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The Annual Diagnostic Prevalence of Ankylosing Spondylitis and Axial Spondyloarthritis in the United States Using Medicare and MarketScan Databases

Jeffrey R. Curtis,[1] [ID] Kevin Winthrop,[2] Rhonda L. Bohn,[3] Robert Suruki,[3] Sarah Siegel,[2] Jeffrey L. Stark,[3] Fenglong Xie,[1] Huifeng Yun,[1] [ID] Lang Chen,[1] and Atul Deodhar[2] [ID]

Objective. The objective of this study was to investigate the diagnostic prevalence of ankylosing spondylitis (AS) and axial spondyloarthritis (axSpA) in the United States and examine treatment patterns for these diseases.

Methods. This retrospective observational cohort study drew from 2006-2014 data in the US Medicare Fee-for-Service and IBM MarketScan databases. AS and axSpA diagnoses were identified through *International Classification of Diseases, Ninth Revision* [ICD-9] codes. Diagnostic prevalence (per 10,000 patients) was calculated as patients with AS and axSpA with full insurance coverage in each calendar year divided by the total patients with full insurance coverage in the same year. Two diagnosis definitions were used: definition 1 (D1), one or more relevant ICD-9 codes from hospital claims or two or more relevant ICD-9 codes from outpatient claims; definition 2 (D2), one or more codes from hospital/outpatient claims. Primary analyses assessed annual AS and axSpA prevalence (D1); sensitivity analyses assessed annual (D2) and 2-year prevalence. Patterns in prevalence and treatment use were analyzed descriptively; no statistical tests were performed.

Results. An increase in AS prevalence (per 10,000 patients) was seen from 2006 to 2014 in primary analyses (Medicare: 2.12-3.60; MarketScan: 0.85-1.42) and sensitivity analyses. A similar trend occurred for axSpA (Medicare: 4.39-6.52; MarketScan: 1.33-2.21). For Medicare, the proportion of patients with AS (D1) using tumor necrosis factor α inhibitors (TNFis), conventional synthetic antirheumatic drugs (csARDs), nonsteroidal antiinflammatory drugs (NSAIDs), opioids, and glucocorticoids remained relatively stable; for MarketScan, TNFi-treated patients increased (51.7% to 65.7%) and NSAID-treated patients decreased (63.5% to 55.7%).

Conclusion. AS and axSpA prevalence may have increased in the United States between 2006 and 2014. Reasons are unknown, but this may be due to increased disease awareness, among other factors.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic and progressive disease that is regarded as one of the most common and severe subtypes of spondyloarthritis (SpA). Although the disease predominantly affects the axial skeleton, some patients have extraspinal manifestations (eg, peripheral arthritis enthesitis, anterior uveitis, psoriasis, and inflammatory bowel disease) (1–3). The burden of AS is associated with reduced health-related quality of life, decreased work productivity, and impaired spinal mobility and physical function (4,5).

AS and nonradiographic axial SpA (nr-axSpA) are subtypes of axial SpA (axSpA); axSpA itself sits under the umbrella term SpA, which also encompasses peripheral SpA. AS, also known

as radiographic axSpA, can be differentiated from nr-axSpA by the presence of definite structural damage to the sacroiliac joints via x-ray imaging, according to the modified New York classification criteria (6–9). Some patients with nr-axSpA progress to AS (10). Accurate estimation of the prevalence of axSpA, including AS, would benefit clinicians, specialty societies (eg, the American College of Rheumatology), health care organizations, and government agencies in planning for the provision of care to these patient populations (4,5).

Based on population screening conducted from 2009 to 2010 as part of the National Health and Nutrition Examination Survey (NHANES), the US population prevalence of axSpA was estimated to be 0.9% on the basis of the Amor criteria and 1.4% on the basis of the European Spondyloarthropathy Study Group (ESSG) criteria (11). The prevalence of AS was 0.5% to 0.6% on the basis of the same survey (12). A 2016 analysis of Kaiser Permanente Northern California (KPNC) electronic health record (EHR) data from the period of 1996-2009 estimated a much lower prevalence in the United States (0.2% for axSpA and 0.1% for AS) (13). This discrepancy in prevalence estimates may have occurred, among other reasons, because the EHR study only captured diagnosed patients, whereas the NHANES survey, given its population-based design, may have also captured undiagnosed patients. Because of improvements in understanding of the axSpA disease spectrum and treatment strategies and the introduction of new treatments, more recent studies of prevalence and treatment patterns are needed.

In addition, although previous studies have examined treatment patterns in patients with AS, including switching and discontinuation of biologics (14) and chronic versus nonchronic use of opioids (15), there remains a need for further investigation of how these treatment patterns may differ between patients with different access to insurance and between older and younger patients (specifically in the Medicare population).

In this study, we investigated the annual diagnostic prevalence of AS and axSpA per 10,000 patients enrolled in two US health care insurance claims databases (Medicare and IBM MarketScan) during the period of 2006-2014. We also descriptively evaluated how the use of treatments for these conditions changed over time.

PATIENTS AND METHODS

Study design and patients. This retrospective observational cohort study was conducted by using 2006-2014 data from two US insurance claims databases. A 5% random sample of all patients enrolled in Medicare, the federal health insurance program for people aged 65 years and older and patients with disabilities, was assessed by using Medicare Fee-for-Service claims data. In addition, the IBM MarketScan Research Databases, which provide one of the largest collections of proprietary claims for privately and publicly insured individuals in the United States, were used; these databases represented health care claims information for individuals enrolled in various employer-sponsored health care plans. Medicare and MarketScan were selected because they complement each other in terms of representativity of the US population, thereby reducing bias in favor of a particular kind of insurance (ie, public or private).

Eligible patients were 20 years of age and older (to avoid overlap with children with juvenile idiopathic arthritis/juvenile spondyloarthritis) and had full-year, continuous medical and pharmacy enrollment in each calendar year from 2006 to 2014.

The study was approved by the institutional review boards of the University of Alabama at Birmingham and Oregon Health & Science University.

Study evaluations. The relevant *International Classification of Disease, Ninth Revision* (ICD-9) diagnosis codes were used to identify AS and axSpA: ICD-9 720.0 for AS or 720.X (X = any digit[s]; defined in ICD-9 as "AS and other inflammatory spondylopathies") for axSpA. Patients with psoriatic arthritis, reactive arthritis, and inflammatory bowel disease–associated arthritis (enteropathic arthritis), the main types of peripheral SpA, would not have been identified by using this method because these diseases have separate ICD-9 diagnosis codes (696.0 for "psoriatic arthropathy," 099.3 for "Reiter's disease," and 713.1 for "arthropathy associated with gastrointestinal conditions other than infections"). Demographic and clinical characteristics, including outpatient visits, the Charlson comorbidity index, and common comorbidities, were captured for patients with AS and axSpA. Annual diagnostic prevalence of AS and axSpA in each database was calculated as the number of patients with AS and axSpA with full insurance coverage (medical and pharmacy) in each calendar year divided by the total number of patients, also with full insurance coverage,

in the same year. All prevalence rates shown are per 10,000 patients; fold changes are also reported to compare the relative change in AS and axSpA diagnostic prevalence in each database between 2006 and 2014.

The primary objective of this analysis was to determine the annual diagnostic prevalence of AS (ICD-9 code 720.0) and axSpA (ICD-9 code 720.X) when defined as one or more ICD-9 diagnosis codes from hospital discharge or two or more diagnosis codes from a rheumatologist outpatient visit (definition 1 [D1]). A sensitivity analysis evaluated the annual diagnostic prevalence of patients with AS and axSpA using an alternative, less stringent definition, whereby only one or more hospital discharge code or one or more code from an outpatient rheumatologist visit was required (definition 2 [D2]). When AS was defined as two or more diagnostic codes from a rheumatologist, the 2016 study of KPNC EHR data found a positive predictive value (PPV) of 81% and a sensitivity of 67%; the same study reported a PPV and sensitivity of 73% and 72%, respectively, when AS was defined as one or more diagnosis codes from a rheumatologist (13).

Because the majority of patients in the Medicare population were expected to be 65 years of age and older because of the eligibility criteria for the program, the annual diagnostic prevalence of axSpA by age group (patients <65 years old and ≥65 years old) between 2006 and 2014 was included as a subgroup analysis in this population. Because Medicare patients younger than 65 years old are generally an understudied population, there remains a need for recent analyses that reveal potential differences in the diagnostic prevalence of AS and axSpA in this subgroup, particularly because these patients are expected to qualify for Medicare through disability rather than age, to inform approaches to care and treatment in this population.

Patients with AS and axSpA who are adequately managed with nonsteroidal antiinflammatory drugs (NSAIDs) and physical therapy may not seek care every year and, therefore, may see a rheumatologist infrequently. Moreover, there are potential cases in which patients may have one outpatient visit toward the end of one calendar year and an additional visit at the beginning of the next; thus, these two visits would span 2 years. For these reasons, 2-year diagnostic prevalence of AS and axSpA was included as an additional sensitivity analysis, calculated as the number of patients with AS and axSpA with full insurance coverage (medical and pharmacy) in a 2-calendar-year period divided by the total number of patients, also with full insurance coverage, in the same 2-year period. Ratios comparing use of D2 over D1 are included to capture proportionality of prevalence change across definitions.

An exploratory objective of the study was to analyze treatments used for AS over time. Five categories of AS treatments—conventional synthetic antirheumatic drugs (csARDs) (16) (including methotrexate [MTX], sulfasalazine [SSZ], and leflunomide), NSAIDs, opioids, glucocorticoids, and biologics (specifically tumor necrosis factor α inhibitors [TNFis], which were the most

widely available biologic over the period of this analysis)—were assessed between 2006 and 2014. Additional information about specific drugs included in the study is provided in the Supplementary Materials.

The annual prevalence of drug use was calculated by dividing the number of patients with one or more prescriptions for that class of drug and a full year of medical and pharmacy coverage by the total number of patients meeting the disease definition (D1 or D2) with a full year of medical and pharmacy coverage in the same calendar year. D2 was used in the treatment patterns analysis in addition to D1 to determine whether any meaningful differences emerge in treatment patterns for AS when diagnostic criteria are relaxed. An additional analysis of drug use by age in the Medicare population was conducted to reveal potential variation in treatment patterns for AS between older (≥65 years old) and younger (<65 years old) patients.

Statistical analysis. Patterns in prevalence over time and between groups, as well as in treatment use, were analyzed descriptively; no statistical tests were performed. All analyses were conducted by using SAS 9.4 (SAS Institute, Inc).

RESULTS

Patient disposition and baseline characteristics. The total number of patients enrolled in the Medicare and MarketScan databases who were eligible for inclusion in this study approximately doubled from 2006 (Medicare: 501,031 patients; MarketScan: 17,562,637 patients) to 2014 (Medicare: 1,046,107; MarketScan: 34,553,135). The mean ages across all years (2006-2014) of patients with AS and axSpA (D1), respectively, were 61.2 years and 65.0 years for Medicare and 47.7 years and 48.4 years for MarketScan. The majority of people who qualify for Medicare are aged 65 years and older. However, more than one fifth of the Medicare patients included in this study who qualified for Medicare because of disability were younger than 65 years of age (2006: n = 136,407 of 501,031 [27.2%]; 2014: n = 210,639 of 1,046,107 [20.1%]). The percentages of patients, respectively, with an AS and axSpA diagnosis (D1) across all years who were women were 37.1% and 57.8% for Medicare and 39.3% and 49.0% for MarketScan. For reference, between 2008 and 2014, the percentage of all Medicare patients who were women ranged from 55.7% to 56.8% (17).

The mean annual numbers of outpatient visits (for all health care services) across all years in patients with AS were 17.5 for Medicare and 11.8 for MarketScan. In patients with axSpA, the mean annual numbers of outpatient visits (for all health care services) across all years were 19.4 for Medicare and 12.6 for MarketScan. Across all years, the Charlson comorbidity index scores were 1.8 for Medicare and 0.6 for MarketScan in patients with AS and 1.9 for Medicare and 0.7 for MarketScan in patients with axSpA (Tables 1 and 2) (18). Across all years, the most common comorbidities among patients

Table 1. Baseline characteristics of patients with AS[a] (ICD-9 code 720.0)

	Medicare (5% random sample)			MarketScan		
	2006	2014	All years	2006	2014	All years
Patient characteristics						
n	106	377	2312	1494	4890	36,079
Age, mean (SD)	57.9 (14.9)	63.8 (13.5)	61.2 (14.1)	47.8 (13.2)	47.8 (13.6)	47.7 (13.6)
Female sex, n (%)	36 (34.0)	138 (36.6)	858 (37.1)	503 (33.7)	1999 (40.9)	14,173 (39.3)
Outpatient visits per year, mean (SD)b	18.0 (12.6)	17.6 (11.2)	17.5 (11.8)	11.4 (7.4)	11.5 (8.0)	11.8 (8.2)
Charlson comorbidity index, mean (SD)	1.4 (1.4)	2.0 (2.0)	1.8 (1.9)	0.5 (0.9)	0.6 (1.0)	0.6 (1.0)
Most common comorbidities, n (%)c						
Diabetes	22 (20.8)	129 (34.2)	679 (29.4)	112 (7.5)	621 (12.7)	3988 (11.1)
Coronary heart disease	27 (25.5)	117 (31.0)	622 (26.9)	98 (6.6)	321 (6.6)	2524 (7.0)
Myocardial infarction	4 (3.8)	40 (10.6)	164 (7.1)	27 (1.8)	94 (1.9)	752 (2.1)
Peripheral vascular disease	12 (11.3)	48 (12.7)	245 (10.6)	11 (0.7)	102 (2.1)	631 (1.7)
Cardiovascular disease	7 (6.6)	43 (11.4)	229 (9.9)	27 (1.8)	137 (2.8)	919 (2.5)
Chronic pulmonary disease	30 (28.3)	101 (26.8)	610 (26.4)	127 (8.5)	584 (11.9)	3787 (10.5)
Renal disease	3 (2.8)	63 (16.7)	296 (12.8)	34 (2.3)	170 (3.5)	1132 (3.1)
Malignancy	8 (7.5)	38 (10.1)	218 (9.4)	66 (4.4)	190 (3.9)	1426 (4.0)
Hypertension	60 (56.6)	266 (70.6)	1494 (64.6)	386 (25.8)	1704 (34.8)	11,456 (31.8)

Abbreviations: AS, ankylosing spondylitis; ICD-9, *International Classification of Diseases, Ninth Revision*.
[a] Defined as at least one ICD-9 diagnosis code of 720.0 from hospital discharge or two diagnosis codes of 720.0 from rheumatologist visit (D1).
[b] Mean number of outpatient visits per year represents all visits, not just those with a rheumatologist.
[c] Comorbidities present in ≥5% of patients are shown; definitions of comorbidities are given in Supplementary Table 1. Medicare data included a 5% random sample of all enrolled patients aged ≥20 years.

with axSpA (present in ≥5% of patients [D1]) included hypertension (70.8%), diabetes (33.8%), and coronary heart disease (29.9%; defined as including acute myocardial infarction, other acute and subacute forms of ischemic heart disease, and unspecified cardiovascular disease) for Medicare and hypertension (33.8%), diabetes (13.0%), and coronary heart disease (7.5%) for MarketScan

(Table 1; ICD-9 codes in Supplementary Table 1). Similarly, the most common comorbidities across all years in patients with AS included hypertension (64.6%), diabetes (29.4%), and coronary heart disease (26.9%) for Medicare and hypertension (31.8%) and diabetes (11.1%) for MarketScan (Table 2; ICD-9 codes in Supplementary Table 1).

Table 2. Baseline characteristics of patients with axSpA[a] (ICD-9 code 720.X)

	Medicare (5% random sample)			MarketScan		
	2006	2014	All Years	2006	2014	All Years
Patient characteristics						
n	220	682	4452	2329	7650	58,758
Age, mean (SD)	63.0 (15.7)	66.1 (13.3)	65.0 (14.6)	48.3 (14.6)	48.3 (14.4)	48.4 (14.8)
Female sex, n (%)	129 (58.6)	374 (54.8)	2572 (57.8)	1012 (43.5)	3851 (50.3)	28,799 (49.0)
Outpatient visits per year, mean (SD)b	20.1 (13.2)	19.4 (12.3)	19.4 (12.2)	11.9 (7.8)	12.4 (8.6)	12.6 (8.9)
Charlson comorbidity index, mean (SD)	1.6 (1.5)	2.1 (2.0)	1.9 (1.9)	0.5 (0.9)	0.7 (1.1)	0.7 (1.1)
Most common comorbidities, n (%)c						
Diabetes	62 (28.2)	244 (35.8)	1502 (33.8)	191 (8.2)	1080 (14.1)	7680 (13.0)
Coronary heart disease	70 (31.8)	217 (31.8)	1329 (29.9)	171 (7.3)	525 (6.9)	4426 (7.5)
Myocardial infarction	11 (5.0)	71 (10.4)	321 (7.2)	42 (1.8)	182 (2.4)	1399 (2.4)
Peripheral vascular disease	34 (15.5)	81 (11.9)	530 (11.9)	28 (1.2)	178 (2.3)	1285 (2.2)
Chronic pulmonary disease	65 (29.5)	196 (28.7)	1284 (28.8)	224 (9.6)	1063 (13.9)	7235 (12.3)
Renal disease	14 (6.4)	122 (17.9)	597 (13.4)	48 (2.1)	284 (3.7)	2148 (3.7)
Malignancy	18 (8.2)	71 (10.4)	450 (10.1)	105 (4.5)	323 (4.2)	2597 (4.4)
Hypertension	142 (64.5)	510 (74.8)	3153 (70.8)	608 (26.1)	2831 (37.0)	19,857 (33.8)

Abbreviations: axSpA, axial spondyloarthritis; ICD-9, *International Classification of Diseases, Ninth Revision*.
[a] Characteristics for axSpA defined as at least one ICD-9 diagnosis code of 720.X from hospital discharge or two diagnosis codes of 720.X from rheumatologist visit, by data source.
[b] Mean number of outpatient visits per year represents all visits, not just those with a rheumatologist.
[c] Comorbidities present in ≥5% of patients are shown; definitions of comorbidities are given in Supplementary Table 1. Medicare data included a 5% random sample of all enrolled patients aged ≥20 years.

Diagnostic prevalence of AS and axSpA. The prevalence of AS (D1) increased between 2006 (Medicare: 2.12 per 10,000 patients; MarketScan: 0.85 per 10,000) and 2014 (Medicare: 3.60 per 10,000 patients, 1.7-fold increase; MarketScan: 1.42 per 10,000 patients, 1.7-fold increase) (Figure 1A). The prevalence of axSpA (D1) increased between 2006 (Medicare: 4.39 per 10,000 patients; MarketScan: 1.33 per 10,000 patients) and 2014 (Medicare: 6.52 per 10,000 patients, 1.5-fold increase; MarketScan: 2.21 per 10,000 patients, 1.7-fold increase) (Figure 1B). As expected, AS and axSpA prevalence calculated by using D2 in the sensitivity analyses was higher than the prevalence estimated by using D1 and increased between 2006 and 2014 (Supplementary Figure 1).

Subgroup analysis by age in Medicare database: younger than 65 years and 65 years and older. The total number of patients with full insurance coverage in the Medicare database (the reference population) was divided into the following groups: younger than 65 years and 65 years and older. The numbers of patients in both these age groups nearly doubled during the study period between 2006 and 2014: the number of patients younger than 65 years was 136,407 in 2006 and rose to 210,639 in 2014, and the number of patients who were 65 years and older increased from 364,624 in 2006 to 835,468 in 2014. Using D1, the prevalence of axSpA in Medicare patients increased between 2006 (<65 years: 7.40 per 10,000 patients; ≥65 years: 3.26 per 10,000 patients) and 2014 (<65 years:
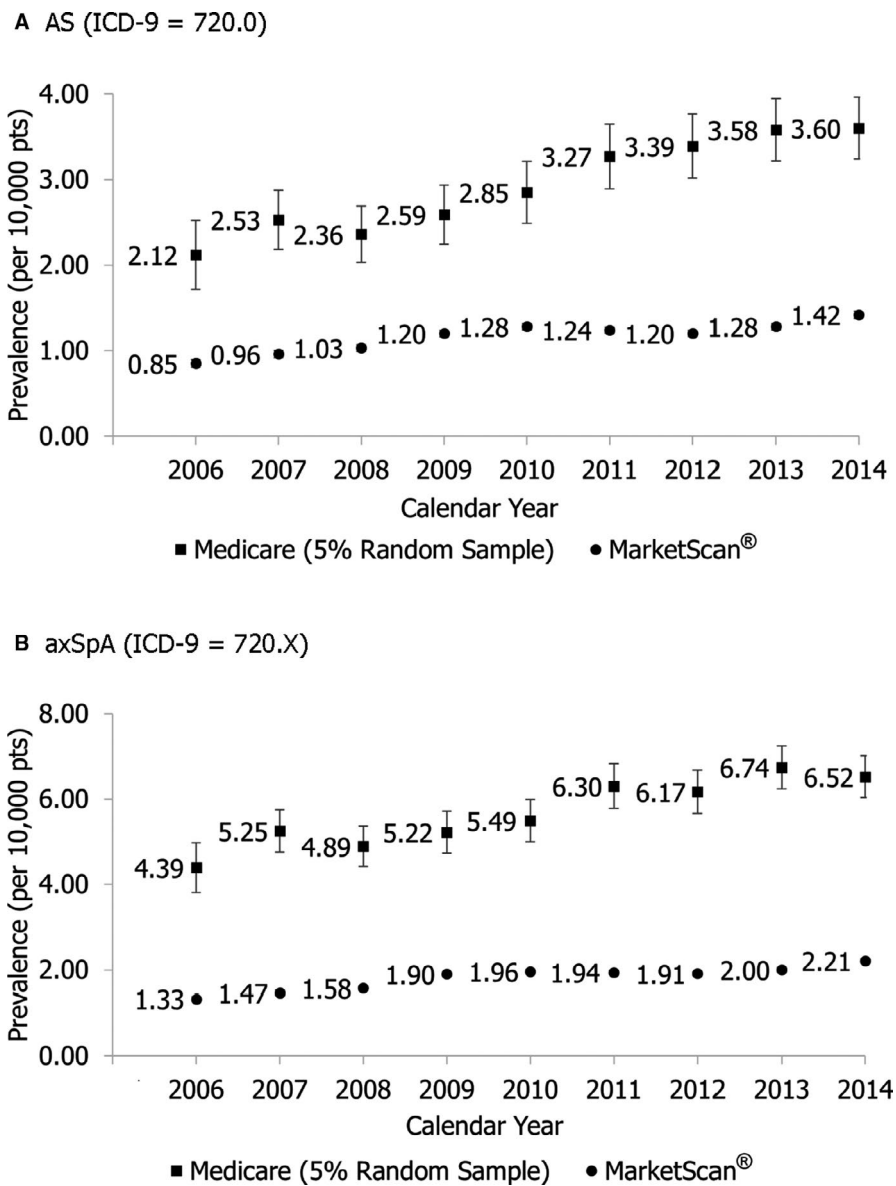
A AS (ICD-9 = 720.0)

B axSpA (ICD-9 = 720.X)

Figure 1.   Annual diagnostic prevalence of ankylosing spondylitis (AS) and axial spondyloarthritis (axSpA) (D1). **A,** AS (*International Classification of Diseases, Ninth Revision* [ICD-9] code 720.0). **B,** axSpA (ICD-9 code 720.X). D1 indicates one or more relevant ICD-9 codes from hospital discharge or two or more relevant ICD-9 codes from rheumatologist visit. Confidence intervals are included for MarketScan data but are small enough that they fall within the size of the plotted data markers. pts, patients.
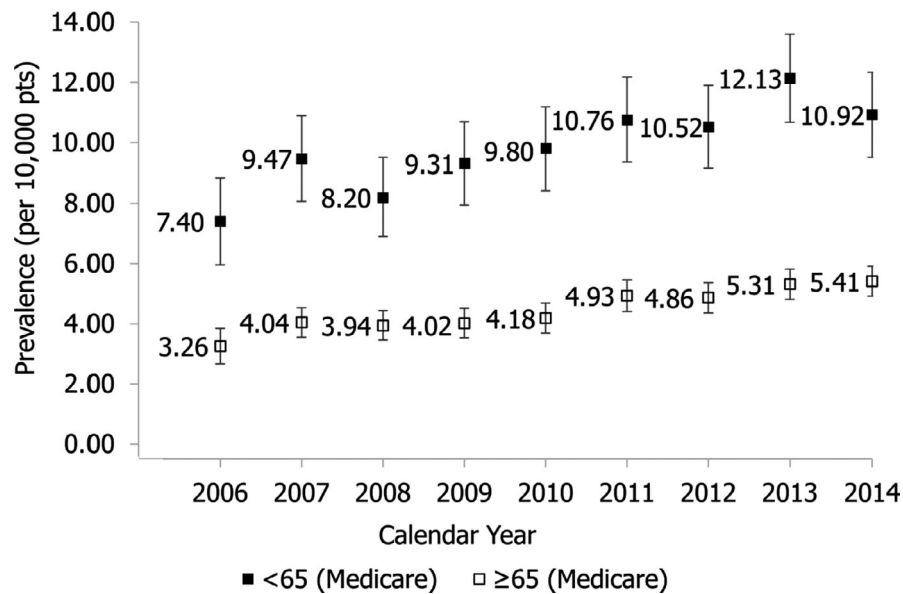
Figure 2. Annual diagnostic prevalence of axial spondyloarthritis (axSpA) by age among Medicare patients (5% random sample) (D1; *International Classification of Diseases, Ninth Revision* [ICD-9] code 720.X). D1 indicates one or more relevant ICD-9 codes from hospital discharge or two or more relevant ICD-9 codes from the rheumatologist visit. Because of Medicare eligibility requirements (patients 65 years of age and older are eligible, whereas patients younger than 65 years of age are only covered if they have certain disabilities or qualifying conditions), diagnostic prevalence rates of spondyloarthritis in these subgroups are not necessarily comparable. pts, patients.

10.92 per 10,000 patients, 1.5-fold increase; ≥65 years: 5.41 per 10,000 patients, 1.7-fold increase) (Figure 2). Similarly, using D2, the prevalence of axSpA increased between 2006 (<65 years: 11.36 per 10,000 patients; ≥65 years: 6.23 per 10,000 patients) and 2014 (<65 years: 16.38 per 10,000 patients, 1.4-fold increase; ≥65 years: 9.46 per 10,000 patients, 1.5-fold increase) (Supplementary Figure 2).

Two-year diagnostic prevalence of AS and axSpA. In Medicare, the 2-year prevalence of AS (per 10,000 patients) increased from 2006-2007 (D1: 3.63; D2: 4.42) to 2012-2013 (D1: 5.33; D2: 6.54). This trend was also reflected in MarketScan; 2-year prevalence rates (per 10,000 patients) were 1.48 (D1) and 2.09 (D2) in 2006-2007, compared with 1.95 (D1) and 2.60 (D2) in 2012-2013 (Supplementary Table 2). The 2-year prevalence of axSpA (per 10,000 patients) also increased in Medicare from 2006-2007 (D1: 8.03; D2: 12.91) to 2012-2013 (D1: 11.07; D2: 17.31). Similar increases in the 2-year prevalence of axSpA were observed in MarketScan; 2-year prevalence rates (per 10,000 patients) were 2.36 (D1) and 3.43 (D2) in 2006-2007, compared with 3.23 (D1) and 4.61 (D2) in 2012-2013 (Supplemental Table 2).

As expected, the 2-year prevalence rates of AS and axSpA were greater when using D2 than when using D1. When using D2 over D1, 2-year AS prevalence (per 10,000 patients) in 2006-2007 was 1.2 times greater in Medicare and 1.4 times greater in MarketScan; in 2012-2013, AS prevalence was 1.2 times greater in Medicare and 1.3 times greater in MarketScan. When using D2 over D1, 2-year axSpA prevalence (per 10,000 patients) in 2006-2007 was 1.6 times greater in Medicare and 1.5 times greater

in MarketScan; in 2012-2013, axSpA prevalence was 1.6 times greater in Medicare and 1.4 times greater in MarketScan. Because the ratios between the prevalence rates measured by using the two definitions did not change over time, even as overall prevalence rates grew, the increase measured is proportional across D1 and D2.

Drug usage over time in AS population. A comprehensive list of drug names is provided in Supplementary Table 3. The proportion of patients with AS (D1) using biologics (TNFis), csARDs (including MTX, SSZ, and leflunomide), opioids, and glucocorticoids remained relatively stable between 2006 and 2014 in the Medicare database, whereas the proportion using NSAIDs decreased from 54.7% in 2006 to 44.6% in 2014 (Figure 3A). In the MarketScan database, the proportion of patients using csARDs, opioids, and glucocorticoids also remained stable across the study period. However, the proportion of patients treated with TNFis increased from 51.7% in 2006 to 65.7% in 2014, and the proportion treated with NSAIDs decreased from 63.5% in 2006 to 55.7% in 2014 (Figure 3B). Sensitivity analyses confirmed these trends in both databases, with the exception of NSAID use in Medicare, which remained stable when D2 was substituted for D1 (Supplemental Figure 3A and B).

Comparing across the databases (D1), a lower proportion of Medicare patients were treated with TNFis compared with MarketScan patients (20.8% vs. 51.7% in 2006, trend seen across all years); the proportion of patients using NSAIDs was also lower in Medicare patients compared with MarketScan patients (54.7% vs. 63.5% in 2006, trend seen across all years). The proportion
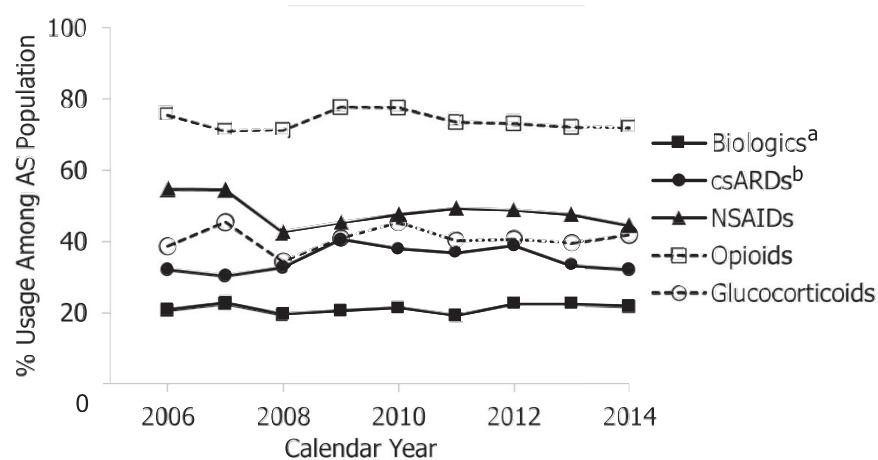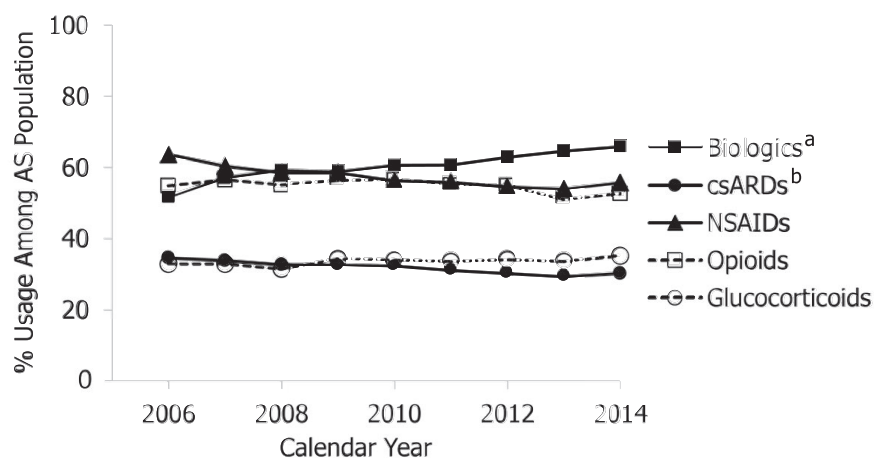
A Medicare (5% Random Sample)

B MarketScan®

Figure 3. Drug use over time in ankylosing spondylitis (AS) population (D1; *International Classification of Diseases, Ninth Revision* [ICD-9] code 720.0). **A,** Medicare (5% random sample). **B,** MarketScan. [a]Tumor necrosis factor α inhibitors. [b]Includes methotrexate, sulfasalazine, and leflunomide. D1 indicates one or more relevant ICD-9 codes from hospital discharge or two or more relevant ICD-9 codes from the rheumatologist visit. csARD, conventional synthetic antirheumatic drug; NSAID, nonsteroidal antiinflammatory drug.

of patients using opioids was generally higher in Medicare than in MarketScan (75.5% vs. 54.8% in 2006, trend seen across all years) (Figure 3A and B).

Subgroup analysis by age in Medicare database: younger than 65 years and 65 years and older. Using D1, a generally higher proportion of Medicare patients younger than 65 years old with AS were treated with csARDs, NSAIDs, opioids, glucocorticoids, and biologics (TNFis) compared with Medicare patients aged 65 years and older. There was a large difference in treatment patterns across subgroups regarding TNFis: approximately one in three patients younger than 65 years old were treated with TNFis across all years, whereas approximately one in fifty patients aged 65 years and older were treated with TNFis

in 2006, increasing to approximately one in ten by 2014. In each age subgroup, opioid use was similar in 2006 and 2014 (Supplementary Figure 4).

DISCUSSION

Our study found that the annual diagnostic prevalence of AS and axSpA in the Medicare and MarketScan databases increased by approximately 1.5- to 1.7-fold during the period from 2006 to 2014. Possible reasons for this include increased awareness and understanding of these diseases among clinicians and other medical care providers in the United States, increased use of magnetic resonance imaging (MRI), and the publication of the Assessment of Spondylo Arthritis international Society (ASAS)

axSpA classification criteria in 2009, which enabled the identification of patients with AS or nr-axSpA (9,19). Although the ASAS classification criteria should not be used for diagnosis, there is evidence that in the absence of diagnostic criteria, the majority of rheumatologists do use them for this purpose (20). Nevertheless, their introduction may have resulted in better disease understanding and awareness, led by scientific studies and clinical trials (21). Because most of the classification criteria were developed in Europe (Amor, ESSG, ASAS), the recognition of these conditions had been better appreciated in European countries than in the United States (7). However, the prevalence estimates in the current study may suggest that both axSpA and AS are becoming more recognized in the United States. In addition, the time to proper diagnosis may be shortening because of increased cooperation among rheumatologists and other specialists.

Discrepancies between the results of prevalence studies may occur because they only assess a proportion of the population for the occurrence of a disease of interest and may use different diagnostic approaches to calculate prevalence (4,7,22). Variability in classification criteria or case definitions, as well as patients' routes to clinical assessment and their access to care, may also impact the estimation of axSpA and AS prevalence (7,22).

A retrospective population-based study conducted in a closed US health care system (Kaiser), by using computerized health care data from an earlier time period slightly overlapping with that of the present study (1996-2009, compared with 2006-2014), found that the diagnostic prevalence rates of AS and axSpA were 10.7 per 10,000 patients and 22.6 per 10,000 patients, respectively (N = 5568) (13). The cases were identified on the basis of the use of a single physician diagnosis code for ICD-9 720.X, which is similar to the methodology used in the current study (D2). These prevalence rates were higher than those in the current analysis, which may be due to better access to rheumatologist care for patients investigated in the Kaiser health care system, thus potentially increasing diagnosis rates.

Diagnostic prevalence estimates derived from the 2009-2010 NHANES study were based on population-level data from 5013 US adults who were classified according to the Amor or ESSG criteria; it estimated the age-adjusted prevalence of AS at 0.5% to 0.6% (52-55 per 10,000 patients) (11,12). These prevalence rates are, as expected, higher in comparison with those in the current study, as they were population based (assessed by using the NHANES survey with a supplement) and might have included undiagnosed patients. Results from population-based and diagnostic prevalence studies are not comparable; both have advantages and limitations. Population-based prevalence studies screen the broader population for cases of disease but require substantial time and resources to be established; diagnostic prevalence studies are less time and resource intensive but capture only patients with diagnostic codes or other designators assigned by examining physicians and, therefore, typically result in lower disease prevalence than that in population prevalence studies.

Although the Medicare program primarily covers patients aged 65 years and older, it also extends to patients younger 65 years old with disabilities; approximately one fifth of the patients with AS and axSpA included in this study were in the latter category. The prevalence of axSpA was greater in the population aged younger than 65 years compared with patients aged 65 years and older in the Medicare population. This is likely due, at least in part, to the Medicare program being available to everyone over the age of 65 but only to people under the age of 65 with disabilities, such as axSpA.

In line with other reports, the patients with AS and axSpA identified in this study had high rates of comorbidities, including hypertension, diabetes, and coronary heart disease, highlighting the need for treatment options that can minimize the impact of these comorbidities on patient quality of life (23,24). The prevalence of comorbidities increased considerably between 2006 and 2014; further research will be needed to examine the cause and impact of these increases.

This study also examined drug usage over time (2006-2014) in patients with AS in both the Medicare and MarketScan databases. The MarketScan database showed an increase in the use of TNFis and a decrease in the use of NSAIDs over the study period (D1 and D2), whereas the Medicare database showed a decrease in the use of NSAIDs (D1), suggesting a trend toward using TNFis over NSAIDs to manage AS. This trend may also be a response to growing evidence reporting reduction of inflammation, improved quality of life in prospective studies, and possible slowing of spinal radiographic progression in retrospective studies in patients with AS treated with TNFis for at least 2 years (25–27). Comparing across the databases, a notably lower proportion of patients were treated with TNFis in Medicare compared with MarketScan, which may reflect differences in coverage between the programs. Variation may also be attributed to the increased burden of comorbidities in older patients, who compose the majority of Medicare beneficiaries; this would be consistent with the lower proportion of patients aged 65 years and older receiving TNFis reported in the Medicare subgroup analysis by age.

In both databases the use of opioids was high despite the use of opioids not being addressed in treatment recommendations for AS and the public health guidance related to misuse of opioids in the United States (16). The high use of opioids among patients with AS identified in the present study, particularly among those with public insurance, is also consistent with previous reporting (15). This suggests further work may be needed to understand and address the pain management needs of patients with AS.

This study used ICD-9 diagnosis codes from hospital or outpatient claims (indicating a rheumatologist visit) for the identification of patients with AS and axSpA. The ICD-9 codes used were 720.0 and 720.X for the diagnosis of AS and axSpA, which have demonstrated high positive predictive values of 83% (28) and

83.3% (29) in patients with AS and axSpA, respectively. These codes showed high sensitivity in patients with AS (91%) (28), but low sensitivity in patients with axSpA (57.3%) (29). ICD-9 codes do not include nr-axSpA subtypes; consequently, there are other forms of SpA that may not have been captured. Therefore, the accuracy of ICD-9 codes in SpA other than AS may need to be investigated further. A new code (M45.A) was recently introduced in the *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) to identify nr-axSpA and will take effect in October 2021 (30); this additional element of specificity afforded by the evolution of the ICD-10 codes will allow this subtype of axSpA to be more easily identified in future real-world databases, given this previously identified limitation (29). The World Health Organization has also released the *International Statistical Classification of Diseases, 11th Revision* (*ICD-11*), which includes more detailed codes for axSpA and its subclasses; axSpA (FA92.0), nr-axSpA (FA92.0Y), peripheral SpA (FA92.1), and axSpA unspecified (FA92.0Z) all have ICD-11 codes. Accurate coding of patients by their medical care providers will benefit future research aiming to examine disease prevalence.

A possible limitation of this study was its retrospective observational design using insurance claims databases. Such administrative data can be affected by coding errors, "rule-out" diagnoses, and limits in the number of diagnoses included in the data set. Additionally, because we required outpatient diagnosis codes to be assigned by rheumatologists or to appear on a hospital claim, patients who were not hospitalized or did not see a rheumatologist (eg, were diagnosed by a primary care physician or chiropractor, orthopedist, or other physician specialty) were not classified as having AS (7).

In conclusion, this study provides the most recent annual diagnostic prevalence rates of axSpA and AS in the United States, on the basis of two large US claims databases in the period from 2006 to 2014. The apparent increases in diagnostic prevalence of both axSpA and AS by more than 1.5-fold between 2006 and 2014 may be due to increased use of sensitive imaging techniques—such as MRI, which has allowed for the detection of sacroiliac joint inflammation, which may not be visible by using conventional x-ray imaging (31)—as well as increased disease awareness and understanding, which may improve patient stratification and personalized treatment once a diagnosis is made. Patients with AS were reported to have increasing use of TNFis, suggesting a shift toward the use of targeted immunomodulatory treatments in this condition. The knowledge of annual diagnostic prevalence of axSpA and AS will help inform the provision of treatment by health care organizations and government agencies.

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AUTHOR CONTRIBUTIONS

ROLE OF THE STUDY SPONSOR

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