EVALUATING THE ASSOCIATION BETWEEN ANTI-TNFα TREATMENT AND MULTIPLE SCLEROSIS RISK IN AUTOIMMUNE CONDITIONS: INSIGHTS FROM HEALTH ADMINISTRATIVE DATA AND METHODOLOGICAL CHALLENGES

by

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Abstract

Objectives: This dissertation aims to compare the risk of multiple sclerosis (MS) in anti-tumor necrosis factor alpha (TNFα) users with nonusers among patients with rheumatic disease (RD) or inflammatory bowel disease (IBD). It also aims to uncover methodological biases in existing research and explore statistical strategies to address these biases, with a particular focus on the issue of sparse data bias.

Methods: Utilizing population-based health administrative data from four Canadian provinces, a nested case-control study was conducted among patients with RD and IBD (2000 to 2018). Any anti-TNFα dispensations in the two years prior to the index date (MS onset) were identified. Causal directed acyclic graphs (cDAGs) were utilized to illustrate biases like confounders, mediators, and collider-stratification bias, which may influence the relationship between anti-TNFα therapy and MS risk. Advanced statistical techniques were applied to mitigate sparse data biases. These techniques included Firth bias adjustment, data augmentation, Markov Chain Monte Carlo (MCMC), Least Absolute Shrinkage and Selection Operator (LASSO), and Ridge regression, and their results and performance were compared against traditional models via simulation studies.

Results: 1) The study found that anti-TNFα therapy was associated with an increased risk of MS in RD patients (pooled incidence rate ratio [IRR]=2.05 [95% confidence interval {CI}, 1.13-3.72]) after adjusting for potential confounders. The number needed to harm was calculated at 2,268 for RD patients. While an increased risk was also observed in IBD patients, the CI was

wider (pooled IRR=1.35 [95% CI, 0.70-2.59]). Sensitivity analyses and the computation of E-values were conducted to strengthen the findings. **2)** When applying various statistical methods to address sparse data issues, data augmentation and MCMC approaches demonstrated superior performance in bias and mean squared error reduction in simulation studies.

Conclusions: The use of anti-TNFα was associated with an increased risk of MS compared with nonusers, especially among patients with RD. The innovative use of cDAGs offers a new perspective on assessing causal relationships and addressing methodological challenges in pharmacoepidemiology. Data augmentation and MCMC approaches should be considered in pharmacoepidemiologic studies with sparse data to avoid drug effect overestimation, which can influence clinical decision-making and public health policies.

Lay Summary

This research investigates whether medications aimed at reducing inflammation, specifically anti-tumor necrosis factor alpha (TNFα) therapy used in inflammatory diseases like arthritis and inflammatory bowel disease (IBD), could increase the risk of developing multiple sclerosis (MS), a nervous system disorder. By analyzing patient data from four Canadian provinces, the study meticulously examines the relationship between the therapy and MS, while also identifying and correcting biases in previous studies. The study found that patients with arthritis who were treated with anti-TNFα therapy were more likely to develop MS compared to those who did not use the therapy. For those with IBD, the increased risk was also observed but with less certain. Given the rarity of MS, the research employed advanced statistical methods to address issues associated with small sample sizes. These insights are vital for healthcare practitioners to weigh the benefits and risks of anti-TNFα therapy, ultimately guiding safer medical decisions.

Preface

The doctoral thesis presented here is a compilation of three separate but related studies, all initiated and conducted by Lingyi Li. The scope of Li's work spanned from the inception of the research questions to the drafting of the final manuscripts. This comprehensive involvement included designing the research methodology, preparing datasets, conducting the statistical analysis, interpreting the findings, and writing the chapters and associated manuscripts. Contributions from co-authors, which comprised members of the doctoral committee, were instrumental in providing methodological guidance, assisting in result interpretation, and refining the manuscripts through editing, with all final submissions receiving their approval. Research funding and data acquisition were led by Dr. J Antonio Aviña-Zubieta and Dr. Mahyar Etminan.

Chapters 1 and 5 constitute original, unpublished material. They were developed with significant guidance and contributions from Drs. J Antonio Aviña-Zubieta, Mahyar Etminan, Helen Tremlett, Gilaad Kaplan, and Hui Xie. I conducted a comprehensive literature search, synthesized the results, and composed the initial drafts of these two chapters. Chapters 2 through 4 have been published or are presently undergoing peer review procedure.

- **Li L**, Etminan M, Kaplan GG, Tremlett H, Xie H, Aviña-Zubieta JA. Multiple sclerosis risk among anti-tumor necrosis factor alpha users: A methodological review of observational studies based on real-world data. Current Drug Safety. 2024;19(2):200-207. doi: 10.2174/1574886318666230726162245 [published, **Chapter 2**]. I designed the study with guidance and input from Dr. Mahyar Etminan. I conducted the literature review,

drafted the manuscript, and incorporated feedback from Drs. J. Antonio Aviña-Zubieta, Gilaad Kaplan, Helen Tremlett, Mahyar Etminan, and Hui Xie.

- **Li L**, Aviña-Zubieta JA, Bernstein CN, Kaplan GG, Tremlett H, Xie H, Peña-Sánchez JN, Marrie RA, Etminan M. Risk of Multiple Sclerosis Among Users of Antitumor Necrosis Factor α in 4 Canadian Provinces: A Population-Based Study. Neurology. 2023;100(6):e558-e567. doi: 10.1212/WNL.0000000000201472 [published, **Chapter 3**]. I designed the study with guidance and input from Drs. Mahyar Etminan, J. Antonio Aviña-Zubieta, Hui Xie, and Helen Tremlett. I conducted the literature review, developed the statistical analysis plan, and executed the data analysis in British Columbia. I managed the coordination of the project and offered guidance to statisticians in other provinces with the support from Drs. Juan-Nicolas Peña-Sánchez, Gilaad Kaplan, Charles Bernstein, and Ruth Ann Marrie. Furthermore, I drafted the manuscript and incorporated feedback from all coauthors.

- **Li L**, Etminan M, Tremlett H, Kaplan GG, Aviña-Zubieta JA, Xie H. Assessing Analytical Methods for Addressing Sparse Data Bias: A Case Study in Pharmacoepidemiology [submitted to a peer-reviewed journal, **Chapter 4**]. I designed the study with guidance and input from Drs. Hui Xie, Mahyar Etminan, J. Antonio Aviña-Zubieta, Helen Tremlett, and Gilaad Kaplan. I conducted the literature review and statistical analysis. I drafted the manuscript and incorporated feedback from all coauthors.

Ethics approval in **Chapter 3** was obtained from the University of British Columbia's Clinical Research Ethics Board (H15-00887), the University of Calgary's Conjoint Health Research Ethics Board (REB16-2375), the University of Saskatchewan Biomedical Research Ethics Board (Bio-REB 2298), and the University of Manitoba Health Research Ethics Board (HS24393). Ethics approval in **Chapter 4** was obtained from the University of British Columbia's Clinical Research Ethics Board (H15-00887).

In **Chapter 3**, all inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not reflect the opinions or policies of the Data Steward(s). This study is based in part on data provided by Alberta Health. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Governments of Alberta. Neither the Government of Alberta nor Alberta Health expressed any opinion in relation to this study. This study is based in part on de-identified data provided by the Saskatchewan Ministry of Health and eHealth Saskatchewan. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan, the Saskatchewan Ministry of Health, or eHealth Saskatchewan. The authors acknowledge the Manitoba Centre for Health Policy for use of the Manitoba Population Research Data Repository under project #2020-069 (HIPC #2020/2021-58). The results and conclusions presented are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred.

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List of Abbreviations

95% CI	95% confidence interval
AS	ankylosing spondylitis
BC	British Columbia
cDAG	causal directed acyclic graphs
CCI	Charlson Comorbidity Index
CNS	central nervous system
DMARD	disease-modifying antirheumatic drug
FDA	Food and Drug Administration
Fc	fragment crystallizable
IBD	inflammatory bowel diseases
ICD	International Classification of Diseases
IFN-γ	interferon gamma
IL	interleukin
IRR	incidence rate ratio
IgG1	immunoglobulin G1
LASSO	Least Absolute Shrinkage and Selection Operator
MCMC	Markov Chain Monte Carlo
MCSE	Monte Carlo standard error
MI	myocardial infarction
ML	maximum likelihood

MS	multiple sclerosis
MSE	mean squared error
NCC	nested case-control
NNH	number needed to harm
NSAIDs	non-steroidal anti-inflammatory drugs
OR	odds ratio
PEG	polyethylene glycol
PPV	positive predictive value
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RD	rheumatic diseases
RR	rate ratio
SD	standard deviation
SE	standard error
SIR	standardized incidence ratios
TNFR	tumor necrosis factor receptor
TNFRSF	tumor necrosis factor receptor superfamily
TNFα	tumor necrosis factor alpha
USA	United States of America

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I must also convey my sincere appreciation to my committee members, Professors Hui Xie, Helen Tremlett, and Gil Kaplan. Their timely critical insights and expert guidance have been essential to the progress and achievements of my PhD work.

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Deep appreciation is due to my friends for their companionship along this extensive journey, to my parents, Su Li and Yuhong Sun, for granting me the liberty to achieve my fullest potential. To my husband, Laowang, for his endless encouragement and support in the pursuit of

my dreams, and to my daughter Naya, who has filled my life with great happiness and shown me how to balance being a mom with the demands of academic study. I am also thankful for my mother-in-law, whose assistance with childcare during the most challenging phases of my PhD was invaluable.

Thinking back to a question from Professor Aviña-Zubieta about which is tougher, being a parent or doing the PhD, I can now say: neither is overly challenging when surrounded by such a strong support system. I'm really lucky to have such a great group of people supporting me.

Dedication

To my family

Chapter 1: INTRODUCTION

1.1 Thesis Organization

This thesis is on the subject of multiple sclerosis (MS) risk associated with the use of anti-tumor necrosis factor alpha (TNFα) in patients with rheumatic diseases (RD) or inflammatory bowel diseases (IBD). The thesis is organized in a manuscript-based format. It consists of five chapters. Chapter one is the introductory chapter and provides the background information and basic concepts for the following chapters within the thesis. First, it reviews the state of knowledge on topics, including a) anti-TNFα; b) MS; c) anti-TNFα and MS; d) causal directed acyclic graphs (cDAGs); e) sparse data bias; f) the use of health administrative datasets; g) purpose; and h) review of thesis chapters. Chapter two presents a methodological review of potential biases of published studies assessing the association between anti-TNFα and MS. It describes how cDAGs can be used to determine those biases when depicting anti-TNFα and its potential to contribute to MS onset. Chapter three evaluates the risk of MS among users of anti-TNFα using population-based cohorts. This chapter quantifies the risk of MS in anti-TNFα users with RD and IBD using population-based health administrative databases from four Canadian provinces. Given the rarity of MS, epidemiological studies examining the association between anti-TNFα and MS often encounter issues of sparse data bias. Chapter four is focused on further discussion of sparse data bias. It evaluates different analytical methods in addressing sparse data bias and compares their performance through simulation studies based on real-life data. The concluding chapter summarizes the findings of the three manuscripts and offers a critical

discussion of the strength, the limitations as well as the relevance of the findings of research in this thesis.

1.2 Anti-Tumor Necrosis Factor Alpha

1.2.1 History and Discovery of Anti-Tumor Necrosis Factor Alpha

In the 1970s, researchers observed certain molecules produced by immune cells with the capability to kill tumor cells, leading to its naming as the TNF (1). This discovery garnered interest in its potential therapeutic applications for cancer patients. However, its clinical use was limited due to severe systemic side effects (2). By the 1980s, advancements in molecular biology and protein purification techniques allowed scientists to isolate and identify a specific molecule named TNFα (3,4). Subsequent research revealed that TNFα is a cytokine intricately involved in systemic inflammation, and it is a member of a group of cytokines that induce the acute phase reaction (5). TNFα is primarily produced by activated macrophages, although other cell types can produce it as well (5). Elevated levels of TNFα have been identified in patients with autoimmune diseases like rheumatoid arthritis and IBD (6,7). Recognizing the role of TNFα in inflammation made it a logical therapeutic target for diseases marked by excessive inflammation (8). This understanding of TNFα's role in inflammation and the subsequent development of therapeutic agents targeting, epitomizes how scientific research can lead to groundbreaking medical treatments.

Infliximab (Remicade®) was one of the first anti-TNFα therapy to be developed, initially approved for use in Crohn's disease in the late 1990s (9). Etanercept (Enbrel®) received Food

and Drug Administration (FDA) approval for the treatment of rheumatoid arthritis later in the same year (10). Other anti-TNFα agents soon followed, including adalimumab (Humira®), golimumab (Simponi®), and certolizumab pegol (Cimzia®). Each of these agents has slight differences but all target and inhibit TNFα function (11). With the success of these agents in treating IBD and rheumatoid arthritis, their use was expanded to other inflammatory conditions such as ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis (12,13). The indications for different types of anti-TNFα are summarized in **Table 1.1**.

Table 1.1 Indication for different types of anti-tumor necrosis factor alpha

Anti-TNFα	Indications
Infliximab	rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, psoriatic arthritis, psoriasis
Etanercept	rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis
Adalimumab	rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, psoriatic arthritis, psoriasis, juvenile idiopathic arthritis
Golimumab	rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis
Certolizumab pegol	rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis

1.2.2 Action of Anti-Tumor Necrosis Factor Alpha and Adverse Events

Anti-TNFα agents work by neutralizing the action of TNFα (14). By binding to TNFα or its receptors, these agents prevent the cytokine from promoting inflammatory responses, thus offering relief in diseases with RD and IBD (15).

Infliximab is a mouse-derived chimeric antibody that targets all forms of human TNFα, effectively preventing TNFα from binding to its soluble and membrane-bound receptors (7,16). Treatment with infliximab enhances the breakdown of cells that produce TNFα, resulting in decreased inflammation (17). Infliximab not only induces cell death but also halts the production of interferon gamma (IFN-γ, i.e., a type of cytokine that plays a vital role in the immune system) in certain T cells (15), leading to reduced inflammation. Additionally, infliximab lowers the levels of specific cell-binding molecules (18). However, the use of infliximab is linked to the occurrence of serious side effects, such as pneumonia, liver toxicity, lymphoma, and a reactivation of tuberculosis (19).

Etanercept is a combined protein containing two similar external regions of tumor necrosis factor receptor (TNFR) 2 connected to a part of the human immunoglobulin G1 (IgG1) (20,21). Although there are multiple versions of etanercept, they differ minimally. Etanercept attaches itself to specific forms of TNFα, rendering them inactive by preventing them from connecting to their receptors (17). It can also bind other members of the lymphotoxin family, such as TNFß, which is a cytokine involved in the regulation of bowel immune cells (22). Etanercept establishes fragile bonds with its target, leading to unstable complexes (23). This is attributed to the absence of a hinge region in its fragment crystallizable (Fc) portion, rendering etanercept being weaker than other blockers (23). It is important to highlight that prolonged use

of etanercept can result in serious infections and sepsis, potentially leading to hospital admission or even fatality (20).

Adalimumab is a fully human IgG1 monoclonal antibody (7,24). Its role is to prevent TNFα from binding to its receptors. The structure of adalimumab is identical to that of natural human IgG1 (24). In patients with rheumatoid arthritis, adalimumab reduces TNFα and interleukin (IL)-6 levels as well as other markers of inflammation (25). Furthermore, adalimumab treatment has been observed to reduce the overproduction of IL-17 by certain cells and increase the number of regulatory T cells (26). Due to its superior tolerance and reduced immunogenicity, adalimumab is effectively utilized for Crohn's disease patients and can be given to those who have experienced infusion reactions to infliximab. Nonetheless, patients undergoing adalimumab treatment have shown various adverse effects, such as thrombocytopenia, leukopenia, the onset of malignancies, and a resurgence of tuberculosis (5,27).

Golimumab is a fully humanized antibody specifically designed to act against TNFα (7,28). Compared to infliximab and adalimumab, golimumab binds more tightly and neutralizes certain TNFα types more effectively, thereby hindering TNFα's biological actions (29). Furthermore, it prevents white blood cells from entering certain areas of inflamed tissue and reduces the production of molecules and proteins that cause inflammation (30). There is less evidence on its potential long-term adverse events in the real-world setting.

Certolizumab pegol is a specially designed antibody that is attached to a polyethylene glycol (PEG) fragment and lacks the Fc region (31). This absence means it does not engage in certain types of cell killing. Its distinctive way of working differentiates it from other TNFα inhibitors. The addition of PEG enables certolizumab pegol to distribute more effectively in

inflamed tissues than infliximab or adalimumab (32). This specialized structure might be the reason behind its heightened effectiveness (33). Furthermore, the attachment of PEG significantly extends the half-life of certolizumab pegol in the body (up to two weeks), potentially due to its increased concentration in inflamed regions (34). Without PEG, the half-life of similar biologic agents is generally shorter (ranging from about 3 days to 20 days) (13). Similar to golimumab, it is less known on potential adverse events on certolizumab pegol (35).

1.2.3 Anti-Tumor Necrosis Factor Alpha Treatment in Rheumatic Diseases and Inflammatory Bowel Diseases

The introduction of anti-TNFα treatments has heralded a revolutionary phase in the treatment of RD and IBD. In the context of rheumatoid arthritis, particularly for those suffering from moderate to severe diseases, it is crucial to understand that rheumatoid arthritis typically involves continuous inflammation, causing joints to become swollen and sensitive (36). Without appropriate treatment, this can evolve into lasting joint damage (37). Therefore, the disease often impairs the social, psychological, and occupational facets of a patient's life (38). The therapeutic response to traditional disease-modifying antirheumatic drugs (DMARDs), though beneficial, often had limitations. For example, these drugs often have a slow onset of action and can lead to potential side effects, including liver toxicity (39). With the emergence of anti-TNFα agents, the landscape of rheumatoid arthritis treatment witnessed a paradigm shift. Beyond the evident relief from pain, these agents have demonstrated a remarkable ability to retard the relentless progression of joint erosion associated with rheumatoid arthritis (40). Improved physical ability, stemming from this treatment approach, has given patients a rejuvenated sense of independence,

rendering daily tasks and self-care more manageable and elevating their quality of life (41). Additionally, by curbing the systemic inflammation inherent to rheumatoid arthritis, some studies also showed that anti-TNFα could potentially reduce the risk of cardiovascular risks, a critical concern for many rheumatoid arthritis patients (42,43).

In the realm of psoriatic arthritis, the therapeutic advantages of anti-TNFα are manifold. Not only do patients witness substantial relief in joint discomfort, characterized by diminished pain, inflammation, and rigidity, but these therapies also adeptly mitigate the skin complications tied to psoriasis (44). This dual-action approach addresses both the skeletal and skin-related symptoms, providing a holistic remedy. Patients were also able to resume previous work and leisure activities (44).

Ankylosing spondylitis, yet another formidable RD challenge, has exhibited marked therapeutic progress with consistent anti-TNFα administration. The use of anti-TNFα has yielded significant improvements over baseline values for various measures of disease activity, including morning stiffness, spinal pain, physical functioning, quality of life, enthesitis, chest expansion, erythrocyte sedimentation rate, and C-reactive protein (45). Furthermore, studies have indicated that the use of anti-TNFα is linked to positive effects on lipid profiles and a decrease in sub-clinical atherosclerosis (46).

Similarly, anti-TNFα agents have been shown to be effective in reducing symptom burden and inflammatory activity in both Crohn's disease and ulcerative colitis, and can induce healing of the intestinal mucosa, which is thought to prevent the development of IBD-related complications and reduce the risk of future flares (47). Additionally, research indicates that employing anti-TNFα therapy leads to fewer hospitalizations and surpasses conventional treatments in enhancing health-related quality of life, including diminishing the necessity for

intestinal resections (48,49). Although anti-TNFα agents are generally well tolerated and have been shown to significantly improve patients' quality of life (50,51), an increased risk of MS has been suspected after their use (52–54).

1.3 Multiple Sclerosis

1.3.1 Epidemiology of Multiple Sclerosis

MS is a chronic, progressive inflammatory disease of the central nervous system (CNS) (55–57). MS is marked by demyelination, where the protective myelin sheath covering nerve fibers gets damaged, leading to axonal loss (55–57). This process of demyelination is fundamental to the onset and progression of MS. As a result, patients with MS often suffer from physical and cognitive impairments, depression, and fatigue, all of which can markedly deteriorate their quality of life (55–57). MS typically presents in young adults and is one of the world's most common neurologic disorders with an estimated global prevalence of 35.9 [95% confidence interval (CI): 35.87-35.95] per 100,000 people in 2020 (58). The number of people with MS worldwide has reached to 2.8 million in 2020 (58). In Canada, the prevalence of MS is one of the highest in the world, estimated at 159 per 100,000 for men and 418 per 100,000 for women (56). As such, MS may affect men and women differently. In the last decade the MS prevalence ratio of women to men has been increasing at a ratio of 2.3-3.5 (59). Some studies have shown that the onset of MS may be earlier in women, and the disease progresses at a lower rate than in men (60). A retrospective study that used survey data from the United States in 2019 estimated that the estimated total economic burden of MS was $85.4 billion, with a direct

medical cost of $63.3 billion and indirect and nonmedical costs of $22.1 billion in the United States (61). According to meta-analyses on the overall economic burden of MS, it is estimated that the lifetime treatment of each MS patient is around $4.1 million dollars (62). Although MS is typically not a fatal disease, patients with MS are estimated to live approximately seven years less than non-MS individuals of similar age (63). Its rising prevalence, combined with relative longevity of patients afflicted with MS, means that MS is projected to cost the Canadian health care system nearly $2.0 billion annually by 2031 (64).

1.3.2 Multiple Sclerosis Prodrome

The MS prodrome refers to early signs and symptoms that manifest before the clinical onset of the disease (65,66). This prodromal phase, which can vary among individuals, might span 5-10 years or more. Notably, individuals in this phase demonstrate increased healthcare utilization, manifesting in more frequent physician visits, hospitalizations, and usage of mental health services (67). Common symptoms during this period include fatigue, pain, migraines, and sleep disturbances. Women might show reduced pregnancy rates and increased hormonal preparation prescriptions (67). Given the MS prodrome, several challenges arise when conducting epidemiological research using health administrative datasets. For example, the gap between the emergence of prodromal symptoms and classical MS onset (which precedes the diagnosis of MS) can be substantial. Administrative datasets might not always capture this latency, skewing the perceived onset or duration of the prodrome.

1.4 Anti-Tumor Necrosis Factor Alpha and Multiple Sclerosis

Initially, the rationale for employing anti-TNFα treatments, such as infliximab and lenercept (another TNFR fusion protein investigated for MS treatment), in patients with MS stemmed from their success in other inflammatory conditions, such as rheumatoid arthritis (68). However, clinical trials and subsequent treatments in MS patients resulted in increased disease activity and exacerbated symptoms. These outcomes indicated a disease-specific response to TNF inhibition that is unique to MS. Treatments that target TNF were not only unsuccessful in managing multiple sclerosis, but they were also associated with a heightened risk of inducing MS in individuals who were administered anti-TNF therapies for conditions other than MS (69).

1.4.1 Postulated Mechanism

The mechanism for anti-TNFα potentially causing MS in persons with RD and IBD is not fully understood. Current hypothesized mechanisms behind this adverse effect lie in the nuanced roles that TNFα plays within the immune system and its signaling pathways. The detrimental impact of anti-TNFα is partly due to their broad action on TNF signaling (69). These treatments inhibit both soluble and membrane-bound TNFα, thereby disrupting the communication through both TNFR1 and TNFR2 (23). This widespread blockade of TNF signaling is problematic because while TNFR1 signaling seems to be associated with beneficial effects like the promotion of remyelination and axonal survival, TNFR2 has been identified as neuroprotective (23). It supports the maturation of oligodendrocytes, which are essential for myelin repair, and fosters the activity of regulatory T-cells, which are vital for controlling the immune response (23).

Genetic factors also appear to influence the response to anti-TNFα (68). Certain genetic variants, particularly those found in the tumor necrosis factor receptor superfamily (TNFRSF)1A gene (70), which codes for the TNFR1, have been linked with an elevated risk of MS. The rs1800693 variant is significant because it increases the production of a soluble form of TNFR1 that naturally neutralizes TNFα (71). While this might seem beneficial, it alters the delicate balance of TNF signaling, which is crucial in the pathophysiology of MS.

Other hypotheses have been put forward to explain the negative outcomes of MS observed among users of anti- TNFα (72). One suggestion is that the inability of anti-TNFα to cross the blood-brain barrier prevents them from directly suppressing demyelination within the CNS. Conversely, these agents may inadvertently promote demyelination by facilitating the entry of peripheral autoreactive T-cells into the CNS. This phenomenon, often referred to as the "lack of entry theory," offers insight into why anti-TNFα might fail to halt demyelination and could even induce MS, as they do not address the CNS pathology directly (73). Moreover, while anti-TNFα may effectively inhibit TNFα activity in the peripheral system, their inability to cross the blood-brain barrier could lead to an accumulation of TNFα within the CNS. This proposed "sponge effect" suggests that, as TNFα is neutralized in the periphery, the gradient across the blood-brain barrier shifts, potentially resulting in increased TNFα concentrations in the CNS, thereby contributing to neuroinflammation and demyelination (73). Another theory is that treatment with anti-TNFα might inadvertently skew cytokine profiles towards a pro-inflammatory state. This is characterized by a reduction in IL-10, which is known for its anti-inflammatory properties, and an increase in IL-12 and IFN-γ, both of which are associated with inflammatory responses. Such alterations in cytokine levels could resemble the cytokine milieu observed in patients with MS, potentially contributing to disease progression rather than

amelioration (74). Additionally, the dysregulation of TNFα has been observed in patients with relapsing-remitting MS, A study (75) highlighted an increased serum capacity to neutralize TNFα in patients with relapsing-remitting MS. These findings suggest that the body's response to TNFα might be altered in relapsing-remitting MS, and that blocking TNFα could trigger demyelinating events by interfering with this delicate balance. Lastly, the administration of anti-TNFα could reveal previously latent infections due to their immunomodulatory effects. Such reactivation of latent infections could, in turn, trigger autoimmune responses within the CNS, leading to demyelination. This risk underscores the complexity of using anti-TNFα in clinical settings, particularly in individuals with underlying infections that could be implicated in the pathogenesis of demyelinating diseases (76).

1.4.2 Summary of Evidence

1.4.2.1 Case Reports and Case Series

A number of case reports and case series have been published on the risk of anti-TNFα and new-onset demyelinating diseases including MS (52,53,72,77). One case series identified a patient presenting with symptoms of MS after using anti-TNFα for only two months (72). In addition, several other case reports have been published documenting demyelinating disease occurring after anti-TNFα treatment, with the affected patients showing neurological symptoms resembling MS (52,53). A case report described a female Caucasian patient affected by psoriatic arthritis from the age of 35 who started on the anti-TNFα etanercept at the age of 53 (78). After 18 months of use, the patient presented with vertigo, gait ataxia, limb incoordination and upper

limb postural and kinetic tremor, bilateral retro-orbital pain, and visual loss. Similar case reports have been published on the risk of demyelinating events (including MS) in patients with IBD who used anti-TNFα (79,80). While case reports on their own cannot demonstrate a clear association between anti-TNFα use and MS, they contribute to forming a robust hypothesis that can be further assessed in the comprehensive epidemiologic study proposed here.

1.4.2.2 Epidemiological Studies and Clinical Trial

To identify epidemiologic studies that have examined the effect of anti-TNFα on the risk of demyelinating diseases including MS, we undertook a search of the literature and used Medline (Ovid) from its inception (1966) to May 2021. We also searched reference lists from retrieved articles and searched for publications from scientists known for publishing in the field of anti-TNFα and demyelinating diseases including MS. The following search terms were used alone and in combination: *tumor necrosis factor inhibitors, anti-TNF, biological agents, biologics, adalimumab, certolizumab pegol, etanercept, infliximab, golimumab, rheumatoid diseases, rheumatoid arthritis, psoriatic arthritis, spondylarthropathies, ankylosing spondylitis, inflammatory bowel diseases, autoimmune diseases of the nervous system, demyelinating autoimmune diseases, multiple sclerosis, neuroinflammatory events, and demyelinating events*. We selected peer-reviewed articles that met the following inclusion criteria: 1) clearly stated case definition of outcome (e.g., MS, self-reported case was not included), 2) reported adjusted odds ratios (ORs), rate ratios (RRs), or standardized incidence ratios (SIRs) with 95% CIs to calculate them and 3) cohort or case-control study designs. Seven epidemiologic studies have investigated the association between anti-TNFα and demyelinating diseases including MS (81–87). Some

results were conflicting and underpowered with the ORs, RRs, or SIRs ranging between 0.56 (95% CI: 0.34-0.90) and 3.48 (95% CI: 1.45-8.37). The summary of these studies is listed in **Table 1.2**.

Table 1.2 Description of epidemiologic studies on the association between anti-tumor necrosis factor alpha and demyelinating diseases including multiple sclerosis

Authors	**Year**	**Data source**	**Event**	**Study Design**	**Sample size**	**Incident cases?**	**Relative risk/odds ratio/standardized incidence ratios (95% CI)**	**Main limitations**
Kunchok et al. (84)	2020	Medical records data from 3 Mayo Clinic locations for patients with RD/IBD	Demyelinating events	Nested case-control study	106 cases and 106 control individuals	No	3.01 (1.55-5.82)	1. small sample sizes 2. residual confounding 3. Not population-based
Kopp et al. (81)	2020	Administrative datasets from Sweden and	Multiple sclerosis	Cohort study	175,520	Yes	0.44 (0.18-1.05) in Sweden and 1.02	1. small sample sizes

		Denmark for patients with RA, PsA, AS		without matching			(0.23-4.46) in Denmark	2. residual confounding
Dreyer et al. (82)	2016	Administrative datasets from Denmark for RA, PsA, AS	Multiple sclerosis	Cohort study without matching	53,723	Yes	1.38 (0.69-2.77) For male: 3.48 (1.45-8.37)	1. small sample sizes 2. residual confounding
Bernatsky et al. (83)	2009	PharMetricx: health claims database in the United States for RA only	Demyelinating events	Nested case-control study	81 cases and 810 control individuals	Yes	1.31 (0.68-2.50)	1. small sample sizes 2. residual confounding 3. Not population-based

Taylor et al. (85)	2021	British Society for Rheumatology Biologics Register for RA	Demyelinating events	Cohort study	13,489	Yes	1.38 (0.96-7.92)	1. small sample sizes 2. residual confounding
Andersen et al. (86)	2015	Danish Civil Registration System for IBD	Demyelinating events	Cohort study	84,843	Yes	2.19 (1.02-4.71)	1. small sample sizes 2. residual confounding 3. Not population-based
Avasarala et al. (87)	2021	Truven Health Market Scan administrative claims database	Multiple sclerosis	Cohort study	208,681	Yes	1.43 (0.062-3.32)	1. small sample sizes 2. residual confounding

		in the United States for IBD						3. Not population-based

RD=rheumatic diseases; IBD=inflammatory bowel diseases; RA=rheumatoid arthritis; PsA=psoriatic arthritis; AS=ankylosing spondylitis

One study (86) analyzed data from the Danish Civil Registration System involving 54,843 IBD patients (1999-2012). This study compared the occurrence of central demyelinating diseases in patients who had been exposed to anti-TNFα with those who had not. The study outcome was the diagnosis of a demyelinating disease like MS, optic neuritis, transverse myelitis, and other central demyelinating diseases. Patients who had a prior history of demyelinating disease or those who used anti-TNFα before 1999 were excluded. The study found that the age-, sex-, and duration of IBD matched hazard ratio for central demyelinating disease comparing anti-TNFα-exposed and unexposed patients was 2.19 (95% CI, 1.02-4.71) among IBD patients, without further adjustment of potential confounders.

Another study (82) examined the risk of MS during anti-TNFα treatment for arthritis. Using the Danish Multiple Sclerosis Registry, the study linked MS patients to the nationwide registry that covers >90% adults with RD treated with biological drugs in Denmark. The study found an increased risk of MS in males with RD (RR=3.48 (95% CI: 1.45-8.37) and in patients with ankylosing spondylitis [RR=5.32 (95% CI: 1.72-16.49)] who were treated for arthritis with anti-TNFα compared to those not using anti-TNFα. However, the study included a very small sample size (only five men with MS had used anti-TNFα) and may have underestimated the risk of MS. Moreover, the study did not control for disease latency (i.e., the possibility that there is a latency period in MS whereby the disease process may have preceded anti-TNFα use leading to reverse causality bias).

A research group (83) conducted a case-control study within a cohort of 104,958 patients with rheumatoid arthritis. Using PharMetrics (1995-2005), a health claims database in the US, patients were entered into the cohort at the date of the first prescription of either a traditional DMARD or a biological agent and were followed until an incident demyelinating event occurred,

death or the end of the study, whichever occurred first. Cases with a demyelinating event and controls were matched on age, sex, and calendar time of cohort entry. Anti-TNFα use during the year before the demyelinating event was defined. The authors reported an adjusted RR of 1.31 (95% CI: 0.68-2.50) in individuals not at high risk for demyelinating events. In addition to matching variables, the conditional logistic regression model was further adjusted for the number of physician visits per year, the use of anakinra, methotrexate, leflunomide, antimalarial agents, other DMARDs, glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), and selective cyclo-oxygenase inhibitors. In that study, PharMetrics is not an optimal database to address the risk of demyelinating events among anti-TNFα users as subjects might drop out of the database upon termination of health coverage. In addition, unnecessary adjustment (i.e., adjustment other than confounders) can also introduce a biased total effect estimation.

A nested case-control (NCC) study (84) that used the medical records of patients with RD or IBD treated at one of three Mayo Clinics, United States of America (USA) (2003-2019) found an OR of 3.09 (95% CI: 1.19-8.04) for the association between anti-TNFα use and incident inflammatory demyelinating events. Cases were matched with controls on sex, year of birth, and autoimmune disease type. They also adjusted for disease duration in the conditional logistic regression model. However, confounding might have been present. Specifically, smoking and comorbidities were not adjusted for in their analysis or considered in the sensitivity analysis. A cohort study (81) using the nationwide clinical rheumatology registers in Sweden and Denmark (2000-2017) suggested no significantly increased risk of MS in anti-TNFα users compared with non-users among RD patients with RR=0.44 (95% CI: 0.18-1.05) in Sweden and RR=1.02 (95% CI: 0.23-4.46) in Denmark. Their multivariable regression model adjusted only for age, sex, and calendar time. In addition to the lack of power, it is possible that residual confounding bias

existed. A more recent study (85) that used data from the British Society for Rheumatology Biologics Register in Rheumatoid Arthritis found an age- and sex-corrected SIR of 1.38 (95% CI: 0.96-1.92) for the association between the use of anti-TNFα and incident demyelinating events without further adjustment when compared with the general UK population. In another study (87), by using the Truven Health Market Scan administrative claims database, it was found that the age- and sex-adjusted RR for IBD patients who used anti-TNFα, in comparison with non-users, was 1.43 (0.062-3.32).

Beyond epidemiological studies, in a double-blind, placebo-controlled trial (88), the anti-TNFα lenercept was administered to 124 patients with relapsing-remitting MS. After 24 weeks, the group who received lenercept reported more MS-related exacerbations than the placebo group (p=0.007). Due to the higher rate of MS flare-ups in the lenercept group, the study was prematurely terminated.

In summary, most studies focus on the outcomes of demyelinating events, which include MS, but do not exclusively examine MS itself. Among those that do treat MS as the outcome, there are several common methodological issues present in the existing epidemiological research regarding the association between anti-TNFα therapy and MS. These include:

(1) Failure to adjust for confounders, residual confounding, and overadjustment for unnecessary covariates (81–87),

(2) Sparse data bias due to limited sample sizes (81–87), and

(3) A lack of population-based studies (83,84,86,87).

To address the bias of residual confounding or overadjustment, we propose using a cDAG to clearly identify all common causes and other pertinent variables related to the anti-TNFα and MS causal question (Section 1.5). Additionally, we suggest employing sparse data

bias analysis techniques to address the challenges posed by small samples (Section 1.6). Finally, we propose utilizing administrative health datasets from four Canadian provinces to remedy the current absence of population-based studies (Section 1.7).

1.5 Causal Directed Acyclic Graphs

CDAG is a graphical tool used primarily to represent and elucidate causal relationships in epidemiologic studies (89). It is directed without cycles, meaning it proceeds in one direction and it never loops back on itself. In a cDAG, the nodes represent variables, such as exposure, outcome, confounder, mediator, and collider (89). Arrows represent the direct causal effects from one variable to another. Alternatively, no direct arrow between two variables suggests no direct causal relationship (89). It helps in study design by identifying which variables should be adjusted for in the analysis and assists in result interpretation, especially in understanding potential biases or alternative explanations for the findings.

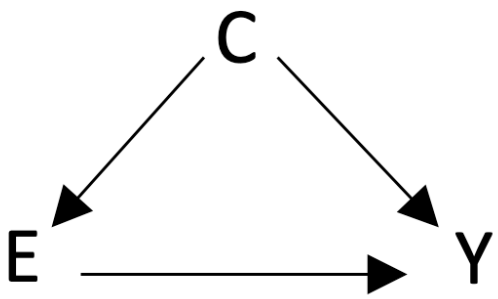
1.5.1 Identifying Bias Structures

1.5.1.1 Confounding

Confounding bias is a widespread issue that can distort the results of epidemiological studies (90). To illustrate, imagine a research group conducting an observational study using extensive health records to investigate the risk of heart attacks among users of a new blood pressure medication. Previous randomized trials had shown that this medication lowered the risk

of heart attacks. However, in the observational study, the researchers find that people taking the medication appear to have a higher risk of heart attacks. This inconsistency could be because of something known as confounding. In this case, the primary reason people are given the medication, like having high blood pressure or other health issues, is the same reason they are at higher risk for heart attacks. So, in the observational study, it might seem like the medication is causing more heart attacks, when in reality, it is the underlying health conditions that are responsible. The basic structure of confounding in cDAG is shown in **Figure 1.1**, where E is the exposure and Y is the outcome, the confounding variable C is associated with both the exposure and the outcome but is not on the causal pathway between the two. Adjustment for C is necessary to control for confounding bias (90).

Figure 1.1 The structure of confounding bias using the causal directed acyclic graph.

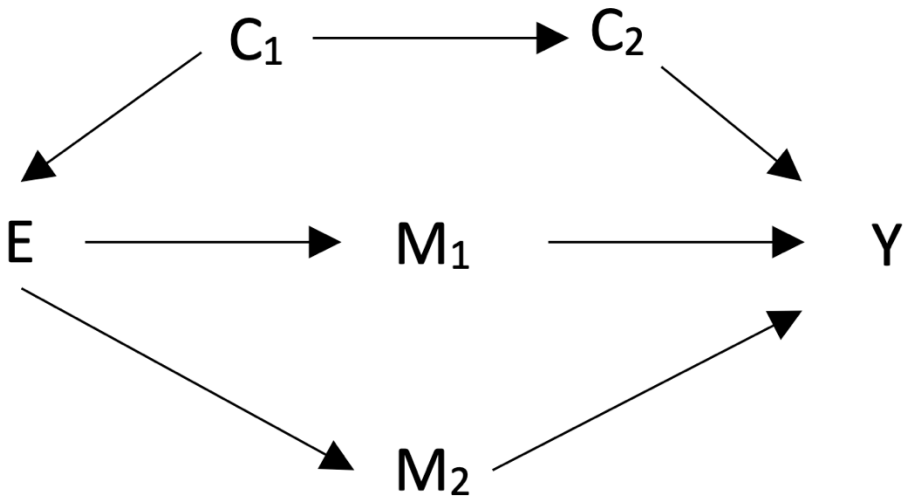


C=confounder; E=exposure; Y=outcome

1.5.1.1.1 Backdoor Path

In the context of cDAGs, a backdoor path between two variables (often an exposure and an outcome) is an alternative, non-causal route that can introduce confounding bias if not properly accounted for (91). It starts from the exposure and ends at the outcome, has at least one arrow pointing towards the exposure (which is why it is "backdoor") (91). As illustrated in **Figure 1.2**, with E as the exposure and Y as the outcome, the only backdoor path is E ← C_1→C_2 → Y, influenced by confounders C_1 and C_2. On the other hand, paths E → M_1 → Y and E → M_2 → Y are not backdoor paths. The goal is to block all backdoor paths between the exposure and the outcome without opening any new biasing paths (e.g., by adjusting for a collider or a mediator). If backdoor paths exist and are not properly controlled for, they can introduce confounding bias, making it difficult to determine the true causal relationship between the exposure and the outcome.

Figure 1.2 Illustration of backdoor path using the causal directed acyclic graph.



E=exposure; Y=outcome; C_1=confounder1; C2=confounder2; M_1=mediator1; M_2=mediator2

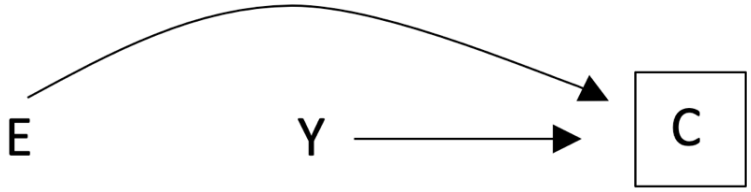
1.5.1.1.2 Least Adjustment Criterion

With a cDAG that depicts our assumptions about causal relationships among variables, it is essential to select variables for adjustment efficiently (92). The least adjustment criterion provides guidance, pointing us to the smallest set of variables necessary to control for, ensuring a direct causal effect estimation between exposure and outcome without confounding bias (92). Referring to **Figure 1.2**, either adjusting for C_1 or C2 effectively blocks the backdoor path E ← C_1→C_2→ Y. It is unnecessary to control for every variable on the backdoor path (92).

1.5.1.2 Collider Stratification Bias

A collider, in epidemiological terms, is a variable that is influenced by two or more other variables (93). Conditioning on a collider or the descendant of a collider (e.g., stratifying by, adjusting for, or selecting based on) can introduce a bias into a study. This bias is known as collider stratification bias, which is also referred to as selection bias. It can distort the observed relationship between other variables (93). To illustrate, imagine a study examines the relationship between sleep and the occurrence of a common cold, but researchers only look at data for people who report having low energy (i.e., by conditioning on energy levels). This can be problematic because among the people who report low energy, there might be those who sleep well but have a cold (hence they feel tired). Also, among the low energy group, there might be those who do not have a cold but just did not sleep well (and therefore feel tired). By only focusing on the low-energy group, the researchers are mixing up the effects of both these reasons for feeling low on energy. In other words, by conditioning on the collider energy levels, the researchers might inadvertently introduce a spurious association between sleep and occurrence of colds (which did not exist before conditioning by energy level as the path between sleep and the occurrence of a common cold was blocked). The structure of a collider is shown in **Figure 1.3**, where E is the exposure and Y is the outcome, and C is the collider. Conditioning on a collider can introduce a biased estimate between the exposure and the outcome (93).

Figure 1.3 The structure of collider bias using the causal directed acyclic graph.



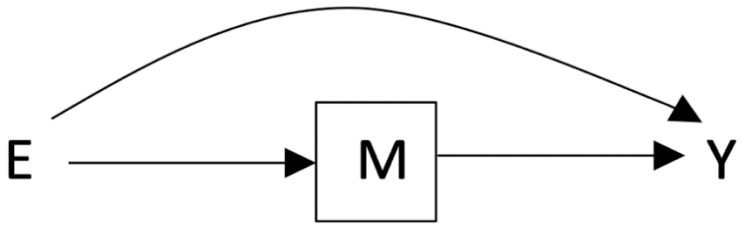
E=Exposure; Y=outcome; C=collider

1.5.1.3 Overadjustment Bias

Mediation, in epidemiological terms, means that an exposure affects an outcome through a third variable, called a mediator (94). When the mediator lies on the causal pathway between the exposure and the outcome, it can be responsible for some or all of the observed relationship. To illustrate, consider an observational study investigating the relationship between physical activity and heart attacks. Researchers notice that individuals who engage in more physical activity have a reduced risk of heart attacks. To understand why this happens, they explore the relationship further and find that regular physical activity also significantly reduces blood pressure. Now, since high blood pressure is a known risk factor for heart attacks, it might be that part of the reason physical activity reduces heart attack risk is through its effect on lowering blood pressure. In this scenario, blood pressure acts as a mediator, as it is a part of the causal pathway through which physical activity affects heart attack risk. The total effect is decomposed

into the natural direct effect (i.e., the effect of physical activity on heart attacks not through blood pressure) and the natural indirect effect (i.e., the effect of blood pressure on the association between physical activity and heart attack) (95). When the aim is to examine the total effect of physical activity on heart attack in observational studies, one should never restrict the study sample to patients with high blood pressure as this approach blocks the indirect effect and leads to an underestimation of the total effect of physical activity on heart attack (95). In this case, the bias of adjusting for a mediator is referred to as over-adjustment bias (94). This can be seen in **Figure 1.4**; M is a mediator between the exposure (E) and the outcome (Y). Its adjustment will bias the total effect of E on Y.

Figure 1.4 The structure of over-adjustment bias using the causal directed acyclic graph.



E=Exposure; Y=outcome; M=mediator

1.6 Sparse Data Bias

As mentioned earlier, sparse data bias in the study of anti-TNFα and MS is mainly due to the small number of MS events. Even outside the context of anti-TNFα and MS, this bias stands out. Historically, it has been overshadowed by more conventional biases in epidemiologic studies, such as confounding, selection bias, and measurement error. In general, sparse data bias emerges when calculating maximum likelihood (ML) estimates with minimal case counts across various exposure, covariate, or outcome levels (96). This can lead to effect estimates that deviate from the null value, giving rise to the term "sparse data bias" (96). Notably, few studies have delved into this bias within the context of matched case-control studies. While conditional logistic regression, employed in matched case-control studies, was initially crafted to counter sparse data bias in logistic regression analysis, achieving this aim demands sizable sample sets (97). Additionally, conditional logistic models might still exhibit significant bias when the events-per-variable ratio (determined by dividing events by covariates) is exceptionally low (96).

Several techniques have been suggested to tackle sparse data bias. These include: (1) Firth bias adjustment (98); (2) penalization via the approximate Bayesian method-data augmentation (99); (3) Markov Chain Monte Carlo (MCMC) Bayesian analyses (100); (4) Least Absolute Shrinkage and Selection Operator (LASSO) regression (101); (5) Ridge regression (102).

1.6.1 Firth Bias Adjustment

Firth's method is particularly useful in the presence of separation, a situation where one or more categories of the predictor variable perfectly predicts the outcome (103). This scenario can lead to infinite ML estimates (103). For illustration, consider an educator analyzing the relationship between students' participation in extracurricular sports, especially chess, and their math exam scores. The data shows that every member of the chess club scored a perfect 100% on their math test, with no students in this group receiving any other score. This uniformity in outcomes can complicate traditional statistical analyses. Using standard methods might overstate the relationship between joining the chess club and excelling in math, implying an infinite or immeasurable effect size. Here, Firth's method steps in, tempering this "infinite impact." Rather than assigning an implausible OR to the chess club's effect on math scores, Firth's method moderates this perfect prediction by adding a penalty term to the likelihood function (103), advocating for a more measured interpretation when confronted with uniform or consistent patterns.

1.6.2 Bayesian Analyses

In the realm of medical research, imagine a scenario where a scientist is keen on understanding the effectiveness of a new drug on a rather rare health condition. The traditional statistical methods might grapple with this because the event, given its rarity, does not provide ample data points which makes it difficult to draw definitive conclusions using regular statistical methods. Enter Bayesian analysis. Unlike conventional techniques that mostly lean on the data at

hand, Bayesian methods have an edge (104). The investigator starts with an existing belief or understanding about the drug's effects. This belief, often born out of previous research or expert insights, is termed as the 'prior' (105). It serves as a backdrop against which the new data is compared. As the research unfolds and the drug is administered to patients, any resulting observations form the 'likelihood'. When this newly acquired data melds with the prior belief, a revised, more informed perspective emerges, termed the 'posterior' distribution (105). Essentially, Bayesian analysis provides a balanced viewpoint, amalgamating both historic insights and fresh data.

1.6.2.1 Markov Chain Monte Carlo Bayesian Analyses

In situations of sparse data bias, MCMC Bayesian analyses usually offer a robust solution (96,105,106). At its core, MCMC is a computer-aided technique that generates samples from a distribution, eliminating the need to understand all its intricate mathematical properties. Therefore, MCMC offers a way to construct the posterior distribution by combining the prior beliefs with the likelihood from the data, effectively painting a spectrum of possible outcomes (107).

The algorithm starts with an initial point, and subsequent points are generated by a predefined stochastic process. As the process iterates, these points form a chain, and under the right conditions, the distribution of points in this chain converges to the desired posterior distribution (100). The beauty of MCMC is its ability to explore high-dimensional parameter spaces and generate samples from intricate posterior distributions, providing comprehensive insight into the possible outcomes and their likelihoods (100). By repeatedly sampling from this

process, MCMC allows for the construction of detailed representations of the posterior distribution, bridging the gap between prior beliefs and observed data (107).

1.6.2.2 Approximate Bayesian Method-Data Augmentation

Data augmentation, in the context of Bayesian analysis, is a powerful technique especially tailored to address challenges arising from sparse data (99). This method involves the addition of latent or unobserved data (referred to as pseudo-data) to the existing dataset, making it richer and more amenable to analysis (99). By integrating this additional structure, data augmentation can streamline the computation and estimation process, particularly in intricate models (99).

The algorithm for data augmentation initiates with the establishment of a prior distribution rooted in background knowledge or expert insights (105). This prior distribution is then transformed into prior data, or pseudo-data. Once this pseudo-data is generated, it is blended with the actual data, providing a combined dataset that facilitates the estimation of the posterior distribution (105). In essence, like MCMC Bayesian analysis, data augmentation serves as a bridge, seamlessly fusing prior beliefs with the observed data, offering a more comprehensive and insightful perspective in situations where data may be scarce (105). While MCMC Bayesian techniques are also adept at addressing sparse data biases, data augmentation often presents a more computationally convenient approach (105), particularly beneficial in scenarios involving non-conjugate priors, where the prior does not neatly align with the likelihood contribution from a dataset (108).

1.6.3 Least Absolute Shrinkage and Selection Operator

Another efficient technique to address this challenge is the LASSO method. Unlike traditional linear regression, LASSO introduces a penalty term to the objective function that is proportional to the absolute values of the coefficients (109). This unique feature of LASSO serves a dual purpose: it not only prevents overfitting by constraining the model's complexity but also promotes sparsity of coefficients by shrinking certain coefficients to exactly zero (101).

To illustrate with an example, imagine researchers are studying the factors affecting house prices in a vast city. They collect data on numerous variables: distance to the city center, number of bedrooms, proximity to schools, age of the house, and so on. However, not all these factors are equally influential. In a typical regression model, researchers might end up with small but non-zero coefficients for many variables, making the model complex and hard to interpret. With LASSO, many of these coefficients would be shrunk to zero, effectively suggesting that those variables do not play a significant role in determining house prices. Thus, a simpler, more interpretable model that focuses on the truly influential variables is derived. LASSO is more useful when the purpose is to predict and it is a modification of the linear regression model (96). It is not surprising that some important confounders in the effect size model would be eliminated by the LASSO regularization.

1.6.4 Ridge Regression Model

The Ridge regression method, like LASSO, is a technique designed to enhance the prediction accuracy and interpretability of statistical models, particularly when dealing with sparse data or multicollinearity (where predictor variables are highly correlated) (110). While LASSO adds a penalty to the absolute value of the coefficients, Ridge regression adds a penalty to the squared value of the coefficients (101). This distinction is fundamental in how the two methods operate.

Imagine a medical researcher aiming to understand the impact of multiple risk factors on a particular health outcome. With a plethora of potential predictors – from age and gender to various biomarkers – the researcher might run into multicollinearity issues. This is where Ridge regression shines. By imposing a penalty on the size of coefficients, Ridge helps in reducing the model's complexity without completely eliminating any predictor, as LASSO might. In mathematical terms, the penalty in Ridge regression is added to the sum of the squared coefficients. This ensures that while some coefficients may be reduced, none are completely set to zero. The end result is a model that balances between fit and complexity, providing a more stable and generalized prediction when dealing with intricate datasets. The choice between LASSO and Ridge will often depend on the specific characteristics and requirements of a given dataset and research question.

1.7 The Use of Health Administrative Datasets

High-quality, comprehensive health administrative data can address the previously mentioned lack of existing population-based studies. The datasets from four western Canadian provinces—British Columbia (BC), Alberta, Saskatchewan, and Manitoba—collectively encompass over 11 million people, nearly one-third of Canada's population. Each province captures nearly 100% of registered residents and their health-related information through comprehensive population-based linked databases. The datasets encompass all provincially funded health care services, which include every healthcare professional visit (111), hospital stays (112), demographic information (113), cancer registry (114), vital statistics (115), and all outpatient or community dispensations of prescription medication (116). Numerous population-based studies have been successfully conducted using these datasets (117–123). The overview of the provincial datasets and population sizes used in our study is listed in **Table 1.3**.

Table 1.3 Overview of the provincial datasets and population sizes

	British Columbia	**Alberta**	**Saskatchewan**	**Manitoba**
Population (2015)	4,848,055	4,067,175	1,098,352	1,278,365
Years of Data Available	1990-2015 (prescription data from 1996)	2008-2015	1998-2017	1984-2018 (prescription data from 1995)

1.8 Purpose

The primary goal of this thesis was to assess the risk of MS among anti-TNFα users, particularly those with RD and IBD, by leveraging population-based health administrative databases from four Canadian provinces. Initially, we aimed to address potential biases from existing epidemiological studies by crafting a cDAG to illustrate the potential impact of anti-TNFα use on the onset of MS. Subsequently, we evaluated the MS risk among anti-TNFα users with RD and IBD across four Canadian provinces. Given the emergence of sparse data bias in existing studies and some of our analyses, our next steps were twofold. Firstly, we compared the risk estimations of MS linked to anti-TNFα use in real-life data, following the application of various methods like Firth bias adjustment, MCMC Bayesian analyses, data augmentation, LASSO regression, and Ridge regression in comparison to conditional logistic regression in sparse data scenarios. Secondly, we appraised the efficacy of these sparse data bias adjustment techniques via simulation studies.

1.9 Overview of Thesis Chapters

This thesis is structured into three main manuscript chapters, situated between an introductory (**Chapter 1**) and a concluding chapter (**Chapter 5**). Collectively, they delve into the implications of anti-TNFα use on MS while factoring in potential biases. A brief overview of the primary focus of each chapter is provided below:

Chapter 2 offers a methodological review of observational studies that discuss the risk of multiple sclerosis among anti-TNFα users. This chapter seeks to address: Do prior epidemiological studies conclusively link the risk of MS demyelinating events with anti-TNFα use in patients with RD or IBD? If these findings are inconclusive, where do the shortcomings lie, and how might we identify and avoid potential biases?

Chapter 3 is an epidemiologic study of a population-based analysis from four Canadian provinces exploring the relationship between anti-TNFα use and MS in cohorts of RD and IBD patients. This chapter probes: Does anti-TNFα use elevate the risk of MS among patients with RD and IBD? If it does, how significant is this risk?

Chapter 4, grounded in real-world data, undertakes a simulation study to contrast various methods for addressing the challenge of sparse data bias. This chapter inquires: When applying methods such as Firth bias adjustment, MCMC Bayesian analyses, data augmentation, LASSO regression, and Ridge regression, how do the outcomes concerning the association between anti-TNFα and MS differ? Which techniques perform the best on sparse data analysis?

Chapter 2: MULTIPLE SCLEROSIS RISK AMONG ANTI-TUMOR NECROSIS FACTOR ALPHA USERS: A METHODOLOGICAL REVIEW OF OBSERVATIONAL STUDIES BASED ON REAL-WORLD DATA

2.1 Introduction

TNFα agents have been shown to significantly improve the quality of life in patients with several chronic immune-mediated inflammatory diseases (16,124–126). However, an increased risk of MS or demyelinating events has been suspected after their use (52,53,72,127,128). One of the first studies that postulated an association between anti-TNFα and MS pathogenesis was a randomized trial that was stopped early due to an increased rate of MS exacerbation among patients who received the drug lenercept (88).

To identify epidemiologic studies that have examined the effect of anti-TNFα on the risk of MS, we undertook a search of the literature and used Medline (Ovid) from its inception (1966) to December 2021. We also searched reference lists from retrieved articles and searched for publications from scientists known for publishing in the field of anti-TNFα and MS. The following search terms were used alone and in combination: *tumor necrosis factor inhibitors, anti-TNF, biological agents, biologics, adalimumab, certolizumab pegol, etanercept, infliximab, golimumab, rheumatoid diseases, rheumatoid arthritis, psoriatic arthritis, spondylarthropathies, ankylosing spondylitis, inflammatory bowel diseases, multiple sclerosis, neuroinflammatory events*, and *demyelinating events.*

We selected peer-reviewed articles that met the following inclusion criteria: 1) clearly stated case definition of MS, 2) reported adjusted ORs, RRs, or SIRs with 95% CIs, and 3) cohort or case-control study designs. Seven epidemiologic studies are included (81–87). Some results were conflicting and underpowered with the ORs, RRs, or SIRs ranging between 0.56 (95% CI: 0.34-0.90) and 3.48 (95% CI: 1.45-8.37) (81–87). These results can be misleading to clinicians, policymakers, and patients, leading to unnecessary prescribing of anti-TNFα or withholding the anti-TNFα from patients at heightened risk of MS who otherwise might benefit from these drugs.

To better understand the conflicting results and identify the structure of potential biases that influence the conflicting results, one can use cDAGs (92,129–131). In this article, we first demonstrate the principles behind how cDAGs work and how they can be used to determine whether there is a confounder, a mediator, or collider-stratification bias and when to appropriately adjust for them in a statistical model. Then, we discuss a case study to show how to control for potential biases by drawing a cDAG. Finally, we critically discuss potential biases that might have led to contradictory findings from previous studies, including confounding, confounding by contraindication, and bias due to measurement error.

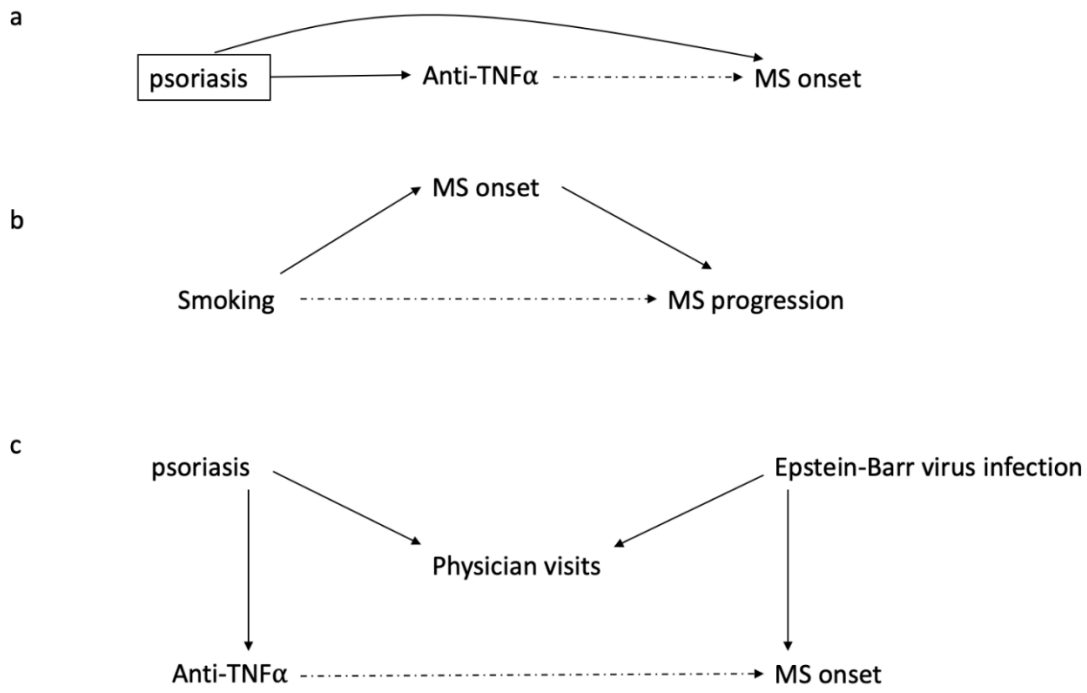
2.2 Use of Causal Diagrams in Assessing the Structure of Confounders, Mediators, and Collider-Stratification Bias

cDAGs can provide a roadmap of all common causes involved in a causal research question by connecting variables using a series of arrows (92,130). An arrow starting from one variable (A) and pointing to another variable (B) means that A causes B (132). Here we describe how cDAGs can be used to demonstrate the structure of confounders, mediators, and collider-stratification bias.

2.2.1 Confounders

Variables that are on a common cause structure are called confounders. Suppose we are interested in the causal effect of anti-TNFα on MS onset (**Figure 2.1 a**). The dotted arrow from anti-TNFα to MS onset shows that this is the causal question under investigation. In addition, there is an arrow pointing from psoriasis to anti-TNFα use (133) and an arrow pointing from psoriasis to MS onset (a backdoor path or an undirected path) (134). Thus, for anti-TNFα use and MS onset, psoriasis is a common cause variable. The presence of a common cause variable can demonstrate a biased association, making it seem like anti-TNFα use is associated with MS onset (135). When researchers are interested in a causal association between anti-TNFα and MS risk, the backdoor path (i.e., the association due to the common cause variable or confounders) should be blocked (91,136), indicated by placing a square box around the common cause variable (137) - psoriasis in the cDAG (**Figure 2.1 a**).

Figure 2.1 Example of a confounder, a mediator and a collider.



a. Example of a confounder. The dotted arrow from anti-TNFα to MS onset shows that this is the causal question under investigation. The causal effect of anti-TNFα on MS onset can be confounded by psoriasis, making psoriasis a confounder. When researchers are interested in the causal effect of anti-TNFα on MS, the association due to the confounder needs to be adjusted for, indicated by placing a square box around the common cause variable - psoriasis in the causal directed acyclic graph. **b.** Example of a mediator. The variable MS onset acts as a mediator because it mediates, at least partially, the effect of smoking on MS progression. The causal effect of smoking on MS progression is biased if the mediator is adjusted for. **c.** Example of a collider. Physician visits act as a collider as it is the common effect of psoriasis and Epstein-Barr virus infections. The effect of anti-TNFα on the risk of MS onset is biased if the data are restricted to those who have visited physicians.

MS=multiple sclerosis; TNF=tumor necrosis factor

2.2.2 Mediators

Mediators are variables that lie along the causal pathway between the exposure and the outcome (138). Suppose we are interested in the total effect of smoking on MS progression. Studies have shown that smoking can increase the risk of developing MS (i.e., MS onset) and smoking is associated with more severe disease and rapid disease progression (139). In the cDAG, there is an arrow pointing from smoking to MS onset and an arrow pointing from MS onset to MS progression (**Figure 2.1 b**). The variable-MS onset acts as a mediator because it mediates, at least partially, the effect of smoking on MS progression. The total effect is decomposed into the natural direct effect (i.e., the effect of smoking on MS progression not through MS onset) and the natural indirect effect (i.e., the effect of MS onset on the association between smoking and MS progression) (95). When the aim is to examine the total effect of smoking on MS progression, one should never restrict the study sample to patients with incident MS as this approach blocks the indirect effect and leads to an underestimation of the total effect of smoking on MS progression. In this case, the bias of adjusting for a mediator is referred to as over-adjustment bias (130,140). When the objective is to examine the direct effect of smoking on MS progression, a mediation analysis is needed to answer this research question (141). One advantage of cDAGs is that they can demonstrate the temporal relationship of variables with respect to their role (e.g., a confounder or a mediator) (142). For example, sometimes a variable can be a mediator if measured after the exposure but a confounder if it is measured before the exposure, in which case, unlike a mediator, it must be adjusted (142).

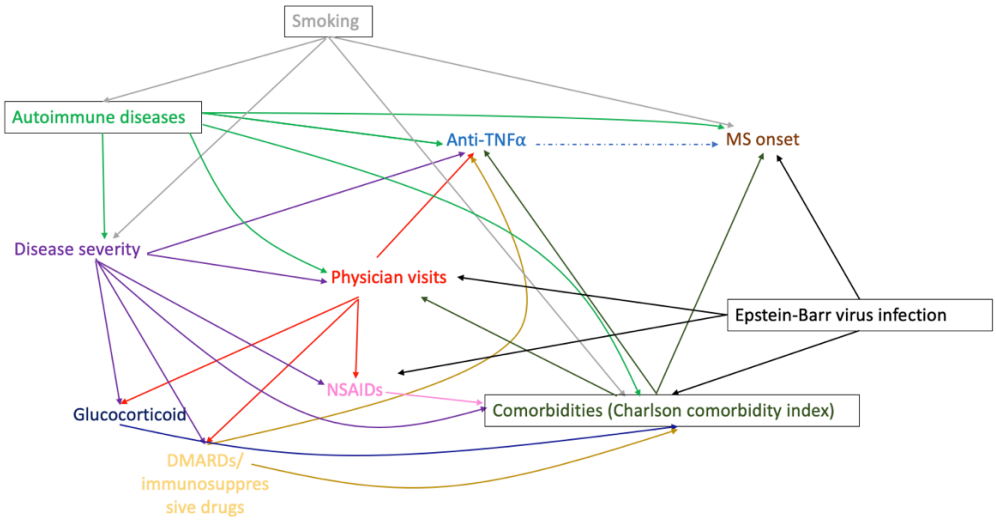
2.2.3 Collider-Stratification Bias (Selection Bias)

A collider is defined as a variable that is a common effect of two other variables (130). Consider researchers wanting to examine the risk of MS onset subsequent to use of anti-TNFα (**Figure 2.1 c**). There are two causal paths from anti-TNFα to MS onset, a direct path and an undirected path or backdoor path. In the undirected or backdoor path, two arrows originate from psoriasis and go to anti-TNFα use and physician visits (the number of physician visits per year), as psoriasis causes both outcomes. Similarly, two arrows originate from Epstein-Barr virus infection and go to MS onset (54) and physician visits. The effect of psoriasis and Epstein-Barr virus infection collide on physician visits, making physician visits a collider. The presence of the collider initially blocks the backdoor path from anti-TNFα to MS onset and means that the blocked backdoor path is not a biasing path (143). However, when a collider is conditioned, collider-stratification bias occurs (144). Suppose researchers want to examine the causal association between anti-TNFα and MS onset, and the data are restricted to those who had physician visits (**Figure 2.1 c**). Conditioning on physician visits makes anti-TNFα and MS associated with each other because a backdoor path previously blocked by the collider is now open from anti-TNFα to MS onset (144). The collider-stratification bias is also known as selection bias in epidemiology (145).

2.3 A Case Study on the Causal Effect of Anti-Tumor Necrosis Factor Alpha Use on the Risk of Developing Multiple Sclerosis

We now illustrate a case study on the causal effect of anti-TNFα use as a trigger of MS onset among patients with autoimmune diseases and show how a cDAG can help us identify potential biases (126). The cDAG for the total effect of anti-TNFα use on MS risk is shown in **Figure 2.2**. To avoid adjusting for mediators, we assume all covariates are measured before the anti-TNFα use.

Figure 2.2 Causal directed acyclic graph for the study examining the risk of multiple sclerosis with use of anti-tumor necrosis factor alpha.



The dotted straight arrow indicates the causal relation under investigation; solid arrows indicate known causal relations. To avoid adjusting for mediator variables, we assume all covariates are measured before the start of exposure. TNFα=tumor necrosis factor alpha; MS=multiple sclerosis; DMARDs= disease-modifying anti-rheumatic drugs; NSAIDs=non-steroid anti-inflammatory drugs

A box has been placed around autoimmune diseases to indicate that the cohort was restricted to patients with autoimmune diseases. Several studies have shown that the risk of MS might be higher in patients with autoimmune diseases, including psoriasis and IBD (134,146,147), so we added the arrow between autoimmune diseases and MS onset. All causes shared by anti-TNFα and MS must be included in a cDAG; we have therefore added the variable comorbidities that the commonly used Charlson Comorbidity Index (CCI) could represent (148). Modification of disease severity is a cause of anti-TNFα use. Disease severity can further influence the risk of comorbidities (149,150). Moreover, disease severity is also a cause for an increased number of physician visits. More frequent physician visits can lead to more intensive use of glucocorticoids, DMARDs/immunosuppressive drugs, NSAIDs, and anti-TNFα. Using glucocorticoids, DMARDs/immunosuppressive drugs, and NSAIDs can further increase the risk of comorbidities (151–154). Smoking is associated with both autoimmune diseases and MS risk and can further cause more severe disease and an increased risk of comorbidities (155,156). Epstein-Barr virus infection can cause the onset of MS (157), an increased number of physician visits, more intensive use of NSAIDs, and can influence the risk of comorbidities (158) (**Figure 2.2**).

The fundamental goal of the cDAG is to adjust or block all the biasing paths and keep open the causal path between anti-TNFα and risk of MS onset, but not to condition on colliders or mediators (159) (**Table 2.1**). Age and sex should be adjusted because they are classic confounders. However, to keep the cDAG simple, these two variables are not shown in **Figure 2.2**. Comorbidities and Epstein-Barr virus infection are common cause variables and need to be adjusted. By adjusting for comorbidities, the open backdoor paths such as *anti-TNFα←physician visits←comorbidities→MS onset* can be eliminated. However, comorbidities are also a collider,

as smoking and DMARDs/immunosuppressive drugs collide on comorbidities. Conditioning on comorbidities would make smoking and DMARDs/immunosuppressive drugs associated with each other. Thus, some undirected biasing paths are now open. For example: *anti-TNFα*← *physician visits*→ *DMARDs/immunosuppressive drugs*→*comorbidities*←*smoking*→*MS onset*. All these backdoor paths are created because of the variable smoking. Therefore, one needs to adjust for smoking to block both existing and new backdoor paths caused by conditioning on a collider. For other variables, such as disease severity, physician visits, use of DMARDs/immunosuppressive drugs, glucocorticoids, and NSAIDs, no biasing paths were created without adjusting for these variables. In addition, these variables are also colliders; adjusting for them would cause extra backdoor paths to open (**Table 2.1**).

Table 2.1 Description of pertinent covariates in the study of anti-tumor necrosis factor alpha use and multiple sclerosis risk, the type of variables in the causal directed acyclic graph structure, and the need for adjustment

Variables	**Type of variables**	**Adjustment, Yes/No**
Smoking	A potential confounder that will create biasing paths	Yes
Comorbidities	A potential confounder that will create biasing paths	Yes
Autoimmune diseases	A potential confounder that will create biasing paths	Yes
Epstein-Barr virus infection	A potential confounder that will create biasing paths	Yes
Physician visits	A confounder, also a collider. No biasing paths were created without adjusting for it.	No
Glucocorticoids	A confounder, also a collider. No biasing paths were created without adjusting for it.	No
NSAIDs	A confounder, also a collider. No biasing paths were created without adjusting for it.	No
DMARDs	A confounder, also a collider. No biasing paths were created without adjusting for it.	No
Disease severity	A confounder, also a collider. No biasing paths were created without adjusting for it.	No

NSAIDs=non-steroid anti-inflammatory drugs; DMARDs= disease-modifying anti-rheumatic drugs.

While the cDAG might incorporate some elements of a mechanistic understanding (for example, by including variables that are known to be causally related based on prior knowledge), it is primarily a statistical tool that is used to guide the analysis and interpretation of data. The relationships represented in the cDAG are typically estimated and tested using statistical methods, which forms the core of the biostatistical approach.

To summarize, for estimating the total effect of anti-TNFα use on the risk of developing MS among patients with autoimmune diseases, other than age and sex, the minimal sufficient adjustment set contains smoking, comorbidities, and Epstein-Barr virus infection (**Table 2.1**).

2.4 Potential Biases in Previous Studies of Multiple Sclerosis risk Among Users of Anti-Tumor Necrosis Factor Alpha

2.4.1 Confounding

Confounding is one of the most prevalent types of bias affecting previous observational studies' validity (160). An NCC study (84) that used the medical records of patients treated at one of three Mayo Clinics, USA (2003-2019) found an OR of 3.09 (95% CI: 1.19-8.04) for the association between anti-TNFα use and incident inflammatory demyelinating events. Cases were matched with controls on sex, year of birth, and autoimmune disease type. They also adjusted for disease duration in the conditional logistic regression model. However, confounding might have been present. Specifically, smoking was not adjusted for or considered in analyses. A cohort study (81) using the nationwide clinical rheumatology registers in Sweden and Denmark (2000-2017) suggested no significantly increased risk of MS in anti-TNFα users compared with non-

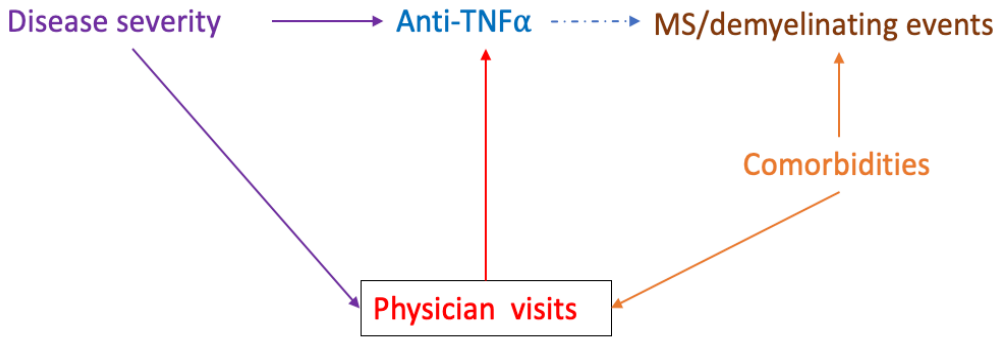
users among patients with RD with RR=0.44 (95% CI: 0.18-1.05) in Sweden and RR=1.02 (95% CI: 0.23-4.46) in Denmark. Their multivariable regression model adjusted only for age, sex, and calendar time. In addition to the lack of power, it is possible that residual confounding bias existed. A more recent study that used data from the British Society for Rheumatology Biologics Register in Rheumatoid Arthritis found an age- and sex-corrected SIR of 1.38 (95% CI: 0.96-1.92) for the association between the use of anti-TNFα and incident demyelinating events without further adjustment when compared with the general UK population (85). To identify potential bias due to confounding, in addition to adjusting for known confounders based on the cDAG, an E-value can be calculated as a sensitivity analysis that permits calculation of the magnitude of an unmeasured confounder that could explain away the specific exposure-outcome association (161).

Although under-adjustment can usually cause residual confounding bias, unnecessary adjustment can also introduce a biased total effect estimation (140). An NCC study was conducted using a United States health claims database from 1995 to 2005 (83), involving a cohort of 104,958 patients diagnosed with rheumatoid arthritis. Patients entered the cohort upon their first prescription of a traditional DMARD or a biological agent and were followed until the occurrence of an incident demyelinating event, death, or the end of the study period, whichever came first. Cases with a demyelinating event and controls were matched on age, sex, and calendar time of cohort entry. Anti-TNFα use during the year before the demyelinating event was defined. The authors reported an adjusted RR of 1.31 (95% CI: 0.68-2.50) in individuals not at high risk for demyelinating events (83). In addition to matching variables, the conditional logistic regression model was further adjusted for the number of physician visits per year, the use of anakinra, methotrexate, leflunomide, antimalarial agents, other DMARDs, glucocorticoids,

NSAIDs, and selective cyclo-oxygenase inhibitors. Based on our cDAG in the previous section, some of the variables adjusted for are not confounders. For example, the number of physician visits per year is a collider. **Figure 2.3** shows part of the cDAG demonstrated in **Figure 2.2**; adjusting for the number of physician visits per year would open the biasing path: *anti-TNFα ←disease severity→physician visits←comorbidities→MS*. The unnecessary adjustment could further augment the bias when the event is rare.

These biases were identified based on the information available in the studies we reviewed without having access to the study protocols or actual data. Thus, we cannot state with certainty if these biases affected the results.

Figure 2.3 A partial causal directed acyclic graph in the study of anti-tumor necrosis factor alpha use and multiple sclerosis risk, physician visits are a collider



The dotted straight arrow indicates the causal relation under investigation; the solid arrows indicate known relations. TNFα=tumor necrosis factor alpha; MS=multiple sclerosis

2.4.2 Confounding by Contraindication

Confounding by contraindication is another form of confounding (162). It usually occurs in observational studies that examine a known adverse drug event. For example, taking glucocorticoids is contraindicated in people with a high risk of myocardial infarction (MI) because of the concern that there is an increased risk of cardiovascular diseases associated with glucocorticoids (154,163) . As such, clinicians may hesitate to prescribe glucocorticoids to patients with a high risk of MI, making it seem like glucocorticoids do not have an effect on MI when in fact it is potentially due to confounding by contraindication. Similarly, as an increasing number of case reports have been published on the risk of anti-TNFα use and new-onset MS over the past 20 years, anti-TNFα use is contraindicated for people with MS-like symptoms or with a family history of MS because of the concern that anti-TNFα can potentially worsen MS (162). Therefore, some clinicians might be withholding anti-TNFα therapy from patients at high risk of MS (164). An observational study attempting to quantify the association could be biased because the anti-TNFα user group would not usually include all patients with MS-like symptoms or with a family history of MS. Ignoring such confounding by contraindication would result in the non-user group appearing to have an artificially higher rate of MS, given the inclusion of patients with a higher risk in the non-user group (162). This bias is reflected in **Figure 2.4**, where the arrow from a family history of MS to anti-TNFα use suggests that patients' family history of MS could affect anti-TNFα use. One way to mitigate this bias is to look at the association between anti-TNFα and MS during the period when the adverse effect was not known. For example, since most case reports that indicated an increased MS risk associated with anti-TNFα were published

after the year 2006 (72), for observational studies, one could estimate the association before the year 2006 to reduce the bias.

Figure 2.4 Causal directed acyclic graph for confounding by contraindication in the anti-tumor necrosis factor alpha and multiple sclerosis study.

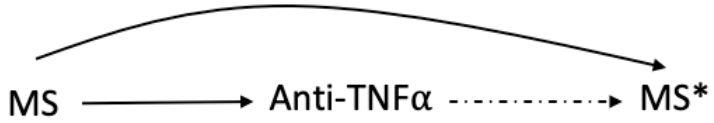
The dotted straight arrow indicates the causal relation under investigation. Same as the causal directed acyclic graph for confounding, family history of MS can affect the use of anti-TNFα, and creates a confounded association between anti-TNFα use and MS. TNF=tumor necrosis factor; MS=multiple sclerosis

2.4.3 Bias Due to Measurement Error

It is common to have measurement errors in studies using health administrative datasets with available and reliable diagnostic coding of disease, but limited information on actual symptom or disease onset (165). Sometimes diagnoses may happen years after early symptoms. Recent studies have shown that the prodromal phase of MS might present 5 or more years prior to the typical symptoms of demyelinating disease (66,166). As such, individuals with early MS symptoms who have not yet been formally diagnosed might be misclassified as not having the disease. Therefore, the association between anti-TNFα and MS diagnosis could be a biased estimate of the association between anti-TNFα and actual MS symptom onset.

The bias due to measurement error may be more profound if the onset of MS affects the use of anti-TNFα. Specifically, clinicians and patients might have decided to discontinue anti-TNFα or not use anti-TNFα, upon patients experiencing early MS symptoms. This bias is also called reverse causality bias or protopathic bias (167), which refers to a situation where early symptoms of the outcome can affect drug use. Like confounding by contraindication, the non-user group might include more persons with MS than would be normally expected, which would bias the effect of anti-TNFα towards the null for the risk of MS. Reverse causality bias or protopathic bias can also be represented by cDAGs (135). In **Figure 2.5**, MS* was used to represent the measurement of MS (i.e., MS diagnosis), as used in some studies using health administrative datasets, and MS was used to represent clinically recognized MS symptom onset (e.g., optic neuritis). Reverse causality bias is usually hard to avoid in studies using health administrative databases, although it can be mitigated by use of all relevant demyelinating disease-related codes to identify the earliest recorded sign of MS onset. One way to reduce the latency of MS diagnosis and to factor in the prodromal phase of MS, is to disregard the period (e.g., 5 years) prior to the date of MS diagnosis or MS onset (168).

Figure 2.5 Causal directed acyclic graph representing the reverse causality bias or protopathic bias in the anti-tumor necrosis factor alpha and multiple sclerosis study.



MS represents the disease onset, MS* represents the measured MS (i.e., MS diagnosis) from utilizing health administrative health databases. This bias is introduced when the onset of MS symptoms affects anti-TNFα use, before the actual diagnosis of MS. TNF=tumor necrosis factor; MS=multiple sclerosis

2.5 Conclusion

In this paper, we have discussed the principles of cDAGs and how cDAGs can allow researchers to visualize the different types of biases. We also discuss potential biases in the literature that might have affected the results of published studies related to the use of anti-TNFα and MS risk (81–86). The novelty of this review lies in its unique application of cDAGs to investigate the relationship between anti-TNFα use and MS, a valuable resource particularly for those in the research and clinical fields who are not well-acquainted with these methods. Additionally, by examining potential biases present in prior research on anti-TNFα and MS, this review not only illuminates past discrepancies but also provides vital guidance that can enhance the validity of future investigations in this area. Clinicians and researchers should be cognizant of these biases when reviewing future studies on this topic.

Chapter 3: RISK OF MULTIPLE SCLEROSIS AMONG USERS OF ANTITUMOR NECROSIS FACTOR ALPHA IN 4 CANADIAN PROVINCES

3.1 Introduction

MS is one of the world's most common neurologic disorders (169), affecting an estimated 2.8 million people worldwide in 2020 (58). Anti-TNFα agents are a class of biologic drugs used for the treatment of several chronic immune-mediated inflammatory diseases such as moderate to severe RD [rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis] and IBD. Although anti-TNFα agents are generally well-tolerated and have been shown to significantly improve patients' quality of life (51,170–172), an increased risk of MS has been suspected after their use (52,53,72,127,128).

One of the first studies that postulated an association with MS pathogenesis was a randomized controlled trial that was stopped early due to an increased MS exacerbation rate among lenercept-treated patients (88). Epidemiologic data suggesting anti-TNFα use may trigger new-onset MS are scarce and contradictory (81–85), mainly due to potential biases such as sparse data bias (82). A 2020 study found that the use of anti-TNFα was associated with an increased risk of overall inflammatory demyelinating events among RD or IBD patients receiving medical care at three Mayo Clinics, USA (84). However, MS was not studied specifically due to the study's small sample size. The use of data from a tertiary referral center also limits its generalizability to the general population.

With the increase in the incidence and prevalence of both RD and IBD worldwide (173–176), the number of anti-TNFα users is also expected to increase. A potential risk of MS among users of anti-TNFα, a drug class for which there might be other safer alternatives (e.g., emerging biologics), could further increase the burden of disease in patients already afflicted with a moderate to severe chronic disease. We aimed to quantify the risk of MS in anti-TNFα users with RD and IBD using population-based health administrative databases from four Canadian provinces.

3.2 Methods

3.2.1 Data Sources

This study was undertaken in four western Canadian provinces: BC, Alberta, Saskatchewan, and Manitoba, which collectively encompassed over 11 million people; nearly one-third of Canada's population. Each province captures nearly 100% of registered residents and their health-related information through comprehensive population-based linked databases. Personal identifiers are used to link records belonging to the same individual across files and over time. Canadian provinces administer publicly funded, universally available health care systems and maintain computerized records related to the provision of these services. These records capture all physician visits (111), hospitalizations (112), demographic data (113), and all outpatient or community dispensations of prescription medication (116). Numerous population-based studies have been successfully conducted using these data sources (120–122,149). An

overview of each province's databases is shown in the **Appendix A. Table 1**. Data for RD and IBD cohorts within each province are saved in different server and can only be analyzed in-house.

3.2.2 Study Design

We undertook two NCC studies for RD and IBD patients age≥18 years, separately, in each province between January 2000 and up until March 2018. The NCC has been deemed the ideal design for drug safety studies in large populations with long follow-ups as it mitigates some of the complexities that might arise when large cohorts are followed for a long period (177). Cohort studies require much larger sample sizes when the outcome is rare (177).

3.2.3 Cohort Definition

Due to data availability, RD cohorts were available in two provinces, BC and Manitoba; each province utilized its internally validated case definition that has been employed previously to identify persons with rheumatoid arthritis (International Classification of Diseases [ICD]-9 714.X) (121,149), ankylosing spondylitis (ICD-9 720.X; ICD-10 M45.X) (178), and psoriatic diseases (ICD-9 696.X; ICD-10 L40.X) (179). Case definitions for RD have a positive predictive value (PPV) of up to 82% (121,149) and are detailed in **Appendix A. Table 2**.

IBD cohorts were identified in the four provinces, selected within each province by internally validated case definitions, using ICD-9 555, 556; ICD-10 K50, K51 (see **Appendix A. Table 2** for details). Case definitions for IBD have a PPV of up to 97% (180,181).

The date after meeting the validated case definition of RD or IBD was defined as the ***cohort entry date***. After identifying the disease cohorts, patients with previous diagnostic codes for MS or any demyelinating events were excluded (the relevant codes are listed below under '*Case and Control Definition*'). Patients were followed from the cohort entry date to (i) death, (ii) MS onset, (iii) termination of health coverage, or (iv) last date of available data.

3.2.4 Case and Control Definition

Cases were identified separately for the RD and IBD cohorts in each province between 1 January 2000 and up to March 2018, and were ascertained using a previously validated and successfully applied algorithm using health administrative data (122). A MS case was defined as a subject who had at least three records related to MS from physician visits (ICD-9 340), hospitalizations (ICD-9 340 or ICD10 G35), or prescription claims specific for MS (**Appendix A Table 3**) in any combination using all available data. This algorithm has a PPV of 99.5% (122). The date of the first ICD-9/10 code for MS or the first code for a demyelinating event (optic neuritis [377.3/H46], acute transverse myelitis [323.82/G37], acute disseminated encephalomyelitis [323/G36.9], demyelinating disease of CNS unspecified [341.9/G37.8], acute disseminated demyelination [G36], or neuromyelitis optica [341.0/G36.0]) was deemed the ***index date*** (MS onset). To ensure MS cases were incident, we required all newly diagnosed MS individuals to have at least 5 years of prior registration in the databases (i.e., "run-in" period) before the index date. The case definition also required patients without having a diagnosis of MS or demyelinating event ever prior to the index date.

Controls were selected from the RD or IBD cohorts using a density-based sampling algorithm (177). First, a risk set of all RD or IBD patients with new onset MS (cases) and their corresponding controls was created. For each case, a pool of controls was identified as all individuals with RD or IBD who had no prior record of MS or a related demyelinating event or prescription filled for an MS drug (**Appendix A. Table 3)** at the index date. Since there is usually little marginal increase in precision from increasing the ratio of controls to cases beyond four (182), from the potential pool of controls, each MS case was matched to up to 5 controls based on the following criteria: (1) birth year±3 years; (2) the same RD or IBD disease duration, thereby controlling for the calendar time bias (183); (3) the same health authority based on each individual's place of residence to ensure that a specific geographic location does not differentially affect anti-TNFα prescribing between cases and controls. Controls were assigned the same index date as their matched case. The density-based sampling approach for control selection has been shown to generate an OR that closely approximates the incidence rate ratio (IRR) derived from a cohort study (177).

3.2.5 Exposure Assessment

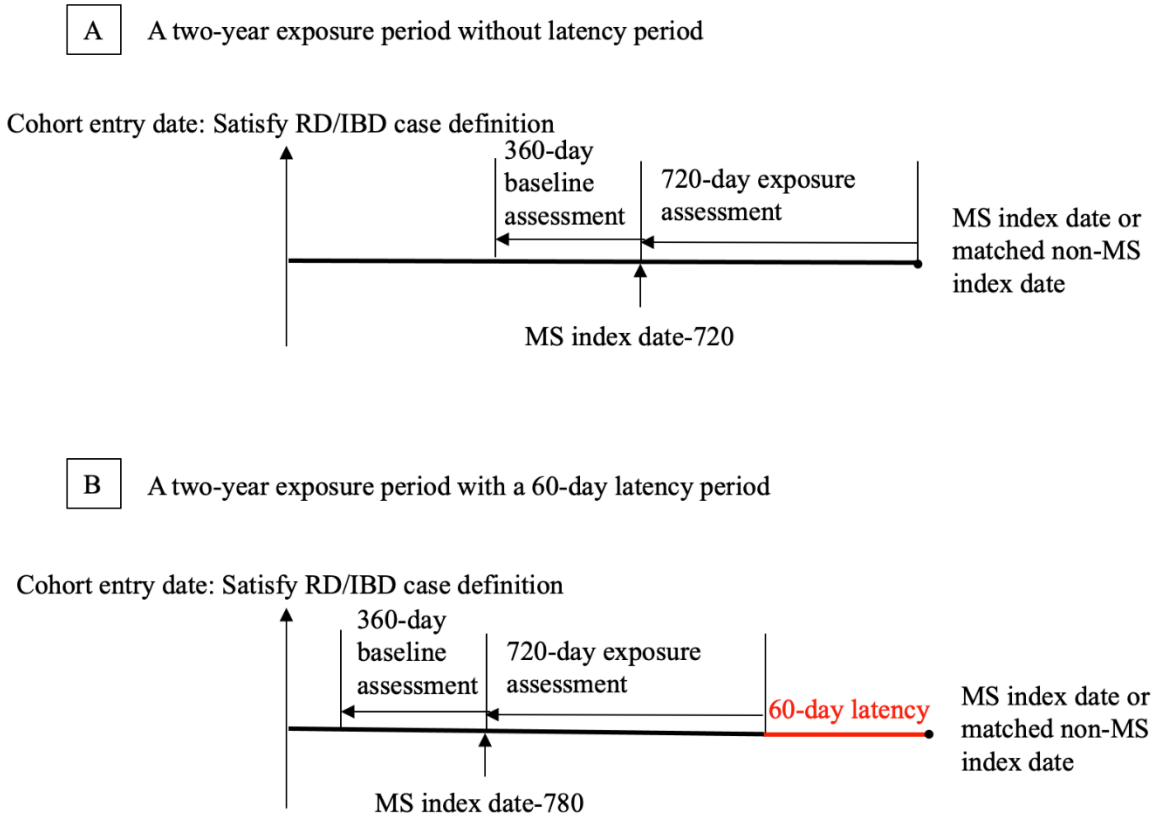
All anti-TNFα drugs approved by Health Canada for the treatment of RD or IBD and dispensed in two years prior to the index date (MS onset) were identified including, adalimumab, certolizumab, etanercept, infliximab, and golimumab (**Appendix A. Table 4)**. Since the risk of MS with anti-TNFα has been reported to occur across a variable time frame (between 2 to 24 months between the initiation of anti-TNFα and onset of MS) (72), we considered different risk periods in relation to anti-TNFα use. For the main analysis, a two-year exposure assessment

period of anti-TNFα use was examined. The use of two years of exposure assessment period may better capture the latency of MS onset. We also examined the risk of anti-TNFα use on MS during a one-year period as a sensitivity analysis since the majority of patients developed MS within one year or less after the therapy initiation (72). The use of anti-TNFα during the exposure assessment period was represented as a binary variable (exposed/unexposed). Specifically, users were defined as individuals with at least one prescription filled for an anti-TNFα agent during the exposure assessment period. The reference comparison group was patients who have not filled a prescription for an anti-TNFα agent in any of the risk periods.

3.2.6 Covariates

All baseline covariates were measured during 360 days preceding the two years exposure assessment period **(Figure 3.1)** to avoid overadjustment bias (i.e., adjusting for mediator variables) (94). In addition to matching variables, the following covariates were considered: sex, number of physician visits and hospitalizations, the CCI (148), and any dispensations for oral glucocorticoids, prescribed NSAIDs, DMARDs, or immunosuppressant drugs. cDAGs were used to select confounding variables for model adjustments (**Figure 2.2)**.

Figure 3.1 A schematic representation of the study design



After satisfying the case definition of RD or IBD, patients were followed until (i) death, (ii) MS onset, (iii) termination of health coverage, or (iv) last date of available data. Among cases and matched general population controls, all anti-TNFα drugs approved by Health Canada for the treatment of RD or IBD and dispensed in two years prior to the index date were identified (A). To account for the latency of MS, a 60-day latency period was applied where the exposure assessment period was pushed back by 60 days (B). Baseline covariates were measured during the 360 days preceding the two years exposure assessment period.

RD=rheumatic diseases; IBD= inflammatory bowel diseases; MS=multiple sclerosis; TNFα= tumor necrosis factor alpha

3.2.7 Statistical Analysis

Baseline covariates between MS patients and controls were compared using descriptive statistics. A conditional logistic regression model was used to obtain IRRs of MS among users and non-users of anti-TNFα. Based on the cDAGs (**Figure 2.2),** in addition to matching variables, sex and CCI were further adjusted. Interaction effect of sex was evaluated by adding an interaction term anti-TNFα*sex in the conditional logistic regression model.

Due to provincial data privacy mandates, we analyzed RD and IBD cohorts, separately, in each province. Then, a meta-analysis was conducted to obtain the pooled estimates across provinces using random-effects models. A test of heterogeneity using Cochrane's Q statistic was performed (184), which describes the percentage of total variation across effect sizes due to heterogeneity rather than chance. An alpha level of $P \leq 0.05$ was used to reject the null hypothesis that the IRRs were statistically the same across all provinces. We calculated the number of patients needed to be treated for one additional patient to be harmed (NNH) for case-control studies using the equation 1/[(OR-1) * unexposed event rate] (185).

3.2.8 Sensitivity Analyses

To further test the robustness of our results, besides the analysis on the risk of anti-TNFα use during a one-year period outlined earlier, two additional sensitivity analyses were performed. First, to account for possible reverse causality bias (which refers to a situation where early symptoms of the outcome could affect anti-TNFα use), a 60-day latency period was applied where the exposure assessment period was pushed back by 60 days **(Figure 3.1 B)**. Specifically,

the first 60 days prior to the index date were disregarded. Second, to estimate the effect of unmeasured confounders (e.g., smoking or Epstein-Barr virus infection), an E-value was calculated (161,186). Specifically, an estimation of the minimum strength of association was calculated, that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away a specific exposure-outcome association (161,186).

SAS V.9.4 was used. Meta-analyses were done with HEpiMA V.2.3.

3.2.9 Standard Protocol Approvals, Registrations, and Patient Consents

No personally identifying information was made available as part of this study. Procedures used were in compliance with BC's Freedom of Information and Privacy Protection Act. Ethics approval was obtained from the University of BC's Clinical Research Ethics Board (H15-00887), the University of Calgary's Conjoint Health Research Ethics Board (REB16-2375), the University of Saskatchewan Biomedical Research Ethics Board (Bio-REB 2298), and the University of Manitoba Health Research Ethics Board (HS24393), which granted a waiver of informed consent because data are deidentified.

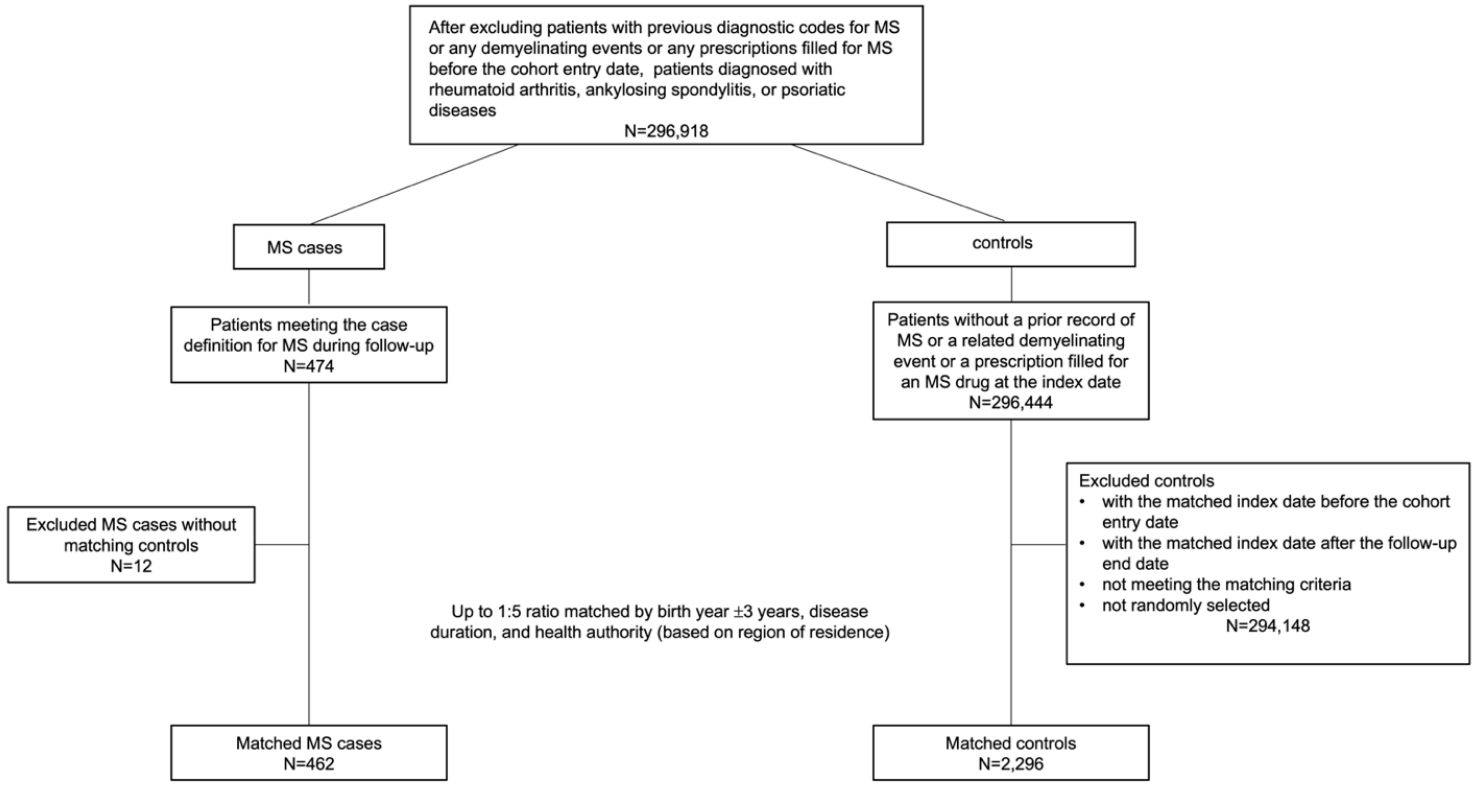
3.2.10 Data Availability Statement

Data for this study reside in limited-access secure research environments. The data cannot leave this secure research environment for legal and ethical reasons.

3.3 Results

After excluding individuals with MS or any demyelinating events before the cohort entry date, in total, we identified 296,918 RD patients in BC and Manitoba combined (**Figure 3.2**). During follow-up, a total of 462 patients developed MS (80.1% female, mean [standard deviation {SD}] age, 47.4 [14.6] years) and were matched with 2,296 controls with RD (59.5% female, mean [SD] age, 47.4 [14.5]). **Table 3.1** summarizes the baseline characteristics of the combined RD cohorts. Compared with controls, MS cases had a higher number of physician visits and hospitalizations, higher use of glucocorticoids, NSAIDs, and DMARDs, as well as higher CCI scores at baseline.

Figure 3.2 Nested case-control inclusion criteria for the rheumatic disease cohorts among the four Canadian provinces.



MS=multiple sclerosis

Table 3.1 Baseline characteristics of the multiple sclerosis cases and matched controls among persons with rheumatic diseases in British Columbia and Manitoba, Canada

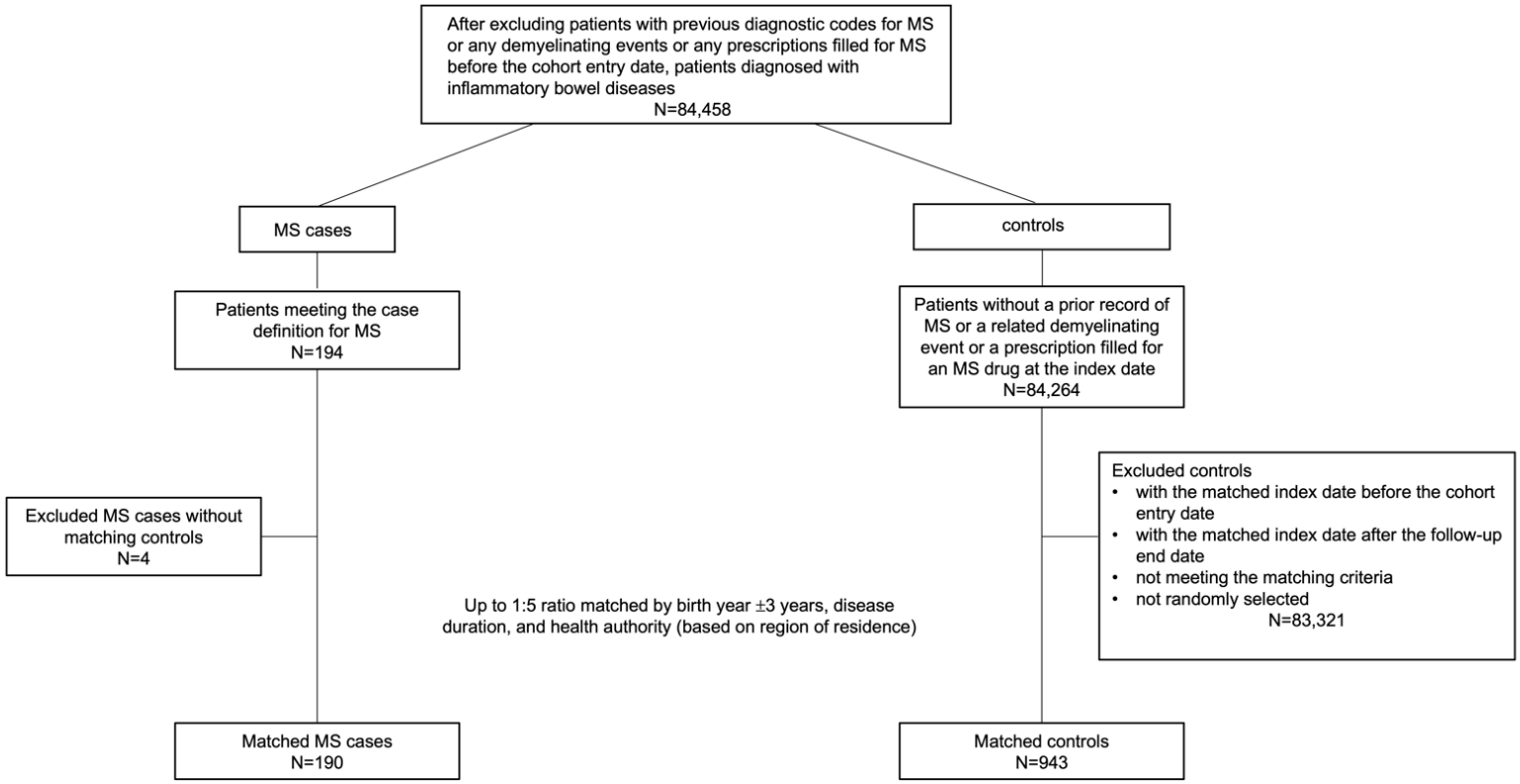
	RD cohorts	
	MS cases (N=462)	**Controls (N=2296)**
Variables[a]		
Age, mean (SD), y	47.39 (14.56)	47.43 (14.50)
Female, n (%)	370 (80.09)	1365 (59.45)
Number of hospitalizations, mean (SD)	0.32 (0.73)	0.22 (0.64)
Number of outpatient visits, mean (SD)	16.72 (17.68)	11.20 (13.22)
Charlson Comorbidity Index, mean (SD)	0.47 (0.97)	0.37 (0.88)
Follow-up duration, mean (SD), days	1986.05 (1495.79)	1981.67 (1498.65)
Glucocorticoid, n (%)	52 (11.26)	202 (8.80)
NSAIDs, n (%)	158 (34.20)	668 (29.09)
DMARDs, n (%)	68 (14.72)	279 (8.80)

RD=rheumatic diseases; MS=multiple sclerosis; NSAIDs=nonsteroidal anti-inflammatory drugs; DMARDs=disease-modifying antirheumatic drugs.

[a]All baseline covariates were measured during 360 days preceding the exposure assessment period.

Among the 84,458 IBD patients from the four provinces combined (**Figure 3.3**), 190 patients developed MS (69.5% female, mean [SD] age, 44.3 [12.3] years) during follow-up, and were matched with 943 controls with IBD (54.1% female, mean [SD] age, 44.2 [12.2]). **Table 3.2** summarizes the baseline characteristics of the IBD cohorts for the four provinces combined. Like the RD cohorts, MS cases had a higher number of physician visits and hospitalizations, higher use of glucocorticoids, and immunosuppressant drugs, as well as higher CCI scores when compared with controls, at baseline.

Figure 3.3 Nested case-control inclusion criteria for the inflammatory bowel diseases cohorts among the four Canadian provinces.



MS=multiple sclerosis

Table 3.2 Baseline characteristics for the multiple sclerosis cases and matched controls among persons with inflammatory bowel diseases in British Columbia, Alberta, Saskatchewan, and Manitoba, Canada

	IBD cohorts	
	MS cases (N=190)	**Controls (N=943)**
Variables[a]		
Age, mean (SD), y	44.30 (12.34)	44.22 (12.23)
Female, n (%)	132 (69.47%)	510 (54.08%)
Number of hospitalizations, mean (SD)	0.60 (1.16)	0.42 (0.99)
Number of outpatient visits, mean (SD)	16.82 (16.34)	12.21 (14.39)
Charlson Comorbidity Index, mean (SD)	0.43 (1.15)	0.32 (0.96)
Follow-up duration, mean (SD), days	1981.01 (1318.88)	1898.58 (1329.02)
Glucocorticoid, n (%)	36 (18.95%)	159 (16.86%)
NSAIDs, n (%)	63 (0.33%)	378 (0.40%)
Immunosuppressant drugs, n (%)	29 (15.26%)	123 (13.04%)

IBD=inflammatory bowel diseases; MS=multiple sclerosis; NSAIDs=nonsteroidal anti-inflammatory drugs.

[a]All baseline covariates were measured during 360 days preceding the exposure assessment period.

We computed the crude incidence rate of MS among incident users of anti-TNFα with respect to MS in each province for the RD and IBD patients separately, during the entire follow-up period. For RD, the crude incidence rate (95% CI) was 0.29 (0.16-0.48)/1,000 person-years for BC, and 0.15 (0.02-0.54)/1,000 person-years for Manitoba. For IBD, the crude incidence rate (95% CI) was 0.26 (0.09-0.61)/1,000 person-years for BC, 0.43 (0.25-0.68)/1,000 person-years for Alberta, 0.41 (0.11-1.05)/1,000 person-years for Saskatchewan, and 0.30 (0.04-1.08)/1,000 person-years for Manitoba.

In the RD cohorts, and across all provinces combined, 18 anti-TNFα users were observed among MS cases compared with 42 anti-TNFα users among controls in the two years prior to the index date (MS onset) (**Table 3.3**). After adjusting for sex and CCI, the corresponding fully adjusted IRR (95% CI) was 2.07 (1.12-3.80) for RD in BC and 1.69 (0.10-28.44) in Manitoba, resulting in a pooled matched IRR (95% CI) of 2.05 (1.13-3.72) for both RD cohorts combined (**Table 3.3** and **Figure 3.4**). The p-value of the interaction term (anti-TNFα*sex) was not statistically significant. The pooled 2-year fully adjusted NNH was 2,268 for RD, meaning that 2,268 patients needed to be treated for one additional patient to be harmed.

In the IBD cohorts, and across all four provinces, 23 anti-TNFα users were observed among MS cases compared with 98 anti-TNFα users among controls (**Table 3.3**). After adjusting for sex and CCI, the corresponding fully adjusted IRR (95% CI) was 2.30 (0.69-7.68) for IBD in BC, 1.57 (0.84-2.96) in Alberta, 0.37 (0.04-3.23) in Saskatchewan, and 0.40 (0.01-3.30) in Manitoba, resulting in a pooled fully adjusted IRR (95% CI) of 1.35 (0.70-2.59) (**Table 3.3** and **Figure 3.4**). The p-value of the interaction term (anti-TNFα*sex) was not statistically significant. Heterogeneity was not found between individual provinces with values of the Cochrane's Q statistic all larger than 0.05 among the RD and IBD cohorts across all provinces (**Figure 3.4**).

Table 3.3 Pooled associations between anti-tumor necrosis factor alpha and subsequent multiple sclerosis during the 2-year exposure assessment period in British Columbia, Alberta, Saskatchewan, and Manitoba, Canada

Category	MS cases	Controls
Pooled RD cohort[a]		
Total No. of MS cases	462	2296
Total No. of anti-TNFα users	18	42
Pooled crude incidence rate ratio (95% CI)	2.22 (1.24-3.96)	1.00 (ref)
Pooled adjusted incidence rate ratio (95% CI)[c]	2.05 (1.13-3.72)	1.00 (ref)
Pooled IBD cohort[b]		
Total No. of MS cases	190	943
Total No. of anti-TNFα users	23	98
Pooled crude incidence rate ratio (95% CI)	1.22 (0.61-2.41)	1.00 (ref)
Pooled adjusted incidence rate ratio (95% CI)[c]	1.35 (0.70-2.59)	1.00 (ref)

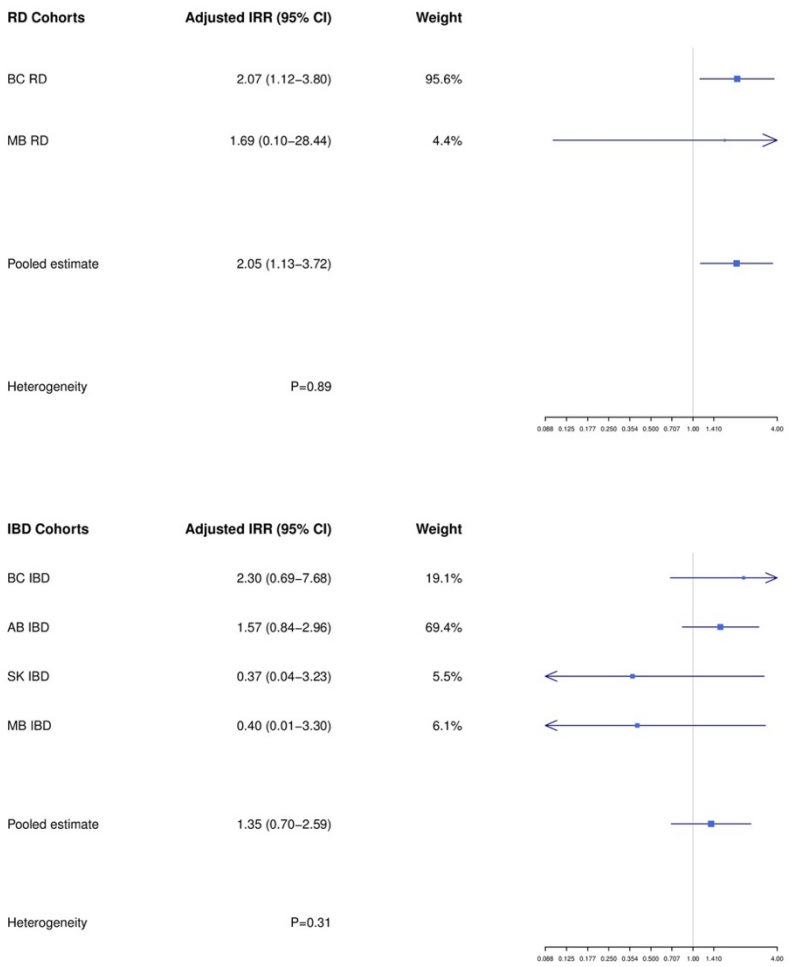
RD=rheumatic disease; IBD=inflammatory bowel diseases; MS=multiple sclerosis; TNFα=tumor necrosis factor alpha

[a]The RD cohort results were available in British Columbia and Manitoba

[b]The IBD cohort results were available in British Columbia, Alberta, Saskatchewan, and Manitoba

[c]In addition to matching variables (i.e., birth year±3 years, disease duration, and the health authority), the conditional logistic regression model was further adjusted for sex and the Charlson Comorbidity Index at baseline

Figure 3.4 The association between anti-tumor necrosis factor alpha and multiple sclerosis among four Canadian provinces



Adjusted IRR and pooled estimates for the association between anti-TNFα and MS in the RD and IBD cohorts, in BC, AB, SK, and MB, Canada

IRR=incidence rate ratio; TNFα= tumor necrosis factor alpha; MS=multiple sclerosis; RD=rheumatic diseases; IBD=inflammatory bowel diseases; BC=British Columbia; AB=Alberta; SK=Saskatchewan; MB=Manitoba

Similar results were found in the sensitivity analyses (**Table 3.4** and **Table 3.5**). Using the E-value metric, the observed IRR for RD would be explained away by an unmeasured confounder that was associated with both anti-TNFα and MS by a RR of at least 3.52-fold each, after adjusting for potential confounders.

Table 3.4 Pooled associations between anti-tumor necrosis factor alpha and subsequent multiple sclerosis during the 1-year exposure assessment period in British Columbia, Alberta, Saskatchewan, and Manitoba, Canada

Category	MS cases	Controls
Pooled RD cohort[a]		
Total No. of MS cases	462	2296
Total No. of anti-TNFα users	18	38
Pooled crude incidence rate ratio (95% CI)	2.43 (1.35-4.37)	1.00 (ref)
Pooled adjusted incidence rate ratio (95% CI)[c]	2.24 (1.22-4.11)	1.00 (ref)
Pooled IBD cohort[b]		
Total No. of MS cases	190	943
Total No. of anti-TNFα users	20	90
Pooled crude incidence rate ratio (95% CI)	1.19 (0.63-2.27)	1.00 (ref)
Pooled adjusted incidence rate ratio (95% CI)[c]	1.29 (0.70-2.36)	1.00 (ref)

Abbreviations: RD, rheumatic disease; IBD, inflammatory bowel diseases; MS, multiple sclerosis; TNFα, tumor necrosis factor alpha

[a]The RD cohort results were available in British Columbia and Manitoba

[b]The IBD cohort results were available in British Columbia, Alberta, Saskatchewan, and Manitoba

[c]In addition to matching variables (i.e., birth year±3 years, disease duration, and the health authority), the conditional logistic regression model was further adjusted for sex and Charlson Comorbidity Index

Table 3.5 Pooled associations between anti-tumor necrosis factor alpha and subsequent multiple sclerosis after applied a 60-day latency period on the 2-year exposure assessment period in British Columbia, Alberta, Saskatchewan, and Manitoba, Canada

Category	MS cases	Controls
Pooled RD cohort[a]		
Total No. of MS cases	462	2296
Total No. of anti-TNFα users	18	42
Pooled crude incidence rate ratio (95% CI)	2.25 (1.25-4.03)	1.00 (ref)
Pooled adjusted incidence rate ratio (95% CI)[c]	2.16 (1.18-3.94)	1.00 (ref)
Pooled IBD cohort[b]		
Total No. of MS cases	190	943
Total No. of anti-TNFα users	23	93
Pooled crude incidence rate ratio (95% CI)	1.35 (0.81-2.25)	1.00 (ref)
Pooled adjusted incidence rate ratio (95% CI)[c]	1.51 (0.89-2.56)	1.00 (ref)

Abbreviations: RD, rheumatic disease; IBD, inflammatory bowel diseases; MS, multiple sclerosis; TNFα, tumor necrosis factor alpha

[a]The RD cohort results were available in British Columbia and Manitoba

[b]The IBD cohort results were available in British Columbia, Alberta, Saskatchewan, and Manitoba

[c]In addition to matching variables (i.e., birth year±3 years, disease duration, and the health authority), the conditional logistic regression model was further adjusted for sex and Charlson Comorbidity Index

3.4 Discussion

In this multi-provincial Canadian population-based study, we found the use of anti-TNFα was associated with an increased risk of MS compared to non-users for RD. The finding of an increased MS risk could help clinicians and RD patients when considering use of anti-TNFα to make more informed treatment decisions. We also found an increased risk of MS among IBD patients but given the observational nature of the study and the wide CIs, further studies are needed to validate these results.

Previous studies linking anti-TNFα use to MS risk have been somewhat mixed. For example, in a double-blind, placebo-controlled trial, the drug lenercept was administrated to 168 patients with clinically definite or laboratory supported definite MS. After 24 weeks, lenercept users reported more MS-related exacerbations than the placebo group (p=0.007), resulting in the manufacturer's decision to terminate the study early (88). An NCC study that used medical records of RD or IBD patients treated at one of three Mayo Clinics in the USA (2003-2019) (84) found that the odds of inflammatory demyelinating events were three times higher among anti-TNFα users when compared with non-users among chronic immune-mediated diseases. The authors did not specifically examine the association between anti-TNFα and MS, but instead looked at all types of inflammatory demyelinating events, and combined RD and IBD, due to the relatively small number of individuals included (N=212). Further, since the Mayo Clinic is a tertiary referral clinic center and only includes insured patients, the study may be subject to referral bias which may also reduce the generalizability of findings. In the same year, others suggested no significantly increased risk of MS in users of anti-TNFα compared with non-users among RD patients (RR=1.02, 95% CI, 0.23-4.46) in a cohort study using the nationwide clinical

rheumatology registers in Sweden and Denmark (2000-2017) (81). However, only six MS cases were identified among anti-TNFα users in Sweden and four in Denmark, resulting in rather wide CIs. The heterogeneity from previous studies can make the results challenging for clinicians and patients to interpret. Thus, our large, population-based, multi-province study, which used a common protocol to combine regions contributes substantially to the understanding of MS risk in persons using anti-TNFα.

The mechanism for anti-TNFα potentially causing MS in persons with RD (and possibly IBD) is not fully understood. Current hypothesized mechanisms involve (72) (1) the increased demyelination through increased ingress of peripheral autoreactive T-cells into the CNS related to anti-TNFα; (2) the aggravation effect of anti-TNFα on CNS demyelination by decreasing TNFR2 which is important for the myelin repair; (3) anti-TNFα can also downregulate IL-10 and upregulate IL-12 and interferon- γ, which can demonstrate a profile like MS; (4) anti-TNFα may not deactivate TNFα in the CNS, facilitating a relatively high concentration of TNFα; (5) MS patients may demonstrate increased serum neutralization capacity of TNFα; and (6) anti-TNFα may also increase the risk of an underlying latent infection, which could lead to demyelination.

The strengths of the study were the use of large Canadian administrative datasets that included the entire RD and IBD cohorts from up to four provinces, limiting selection bias and maximizing the generalizability of findings. Selecting confounding variables based on cDAGs enabled our study to be less prone to confounding by indication. Moreover, we used a highly accurate case definition for MS. Finally, implementation of a MS latency period in the analysis may help to control for reverse causality bias.

The limitations deserve comment. The main contribution to these results was from BC and Alberta. Data from the provinces of Saskatchewan and Manitoba had lower weights mainly

due to smaller sample sizes, hence relatively lower precision **(Figure 3.4)**. The association between anti-TNFα and MS risk was not consistent in the IBD cohort, possibly due to the smaller cohort size or different disease states. As with all pharmacoepidemiologic studies using health administrative databases, we only have information on dispensation of prescription drugs and not their actual intake. However, since anti-TNFα agents are administered intravenously or subcutaneously and require special approvals for government-funded access, misclassification of anti-TNFα use is highly unlikely. We did not have information on lifestyle-related factors such as smoking. However, through our sensitivity analysis using the E-value, the observed IRR for RD would be hard to explain away. Health administrative databases capture information on diagnosis, but not necessarily on MS symptoms (which could indicate early disease onset). A previous study has shown that the prodromal phase to MS might present 5 or more years prior to the typical symptoms of demyelinating disease (66). As such, subjects exhibiting early MS symptoms or MS prodrome who have not yet been diagnosed might be misclassified as controls. However, this type of misclassification which is nondifferential usually leads to an underestimation of the risk of MS with the use of anti-TNFα. It is also possible that our results may be subject to ascertainment bias. Specifically, there might be more screening and surveillance of demyelination among users of anti-TNFα compared with non-users. However, because of the concern that anti-TNFα use might lead to MS, clinicians might be withholding anti-TNFα to patients with symptoms that might resemble MS or those with family history of MS. Thus, confounding by contraindication might also mean that our estimates are conservative, and our results are potentially an underestimation of the true risk.

3.5 Conclusion

In conclusion, this is the largest population-based study to date utilizing health administrative datasets from four Canadian provinces to demonstrate that the use of anti-TNFα was associated with an increased risk of incident MS among patients with RD when compared with non-users. The finding of the increased MS risk could help clinicians and patients with RD who require anti-TNFα to make better informed decisions regarding treatment. Specifically, clinicians and patients can weigh the risk-quality of life trade-offs between using an anti-TNFα drug or choosing other available alternative medications that are comparable in efficacy, but have not been associated with MS (187,188).

Chapter 4: ASSESSING ANALYTICAL METHODS FOR ADDRESSING SPARSE DATA BIAS: A CASE STUDY IN PHARMACOEPIDEMIOLOGY UTILIZING CONDITIONAL LOGISTIC REGRESSION

4.1 Introduction

Sparse data bias is a unique type of bias that has traditionally received less attention than other classical forms of bias in epidemiologic research including confounding, selection bias, and measurement error. Sparse data bias can arise when calculating the ML estimates of ratio with low case counts for different exposure, covariate, or outcome levels, resulting in effect estimates that tend to deviate from the null, hence the term "sparse data bias" (96). The implications of this bias in pharmacoepidemiologic research can be significant, as overestimation of adverse effects linked to widely used medications can lead to serious clinical and public health consequences. For example, an inflated estimation of a particular drug's adverse events could discourage patients from adhering to a possibly effective medication, leading to potentially harmful health outcomes.

To date, pharmacoepidemiologic studies addressing sparse data bias are scant. Specifically, there is a paucity of studies that have examined sparse data bias in matched case-control studies. Although conditional logistic regression that is used in matched case-control studies was originally designed to mitigate the sparse data bias in logistic regression analysis (97), it still necessitates large sample sizes to be able to achieve this purpose. Moreover, conditional logistic models can still show significant bias if the ratio of events per variable

(computed by dividing the number of events by the number of covariates) is excessively low (96).

As an example of a sparse data issue, members of our team recently published an NCC study investigating the association between anti- TNFα and the risk of MS (126). This study reported an adjusted RR of 0.40 (95% CI 0.01-3.30) in a stratified analysis for the association between anti-TNFα and MS. To tackle the issue of sparse data, we will use data from this study as an example to illustrate how several methods can be used to handle sparse data bias and evaluate their performance relative to one another.

Several methods have been proposed to address sparse data bias, including: (1) Firth bias adjustment (98); (2) penalization via the approximate Bayesian method-data augmentation (99); (3) MCMC Bayesian analyses (100); (4) LASSO regression (101); (5) Ridge regression (102). It has been demonstrated that Bayesian methods and their equivalent approaches offer significant benefits over conventional frequentist methods (105). Moreover, data augmentation involves a similar number of steps and produces comparable results to MCMC Bayesian analyses while running faster (105). However, no studies have compared the performance of these methods in the context of a pharmacoepidemiologic study.

The objectives of this study are: (1) to compare the estimation results on the risk of MS associated with the use of anti-TNFα using a real-life data in a sparse data setting with conditional logistic regression after applying methods such as Firth bias adjustment, data augmentation, MCMC Bayesian analyses, LASSO regression, and Ridge regression; and (2) to evaluate the performance of these sparse data bias adjustment approaches through simulation studies.

4.2 Methods

4.2.1 Data Source and Cohort Definition

We utilized a real-world dataset to compare results from different methods, and our simulation data was also designed to emulate the large population-based health database from the province of BC, Canada (126). Population Data BC provides researchers with access to data on all provincially funded health care services since 1990, reflecting the universal health care coverage available to all residents in the province (population ~ 4.7 million). This includes data on all healthcare professional visits (111), hospitalizations (112), demographic data (113), BC cancer registry (114), and vital statistics (115). Furthermore, Population Data BC facilitated linkage with the comprehensive prescription drug database PharmaNet (116), which captures all outpatient and community dispensed medications for all residents since 1996. Numerous population-based studies have been successfully conducted using health administrative data in BC (118,119,126).

To examine the risk of anti-TNFα use with MS, we undertook an NCC study. We initially created a cohort of patients with IBD residing in BC between January 2000 and December 2006, identified using validated case definitions. Any anti-TNFα dispensation in the two years prior to the index date (MS onset) was identified. Incident-onset MS cases were ascertained using a validated algorithm. Up to five controls were matched to each MS case based on birth year ±3 years, disease duration, and health authority (based on region of residence). We call this cohort the anti-TNFα and MS cohort. A detailed description of the data and study design can be found

in Chapter 3 (126). In addition to matching variables, confounding variables for the association between anti-TNFα and MS included sex and the CCI (148).

4.2.2 Description of the Methods

4.2.2.1 Firth Bias Adjustment

Firth bias adjustment is a statistical correction method used to mitigate the bias in ML estimates, especially in situations where sample sizes are small or data is sparse; It achieves the bias adjustment by incorporating a penalty term into the likelihood function (103), particularly for exponential family models (98). This penalty term can be viewed as an analogue to the Jeffreys prior, which is a non-informative prior that ensures the posterior distribution is proper even in the case of small sample sizes, thus avoiding infinite estimates (98). Firth can be applied to a variety of models beyond logistic regression, including generalized linear models and Cox regression models (189). The relationship between the partial likelihood in Cox regression and conditional likelihood for matched case-control studies suggests that the same type of penalization used in Firth's method may also be applicable to conditional logistic regression models (103). It has been shown that the profile likelihood CI is statistically more robust than the Wald CI when dealing with sparse data (190).

4.2.2.2 Approximate Bayesian Method-Data Augmentation

Most statistical analyses adopt a frequentist approach. In this approach, the likelihood of observing the given data is computed for various parameter values. We then use this likelihood to make decisions about the model parameters, typically selecting the parameters that maximize this likelihood. In contrast, Bayesian methods combine what we previously believed about the model parameters (*prior* probabilities) with the current data. From this combination, we get updated probabilities called '*posterior* probabilities' for those parameters (105). By selecting appropriate prior distributions from the literature, Bayesian techniques can surpass traditional frequentist methods in terms of mean squared error (MSE) of estimates, particularly in situations where the data are sparse (105). Data augmentation is an approximate Bayesian analysis method that involves artificially increasing the size of a dataset by creating augmentations of existing data, enhancing its diversity and potentially improving model training and accuracy. The process of data augmentation commences with the conversion of prior distributions into prior-data records. By incorporating these records, we can employ traditional analysis techniques on an enriched dataset, allowing for more robust and comprehensive results. Data augmentation produces results that are comparable to those obtained from analyses based on posterior sampling (99), but runs much faster than simulation methods such as MCMC which we will introduce below.

In order to construct the prior data, we need to begin by specifying an interval to ensure the true effect is not huge (96). For example, based on previous studies (84,86,87,126), the pooled RR or ORs for anti-TNFα and MS was 1.92 (95% CI 1.34-2.75) among patients with IBD. To ensure that the prior intervals encompass the full range of reasonable possibilities for

the effect of for anti-TNFα (105) , we choose a normal distribution prior with a 95% CI of 0.5 and 8. This led to a prior centre of β_{prior} of $\ln(OR_{prior})=[\ln(0.5)+\ln(8)]/2=\ln(2)$ and a variance of $\nu_{prior}=\{[\ln(8)-\ln(0.5)]/(2*1.96)\}^2=0.5$. We also need to set additional variables in the prior data. The explanation and values for those additional variables have been listed in the **Appendix B. Table 1**.

After setting the prior data, a Cox proportional-hazard regression model was used to get the posterior estimates for the conditional logistic regression model, along with the profile likelihood intervals (105).

4.2.2.3 Markov Chain Monte Carlo Bayesian Analyses

MCMC is a computer-driven sampling method that characterizes a distribution by randomly drawing values from it, without the need to know all of its mathematical properties (107). The term MCMC combines two concepts: Monte Carlo and Markov Chain (107).

Monte Carlo simulation refers to the estimation of distribution properties by examining random samples. For instance, to find the mean of a normal distribution, instead of deriving it directly from the distribution's equations, the Monte Carlo approach would involve obtaining a large number of random draws from the distribution and computing the sample mean of those draws. This method is particularly beneficial when generating random samples is straightforward; it simplifies the computational process by circumventing the direct evaluation of complex underlying equations, thus reducing computational time and resource demands (107). Markov Chain pertains to the unique sequential process employed to generate these random draws. Each random draw serves as a steppingstone for generating the next draw, such that each

new draw depends on the one preceding it, without relying on any draws further back in the sequence (107).

MCMC has been proven to be a valuable tool in Bayesian inference (100), especially when dealing with complex posterior distributions that are challenging to analyze directly. With MCMC, one can estimate various aspects of the posterior distribution that cannot be evaluated analytically. Bayesian inference leverages observed data to update prior beliefs about one or more parameters, leading to a new set of posterior beliefs about those same parameters (107). Like the data augmentation approach, MCMC requires extra labour beyond standard programming. To be comparable with the data augmentation demonstrated above, a normal distribution prior of the anti-TNFα regressor with mean of ln(2) and variance of 0.5 was chosen. As the data augmentation approach, after setting the prior distribution, the Cox proportional-hazard regression model was used to get the posterior estimates as well as the profile likelihood intervals for the conditional logistic regression.

To assess the robustness of our results, we performed a sensitivity analysis to evaluate the results of data augmentation and MCMC methods after applying a wider and weaker normal distribution prior with a 95% CI of 0.1 and 16. This 95 % CI leads to a prior mean of ln(1.265) and a variance of 1.675.

4.2.2.4 Least Absolute Shrinkage and Selection Operator

The LASSO method adjusts the linear regression model by introducing a penalty for the size of the coefficients. This ensures that coefficients don't become too large and potentially overfit the data (109). LASSO regression is also known as L1 regularization. In conditional

logistic regression, the LASSO method involves maximizing the conditional log-likelihood function penalized by the L1- norm of the unknown coefficient vector, or equivalently, minimizing the negative objective function (191). This penalty term helps to shrink the coefficients of the variables that are not important or relevant to the outcome down to zero, effectively eliminating them from the model (101). By shrinking the coefficients of the irrelevant variables to zero, LASSO can help to identify the variables that are most important for predicting the outcome. LASSO mitigates the impact of sparse data bias by shrinking the effect estimates. In the effect size model, there's a possibility that the coefficient of our main exposure will shrink to zero when using LASSO regression. Therefore, LASSO is more commonly used when the primary goal is prediction.

4.2.2.5 Ridge Regression Models

In contrast, Ridge regression which is also referred to as L2 regularization adds a penalty term proportional to the square of the coefficients (101). This has the effect of shrinking the coefficients of less important variables towards zero, but they are still retained in the model with smaller weights (101). Like LASSO regression, the Ridge regression is also more commonly used when the research aim is prediction. The main difference between LASSO and Ridge is that LASSO tends to produce sparse models, where only a subset of the variables is included, while Ridge tends to produce dense models, where all variables are included, but some have smaller weights. There are a few publicly available R packages that conduct the LASSO and Ridge regression for conditional logistic models (191). In this paper, we used the clogitL1 method (192) which enables researchers to conduct the many-to-many match in some circumstances.

4.3 Results

Among 34,294 IBD patients, a total of 26 MS patients with index date before December 2006 were matched to 129 controls on birth year ±3 years, disease duration, and health authority (based on region of residence). One anti-TNFα user was observed among MS cases compared with one anti-TNFα user among controls. Upon adjusting for sex and the CCI, the fully adjusted OR (95% CI) in the conditional logistic regression model without sparse data bias adjustment was 5.31 (0.18 to 161.63) (**Table 4.1**). This estimate was indicative of sparse data bias, as indicated from the wide CIs. After applying the Firth bias adjustment method, the corresponding OR (95% CI) was 5.08 (0.35-79.57). Utilizing the data augmentation method with a prior OR (95% CI) of 2 (0.5-8), the fully adjusted OR (95% Credible Interval) equated to 2.37 (0.66-8.35). Implementing the MCMC sparse data adjustment method with a prior mean of ln(2), and a prior variance of 0.5, the fully adjusted OR (95% Credible Interval) was 2.36 (0.66 to 8.33). Conversely, the LASSO approach resulted in a coefficient of zero for the anti-TNFα variable, indicating its exclusion from the model. This outcome suggests that, within the context of the other variables in the model, anti-TNFα does not provide additional predictive value and is deemed non-essential by the algorithm's regularization process, which penalizes less informative predictors as part of its optimization. For Ridge regression, the OR (95% CI) was 1.06 (0.98 to 1.15).

During the sensitivity analysis, the data augmentation method was applied to the anti-TNFα and MS cohort (**Table 4.1**) using a prior OR (95% CI) of 1.265 (0.1 to 16). The resulting fully adjusted OR (95% Credible Interval) was 2.28 (0.32-16.38). In a similar manner, the

MCMC method with a prior mean of ln(1.265) and a variance of 1.675 produced an OR (95% Credible Interval) of 2.22 (0.29-15.31) (**Table 4.1**).

Table 4.1 Odds ratios for the association between anti-tumor necrosis factor alpha and multiple sclerosis among patients with inflammatory bowel diseases in the real-world data using conditional logistic regression with and without sparse data bias adjustment

	Adjusted OR (95% limits)
ML method	5.31 (0.18 to 161.63)
Firth	5.08 (0.35-79.57)
Data augmentation with a prior OR (95% CI) of 2 (0.5 to 8)	2.37 (0.66-8.35)
MCMC with prior a mean of ln(2) and variance of 0.5	2.36 (0.66 to 8.33)
LASSO	1.0 (1.0-1.0)
Ridge	1.06 (0.98 to 1.15)
Data Augmentation with a prior OR (95% CI) of 1.265 (0.1 to 16)	2.28 (0.32-16.38)
MCMC with a prior mean of ln(1.265) and a variance of 1.675	2.22 (0.29-15.31)

ML=maximum likelihood; OR=odds ratio; MCMC=Markov Chain Monte Carlo.

4.4 Simulation Study

Our goal was to compare the performance of several methods using simulated datasets, including ML estimate method, Firth, data augmentation, MCMC, LASSO, and Ridge, in a sparse data setting, to identify the most robust method. We conducted simulation studies using SAS 9.4 (SAS Institute, Cary, NC, USA) and RStudio (Version 1.3.1093).

4.4.1 Data-generating Mechanism

We generated the simulation dataset based on the anti-TNFα and MS cohort described above. The dataset contains a source population of 34,294 (derived from the total number of IBD patients in the real-life data). The distribution of the following variables originated from our NCC study. Specifically, anti-TNFα and sex followed a Bernoulli distribution with probabilities of $\pi_{\text{anti-TNF}\alpha}$=0.0129, π_{male}=0.37, respectively. Age followed a normal distribution with a mean (μ) of 48 and a SD (σ) of 12. The CCI (148) is modeled with a multinomial distribution, denoted by *Multi*(0.82, 0.13, 0.03, 0.003, 0.003, 0.003,0.003, 0.005, 0.001, 0.002). This distribution corresponds to the actual set of values observed in the data, ranging from 0 to 9. The distribution of patients accessing health care across the five health authority areas was modeled using a multinomial distribution, with the probabilities for each area set with *Multi*(0.16, 0.37, 0.21, 0.16, 0.11). The number of years a person has had the disease, as determined by the year of IBD index date, follows a multinomial distribution. This distribution is denoted by *Multi*(0.036, 0.143, 0.107, 0.107, 0.107, 0.071, 0.107, 0.036, 0.036, 0.071, 0.071, 0.036, 0.036, 0.036) and corresponds to the distinct years ranging from 1990 to 2003 as observed in the actual data. All variables included in the statistical model were treated as quantitative variables.

After creating the above variables in the simulated dataset, we established the true estimate as 0.65 (OR=1.92) from the pooled results in existing studies for anti-TNFα and MS $_{\text{risk}}$ among IBD patients. Based on the real-life data, the coefficient estimates for other variables were as follows: age at -0.04, sex at 1.00, CCI at 0.21, health authority at 0.01, and year of the IBD index date at 0.02.

The binary outcome for MS was generated through a Bernoulli distribution, with the probability represented as $\pi_{MS}=\exp(\beta_0+\beta^T X_i)/[1+\exp((\beta_0+\beta^T X_i)]$. In the simulation, to ensure that the simulated datasets exhibit similar levels of sparsity and the related issues as the real-world dataset, we determined β_0 based on the expected number of events (26 MS cases in our original cohort), true estimates, and the probability of covariates, arriving at a β_0 value of -6.30.

In order to generate the matched case-control data, we created a matched sample by random matching of approximately 26 MS cases with up to five non-MS controls, based on age, years of disease duration, and the same health authority within the source population. We then evaluated the coefficient estimate of $x_{\text{anti-TNF}\alpha}$ (also referred to as the target) in the simulated matched sample, denoted as $\beta_{\text{anti-TNF}\alpha}$ or the posterior median of $\beta_{\text{anti-TNF}\alpha}$, using methods for comparison, all of which utilized the conditional logistic regression model. This process was repeated 1,000 times, following the previously outlined procedure and resulting in 1000 target estimates.

4.4.2 Performance Measures

We computed the **bias** for the anti-TNFα estimate, defined as the difference between the estimated $\beta_{\text{anti-TNF}\alpha}$ (or the posterior median of $\beta_{\text{anti-TNF}\alpha}$) and the true estimate. We also calculated the **empirical standard error**, which estimates the SD of the anti-TNFα estimate across the 1,000 replications. Furthermore, we determined the **MSE** of the estimate, which assesses the accuracy of the estimates by measuring their squared deviation from the true parameter. Additionally, since performance measures are themselves subject to inaccuracy, we

reported the **Monte Carlo standard error (MCSE)** to measure the uncertainty resulting from a finite number of simulation repetitions. The detailed calculations of these measurements are provided in **Table 4.2**.

Table 4.2 Summary statistics for performance measurement of the simulation study

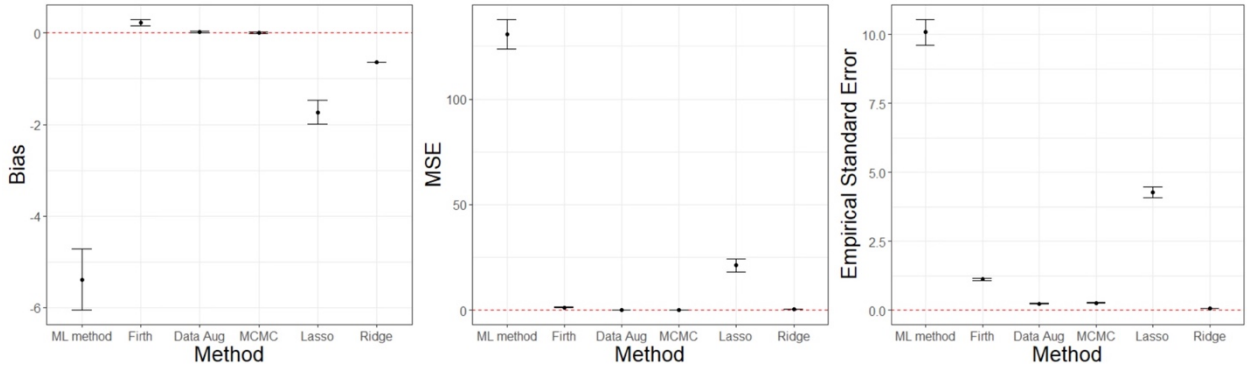
Summary Statistics	**Calculation**
bias	$\frac{1}{n_{\text{sim}}}\sum_{i=1}^{n_{\text{sim}}}(\hat{\theta}_i - \theta)$
Monte Carlo SE for bias	$\sqrt{\frac{\frac{1}{n_{\text{sim}}-1}\sum_{i=1}^{n_{\text{sim}}}(\hat{\theta}_i - \bar{\theta})^2}{n_{\text{sim}}}}$
empirical SE	$\sqrt{\frac{1}{n_{\text{sim}}-1}\sum_{i=1}^{n_{\text{sim}}}(\hat{\theta}_i - \bar{\theta})^2}$
Monte Carlo SE for empirical SE	$\frac{\widehat{\text{empirical SE}}}{\sqrt{2(n_{\text{sim}}-1)}}$
MSE	$\frac{1}{n_{\text{sim}}}\sum_{i=1}^{n_{\text{sim}}}(\hat{\theta}_i - \theta)^2$
Monte Carlo SE for MSE	$\sqrt{\frac{\sum_{i=1}^{n_{\text{sim}}}[(\hat{\theta}_i - \theta)^2 - \widehat{MSE}]^2}{n_{\text{sim}}(n_{\text{sim}}-1)}}$

SE=standard error; MSE=mean squared error

4.4.3 Results from the Simulation Study

Figure 4.1 and **Table 4.3** encapsulate the performance evaluation of six analytical methods - ML estimate, Firth, data augmentation, MCMC, LASSO, and Ridge - assessed on a set of 1,000 simulated datasets. Among the array of methods evaluated, the ML method shows a significant bias (MCSE) of -5.387 (0.340) and a MSE of 130.620 (3.639), indicating poor performance. In comparison, LASSO and Ridge have a smaller bias and MSE than ML. For the Firth method, the bias (MCSE) in point estimates is relatively low at 0.227 (0.038). The MSE (MCSE) is at 1.302 (0.080). The empirical standard error (MCSE) for Firth is 1.119 (0.027), which is higher than data augmentation and MCMC, but significantly lower than that of the ML method. Data augmentation and MCMC outperformed the others on the measurement of bias and MSE. The bias (MCSE) for data augmentation was 0.022 (0.008) and was 0.010 (0.010) for MCMC. The MSE (MCSE) for data augmentation and MCMC was found to be 0.059 (0.003) and 0.071 (0.003), respectively. Upon evaluation of the empirical standard error (MCSE), it was observed that the data augmentation and MCMC methods achieved values of 0.242 (0.005) and 0.267 (0.006), respectively.

Figure 4.1 Bias, mean square error, and empirical standard error with Monte Carlo standard error of $\beta_{anti\text{-}TNF\alpha}$ for the Maximum likelihood method, Firth, data augmentation, Markov Chain Monte Carlo, Least Absolute Shrinkage and Selection Operator, and Ridge comparison over 1,000 replications.



MSE=mean squared error; MCMC= Markov Chain Monte Carlo; aug=augmentation; ML=maximum likelihood; LASSO= Least Absolute Shrinkage and Selection Operator

Table 4.3 Bias, mean squared error, and empirical standard error with Monte Carlo standard error for maximum likelihood method, Firth method, data augmentation with a prior odds ratio (95% CI) of 2 (0.5 to 8), Markov Chain Monte Carlo method with a prior mean of ln(2) and variance of 0.5, Least Absolute Shrinkage and Selection Operator and Ridge derived from the 1000 simulated datasets.

	Sample Size	**Bias in point estimate (MCSE)**	**MSE (MCSE)**	**Empirical standard error (MCSE)**
ML	1000	-5.387 (0.340)	130.620 (3.639)	10.085 (0.241)
Firth	1000	0.227 (0.038)	1.302 (0.080)	1.119 (0.027)
Data Augmentation	1000	0.022 (0.008)	0.059 (0.003)	0.242 (0.005)
MCMC	1000	0.010 (0.010)	0.071 (0.003)	0.267 (0.006)
LASSO	1000	-1.730 (0.135)	21.259 (1.578)	4.276 (0.096)
Ridge	1000	-0.638 (0.002)	0.412 (0.002)	0.066 (0.002)

MSE=mean squared error; MCSE=Monte Carlo standard error; ML=maximum likelihood; OR=odds ratio; MCMC=Markov Chain Monte Carlo; LASSO= Least Absolute Shrinkage and Selection Operator

4.5 Discussion

We investigated the performance of a number of strategies available to tackle sparse data bias in an NCC study that yielded estimates indicative of sparse data bias from a conditional logistic regression model. When the event counts are low and the distribution of the relevant covariate is considerably uneven, the ML estimate and LASSO techniques exhibited substantial bias in the corresponding MSE, and empirical standard error. Data augmentation and MCMC approaches demonstrated the best performance with the lowest bias and MSE. Firth and Ridge methods yielded commendable outcomes, showcasing lower bias, MSE, and empirical standard error when compared against ML and LASSO. However, it didn't outperform Bayesian approaches. While the Firth penalty aligns with the Jeffreys prior in Bayesian analysis, the Jeffreys prior underlying the Firth penalty can generate spurious estimates that fall outside the range of both the prior median and the ML estimates (189). Therefore, the application of Firth's method does not guarantee effectively diminishing the biased estimation of the OR with sparse data.

When utilizing LASSO and Ridge regression in effect size models to investigate the causal effect of a target, it is essential to be aware of their inherent risks and limitations. In order to maximize the conditional log-likelihood function, LASSO is known for pushing some coefficients to zero, resulting in a sparse model. As observed in **Table 4.1**, when applying LASSO to anti-TNFα and MS cohort, it sets the effect of anti-TNFα to zero in that dataset. Even though Ridge regression shrinks coefficients towards zero without completely eliminating them, it does not fully resolve the issue and can lead to an underestimation of the true effect sizes in the

model. Therefore, both LASSO and Ridge regression are more commonly used in predictive models, and might not be an optimal method for causal questions.

The selection of priors in Bayesian or approximate Bayesian analyses can be contentious due to the subjective nature of defining their distribution. In data augmentation, we chose a prior OR (95% CI) of 2 (0.5 to 8), and for the MCMC method, we used a prior mean of ln(2) and a variance of 0.5, based on the results of a meta-analysis from previous studies. As it is recommended to consider a broader prior interval, resulting in weaker penalties (96), we applied a wider and weaker prior interval in the sensitivity analysis with OR (95% CI) of 1.265 (0.1 to 16) in data augmentation and a prior mean of ln(1.265) and a variance of 1.675 in the MCMC analysis. The ORs for the association between anti-TNFα and MS in the anti-TNFα and MS cohort remained similar.

The publication of pharmacoepidemiologic studies prone to sparse data bias will continue to grow, particularly with studies that aim to quantify rare adverse events. The methods to combat sparse data bias, as discussed in this paper, are still underutilized. The results of our study demonstrate that pharmacoepidemiologic studies with sparse data bias, especially those using conditional logistic regression, can employ methods like data augmentation and MCMC with carefully chosen priors to tackle the sparse data issue.

Chapter 5: DISCUSSION AND CONCLUSIONS

The concluding chapter of this thesis wraps up the work by summarizing the key findings, evaluating the strengths and limitations, outlining the implications for clinical practice, and suggesting avenues for future research.

5.1 Summary of Key Findings

This dissertation unfolds through three sequential studies that scrutinize the risk of MS linked to the use of anti-TNFα in individuals with RD and IBD, identify potential methodological issues, and develop strategies to address these issues. In Chapter 2 (193), I delve into the concepts of cDAGs, demonstrating how they help researchers identify various biases like confounders, mediators, and collider-stratification bias. Through a case study, the process of crafting a cDAG to understand the causal relationship between anti-TNFα and the likelihood of MS was illustrated. The chapter also sheds light on potential biases in existing literature that might have influenced study outcomes pertaining to anti-TNFα and the risk of MS, such as confounding, contraindication-related confounding, and biases stemming from measurement inaccuracies. What sets this review apart is its novel use of cDAGs to delve into the connection between anti-TNFα and MS, making it an indispensable guide, especially for those in research and clinical sectors unfamiliar with these techniques. By scrutinizing biases in earlier research concerning anti-TNFα and MS, this review clarifies past inconsistencies and offers crucial insights to improve the accuracy of subsequent studies in this domain.

In Chapter 3 (126), this largest population-based study to date quantified the risk of MS associated with the use of anti-TNFα, beginning with the compilation of a substantial cohort from four Canadian provinces, consisting of 296,918 patients with RD and 84,458 with IBD. Subsequently, I carried out an NCC study within these RD and IBD populations. Incident-onset MS cases were ascertained using a validated algorithm (122). Up to five controls were matched to each MS case based on birth year ±3 years, disease duration, and health authority (based on region of residence) by using the density-based sampling algorithm. Any anti-TNFα dispensation in the two years prior to the index date (MS onset) was identified. This research represents the inaugural analysis of MS risk among anti-TNFα users versus non-users from four Canadian provinces. Additionally, I carried out two sensitivity analyses: 1) accounting for potential reverse causality bias by implementing a 60-day latency window, and 2) deriving an E-value to consider the potential impact of undetected confounders (161). The findings revealed that the use of anti-TNFα was associated with an increased risk of MS compared to non-users for RD (pooled RR=2.05 [95% CI, 1.13-3.72]) after adjusting for potential confounders, which included matching variables, sex, and CCI at baseline. The number needed to harm was 2,268, suggesting that for every 2,268 RD patients treated with anti-TNFα, there would be an additional MS case. I also found an increased risk of MS among IBD patients but with a wide CI (pooled RR=1.35 [95% CI, 0.70-2.59]).

It should be emphasized that finding an association does not necessarily confirm a causal relationship. Although our study observed a higher risk of developing MS among users of anti-TNFα in the RD patients, we cannot establish with absolute certainty that anti-TNFα therapies cause MS. This is despite our belief that unmeasured confounding, especially confounding by

disease severity, is unlikely to have biased our results. Finally, our results are in line with a number of case series and epidemiological studies that have also shown a risk.

Our study in Chapter 3 provided some insights that were acknowledged in an accompanying editorial (194). The editorial highlighted the robustness of our datasets, which encompassed almost 100% of residents from four Canadian provinces. It also praised the highly validated algorithms I employed to identify patients with RD, IBD, and MS. Additionally, the editorial commended our meticulous efforts to curtail potential biases and extract the most valuable insights from the administrative data.

In both prevailing research on this subject and my own work, the significant methodological difficulties presented by infrequent exposures and outcomes prompted me to explore in-depth statistical techniques that could counter or alleviate the effects of sparse data bias.

In Chapter 4, I assessed the outcomes of applying diverse methods, such as Firth bias adjustment, data augmentation, MCMC Bayesian analyses, LASSO regression, and Ridge regression, against conditional logistic regression in the context of real-life data on anti-TNFα and MS. In contrast to the traditional conditional logistic regression that indicated an adjusted OR of 5.31 (95% CI, 0.18-161.63) for the link between anti-TNFα usage and MS within the IBD cohort, alternative statistical methods presented modified results. The Firth method revealed an adjusted OR of 5.08 (95% CI, 0.35-79.57). The data augmentation approach, starting with an assumed OR of 2 (95% CI, 0.5-8), yielded an adjusted OR of 2.37 (95% Credible Interval, 0.66-8.35). Furthermore, the MCMC technique, with a prior mean of the natural logarithm of 2 and a variance of 0.5, resulted in an adjusted OR of 2.36 (95% Credible Interval, 0.66 to 8.33). The LASSO approach resulted in a coefficient of zero for the anti-TNFα variable, indicating its

exclusion from the model. The Ridge showed an adjusted OR of 1.06 (95% CI, 0.98 to 1.15). In the simulation study based on our real-life data, the traditional conditional logistic regression and LASSO techniques exhibited substantial bias in the corresponding MSE and empirical standard error. Data augmentation and MCMC approaches demonstrated the best performance with the lowest bias and MSE. Firth and Ridge methods yielded commendable outcomes, showcasing lower bias and MSE when compared against traditional logistic regression and LASSO regression. However, it did not outperform data augmentation and MCMC approaches.

5.2 Strengths and Limitations

5.2.1 Strengths

While a randomized controlled trial remains the gold standard for assessing the adverse effects of MS in RD and IBD patients, ethical concerns arising from an earlier trial halted due to increased MS exacerbation rates among lenercept-treated individuals make such a trial improbable. Therefore, this study serves as the next best alternative. I adopted a detailed and careful strategy, choosing an NCC design utilizing a density-based sampling method. This algorithm helps to reduce selection bias by ensuring that controls reflect the distribution of exposure among the at-risk population each time a case is identified. Such a design guarantees that the OR produced is an accurate reflection of the IRR that one would obtain from a cohort study (195).

The study adopts a comprehensive population-based methodology, using an extensive administrative dataset from four Canadian provinces that captures information on all legal

residents. This broad coverage mitigates selection biases and bolsters the generalizability of our results. Furthermore, I used the strictest case definitions for RD, IBD, and MS. The PPV for RD was as high as 82%, for IBD it reached 97%, and for MS, it was 99.5%. This ensured that I selected the true cases of patients, minimizing selection bias, and enhancing the accuracy and generalizability of our findings. After using the validated algorithm to define MS cases, I defined the index date as the date of the first ICD-9/10 code for MS or the first code for a demyelinating event to ensure that only incident MS cases are captured, which included: optic neuritis, acute transverse myelitis, acute disseminated encephalomyelitis, demyelinating disease of the CNS unspecified, acute disseminated demyelination, or neuromyelitis optica. I also required all newly diagnosed MS individuals to have at least 5 years of prior registration in the mandatory provincial health system (known as the "run-in" period) before the index date and imposed a 60-day latency period in our sensitivity analysis to best capture the onset of MS.

Moreover, selecting confounding variables based on cDAGs allows my study to be less susceptible to confounding bias, overadjustment bias, and collider bias. These biases commonly appear in existing epidemiological studies examining the association between anti-TNFα and MS. Sparse data bias is a frequent issue in pharmacoepidemiologic studies, yet few studies address this problem. I explored four modern methods, including Bayesian analysis and machine learning techniques, to tackle sparse data bias. Through simulation studies, I evaluated their performance, shedding light on the challenges of sparse data bias and offering potential solutions. Simulation data that are based on actual datasets serves as a valuable tool, potentially increasing the reliability of research outcomes.

5.2.2 Limitations

While I've made extensive efforts to minimize potential biases, several limitations persist in this dissertation. First, health administrative databases include diagnostic ICD codes but may not always reflect the earliest clinical signs of MS. Previous research indicates that the prodromal phase for MS might emerge 5 or more years before the typical demyelinating disease symptoms (66,67). Consequently, subjects exhibiting early MS symptoms or MS prodrome who have not yet been diagnosed might be misclassified as controls. However, this type of misclassification, which is nondifferential usually leads to an underestimation of the risk of MS with the use of anti-TNFα.

Similar to other research that relies on health administrative data, our study did not include information on lifestyle behaviors such as smoking. Nevertheless, our sensitivity analysis, employing the E-value, indicates that the observed IRR for RD would be explained away by an unmeasured confounder that was associated with both anti-TNFα and MS by a RR of at least 3.52-fold each, after adjusting for potential confounders.

Although our data encompass four Canadian provinces, the association between anti-TNFα and MS risk wasn't consistent within the IBD cohort, potentially due to the rarity of MS events. Similarly, I was unable to analyze the association between anti-TNFα and MS occurrence in the RD and IBD subpopulations, as well as the specific impact of different anti-TNFα treatments on MS risk, because the sample sizes were too small.

Given concerns that anti-TNFα use might induce MS, clinicians might hesitate to prescribe it to patients showing MS-like symptoms or those with a familial MS history. Such contraindication could mean our estimates are conservative, leading to potential

underestimations of the actual risk. Lastly, like all pharmacoepidemiologic studies based on health administrative databases, we have records of prescription drug dispensations, but not necessarily their consumption. However, given that anti-TNFα treatments are typically given intravenously or subcutaneously and necessitate specific approvals for publicly-funded access, misclassification of their use seems improbable.

5.3 Significance and Contributions of Research

Past investigations into the association between anti-TNFα and MS were fraught with varying degrees of bias. Recognizing and understanding these biases is paramount for clinicians and researchers when dissecting future studies in this arena. An invaluable tool for this task is the crafting of a cDAG, which serves as a visual guide to pinpoint these biases effectively. The insights gained from Chapter 2's in-depth exploration of cDAGs empower clinicians with a systematic approach to identify and evaluate potential biases when deliberating treatment options. This is especially pivotal when interpreting the nuanced relationship between anti-TNFα and the risk of MS.

Our study, drawing on population-based data from four Canadian provinces, identified an increased association between MS and the use of anti-TNFα therapy among patients with RD. This revelation allows for a more informed dialogue between clinicians and patients. They can now judiciously assess the balance between the potential risks and the quality-of-life improvements offered by anti-TNFα. In instances where the associated MS risk becomes a significant concern, they might contemplate alternative treatments that, while exhibiting similar efficacy, do not carry this specific risk.

Furthermore, Chapter 4 equips researchers with innovative statistical techniques tailored to combat the challenges of sparse data bias. To date, pharmacoepidemiologic studies addressing sparse data bias are scant. The significance of this bias cannot be overstated, as it may result in the overestimation of a drug's adverse effects. Such exaggerations could deter patients from continuing with treatments that might be beneficial, potentially leading to detrimental health outcomes. Our research has shown that in the realm of pharmacoepidemiology, particularly in studies utilizing conditional logistic regression that are prone to sparse data bias, methodologies like data augmentation and MCMC with judiciously selected prior information can be effectively applied to address this challenge. This, in turn, can profoundly influence and refine treatment decisions, ultimately benefiting patient care.

5.4 Implication for Future Research

Our research sheds light on different aspects of the risk of MS among RD and IBD patients while also points out areas that warrant further exploration.

In our study, the risk of MS associated with particular subtypes of RD and IBD, such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and colitis, was not discernible due to an inadequate sample size. Hence, I suggest that subsequent research with larger sample sizes focusing on these specific subgroups of RD and IBD would be both viable and beneficial.

Given that subjects exhibiting early MS symptoms or MS prodrome who have not yet been diagnosed might be misclassified as controls in the administrative datasets, there is an opportunity to enhance accuracy through the application of advanced machine learning methods.

This is particularly relevant for understanding the relationship between anti-TNFα and MS. Specifically, employing supervised learning and deep learning algorithms could be a promising approach. These algorithms aim to determine a binary outcome, signifying either the occurrence or non-occurrence of MS onset, utilizing meticulously chosen predictor variables or features. To optimize the predictive capability and avoid overfitting, it is essential to partition the dataset into training, validation, and testing subsets. Utilizing the most effective algorithm identified from this process can subsequently pave the way for more accurate future predictions of MS onset, thereby minimizing potential biases.

While our dataset did not account for the potential confounders like smoking, I did compute an E-value. However, future investigations leveraging population-based datasets that incorporate unmeasured confounders in our datasets would be of great significance. Moreover, for forthcoming pharmacoepidemiologic studies with issues of sparse data bias, I recommend adopting methodologies such as data augmentation and MCMC. The judicious selection of suitable priors is especially crucial to mitigate the challenges posed by potential sparse data bias.

5.5 Conclusion

The research detailed in this thesis offers clinically relevant and innovative insights into the potential risks of anti-TNFα on MS for patients with RD and IBD. I identified a pronounced association between the use of anti-TNFα and an increased incidence of MS among RD patients relative to non-users. I have mitigated potential biases through the use of extensive population-based data spanning four Canadian provinces, employing rigorously validated case definitions to pinpoint RD, IBD, and MS cases. By implementing a cDAG, I have navigated around common

issues such as confounding, overadjustment, and collider-stratification, and I have introduced effective strategies to address the challenge of sparse data bias. These methodological improvements set a new course for subsequent research in pharmacoepidemiology. Together, these initiatives have addressed critical gaps in existing research, providing valuable information that can assist healthcare providers and patients in making well-informed choices regarding anti-TNFα therapy.

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Appendices

Appendix A : Dataset description, disease and medication identification codes

Appendix A. Table A.1 Overview of the provincial datasets and population sizes

	British Columbia	**Alberta**[a]	**Saskatchewan**[a]	**Manitoba**
Population (2015)	4,848,055	4,067,175	1,098,352	1,278,365
Years of Data Available	1990-2015 (prescription data from 1996)	2008-2015	1998-2017	1984-2018 (prescription data from 1995)
Number of RD Patients	282,893	N/A	N/A	14,025 (rheumatoid arthritis only)
Number of IBD patients	34,328	33,984	7,933	8,213

RD=rheumatic diseases; IBD=inflammatory bowel diseases; N/A=not available

[a]The RD cohorts were not available in Alberta and Saskatchewan

Appendix A. Table A.2 Case definitions of rheumatic diseases and inflammatory bowel diseases within each province

	British Columbia	**Alberta**[a]	**Saskatchewan**[a]	**Manitoba**
RD case definition	**Rheumatoid Arthritis:** at least two outpatient visits at least 2 months apart within a 5-year period with an ICD-9 code for rheumatoid arthritis (714.X) **Ankylosing Spondylitis:** at least two diagnostic codes from either outpatient (ICD-9 720.X) or hospitalizations (ICD-9 720.X; ICD-10 M45.X) at least 2 months apart within a 2-year period. **Psoriatic Diseases:** at least one diagnostic code (ICD-9 696.X) for psoriatic diseases by a rheumatologist/dermatologist; or at least two diagnostic	N/A	N/A	**Rheumatoid Arthritis:** If resident in Manitoba ≥2 years: At least 5 hospitalizations (ICD-9 714; ICD-10 M05, M06) or outpatient visits (ICD-9 714). If resident in Manitoba <2 years: At least 3 hospitalizations (ICD-9 714;

	codes for psoriatic diseases at least two months apart within a two-year period by a non-rheumatologist/dermatologist; or at least one hospitalization with diagnostic code for psoriatic diseases (ICD-9 696.X; ICD-10 L40.X).			ICD-10 M05, M06) or outpatient visits (ICD-9 714).
IBD case definition	At least four outpatient visits with diagnostic codes for IBD (ICD-9 555 or 556) within two years or at least two hospitalizations with diagnostic codes for IBD (ICD-9 555, 556; ICD-10 K50 or K51) within two years	At least four outpatient visits, or two hospitalizations or two medical contacts in the Ambulatory Care Classification System database with	If resident in Saskatchewan ≥2 years: At least 5 hospitalizations (ICD-9 555 or 556; ICD-10 K50 or K51) or outpatient visits (ICD-9 555 or 556)	If resident in Manitoba ≥2 years: At least 5 hospitalizations (ICD-9 555 or 556; ICD-10 K50 or K51) or outpatient visits (ICD-9 555 or 556)

		an IBD diagnostic code (ICD-9 555, 556; ICD-10 K50 or K51) within a two-year period	If resident in Saskatchewan <2 years: At least 3 hospitalizations (ICD-9 555 or 556; ICD-10 K50 or K51) or outpatient visits (ICD-9 555 or 556)	If resident in Manitoba <2 years: At least 3 hospitalizations (ICD-9 555 or 556; ICD-10 K50 or K51) or outpatient visits (ICD-9 555 or 556)

RD=rheumatic diseases; IBD=inflammatory bowel diseases; N/A=not available

[a]The RD cohorts were not available in Alberta and Saskatchewan

Appendix A. Table A.3 Disease-modifying drugs approved by Health Canada over the study period (2000-2018) for the treatment of multiple sclerosis and their drug identification numbers

Drug name	**Drug identification number** (assigned by Health Canada)
Extavia	02337819
Betaseron	02169649
Rebif	02237319, 02277492, 02237317, 02237320, 02281708, 02318253, 02318261, 02318288
Avonex	02237770, 02269201
Copaxone	02245619, 02233014, 02441446, 02456915, 02460661
Tysabri	02286386
Aubagio	02416328
Gilenya	02365480
Tecfidera	02404508, 02420201
Lemtrada	02418320
Plegridy	02444399, 02444402, 02444372, 02444380
Zinbryta	02459620, 02459639

Appendix A. Table A.4 Anti-tumor necrosis factor alpha drugs approved by Health Canada for the treatment of rheumatoid diseases and inflammatory diseases and their drug identification numbers

Drug name	**Drug identification number** (assigned by Health Canada)
Adalimumab	2258595, 2458349, 2458357, 2466872
Certolizumab	2331675, 2465574
Etanercept	2242903, 2242903, 2274728, 2455323, 2455331, 2462850, 2462869, 2462877, 66123997
Infliximab	2244016, 2419483, 2419475
Golimumab	2324784, 2324776, 2413175, 2413183, 2417472

Appendix B : Data augmentation prior data information

Appendix B. Table B.1 Variables in the prior data augmentation for the conditional logistic regression with prior distribution N(ln(2),0.5), S=10

	Case $2/v \times S^2$	**TNFi** $1/S$	**H** $-m/S$	**M** $2A$
Exposed	800	0.1	-0.0693	1600
Unexposed	800	0	0	1600

We need to set the following variables in the prior data: (1) A (case)= the number of cases represented by the data record. A is 1 for all actual cases and 0 for all actual controls. For the normal distribution prior records, A can be represented by $2/\nu_{prior}=4$. (2) M=the total number of subjects represented by the record. M is set to 1 for all actual-data records. For the grouped prior data records, M=2A=8. Thus, the proportion of cases in the record is A/M, which in the ungrouped actual-data record is 1 (1/1) for cases and 0 (0/1) for controls, for the prior records, it is A/2A=1/2. (3) H=the 'offset' variable if the prior center β_{prior} is not zero. We set H=0 for all actual records. For the prior data records, we set $H=-\beta_{prior}=-0.69$. (4) The regressor value in the prior-data record to represent users of anti-TNFα was set $X_{anti\text{-}TNF\alpha}=1$, all other regressors in this prior record are set to 0. For the actual records, no change is made to the regressor values. (5) S=the rescaling factor. it is possible to impose perfectly normal priors by utilizing a rescaling factor S that is divided into all the regressor values in the prior data, including the offset H. The prior A and M can then be inflated by a factor of S^2 to compensate. To illustrate, if S equals 10, the prior record for anti-TNFα and MS can be expressed as $A=4\times S^2=400$, M=800, H=-0.69/S=-0.069, and the anti-TNFα regressor value=1/10=0.1 which indicates the prior record is for anti-TNFα.