RESEARCH ARTICLE

Risk of Multiple Sclerosis Among Users of Antitumor Necrosis Factor α in 4 Canadian Provinces

A Population-Based Study

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Abstract

Background and Objectives

Antitumor necrosis factor α (TNFα) agents are a class of biologic drugs used for the treatment of several immune-mediated conditions. An increased risk of multiple sclerosis (MS) with their use has been suggested, but studies have been limited. Relevant population-based epidemiologic data linking anti-TNFα to MS are scarce. The objective was to compare the risk of MS in anti-TNFα users with nonusers among patients with rheumatic disease (RD) or inflammatory bowel disease (IBD).

Methods

A nested case-control study was conducted. Population-based health care–linked databases from 4 Canadian provinces were used. All patients with RD or IBD residing within a participating province between January 2000 and March 2018 were identified by validated case definitions. Any anti-TNFα dispensation in the 2 years before the index date (MS onset) was identified. Incident onset MS cases were ascertained using a validated algorithm. Up to 5 controls were matched to each MS case based on birth year ±3 years, disease duration, and health authority (based on region of residence). Conditional logistic regressions were used to calculate the incidence rate ratio (IRR) after adjusting for potential confounders. A meta-analysis was conducted to provide pooled estimates across provinces using random-effects models.

Results

Among 296,918 patients with RD patients, 462 MS cases (80.1% female, mean [SD] age, 47.4 [14.6] years) were matched with 2,296 controls (59.5% female, mean [SD] age, 47.4 [14.5] years). Exposure to anti-TNFα occurred in 18 MS cases and 42 controls. After adjusting for matching variables, sex, and the Charlson Comorbidity Index, the pooled IRR was 2.05 (95% CI, 1.13–3.72). Among 84,458 patients with IBD, 190 MS cases (69.5% female, mean [SD] age, 44.3 [12.3] years) were matched with 943 controls (54.1% female, mean [SD] age, 44.2 [12.2] years). Exposure to anti-TNFα occurred in 23 MS cases and 98 controls. The pooled adjusted IRR was 1.35 (95% CI, 0.70–2.59).

Discussion

The use of anti-TNFα was associated with an increased risk of MS compared with nonusers, especially among patients with RD. These findings could help clinicians and patients with RD to make more informed treatment decisions. Further studies are needed to validate these results for patients with IBD.

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Glossary

CCI = Charlson Comorbidity Index; **cDAG** = causal direct acyclic graph; **DMARD** = disease-modifying antirheumatic drug; **IBD** = inflammatory bowel disease; **IRR** = incidence rate ratio; **MS** = multiple sclerosis; **NCC** = nested case control; **NSAID** = nonsteroidal anti-inflammatory drug; **RD** = rheumatic disease; **TNFα** = tumor necrosis factor α.

Multiple sclerosis (MS) is one of the world's most common neurologic disorders,[1] affecting an estimated 2.8 million people worldwide in 2020.[2] Antitumor necrosis factor α (TNFα) agents are a class of biologic drugs used for the treatment of several chronic immune-mediated inflammatory diseases such as moderate to severe rheumatic diseases (RDs) [rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis] and inflammatory bowel diseases (IBDs). Although anti-TNFα agents are generally well-tolerated and have been shown to significantly improve patients' quality of life,[3-6] an increased risk of MS has been suspected after their use.[7-11]

One of the first studies that postulated an association with MS pathogenesis was a randomized controlled trial that was stopped early because of an increased MS exacerbation rate among lenercept-treated patients.[12] Epidemiologic data suggesting anti-TNFα use may trigger new onset MS are scarce and contradictory,[13-17] mainly because of potential biases such as sparse data bias.[16] A 2020 study found that the use of anti-TNFα was associated with an increased risk of overall inflammatory demyelinating events among patients with RD or IBD receiving medical care at 3 Mayo Clinics, USA.[13] However, MS was not studied specifically because of 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,[18-21] 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 4 Canadian provinces.

Methods

Data Sources

This study was undertaken in 4 western Canadian provinces: British Columbia, 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,[22] hospitalizations,[23] demographic data,[24] and all outpatient or community dispensations of prescription medication.[25] Numerous population-based studies have been successfully conducted using these data sources.[26-29] An overview of each province's databases is presented in eTable 1 (links.lww.com/WNL/C454). Data for RD and IBD cohorts within each province are saved in different server and can only be analyzed in-house.

Study Design

We undertook 2 nested case-control (NCC) studies for patients with RD and IBD age18 years or older, separately, in each province between January 2000 and March 2018. The NCC has been deemed the ideal design for drug safety studies in large populations with long follow-ups because it mitigates some of the complexities that might arise when large cohorts are followed for a long period.[30] Cohort studies require much larger sample sizes when the outcome is rare.[30]

Cohort Definition

Owing to data availability, RD cohorts were available in 2 provinces, British Columbia and Manitoba; each province used its internally validated case definition that has been used previously to identify persons with rheumatoid arthritis (ICD-9 714.X),[26,28] ankylosing spondylitis (ICD-9 720.X; ICD-10 M45.X),[31] and psoriatic diseases (ICD-9 696.X; ICD-10 L40.X).[32] Case definitions for RD have a positive predictive value (PPV) of up to 82%[26,28] and are presented in eTable2 (links.lww.com/WNL/C454).

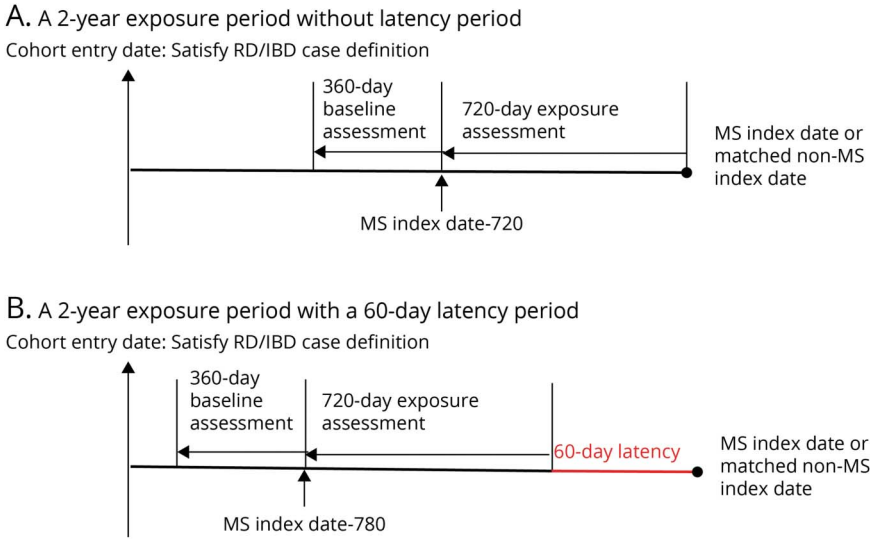
IBD cohorts were identified in the 4 provinces, selected within each province by internally validated case definitions, using ICD-9 555, 556; ICD-10 K50, K51 (see eTable 2 for details, links.lww.com/WNL/C454). Case definitions for IBD have a PPV of up to 97%.[33,34]

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 (1) death, (2) MS onset, (3) termination of health coverage, or (4) last date of available data.

Case and Control Definition

Cases were identified separately for the RD and IBD cohorts in each province between January 2000 and March 2018 and

Figure 1 Schematic Representation of the Study Design



After satisfying the case definition of rheumatic diseases (RDs) or inflammatory bowel diseases (IBDs), patients were followed until (1) death, (2) multiple sclerosis (MS) onset, (3) termination of health coverage, or (4) last date of available data. Among cases and matched general population controls, all antitumor necrosis factor α (TNFα) drugs approved by Health Canada for the treatment of RD or IBD and dispensed in 2 years before 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 2-year exposure assessment period.

were ascertained using a previously validated and successfully applied algorithm using health administrative data.[29] A MS case was defined as a subject who had at least 3 records related to MS from physician visits (ICD-9 340), hospitalizations (ICD-9 340 or ICD10 G35), or prescription claims specific for MS (eTable 3, links.lww.com/WNL/C454) in any combination using all available data. This algorithm has a PPV of 99.5%.[29] 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 before the index date.

Controls were selected from the RD or IBD cohorts using a density-based sampling algorithm.[30] First, a risk set of all patients with RD or IBD with new onset MS (cases) and their corresponding controls was created. For each case, a pool of controls was identified as all with RD or IBD who had no prior record of MS or a related demyelinating event or prescription filled for an MS drug (eTable 3, links.lww.com/WNL/C454) at the index date. Because there is usually little marginal increase in precision from increasing the ratio of controls to cases beyond 4,[35] 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[36]; and (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.[30]

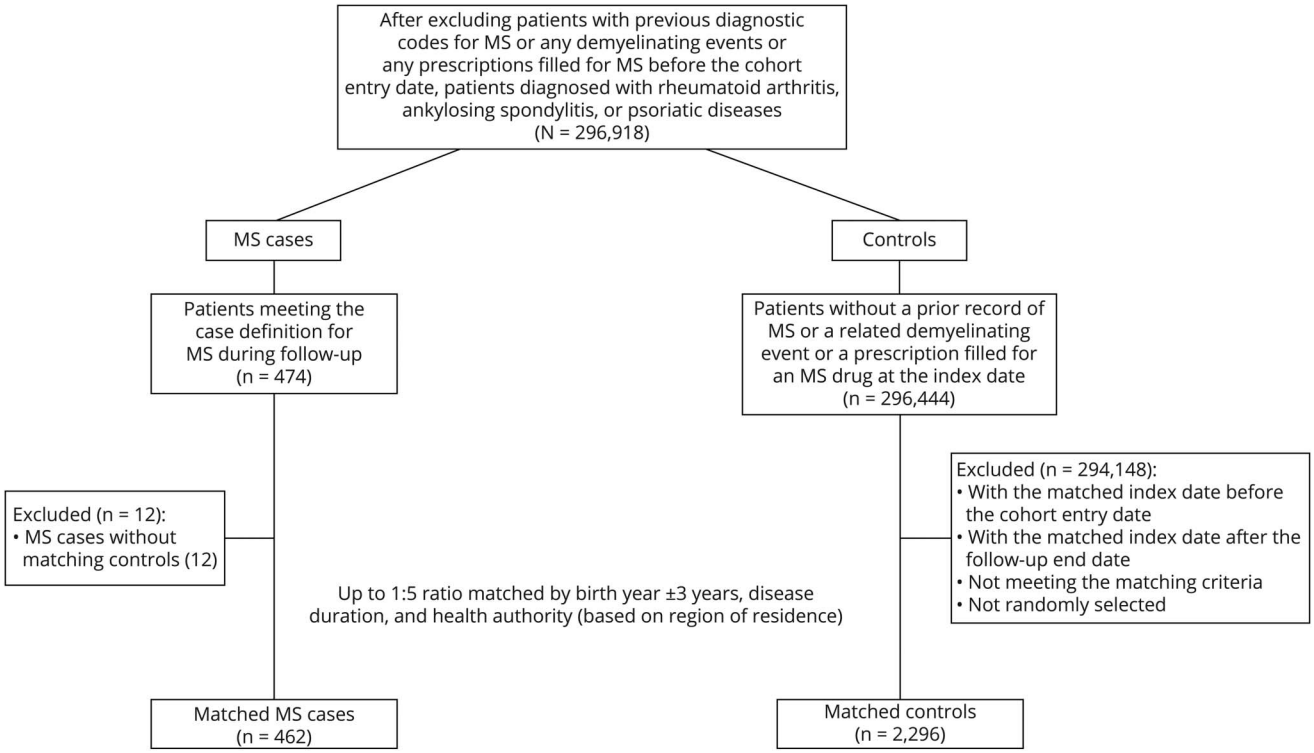
Exposure Assessment

All anti-TNFα drugs approved by Health Canada for the treatment of RD or IBD and dispensed in 2 years before the index date (MS onset) were identified including, adalimumab, certolizumab, etanercept, infliximab, and golimumab (eTable 4, links.lww.com/WNL/C454). Because 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),[11] we considered different risk periods in relation to anti-TNFα use. For the main analysis, a 2-year exposure assessment period of anti-TNFα use was examined. The use of 2 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 1-year period as a sensitivity analysis because most patients developed MS within 1 year or less after the therapy initiation.[11] 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 1 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.

Covariates

All baseline covariates were measured during 360 days preceding the 2 years exposure assessment period (Figure 1A) to

Figure 2 Nested Case-Control Inclusion Criteria for the Rheumatic Diseases (RD) Cohorts Among the 4 Canadian Provinces



Abbreviation: MS = multiple sclerosis.

avoid overadjustment bias (i.e., adjusting for mediator variables).[37] In addition to matching variables, the following covariates were considered: sex, number of physician visits and hospitalizations, the Charlson Comorbidity Index (CCI),[38] and any dispensations for oral glucocorticoids, prescribed nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), or immunosuppressant drugs. Causal direct acyclic graphs (cDAGs) were used to select confounding variables for model adjustments (eFigure 1, links.lww.com/WNL/C454).

Statistical Analysis

Baseline covariates between patients with MS and controls were compared using descriptive statistics. A conditional logistic regression model was used to obtain IRRs of MS among users and nonusers of anti-TNFα. Based on the cDAGs (eFigure 1, links.lww.com/WNL/C454), 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.

Owing 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 Q statistic was performed,[39] which describes the percentage of total variation across effect sizes because of 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 needed to harm (NNH), which represents the number of patients needed to be treated for 1 additional patient to be harmed for case-control studies using equation $1/[(\text{OR-1}) \times \text{unexposed event rate}]$.

Sensitivity Analyses

To further test the robustness of our results, besides the analysis on the risk of anti-TNFα use during a 1-year period outlined earlier, 2 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 1B). Specifically, the first 60 days before the index date were disregarded. Second, to estimate the effect of unmeasured confounders (e.g., smoking), an E-value was calculated.[41,42] Specifically, an estimation of the minimum strength of association was calculated that an unmeasured confounder would need to have with both exposure and outcome to fully explain away a specific exposure-outcome association.[41,42]

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

Table 1 Baseline Characteristics of the MS Cases and Matched Controls Among Persons With RD 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)	1,365 (59.45)
No. of hospitalizations, mean (SD)	0.32 (0.73)	0.22 (0.64)
No. 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 (1,495.79)	1981.67 (1,498.65)
Glucocorticoid, n (%)	52 (11.26)	202 (8.80)
NSAIDs, n (%)	158 (34.20)	668 (29.09)
DMARDs, n (%)	68 (14.72)	279 (8.80)

Abbreviations: DMARDs = disease-modifying antirheumatic drugs; MS = multiple sclerosis; NSAIDs = nonsteroidal anti-inflammatory drugs; RD = rheumatic disease.
[a] All baseline covariates were measured during 360 days preceding the exposure assessment period.

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 British Columbia's Freedom of Information and Privacy Protection Act. Ethics approval 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), which granted a waiver of informed consent because data are deidentified.

Data Availability

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

Results

After excluding individuals with MS or any demyelinating events before the cohort entry date, in total, we identified 296,918 patients with RD in British Columbia and Manitoba combined (Figure 2). During follow-up, a total of 462 patients developed MS (80.1% female, mean [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] years). Table 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; and higher CCI scores at baseline.

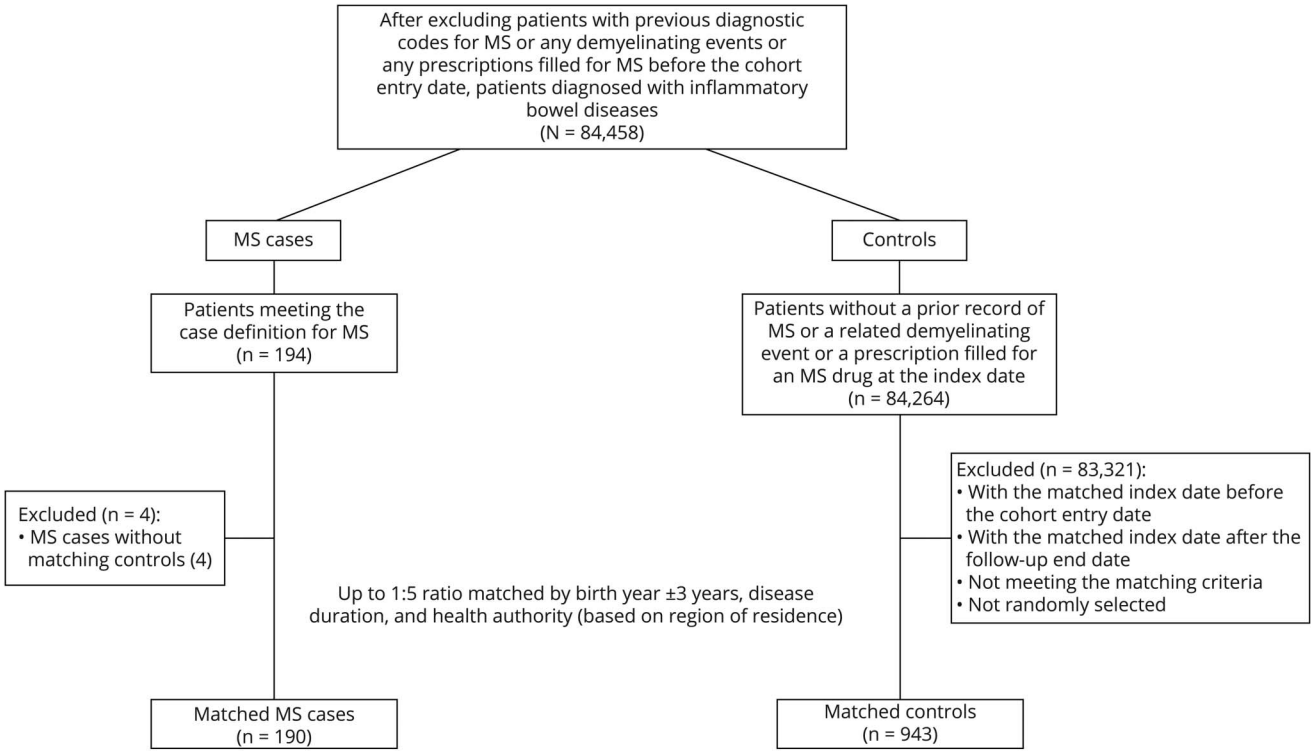
Among the 84,458 patients with IBD from the 4 provinces combined (Figure 3), 190 patients developed MS (69.5% female, mean [SD] age, 44.3 [12.3] years) during follow-up and were matched with 943 controls with IBD (54.1% female, mean [SD] age, 44.2 [12.2] years). Table 2 summarizes the baseline characteristics of the IBD cohorts for the 4 provinces combined. Like the RD cohorts, MS cases had a higher number of physician visits and hospitalizations, higher use of glucocorticoids and immunosuppressant drugs, and higher CCI scores when compared with controls at baseline.

We computed the crude incidence rate of MS among incident users of anti-TNFα with respect to MS in each province for the patients with RD and IBD 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 British Columbia 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 British Columbia, 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 2 years before the index date (MS onset) (Table 3). After adjusting for sex and CCI, the corresponding fully adjusted IRR (95% CI) was 2.07 (1.12–3.80) for RD in British Columbia 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 and Figure 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 1 additional patient to be harmed.

In the IBD cohorts and across all 4 provinces, 23 anti-TNFα users were observed among MS cases compared with 98 anti-TNFα users among controls (Table 3). After adjusting for sex and CCI, the corresponding fully adjusted IRR (95% CI) was 2.30 (0.69–7.68) for IBD in British Columbia, 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 and Figure 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 Q statistic all larger than 0.05 among the RD and IBD cohorts across all provinces (Figure 4).

Figure 3 Nested Case-Control Inclusion Criteria for Inflammatory Bowel Diseases (IBD) Cohorts Among the 4 Canadian Provinces



Abbreviation: MS = multiple sclerosis.

Similar results were found in the sensitivity analyses (eTable 5 and eTable 6, links.lww.com/WNL/C454). 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 risk ratio of at least 3.52-fold each, after adjusting for potential confounders.

Discussion

In this multiprovincial Canadian population-based study, we found that the use of anti-TNFα was associated with an increased risk of MS compared with nonusers for RD. The finding of an increased MS risk could help clinicians and patients with RD when considering the use of anti-TNFα to make more informed treatment decisions. We also found an increased risk of MS among patients with IBD, but given the observational nature of this study and the wide confidence intervals, 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.[12] A NCC study that used medical records of patients with RD or IBD treated at 3 Mayo Clinics in the United States (2003–2019)[13] found that the odds of inflammatory demyelinating events were 3 times higher among anti-TNFα users when compared with nonusers 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, because of the relatively small number of individuals included (N = 212). Furthermore, because the Mayo Clinic is a tertiary referral clinic center and only includes insured patients, this study may be subject to referral bias which may also reduce the generalizability of findings. In the same year, others suggested that no significantly increased risk of MS in users of anti-TNFα compared with nonusers among patients with RD (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).[15] However, only 6 MS cases were identified among anti-TNFα users in Sweden and 4 in Denmark, resulting in rather wide confidence intervals. The heterogeneity from previous studies can make the results challenging for clinicians and patients to interpret. Thus, our large, population-based, multiprovince study, which used a common protocol to combine regions, contributes substantially to the understanding of MS risk in persons using anti-TNFα.

Table 2 Baseline Characteristics for the MS Cases and Matched Controls Among Persons With IBD 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 (1,318.88)	1898.58 (1,329.02)
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%)

Abbreviation: 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.

Table 3 Pooled Associations Between Anti-TNFα and Subsequent MS 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)

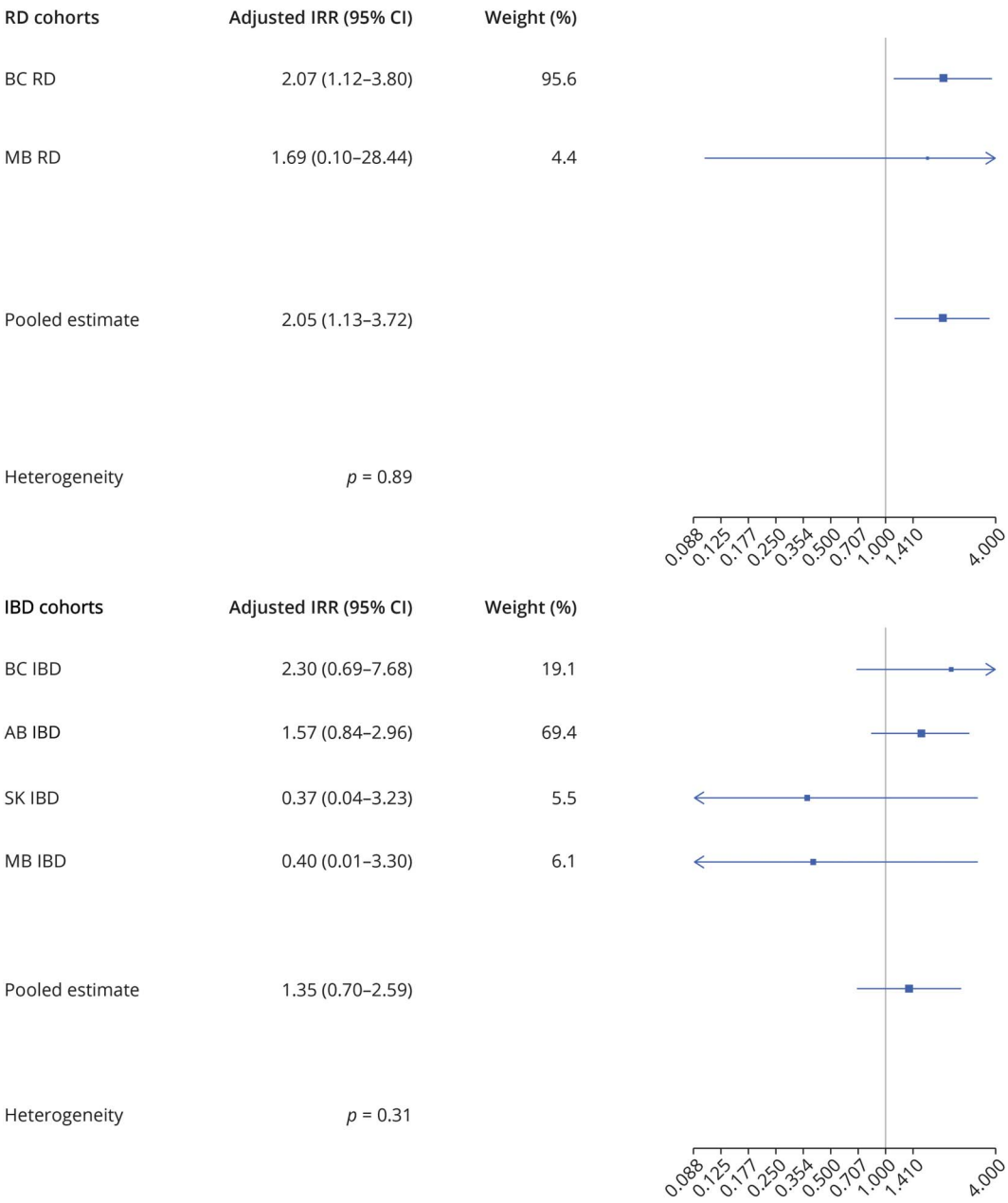
Abbreviations: IBD = inflammatory bowel diseases; MS = multiple sclerosis; RD = rheumatic disease; TNFα = tumor necrosis factor α.
[a] The RD cohort results were available in British Columbia and Manitoba.
[b] The IBD cohort results were available in British Columbia, Alberta, Saskatchewan, and Manitoba.
[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.

The mechanism for anti-TNFα potentially causing MS in persons with RD (and possibly IBD) is not fully understood. Current hypothesized mechanisms involve[11] (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 TNF receptor 2 which is important for the myelin repair; (3) anti-TNFα can also downregulate interleukin-10 and upregulate interleukin-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) patients with MS 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 this study were the use of large Canadian administrative data sets that included the entire RD and IBD cohorts from up to 4 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 British Columbia and Alberta. Data from the provinces of Saskatchewan and Manitoba had lower weights mainly because of smaller sample sizes, hence relatively lower precision (Figure 4). The association between anti-TNFα and MS risk was not consistent in the IBD cohort, possibly because of 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, because 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 before the typical symptoms of demyelinating disease.[43] 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

Figure 4 Association Between Antitumor Necrosis Factor α and Multiple Sclerosis Among 4 Canadian Provinces



Adjusted IRR and pooled estimates for the association between antitumor necrosis factor α (TNFα) and multiple sclerosis (MS) in the rheumatic disease (RD) and inflammatory bowel disease (IBD) cohorts in British Columbia (BC), Alberta (AB), Saskatchewan (SK), and Manitoba (MB), Canada.

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 nonusers. 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 a 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.

In conclusion, this is the largest population-based study to date using health administrative data sets from 4 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 nonusers. The finding of the increased MS risk could help clinicians and patients with RD who requires 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.[44,45]

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