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Sex differences in time to initiate NSAIDs or bDMARDs among patients with axial spondyloarthritis

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ABSTRACT

Objective: We evaluated sex differences in time to initiation of nonsteroidal anti-inflammatory agents (NSAIDs) or biologic disease modifying antirheumatic drugs (bDMARDs) among patients with axial spondyloarthritis (axSpA).

Methods: Using the 2013-2018 IBM® MarketScan® Database, we identified 174,632 axSpA patients aged ≥18 years. We evaluated the time between axSpA diagnosis and the first prescription NSAID dispensing (among those with no baseline NSAIDs use) or bDMARDs infusion/procedure claim (among those dispensed ≥ two different prescription NSAIDs in the baseline period). Adjusted hazard ratios (aHR) for time to initiation of NSAIDs or bDMARDs were computed using survival analyses. Cox proportional hazard models estimated associations between sex and predictors of treatment initiation.

Results: Average age at diagnosis was 48.2 years, 65.7% were females, and 37.8% had ≥ one NSAIDs dispensing before axSpA diagnosis. Of those without dispensing for ≥ two different prescription NSAIDs before diagnosis, NSAIDs were initiated earlier in females than males (NSAID initiators: Females (32.9%), Males (29.3%); aHR: 1.14, 95% CI: 1.11-1.16). Among those with ≥ two different prescription NSAIDs dispensations in the baseline period, 4.2% initiated a bDMARD while 77.9% continued NSAIDs use after diagnosis. Time to bDMARDs initiation was longer for females than males (aHR:0.61, 95% CI:0.52-0.72), but bDMARDs were initiated sooner among those with NSAIDs use in the baseline period.

Conclusion: Prescription NSAID use was more common than initiation of bDMARDs among patients newly diagnosed with axSpA. Females appeared more likely to continue NSAIDs after diagnosis, and the time to initiation of bDMARDs was longer for females than males.

Keywords: Spondyloarthritis, Nonsteroidal Antiinflammatory Drugs (Nsaids), Disease-Modifying Antirheumatic Drugs (Dmards),

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Significance and Innovations

- Our data showed that use of prescribed NSAIDs was more common than initiation of bDMARDs among patients with newly diagnosed axSpA, suggesting that treatment guidelines pertaining to the use of bDMARDs are being followed for axSpA.
- While females were more likely than males to continue use of NSAIDs, time to initiation of bDMARDs was longer for females.

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INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease affecting approximately 1.7 to 2.7 million (0.9% to 1.4%) American adults (1,2). (3) Despite recent studies having suggested that the prevalence of axSpA does not differ by sex (3) (5,6), females with axSpA exhibit different clinical manifestations and extent of radiographic damage compared to males (4). Extra-articular manifestations, such as enthesitis and inflammatory bowel disease, occur more frequently and are more severe in females than in males (5).

First line therapy for axSpA includes prescription of nonsteroidal anti-inflammatory drugs (NSAIDs) for a period of at least 4 weeks (6). Guidelines from rheumatological societies recommend that physicians consider alternative treatment options, such as biologic disease modifying anti-rheumatic drugs (bDMARDs), based upon disease severity (6–10). Biologic DMARDs, including tumor necrosis factor (TNF) inhibitors and interleukin (IL) inhibitors (e.g., IL-17), are effective in relieving symptoms, controlling disease activity, and improving physical function (6,7).

Research on sex differences in patterns of treatment initiation after a diagnosis of axSpA is extremely limited. Previous studies have focused primarily on treatment outcomes and high costs associated with bDMARDs in small non-representative samples (10–12). To the best of our knowledge, only one other study has assessed the time to bDMARD initiation in patients with axSpA (13). However, that study was conducted in Europe in a single center clinic-based sample.

Using national medical claims and encounters data from commercially insured US individuals, this study examined: 1) differences in time to NSAID or bDMARD initiation by sex among patients with axSpA; and 2) the extent to which factors associated with NSAID or bDMARD use in axSpA differ by sex. We hypothesized that

time to treatment initiation would be longer in women, since women have been found to be more reluctant to initiate treatment due to potential adverse effects or medication hesitancy (14–16).

METHODS

The UMass Chan Medical School Institutional Review Board considered this study to be not human subjects research, as it used a secondary, deidentified database.

Data Source

We used data from the IBM® MarketScan® Commercial Claims and Encounters Database (Jan 01, 2013 - Dec 31, 2018), a collection of US national medical claims and encounters data from commercially insured individuals (17). This database contains deidentified, individual-level data about inpatient and outpatient services rendered. It also includes data on patient demographics, outpatient pharmacy prescription claims, and information about annual enrollment in healthcare plans for each individual.

Study design

We considered the date of the first recorded axSpA diagnosis to be the index date (Supplemental Figure S1). The baseline period was defined as the 12-month period prior to the index date; the follow-up period was defined as the time-period following the index date (i.e., after the first recorded axSpA diagnosis). No minimum duration was required for the follow-up period.

Identification of axSpA cohort and analytic sample

Patients were eligible for inclusion in this study if they met one of the following criteria: (i) at least one diagnosis of axSpA during an inpatient visit; (ii) a diagnosis of

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axSpA recorded during each of at least two outpatient visits that occurred on different dates, at least 7 days apart; (iii) at least one outpatient diagnosis of axSpA made by a rheumatologist; or (iv) at least one diagnosis of axSpA during an outpatient visit and at least one dispensing of a conventional synthetic or biologic disease modifying antirheumatic drug (DMARD) (18–21). Targeted synthetic DMARDs, the janus kinase inhibitors tofacitinib and upadacitinib, were not included as these had not yet been approved by the Food and Drug Administration (FDA) for treatment of axSpA during the observation window. The International Classification of Diseases, Ninth Revision (ICD-9)/ International Classification of Diseases, Tenth Revision (ICD-10) codes used to identify axSpA cohort are provided in Supplemental Table S1.

Patients who satisfied one of the four axSpA criteria were identified (N=392,802) and those who were continuously enrolled within the MarketScan® database and who had both medical and pharmacy coverage for ≥12 months prior to their axSpA diagnosis (N=196,573) were ascertained (Supplemental Figure S2). After restricting the sample to those aged ≥18 years (N=191,569), the final analytic sample was limited to newly diagnosed patients, i.e., those who had no prior diagnosis of axSpA and had no record of a prescription for a bDMARD having been dispensed during the 12-month look back period before the index date (N=184,178). Lastly, to ensure initiation of axSpA-specific bDMARDs, we excluded individuals with other inflammatory diseases for which bDMARD treatment is indicated (rheumatoid arthritis (RA), psoriatic arthritis (PsA), and inflammatory bowel disease) (N=174,632).

Operational definition of sex

Sex was used as a biological variable from the index diagnosis because axSpA symptoms and clinical manifestations (4) may differ between females and males. In axSpA, female sex has been associated with poorer tolerance (e.g., side effects) of

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bDMARDs (4,22,23), which might impact a healthcare provider's decision to prescribe a bDMARD. For all analyses, we used males as the referent group.

Operational definition of pharmacological treatments

Treatment guidelines for axSpA recommend sequential therapeutic trials of two different prescription NSAIDs before initiating bDMARD therapy. In a retrospective, observational study, 43.0% patients with ankylosing spondylitis (AS) patients reported taking NSAIDs for pain relief either before or at the time of having received a physician-confirmed diagnosis of axSpA (24). In clinical practice, if a patient took NSAIDs to treat back pain prior to their diagnosis of axSpA, this can be considered as a therapeutic trial of NSAIDs when disease severity prompts consideration of prescription of a bDMARD (7).

Prescription NSAIDs

Because a therapeutic trial of a prescription NSAID is often initiated to treat back pain before a patient is diagnosed with axSpA, we created a variable to record NSAIDs use during the 12 months before the initial diagnosis of axSpA. Prescription NSAIDs include aspirin, celecoxib, diclofenac, ibuprofen, indomethacin, ketoprofen, meloxicam, naproxen, piroxicam, and sulindac. For patients who did not take an NSAID during the baseline period, we calculated the time to NSAID initiation as the time from the index date to the first dispensing of an NSAID after the diagnosis of axSpA. For patients who never began taking an NSAID throughout the study period, survival time in months was calculated as the time from the index date to the end of the study period or end of insurance coverage (whichever came first).

bDMARD initiation

Initiation of a bDMARD was defined as the first dispensing or administration of a bDMARD during the follow-up period after a diagnosis of axSpA. Biologic DMARDs

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include TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) and non-TNF biologic medications (secukinumab, ixekizumab, ustekinumab). For patients who had taken at least two different prescription NSAIDs during the baseline period, the time to bDMARD initiation was calculated as the time from the index date to the first prescription and/or infusion procedure claim for any bDMARD after the diagnosis of axSpA (Supplemental Figure S1).

Claims for medication dispensing were identified using National Drug Codes (NDC) and claims for infusions were identified using Healthcare Common Procedure Coding System (HCPCS) codes (Supplemental Table S2). Using the dispensing date of an individual bDMARD prescription or infusion, a binary variable was created to indicate bDMARD initiation during the follow-up period. All patients were followed until treatment with a bDMARD was initiated, the patient ended their continuous enrollment for medical and pharmacy coverage within the IBM® MarketScan® Commercial Claims and Encounters Database, or the study ended, whichever came first.

Other medications used to manage axSpA, RA, and PsA symptoms

Binary variables (yes/no) were created to determine filling of prescriptions for other medications, including conventional synthetic DMARDs (csDMARDs; sulfasalazine), short-term oral corticosteroids (dexamethasone, hydrocortisone, methylprednisolone, prednisone, triamcinolone), and opioids (codeine, hydrocodone, morphine, oxycodone, pentazocine, propoxyphene, tramadol), during each of two time periods: 1) the baseline period; and 2) the follow-up period between the index date and end of the study. The prescriptions filled were identified using NDC codes in the prescription drug tables (commercial claims and encounters data: outpatient pharmaceutical claims (CCAE-D)/2013-2018).

Other Covariates

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Sociodemographic and clinical characteristics collected during the baseline period included age in years at the time of the first recorded axSpA diagnosis, calendar year using the index date, geographic region (Northeast, North central, South, West), and health insurance plan type (health maintenance organization [HMO], preferred provider organization [PPO], consumer-directed/high deductible health plan [CDHP/HDHP], other). The Charlson Comorbidity Index score (25–27) was calculated using medical comorbidities captured by ICD-9/10 codes occurring during the baseline period. A binary variable (yes/no) was then created based on the Charlson Comorbidity Index score to indicate the presence of comorbidities. Binary variables (present/absent) were created initially to indicate the presence of each extraarticular manifestation, which were identified by the presence of claims during the baseline period: iritis/uveitis, and psoriasis. Initially, binary variables were created to signify the presence of each extraarticular manifestation, but we subsequently combined these into a single composite binary variable (yes/no) to indicate the presence of extraarticular manifestations. We enumerated healthcare utilization during the baseline period and during the follow-up period between the index date and the study's ending date: inpatient visits (0, 1, ≥2); emergency room (ER)/urgent care visits (0, 1, ≥2); and outpatient visits to healthcare providers, including rheumatologists, primary care providers, and other specialists (orthopedic surgeons/pain specialists) (0, 1, ≥2) (Supplemental Table S3).

Statistical Analysis

Descriptive statistics were used to describe baseline sociodemographic and clinical characteristics among patients with axSpA stratified by sex, with means and standard deviations (SD). Standardized mean differences were calculated for continuous variables and proportions were calculated for categorical variables. Differences in median follow-up time were examined by sex. The proportion of patients

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initiating prescription NSAIDs and the proportion initiating bDMARDs was estimated overall and by baseline NSAID use for bDMARDs initiators. The median times to initiation of NSAIDs and to initiation of bDMARDs were calculated overall and by sex. The bivariate relationships between sex and initiation of each treatment were examined separately for NSAIDs and for bDMARDs, with additional analyses stratified by baseline NSAID use for patients initiating bDMARDs. The proportion of patients for whom a medication of another class used to manage axSpA (i.e., corticosteroids, csDMARDs, and opioids) was dispensed during the baseline and follow-up periods were calculated overall and by sex.

Survival analyses were conducted to examine and compare possible differences in the time to initiation of treatment between female and male patients with axSpA. Models were run separately for initiation of NSAIDs and initiation of bDMARDs, with the latter model stratified by baseline NSAID use. Survival time to treatment initiation was reported in months and all analyses accounted for censoring by death, patient-specific end of continuous enrollment, and end of study period (28). In each model, the proportional hazards assumption was assessed using log-log survival curves and Schoenfeld residuals goodness of fit test (29). Kaplan-Meier estimates of survival probabilities with corresponding 95% confidence intervals (CI) and log-rank tests were used to compare time to treatment initiation by sex (26). Cox proportional hazard models that adjusted for demographic and clinical covariates were used to examine differences in time to treatment initiation between females and males with axSpA. Associations between sex and predictors of treatment initiation were assessed using sex-stratified Cox proportional hazards models (30). Adjusted hazard ratios (aHR) and 95% confidence intervals (CI) were derived from these models. Differences between females and males for each independent predictor were quantified by testing for statistical interaction (31). To further evaluate potential misclassification bias, sensitivity

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analyses were conducted by using restricted ICD-9/10 codes (ICD-9:720.0 and 720.X and ICD-10: M45x), ICD-9 codes only (not including ICD-10 codes), and ICD-9/10 codes that were recorded from rheumatologist only (defined by provider type) for the diagnosis of AS and axSpA (18–20). Statistical significance for the interaction term was defined as a p-value of <0.05.

RESULTS

Characteristics of patients with axSpA

For bDMARD initiation, the median follow-up time after axSpA diagnosis was 16.4 months for females (IQR: 23.1) and 15.8 months for males (IQR: 22.8); for NSAID initiation, the median follow-up time was 10.2 months for females (IQR: 17.7) and 10.6 months for males (IQR: 18.3). Overall, baseline demographic and clinical characteristics were similar between females and males (Table 1). The average age at diagnosis was 48.2 years, (SD=11.6), 65.7% of patients were female, and 49.4% were from the South. Approximately one in four of patients had been diagnosed before the age of 40 years.

During the 12-month baseline period, 6.1% of patients (females: 7.3%, males: 3.9%) had a claim for a rheumatologist visit, 84.0% (females: 85.6%, males: 80.8%) had a claim for a PCP visit, and 31.7% (females: 32.6%, males: 29.7%) had a claim for a visit to another specialist (orthopedic surgeon/pain specialist) (Table 1). With respect to indicators of healthcare utilization, 21.4% (females: 22.9%, males: 18.5%) had an urgent care/ER visit, and 8.8% (females: 9.5%, males: 7.5%) had been hospitalized at least once. During the baseline period (Table 1), while 16.7% (females: 17.7% males: 14.6%) had filled a prescription for a short-term oral corticosteroid, only 1.3% (females: 1.6%, males: 0.7%) had filled a prescription for a csDMARD, and 4.7% (females: 5.0%, males: 4.2%) had filled a prescription for an opioid.

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During the follow-up period, 11.8% of females had a claim for a visit to a rheumatologist, 85.0% had a claim for a visit to a PCP, and 43.8% had a claim for a visit to either a pain specialist or an orthopedic surgeon (Table 1). In addition, 14.9% of patients (females: 15.8%, males: 13.2%) had a claim for an inpatient hospitalization and 26.8% (females: 28.3%, males: 23.7%) had a claim for an urgent care/ER visit (Table 1). While 23.3% of patients (females: 24.8%, males: 20.4%) had filled a prescription for a short-term oral corticosteroid during the follow-up period, only 7.2% of patients (females: 7.7%, males: 6.3%) had filled a prescription for an opioid and 2.7% of patients (females: 3.2%, males: 1.7%) had filled a prescription for a csDMARD (Table 1).

Prescription NSAIDs use

Of the 174,632 patients with axSpA, 57.4% filled a prescription for an NSAID during the study period. In the year before their axSpA diagnosis, at least one prescription NSAID had been dispensed to 37.8% of patients (females: 39.7%; males: 34.1%) (data not shown). Of the 108,692 patients without any prescription NSAIDs dispensed during the baseline period (Table 2), 32.9% of females and 29.3% of males initiated NSAID therapy during the follow-up period. The median time to NSAID initiation after axSpA diagnosis was 5.4 months (IQR 13.1) for females and 5.2 months (IQR 13.7) for males. The most commonly initiated NSAIDs was meloxicam (8.9%), followed by ibuprofen (7.7%), diclofenac (6.8%) and naproxen (5.0%).

For time-to-initiate any NSAID or bDMARD following diagnosis, the proportional hazards assumption was met. Prescription NSAIDs were initiated earlier in females than in males (aHR: 1.14, 95% CI: 1.11-1.16) and in patients older than 30 years compared with those between the ages of 18 and 30 years ($aHR_{31\text{-}40\ years}$: 1.09, 95% CI: 1.05-1.14) (Table 3). NSAIDs were initiated earlier for those patients who had filled prescriptions for csDMARDs (aHR: 1.13, 95% CI: 1.01-1.26), short-term oral corticosteroids (aHR:

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1.44, 95% CI: 1.40-1.49), or opioids (aHR: 1.36, 95% CI: 1.29-1.44) during the 12 months before diagnosis than for patients who had not filled a prescription for these medications. Compared to axSpA patients living in the Northeast, NSAIDs initiation was significantly greater among axSpA patients living in the South (aHR: 1.19, 95% CI: 1.15-1.23) (Table 3) and was earlier among females than males (8.2% increase in HR for female vs male) (Table 5). However, the time to NSAID initiation was longer for females over 30 years of age relative to that for males older than 30 years (decrease in HR for female vs male; 31-40 years: 12.4%; 41-50 years: 20.4%; 51-60 years: 26.4%; >60 years: 27.6%).

Initiation of bDMARDs

The median time to bDMARD initiation after diagnosis of axSpA was 4.8 months (IQR 12.4) for females and 3.0 months (IQR 8.3) for males (Table 2). During the follow-up period, 2.4% of axSpA patients (2.1% females, 3.0% males) initiated a bDMARD after having been diagnosed with axSpA. Among the axSpA patients who initiated bDMARD treatment during the follow-up period, 1.4% were dispensed adalimumab and 0.5% were dispensed etanercept. The time to initiation of bDMARDs was longer for females than for males (aHR: 0.63, 95% CI: 0.59-0.67) (Table 3).

In the overall sample, time to bDMARD initiation was significantly longer among those axSpA patients older than 30 years, compared to those between the ages of 18 and 30 years, ($aHR_{51\text{-}60\ yrs}$: 0.39, 95% CI: 0.36-0.44; $aHR_{>60\ yrs}$: 0.26, 95% CI: 0.23-0.30) and among those living in the North central (aHR: 0.82, 95% CI: 0.73-0.91) and Southern (aHR: 0.86, 95% CI: 0.78-0.94) regions of the US, compared to those living in the Northeast (Table 3). The time to initiate bDMARDs was shorter among axSpA patients with pre-existing comorbidities (aHR: 1.43, 95% CI: 1.34-1.54) and extra-articular manifestations (aHR: 6.62, 95% CI: 6.01-7.30) than among those without these

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comorbidities (Table 3). Similarly, use of NSAIDs (aHR: 1.89, 95% CI: 1.78-2.02), csDMARDs (aHR: 4.87, 95% CI: 4.32-5.50), or short-term oral corticosteroids (aHR: 1.50, 95% CI: 1.40-1.62) during the baseline period was associated with earlier initiation of bDMARDs during the follow-up period (Table 3).

Among those who had been dispensed at least two different prescription NSAIDs during the baseline period, 3.7% of females and 5.4% of males subsequently filled a prescription for a bDMARD (Table 2). The median time to initiation of a bDMARD was 3.7 months for females (IQR 11.0) and 2.3 months (IQR 6.6) for males. The time to initiation of bDMARDs was significantly longer for females than for males (aHR:0.61, 95% CI:0.52-0.72) (Table 4). Compared to axSpA patients between the ages of 18 and 30 years, bDMARDs were initiated earlier among females than males older than 30 years of age (Table 6). While the time to bDMARD initiation was shorter for females relative to that for males for patients with pre-existing comorbidities (18.6% increase in HR for female vs male), it was longer among those who had been dispensed a short-term oral corticosteroid in the baseline period (14.8% decrease in HR for female vs. male). Similar associations were observed between sex and predictors of treatment initiation among those with dispensations for at least two different prescription NSAIDs before an axSpA diagnosis (Supplemental Table S4). Overall, results from the sensitivity analyses using restricted ICD codes were qualitatively similar to the primary findings (Supplemental Table S5 – Table S12).

DISCUSSION

Using national medical claims and encounters data from commercially insured patients in the US with newly diagnosed axSpA, we found that nearly one in three patients with axSpA had followed the guidelines recommended by the ACR with initiation of treatment with prescription NSAIDs after their index diagnosis. A very low

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proportion of females and males with axSpA initiated a bDMARD during the study period. Dispensing of prescription NSAIDs occurred more often for females than males. While females initiated NSAID treatment earlier after the diagnosis of axSpA than did males, bDMARD initiation was delayed in females compared to males.

In our study, only 2.4% of newly diagnosed axSpA patients initiated a bDMARD. Males were dispensed bDMARDs earlier than females, albeit the median time difference was only a few months. In the sex stratified analyses, bDMARD initiation was delayed in both sexes for individuals older than 30 years of age. However, compared to males, bDMARDs were initiated sooner among females 40 to 60 years old and in those with pre-existing comorbidities. Given the longer diagnostic delay and more severe extra-articular manifestations in females with axSpA compared to males (4), females might more likely be diagnosed at a more advanced stage of the disease compelling earlier treatment initiation.

Our finding that initiation of bDMARDs was low in both sexes is consistent with the results of previous research. A Taiwanese study using claims data reported bDMARDs initiation in only 1.3% of patients with ankylosing spondylitis (32). Similarly, two studies from Sweden and Canada found that 4.0% and 4.1% of patients with newly diagnosed rheumatic disease initiated a bDMARD (33,34). The relatively short duration of the follow-up period in our study could have contributed to the observed low frequency of bDMARD claims. Indeed, a 10-year delay from disease diagnosis to bDMARD initiation has been observed in over 60% of patients with ankylosing spondylitis treated with bDMARDs (35). On the other hand, the use of bDMARDs to treat axSpA is recommended only after inadequate response to two different prescription NSAIDs. Thus, our results suggest that treatment guidelines for axSpA pertaining to the use of bDMARDs are being followed.

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Despite guidelines recommending that NSAIDs be prescribed as first-line therapy for axSpA (7), only 57.4% of patients in our study had filled a prescription for an NSAID throughout the study period. A recent systematic review reported wide variation in the proportion of patients with axSpA using NSAIDs, ranging from 11.8% to 82.8% (36). Although the results of our analysis are consistent with those of similar studies, in which 35.0% to 50.0% of axSpA/ankylosing spondylitis patients had been prescribed NSAIDs (37,38), other studies have reported NSAID use by 70.0-80.0% of patients with a diagnosis of ankylosing spondylitis (39,40). Because we used claims data, we cannot determine whether patients who were prescribed NSAIDs also filled the prescription. Furthermore, information regarding use of over-the-counter pain medications was not available in our data source.

Early initiation of treatment for axSpA is crucial to retard disease progression (41). Clinical guidelines from the ACR recommend initiation of treatment with NSAIDs soon after diagnosis. However, in our study, treatment with NSAIDs or bDMARDs had not been initiated in 42.1% of axSpA patients following their diagnosis. Our finding is consistent with that of studies that examined time to treatment initiation among patients with other rheumatic conditions, in which 37.0%, and 51.4% did not initiate appropriate treatment within 12 months of diagnosis (42,43). One possible explanation for not having initiated NSAID or bDMARD treatment could be that 16.7% and 23.3% of patients had been treated with short-term oral corticosteroids during the baseline and follow-up periods. Concurrent use of NSAIDs with corticosteroids is not recommended since it may increase the potential for developing gastric ulceration and bleeding (44,45). Future studies to identify the potential factors contributing to treatment non-initiation among patients with axSpA are warranted.

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Our study is unique in that we evaluated the extent to which factors associated with initiation of bDMARDs differ by sex among axSpA patients in the US. We found that bDMARDs initiation, both among those with and without prescription NSAIDs dispensed at baseline, was delayed in females with axSpA compared to males. While males with ankylosing spondylitis typically experience rapid symptomatic relief (22,23,46), females respond less favorably to treatment with bDMARDs (4).Generally, females are more reluctant to initiate medications with potential adverse effects even when medication benefits outweigh the risks (14–16). The extent to which these factors may influence the decision by healthcare providers to initiate bDMARDs treatment for axSpA patients requires further investigation.

Study Strengths and Limitations

The study population included commercially insured adults in the US and may not be representative of the entire US population, i.e., publicly insured, and uninsured. Patients were included in the study sample based on the presence of specific diagnostic codes (47,48), which sometimes may be used incorrectly. Indeed, we observed higher proportion of women in our study sample indicating the potential for differential misclassification (i.e., women might be more likely to be misclassified than men). While we acknowledge the potential of misclassification using claims data, the criteria (18–21) and ICD 9/10 codes used for cohort identification have shown moderate positive predictive values (range:71%-83%) (18,20,49). To further evaluate potential misclassification bias, results from sensitivity analyses were qualitatively similar to the primary findings. Our data source lacked information on race/ethnicity, socioeconomic status, and disease severity, characteristics which may influence treatment initiation. In addition, considering that axSpA patients may utilize over-the-counter NSAIDs, prescription of NSAIDs may underestimate NSAID use and the true NSAIDs initiation

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rates. However, this underestimation likely is non-differential by sex (50). Further, prescription fills were used to assess medication exposure; filling of a prescription does not necessarily imply that the patient took the medication. Despite these limitations, our study has some notable strengths. To our knowledge, this study is the first to evaluate sex differences in the time to initiate NSAIDs or bDMARDs among US patients with axSpA. Use of a retrospective claims database provided a large sample size which permitted examination of patterns of medication use and healthcare utilization by axSpA patients both before and after diagnosis.

CONCLUSION

Use of prescription NSAIDs was more common than initiation of bDMARDs in patients with newly diagnosed axSpA. The decision to initiate a bDMARD in axSpA is complex for patients, physicians, and payers because of the high cost of these medications, as well as the requirement by many payers for prior authorization. In our study, females appeared more likely to continue NSAIDs use, and the time to initiate bDMARDs was longer for females than males. This emphasizes the need for additional research to determine whether low initiation rates of bDMARDs after treatment with two different prescription NSAIDs among females with a diagnosis of axSpA, compared to that among males, represents a missed opportunity to prevent disease progression and improve quality of life for this patient population.

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Table 1. Demographic and clinical characteristics of females and males with axSpA.

Patient characteristic	Overall N=174,632	Females N=114,800	Male N=59,832	Standardized mean difference
Age at diagnosis in years, mean (SD)	48.2 (11.6)	48.2 (11.5)	48.2 (11.8)	-0.0033
Age group at diagnosis, %				
18 to 30 years	9.3	9.1	9.7	0.0213
31 to 40 years	16.1	16.2	16.0	-0.0056
41 to 50 years	25.0	25.1	24.6	-0.0124
51 to 60 years	34.7	35.0	34.2	-0.0156
> 60 years	14.9	14.6	15.5	0.0243
Calendar year, %				
2014	24.8	25.1	24.4	-0.0195
2015	19.9	20.1	19.6	-0.0124
2016	22.3	22.3	22.3	-0.0011
2017	17.7	17.5	18.0	0.0114
2018	15.4	15.0	16.0	0.026
Geographic region, %				
Northeast	14.4	14.1	15.1	0.0281
North central	22.2	22.1	22.4	0.0079
South	49.4	50.0	48.2	-0.0351
West	13.3	13.1	13.6	0.0144
Health insurance plan type, %				
HMO	8.7	8.7	8.7	-0.0019
PPO	59.6	59.5	59.8	0.0046

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CDHP/HDHP	21.0	20.7	21.7	0.0230
Other[++]	10.6	11.0	9.8	-0.0382
Pre-existing comorbidities*, %	24.0	26.5	21.8	-0.1106
Extra-articular manifestations, %	1.9	1.8	2.0	0.014
Healthcare utilization in the baseline period (12 months before axSpA index date)				
Rheumatologist visits, %				
0	93.9	92.7	96.1	0.1448
1	2.7	3.1	2.0	-0.0668
≥ 2	3.4	4.2	1.9	-0.1324
Primary care provider visits, %				
0	16.0	14.4	19.2	0.13
1	12.9	12.4	13.8	0.0403
≥ 2	71.1	73.2	67.0	-0.1358
Other specialist visits (orthopedic surgeon/pain specialist), %				
0	68.4	67.4	70.3	0.0624
1	11.1	11.3	10.7	-0.019
≥ 2	20.6	21.3	19.0	-0.0572
Hospitalizations, %				
0	91.2	90.6	92.5	0.0699
1	5.9	6.5	4.7	-0.0773
≥ 2	2.9	3.0	2.8	-0.0103
Urgent care/ER visits, %				
0	78.6	77.1	81.5	0.1082
1	12.8	13.4	11.7	
≥ 2	8.6	9.5	6.8	-0.051
Use of other axSpA medication, %				-0.0984
Conventional synthetic DMARDs	1.3	1.6	0.7	-0.0814
NSAIDs	37.8	39.7	34.1	-0.1146
Corticosteroids (short-term use)	16.7	17.7	14.6	-0.0837
Opioids	4.7	5.0	4.2	-0.0413
Healthcare utilization in the follow-up period (time-period after axSpA index date)				
Rheumatologist visits, %				
0	89.2	88.1	91.3	0.1036
1	3.1	3.4	2.5	-0.057
≥ 2	7.7	8.4	6.3	-0.0836
Primary care provider visits, %				
0	16.2	14.9	18.5	0.0961
1	10.5	10.1	11.3	0.0371
≥ 2	73.3	74.9	70.2	-0.106
Other specialist visits, %				

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0	57.5	56.2	59.9	0.0749
1	10.9	11.1	10.5	-0.0186
≥ 2	31.6	32.7	29.6	-0.0672
Hospitalizations, %				
0	85.1	84.3	86.8	0.0737
1	8.8	9.6	7.3	-0.0836
≥ 2	6.1	6.2	5.9	-0.0113
Urgent Care/ER visits, %				
0	73.2	71.6	76.3	0.1057
1	13.6	13.9	13.0	-0.0264
≥ 2	13.2	14.4	10.7	-0.1127
Use of other axSpA medications, %				
Conventional synthetic DMARDs	2.7	3.2	1.7	-0.095
Corticosteroids	23.3	24.8	20.4	-0.1057
Opioids	7.2	7.7	6.3	-0.0539

HMO=Health maintenance organization, PPO=Preferred provider organization, CDHP=Consumer directed health plan, HDHP=High deductible health plan, ER=Emergency room, DMARDs=Disease modifying antirheumatic drugs, NSAIDs=Nonsteroidal anti-inflammatory drugs.

+ Other/Unknown includes long term disability, COBRA continued, surviving spouse/dependent and other/unknown

++Other includes Basic, Comprehensive, EPO, POS, and POS with capitation

* From inpatient/outpatient claims in the 12 months prior to index date- calculated using Charlson Comorbidity Index

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Table 2. Prescribing patterns among females and males with axSpA during the follow-up period.

Patient characteristic	Overall	Females	Males	Standardized mean difference
Among those without bDMARDs dispensations in the baseline period	**N=174,632**	**N=114,800**	**N=59,832**	
Any bDMARDs initiation, %	2.4	2.1	3.0	0.0574
TNF inhibitors				
Infliximab	0.2	0.2	0.3	0.0154
Adalimumab	1.4	1.1	1.8	0.0537
Golimumab	0.1	0.1	0.1	0.0002
Etanercept	0.5	0.5	0.7	0.0239
Certolizumab	0.1	0.1	0.04	-0.0073
Non-TNF inhibitors				
Secukinumab	0.2	0.2	0.3	0.0079
Ustekinumab	0.03	0.03	0.02	-0.0107
Ixekizumab	0.01	0.01	0.02	0.0009
Time to first bDMARDs medication since diagnosis in months*, Median (IQR)	3.9 (10.9)	4.8 (12.4)	3.0 (8.3)	-0.2439
Among those *without* dispensations for prescription NSAIDs in baseline period	**N=108,692**	**N=69,280**	**N=39,412**	
Any NSAIDs initiation, %	31.6	32.9	29.3	-0.0788
Naproxen	5.0	5.1	4.9	-0.0087
Ibuprofen	7.7	8.5	6.3	-0.0828
Indomethacin	0.7	0.4	1.1	0.0752
Diclofenac	6.8	7.2	6.2	-0.0408
Sulindac	0.1	0.1	0.1	0.0009
Piroxicam	0.2	0.2	0.2	0.003
Ketoprofen	0.1	0.1	0.04	-0.0107
Aspirin	0.4	0.4	0.5	0.0229
Meloxicam	8.9	9.1	8.3	-0.0291
Celecoxib	1.7	1.8	1.6	-0.0192
Time to first NSAIDs since diagnosis in months*, Median (IQR)	5.3 (13.3)	5.4 (13.1)	5.2 (13.7)	0.0012
Among those *with* dispensations for two different prescription NSAIDs in the baseline period**	**N=16,712**	**N=11,907**	**N=4,805**	
Any bDMARDs initiation, %	4.2	3.7	5.4	
TNF inhibitors				
Infliximab	1.4	1.2	1.7	0.0423
Adalimumab	2.4	2.0	3.2	0.0746
Golimumab	0.1	0.1	0.1	0.0021
Etanercept	1.1	0.9	1.4	0.0423
Certolizumab	0.1	0.2	0.1	-0.0292
Non-TNF inhibitors				
Secukinumab	0.3	0.3	0.4	0.0221

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Ustekinumab	0.1	0.1	0.04	-0.0041
Ixekizumab	0.02	0.02	0.02	0.0029
Time to first bDMARDs medication since diagnosis in months*, Median (IQR)	3.0 (9.5)	3.7 (11.0)	2.3 (6.6)	-0.2162
Continued use of NSAIDs, %	77.9	79.1	74.7	-0.1056

*Among patients who had any bDMARDs initiation after axSpA diagnosis. IQR=Interquartile range, DMARDs=Disease modifying antirheumatic drugs, NSAIDs=Nonsteroidal anti-inflammatory drugs.

**Of the 49,228 patients with prescription claims for only one NSAID in the baseline period, 65.6% (females: 66.3%, males: 64.0%) continued to fill prescriptions for NSAIDs in the follow-up period.

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Table 3. Cox proportional hazard model predicting time-to-initiate any NSAIDs or bDMARDs following diagnosis.

	Time to initiate any prescription NSAIDs (n=108,692)				Time to initiate any bDMARDs (n=174,632)			
	Crude Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI	Crude Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI
Female	1.15	1.13 - 1.18	1.14	1.11 - 1.16	0.69	0.65 - 0.73	0.63	0.59 - 0.67
Age group at diagnosis								
18 to 30 years	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
31 to 40 years	1.12	1.07 - 1.17	1.09	1.05 - 1.14	0.81	0.73 - 0.89	0.75	0.67 - 0.83
41 to 50 years	1.18	1.14 - 1.23	1.15	1.10 - 1.20	0.65	0.59 - 0.72	0.57	0.52 - 0.63
51 to 60 years	1.20	1.15 - 1.24	1.15	1.10 - 1.20	0.48	0.44 - 0.53	0.39	0.36 - 0.44
> 60 years	1.11	1.06 - 1.17	1.07	1.02 - 1.12	0.33	0.28 - 0.37	0.26	0.23 - 0.30
Calendar year								
2014	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
2015	1.14	1.11 - 1.18	1.12	1.08 - 1.15	1.05	0.96 - 1.14	0.97	0.89 - 1.07
2016	1.19	1.16 - 1.23	1.16	1.13 - 1.20	1.13	1.03 - 1.23	1.04	0.94 - 1.13
2017	1.22	1.18 - 1.26	1.18	1.14 - 1.22	1.35	1.23 - 1.49	1.19	1.07 - 1.31
2018	1.20	1.15 - 1.26	1.17	1.12 - 1.22	1.53	1.37 - 1.71	1.33	1.19 - 1.49
Geographic region								
Northeast	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
North central	0.99	0.96 - 1.03	0.98	0.95 - 1.02	0.80	0.73 - 0.89	0.82	0.73 - 0.91
South	1.20	1.16 - 1.24	1.19	1.15 - 1.23	0.85	0.77 - 0.93	0.86	0.78 - 0.94
West	1.02	0.98 - 1.06	1.04	0.99 - 1.08	1.31	1.18 - 1.45	1.36	1.21 - 1.49
Health insurance plan type								

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HMO	1.09	1.05 - 1.14	1.09	1.05 - 1.14	1.09	0.98 - 1.21	1.04	0.94 - 1.16
PPO	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
CDHP/ HDHP	1.04	1.02 - 1.08	1.05	1.02 - 1.08	1.00	0.92 - 1.08	0.96	0.89 - 1.04
Other[++]	1.03	0.99 - 1.06	1.01	0.98 - 1.05	0.97	0.88 - 1.08	1.08	0.97 - 1.20
Pre-existing comorbidities[*]	1.12	1.09 - 1.15	1.04	1.01 - 1.07	1.54	1.45 - 1.64	1.43	1.34 - 1.54
Extraarticular manifestations	1.02	0.94 - 1.10	0.99	0.92 - 1.07	7.20	6.71 - 7.71	6.62	6.01 - 7.30
Baseline conventional synthetic DMARD use	1.31	1.18 - 1.47	1.13	1.01 - 1.26	7.64	6.95 - 8.40	4.87	4.32 - 5.50
Baseline NSAID use	Not applicable				1.91	1.80 - 2.03	1.89	1.78 - 2.02
Baseline corticosteroid use	1.52	1.47 - 1.56	1.44	1.40 - 1.49	1.82	1.70 - 1.95	1.50	1.40 - 1.62
Baseline opioid use	1.47	1.40 - 1.55	1.36	1.29 - 1.44	1.11	0.97 - 1.27	0.94	0.82 - 1.09

HMO=Health maintenance organization, PPO=Preferred provider organization, CDHP=Consumer directed health plan, HDHP=High deductible health plan, DMARDs=Disease modifying antirheumatic drugs, NSAIDs=Nonsteroidal anti-inflammatory drugs.

[++]Other includes Basic, Comprehensive, EPO, POS, and POS with capitation

* From inpatient/outpatient claims in the 12 months prior to index date- calculated using Charlson Comorbidity Index

The Cox proportional hazard models were adjusted for demographic and clinical covariates (age group, calendar year, region, employment status of beneficiary, health plan type, pre-existing comorbidities, and presence of extra-articular manifestations) and use of other axSpA medications in the baseline period (yes/no for conventional synthetic DMARDs, NSAIDs, Corticosteroids, opioids).

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Table 4. Cox proportional hazard model predicting time-to-initiate bDMARDs following diagnosis among axSpA patients with claims for nonsteroidal anti-inflammatory drugs (NSAIDs) in the baseline period (n=16,712).

	Time to initiate any bDMARDs use			
	Crude Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI
Female	0.67	0.57 - 0.78	0.61	0.52 - 0.72
Age group at diagnosis				
18 to 30 years	Ref	Ref	Ref	Ref
31 to 40 years	0.57	0.44 - 0.72	0.56	0.43 - 0.72
41 to 50 years	0.41	0.32 - 0.51	0.43	0.34 - 0.55
51 to 60 years	0.28	0.22 - 0.35	0.28	0.22 - 0.36
> 60 years	0.17	0.12 - 0.24	0.17	0.12 - 0.24
Calendar year				
2014	Ref	Ref	Ref	Ref
2015	1.12	0.89 - 1.40	1.09	0.86 - 1.37
2016	1.11	0.89 - 1.40	1.11	0.88 - 1.40
2017	1.22	0.95 - 1.56	1.16	0.90 - 1.49
2018	1.64	1.26 - 2.14	1.49	1.14 - 1.96
Geographic region				
Northeast	Ref	Ref	Ref	Ref
North central	0.72	0.55 - 0.94	0.81	0.61 - 1.07
South	0.84	0.67 - 1.05	0.92	0.73 - 1.16
West	1.30	0.99 - 1.71	1.34	1.01 - 1.76
Health insurance plan type				
HMO	0.87	0.67 - 1.14	0.91	0.70 - 1.19
PPO	Ref	Ref	Ref	Ref
CDHP/HDHP	0.89	0.73 - 1.08	0.84	0.69 - 1.02
Other[++]	0.94	0.73 - 1.20	1.05	0.82 - 1.35
Pre-existing comorbidities[*]	1.45	1.25 - 1.69	1.33	1.13 - 1.57
Extraarticular manifestations	6.19	4.79 - 8.01	5.31	4.08 - 6.92
Baseline conventional synthetic DMARD use	7.03	5.61 – 8.82	5.63	4.41- 7.17
Baseline corticosteroid use	1.55	1.33 - 1.80	1.37	1.17- 1.61
Baseline opioid use	0.84	0.64 - 1.10	0.78	0.59 - 1.03

HMO=Health maintenance organization, PPO=Preferred provider organization, CDHP=Consumer directed health plan, HDHP=High deductible health plan, DMARDs=Disease

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modifying antirheumatic drugs. [++]Other includes Basic, Comprehensive, EPO, POS, and POS with capitation

* From inpatient/outpatient claims in the 12 months prior to index date- calculated using Charlson Comorbidity Index

The Cox proportional hazard models were adjusted for demographic and clinical covariates (age group, calendar year, region, employment status of beneficiary, health plan type, pre-existing comorbidities, and presence of extra-articular manifestations) and use of other axSpA medications in the baseline period (yes/no for conventional synthetic DMARDs, NSAIDs, Corticosteroids, opioids).

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Table 5. Association of sex with baseline predictors of NSAID initiation in axSpA.

	Adjusted HR	95% CI		P value*
Age group at diagnosis				
18 to 30 years	Ref	Ref	Ref	
31 to 40 years				0.012
Female	1.05	0.99	1.11	
Male	1.18	1.09	1.28	
41 to 50 years				<.0001
Female	1.08	1.02	1.13	
Male	1.30	1.21	1.40	
51 to 60 years				<.0001
Female	1.06	1.01	1.11	
Male	1.34	1.25	1.44	
> 60 years				<.0001
Female	0.98	0.92	1.04	
Male	1.25	1.15	1.36	
Calendar year				
2014	Ref	Ref	Ref	
2015				0.74
Female	1.11	1.07	1.15	
Male	1.12	1.07	1.18	
2016				0.59
Female	1.16	1.12	1.20	
Male	1.18	1.12	1.24	
2017				0.17
Female	1.16	1.11	1.21	
Male	1.22	1.15	1.29	
2018				0.013
Female	1.12	1.06	1.18	
Male	1.25	1.17	1.35	
Geographic region				
Northeast	Ref	Ref	Ref	
North central				0.33
Female	1.00	0.95	1.04	
Male	0.96	0.90	1.02	
South				0.018
Female	1.22	1.17	1.27	
Male	1.12	1.06	1.19	
West				0.49
Female	1.05	0.99	1.10	
Male	1.02	0.95	1.09	
Health insurance plan type				
Health Maintenance Organization (HMO)				0.32
Female	1.11	1.06	1.16	

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Male	1.06	0.99	1.14	
Preferred Provider Organization (PPO)	Ref	Ref	Ref	
CDHP/HDHP				0.14
Female	1.06	1.03	1.10	
Male	1.02	0.97	1.07	
Other[++]				0.73
Female	1.02	0.98	1.06	
Male	1.00	0.94	1.07	
Pre-existing comorbidities[**]				0.96
Female	1.04	1.01	1.07	
Male	1.04	0.99	1.09	
Presence of extraarticular manifestations				0.20
Female	0.95	0.86	1.05	
Male	1.06	0.93	1.21	
Baseline non-biologic DMARD use				0.89
Female	1.13	1.00	1.28	
Male	1.15	0.88	1.51	
Baseline corticosteroid use				0.30
Female	1.48	1.40	1.56	
Male	1.43	1.38	1.48	
Baseline opioid use				0.99
Female	1.36	1.24	1.50	
Male	1.36	1.28	1.45	

[*]P-value is from the interaction of sex with each covariate. CDHP=Consumer directed health plan, HDHP=High deductible health plan, DMARDs=Disease modifying antirheumatic drugs, NSAIDs=Nonsteroidal anti-inflammatory drugs.

[+]Other/Unknown includes long term disability, COBRA continuee, surviving spouse/dependent and other/unknown

[++]Other includes Basic, Comprehensive, EPO, POS, and POS with capitation

[*]From inpatient/outpatient claims in the 12 months prior to index date- calculated using Quan's comorbidity index

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Table 6. Association of sex with baseline predictors of bDMARD initiation in axSpA.

	Adjusted HR	95% CI		P value*
Age group at diagnosis				
18 to 30 years	Ref	Ref	Ref	
31 to 40 years				
Female	0.77	0.67	0.89	0.50
Male	0.72	0.62	0.84	
41 to 50 years				
Female	0.63	0.55	0.73	0.03
Male	0.50	0.43	0.58	
51 to 60 years				
Female	0.44	0.38	0.50	0.02
Male	0.35	0.30	0.40	
> 60 years				
Female	0.28	0.23	0.34	0.21
Male	0.24	0.19	0.29	
Calendar year				
2014	Ref	Ref	Ref	
2015				
Female	0.96	0.85	1.08	0.70
Male	0.99	0.86	1.14	
2016				
Female	1.05	0.93	1.19	0.68
Male	1.01	0.88	1.16	
2017				
Female	1.17	1.03	1.33	0.77
Male	1.20	1.04	1.40	
2018				
Female	1.31	1.13	1.52	0.73
Male	1.36	1.05	1.61	
Geographic region				
Northeast	Ref	Ref	Ref	
North central				0.26
Female	0.86	0.75	1.00	
Male	0.77	0.65	0.90	
South				
Female	0.91	0.81	1.03	0.16
Male	0.80	0.70	0.91	
West				
Female	1.40	1.21	1.62	0.49
Male	1.30	1.11	1.52	
Health insurance plan type				
Health Maintenance Organization (HMO)				0.19
Female	0.98	0.85	1.31	

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Male	1.13	0.96	1.33	
Preferred Provider Organization (PPO)	Ref	Ref	Ref	
CDHP/HDHP				0.48
Female	0.97	0.88	1.08	
Male	0.93	0.83	1.05	
Other[++]				0.85
Female	1.09	0.95	1.24	
Male	1.07	0.90	1.26	
Pre-existing comorbidities[**]				
Female	1.56	1.42	1.70	0.0059
Male	1.27	1.14	1.42	
Presence of extraarticular manifestations				
Female	6.89	6.06	7.83	0.33
Male	6.25	5.38	7.25	
Baseline non-biologic DMARD use				
Female	4.63	4.00	5.37	0.39
Male	5.20	4.18	6.46	
Baseline NSAID use				
Female	1.91	1.76	2.08	0.67
Male	1.86	1.69	2.05	
Baseline corticosteroid use				
Female	1.42	1.30	1.56	0.08
Male	1.63	1.45	1.82	
Baseline opioid use				
Female	1.01	0.86	1.20	0.16
Male	0.82	0.64	1.05	

[*]P-value is from the interaction of sex with each covariate. CDHP=Consumer directed health plan, HDHP=High deductible health plan, DMARDs=Disease modifying antirheumatic drugs, NSAIDs=Nonsteroidal anti-inflammatory drugs.

[+]Other/Unknown includes long term disability, COBRA continuee, surviving spouse/dependent and other/unknown

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[**]From inpatient/outpatient claims in the 12 months prior to index date- calculated using Quan's comorbidity index

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