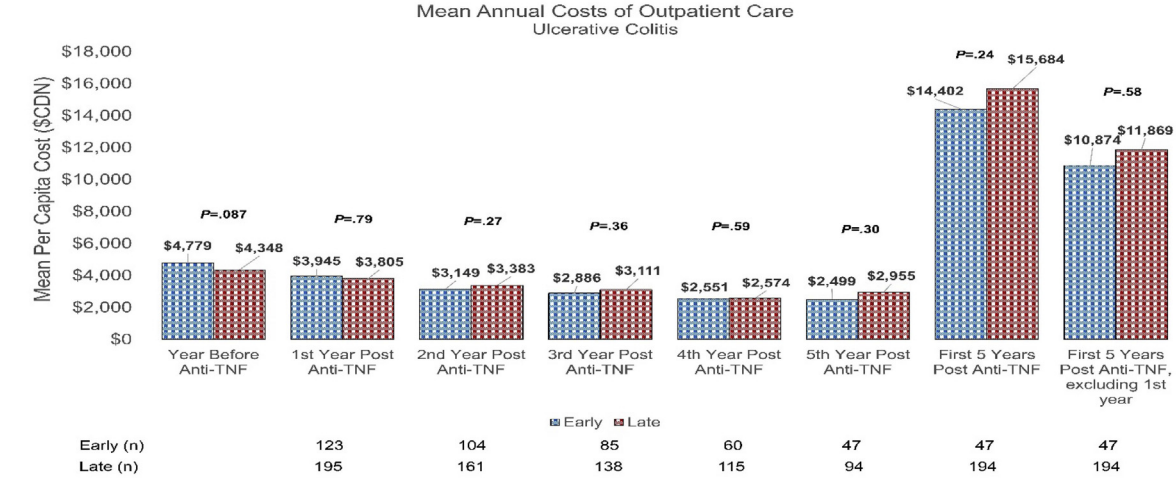
Supplementary Figure 6. IPTW-adjusted incidence rates for mean annual direct costs pre and post anti-TNF initiation for UC.



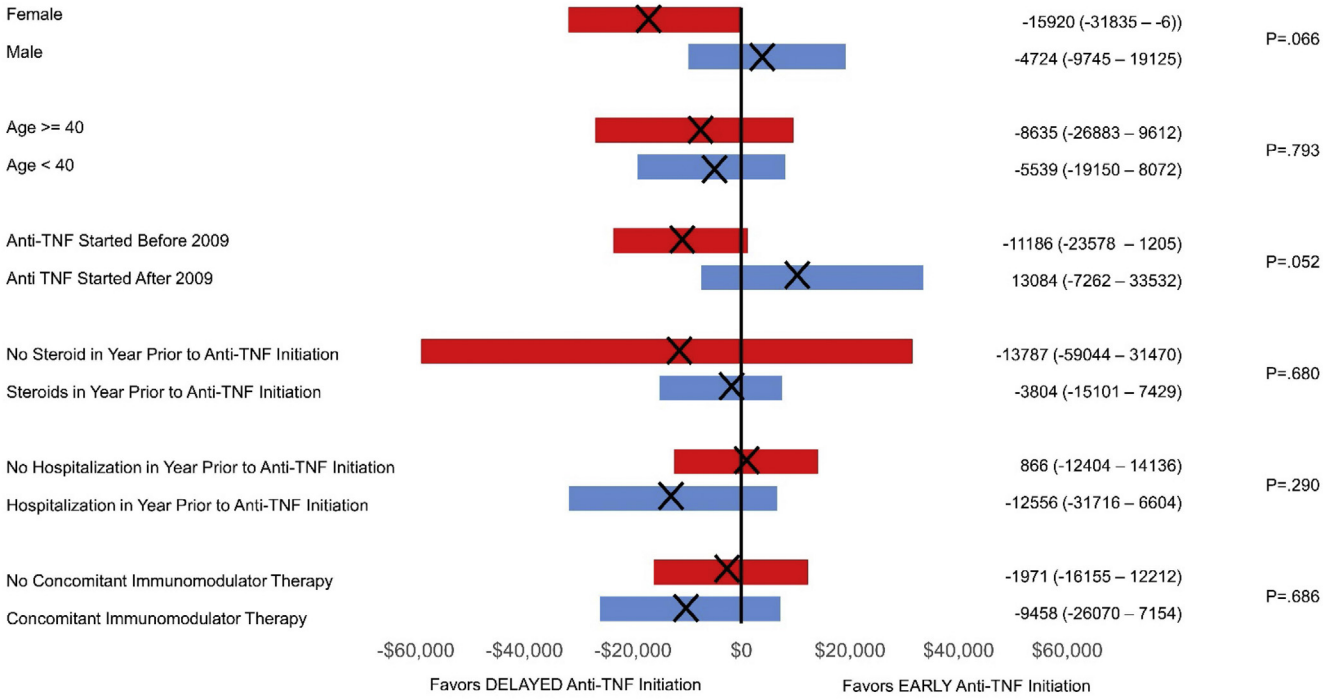
Supplementary Figure 7. Unadjusted incidence rates for IBD-specific outcomes pre and post anti-TNF initiation for UC.







Supplementary Figure 8. Unadjusted incidence rates for mean annual direct costs pre and post anti-TNF initiation for UC.



Supplementary Figure 9. Cumulative difference in IPTW-adjusted costs in first 5 years following anti-TNF initiation between early and late initiators with UC.

Supplementary Table 1. ICD-9 and CCI Codes for Resective Intestinal Surgery

	Code
Incision, excision, and anastomosis of intestine	
Other excision of small intestine	45.6
Multiple segmental resection of small intestine	45.61
Other partial resection of small intestine	45.62
Duodenectomy, ileectomy, jejunectomy	
Total removal of small intestine	45.63
Other open and other partial excision of large intestine	45.7
Segmental resection for multiple traumatic lesions of large intestine	45.71
Open and other cecectomy/resection of cecum and terminal ileum	45.72
Open and other right hemicolectomy/ileocolectomy/right radical colectomy	45.73
Open and other resection of transverse colon	45.74
Open and other left hemicolectomy	45.75
Open and other sigmoidectomy	45.76
Other and unspecified partial excision of large intestine/enterocolectomy NEC	45.79
Total intra-abdominal colectomy/excision of cecum, colon, and sigmoid	45.8
Laparoscopic total intra-abdominal colectomy	45.81
Open total intra-abdominal colectomy	45.82
Other and unspecified total intra-abdominal colectomy	45.83
Resection of exteriorized segment of small intestine	46.02
Resection of exteriorized segment of large intestine	46.04
Resection of exteriorized segment of intestine NOS	
Second-stage Mikulicz operation	
Operations on rectum, rectosigmoid, and perirectal tissue	
Rectal pull-through operations	48.4x
Abdominoperineal resection of rectum	48.5
Abdominoperineal resection of the rectum, NOS	48.5
Laparoscopic abdominoperineal resection of the rectum	48.51
Open abdominoperineal resection of the rectum	48.52
Other abdominoperineal resection of the rectum	48.59
Other resection of rectum	48.6
Transsacral rectosigmoidectomy	48.61
Anterior resection of rectum with synchronous colostomy	48.62
Other anterior resection of rectum	48.63
Posterior resection of rectum	48.64
Duhamel resection of rectum	48.65
Duhamel abdominoperineal pull-through	
Other	48.69
Partial proctectomy	
Rectal resection NOS	

Supplementary Table 1. Continued

	Code
Laparoscopic surgery	
17.3 Laparoscopic partial excision of large intestine	17.3
17.31 Laparoscopic multiple segmental resection of large intestine	17.31
17.32 Laparoscopic cecectomy	17.32
17.33 Laparoscopic right hemicolectomy	17.33
17.34 Laparoscopic resection of transverse colon	17.34
17.35 Laparoscopic left hemicolectomy	17.35
17.36 Laparoscopic sigmoidectomy	17.36
17.39 Other laparoscopic partial excision of large intestine	17.39

CCI Codes for Surgery	
Resections with anastomoses	
1.NK.87	Excision partial, small intestine
1.NK.87.DA	Simple excision, laparoscopic
1.NK.87.LA	Simple excision, open
1.NK.87.DN	Enterocolostomy anastomosis, laparoscopic
1.NK.87.RE	Enterocolostomy anastomosis, open
1.NK.87.DP	Enteroenterostomy anastomosis, laparoscopic
1.NK.87.RF	Enteroenterostomy anastomosis, open
1.NM.87	Excision partial, large intestine
1.NM.87.DA	Simple excision, laparoscopic
1.NM.87.LA	Simple excision, open
1.NM.87.DF	Colocolostomy anastomosis, laparoscopic
1.NM.87.RN	Colocolostomy anastomosis, open
1.NM.87.DE	Colorectal anastomosis, laparoscopic
1.NM.87.RD	Colorectal anastomosis, open
1.NM.87.DN	Enterocolostomy anastomosis, laparoscopic
1.NM.87.RE	Enterocolostomy anastomosis, open
1.NQ.87	Excision partial, rectum (includes proctocolectomy, procto-sigmoidectomy, pull through, rectosigmoidectomy, anterior resection)
1.NQ.87.LA	Closure by apposition, open
1.NQ.87.DA	Closure by apposition, laparoscopic
1.NQ.87.RD	Colorectal anastomosis, open
1.NQ.87.DE	Colorectal anastomosis, laparoscopic
1.NM.89	Excision total, large intestine
1.NM.89.DF	Ileorectal anastomosis, laparoscopic
1.NM.89.RN	Ileorectal anastomosis, open
1.NM.91	Excision radical, large intestine (including en bloc resection)

Supplementary Table 1. Continued

CCI Codes for Surgery	
Resections with anastomoses	
1.NM.91.DF	Colocolostomy anastomosis, laparoscopic
1.NM.91.RN	Colocolostomy anastomosis, open
1.NM.91.DE	Colorectal anastomosis, laparoscopic
1.NM.91.RD	Colorectal anastomosis, open
1.NM.91.DN	Enterocolostomy anastomosis, laparoscopic
1.NM.91.RE	Enterocolostomy anastomosis, open
1.NQ.89	Excision total, rectum
1.NQ.89.SF	Coloanal anastomosis, abdominal anterior approach
1.NQ.89.KZ	Coloanal anastomosis, abdominoperineal approach
1.NQ.89.GV	Coloanal anastomosis, combined endoscopic approach
1.NQ.89.SF	Pouch formation, abdominal anterior approach
1.NQ.89.KZ	Pouch formation, abdominoperineal approach
1.NK.87	Excision partial, small intestine
1.NK.87.DX	Stoma formation with distal closure, laparoscopic
1.NK.87.TF	Stoma formation with distal closure, open
1.NK.87.DY	Stoma formation with mucous fistula, laparoscopic
1.NK.87.TG	Stoma formation with mucous fistula, open
1.NM.87	Excision partial, large intestine
1.NM.87.DX	Stoma formation and distal closure, laparoscopic
1.NM.87.TF	Stoma formation and distal closure, open
1.NM.87.DY	Stoma formation with mucous fistula, laparoscopic
1.NM.87.TG	Stoma formation with mucous fistula, open
1.NQ.87	Excision partial, rectum (includes proctocolectomy, procto-sigmoidectomy, pull through, rectosigmoidectomy, anterior resection)
1.NQ.87.LA	Closure by apposition, open
1.NQ.87.DA	Closure by apposition, laparoscopic
1.NQ.87.RD	Colorectal anastomosis, open
1.NQ.87.DE	Colorectal anastomosis, laparoscopic
1.NQ.87.TF	Colostomy with Hartman or submucosal fistula, open
1.NQ.87.DX	Colostomy with Hartman or submucosal fistula, laparoscopic
1.NM.89	Excision total, large intestine
1.NM.89.DX	Stoma formation with distal closure, laparoscopic
1.NM.89.TF	Stoma formation with distal closure, open
1.NM.91	Excision radical, large intestine (including en bloc resection)
1.NM.91.DX	Stoma formation with distal closure, laparoscopic
1.NM.91.TF	Stoma formation with distal closure, open
1.NM.91.DY	Stoma formation with mucous fistula, laparoscopic

Supplementary Table 1. Continued

CCI Codes for Surgery	
Resections with anastomoses	
1.NM.91.TG	Stoma formation with mucous fistula, open
1.NQ.89	Excision total, rectum
1.NQ.89.RS	Stoma formation with distal closure, anterior approach
1.NQ.89.LH	Stoma formation with distal closure, abdominoperineal
1.NQ.89.AB	Stoma formation with distal closure, combined endoscopic
1.NQ.89.RS	Continent ileostomy formation, anterior approach
1.NQ.89.LH	Continent ileostomy formation, abdominoperineal approach

CCI, Canadian Classification of Health Interventions; *ICD-9*, International Classification of Diseases, ninth revision; *NOS*, not otherwise specified.