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Comparison of Men and Women With Axial Spondyloarthritis in the US-based Corrona Psoriatic Arthritis/Spondyloarthritis Registry

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ABSTRACT. ***Objective.*** To compare patient characteristics and disease burden between men and women with axial spondyloarthritis (axSpA) in the US-based Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) Registry.

Methods. Patients aged ≥ 18 years with axSpA enrolled in the Corrona PsA/SpA Registry between March 2013 and November 2018 who were not concurrently diagnosed with PsA were included. Patient demographics, clinical characteristics, disease activity, patient-reported symptoms, work productivity, and treatment history at enrollment were compared between men and women, using *t* tests or Wilcoxon rank-sum tests for continuous variables and chi-square or Fisher exact tests for categorical variables.

Results. Of 498 patients with axSpA and available sex information, 307 (61.6%) were men and 191 (38.4%) were women. Compared with men, women had higher disease activity as measured by Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, and physician global assessment, and had higher tender/swollen joint counts and enthesitis scores (all $P \leq 0.01$). Women also had worse patient-reported symptoms (pain, fatigue, Health Assessment Questionnaire for the Spondyloarthropathies, and EuroQol visual analogue scale; all $P < 0.05$), had greater work and activity impairment, and were less likely to work full time than men. Prior conventional synthetic disease-modifying antirheumatic drug and prednisone use was more common in women than in men (both $P < 0.05$). Additionally, women were more likely to have diagnoses of depression and fibromyalgia (both $P < 0.01$).

Conclusion. In this US registry of patients with axSpA, women had higher overall disease burden and more peripheral manifestations than men. Improved awareness of sex differences in the presentation of axSpA may aid physicians in earlier identification and improved disease management.

Key Indexing Terms: ankylosing spondylitis, epidemiology, registry, sex, spondyloarthropathy

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease that primarily affects the axial skeleton, causing inflammation of the vertebral joints that can lead to spinal fusion; peripheral joints and entheses are also frequently involved.[1] The leading symptom of axSpA is chronic inflammatory back pain (IBP); other symptoms include arthritis, enthesitis, and extra-articular manifestations such as uveitis, psoriasis, and inflammatory bowel disease.[2] AxSpA encompasses both patients with sacroiliitis visible on imaging (ankylosing spondylitis [AS] or radiographic axSpA [r-axSpA]) and those without radiographic

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evidence of damage in the sacroiliac joints (nonradiographic axSpA [nr-axSpA]).[1] Patients with nr-axSpA may eventually develop radiographically evident damage[3]; however, this may take years to develop or may not develop at all, which can complicate early disease identification and delay management.[3,4] Patients with axSpA often experience reduced health-related quality of life (QOL) due to pain, stiffness, fatigue, and impaired physical function,[5] and have increased risk of developing comorbidities, such as cardiovascular disease, osteoporosis, depression, and anxiety.[6,7] Failure to diagnose axSpA in the early stages can result in delayed treatment and worse patient outcomes.[8]

AxSpA, particularly AS, has historically been considered a disease that predominantly affects men,[9,10,11] partly due to the perception of AS as the prototypical form of the disease, as well as classification criteria focused on axial symptoms and the presence of discernable radiographic structural damage.[12,13] The prevalence of definitive sacroiliitis and radiographic spinal damage is lower in women than in men,[14,15,16,17] which may contribute to underrecognition of axSpA in women. Additionally, women with axSpA are more likely to have peripheral symptoms[17,18,19,20,21] and extraarticular manifestations,[17,22,23] which can lead to misdiagnosis. Previous evidence and a broader definition of axSpA that includes nr-axSpA and peripheral symptoms suggest that the prevalence of axSpA overall, and particularly nr-axSpA, may be comparable between men and women.[11,16,17,24–27]

Limited information is available on the overall disease burden of axSpA in women, particularly in the US. Women are generally underrepresented in clinical studies, and much of the available data on axSpA disease burden in women are derived from patients with AS.[11] Considering our limited historical understanding of sex differences in axSpA, it is important to better characterize differences in disease presentation between men and women to ensure that women are represented in clinical studies and routine practice. A thorough understanding of these differences may lead to improved identification of patients with axSpA and earlier diagnosis. Therefore, the objective of this study was to characterize and compare men and women with axSpA in a real-world population of patients seen in routine US clinical practice.

METHODS

Study population. The Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) Registry is a large, independent, prospective, observational cohort initiated in March 2013 that comprises patients diagnosed with PsA or SpA by a rheumatologist. Patients are recruited by 61 participating rheumatologists from 58 private and academic practice sites across 30 states in the US. As of November 1, 2019, the registry included data on approximately 4095 patients with PsA/SpA from 16,687 patient visits.

Participating investigators were required to obtain full board approval for conducting noninterventional research with a limited dataset involving human participants. The Corrona PsA/SpA Registry and its investigators have been reviewed and approved by a central institutional review board (IRB; New England Independent Review Board No. 120160070). Academic investigative sites that did not receive a waiver to use the central IRB obtained approval from their respective governing IRBs. All research was conducted in compliance with the current (2013) Declaration of Helsinki. All registry participants were required to provide written informed consent and authorization prior to participating.

This study included all patients aged ≥ 18 years with axSpA who were enrolled in the Corrona PsA/SpA Registry between March 2013 and November 2018. AxSpA was defined using the Assessment of Spondylo-Arthritis international Society (ASAS)[12] and modified New York[13] classification criteria, and included both AS (r-axSpA) and nr-axSpA. Patients with a concurrent diagnosis of PsA were excluded.

Outcomes and assessments. Data were collected at registry enrollment using questionnaires from patients and their treating rheumatologists at office visits and included patient demographics, clinical characteristics, history of physician-reported comorbidities, treatment history, laboratory measurements, disease activity measures, and patient-reported outcome (PRO) measures. Disease activity measures and clinical features included the Ankylosing Spondylitis Disease Activity Score (ASDAS); Bath AS Disease Activity Index (BASDAI); Bath AS Functional Index (BASFI); spinal mobility measures (lumbar flexion using the modified Schober test and occiput-to-wall distance); presence of IBP, enthesitis, and dactylitis; 68-joint tender joint count (TJC)/66-joint swollen joint counts (SJC); and physician global assessment (visual analog scale [VAS] 0–100). PRO measures included patient-reported pain and fatigue (VAS 0–100), morning stiffness, patient global assessment (VAS 0–100), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S; 0–3), and EuroQol VAS (EQ VAS; 0–100; higher scores indicate better general health). Work productivity was assessed using the Work Productivity and Activity Impairment questionnaire.

Statistical analysis. For the primary analysis, enrollment characteristics were compared between men and women with axSpA. In a secondary analysis, patients were stratified by rheumatologist-reported diagnosis of AS or nr-axSpA, and enrollment characteristics were compared between men and women with AS and between men and women with nr-axSpA. For continuous variables, *P* values were calculated using *t* tests for variables with approximately normal distribution (assessed using the Shapiro-Wilk test for normality) or nonparametric Wilcoxon rank-sum tests for variables with evidence of skewed or non-normal distribution. For categorical variables, *P* values were calculated using chi-square tests for variables with expected frequency ≥ 5 or Fisher exact tests for variables with frequency < 5. Statistical analyses were performed using Stata 15.1 (StataCorp LP).

RESULTS

Demographics and defining clinical characteristics. Of 504 patients meeting the criteria for axSpA without a concurrent diagnosis of PsA, 498 had sex information available (307 [61.6%] men, 191 [38.4%] women). A total of 414 patients had a diagnosis of AS, of whom 408 had sex information available (252 [61.8%] men, 156 [38.2%] women). Ninety patients had a diagnosis of nr-axSpA, of whom 55 (61.1%) were men and 35 (38.9%) were women.

Patient demographics and clinical characteristics are shown in Table 1. Women and men were of comparable age and most patients in both groups were White. Differences in axSpA symptom duration and time from symptom onset to diagnosis between women and men were not significant. Differences in demographics and clinical characteristics between men and women with AS and between men and women with nr-axSpA were generally similar to those in the overall population of patients with axSpA (Supplementary Table 1, available with the online version of this article).

Disease activity and clinical features. Women had higher disease activity and greater functional impairment than men as reflected by higher BASDAI and BASFI scores (Table 2). ASDAS was numerically higher in women, although this difference did not

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Table 1. Patient demographics and defining clinical characteristics in men and women with axSpA at enrollment[a].

	Overall, N = 504[b]	Men, n = 307	Women, n = 191	*P*[c]
Diagnosis, n (%)				
AS	414 (82.1)	252 (82.1)	156 (81.7)	0.91
nr-axSpA	90 (17.9)	55 (17.9)	35 (18.3)	
Age, yrs, mean (SD)	47.4 (13.7)	47.3 (13.9)	47.7 (13.5)	0.75[d]
Race, n (%)				
White	449 (91.8)	276 (91.4)	172 (92.5)	0.08[e]
Black	9 (1.8)	3 (1.0)	6 (3.2)	
Other	31 (6.3)	23 (7.6)	8 (4.3)	
BMI, kg/m^2, mean (SD)	29.9 (7.1)	29.8 (6.0)	30.0 (8.5)	0.32[d]
BMI category, kg/m^2, n (%)				
Normal/underweight, < 25	124 (25.2)	64 (21.5)	60 (31.7)	0.04[f]
Overweight, 25 to < 30	157 (31.9)	102 (34.3)	54 (28.6)	
Obese, ≥ 30	211 (42.9)	131 (44.1)	75 (39.7)	
Symptom duration, yrs, mean (SD)	16.8 (12.1)	17.6 (12.3)	15.7 (11.6)	0.09[d]
Disease duration, yrs, mean (SD)	9.5 (10.5)	10.3 (10.8)	8.2 (9.9)	0.02[d]
Time from symptom onset to diagnosis, yrs, mean (SD)	7.3 (8.9)	7.3 (8.9)	7.6 (9.0)	0.79[d]
HLA-B27 positive, n (%)	354 (70.2)	224 (73.0)	124 (64.9)	0.06[f]

[a] All values were calculated based on available data, and all variables had < 20% missing data. [b] Six patients did not have sex information available at enrollment or follow-up. [c] *P* values compared men vs women with axSpA. *P* values calculated using [d] Wilcoxon rank-sum test, [e] Fisher exact test, and [f] chi-square test. AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; nr-axSpA: nonradiographic axial spondyloarthritis.

Table 2. Disease activity and clinical features in men and women with axSpA at enrollment[a].

	Overall, N = 504[b]	Men, n = 307	Women, n = 191	*P*[c]
ASDAS	2.7 (1.1)	2.6 (1.2)	2.8 (0.9)	0.07[d]
BASDAI, 0–10	4.5 (2.4)	4.2 (2.5)	4.9 (2.3)	< 0.01[e]
BASFI, 0–10	3.6 (2.8)	3.4 (2.8)	4.1 (2.7)	< 0.01[e]
Inflammatory back pain, n (%)	305 (60.5)	191 (62.2)	110 (57.6)	0.31[f]
Lumbar flexion (modified Schober test), cm	4.7 (4.3)	4.6 (4.5)	4.8 (4.0)	0.43[e]
Occiput to wall, cm	4.6 (6.9)	5.8 (7.7)	2.7 (5.0)	< 0.01[e]
Enthesitis, n (%)	133 (26.4)	62 (20.2)	71 (37.2)	< 0.01[f]
SPARCC Enthesitis Index, 1–16	4.1 (3.0)	3.2 (2.4)	4.8 (3.2)	< 0.01[e]
Dactylitis, n (%)	12 (2.4)	9 (2.9)	3 (1.6)	0.39[g]
Dactylitis count (1–20)	2.9 (3.2)	3.4 (3.5)	1.3 (0.6)	0.37[e]
Tender joint count (0–68)	3.1 (7.1)	1.8 (4.7)	5.1 (9.6)	< 0.01[e]
Swollen joint count (0–66)	0.7 (2.4)	0.6 (2.5)	0.9 (2.2)	0.01[e]
CRP, mg/L	10.0 (21.0)	11.6 (25.6)	7.8 (11.5)	0.53[e]
ESR, mm/h	15.3 (18.1)	13.4 (17.3)	18.0 (19.0)	< 0.01[e]
PGA (VAS 0–100)	27.5 (23.0)	25.7 (23.4)	30.8 (22.2)	< 0.01[e]

Values are mean (SD) unless otherwise indicated. [a] All values were calculated based on available data, and all variables had < 20% missing data except for ASDAS (n = 305), CRP (n = 325), and ESR (n = 309). [b] Six patients did not have sex information available at enrollment or follow-up. [c] *P* values compared men vs women with axSpA. *P* values calculated using [d] 2-sample *t* test, [e] Wilcoxon rank-sum test, [f] chi-square test, and [g] Fisher exact test. ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PGA: physician global assessment; SPARCC: Spondyloarthritis Research Consortium of Canada; VAS: visual analog scale.

achieve statistical significance. The prevalence of IBP was comparable between women and men (57.6% vs 62.2%; $P = 0.31$), but women reported greater IBP severity as assessed by BASDAI Question 2 (Figure 1). Lumbar flexion was comparable between women and men, but women had a significantly lower occiput-to-wall distance. A higher proportion of women had enthesitis (37.2% vs 20.2%; $P < 0.01$), with higher Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index

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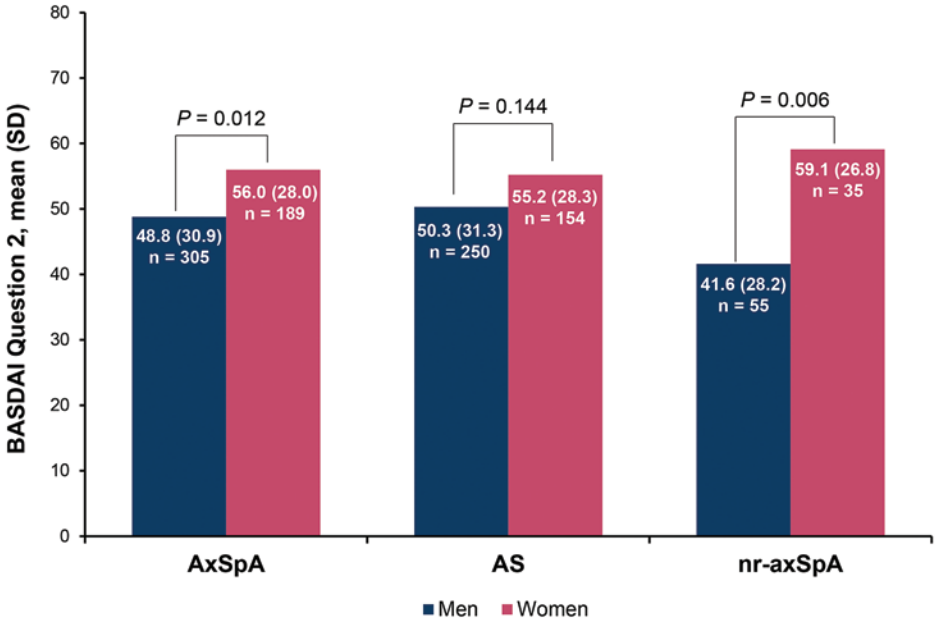

Figure 1. Patient-reported severity of inflammatory neck, back, or hip pain in men and women with axSpA. Results are mean (SD) of BASDAI Question 2: "How would you describe the overall level of inflammatory neck, back, or hip pain you have had?" Severity is rated on a scale of 0 (none) to 10 (very severe). *P* values were calculated using Wilcoxon rank-sum tests. AS: ankylosing spondyloarthritis; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; nr-axSpA: nonradiographic axial spondyloarthritis.

scores and higher TJCs and SJCs compared with men. Among patients with available laboratory measures, C-reactive protein (CRP) levels were comparable between women and men, but women had a higher erythrocyte sedimentation rate (ESR) than men. Women also had higher physician global assessment scores than men.

Similar trends in disease activity and clinical characteristics were observed when patients were stratified by diagnosis of AS or nr-axSpA (Supplementary Table 2, available with the online version of this article). However, mean SJCs and SPARCC Enthesitis Index scores were comparable between men and women with AS, whereas women with nr-axSpA had worse scores for both measures than men with nr-axSpA. Prevalence and severity of IBP were comparable between men and women with AS (Figure 1; Supplementary Table 2). In contrast, a lower proportion of women with nr-axSpA had IBP but reported greater IBP severity than men with nr-axSpA. In contrast to the overall population and patients with AS, women with nr-axSpA had higher ASDAS scores but similar occiput-to-wall distance and physician global assessment scores compared with men with nr-axSpA.

PRO measures and work productivity and activity impairment. Women reported worse pain and fatigue scores than men (Table 3). Although patient global assessment scores were comparable between women and men, women had worse HAQ–Disability Index (HAQ-DI), HAQ-S, and EQ VAS scores than men. Women were less likely to work full time and reported higher percentages for impairment while working, overall work impairment, and activity impairment than men.

Differences in PRO measures between men and women after stratification by diagnosis of AS or nr-axSpA were generally comparable to those observed in the overall population (Supplementary Table 3, available with the online version of this article). However, men and women with AS reported comparable pain scores, whereas women with nr-axSpA reported worse pain than men with nr-axSpA.

Treatment history. The proportions of women and men with prior (33.0% vs 29.0%) and current (66.5% vs 70.4%) biologic use, and current conventional synthetic disease-modifying antirheumatic drug (csDMARD) use (24.6% vs 20.5%) were comparable (Table 4). However, higher proportions of women had prior csDMARD use (22.0% vs 13.4%; $P = 0.01$) and women had used a greater number of prior csDMARDs than men. Additionally, higher proportions of women had prior (15.7% vs 8.8%; $P = 0.02$) or current (9.9% vs 2.9%; $P < 0.01$) prednisone as well as nonsteroidal antiinflammatory drug (NSAID) use compared with men. Comparisons of treatment profiles between men and women with AS and between men and women with nr-axSpA generally reflected those in the overall population of patients with axSpA (Supplementary Table 4, available with the online version of this article).

Comorbidities. The prevalence of comorbidities was generally comparable between men and women (Table 5). However, higher proportions of women had diagnoses of depression (25.7% vs 12.1%; $P < 0.01$) and fibromyalgia (FM; 10.5% vs 1.0%; $P < 0.01$) compared with men. Differences in the prevalence of comorbidities between men and women with AS and between men and women with nr-axSpA were similar to those in the overall population of patients with axSpA (Supplementary Table 5, available with the online version of this article). Overall,

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Table 3. Patient-reported outcome measures and work productivity and activity impairment in men and women with axSpA at enrollment[a].

	Overall, N = 504[b]	Men, n = 307	Women, n = 191	*P*[c]
Patient pain, VAS 0–100	47.8 (29.6)	45.3 (30.5)	51.6 (27.8)	0.03[d]
Patient fatigue, VAS 0–100	48.6 (28.7)	45.4 (29.1)	53.9 (27.4)	< 0.01[d]
Morning stiffness, min, n (%)				
< 30	132 (26.8)	88 (29.4)	43 (22.6)	0.10[e]
≥ 30	360 (73.2)	211 (70.6)	147 (77.4)	
PtGA (VAS 0–100)	52.3 (32.4)	52.2 (32.5)	52.5 (33.1)	0.82[d]
HAQ-DI, 0–3	0.66 (0.64)	0.58 (0.62)	0.80 (0.65)	< 0.01[d]
HAQ-S, 0–3	0.67 (0.64)	0.59 (0.62)	0.82 (0.65)	< 0.01[d]
EQ VAS, 0–100[f]	64.0 (22.4)	66.2 (22.2)	61.1 (22.4)	< 0.01[d]
Employment				
Work status, n (%)				
Full time	292 (58.6)	190 (62.1)	102 (53.7)	< 0.01[e]
Part time	31 (6.2)	11 (3.6)	20 (10.5)	
Disabled	74 (14.9)	49 (16.0)	24 (12.6)	
Retired	60 (12.0)	38 (12.4)	22 (11.6)	
Other	41 (8.2)	18 (5.9)	22 (11.6)	
Current employment, n (%)	328 (66.1)	206 (67.8)	121 (64.0)	0.39[e]
WPAI domains				
% Work time missed	6.9 (18.0)	6.7 (18.4)	7.3 (17.4)	0.33[d]
% Impairment while working	28.8 (26.0)	24.9 (23.8)	35.4 (28.5)	< 0.01[d]
% Overall work impairment	31.3 (27.9)	28.4 (27.1)	36.4 (28.6)	0.03[d]
% Activity impairment	39.9 (30.2)	36.1 (29.7)	45.9 (30.0)	< 0.01[d]

Values are mean (SD) unless otherwise indicated. [a] All values were calculated based on available data, and all variables had < 20% missing data except for patient global assessment (n = 144), HAQ-DI (n = 392), HAQ-S (n = 392), % work time missed (n = 299), % impairment while working (n = 313), and % overall work impairment (n = 289). [b] Six patients did not have sex information available at enrollment or follow-up. [c] *P* values compared men vs women with axSpA. *P* values calculated using [d] Wilcoxon rank-sum test and [e] chi-square test. [f] Higher scores indicate better general health. axSpA: axial spondyloarthritis; EQ VAS: EuroQol visual analog scale; HAQ-DI: Health Assessment Questionnaire–Disability Index; HAQ-S: Health Assessment Questionnaire for the Spondyloarthropathies; PtGA: patient global assessment; VAS: visual analog scale; WPAI: Work Productivity and Activity Impairment questionnaire.

18 of 408 (4.4%) patients with AS and 5 of 90 patients (5.6%) with nr-axSpA had FM. A higher proportion of women with AS had FM than men with AS (10.3% vs 0.8%; $P < 0.01$). The proportion of women with nr-axSpA who had FM was higher than the proportion of men with nr-axSpA, but this difference did not reach statistical significance (11.4% vs 1.8%; $P = 0.07$).

DISCUSSION

This real-world study of patients with axSpA enrolled in the Corrona PsA/SpA Registry is one of the first to evaluate differences in clinical and patient-reported disease burden between men and women with axSpA in the US. Differences in clinical characteristics, disease activity, and PRO measures between men and women with axSpA were maintained when patients were stratified by diagnosis of AS or nr-axSpA, although these differences were less pronounced between men and women with AS. Overall, we found that women had more peripheral axSpA manifestations than men, including more peripheral arthritis and enthesitis.

Our results are consistent with findings from prior studies. The majority of studies that have evaluated disease burden in men vs women with axSpA have shown worse BASDAI scores, pain, fatigue, and QOL in women than in men.[11] We also observed worse functional status, as evidenced by higher BASFI, HAQ-DI, and HAQ-S scores in women than in men, which is consistent with other real-world cohort studies.[15,17] In prior studies, women were more likely to have peripheral symptoms, such as enthesitis and tender or swollen joints, than men.[17–23] We observed similar features in our study population. This increased prevalence of peripheral symptoms in woman is relevant, as peripheral axSpA symptoms were deprioritized in prior classification criteria. Updated classification criteria now include nonradiographic sacroiliac magnetic resonance imaging manifestations and peripheral symptoms more prominently, rather than focusing primarily on axial components.[24,26,28,29]

Both men and women experience a substantial delay in diagnosis of axSpA; estimates suggest an average of 5–14 years between symptom onset and diagnosis.[8] Previous studies have shown a longer delay in women than in men, which may be partly due to historical emphasis on axial symptoms for diagnosis.[30] In contrast, we observed a comparable delay between men and women (7.3 vs 7.6 yrs), which may reflect the ability of rheumatologists participating in the Corrona Registry to better detect axSpA due to training and routine patient visits. Most

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Table 4. Prior and current treatments in men and women with axSpA at enrollment[a].

	Overall, N = 504[b]	Men, n = 307	Women, n = 191	*P* [c]
Prior medication use				
Biologics	154 (30.6)	89 (29.0)	63 (33.0)	0.35
0	350 (69.4)	218 (71.0)	128 (67.0)	0.62
1	98 (19.4)	57 (18.6)	39 (20.4)	
≥ 2	56 (11.1)	32 (10.4)	24 (12.6)	
csDMARDs	85 (16.9)	41 (13.4)	42 (22.0)	0.01
0	419 (83.1)	266 (86.6)	149 (78.0)	0.03
1	64 (12.7)	32 (10.4)	30 (15.7)	
≥ 2	21 (4.2)	9 (2.9)	12 (6.3)	
Prednisone	59 (11.7)	27 (8.8)	30 (15.7)	0.02
Current medication use				
Biologics	347 (68.8)	216 (70.4)	127 (66.5)	0.37
csDMARDs	111 (22.0)	63 (20.5)	47 (24.6)	0.29
Prednisone	28 (5.6)	9 (2.9)	19 (9.9)	< 0.01
Analgesics (excluding NSAIDs)	10 (2.0)	4 (1.3)	6 (3.1)	0.19
Opioids	15 (3.0)	8 (2.6)	7 (3.7)	0.59
NSAID use				
Never	419 (83.1)	266 (86.6)	148 (77.5)	0.03
Prior use	24 (4.8)	11 (3.6)	13 (6.8)	
Current use	61 (12.1)	30 (9.8)	30 (15.7)	

Values are presented as n (%). [a] All values were calculated based on available data, and all variables had < 20% missing data. [b] Six patients did not have sex information available at enrollment or follow-up. [c] *P* values compare men vs women with axSpA and were calculated using chi-square tests, except analgesic and opioid use, which were calculated using Fisher exact tests. axSpA: axial spondyloarthritis; csDMARD: conventional synthetic disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug.

Table 5. Prevalence of select comorbidities in men and women with axSpA at enrollment.

Comorbidity[a]	Overall, N = 504[b]	Men, n = 307	Women, n = 191	*P* [c]
Hypertension	161 (31.9)	103 (33.6)	55 (28.8)	0.27
Depression	87 (17.3)	37 (12.1)	49 (25.7)	< 0.01
Hyperlipidemia	77 (15.3)	48 (15.6)	28 (14.7)	0.77
Uveitis	60 (11.9)	30 (9.8)	27 (14.1)	0.14
Cardiovascular disease[d]	47 (9.3)	30 (9.8)	16 (8.4)	0.60
Diabetes mellitus	34 (6.7)	21 (6.8)	12 (6.3)	0.81
Psoriasis	30 (6.0)	18 (5.9)	10 (5.2)	0.77
Serious infection[e]	30 (6.0)	19 (6.2)	10 (5.2)	0.66
Fibromyalgia	24 (4.8)	3 (1.0)	20 (10.5)	< 0.01
Any cancer (excluding NMSC)	22 (4.4)	13 (4.2)	9 (4.7)	0.80
Ulcerative colitis	22 (4.4)	9 (2.9)	13 (6.8)	0.04
Anxiety	17 (3.4)	7 (2.3)	10 (5.2)	0.08

Values are presented as n (%). [a] All values were calculated based on available data, and all variables had < 20% missing data. [b] Six patients did not have sex information available at enrollment or follow-up. [c] *P* values compare men vs women with axSpA and were calculated using chi-square tests. [d] Combined histories of myocardial infarction, acute coronary syndrome, coronary artery disease, congestive heart failure, peripheral arterial thromboembolic event, peripheral artery disease, cardiac revascularization procedure, ventricular arrhythmia, cardiac arrest, unstable angina, stroke, transient ischemic attack, peripheral ischemia or gangrene (necrosis), pulmonary embolism, carotid artery disease, or other cardiovascular event. [e] Includes infections that led to hospitalization or intravenous antibiotics: joint/bursa, cellulitis, sinusitis, diverticulitis, sepsis, pneumonia, bronchitis, gastroenteritis, meningitis, urinary tract infection, upper respiratory tract infection, *Mycobacterium tuberculosis*, or infection of other specified site. axSpA: axial spondyloarthritis; NMSC: nonmelanoma skin cancer.

patients initially see nonrheumatology healthcare providers for back pain or nonaxial symptoms, and unfamiliarity with axSpA manifestations may delay referral to rheumatologists.[30,31] Updated classification criteria and referral recommendations that account for peripheral symptoms, as well as increased access to educational and public awareness programs, have improved

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referral rates for patients with potential axSpA to rheumatologists and reduced diagnosis delay[29,31,32,33]; however, the average delay of > 7 years suggests additional educational efforts may be needed.

Whereas several previous studies of patients with AS have suggested comparable or greater disease burden in women than in men,[15,19,20,21] limited information is available regarding sex differences in patients with nr-axSpA. In our study population, women with nr-axSpA had worse disease activity and QOL than men, and our results show more pronounced sex differences in patients with nr-axSpA than in patients with AS. Whereas men and women with AS had comparable SJCs, SPARCC Enthesitis Index scores, ASDAS scores, and patient-reported pain, scores for these measures were worse in women than in men with nr-axSpA. Additionally, although the prevalence and severity of IBP were comparable between men and women with AS, the prevalence of IBP was lower among women than men with nr-axSpA; however, women reported greater IBP severity.

There are several potential reasons for the differences in symptoms between men and women with axSpA. First, genetic differences between men and women may result in differential disease expression and progression. In 1 study, men with AS had higher levels of tumor necrosis factor-α (TNF-α), interleukin (IL)-17, and Th17 cells than women with AS.[34] IL-17 facilitates osteoblastic differentiation and proliferation, promoting new bone formation,[35,36] and works synergistically with TNF-α to stimulate inflammatory pathways that lead to bone damage,[37] which may contribute to the higher prevalence of radiographic progression in men than in women. Sex-specific differences in the expression or allele variants of other genes implicated in axSpA have also been identified.[11] Further research may elucidate additional genetic mechanisms in the differential disease progression between men and women with axSpA.

Second, the greater disease burden in women may be partially due to central sensitization[38]: hypersensitivity to painful and/or inflammatory stimuli due to dysregulation in the central nervous system that can lead to chronic pain, perceived pain intensity disproportionate to the intensity of the stimulus, or pain perceived in areas where trauma or inflammation has not occurred.[39] Central sensitization is more common in women than in men.[38,40,41] Because symptoms of central sensitization overlap those of inflammatory rheumatic diseases, it can be challenging to determine disease severity due to the primary rheumatic disease vs the burden of central sensitization, particularly when evaluating outcome measures that rely on patient-reported symptoms.[38,42,43] For example, it may be difficult to distinguish true enthesitis resulting from inflammation of the entheses vs entheseal tenderness due to central sensitization when using clinical examinations that rely on palpitation of tender entheseal insertion sites. Use of imaging techniques and development of more sensitive screening tools may help improve differentiation between central sensitization and axSpA or other rheumatic diseases in the future, but these methods are not commonly employed in longitudinal observational cohort studies due to time and cost.[38,42] Distinguishing the degree of symptoms due to central sensitization from that of axSpA is important to guide treatment decisions and accurately assess treatment response.

Third, the higher prevalence of peripheral symptoms in women may contribute to differences in treatment profiles between men and women that can affect disease progression. A previous study using US claims data found that women with AS were less likely to receive biologics and more likely to receive csDMARDs, NSAIDs, muscle relaxants, anticonvulsants, opioids, and glucocorticoids compared with men.[27] Use of csDMARDs and prednisone was also higher in women with AS than in men with AS in the PSOAS study, but biologic use was comparable between men and women.[15] Biologic use was also comparable between men and women in our study population, whereas csDMARD, prednisone, and NSAID use were higher in women than in men. The ASAS/European League Against Rheumatism management guidelines for axSpA indicate that csDMARDs, particularly sulfasalazine, may be used in patients with peripheral arthritis;[44] thus the higher csDMARD use among women may reflect the higher burden of peripheral symptoms. Prednisone may be used for symptomatic treatment of other seronegative arthropathies, such as PsA or reactive arthritis, in which the symptoms mimic peripheral axSpA manifestations,[45,46] but it is not recommended for the treatment of axSpA. The increased prednisone use in women may reflect greater potential for misdiagnosis with seronegative peripheral arthritis in women with early axSpA presenting with a high degree of peripheral, rather than axial, symptoms. Misdiagnosis can delay appropriate disease management, resulting in continued disease progression that may lead to worse clinical, economic, and QOL outcomes.[8] These results suggest a need for greater awareness of peripheral axSpA manifestations and improved screening to ensure prompt diagnosis and appropriate treatment.

Finally, the differences in functional and PRO measures between men and women with axSpA may be influenced by differences in the type of work and daily activities that men and women perform and how the disease affects these day-to-day activities. For example, women are more likely to engage in child and elderly care, perform unpaid labor in the home and workplace, and use public transportation for daily travel than men.[47] These activities likely result in different physical and psychological stresses than corporate and administrative positions, manual labor occupations, and driving, which are more common among men.[47] Additionally, mechanical and physical stress differs between men and women in manual labor occupations and other physically demanding activities.[47] Several studies have shown that women with axSpA have worse PROs than men,[11] and some have also shown greater functional impairment in women despite comparable or less radiographic damage than men.[15,17] We observed higher pain, fatigue, and HAQ scores as well as greater work and activity impairment in women in our study population than in men. The higher burden of peripheral symptoms in women may contribute to the greater functional impairment and worse QOL observed in women with axSpA, in part due to the effect of these peripheral symptoms on the work and activities women perform.

Patients in the Corrona Registry are routinely seen and treated by rheumatologists voluntarily participating in the registry and may not be representative of all US patients with axSpA, many

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of whom are not being treated by a rheumatologist. A reduced number of patients had data available for ASDAS, CRP, and ESR, and because Corrona does not require laboratory tests, these missing data may reflect practice patterns of the investigators. Data on radiographic progression were not collected; thus, no associations can be made between disease burden and level of radiographic damage. Diagnosis of FM was based on physician judgment, the prevalence of which may be underrepresented in this dataset. The Corrona Registry is currently incorporating the Widespread Pain Index and the Symptom Severity scale, a validated quantitative measure of central sensitization,[48,49] to better assess FM in future analyses. The presence of depression was also based on physician judgment and the prevalence may be over- or underestimated in this dataset. The small sample size of patients with nr-axSpA may have limited the detection of statistically significant differences between men and women with nr-axSpA. Due to the descriptive, cross-sectional nature of this study, no longitudinal analyses were conducted to assess differences in disease outcomes over time between men and women.

In this US registry of patients with axSpA, women had greater overall disease burden compared with men, including higher disease activity, worse patient-reported symptoms, and greater work productivity impairment. We observed similar results when patients were stratified by diagnosis of AS or nr-axSpA. Women demonstrated less impairment of spinal mobility but increased signs of peripheral arthritis, suggesting that conventional definitions of axSpA centered around axial symptoms may need to be broadened to include peripheral manifestations in women. A substantial delay in diagnosis was observed in both men and women; greater awareness of peripheral axSpA symptoms may reduce delayed or missed diagnoses. Improved awareness of sex differences in the presentation of axSpA may aid physicians in earlier identification and improved disease management. Further studies are needed to better understand the differences in disease progression and outcomes in men vs women with axSpA.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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