Healthcare Utilization and Cost Burden with Switching or Cycling After Starting anti-TNFs in IBD: A Retrospective Cohort Analysis

Janice Jang

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

University of Washington

2026

Committee:

Kyu Eun Lee

Noemi Kreif

Program Authorized to Offer Degree:

College of Pharmacy

University of Washington

Abstract

Healthcare Utilization and Cost Burden with Switching or Cycling After Starting anti-TNFs in IBD: A Retrospective Cohort Analysis

Janice Jang

Chair of the Supervisory Committee:

Kyu Eun Lee

Objective: To compare the healthcare utilization and cost burden between patients who cycle to a different anti-TNF and patients who switch to a different mechanism of action medication within ulcerative colitis (UC) and Crohn's disease (CD).

Methods: We conducted a retrospective cohort study using Merative Marketscan claims data from January 2016 to December 2024. UC and CD patients were identified as having at least two UC or CD outpatient claims or one inpatient claim in the 6 months prior to their first anti-TNF. The index date is when the patient switches or cycles, i.e., the fill of the second drug. Primary healthcare utilization outcomes were the number of inpatient admissions, inpatient length of stay, the number of outpatient visits, and the number of emergency room visits. The primary healthcare cost outcomes were total healthcare expenditure, medical expenditure, and pharmacy/medication expenditure. Secondary outcomes consisted of non-persistence of the index biologic, defined by a 90-day gap in therapy, and corticosteroid use of greater than 60 consecutive days. Inverse probability of treatment weighting was used to adjust for potential confounding variables in the observational data.

Results: In the 12-month follow-up, UC cyclers were associated with a 0.2-day increase in length of stay (95% CI -1.18, 1.57), a 0.05 decrease in hospital admissions (95% CI -0.13, 0.03), 1.18 increase in outpatient visits (95% CI -0.23, 2.58), and a 0.5 increase in ER visits (95% CI -1.01, 2.01), which were statistically nonsignificant. In CD patients, cyclers had a slightly higher mean length of stay in days (ATE 0.11; 95% CI -1.44, 1.37), number of hospital admissions (ATE 0.04; 95% CI -0.07, 0.14), and number of ER visits (ATE 0.59; 95% CI -0.7, 1.88). The mean number of outpatient visits was 0.21 lower in the

cycling group compared to the switching group in CD (ATE -0.21; 95% CI -1.94, 3.69). Healthcare utilization outcomes for CD were not statistically significant. UC patients who cycled had lower mean total healthcare expenditure (ATE -13012.44; 95% CI -32105, 5101), pharmacy expenditure (ATE -2595.93; 95% CI -20764, 17397), and medical expenditure (ATE -5592.17; 95% CI -11986, 1697) compared to switchers, but were statistically nonsignificant. In CD, cycling was associated with significantly lower total healthcare expenditures (ATE -54352.72; 95% CI -67382, -39816) and significantly lower pharmacy expenditures (ATE -53136.04; 95% CI -63709, -41280). Cycling was also associated with slightly higher mean medical expenditure in CD (ATE 441.88; 95% CI -11177.9, 43943.8) but was not statistically significant.

Conclusion: Overall, within IBD, cycling between anti-TNFs was not associated with consistently higher healthcare utilization than switching to a non-anti-TNF, but it was linked to lower healthcare expenditures in CD patients.

Table of Contents

1. Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, immunological disease with a progressive nature.[1] The disease is characterized by inflammation that may affect any part of the gastrointestinal tract in CD or be limited to the colon in UC.[1] Patients with IBD experience weight loss, diarrhea, and persistent abdominal pain.[2] Often, IBD patients may also present with extraintestinal symptoms such as osteoporosis and skin, joint, liver, and eye conditions, which can have a significant impact on a patient's quality of life and higher economic burden.[1] The mean direct annual cost of treating CD was estimated to be $12,000 and $9,000 for UC in 2021 USD, which would be an estimated $50 billion annual cost of IBD in the U.S.[3,4] These costs were estimated after the market entry of anti-tumor necrosis factor (anti-TNF) biologics and do not account for increased costs associated with more recently approved medications.[4] Furthermore, the prevalence of IBD has been increasing in the past few decades, as suggested by a 23.5% increase in prevalence between 1990 and 2017.[5,6] The U.S. has had the highest age-standardized prevalence rate of IBD, with a prevalence of approximately 0.7% of the U.S. population.[4,7]

Goals of treatment for CD and UC include maintaining steroid-free remission to promote mucosal healing, prevent hospitalizations, and improve quality of life.[8,9] The choice of therapy involves considerations of the patient's disease severity and prior medication response.[10] Medications available for maintenance of moderate to severe CD and UC include immunomodulators (azathioprine and 6-mercaptopurine), anti-tumor necrosis factors (anti-TNFs), integrin inhibitors (vedolizumab and natalizumab), anti-interleukin therapy (ustekinumab, risankizumab, mirikizumab, guselkumab), and Janus Kinase inhibitors (e.g., upadacitinib). While corticosteroids have been used in moderate to severe UC and CD as a bridge to advanced therapy during induction of remission, the American College of Gastroenterology clinical practice guidelines for UC and the American Gastroenterology Association clinical practice guidelines for CD recommend against using corticosteroids to maintain remission.[11,12] Continued use of corticosteroids increases the risk of morbidity and mortality in IBD in comparison to other treatment agents.[13,14]

The mainstay of advanced biologic therapy for moderate-to-severely active CD and UC is anti-TNF agents, including infliximab, adalimumab, and certolizumab pegol.[15] However, up to 20% to 30% of patients may be non-responsive to anti-TNF induction therapy, and patients initially responsive to induction therapy may lose treatment effect after a few years as a secondary non-responder during maintenance treatment.[8,9] Reasons for a primary non-response or loss of response may include suboptimal drug serum concentrations, intestinal infections, and functional bowel symptoms.[8] The current American College of Gastroenterology clinical guidelines for UC recommend that primary nonresponders to anti-TNF therapy should be considered for a medication with a different mechanism of action, like an integrin-

inhibitor or anti-interleukin therapy, rather than cycling within anti-TNF agents, i.e., going from one anti-TNF agent to another anti-TNF agent.[8] Non-responders with an adequate drug serum concentration may particularly benefit more from a different mechanism of action rather than cycling.[8] Approximately 50% - 65% of primary non-responders who receive a second TNF-inhibitor, after being refractory to their first anti-TNF, may achieve remission, but a substantial proportion will ultimately lose response to TNF-inhibitors.[16,17]

Previous studies have reported that patients with IBD who switched to a different mechanism of action had higher treatment persistence, i.e., were less likely to discontinue their medication, during the maintenance phase compared to those who cycled between anti-TNF agents.[18–21] Additionally, IBD patients who switched to a different mechanism of action had a lower likelihood of re-switching therapy compared to anti-TNF cyclers.[20–22] UC patients who cycled were 1.82 times more likely to discontinue their index biologic compared to switchers (HR 1.82; 95% CI 1.14, 2.89). Also, CD patients who cycled were 1.71 times more likely to discontinue their index biologic compared to switchers (HR 1.71; 95% CI 1.25, 2.34). Hupé et al. showed that patients with UC who had previously failed anti-TNF therapy had higher clinical remission when switching to vedolizumab than when cycling to infliximab.[23] However, there is an evidence gap in evaluating the downstream healthcare resource utilization and cost differences between switching mechanisms of action and cycling within anti-TNF agents. Treatment discontinuation and delayed clinical remission associated with cycling between anti-TNF agents may lead to greater healthcare utilization and higher overall costs. In this study, we aim to investigate the healthcare utilization and economic burden associated with cycling within anti-TNF agents compared to switching to a different mechanism of action after the first-line anti-TNF therapy, among IBD patients using real-world data in the United States.

2. Methods

2.1 Study Design and Data Source

This study was a retrospective cohort study of individuals with IBD who initiated an anti-TNF and switched or cycled to a different IBD drug during January 1, 2016, and December 31, 2024 (Figure 1). We used Merative MarketScan Commercial Database, Merative MarketScan Medicare Database, and Merative MarketScan Multi-State Medicaid Database for de-identified claims data. The Commercial Database contains healthcare data for active employees and persons not yet eligible for Medicare. The Medicare Database consists of claims from Medicare-eligible retirees, including individuals with employer-sponsored Medicare Supplemental and Medicare Advantage Plans. The Medicaid Database pools healthcare claims of Medicaid enrollees of state-level programs, including fee-for-service and managed care plans. All three databases contain claims for inpatient and outpatient encounters and

prescription drug fills. The data is de-identified and fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. This study was exempt from IRB approval, as it did not use any patient-identifiable data. International Classification of Diseases 10th Revision, Clinical Modification (ICD-10-CM) codes were utilized to identify diagnoses, National Drug Codes (NDC) were used to identify medications, and Current Procedural Terminology, 4th Edition (CPT-4) were used to identify healthcare procedures.

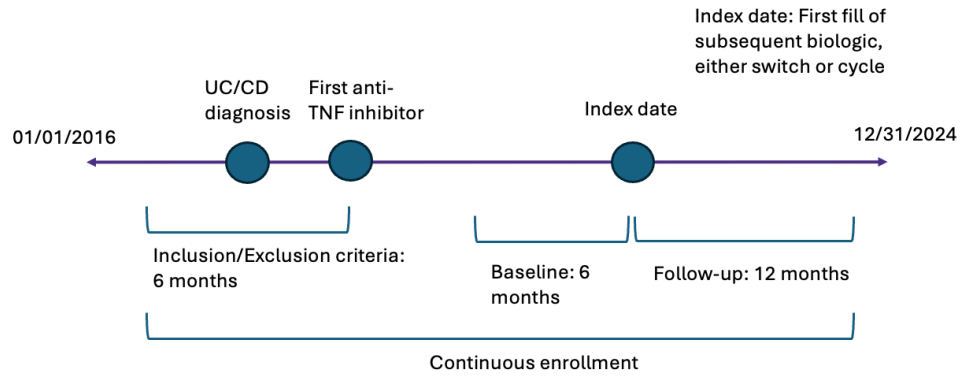


Figure 1: Study Timeline

2.2 Cohort Selection

We identified patients whose earliest claim for an anti-TNF medication was between January 1, 2016, and December 31, 2024. Individuals with a claim for an anti-TNF between January 1, 2010, and December 31, 2015, were excluded. Anti-TNF medications include adalimumab, infliximab, certolizumab pegol, golimumab, and their corresponding biosimilars (Appendix 8.4). Individuals had to have at least 1 inpatient diagnosis or 2 outpatient diagnoses for either UC (K51.x) or CD (K50.x) within the last 6 months before their first anti-TNF. If the individual had both a diagnosis of UC and CD in the 6 months prior to their first anti-TNF, they were excluded from the cohort. During the 6 months before the first anti-TNF, individuals who had filled other biologics or small synthetic drugs (Table 8.2) were excluded. In addition, individuals with claims for IBD-related procedures, such as colectomy, proctectomy, and anorectal procedures (Table 8.1) or a diagnosis of other immune-mediated diseases, such as ankylosing spondylitis, hidradenitis suppurativa, juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis, relapsing polychondritis, and uveitis (Table 8.1) in the 6 months before the first anti-TNF were excluded from the cohort. Diagnosis of any type of malignancy, as well as primary and secondary malignant neoplasms (Table 8.1), was also an exclusion if it was identified in those 6 months. Patients had to be at least 18 years old at the time of their first anti-TNF.

The control cohort ("switchers") was identified as individuals who filled a medication with a different mechanism of action, including sphingosine 1-phosphate (S1P) modulators, integrin receptor antagonists, Janus kinase (JAK) inhibitors, and interleukin-23 inhibitors after their first anti-TNF and within 90 days after the last day's supply of the first anti-TNF. The treatment cohort ("cyclers") was identified as individuals who filled a different anti-TNF from their first anti-TNF after the date of their first anti-TNF and within 90 days after the last day's supply of the first anti-TNF. A 90-day period after the last day's supply for the anti-TNF was chosen as a grace period. Biosimilar medications are considered to be bioequivalent to their reference product and were not considered as a different anti-TNF from their reference product in this study. The index date is identified as the date the person picked up their second-line biologic agent, i.e., the date the individual is identified as either a switcher or cycler. The follow-up time period is 1 year after the index date. Continuous enrollment was applied from 6 months prior to the first anti-TNF claim to 1 year after the index date.

2.3 Baseline Characteristics

Baseline characteristics were gathered from the index date to 6 months in the pre-index period. Information about age, sex, insurance (commercial, Medicare, Medicaid), index year, baseline anti-TNF medication, index medication, and region (Northeast, North Central, South, West, Unknown) was retrieved for baseline characteristics. The Medicaid Database does not contain region information, so enrollees from the Medicaid Database were coded as Unknown region. Utilizing the comorbidity package in R, the unweighted Charlson Comorbidity Index (CCI), Quan-weighted CCI, unweighted Elixhauser Comorbidity Index (EI), and van Walraven-weighted EI were assessed using ICD-10 codes for each individual. CCI, which predicts a patient's mortality based on their set of comorbidities, from a study in 1984, was reevaluated by a study by Quan, in which they kept 12 of the comorbidities from the original 17 based on more recent data.[24] EI accounts for 30 comorbidities and was re-weighted to better predict mortality by van Walraven et al.[25,26] The number of hospital admissions and baseline healthcare costs from the 6-month pre-index period were evaluated. Baseline medication use, including 5-aminosalicylates (5-ASA), corticosteroids, and corticosteroids of greater than 60-day supply, was also included in the baseline characteristics. Concomitant use of corticosteroids was shown to be a predictor of anti-TNF failure (HR 2.04; 95% CI 1.18, 3.55).[27] Additionally, 5-ASA is a common treatment in UC patients and is frequently used in CD patients, and can be used in uncontrolled disease. We observed extraintestinal manifestations from the pre-index period and grouped them by disease state (Table 8.1 To characterize persistence of the first anti-TNF, we calculated the total number of continuous days on the first anti-TNF and total time between the first anti-TNF to index date, which includes gaps in between prescriptions. Continuous days of a medication were defined as medications filled within 1.5 times the days' supply after the last day's supply of the previous fill (imputation rules; Table 8.4).

2.4 Outcomes

The primary outcomes for healthcare utilization were all-cause hospitalizations, consisting of the number of inpatient (IP) admissions and the number of IP days, the number of all-cause outpatient (OP) visits, and the number of all-cause emergency room (ER) visits. For cost, primary outcomes were medical costs, medication costs, and total healthcare costs, defined by both medical and medication costs. Medical costs were adjusted to 2024 USD using the Medical Care Consumer Price Index for All Urban Consumers (CPI-U), and pharmacy costs were adjusted to 2024 USD using the Prescription Drugs CPI-U. Secondary outcomes included non-persistence of index biologic, i.e., between the second- and third-line biologic, and prolonged CS use defined as >60 consecutive days' supply in the follow-up period. Secondary outcomes are measured as binary outcomes. Additionally, exploratory outcomes: UC-/CD-related IP admission and number of IP days, UC-/CD-related OP visits, and UC-/CD-related ER visits were observed.

2.5 Statistical Analysis

R statistical software was utilized for the data analysis. For baseline characteristics, categorical variables from the study cohort are presented as frequencies and proportions, and continuous variables are presented with means and standard deviations (SD).

2.5.1 Inverse Probability of Treatment Weighting

In our study, the cycling cohort was the treatment group, and switching was the control group. The treatment effect was estimated for the UC and CD study populations, separately, targeting the average treatment effect in the populations (ATE). ATE consists of comparing outcomes of two counterfactual scenarios: one where the entire study population cycles compared to one where the entire study population switches.[28] We controlled for confounding, since switchers and cyclers may differ in ways that independently affect healthcare utilization and cost outcomes. To account for observed confounders, we adjusted using propensity score estimates. The propensity score is the probability that an individual is cycled, conditional on their observed baseline covariates.[29] The probability of cycling was modeled using a logistic regression, i.e., a generalized linear model with a logit link (Eq.1). The covariates which we identified as confounders and included in the logistic regression were age, sex, van-Walraven weighted EI, Quan-weighted CI, number of continuous days on the first anti-TNF, healthcare expenditure in the pre-index period, hospitalization (binary) in the pre-index period, continuous CS use > 60 days, region, 5-ASA use, any CS use, dermatologic extraintestinal manifestations (EIM), musculoskeletal EIM, hepatobiliary EIM, ophthalmologic EIM, and insurance (Table 1). Prior hospitalization, greater comorbidity, and higher baseline healthcare spending reflect overall higher burden of disease and can be a strong independent predictor of healthcare utilization and spending. Concomitant medication use, such as

5-ASA and CS, as well as the presence of EIMs, can be associated with treatment decisions and higher utilization of medical care, as use of concomitant medications and presence of EIMs indicate uncontrolled and a more extensive, systematic disease. We applied inverse probability treatment weights (IPTW) derived from propensity score estimates. The datasets are reweighted according to the inverse of the propensity score, where cyclers receive a weight of $1/\pi_i$, and switchers receive a weight of $(1/(1 - \pi_i)$, to estimate the ATE. Weights were calculated using the R WeightIt package.[30] Balance was assessed in the reweighted data according to SMDs. We considered covariates with an SMD below 0.1 to be well balanced.[29]

$$\ln(\frac{p}{1-p}) = \beta_0 + \beta_1 sex + \beta_2 age + \beta_3 score\_uw\_charl + \beta_4 score\_quan + \beta_5 score\_uw\_elix + \beta_6 score\_vw + \beta_7 asa + \beta_8 cs + \beta_9 cs\_60 + \beta_{10} total\_covered + \beta_{11} eim\_eye + \beta_{12} eim\_joint + \beta_{13} eim\_hepato + \beta_{14} eim\_derm + \beta_{15} hosp + \beta_{16} insurance + \beta_{17} totalpay. \quad (1)$$

Table 1: Definitions and Coding of Model Variables

Variable	Definition	Type/Coding
sex	Patient sex	Binary (0= male; 1 = female)
age	Age in years	Continuous
score_uw_charl	Unweighted Charlson Comorbidity Index	Continuous
score_quan	Quan-weighted Charlson Comorbidity Index	Continuous
score_uw_elix	Unweighted Elixhauser Comorbidity Index	Continuous
score_vw	Van Walraven-weighted Elixhauser Comorbidity Index	Continuous
asa	5-aminosalicylate (5-ASA) use	Binary (0 = no use; 1 = any use)
cs	Any corticosteroid use	Binary (0 = no use; 1 = any use)
cs_60	Corticosteroid use for >60 continuous days	Binary (0 = ≤60 days / none; 1 = >60 days)
total_covered	Total continuous days on first anti-TNF agent	Continuous (days)
eim_eye	Ophthalmologic extraintestinal manifestation (EIM)	Binary (0 = absent; 1 = present)
eim_joint	Musculoskeletal EIM	Binary (0 = absent; 1 = present)

eim_hepato	Hepatopancreatobiliary EIM	Binary (0 = absent; 1 = present)
eim_derm	Dermatologic EIM	Binary (0 = absent; 1 = present)
hosp	Any hospitalization	Binary (0 = none; 1 = ≥1 hospitalization)
insurance	Insurance type	Medicare; Medicaid; reference = Commercial
totalpay	Baseline total healthcare cost	Continuous (USD)

2.5.2 Healthcare Utilization and Costs

Regression was adjusted by covariates that remained unbalanced after propensity score estimation. For the analysis of the outcomes for UC patients, regression was adjusted by index year. The index year was not a covariate included in the propensity score regression, thus was included to adjust for the regression model. For the analysis of the outcomes for CD patients, regression was adjusted by index year and by the number of continuous days on the first anti-TNF and healthcare expenditure in the pre-index period, due to remaining imbalance after propensity score estimation, with the exception of the number of ER visits, which was regressed on only the number of continuous days on the first anti-TNF and index year due to the algorithm's inability to converge.

For inpatient admissions, underdispersion occurred where the variance was less than the mean. Having more than 1 inpatient admission was rare; only 1 patient in the CD group had 2 admissions. With underdispersion, the standard errors are more conservative and can tend to give false negative results.[31] Inpatient admissions were modeled using a Poisson regression. Other healthcare utilization outcomes were overdispersed, with variance greater than the mean, and the deviance statistic testing goodness of fit showed evidence of lack of fit with the Poisson regression. With overdispersion, the standard error estimates may come out too small and lead to wrong conclusions that there is a meaningful effect when there is not.[32] To account for overdispersion, IP length of stay, ER visits, and OP visits were modeled using negative binomial regression. Negative binomial models have two parameters: the mean and the over-dispersion parameter θ to account for overdispersion. Outcomes modeled using quasi-Poisson were attached to the appendix, as negative binomial and quasi-Poisson models have differences in weighting the observations. Incidence rate ratios (IRR) were estimated for healthcare utilization outcomes.

For cost outcomes, including total healthcare cost, medical cost, and pharmacy cost, the distribution was right-skewed, with many individuals having zero cost outcomes. The healthcare utilization costs and predictor variable relationship were modeled with a two-part model. The first part of the model used

logistic regression to estimate the probability of any costs occurring. Among those with non-zero costs, mean costs were modeled using a generalized linear model (GLM) with a gamma distribution and a log link. Secondary outcomes: non-persistence of index biologic, i.e., between the second- and third-line biologic, and prolonged CS use, defined as >60 consecutive days' supply, were modeled using logistic regression. MASS, stats, and glm2 packages were utilized in R for regression models.

Average treatment effects (ATE) were estimated for all outcomes. Treatment effects are estimated by the g-computation method. For healthcare utilization outcomes, robust standard errors were calculated for confidence intervals.[33] For healthcare expenditure outcomes, a fractional weighted bootstrap with 1000 bootstrap replications was used to calculate confidence intervals.[33,34] In R, package marginaleffects was used to calculate ATE and robust standard errors, and the package boot was used to calculate bootstrapped confidence intervals.[33]

3. Results

A total of 29,934 individuals with IBD were identified to have a first anti-TNF fill between January 1, 2016, and December 31, 2024. After applying the inclusion and exclusion criteria, 1,262 of those individuals filled a different MOA drug or a different anti-TNF medication (Figure 6.1). We identified 532 individuals for UC and 730 individuals for CD to be included in the data analysis. Of the 532 individuals with UC, 425 were in the switching cohort, and 107 were in the cycling cohort. Of the 730 individuals with CD, 605 individuals were in the switching cohort, and 125 were in the cycling cohort.

3.1 Baseline Characteristics

Baseline characteristics of the cohorts pre- and post-weighting are shown in Table 7.1 for UC and Table 7.2 for CD. Before weighting, for both UC and CD groups, the switching cohort had a higher mean healthcare spending in the 6-month pre-index compared to the cycling cohort. Mean healthcare spending in the 6-month baseline was $62,285.30 for CD switchers and $48,319.20 for CD cyclers, while $59,539.20 for UC switchers and $49,843.90 for UC cyclers. Additionally, prior to weighting, the switching cohort had a higher mean total continuous duration of the first anti-TNF compared to the cycling cohort. Most patients in either cohort for UC and CD were on adalimumab for their first anti-TNF; 91.5% for the switching cohort and 68.2% for the cycling cohort in UC, and 89.9% for the switching cohort and 65.6% for the cycling cohort in CD. As 2nd line medication, the majority of patients in the switching cohort for UC and CD filled an interleukin-23 inhibitor, while 43.2% of CD patients in the cycling cohort filled certolizumab, and 38.3% of UC patients in the cycling cohort filled golimumab as their 2nd line. The index year was concentrated in later years for the cycling cohort (around 2016 compared to the switching cohort, which was more concentrated in the earlier years. This reflects the

different approval dates for the medications, with non-anti-TNF medications being approved more recently compared to the anti-TNFs (Table 8.2).

IPTW improved the balance between the cohorts. The covariates were well balanced after IPTW for both UC and CD, as shown by Figures 6.2 and 6.3, with the exception of the number of continuous days on the first anti-TNF drug and baseline 6-month healthcare cost covariates in the CD group.

3.2 Regression Analysis

Coefficients and standard errors from the regression analysis for healthcare utilization outcomes are shown in Table 7.3. For UC patients, cyclers compared to switchers had an average of 0.18 more outpatient visits per (95% CI -0.23, 2.58), but this was not statistically significant. Cyclers with UC had lower rates in IP admissions and higher rates of ER visits and IP length of stay compared to switchers, but these findings were also not statistically significant. For CD patients, cyclers had higher rates of IP admissions, ER visits, and IP length of stay, and lower rates of OP visits compared to switchers, but these results were also not statistically significant. These findings can further be corroborated by the average treatment effects for UC and CD (Table 7.6).

Coefficients and standard errors from the regression analysis for healthcare cost outcomes are shown in Table 7.4. CD patients who cycled had an average $54,352.72 (95% CI -67382, -39816) lower total healthcare cost compared to patients who switched in the 1-year follow-up period, driven primarily by lower per-user cost rather than probability of incurring any cost. In addition, cycling patients had $53,136.04 (95% CI -63709, -41280) lower pharmacy expenditure compared to switching in CD, which is also primarily attributable to lower per-user cost. Cycling on average had higher medical expenditure (IP, OP, and ER costs) compared to switching among CD patients, but the difference was not statistically significant. Among UC patients, total healthcare expenditure, medical expenditure, and pharmacy expenditure were on average lower in the group that cycled versus switched, but was not statistically significant.

When outcomes were limited to only UC-related claims, the average number of outpatient visits in the cycling cohort was 0.33 higher, but the outcome was statistically nonsignificant (ATE 0.33; 95% CI -0.92, 1.58). In the UC cohort, average length of stay (-0.16) and hospital admissions (0.05) were lower in the cycling cohort (Figure 6.3.7). Minimal differences in the ATE outcomes were seen for CD-related outcomes (Figure 6.3.8).

ATE of secondary outcomes: non-persistence of an index drug, defined by a gap of 90 days between the last day supply and the next fill, and continuous CS use of > 60 days, are illustrated by Figures 6.3.5 and 6.3.6. ATEs for secondary outcomes were not statistically significant.

4. Discussion

In this retrospective, cohort study, cycling between anti-TNF medications was not associated with an increased rate of healthcare utilization in CD patients. Cycling was also not associated with an increased rate of healthcare utilization outcomes for UC patients. Cycling was associated with a decreased average total healthcare spending and pharmacy spending in CD patients, but not in UC patients.

Among CD patients, cycling was associated with a significant decrease in pharmacy expenditure after receiving the second-line treatment, which contributed to the overall reduction in total healthcare expenditure. This finding suggests that the costs of newer advanced therapy used as the second-line treatment outweigh any potential costs from continuing a first-line therapy with the same mechanism of action, particularly when patients are non-responsive. Lower pharmacy spending among cycling patients could reflect the higher costs of non-anti-TNF therapies, which had limited generic or biosimilar competition during the study period. [add the estimates of finishing a course of treatment with non-anti-TNF vs. anti-TNF here] By contrast, multiple biosimilars for adalimumab and infliximab were available by 2024, contributing to reduced prices for anti-TNF agents. [35] In the non-anti-TNF class, natalizumab was the only one with a non-branded alternative during the study period, with a biosimilar being approved in 2023; however, no individuals in my study were identified to have switched to natalizumab.[35] Biosimilars of ustekinumab were approved in 2025, which occurred outside our study period. [35] [36363636]Comparing the UC to CD group, UC patients also had a decrease in average total healthcare expenditures, pharmacy expenditures, and medical expenditures in the cycling group compared to switching, but this was not statistically significant. There is a likelihood that the study was underpowered to detect a meaningful effect size. The numerically lower spending on medications for UC patients could be due to the same reasons as that of the CD cohort.

Our findings suggest that cycling did not significantly increase healthcare resource utilization in UC and CD patients. This may be explained by the fact that 50-65% of patients who were non-responsive to their first anti-TNF can develop a response to their second anti-TNF. Reasons a patient may discontinue anti-TNF therapy are likely mostly due to primary nonresponse and loss of response, but a portion of the patients are discontinuing due to adverse events such as acute infusion reactions. One study suggests round 20.6% of CD patients discontinued infliximab and were treated with certolizumab because of acute infusion reactions.[36] Another found that an estimated 25% of discontinuation occurred due to loss of response, and 11% occurred due to side effects.[37] From one Belgian hospital, 28.5% of IBD patients discontinued due to adverse events, and 34% and 34.5% from primary non-response and loss of response, respectively.[38] Patients who discontinue due to an adverse event rather than a lack of response may be responsive to their second anti-TNF. A meta-analysis evaluating switching from infliximab to either

adalimumab or certolizumab in CD patients found higher remission rates for patients in their second anti-TNF who discontinued due to intolerance (61%) compared to primary non-response (30%) or loss of response (45%).[39] Additionally, loss of response could also be driven by the formation of anti-drug antibodies by an immune reaction.[40] Patients with low drug levels of the first anti-TNF without anti-drug antibodies may benefit from cycling to a second anti-TNF. [41] As a result, the lack of difference in healthcare utilization could be explained by the portion of the cycling cohort having the potential to respond to their second anti-TNF therapy.

To my knowledge, this is the first study that looked at cost burden outcomes between switchers and cyclers in IBD. Previous studies have primarily focused on persistence in therapy and prolonged corticosteroid use between patients who switched or cycled anti-TNFs in either UC or CD. Based on results on our secondary outcomes, non-persistence of the index biologic, defined by a gap of 90 days, and CS use of > 60 consecutive days were both not significantly different between the cycle and switch cohorts. In a study comparing cycling and switching in UC patients, persistence was shown to be 1.92 times higher in the switching versus cycling group (HR 1.92, p-value <0.001).[42] Persistence in that study was defined as > 120-day therapy gap for ustekinumab, vedolizumab, and infliximab, and > 60-day therapy gap for adalimumab and golimumab at 12 months after the maintenance phase. Additionally, they found 60.1% of the switch cohort and 49.3% of the cycle cohort to be CS-free after 12 months. A similar retrospective cohort study in patients with CD comparing patients who cycled between anti-TNF and patients who switched to either ustekinumab or vedolizumab found that patients who switched were 1.44 times more persistent on their therapy but similar in their corticosteroid-free persistence.[19] A different study using German claims data found that, among UC, discontinuation of the second-line medication in cyclers was 1.82 times higher than switchers (HR 1.82; 95% CI 1.14, 2.89), and initiation of prolonged CS therapy was 2.02 times higher in cyclers compared to switchers (HR 2.02; 95% CI 1.01, 4.01).[21] In this study, switchers were patients who started vedolizumab or ustekinumab after first anti-TNF. Our findings are different than expected based on previous studies. One potential reason for the difference could be that previous studies have defined switchers to those who changed their medication either to ustekinumab and vedolizumab. This study included S1P modulators, JAK inhibitors, and more recent medications like risankizumab in the definition of switchers to include all other possible medications a patients may choose to get a different mechanism of action therapy. Additionally, this study does not define a separate induction and maintenance period after the index date, so outcomes are being collected from both the induction and maintenance phases.

This study has several limitations. First, this study assumes that the majority of patients who cycle are discontinuing their first anti-TNF due to lack of response. The reason behind discontinuing the first anti-

TNF was not observed for this study, mainly due to limitations of using claims data. Drug levels and antibody lab results are not available, which makes it difficult to assess whether patients were non-responsive to their medication and be able predict future response to another anti-TNF. Next, treatment patterns after the first change in the medication were not observed. That is, any cycling or switching after the index date was not assessed. In addition, we only had a 12-month follow-up period and were limited to seeing effects in short-term outcomes. Depending on how long the individual was on the first anti-TNF, there is a period of time between the first anti-TNF claim and the index date where treatment patterns are not assessed. The pre-index period was only 6 months before the index date, where baseline characteristics were gathered. Next, comorbidities indices and extraintestinal manifestation diagnoses were utilized in this study as proxies to disease severity. Finally, while confounding was adjusted by IPTW, residual confounding may remain due to unobservable characteristics in the data.

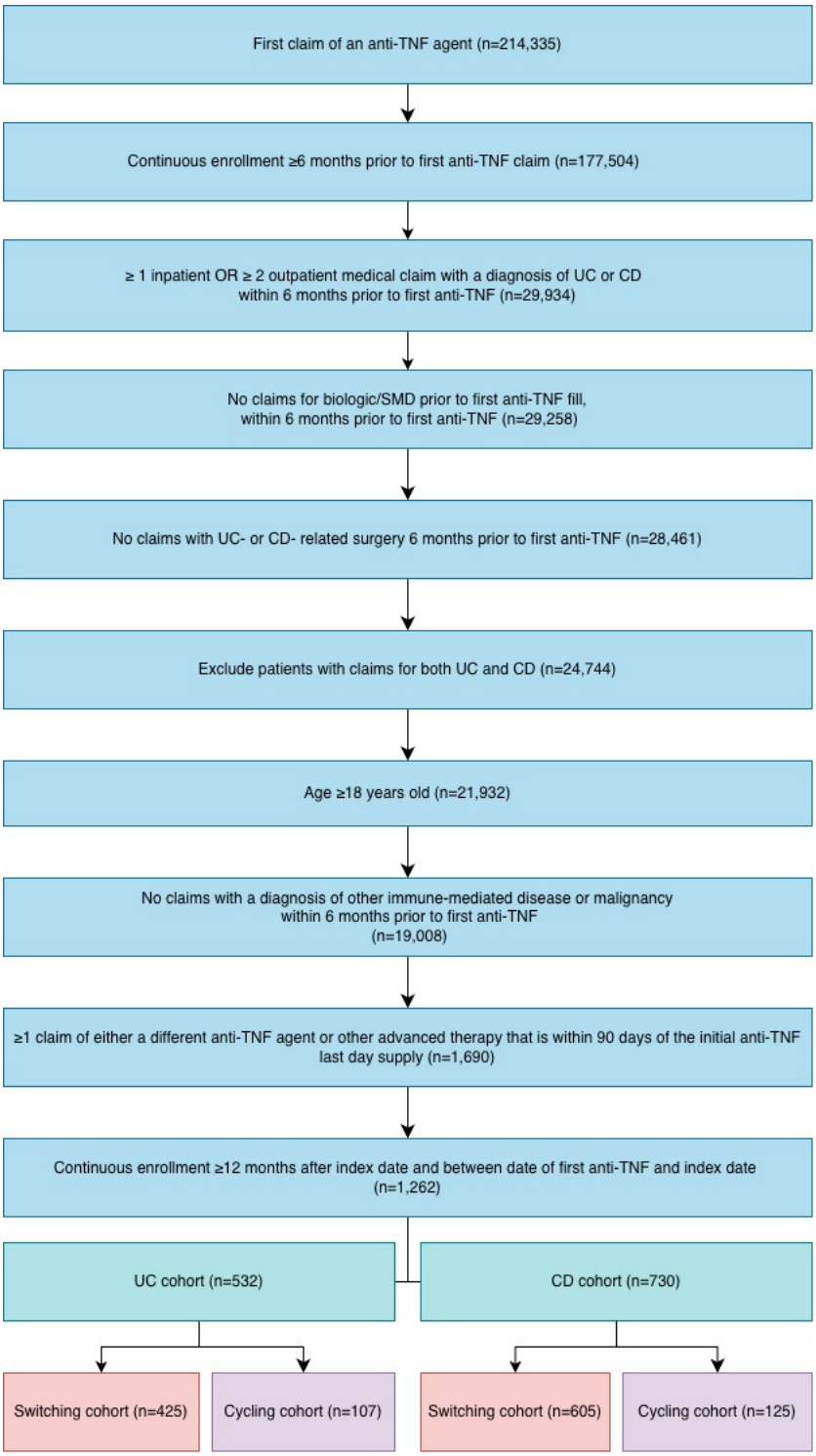
The future direction of this research could be to compare outcomes between different medication classes within the non-anti-TNFs, as well as assess for incidences of injection site or infusion site reactions prior to the index date.

5. Conclusion

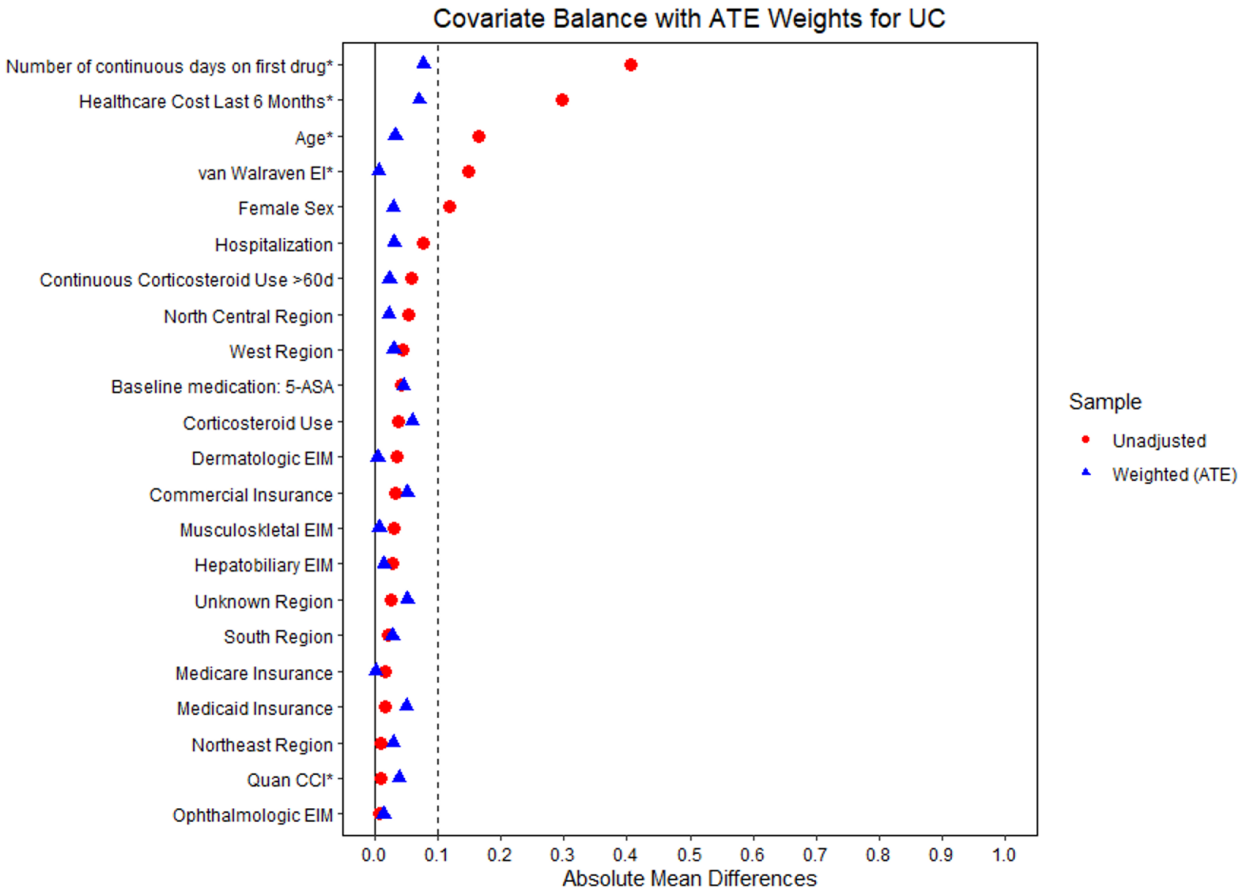
In conclusion, this retrospective cohort study found that cycling between anti-TNFs was not associated with broadly increased healthcare utilization compared with switching to a non-anti-TNF therapy among patients with IBD. Total healthcare expenditure and pharmacy expenditure were, on average, lower in the cycling cohort compared to the switching cohort in CD patients. These findings suggest that the economic implications of cycling versus switching may differ by IBD subtype and outcome measure.

6. Figures

6.1 Cohort Identification Flowchart

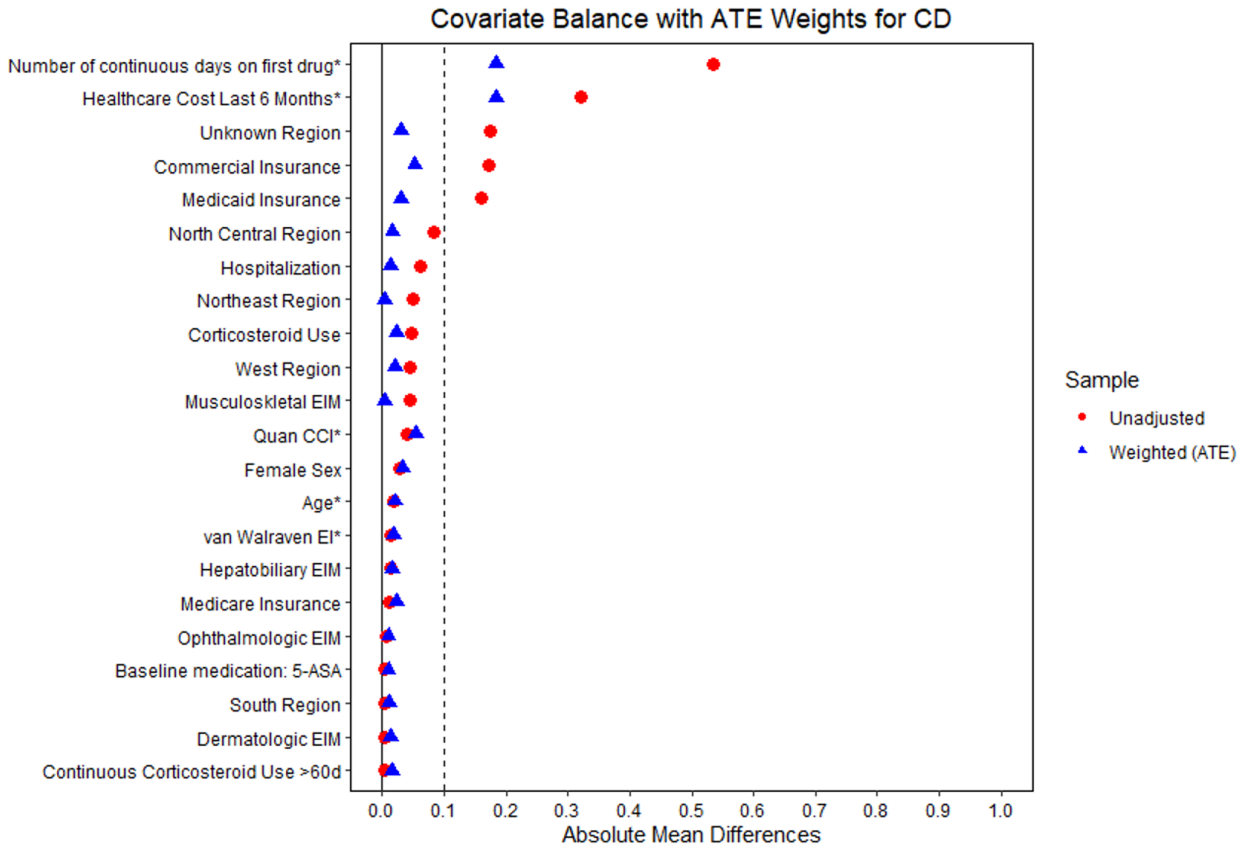


6.2.1 Covariate Balance with ATE Weighting in UC



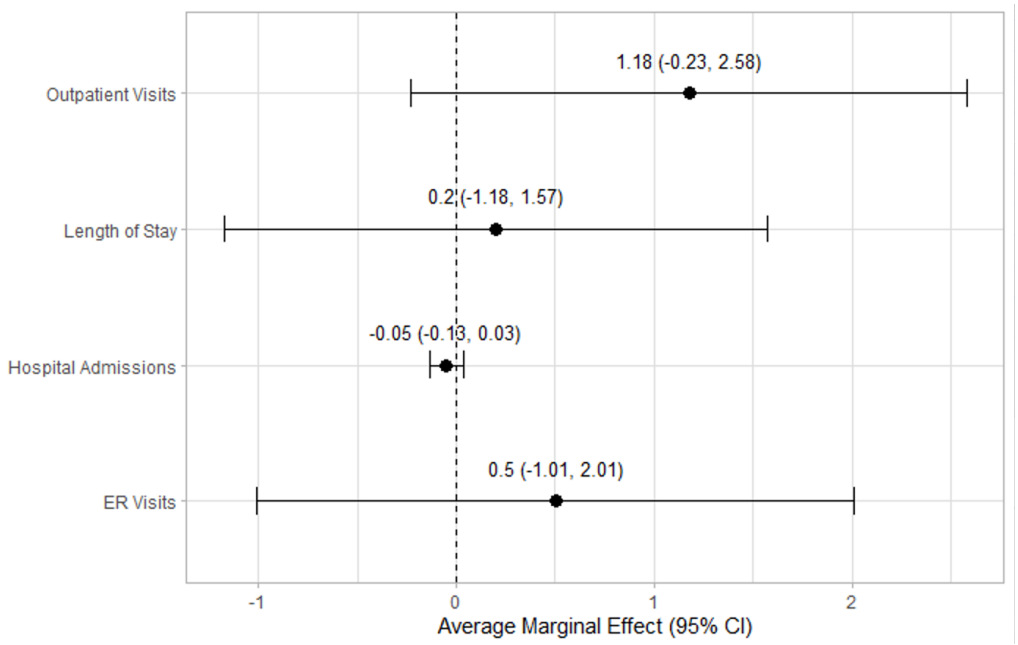
* = standardized mean differences

6.2.2 Covariate Balance with ATE Weighting in CD

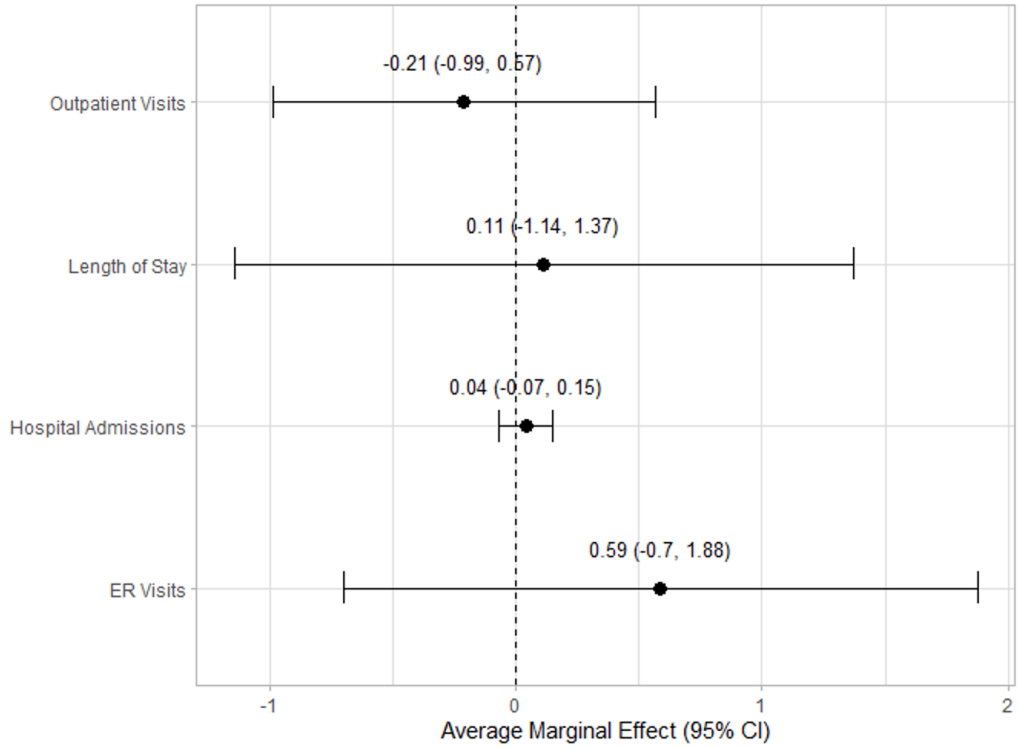


* = standardized mean differences

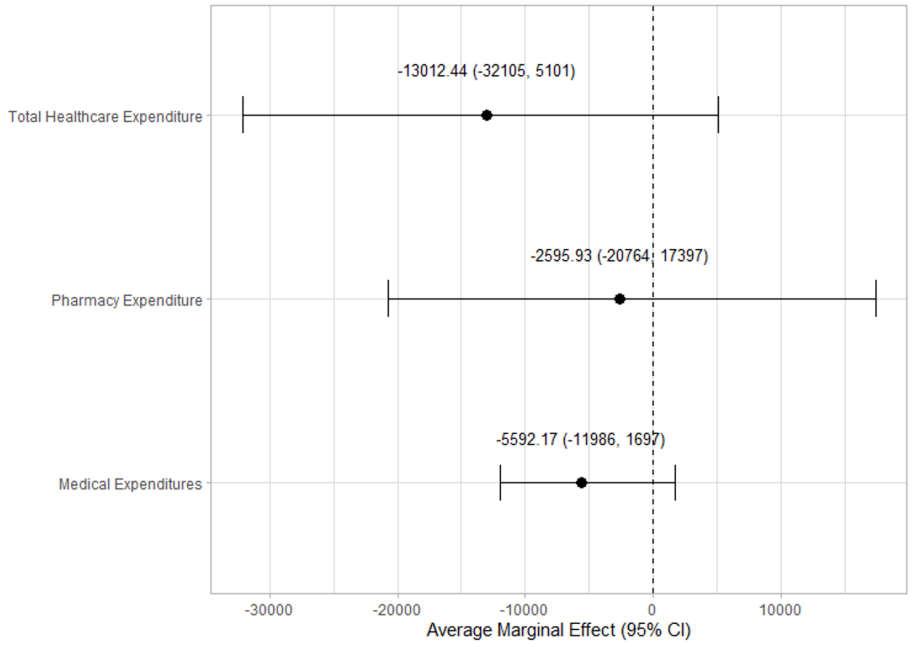
6.3.1 Average Treatment effects of Cycling on Healthcare Utilization for UC



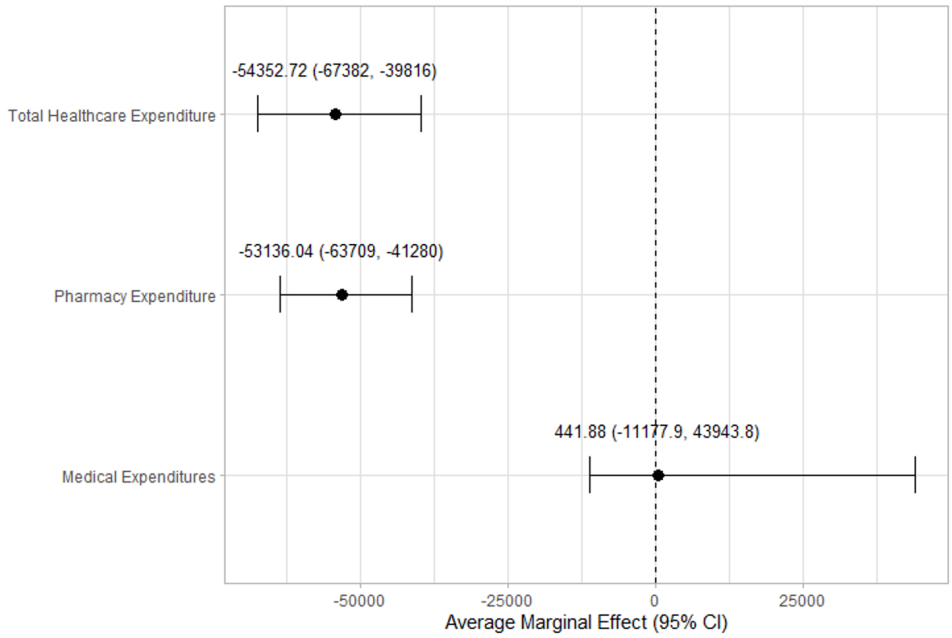
6.3.2 Average Treatment effects of Cycling on Healthcare Utilization for CD



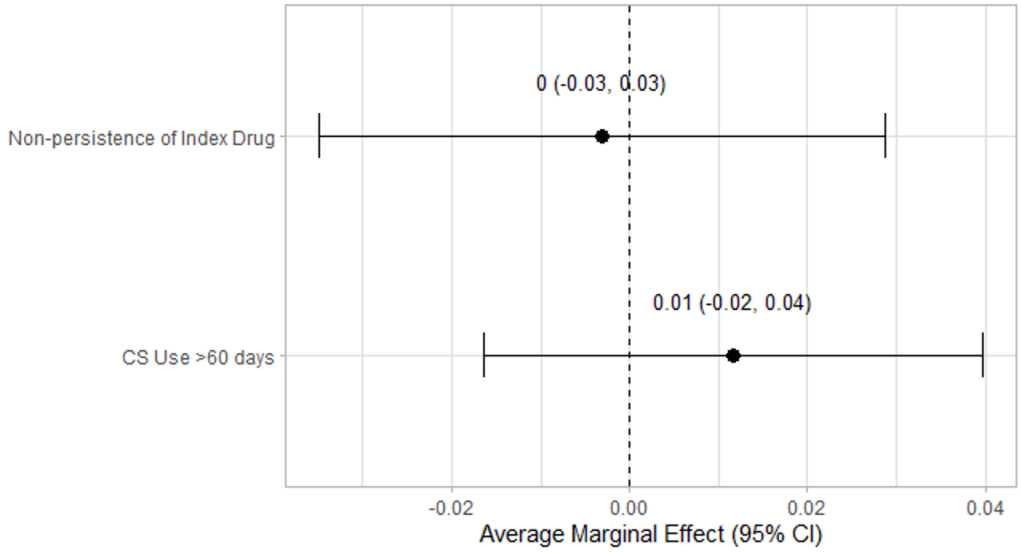
6.3.3 Average Treatment Effects of Cycling on Healthcare Expenditures for UC



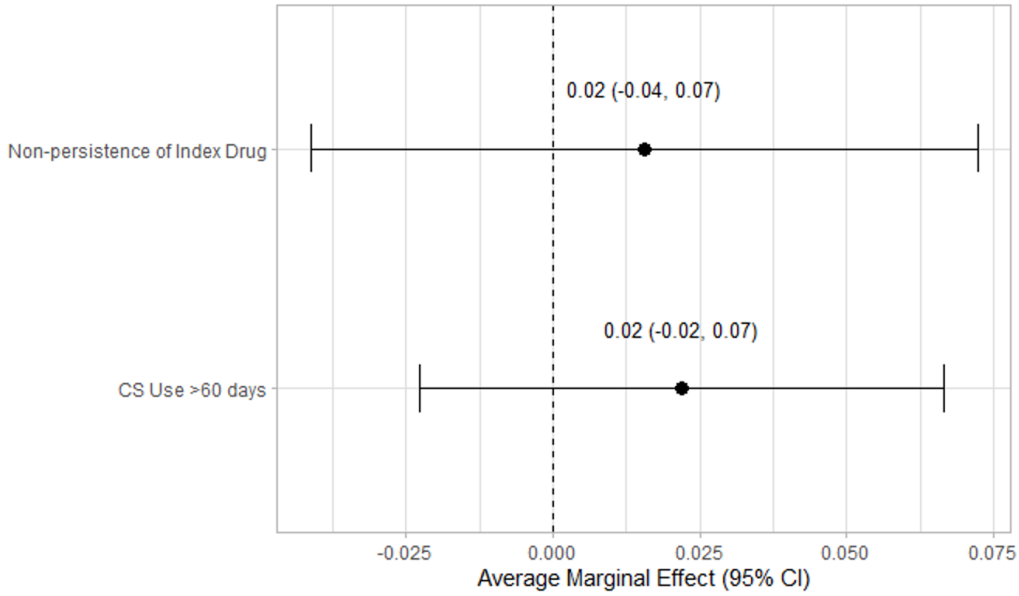
6.3.4 Average Treatment Effects of Cycling on Healthcare Expenditures for CD



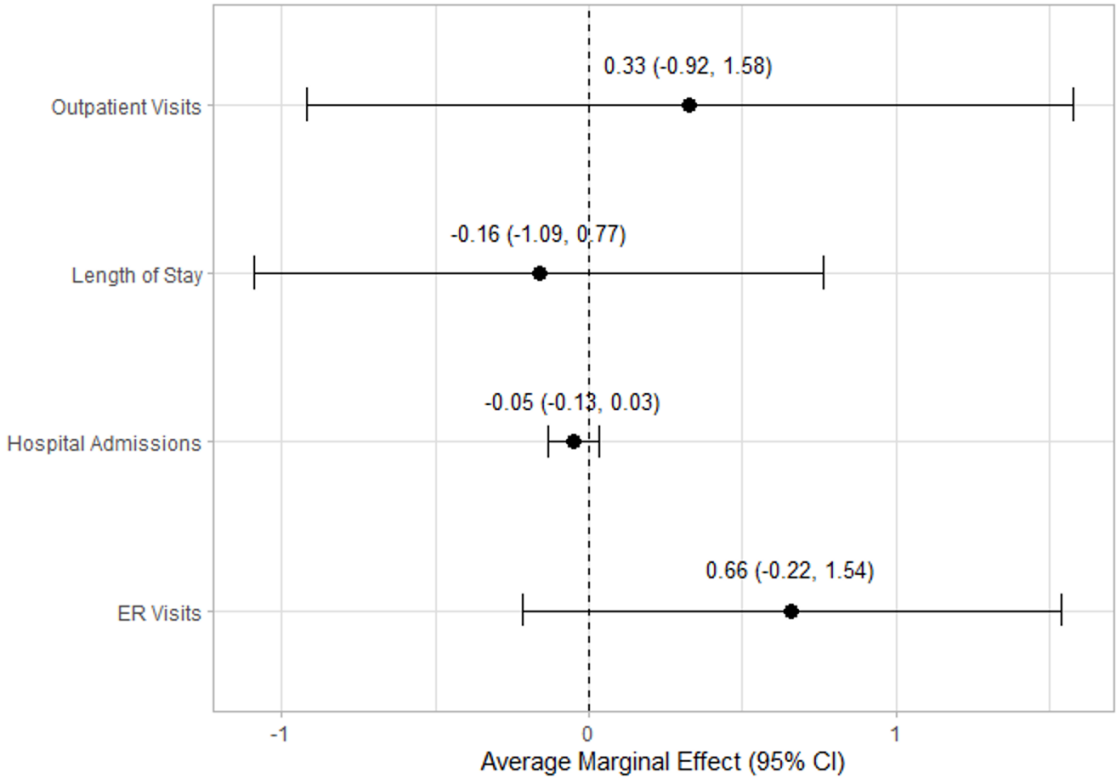
6.3.5 Average Treatment effects of Cycling on Secondary Outcomes for CD



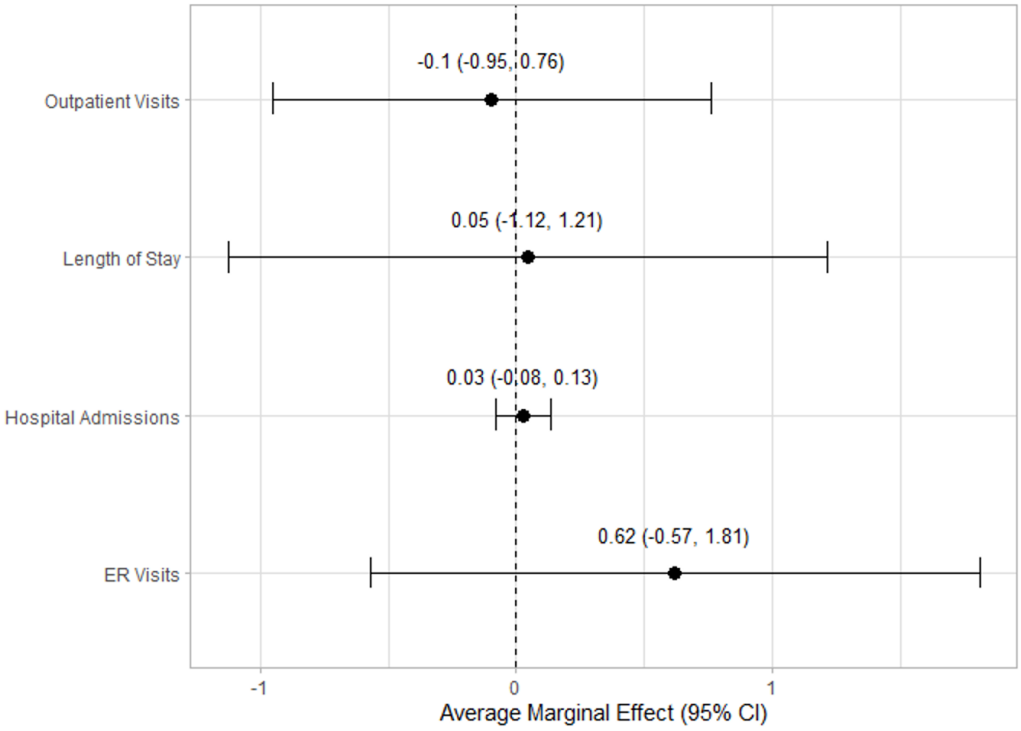
6.3.6 Average Treatment effects of Cycling on Secondary Outcomes for UC



6.3.7 Average Treatment effects of Cycling on Healthcare Utilization Outcomes for UC (Diagnosis code of UC or CD)



6.3.8 Average Treatment effects of Cycling on Healthcare Utilization Outcomes for CD (Diagnosis code of UC or CD)



7. Tables

7.1 Baseline Characteristics of Weighted and Unweighted Cohorts for UC

Characteristics	Before Weighing		After Weighing		
	Switching Cohort	Cycling Cohort	Switching Cohort	Cycling Cohort	Absolute SMD
N=	425	107	415.65	68.83	--
Sex, n (%)					
Male	217 (51.1)	42 (39.3)	(49.23)	(52.18)	--
Female	208 (48.9)	65 (60.7)	(50.77)	(47.82)	0.060
Unweighted CCI, mean (SD)	0.3 (0.5)	0.3 (0.6)	--	--	--
Quan-weighted CCI, mean (SD)	0.2 (0.6)	0.2 (0.6)	0.24 (0.62)	0.26 (0.70)	0.040
Unweighted EI, mean (SD)	1.3 (1.5)	1.7 (1.7)	--	--	--
van-Walraven EI, mean (SD)	0.7 (4.2)	1.4 (5.3)	0.86 (4.27)	0.83 (4.70)	0.006
Baseline medications, n (%)					
5-ASA	209 (49.2)	57 (53.3)	(50.20)	(54.77)	0.092
Corticosteroid use	294 (69.2)	78 (72.9)	(69.66)	(63.68)	0.132
Corticosteroid use > 60 days	172 (40.5)	37 (34.6)	(39.16)	(36.86)	0.047
Index year, n (%)					
2016	12 (2.8)	18 (16.8)	--	--	--
2017	20 (4.7)	19 (17.8)	--	--	--
2018	34 (8.0)	23 (21.5)	--	--	--
2019	51 (12.0)	26 (24.3)	--	--	--
2020	69 (16.2)	10 (9.3)	--	--	--
2021	57 (13.4)	4 (3.7)	--	--	--
2022	84 (19.8)	5 (4.7)	--	--	--
2023	98 (23.1)	2 (1.9)	--	--	--
Time between first fill and index date, mean (SD)	391.1 (385.8)	265.8 (315.3)	--	--	--
Extraintestinal manifestations (EIM), n (%)					
dermatologic	43 (10.1)	7 (6.5)	(9.46)	(9.95)	0.018
ophthalmologic	15 (3.5)	3 (2.8)	(3.31)	(1.90)	0.081
musculoskeletal	21 (4.9)	2 (1.9)	(4.32)	(3.63)	0.038
hepatopancreaticobiliary	32 (7.5)	11 (10.3)	(8.08)	(9.56)	0.052

Age, mean (SD)	42.7 (13.2)	40.4 (15.0)	42.35 (13.40)	42.81 (14.44)	0.033
Name of first anti-TNF, n (%)					
adalimumab	389 (91.5)	73 (68.2)	--	--	--
certolizumab	4 (0.9)	0 (0.0)	--	--	--
golimumab	11 (2.6)	14 (13.1)	--	--	--
infliximab	21 (4.9)	20 (18.7)	--	--	--
Name of second-line drug, n (%)					
adalimumab	--	34 (31.8)	--	--	--
certolizumab	--	5 (4.7)	--	--	--
golimumab	--	41 (38.3)	--	--	--
infliximab	--	27 (25.2)	--	--	--
ozanimod	10 (2.4)	--	--	--	--
risankizumab	1 (0.2)	--	--	--	--
tofacitinib	98 (23.1)	--	--	--	--
upadacitinib	55 (12.9)	--	--	--	--
ustekinumab	187 (44.0)	--	--	--	--
vedolizumab	74 (17.4)	--	--	--	--
Hospitalizations, n (%)	55 (12.9)	22 (20.6)	(14.33)	(17.47)	0.085
Total continuous duration of first anti-TNF, mean (SD)	335.6 (354.5)	212.3 (242.8)	312.68 (333.91)	336.32 (371.62)	0.078
Insurance, n (%)					
Commercial	359 (84.5)	87 (81.3)	(83.73)	(78.54)	0.138
Medicaid	57 (13.4)	16 (15.0)	(13.78)	(18.80)	0.144
Medicare	9 (2.1)	4 (3.7)	(2.49)	(2.66)	0.010
Healthcare cost baseline 6 months, mean (SD)	59,539.2 (30,199.2)	49,843.9 (22,366.2)	61,022.91 (31,583.87)	58,978.75 (26,869.96)	0.071
Region, n (%)					
Northeast	68 (16.0)	16 (15.0)	(15.99)	(18.94)	0.082
North Central	81 (19.1)	26 (24.3)	(19.94)	(17.69)	0.055
South	180 (42.4)	43 (40.2)	(42.07)	(39.23)	0.058
West	39 (9.2)	5 (4.7)	(8.22)	(5.15)	0.121
Unknown	57 (13.4)	17 (15.9)	(13.78)	(18.98)	0.147

7.2 Baseline Characteristics of Weighted and Unweighted Cohorts for CD

Characteristics	Before Weighing	After Weighing

	Switching Cohort	Cycling Cohort	Switching Cohort	Cycling Cohort	Absolute SMD
N=	605	125	588.65	91.07	
Sex, n (%)					
Male	249 (41.2)	55 (44.0)	(41.61)	(38.74)	
Female	356 (58.8)	70 (56.0)	(58.40)	(61.79)	0.068
Unweighted CCI, mean (SD)	0.4 (0.7)	0.4 (0.7)	--	--	--
Quan-weighted CCI, mean (SD)	0.4 (0.9)	0.4 (0.7)	0.41 (0.87)	0.46 (0.86)	0.054
Unweighted EI, mean (SD)	1.4 (1.7)	1.9 (1.8)	--	--	--
van-Walraven EI, mean (SD)	1.7 (5.4)	1.6 (5.5)	1.66 (5.41)	1.76 (5.25)	0.018
Baseline medications, n (%)					
5-ASA	90 (14.9)	18 (14.4)	(14.64)	(13.61)	0.029
Corticosteroid use	334 (55.2)	75 (60.0)	(55.87)	(53.48)	0.048
Corticosteroid use > 60 days	148 (24.5)	31 (24.8)	(24.41)	(22.78)	0.038
Index year, n (%)					
2016	3 (0.5)	15 (12.0)	--	--	--
2017	44 (7.3)	21 (16.8)	--	--	--
2018	70 (11.6)	29 (23.2)	--	--	--
2019	107 (17.7)	21 (16.8)	--	--	--
2020	94 (15.5)	15 (12.0)	--	--	--
2021	83 (13.7)	11 (8.8)	--	--	--
2022	105 (17.4)	6 (4.8)	--	--	--
2023	99 (16.4)	7 (5.6)	--	--	--
Time between first fill and index date, mean (SD)	503.9 (441.8)	296.3 (253.4)	--	--	--
Extraintestinal manifestations (EIM), n (%)					
dermatologic	109 (18.0)	23 (18.4)	(18.13)	(19.50)	0.036
ophthalmologic	23 (3.8)	4 (3.2)	(3.63)	(2.56)	0.058
musculoskeletal	40 (6.6)	14 (11.2)	(7.40)	(7.85)	0.016
hepatopancreaticobiliary	66 (10.9)	12 (9.6)	(10.81)	(12.45)	0.054
Age, mean (SD)	40.7 (13.5)	40.4 (13.4)	40.64 (13.58)	40.36 (12.86)	0.021
Name of first anti-TNF, n (%)					
adalimumab	544 (89.9)	82 (65.6)	--	--	--
certolizumab	26 (4.3)	12 (9.6)	--	--	--

infliximab	35 (5.8)	31 (24.8)	--	--	--
Name of second-line drug, n (%)					
adalimumab	--	40 (32.0)	--	--	--
certolizumab	--	54 (43.2)	--	--	--
golimumab	--	1 (0.8)	--	--	--
infliximab	--	30 (24.0)	--	--	--
guselkumab	1 (0.2)	--	--	--	--
risankizumab	32 (5.3)	--	--	--	--
tofacitinib	1 (0.2)	--	--	--	--
upadacitinib	23 (3.8)	--	--	--	--
ustekinumab	520 (86.0)	--	--	--	--
vedolizumab	28 (4.6)	--	--	--	--
Hospitalizations, n (%)	103 (17.0)	29 (23.2)	(17.89)	(16.45)	0.036
Total continuous duration of first anti-TNF, mean (SD)	431.5 (413.7)	250.5 (241.3)	400.54 (393.74)	338.17 (299.04)	0.184
Insurance, n (%)					
Commercial	492 (81.3)	80 (64.0)	(78.29)	(72.94)	0.122
Medicaid	106 (17.5)	42 (33.6)	(20.34)	(23.38)	0.071
Medicare	7 (1.2)	3 (2.4)	(1.37)	(3.68)	0.175
Healthcare cost baseline 6 months, mean (SD)	62,285.3 (41,716.4)	48,319.2 (35,984.4)	63,606.59 (44,363.07)	55,757.46 (43,701.43)	0.184
Region, n (%)					
Northeast	98 (16.2)	14 (11.2)	(15.25)	(14.87)	0.011
North Central	118 (19.5)	14 (11.2)	(18.06)	(16.34)	0.048
South	225 (37.2)	47 (37.6)	(37.29)	(38.47)	0.024
West	57 (9.4)	6 (4.8)	(8.62)	(6.49)	0.083
Unknown	107 (17.7)	44 (35.2)	(20.79)	(23.83)	0.070

7.3 Results for Healthcare Resource Utilization

7. 3.1 Number of Inpatient Admissions for UC (Poisson Regression)

Covariates	Estimate	Std. Error
Cycling (treatment)	-0.367	0.308
Index Year 2017	-0.254	0.506
Index Year 2018	-0.395	0.470
Index Year 2019	-0.815	0.479
Index Year 2020	-0.667	0.462
Index Year 2021	-0.865	0.514
Index Year 2022	-0.951	0.487
Index Year 2023	-1.222*	0.507
Significance levels: * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$		

7.3.2 Number of Inpatient Admissions for CD (Poisson Regression)

Covariates	Estimate	Std. Error
Cycling (treatment)	0.188	0.232
Total continuous duration of first anti-TNF	< 0.001	< 0.001
Index Year 2017	0.797	1.001
Index Year 2018	1.229	0.971
Index Year 2019	1.199	0.975
Index Year 2020	1.180	0.979
Index Year 2021	0.558	1.007
Index Year 2022	1.407	0.981
Index Year 2023	0.641	1.001
Baseline 6-month healthcare cost	< 0.001	< 0.001
Significance levels: * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$		

7.3.3 Number of Inpatient Days for UC

	Negative binomial	
Covariates	Estimate	Std. Error
Cycling (treatment)	0.153	0.522
Index Year 2017	0.055	1.101
Index Year 2018	-0.824	1.011
Index Year 2019	-0.437	0.962
Index Year 2020	-0.469	0.970
Index Year 2021	-0.853	1.024
Index Year 2022	-1.267	0.984
Index Year 2023	-1.735	0.985
	AIC: 947.59 BIC: 990.3555	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.3.4 Number of Inpatient Days for CD

	Negative binomial	
Covariates	Estimate	Std. Error
Cycling (treatment)	0.060	0.413
Total continuous duration of first anti-TNF	- < 0.001	< 0.001
Index Year 2017	0.515	1.125
Index Year 2018	1.367	1.087
Index Year 2019	1.125	1.092
Index Year 2020	1.141	1.103
Index Year 2021	0.167	1.124
Index Year 2022	1.302	1.115
Index Year 2023	0.642	1.121
Baseline 6-month healthcare cost	< 0.001	< 0.001
	AIC: 1657.1 BIC: 1712.226	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.3.5 Number of ER Visits for UC

	Negative binomial	
Covariates	Estimate	Std. Error
Cycling (treatment)	0.262	0.370
Index Year 2017	-0.804	0.788
Index Year 2018	0.029	0.710
Index Year 2019	-1.067	0.687
Index Year 2020	0.462	0.682
Index Year 2021	0.441	0.718
Index Year 2022	-0.163	0.692
Index Year 2023	-0.108	0.689
	AIC: 1387.4 BIC: 1430.163	

Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001

7.3.6 Number of ER Visits for CD

	Negative binomial	
Covariates	Estimate	Std. Error
Cycling (treatment)	0.235	0.316
Total continuous duration of first anti-TNF	< 0.001	< 0.001
Index Year 2017	1.420	0.930
Index Year 2018	2.055*	0.902
Index Year 2019	2.176 *	0.905
Index Year 2020	2.108*	0.913
Index Year 2021	1.349	0.928
Index Year 2022	2.289 *	0.922
Index Year 2023	1.591	0.926
	AIC: 2158.4 BIC: 2208.914	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.3.7 Number of Outpatient Visits for UC

	Negative binomial	
	Coefficients	SE
Cycling (treatment)	0.298 **	0.102
Index Year 2017	0.015	0.215
Index Year 2018	-0.096	0.198
Index Year 2019	-0.156	0.189
Index Year 2020	0.071	0.190
Index Year 2021	-0.367	0.205
Index Year 2022	-0.157	0.194
Index Year 2023	-0.157	0.193
	AIC: 2517.9 BIC: 2560.667	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.3.8 Number of Outpatient Visits for CD

	Negative binomial	
	Coefficients	SE
Cycling (treatment)	-0.061	0.099
Total continuous duration of first anti-TNF	- < 0.001	< 0.001
Index Year 2017	0.260	0.271
Index Year 2018	0.163	0.263
Index Year 2019	0.358	0.264
Index Year 2020	0.249	0.267
Index Year 2021	0.102	0.271

Index Year 2022	0.054	0.271
Index Year 2023	0.127	0.271
Baseline 6-month healthcare cost	< 0.001**	< 0.001
	AIC: 3371.8 BIC: 3426.93	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.4 Results for Healthcare Expenditures

7.4.1 Total Healthcare Expenditures for UC

	Two Part Model			
	Binomial (logit link)		GLM	
	Coefficients	SE	Coefficients	SE
Cycling (treatment)	-0.4214	0.6092	-0.10974	0.07027
Index Year 2017	16.5687	1776.3397	0.34500 *	0.14642
Index Year 2018	0.5758	1.1790	0.29248 *	0.13487
Index Year 2019	0.6207	1.1143	0.15278	0.12881
Index Year 2020	-0.3534	1.0030	0.52059 ***	0.13060
Index Year 2021	-0.9381	1.0042	0.49386 ***	0.13959
Index Year 2022	16.4125	1148.2468	0.64565 ***	0.13112
Index Year 2023	0.6047	1.1621	0.56786 ***	0.13107
	AIC: 159.38 BIC: 197.8674		AIC: 12830 BIC: 12872.72	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001				

7.4.2 Total Healthcare Expenditures for CD

	Two Part Model			
	Binomial (logit link)		GLM	
	Coefficients	SE	Coefficients	SE
Cycling (treatment)	0.4872	0.4953	-0.5344 ***	0.05709
Total continuous duration of first anti-TNF	-0.0002835	0.0003578	0.00001578	0.00005387
Index Year 2017	-13.47	599.4	0.2252	0.1483
Index Year 2018	-12.90	599.4	0.3193 *	0.1432
Index Year 2019	-13.40	599.4	0.3794 **	0.1442
Index Year 2020	-14.30	599.4	0.4590 **	0.1461
Index Year 2021	-14.20	599.4	0.4069 **	0.1488
Index Year 2022	-13.41	599.4	0.4612 **	0.1473
Index Year 2023	-13.05	599.4	0.2934 *	0.1480
Baseline 6-month healthcare cost	--	--	0.000005032 ***	0.0000004694
	AIC: 356.5 BIC: 402.429		AIC: 16867 BIC: 16921.02	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001				

7.4.3 Medical Expenditures (IP, OP, and ER costs) for CD

	Two Part Model			
	Binomial (logit link)		GLM	
	Coefficients	SE	Coefficients	SE
Cycling (treatment)	0.4184265	0.4147614	-0.02680	0.1959
Total continuous duration of first anti-TNF	-0.0001345	0.0003231	-0.00009706	0.0001846
Index Year 2017	0.8720157	0.8313799	0.01131	0.5436

Index Year 2018	1.5170842	0.8430936	0.2551	0.5258
Index Year 2019	1.2094556	0.8117466	-0.007060	0.5287
Index Year 2020	0.4911412	0.7904909	0.1946	0.5346
Index Year 2021	0.6435695	0.8121515	-0.4162	0.5430
Index Year 2022	0.7321735	0.8123527	0.2730	0.5406
Index Year 2023	1.4001551	0.8539085	0.02696	0.5409
Baseline 6-month healthcare cost	--	--	0.00001154 ***	0.000001612
	AIC: 453.35 BIC: 499.2831		AIC: 14095 BIC: 14148.72	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001				

7.4.4 Medical Expenditures (IP, OP, and ER costs) for UC

	Two Part Model			
	Binomial with Logit		GLM	
	Coefficients	SE	Coefficients	SE
Cycling (treatment)	-0.05626	0.55245	-0.2848	0.1884
Index Year 2017	16.21141	1080.86189	0.3105	0.3950
Index Year 2018	1.21456	1.04351	0.1297	0.3647
Index Year 2019	1.27362	0.96946	-0.1554	0.3488
Index Year 2020	0.22177	0.81304	-0.3400	0.3544
Index Year 2021	-0.67040	0.78849	-0.3511	0.3815
Index Year 2022	0.43906	0.84944	-0.4444	0.3581
Index Year 2023	0.30534	0.83454	-0.5891	0.3573
	AIC: 247.75 BIC: 286.2445		AIC: 10914 BIC: 10955.77	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001				

7.4.5 Pharmacy Expenditures for CD

	Two Part Model			
	Binomial with Logit		GLM	
	Coefficients	SE	Coefficients	SE
Cycling (treatment)	0.3815	0.4347	-0.6474 ***	0.06020
Total continuous duration of first anti-TNF	-0.0002671	0.0003458	0.00006012	0.00005628
Index Year 2017	-13.53	600.0	0.2429	0.1548
Index Year 2018	-13.69	600.0	0.3422 *	0.1496
Index Year 2019	-13.55	600.0	0.4327 **	0.1506
Index Year 2020	-14.59	600.0	0.5200 ***	0.1529
Index Year 2021	-14.40	600.0	0.5333 ***	0.1555
Index Year 2022	-13.49	600.0	0.4769 **	0.1538
Index Year 2023	-13.14	600.0	0.3067 *	0.1545
Baseline 6-month healthcare cost	--	--	0.000002093 ***	0.0000004981
	AIC: 396.05 BIC: 441.9782		AIC: 16426 BIC: 16480.3	

Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001

7.4.6 Pharmacy Expenditures for UC

	Two Part Model			
	Binomial (logit link)		GLM	
	Coefficients	SE	Coefficients	SE
Cycling (treatment)	-0.2102	0.5924	-0.02191	0.07779
Index Year 2017	16.5953	1780.5765	0.36771 *	0.16190
Index Year 2018	0.5993	1.1783	0.37733 *	0.14913
Index Year 2019	0.2428	1.0408	0.31873 *	0.14264
Index Year 2020	-0.2719	0.9985	0.83927 ***	0.14441
Index Year 2021	-1.0388	0.9832	0.84737 ***	0.15487
Index Year 2022	16.5220	1149.0801	1.02001 ***	0.14500
Index Year 2023	0.7250	1.1513	0.94939 ***	0.14495
	AIC: 171.22 BIC: 209.713		AIC: 12573 BIC: 12615.29	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001				

7.5 Incidence Rate Ratios

7.5.1 Incidence Rate Ratios for Healthcare Utilization for UC

Outcome	Model	IRR (95% CI)
Inpatient admissions	Poisson	0.69 (0.38, 1.27)
Inpatient length of stay	Negative Binomial	1.17 (0.42, 3.24)
ER visits	Negative Binomial	1.3 (0.63, 2.68)
Outpatient visits	Negative binomial	1.35 (1.10, 1.64)

7.5.2 Incidence Rate Ratios for Healthcare Utilization for CD

Outcome	Model	IRR (95% CI)
Inpatient admissions	Poisson	1.21 (0.77, 1.9)
Inpatient length of stay	Negative Binomial	1.06 (0.47, 2.39)
ER visits	Negative Binomial	1.27 (0.68, 2.35)
Outpatient visits	Negative binomial	0.94 (0.77, 1.14)

7.6 Average Treatment effects

7.6.1 Average Treatment effects of Cycling on Healthcare Utilization for UC

Outcome	Model	ATE (95% CI)
Inpatient admissions	Poisson	-0.0491 (-0.13, 0.03)
Inpatient length of stay	Negative Binomial	0.1988 (-1.18, 1.57)
ER visits	Negative Binomial	0.5031 (-1.01, 2.01)
Outpatient visits	Negative binomial	1.1773 (-0.23, 2.58)

7.6.2 Average Treatment effects of Cycling on Healthcare Utilization for CD

Outcome	Model	ATE (95% CI)

Inpatient admissions	Poisson	0.0403 (-0.07, 0.14)
Inpatient length of stay	Negative Binomial	0.1122 (-1.44, 1.37)
ER visits	Negative Binomial	0.5871 (-0.7, 1.88)
Outpatient visits	Negative binomial	-0.2107 (-1.94, 3.69)

7.6.3 Average Treatment effects of Cycling on Cost Outcomes for UC

Outcome	Model	ATE (95% CI)
Total Healthcare Expenditure	Two-part	-13012.44 (-32105, 5101)
Medical Expenditure	Two-part	-5592.169 (-11986, 1697)
Pharmacy Expenditure	Two-part	-2595.927 (-20764, 17397)

7.6.4 Average Treatment effects of Cycling on Cost Outcomes for CD

Outcome	Model	ATE (95% CI)
Total Healthcare Expenditure	Two-part	-54352.72 (-67382, -39816)
Medical Expenditure	Two-part	441.8819 (-11177.9, 43943.8)
Pharmacy Expenditure	Two-part	-53136.04 (-63709, -41280)

7.7 Secondary Outcomes

7.7.1 Non-persistence of the Index Biologic for UC

	Binomial (logit link)	
	Coefficients	SE
Cycling (treatment)	0.582	0.676
Index Year 2017	15.892	1230.776
Index Year 2018	15.515	1230.776
Index Year 2019	14.879	1230.776
Index Year 2020	14.382	1230.776
Index Year 2021	15.460	1230.776
Index Year 2022	15.363	1230.776
Index Year 2023	14.192	1230.776
	AIC: 135.14 BIC: 173.6268	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.7.2 Non-persistence of the Index Biologic for CD

	Binomial (logit link)	
	Coefficients	SE
Cycling (treatment)	-0.1240	0.6915
Total continuous duration of first anti-TNF	-0.001050	0.0008620
Index Year 2017	-0.04122	4947
Index Year 2018	17.57	4431
Index Year 2019	17.61	4431
Index Year 2020	16.70	4431
Index Year 2021	17.27	4431

Index Year 2022	17.35	4431
Index Year 2023	0.1596	4752
Baseline 6-month healthcare cost	0.000005074	0.000003195
	AIC: 186.09 BIC: 236.6185	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.7.3 Prolonged CS Use > 60 Days Consecutive Use for UC

	Binomial (logit link)	
	Coefficients	SE
Cycling (treatment)	0.7225	0.6975
Index Year 2017	16.1698	1072.9789
Index Year 2018	1.4324	1.1455
Index Year 2019	0.5960	0.8745
Index Year 2020	0.3870	0.8453
Index Year 2021	0.6019	0.9158
Index Year 2022	1.9197	1.1203
Index Year 2023	1.3532	0.9617
	AIC: 185.02 BIC: 223.514	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.7.4 Prolonged CS Use > 60 Days Consecutive Use for CD

	Binomial (logit link)	
	Coefficients	SE
Cycling (treatment)	0.3530	0.6443
Total continuous duration of first anti-TNF	0.001135	0.0007221
Index Year 2017	0.2101	1.140
Index Year 2018	2.243	1.475
Index Year 2019	0.9919	1.187
Index Year 2020	1.194	1.238
Index Year 2021	0.5917	1.198
Index Year 2022	0.07868	1.146
Index Year 2023	0.3622	1.173
Baseline 6-month healthcare cost	0.00001240 *	0.000006147
	AIC: 241.5 BIC: 292.0243	
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

References

1. Malik TF, Aurelio DM. Extraintestinal Manifestations of Inflammatory Bowel Disease. *StatPearls*. Published online March 6, 2023. Accessed October 22, 2025. https://www.ncbi.nlm.nih.gov/books/NBK568797/

2. Bruner LP, White AM, Proksell S. Inflammatory Bowel Disease. *Primary Care: Clinics in Office Practice*. 2023;50(3):411-427. doi:10.1016/J.POP.2023.03.009

3. Burisch J, Zhao M, Odes S, et al. The cost of inflammatory bowel disease in high-income settings: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol*. 2023;8(5):458-492. doi:10.1016/S2468-1253(23)00003-1

4. Burisch J, Claytor J, Hernandez I, Hou JK, Kaplan GG. The Cost of Inflammatory Bowel Disease Care: How to Make it Sustainable. *Clinical Gastroenterology and Hepatology*. 2025;23(3):386-395. doi:10.1016/j.cgh.2024.06.049

5. Alatab S, Sepanlou SG, Ikuta K, et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020;5(1):17-30. doi:10.1016/S2468-1253(19)30333-4

6. Caron B, Honap S, Peyrin-Biroulet L. Epidemiology of Inflammatory Bowel Disease across the Ages in the Era of Advanced Therapies. *J Crohns Colitis*. 2024;18(Suppl 2):ii3. doi:10.1093/ECCO-JCC/JJAE082

7. Lewis JD, Parlett LE, Jonsson Funk ML, et al. Incidence, Prevalence, and Racial and Ethnic Distribution of Inflammatory Bowel Disease in the United States. *Gastroenterology*. 2023;165(5):1197-1205.e2. doi:10.1053/j.gastro.2023.07.003

8. Rubin DT, Ananthakrishnan AN, Siegel CA, Barnes EL, Long MD. ACG Clinical Guideline Update: Ulcerative Colitis in Adults. *American Journal of Gastroenterology*. 2025;120(6):1187-1224. doi:10.14309/AJG.0000000000003463

9. Lichtenstein GR, Loftus E V., Afzali A, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *American Journal of Gastroenterology*. 2025;120(6):1225-1264. doi:10.14309/AJG.0000000000003465

10. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *The Lancet*. 2017;389(10080):1741-1755. doi:10.1016/S0140-6736(16)31711-1

11. Singh S, Loftus E V., Limketkai BN, et al. AGA Living Clinical Practice Guideline on Pharmacological Management of Moderate-to-Severe Ulcerative Colitis. *Gastroenterology*. 2024;167(7):1307-1343. doi:10.1053/j.gastro.2024.10.001

12. Feuerstein JD, Ho EY, Shmidt E, et al. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. *Gastroenterology*. 2021;160(7):2496-2508. doi:10.1053/j.gastro.2021.04.022

13. George J, Singh S, Dulai PS, et al. Corticosteroid-Free Remission vs Overall Remission in Clinical Trials of Moderate–Severe Ulcerative Colitis and Crohn's Disease. *Inflamm Bowel Dis*. 2019;26(4):515. doi:10.1093/IBD/IZZ193

14. Barkan R, Shpoker L, Abboud R, et al. Factors associated with corticosteroid use in Crohn's disease and ulcerative colitis patients in Israel: A multicenter cross-sectional study. *Digestive and Liver Disease*. 2024;56(5):744-748. doi:10.1016/j.dld.2024.01.180

15. Bressler B. Is there an optimal sequence of biologic therapies for inflammatory bowel disease? *Therap Adv Gastroenterol*. 2023;16:17562848231159452. doi:10.1177/17562848231159452

16. Casanova MJ, Chaparro M, Mínguez M, et al. Effectiveness and Safety of the Sequential Use of a Second and Third Anti-TNF Agent in Patients With Inflammatory Bowel Disease: Results From the Eneida Registry. *Inflamm Bowel Dis*. 2020;26(4):606-616. doi:10.1093/IBD/IZZ192

17. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol*. 2016;7. doi:10.1038/CTG.2015.63

18. Zhdanava M, Burbage S, Boonmak P, et al. Treatment Persistence Among Anti-Tumor Necrosis Factor–experienced Patients With Ulcerative Colitis Switching to a Biologic With a Different Mode of Action or Cycling to Another Anti–Tumor Necrosis Factor Agent. *Clin Ther*. 2025;47(3):204-211. doi:10.1016/j.clinthera.2024.12.002

19. Zhdanava M, Kachroo S, Manceur AM, et al. Persistence Among Patients with Crohn Disease Previously Treated with an Anti-tumor Necrosis Factor Inhibitor and Switching or Cycling to Another Biologic Agent. *Clin Ther*. 2023;45(8):770-777. doi:10.1016/j.clinthera.2023.06.013

20. Gorritz M, Tuly R, Sun K, et al. S993 Treatment Persistence and Augmentation Differences Across Second-Line Treatment Strategies Among TNFi Experienced Ulcerative Colitis Patients: TNFi Cyclers vs MOA Switchers. *American Journal of Gastroenterology*. 2023;118(10S):S753-S753. doi:10.14309/01.AJG.0000953612.50792.A1

21. Zhuleku E, Wirth D, Nissinen R, et al. Switching within versus out of class following first-line TNFi failure in ulcerative colitis: real-world outcomes from a German claims data analysis. *Therap Adv Gastroenterol*. 2024;17. doi:10.1177/17562848241262288

22. Zhuleku E, Antolin-Fontes B, Borsi A, et al. Real-world outcomes associated with switching to anti-TNFs versus other biologics in Crohn's Disease patients: A retrospective analysis using German claims data. *Therap Adv Gastroenterol*. 2022;15. doi:10.1177/17562848221130554;CTYPE:STRING:JOURNAL

23. Hupé M, Rivière P, Nancey S, et al. Comparative efficacy and safety of vedolizumab and infliximab in ulcerative colitis after failure of a first subcutaneous anti-TNF agent: a multicentre cohort study. *Aliment Pharmacol Ther*. 2020;51(9):852-860. doi:10.1111/APT.15680

24. Quan H, Li B, Couris CM, et al. Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries. *Am J Epidemiol*. 2011;173(6):676-682. doi:10.1093/AJE/KWQ433

25. Van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care*. 2009;47(6):626-633. doi:10.1097/MLR.0B013E31819432E5

26. Oterino-Moreira I, Lorenzo-Martínez S, López-Delgado Á, Pérez-Encinas M. Comparison of Three Comorbidity Measures for Predicting In-Hospital Death through a Clinical Administrative Nacional Database. *Int J Environ Res Public Health*. 2022;19(18):11262. doi:10.3390/IJERPH191811262

27. Mpakogiannis KC, Chasani P, Mastorogianni IN, Katsanos KH, Fousekis FS. Predictors of First Anti-TNF Treatment Failure in Patients with Inflammatory Bowel Disease: A Single-Center Cohort Study. *Biomedicines*. 2026;14(5):984. doi:10.3390/BIOMEDICINES14050984

28. Greifer N, Stuart EA. Choosing the Causal Estimand for Propensity Score Analysis of Observational Studies. Published online June 19, 2021. Accessed June 7, 2026. https://arxiv.org/pdf/2106.10577

29. Austin PC, Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *STATISTICS IN MEDICINE Statist Med*. 2009;28:3083-3107. doi:10.1002/sim.3697

30. Greifer N. WeightIt: Weighting for Covariate Balance in Observational Studies . Preprint posted online 2026. Accessed June 7, 2026. https://ngreifer.github.io/WeightIt/

31. Zeviani WM, Ribeiro Jr EE, Bonat WH. Regression Models for Count Data: beyond the Poisson model. March 17, 2017. Accessed June 10, 2026. https://cursos.leg.ufpr.br/rmcd/introduction.html

32. Harrison XA. Using observation-level randomeffects to model overdispersion in count data in ecology and evolution. *PeerJ*. 2014;2014(1):e616. doi:10.7717/PEERJ.616/SUPP-1

33. Greifer N. Estimating Effects After Weighting (WeightIt). April 22, 2026. Accessed June 10, 2026. https://ngreifer.github.io/WeightIt/articles/estimating-effects.html#reporting-results

34. Austin PC. Bootstrap vs asymptotic variance estimation when using propensity score weighting with continuous and binary outcomes. *Stat Med*. 2022;41(22):4426-4443. doi:10.1002/SIM.9519;PAGE:STRING:ARTICLE/CHAPTER

35. Biosimilar Approvals. AJMC. December 22, 2025. Accessed June 8, 2026. https://www.centerforbiosimilars.com/biosimilar-approvals

36. Moon W, Pestana L, Becker B, et al. Efficacy and safety of certolizumab pegol for Crohn's disease in clinical practice. *Aliment Pharmacol Ther*. 2015;42(4):428-440. doi:10.1111/APT.13288

37. Schultheiss JPD, Mahmoud R, Louwers JM, et al. Loss of response to anti-TNFα agents depends on treatment duration in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2021;54(10):1298-1308. doi:10.1111/APT.16605;WGROUP:STRING:PUBLICATION

38. Alsoud D, Verstockt B, Vermeire S. Letter: immunogenicity is not the root cause for loss of response to anti-TNF agents in patients with IBD in TDM era. *Aliment Pharmacol Ther*.

2022;55(7):885-886. doi:10.1111/APT.16797;JOURNAL:JOURNAL:13652036;PAGE:STRING:ARTICLE/CHAPTER

39. Gisbert JP, Marín AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: The efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. *Aliment Pharmacol Ther*. 2015;41(7):613-623. doi:10.1111/APT.13083

40. Chanchlani N, Lin S, Bewshea C, et al. Mechanisms and management of loss of response to anti-TNF therapy for patients with Crohn's disease: 3-year data from the prospective, multicentre PANTS cohort study. *Lancet Gastroenterol Hepatol*. 2024;9(6):521-538. doi:10.1016/S2468-1253(24)00044-X

41. Roblin X, Vérot C, Paul S, et al. Is the Pharmacokinetic Profile of a First Anti-TNF Predictive of the Clinical Outcome and Pharmacokinetics of a Second Anti-TNF? *Inflamm Bowel Dis*. 2018;24(9):2078-2085. doi:10.1093/IBD/IZY111

42. Zhdanava M, Burbage S, Boonmak P, et al. Treatment Persistence Among Anti-Tumor Necrosis Factor–experienced Patients With Ulcerative Colitis Switching to a Biologic With a Different Mode of Action or Cycling to Another Anti–Tumor Necrosis Factor Agent. *Clin Ther*. 2025;47(3):204-211. doi:10.1016/J.CLINTHERA.2024.12.002

43. Janssen Announces U.S. FDA Approval of STELARA® (ustekinumab) for the Treatment of Adults with Moderately to Severely Active Ulcerative. Accessed November 9, 2025. https://www.jnj.com/media-center/press-releases/janssen-announces-u-s-fda-approval-of-stelara-ustekinumab-for-the-treatment-of-adults-with-moderately-to-severely-active-ulcerative

8.0 Appendix

8.1 Exclusion Criteria Extraintestinal Manifestation Diagnoses ICD-10 Codes

EIM Group	Diagnosis	ICD-10
Eye (ophthalmologic)	Scleritis/episcleritis/scleromalacia	H15
	Uveitis iridocyclitis	H20
	Corneal ulcers	H160
	Retinal vascular disease	H34, H350, H351, H352
	Conjunctivitis	H10
	Blepharitis	H010
	Cataract	H288
Hepatopancreaticobiliary	Cholelithiasis	K80
	Sclerosing cholangitis	K830
	Acute pancreatitis	K85, K861
	Bile duct carcinoma	C221, C240, C241, C248, C249
	Autoimmune chronic active hepatitis/autoimmune hepatitis	K759, K754, K758, K732
	Cirrhosis	K74
	Granulomatous disease	D71
	Fatty liver	K760
	Bile acid malabsorption	K908
	Calculus of gallbladder	K802, K803
	Splenic rupture	D735
Dermatologic	Aphthous stomatitis	K12
	Psoriasis	L40
	Erythema nodosum	L52
	Pyoderma gangrenosum	L88
	Sweet's syndrome	L982
	Necrotizing vasculitis	M30, M31
	Fistulas and fissures	K60
	Fistula anal	K603, K604, K605
	Fistula intestine	N321, N832A, K32C, D, F, G
	Acrodermatitis enteropathica	E832
	Thrombocytopenic purpura	M311
	Purpura	D69
	Glossitis	K140
	Vitiligo	L80
	Amyloidosis	E85
	Abscesses	K61
Musculoskeletal	Rheumatoid arthritis	M05, M06
	Psoriatic arthritis	M07
	Ankylosing spondylitis	M45
	Sacroiliitis	M461, M43.2
	Osteoporosis	M80, M81, M82
	Osteomalacia	M83
	Systematic lupus erythematosus (SLE)	M32
	Clubbing	R683

	Periostitis	M901
	Aseptic necrosis	M87, M905
	Polymyositis	M33.2
Malabsorption and anemia		K908, K909, D500, D509

8.2 FDA Approval Dates: Biologic/Target Small Synthetic Medications for IBD

Medication	FDA Approval date
Anti-TNFs	
infliximab	CD in 8/1998 and UC in 10/2006
adalimumab	CD in 2/2007 and UC in 9/2012
golimumab	UC in 5/2013
certolizumab pegol	CD in 4/2008
Interleukin-23 inhibitor	
ustekinumab	CD in 9/2016 and UC in 10/2019[43]
risankizumab-rzaa	CD and UC in 6/2022
mirikizumab-mrkz	CD in 1/2025 and UC in 10/2023
guselkumab	CD in 3/2025 and UC in 9/2024
Integrin receptor antagonists	
vedolizumab	CD and UC in 5/2014
natalizumab	CD in 1/2008
Janus Kinase (JAK) inhibitors	
upadacitinib	CD in 3/2023 and UC in 4/2022
tofacitinib	UC in 5/2018
Sphingosine 1-phosphate (S1P) modulators	
etrasimod	UC in 10/2023
ozanimod	UC in 3/2020

8.4 Imputation Rules for Continuous Fills

- Grace days after the last day of supply, calculated by days' supply x 1.5
- If the days' supply is missing, then:

Medication	Imputed days' supply for NDC codes
Adalimumab	28 days
Ustekinumab, Mirikizumab	56 days
Vedolizumab	56 days
Vedolizumab SC	14 days
Certolizumab Pegol	28 days
Golimumab	28 days
Infliximab	56 days
Infliximab SC	14 days
Upadacitinib, Tofacitinib, Ozanimod, Etrasimod	30 days

8.5 Regression Equations

- Poisson (UC)
  - $\log(\mu_i) = \beta0 + \beta1 \cdot \text{group\_bin}_i + \Sigma\, \gamma k \cdot I(\text{index\_year}_i = k)$
  - $\text{Var}(Y_i) = \mu_i$
- Negative Binomial (UC)
  - $\log(\mu_i) = \beta0 + \beta1 \cdot \text{group\_bin}_i + \Sigma\, \gamma k \cdot I(\text{index\_year}_i = k)$
  - $\text{Var}(Y_i) = \mu_i + \mu_i^2 / \theta$
- Quasi-Poisson (UC)
  - $\log(\mu_i) = \beta0 + \beta1 \cdot \text{group\_bin}_i + \Sigma\, \gamma k \cdot I(\text{index\_year}_i = k)$
  - $\text{Var}(Y_i) = \varphi \cdot \mu_i$
- Two-part model (UC)
  - $\text{logit}(\pi_i) = \log(\pi_i / (1 - \pi_i)) = \alpha0 + \alpha1 \cdot \text{group\_bin}_i + \Sigma\, \delta k \cdot I(\text{index\_year}_i = k)$ where $\pi_i = \Pr(Y_i > 0)$
  - $\log(\mu_i) = \beta0 + \beta1 \cdot \text{group\_bin}_i + \Sigma\, \gamma k \cdot I(\text{index\_year}_i = k)$ where $\mu_i = E(Y_i \mid Y_i > 0)$
  - $E(Y_i) = \pi_i \cdot \mu_i$

7.3.3 Number of Inpatient Days for UC

	Quasipoisson	
Covariates	Estimate	Std. Error
Cycling (treatment)	0.083	0.365
Index Year 2017	0.038	0.623
Index Year 2018	-0.842	0.688
Index Year 2019	-0.367	0.579
Index Year 2020	-0.450	0.596
Index Year 2021	-0.867	0.702
Index Year 2022	-1.262	0.715
Index Year 2023	-1.738*	0.803
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.3.4 Number of Inpatient Days for CD

	Quasipoisson	
Covariates	Estimate	Std. Error
Cycling (treatment)	0.195	0.399
Total continuous duration of first anti-TNF	- < 0.001**	0.001
Index Year 2017	0.352	0.678
Index Year 2018	-0.409	0.748
Index Year 2019	0.340	0.651
Index Year 2020	0.145	0.664
Index Year 2021	-0.370	0.778
Index Year 2022	-0.734	0.786
Index Year 2023	-1.156	0.879
Baseline 6-month healthcare cost	< 0.001	< 0.001
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.3.5 Number of ER Visits for UC

	Quasipoisson	
Covariates	Estimate	Std. Error
Cycling (treatment)	0.271	0.302
Index Year 2017	-0.722	0.783
Index Year 2018	0.118	0.578
Index Year 2019	-0.976	0.676
Index Year 2020	0.528	0.542
Index Year 2021	0.560	0.564
Index Year 2022	-0.099	0.590
Index Year 2023	-0.032	0.584
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.3.6 Number of ER Visits for CD

	Quasipoisson	
Covariates	Estimate	Std. Error
Cycling (treatment)	0.179	0.255
Total continuous duration of first anti-TNF	< 0.001	< 0.001
Index Year 2017	1.431	1.636
Index Year 2018	2.018	1.606
Index Year 2019	2.203	1.605
Index Year 2020	2.108	1.609
Index Year 2021	1.419	1.631
Index Year 2022	2.296	1.611
Index Year 2023	1.585	1.625
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.3.7 Number of Outpatient Visits for UC

	Quasipoisson	
	Coefficients	SE
Cycling (treatment)	0.314 **	0.117
Index Year 2017	0.008	0.244
Index Year 2018	-0.108	0.227
Index Year 2019	-0.149	0.218
Index Year 2020	0.109	0.215
Index Year 2021	-0.343	0.246
Index Year 2022	-0.149	0.226
Index Year 2023	-0.143	0.226
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.3.8 Number of Outpatient Visits for CD

	Quasipoisson

	Coefficients	SE
Cycling (treatment)	-0.065	0.118
Total continuous duration of first anti-TNF	- < 0.001	< 0.001
Index Year 2017	0.242	0.337
Index Year 2018	0.140	0.329
Index Year 2019	0.329	0.328
Index Year 2020	0.206	0.333
Index Year 2021	0.072	0.340
Index Year 2022	0.026	0.339
Index Year 2023	0.106	0.338
Baseline 6-month healthcare cost	< 0.001**	< 0.001
Significance levels: * p < 0.05 ** p < 0.01 *** p < 0.001		

7.5 Incidence Rate Ratios

7.5.1 Incidence Rate Ratios for Healthcare Utilization for UC

Outcome	Model	IRR (95% CI)
Inpatient length of stay	Quasipoisson	1.09 (0.53, 2.22)
ER visits	Quasipoisson	1.31 (0.73, 2.37)
Outpatient visits	Quasipoisson	1.37 (1.09, 1.72)

7.5.2 Incidence Rate Ratios for Healthcare Utilization for CD

Outcome	Model	IRR (95% CI)
Inpatient length of stay	Quasipoisson	1.22 (0.56, 2.66)
ER visits	Quasipoisson	1.2 (0.73, 1.97)
Outpatient visits	Quasipoisson	0.94 (0.74, 1.18)

7.6 Average Treatment effects

7.6.1 Average Treatment effects of Cycling on Healthcare Utilization for UC

Outcome	Model	ATE (95% CI)
Inpatient length of stay	Quasipoisson	0.106 (-1.27, 1.48)
ER visits	Quasipoisson	0.524 (-1.389, 2.44)
Outpatient visits	Quasipoisson	1.248 (-0.219, 2.71)

7.6.2 Average Treatment effects of Cycling on Healthcare Utilization for CD

Outcome	Model	ATE (95% CI)
Inpatient length of stay	Quasipoisson	0.261 (-1.341, 1.864)
ER visits	Quasipoisson	0.435 (-0.903 1.773)
Outpatient visits	Quasipoisson	-0.224 (-0.994, 0.546)

8.4 Relevant Medication NDCs

Medication Class	Medication Name	NDC
Anti-tumor necrosis factors (anti-TNF)	adalimumab	0025-0325-01 0025-0325-02 0025-0328-02 0025-0333-02 0069-0325-01 0069-0325-02 0069-0328-02 0069-0333-02 72606-022-01 72606-022-02 72606-022-03 72606-022-08 72606-022-09 72606-022-10 72606-022-11 72606-022-12 72606-040-01 72606-040-02 72606-040-03 72606-040-04 72606-040-05 72606-041-01 72606-040-06 61314-391-64 61314-327-20 61314-327-64 83257-020-42 83257-021-42 83257-022-32 61314-332-64 72606-022-04 72606-022-05 72606-022-06 72606-022-07 61314-325-20 65219-612-99 65219-620-20 65219-612-69 65219-612-89 82009-144-22 82009-146-22 82009-148-22 0597-0545-22

		0597-0555-80 0597-0565-20 0597-0575-50 0597-0585-89 0597-0595-20 82009-150-22 83457-187-01 83457-186-01 51759-360-02 51759-361-17 82009-156-22 82009-158-22 55513-399-01 55513-400-01 55513-400-02 55513-400-91 55513-410-01 55513-410-02 55513-411-01 55513-413-01 55513-479-01 55513-479-02 55513-480-01 55513-480-02 55513-481-01 55513-481-02 84612-399-01 84612-479-01 55513-482-01 55513-482-02 72511-400-01 72511-400-02 72511-482-01 72511-482-02 84612-479-02 84612-481-01 84612-481-02 84612-482-01 84612-482-02 72511-399-01 72511-479-02 72511-481-02 0597-0370-45 0597-0370-82 0597-0375-16 0597-0375-23 0597-0375-48 0597-0375-97 0597-0400-89 0597-0405-80 0597-0485-20 0597-0485-46 0597-0495-47 0597-0495-50 78206-183-01 78206-184-01 78206-185-01 78206-186-01 78206-187-01 78206-187-59 50090-6705-0 50090-6706-0 50090-6707-0 83257-016-42 83257-017-42 83257-019-32 0074-0124-01 0074-0124-02 0074-0124-03 0074-0124-04 0074-0124-74 0074-0243-02 0074-0554-01 0074-0554-02 0074-0554-71 0074-0554-74 0074-0616-02 0074-0616-71 0074-0817-02 0074-1539-03 0074-2540-01 83457-124-02 83457-243-02 83457-554-02 83457-616-02 83457-817-02 50090-4487-0 0074-3799-02 0074-4339-02 61314-454-20 61314-454-36 61314-454-68 61314-473-20 83457-100-01 83457-101-01 83457-102-01 83457-103-01 83457-107-01 83457-108-01 83457-112-01 83457-113-01 61314-473-64 61314-473-92 61314-476-64 61314-509-64 61314-517-36 61314-531-64 65219-558-08 65219-554-08 65219-554-28 65219-554-38 51759-386-22 51759-402-02 51759-402-17 51759-412-22 51759-523-21 51759-274-17 50090-7718-0 72606-063-01 72606-023-01 72606-023-02 72606-023-03 72606-023-04 72606-023-05 72606-023-07 72606-023-08 72606-024-01 72606-030-01 72606-030-02 72606-030-03 72606-030-04 72606-030-05 72606-030-06 72606-030-07 72606-030-08 72606-030-09 72606-030-10

		72606-030-11 72606-030-12 72606-030-13 72606-030-14 72606-039-01 72606-046-01 70114-210-02 70114-220-02 71288-815-81 71288-816-81
	certolizumab pegol	50474-700-61 50474-700-62 50474-710-79 50474-710-80 50474-710-81 50474-750-10
	infliximab	55513-670-21 55513-670-01 0069-0809-01 57894-160-01 57894-030-01 78206-162-01 72606-025-01 72606-025-02 72606-025-03 72606-025-04 72606-025-05 72606-025-06 72606-025-08 72606-025-09 72606-025-10 72606-025-07 72606-025-11 72606-025-12 72606-047-01
	golimumab	57894-070-89 57894-070-90 57894-071-01 57894-071-02 57894-071-89 57894-071-90 57894-070-02 57894-070-01 57894-350-01 57894-350-89
Sphingosine 1-phosphate (S1P) modulators	ozanimod	59572-810-07 59572-810-97 59572-820-30 59572-890-28 59572-890-98
	etrasimod	63539-274-28 0069-0274-30 63539-274-30
Integrin receptor antagonist	natalizumab	61314-543-94 64406-008-01
	vedolizumab	64764-300-20 64764-107-11 64764-108-21
Janus kinase (JAK) inhibitors	tofacitinib	63539-029-02 0069-0501-30 0069-0502-30 0069-1001-01 0069-1002-01 0069-1029-02 63539-012-02 63539-016-02 63539-501-14 63539-501-30 63539-502-30
	upadacitinib	0074-1043-14 0074-1043-28 0074-2306-30 0074-2306-70 0074-2310-20 0074-2310-30 0074-2320-01 0074-2320-70
Interleukin-23 inhibitor	mirikizumab	0002-1442-11 0002-3116-11 0002-3116-61 0002-7717-61 0002-8011-61 0002-7575-01 0002-8011-27 0002-7717-11 0002-7722-11 0002-8870-27
	guselkumab	57894-640-06 57894-651-92 57894-640-01 57894-640-04 57894-640-11 57894-640-99 57894-651-04 57894-650-02 57894-651-02 57894-651-22

	risankizumab	0074-1050-01 0074-1050-70 0074-1065-01 0074-1065-02 0074-1070-01 0074-1070-02 0074-2100-01 0074-2100-70 0074-7042-04 0074-5015-01 0074-5015-02 0074-7040-02 0074-8300-01 0074-8350-01
	ustekinumab	69448-019-26 69448-017-63 69448-018-63 51407-929-11 51407-930-11 51407-931-11 65219-824-01 65219-826-26 65219-828-05 65219-822-05 83457-651-01 83457-652-01 61314-651-94 61314-651-01 61314-652-01 61314-654-94 83457-651-96 83457-652-96 51759-505-32 50090-7769-0 51759-607-32 51759-708-13 51759-505-13 0143-9168-01 0143-9169-01 0143-9170-01 0143-9171-01 57894-054-16 57894-054-27 57894-060-02 57894-060-03 57894-060-04 57894-061-03 57894-061-04 72606-027-01 72606-028-01 72606-029-01 57894-440-01 57894-440-03 57894-441-01 57894-444-01 65219-862-01 65219-866-26 51759-414-32 51759-413-32 51759-709-32 51759-710-32 82009-160-11 82009-162-11 82009-163-94 84612-055-01 84612-066-01 84612-076-01 84612-089-01 84612-855-01 84612-876-01 84612-889-01 83257-023-41 83257-024-11 83257-025-41 83257-026-11
5-ASA	Sulfasalazine	00005396031 00013010101 00013010105 00013010110 00013010111 00013010120 00013010130 00013010201 00013010205 00013010220 00013010250 00013010260 00016010110 00016010306 00032208001 00032208010 00093323401 00093323405 00093323410 00102275501 00150115240 00150115280 00157069601 00157069605 00182101601 00182101605 00182101610 00223172701 00223172702 00223172705 00228239910 00228239950 00254590528 00302671001 00302671005 00302671201 00302671205 00304026900 00304026901 00304026905 00304117901 00349234900 00349234901 00349234905 00349829201 00349829205 00359036710 00359037010 00359037040 00359037050 00364044401 00364044405 00364068801 00368102001 00405495601 00405495602 00536461301 00536461305 00536461701 00536461705

		00536461710 00537614801 00537614805 00537614810 00580033101 00580033105 00580146001 00580146005 00591079601 00591079605 00591079610 00591550301 00591550303 00591550304 00603580104 00603580121 00603580128 00603580132 00603580221 00603580228 00603580321 00603580325 00615152201 00615152205 00615152213 00677014701 00677014705 00677048301 00677048305 00686004420 00719192710 00719192810 00719192812 00719192813 00725005901 00725005904 00725005905 00725005910 00725013101 00725013105 00725013110 00779105225 00779105227 00781104501 00781104505 00814723014 00814723028 00814723114 00814723128 00839609806 00839609812 00839609816 00839674406 00839674412 00904115140 00904115160 00904115180 00904115240 00904115260 00904115261 00904115270 00904115280 00948520201 01050115260 05364061305 10544028830 11845012101 11845012103 12071034101 12071034105 12071034199 17022838002 17236028501 17236028505 17236028510 17236029101 17236029105 23155001901 23490631300 33261075600 33261075602 33261075630 33261075660 33261075695 35470005901 35470005905 38779017604 38779017605 38779017608 38779017609 38779017610 38779017625 38779017644 47202237101 47202237102 47202271001 49452752301 49452752302 49452752303 49452752304 49452752305 49727004204 49999098100 50090008604 50090201304 50090693600 50268073011 50268073015 50430004003 50430004005 50430004006 51079004420 51079004440 51079004450 51382010701 51382010705 51432044103 51432044105 51432044200 51432044203 51432044205 51552104405 51655011177 51728004601 51728004605 51728064801 51728064805 51927104500 52446044621 52544079601 52544079605 52544079610 53258017213 53489014701 53489014705 53489014710 54274000410 54274000430 54274005210 54274005230 54569031300 54569031301 54569031303 54569031304

		54868112301 54868113800 54868113801 54868113803 54868113804 54868113805 54868113806 54868113807 54868113808 54868113900 55045349601 55289017610 55289017640 56126030611 58016007400 58016007430 58016007460 58016007490 59762010401 59762010402 59762010405 59762010406 59762500001 59762500002 59762500005 59762500006 60346081240 60346081294 61392014730 61392014731 61392014732 61392014739 61392014745 61392014751 61392014754 61392014760 61392014790 61392014791 62135096001 62135096005 62135096010 62135096031 62991270401 62991270403 62991270404 66336056430 99999500060
	Balsalazide Disodium	00054007928 00378675082 00591357035 42291015728 50268010211 50268010213 54868613700 55700027030 60505257507 65649010102 65649010150 65649010202 68084079932 68084079933 68682075002 60429095228 72789014969 51407082028 72162209502 70710162601
	Mesalamine	00023585318 00023590118 00032192428 00032192482 00032192824 00032192846 00037002207 00037002228 00037006603 00037006605 00088201046 00088201080 00088201090 00093590786 00093688871 00093922489 00149075202 00149075206 00149075215 00149078301 00378137578 00378740178 00378923093 00430075227 00430075327 00430078327 00472191501 00472191530 00480755080 00527301248 00574725003 00591224522 00781708806 00781708833 00832605612 00904683204 16714024501 16714024530 16714083001 21922004547 21922004549 31722000530 31722000532 31722004312 42291048918 42291056318 42291056412 43386051087 45802009828 45802009846 45802009851 45802092341 45802092349 45802092949 49452045001 49452045002 49452045003 49452045004 49452045005 49452045006 49999096918 50090300200 50268057711 50268057715 50532006603 50532006605 51407027412 51407090012 51552132604 51552132605 51552132606 51927107800 54092010001 54092018980 54092018981

		54092019112 54092019180 54092047602 54092047612 54569479300 54569673300 54868251500 54868251501 54868251502 54868251503 54868251504 54868251505 54868519900 54868530200 54868530201 54868614700 54868615000 55154230506 55289083330 58914050018 58914050056 58914050118 58914050142 58914050156 59651039708 59762011701 59762011803 60687026425 60687026495 60687034725 60687034795 60687039725 60687039795 60687040825 60687040895 60687055632 60687055633 60687065032 60687065033 62135071412 62135071460 62332072435 62559042007 62559042011 62991270501 62991270502 62991270503 63304008913 63304017513 63629867801 64980028203 65649010302 66336050390 66993095077 67877071712 68220002207 68220002228 68220006603 68220006605 68220006607 68220006628 68382043528 68382045219 68382048428 68382064928 68382071119 68682011320 69238127403 69918056030 70710130207 70748021416 72162180403 72162221302 72162223102 72162230202 72162230204
	Olsalazine Sodium	00013010501 00013010520 00037686010 50474060001 50474060025 53014072671 53014072682 68220016010