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Does Gender Impact a Diagnosis of Ankylosing Spondylitis?

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Objective. The study objective was to explore differences in ankylosing spondylitis (AS) diagnosis experiences between men and women by examining the coding of health events over the 2 years preceding AS diagnosis.

Methods. Claims data (January 2006–April 2019) from the MarketScan databases were examined. Patients who had received two or more AS diagnoses at least 30 days apart and had at least 2 years of insurance enrollment before their first AS diagnosis were analyzed. Men were matched 1:1 to women by age, diagnosis date, insurance type, and enrollment duration. Health events (diagnosis and provider codes) were examined over 2 years before AS diagnosis and stratified by gender. Data were analyzed using univariate χ^2 tests.

Results. Among 7744 patients, 274 of 1906 AS-related codes showed statistically significant differences between men and women. Women received more diagnosis codes than men across diagnoses and providers; the largest difference in diagnosis codes among women versus men was in peripheral symptom coding (57.7% vs. 43.9%, respectively). More women than men received diagnosis codes for depression (21.2% vs. 9.8%) and other musculoskeletal symptoms (52.8% vs. 40.0%); only gout was more common in men (6.5%) than in women (2.2%). Among men, backache codes gradually increased 12 months before AS diagnosis, whereas axial and sacroiliitis coding increased sharply immediately before diagnosis. The greatest difference in physician types visited was for rheumatologists: 64.2% of women had visits compared with 45.1% of men.

Conclusion. Further investigation into the dissimilarities in diagnostic experiences between men and women is needed to determine whether differences are due to disease phenotype or potential cognitive bias influencing diagnostic decision-making.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic progressive disease characterized by the inflammation of the axial skeleton, peripheral joints, and entheses (1,2). The true prevalence of axSpA is not known, largely as a result of significant delays in axSpA diagnosis and the under-recognition of the disease by health care professionals who see patients with chronic back pain (3). Nevertheless, the National Health and Nutrition Examination Survey conducted in 2009-2010 estimated that the prevalence of axSpA ranges from 0.9% to 1.4% among the adult population in the United States (3,4). On average, patients experience symptoms for 5 to 14 years before receiving a diagnosis of axSpA (5–7). Diagnosis delay is partly attributed to the challenges in differentiating inflammatory back pain—a key clinical feature of axSpA affecting the spine and sacroiliac joints—from other forms of chronic back pain in the general population (8–10). An earlier diagnosis and the

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prompt treatment of disease may significantly ameliorate the burden of disease, resulting in better quality of life; nonetheless, misdiagnoses, delays in diagnosis, and underdiagnosis persist (3,11).

The term axSpA encompasses patients with radiographic sacroiliitis visible on imaging (ankylosing spondylitis [AS]) and those without evidence of radiographic damage in the sacroiliac joints (non-radiographic axSpA) (12). Historically, AS was considered a disease that primarily affected men (13–15). Some investigations have revealed the prevalence of sacroiliitis and the severity of radiographic spinal damage to be lower in women than in men, contributing to the under-recognition of AS among women (16). In addition, other studies have shown that women with AS are more likely than men to have peripheral arthritis and extra-articular manifestations (eg, enthesitis, psoriasis, and inflammatory bowel disease), leading to misdiagnosis or longer delays in diagnosis (17–19) despite a similar age of disease onset among both men and women or even slightly earlier among women (20,21). Although a Canadian cross-sectional study reported that women were more likely to seek routine health care consults compared with men (22), it is unclear whether true biologic differences in AS disease characteristics exist between men and women, or whether implicit bias exists in the diagnostic process that creates differences in diagnostic delay based on gender. Better understanding and characterization of these distinctions and a greater awareness of the differences in overall disease burden and presentation among men and women with AS could lead to improved disease management (23).

Health care claims databases provide a diverse set of information, such as coding of health events, that can be used to gain a better understanding of the experience of the patient in their journey to an AS diagnosis. We sought to specifically understand the contrasts between men and women in their pathway to AS diagnosis by using administrative claims data to analyze health events (ie, diagnosis codes and provider specialties consulted by patients) before AS diagnosis. Our study may help clarify whether true gender differences exist in the presentation and natural history of axSpA or whether there exist differences in the diagnostic algorithms or workup between men and women.

PATIENTS AND METHODS

Data source and variables. This retrospective cohort study used administrative claims data from the Truven MarketScan research databases (24) from January 2006 to April 2019. As of 2020, the Truven MarketScan databases comprise more than 263 million patients, allowing concurrent analysis of integrated pooled data from multiple sources, such as employers, state agencies, and various health plans. Available data sets include claims for inpatient and outpatient services and outpatient prescription drugs; these claims data are linked from hospital discharge records, electronic medical records, laboratory results, mortality data, and employer records (eg, absenteeism, disability, and workers' compensation). Use of these databases allows for longitudinal tracking of patient data across the care continuum, from the initial provider visit to carve-out care—ie, the subcontracting of certain health care services to a third-party insurance plan or network. Variables, derived entirely from the Truven MarketScan databases, include sequence of health events and patient demographics.

Study population and data analysis. Patients with AS must have satisfied the following criteria for inclusion in the analysis: the receipt of two diagnoses of AS (specified by the International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification [ICD-9-CM and ICD-10-CM]) at least 30 days apart and 2 or more years of continuous insurance enrollment before receiving an AS diagnosis. The following ICD-9-CM and ICD-10-CM diagnosis codes were included: 720.0 (AS and other inflammatory spondylopathies), M08.1 (juvenile AS), and M45.0-9 (AS). For the purpose of this study and for consistency, we are classifying disease as "AS"; however, we recognize that during the duration of our study period (2006-2019), it is likely that clinicians may have coded patients in the wider axSpA disease spectrum as having "AS" because there were no diagnosis codes for non-radiographic axSpA at the time. Men with AS were matched 1:1 to women with AS by age (within 5 years), date of AS diagnosis (within 1 year), insurance type (commercial, supplemental Medicare, Medicaid), and enrollment duration (within 1 year). Demographic data collected included age, gender, work status, US geographic location, insurance type, index date (date of first AS diagnosis), and service date of health event.

Health event data were extracted every 6 months for the 2 years before AS diagnosis. A health event referred to any health service provided to the patient before their first AS diagnosis as compiled from their medical and pharmacy claims history. A sequence of health events was the consecutive order of events arranged by the service date provided in the claims database. Health events comprised diagnosis codes specified by ICD-9-CM and ICD-10-CM and specialty physician types (eg, general practitioners, dermatologists, and rheumatologists) as specified by the Truven MarketScan databases. To identify codes that were relevant to AS, an initial comparison was made between the patients with AS enrolled in this study and randomly selected demographically matched controls from the Truven MarketScan database. Codes that were significantly present in the AS group, but not in the control group, were kept. We identified a total of 1906 AS-related codes for diagnoses, specialties, procedures, and drugs that were then examined for gender differences. Results were additionally stratified by men versus women and analyzed using univariate χ^2 tests. P values less than the Bonferroni-corrected significance threshold of 0.05/1906 were used as a cutoff for statistical significance.

This study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology, the Strengthening the Reporting of Observational Studies in Epidemiology guidelines, and the ethical principles in the Declaration of Helsinki. All records are in full compliance with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996. Because this study is a retrospective examination of deidentified claims data in compliance with US patient confidentiality requirements and did not involve the collection, use, or transmittal of individually identifiable data, institutional review board approval for patient consent was not required.

RESULTS

Patient disposition and demographics. Of the more than 265 million covered patients in the Truven MarketScan databases, 4281 women and 4105 men were eligible for the analysis; of these, 3872 men and women (7744 total) were matched and included in our study, dropping 409 women and 233 men (<10%) from the analysis. The baseline demographics of men and women with AS are shown in Table 1. The mean (SD) age for men was 45.1 (14.4) years and for women was 45.3 (14.1) years. Women were less likely than men to be working full time (41.2% vs. 47.1%). Overall, 74.9% and 81.4% of men and women, respectively, were diagnosed with AS by a rheumatologist; approximately 5% of both men and women received their diagnosis from a general practitioner.

Patient diagnosis history and specialty physician analyses. Of the 1906 codes examined for differences between women and men, 274 codes across diagnoses (n = 100), specialties (n = 12), procedures (n = 111), and drugs (n = 51) showed statistically significant differences—ie, meeting the Bonferroni-corrected significance threshold of 0.05/1906. In general, women received more codes than men across diagnoses and providers

Table 1. Baseline demographics of men and women diagnosed with AS[a,b]

Characteristic	Men (N = 3872)	Women (N = 3872)
Age, mean (SD), y	45.1 (14.4)	45.3 (14.1)
Work status, %		
Active full time	47.1	41.2
Active part time	0.5	1.3
Early retiree	6.1	5.0
Medicare-eligible retiree	6.2	6.7
Insurance type, %		
Commercial	90.2	90.2
Medicaid	1.2	1.2
Medicare	8.6	8.6
US geographic region, %		
Northeast	18.2	18.3
North Central	18.0	14.2
South	43.4	46.8
West	18.8	18.9
Unknown	1.7	1.8
Diagnosing physician, %		
Rheumatologist	74.9	81.4
General practitioner	5.7	4.5
Other	19.5	14.0

Abbreviations: AS, ankylosing spondylitis; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.
[a]Patients with AS must have satisfied the following criteria for inclusion in the analysis: the receipt of two diagnoses of AS, specified by ICD-9-CM and ICD-10-CM, ≥30 days apart and ≥2 years of continuous insurance enrollment before receiving an AS diagnosis (the following ICD-9-CM and ICD-10-CM diagnosis codes were included: 720.0 [AS and other inflammatory spondylopathies], M08.1 [juvenile AS], and M45.0-9 [AS]).
[b]Men with AS were matched 1:1 to women with AS by age (within 5 years), date of AS diagnosis (within 1 year), insurance type (commercial, supplemental Medicare, Medicaid), and enrollment duration (within 1 year).

Table 2. Differences in the proportion of men versus women who had different categorized diagnostic features in the 2 years before ankylosing spondylitis diagnosis

Grouped diagnoses, %	Men	Women	Difference
Peripheral[a]	43.9	57.7	−13.7*
mSK NOS	40.0	52.8	−12.8*
Unspecified	46.9	59.6	−12.7*
Depression	9.8	21.2	−11.4*
Other malaise and fatigue	18.1	28.2	−10.1*
Skin	26.9	36.4	−9.4*
Rheumatoid arthritis	12.0	20.9	−8.9*
Inflammatory polyarthropathy[b]	11.9	20.7	−8.8*
Osteoarthritis	25.5	34.0	−8.5*
GERD	13.1	21.0	−8.0*
Spondylopathy	17.6	24.0	−6.4*
Enthesitis	11.7	17.5	−5.8*
Axial[c]	50.0	54.6	−4.7
Fibromyalgia	0.7	4.3	−3.6*
Obesity	5.3	8.8	−3.4*
Sacroiliitis	8.8	12.1	−3.4*
Backache	20.1	22.9	−2.8
Inflammatory bowel disease	5.6	5.4	0.1
Psoriasis	4.0	3.4	0.6
Psoriatic arthritis	5.3	4.6	0.8
Gout	6.5	2.2	4.3*

Abbreviations: GERD, gastroesophageal reflux disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; mSK NOS, musculoskeletal not otherwise specified.
Note: Differences represent the proportion of men minus the proportion of women with diagnosis coding. Green shading (negative values) indicates that the event was more common in women.
[a]Peripheral comprises more than 150 codes related to pain or arthritis in hands/wrists, elbows, arms, feet/ankles, knees, and legs and includes codes for rheumatoid arthritis, osteoarthritis, and enthesitis.
[b]Inflammatory polyarthropathy includes codes for inflammatory polyarthropathy (ICD-10-CM, M064), unspecified inflammatory polyarthropathy (ICD-9-CM, 714.9), and other specified inflammatory polyarthropathies (ICD-9-CM, 714.89).
[c]Axial comprises more than 50 codes relating to axial disorders and syndromes and includes codes for spondylopathy, sacroiliitis, and backache.
* *P* value less than the Bonferroni-corrected significance threshold of 0.05/1906.

Table 3. Differences in the proportion of men versus women who visited different specialties during the 2 years before ankylosing spondylitis diagnosis

Specialty, %	Men	Women	Difference
Rheumatology	45.1	64.2	−19.1*
Pathology	30.8	49.4	−18.6*
Radiology	67.1	82.3	−15.2*
Acute care hospital	68.1	81.6	−13.5*
Anesthesiology	24.1	37.1	−13.0*
Laboratory	58.6	69.8	−11.2*
Gastroenterology	18.8	27.0	−8.3*
Neurology	11.0	19.2	−8.2*
Imaging center	10.1	15.5	−5.4*
Ambulatory surgery centers	11.9	16.8	−4.9*
Psychiatry/psychology	7.4	12.0	−4.6*
Cardiovascular disease/ cardiology	20.1	24.6	−4.5*
Therapy (physical)	19.7	24.2	−4.5*
Orthopedic surgery	32.9	37.2	−4.3
General practice	86.1	89.5	−3.4

Note: Differences represent the proportion of men minus the proportion of women with specialty coding. Green shading (negative values) indicates that the event was more common in women.
* *P* value less than the Bonferroni-corrected significance threshold of 0.05/1906.

(Tables 2 and 3). Compared with men, women also had more diagnosis coding for peripheral signs and symptoms (57.7% vs. 43.9%), a variety of nonspecific musculoskeletal symptoms (52.8% vs. 40.0%), unspecified coding (59.6% vs. 46.9%), and depression (21.2% vs. 9.8%) (all $P < 0.05/1906$). Coding for axial symptoms, backache, inflammatory bowel disease, psoriasis, and psoriatic arthritis was similar between men and women. Of the codes examined, only gout was significantly more common in men than in women (6.5% vs. 2.2%) ($P < 0.05/1906$).

These differences were observed throughout the 2 years before AS diagnosis. Women generally showed increased coding for most diagnoses during the entire 2-year period leading up to AS diagnosis. Furthermore, we observed that coding for backache gradually increased in men starting at 12 months before their AS diagnosis, whereas axial and sacroiliitis coding increased sharply in men immediately before AS diagnosis (Figure 1). Similar trends over time were observed among the subgroup of patients who were diagnosed with AS by rheumatologists only (Supplementary Figure S1). When looking at physician types visited in the 2 years before AS diagnosis, women had a significantly greater number of visits than men for nearly all specialty types (Table 3). The greatest difference was observed for rheumatologists: 64.2% of women had visits versus 45.1% of men ($P < 0.05/1906$).

DISCUSSION

This analysis examined a clinically relevant subset of health events (ie, diagnosis codes and health care provider specialties seen by patients) using the Truven MarketScan research databases before AS diagnosis in men versus women. Our study revealed differences in number and composition of coding between men and women during the 2-year period leading up to diagnosis of AS. The greatest variations in diagnoses observed were for peripheral versus axial coding, unspecified coding, musculoskeletal signs and symptoms, and depression. These findings, over a range of codes, are consistent with the possibility of differences in disease phenotype between men and women that results in divergent pathways to a diagnosis of AS. However, an alternative explanation for these findings is possible, ie, that a

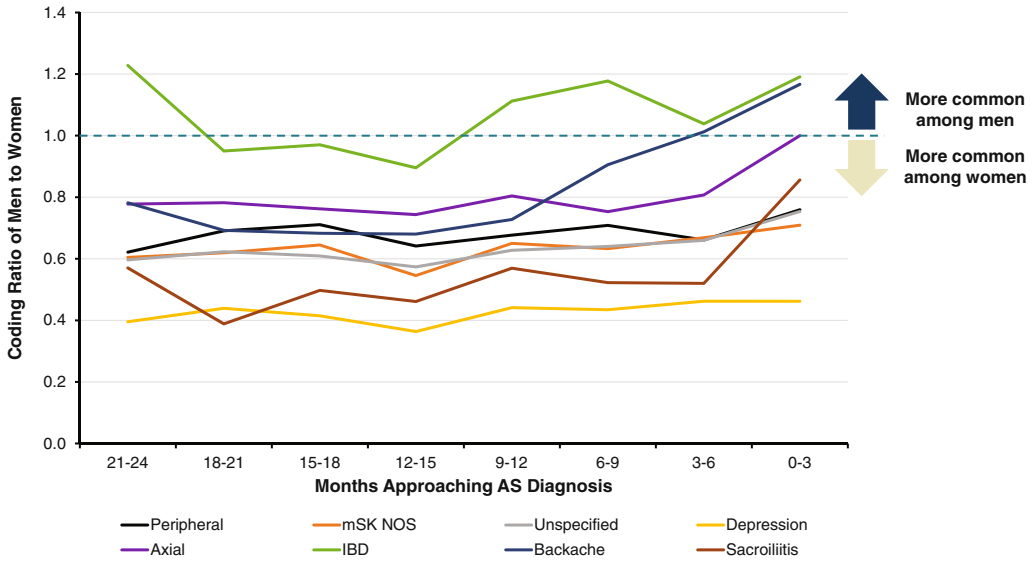

Figure 1. Differences in diagnosis codes among men and women with AS in the 2 years before its diagnosis. AS, ankylosing spondylitis; IBD, inflammatory bowel disease; mSK NOS, musculoskeletal not otherwise specified.

cognitive bias exists, providing a framework for the health care practitioner to use different tools and testing events when making a diagnosis of AS—and more broadly axSpA—in women.

Health care claims data have been used to analyze diagnostic prevalence, health care utilization, and treatment patterns among patients with AS in the United States (25–28); however, to our knowledge, this was the first study to have used claims data to evaluate the diagnostic experience of men and women with AS in their pursuit of a diagnosis. In general, the women with AS in our study received more diagnosis codes than men, pointing to differences between men and women in the pathways to AS diagnosis. Additionally, a greater number of visits to rheumatologists by women versus men supports the hypothesis that there is a greater challenge to clinicians in diagnosing the AS disease spectrum in women than in men. It is not clear whether this represents true disease spectrum differences in disease presentation or implicit diagnostic bias considering the historical context that AS was believed to predominantly affect men (13–15).

Women with AS in our study received significantly more diagnosis codes for peripheral symptoms in the 2 years preceding an AS diagnosis than men. The higher frequency of peripheral symptoms among women in our study is in agreement with previous reports (17,19,29,30); this is pertinent because the AS classification criteria were amended to include an equal consideration of both axial and peripheral manifestations of the disease (7,31–33). Additionally, because it has been shown in other studies that—compared with men—women with AS are not as likely to receive biologics as treatment for AS and are more likely to receive other therapies such as disease-modifying antirheumatic drugs, corticosteroids, prednisone, and opioids (16,26), symptomatic relief from these medications may perpetuate potential misdiagnosis, especially in women with early AS.

The gender differences seen in our study were previously reported, indicating the possibility of variation in AS manifestations between women and men. AS may manifest differently among women because of distinct immunologic (34,35) and genetic (36,37) responses to the disease compared with men. Enthesitis (30,38) and AS disease burden (39–41) are reportedly more severe among women than among men. The greater level of disease burden in women may partly be attributed to the phenomenon of central sensitization, as characterized by perceived pain due to dysregulation of the central nervous system (42). In the current study, fibromyalgia was more commonly diagnosed in women than in men (4.3% vs. 0.7%)—in agreement with other reports (42–44). Because of the overlap of symptoms of central sensitization and inflammatory rheumatic diseases, ascertaining overall disease severity may be difficult (42,45). The use of imaging and more sensitive screening tools may help to differentiate these two conditions, although these methods are not commonly used in routine clinical practice because of time and cost (42,45).

In the 2 years preceding AS diagnosis in this analysis, more women than men sought medical care from health care providers. This is consistent with studies showing that women are more likely than men to use primary health care for physical and mental health symptoms, as well as serious illnesses, suggesting that gender differences in health care–seeking behavior may influence differences between men and women in the overall journey to diagnosis (22,46,47). It is well documented that patients experiencing chronic back pain receive initial treatment from nonrheumatology health care providers, especially primary care physicians (5), possibly delaying diagnosis. In our study, the greatest difference was noted for rheumatologists; 64.2% of women had visits compared with 45.1% of men. This observation may support the premise that diagnosing the AS disease spectrum is more challenging in women than in men. The difference in AS manifestation, drug prescribing patterns, and diagnosis journey among men and women may warrant an assessment of the physician–patient encounter, beyond office visit notes, to gain a better overall understanding of the doctor–patient relationship and how patients' health is being discussed. In this regard, several relationship assessment instruments are available (48) and may help in evaluating the possibility that women undergo a different diagnostic algorithm/workup than men before receiving a diagnosis of AS.

As with any analysis of administrative claims data, miscoding by health care providers may have occurred. Some health care services may be excluded from claims databases, thus causing underrating of overall disease and economic burden. ICD-9-CM and ICD-10-CM codes are used for billing and may not reflect an accurate diagnosis; there was also no independent confirmation of patient diagnoses. Furthermore, ICD codes do not always comprehensively encompass the full spectrum of disease. For example, because of the lack of an ICD code for non-radiographic axSpA at the time of this analysis (ie, before April 2019), our sample population may more broadly represent the spectrum of axSpA. The AS diagnosis was made by any qualified physician and was not required to be from a rheumatologist. This is relevant because, in 2015, the rheumatologist workforce was estimated to be 24 adult rheumatologists for every 1 million adults and 3 pediatric rheumatologists for every 1 million children; by 2025, every region within the United States is anticipated to experience a decrease in the number of practicing rheumatologists, underlying the importance of including diagnoses made from all qualified physicians (49). On the other hand, the nature of the way data were collected—ie, claims that were mostly from individuals with commercial insurance through a larger employer or with Medicare—meant that the distribution of age at diagnosis in this study may have skewed higher than what is typically observed in clinical practice. Although diagnostic journeys frequently take longer than the 2-year timeframe chosen for this

study, limiting coding events to 2 years preceding an AS diagnosis may more likely capture health events directly leading to AS diagnosis, whereas a longer timeframe would potentially collect unrelated events that would make interpretation difficult. Although this approach might miss some relevant health events, this strategy was chosen to identify records specifically related to AS diagnosis.

In summary, our study highlights differences in the AS diagnosis journey between men and women from a health systems perspective, suggesting the possibility of fundamental differences in disease presentation and/or disease management in a disease for which heterogeneity is often the rule. Conversely, the data also suggest that cognitive bias may influence diagnostic decision-making in a complex disease spectrum such as axSpA, for which no specific definitive diagnostic tests exist. It is possible that more errors would occur when a woman presents to a provider whose expectation is that AS is much more common in men. These differences may contribute to a delayed journey to diagnosis of AS for women compared with men, which merits further investigation into whether the disease phenotype is fundamentally different between men and women or whether there is a mindset by clinicians that women are to be managed differently than men in the diagnostic process. The already substantial financial burden associated with AS (25) may be exacerbated by the high volume of non-AS diagnoses claims, potentially indicating misdiagnoses. We propose further investigation into these differences, because timelier diagnosis and treatment could significantly reduce the burden of disease.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. All authors had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Novartis Pharmaceuticals Corporation participated in the study design, data collection, data analysis, interpretation of data, and review and approval of the manuscript. Authors had full control of the content and made the final decision on allaspects of this publication. Publication of this article was not contingent upon approval by Novartis Pharmaceuticals Corporation.

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