



Sex differences in axial spondyloarthritis: biological mechanisms, clinical phenotypes, and therapeutic implications - a narrative review

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Abstract

Sex differences in axial spondyloarthritis (axSpA) are gaining recognition as clinically significant, but they are still not well incorporated into diagnostic practice and outcome assessment. Although long viewed as a predominantly male disease, axSpA affects women at nearly comparable rates and often follows a distinct phenotype. These differences extend beyond variations in severity and appear to reflect different biological and clinical expressions of disease.

Women with axSpA typically report higher levels of pain, fatigue, and disease activity, frequently alongside lower inflammatory markers and slower radiographic progression. They also experience longer diagnostic delays and more often present with peripheral manifestations or overlapping pain conditions such as fibromyalgia. In contrast, men more commonly exhibit the classical axial phenotype, elevated C-reactive protein, and greater structural damage. This discordance between symptom burden and objective inflammation creates challenges for disease assessment, as conventional tools may not perform equally across sexes. Emerging evidence also indicates sex-related differences in treatment response and drug persistence.

Recognizing sex as a biological determinant of disease expression, rather than merely a covariate for statistical adjustment, offers an opportunity to improve diagnostic precision, refine outcome interpretation, and support more individualized patient care.

Keywords: axial spondyloarthritis, sex differences, patient-reported outcomes, biologic therapy, personalized medicine

Introduction

Spondyloarthritis (SpA) comprises a heterogeneous group of chronic immune-mediated inflammatory diseases characterized by axial and/or peripheral musculoskeletal involvement, enthesitis, and extra-musculoskeletal manifestations [1]. This review centers on axial spondyloarthritis (axSpA) and draws on evidence from the broader SpA spectrum to inform diagnostic approaches, treatment trajectories, and long-term outcomes.

For decades, axSpA was regarded as a predominantly male disease, largely

because early research and clinical recognition focused on its radiographic phenotype, historically termed ankylosing spondylitis (AS), which was the most clinically recognizable and extensively studied phenotype [2,3]. However, the development and validation of the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA, together with the formal recognition of non-radiographic axSpA (nr-axSpA), have since broadened the spectrum and revealed a more balanced sex distribution, particularly among patients

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without definite radiographic sacroiliitis [2,4,5].

A precise distinction between sex and gender is important in this context. In this review, we use the term sex to refer to biological attributes, including chromosomal, hormonal, anatomical, and physiological characteristics, and gender to refer to socially constructed roles, behaviors, expectations, and interactions with the healthcare system. Although many studies on axSpA have historically used “sex” and “gender” interchangeably, this distinction is increasingly important. Biological sex may influence immune regulation, hormonal signaling, bone remodeling and structural progression, whereas gender-related factors may shape symptom interpretation, healthcare-seeking behavior, diagnostic pathways and treatment access [3,6–8]. Therefore, when discussing published studies, we retain the terminology used by the original authors but interpret findings according to whether they primarily reflect biological or sociocultural mechanisms.

Several reviews have examined sex and gender differences in axSpA, including the comprehensive synthesis by Rusman et al. published in 2020, which summarized the evidence available at that time on diagnostic delay, clinical phenotype, and treatment response [3]. Since then, the evidence base has expanded substantially.

The present review integrates more recent findings from large multinational registries and cohorts, including EuroSpA, IMAS, ASAS-perSpA, REGISPON-3, and the Swiss Clinical Quality Management cohort, together with newer sex-stratified imaging and transcriptomic studies. It also proposes a sex-informed, domain-based framework for interpreting discordance between patient-reported outcomes (PROs) and objective measures of inflammation and structural damage. To our knowledge, this clinically oriented framework has not been explicitly articulated in previous narrative reviews of axSpA.

Sex- and gender-related differences have important clinical consequences, beginning with the diagnostic pathway. Women with axSpA are more likely than men to experience diagnostic delay, a finding consistently reported across observational studies, international surveys, and systematic reviews [3,9–12]. This delay appears to be multifactorial. Women less often present with the classical combination of radiographic sacroiliitis, elevated C-reactive protein (CRP), and HLA-B27 positivity, and more often present with a broader symptom profile that may include peripheral manifestations, widespread pain, fatigue, or fibromyalgia overlap [3,9,10,13]. Historical perceptions of axSpA as a male disease may also continue to influence clinical suspicion and referral patterns [3,6].

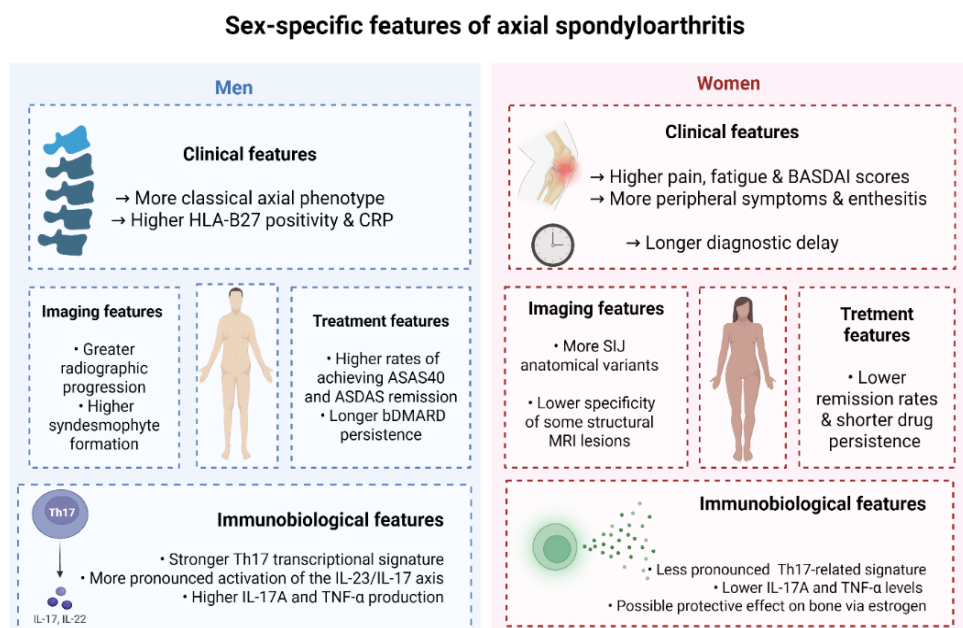


Figure 1. Sex dimorphism in axial spondyloarthritis (created with BioRender).

Legend: Schematic overview of reported sex-related differences in axSpA across clinical, imaging, treatment and immunobiological domains. These features represent group-level trends and should not be interpreted as fixed characteristics of individual patients.

Abbreviations: ASAS40, Assessment of SpondyloArthritis international Society 40% response; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying antirheumatic drug; CRP, C-reactive protein; MRI, magnetic resonance imaging; SIJ, sacroiliac joint.

Beyond diagnosis, sex differences are reflected in disease expression. Women generally report higher levels of pain, fatigue, and functional impairment, together with worse health-related quality of life. Men more often exhibit elevated inflammatory markers, HLA-B27 positivity, MRI inflammation, and greater structural damage, including syndesmophyte formation [3,13–16]. This divergence gives rise to one of the central paradoxes in axSpA: a higher symptom burden in women that frequently coexists with lower levels of conventional objective inflammation.

From a biological perspective, sexual dimorphism in immune responses offers a plausible explanatory framework. Differences between sexes in innate and adaptive immune activation, including variation in T- and B-cell responses and cytokine pathways such as the IL-23/IL-17 axis, have been described, and a sex-related Th17 transcriptional signature has been reported in AS [17–19].

Taken together, sex-related differences span clinical presentation, imaging findings, treatment response, and immunobiological mechanisms, as summarized in figure 1. Sex should therefore be seen as a determinant of disease expression with clinical implications, not just a covariate.

Methods

This narrative review was informed by a targeted search of PubMed and Google Scholar for articles published between January 2000 and April 2026. The search was supplemented by manual screening of the reference lists of key studies and recent reviews addressing sex and gender differences in spondyloarthritis. Search strategies combined terms related to axial spondyloarthritis and ankylosing spondylitis with terms covering sex and gender differences, diagnostic delay, immunological pathways, sacroiliac joint anatomy, MRI findings, radiographic progression, treatment response, drug persistence, and patient-reported outcomes.

The evidence considered included observational cohorts and registries, randomized controlled trials reporting sex-disaggregated outcomes, systematic reviews and meta-analyses, and relevant imaging and mechanistic studies. Particular emphasis was placed on evidence published after 2020, including large multinational registries and long-term cohort studies, while earlier publications were retained when they provided important epidemiological or biological context. As this was a narrative review, study selection was not based on a formal systematic-review protocol, and no structured risk-of-bias assessment was performed.

Clinical phenotype and diagnostic differences

The clinical expression of axSpA differs meaningfully between sexes, although the distinction is subtler than a simple axial-versus-peripheral divide.

Symptom burden and patient-reported outcomes

Across multiple cohorts, women report higher

pain, fatigue and disease activity, reflected in elevated BASDAI scores and worse quality of life [3,10,13]. In the DESIR cohort, women with recent-onset axSpA had higher disease activity and worse function, whereas men were more frequently HLA-B27-positive and showed greater objective inflammation (elevated CRP and MRI changes) [15]. Similar patterns appear in registries and systematic reviews, with women showing higher patient-reported burden and men more objective or structural markers [10,11,20].

Recent studies focused on PROs reinforce this pattern. In the ASAS-perSpA study, female sex was associated with less favourable outcomes across the SpA spectrum, including higher BASDAI and worse ASAS-HI and EQ-5D scores, while CRP did not differ by gender [21]. BASDAI was more influenced by gender than ASDAS, supporting the need to interpret outcome measures according to what they actually capture [21]. EuroSpA data from over 13 000 patients initiating first-line TNFi showed that women had worse BASDAI and BASFI scores at baseline; these differences widened after six months and persisted independently of baseline clinical characteristics [22].

This symptom-inflammation mismatch does not imply lack of disease validity in women. Rather, it reflects a complex phenotype involving inflammatory, mechanical, and pain-processing factors. Women more frequently present with enthesitis, peripheral symptoms and widespread pain, complicating early classification [3,6,13]. Fibromyalgia, which is common in axSpA and more prevalent in women, can amplify pain, fatigue and BASDAI scores independently of objective inflammation [23,24]. This overlap is clinically important because it risks both under-recognition of axSpA (when symptoms are attributed solely to fibromyalgia) and overestimation of inflammatory activity (when high PROs are interpreted without sufficient context).

Potential biological mechanisms contributing to sex differences

Biological mechanisms may contribute to these phenotypic differences. Men with axSpA demonstrate a more pronounced Th17 transcriptional signature and higher circulating levels of IL-17A and TNF- α compared with women, suggesting stronger engagement of the IL-23/IL-17 axis in male patients [17,18]. However, the available evidence remains limited to a small number of transcriptomic and cytokine studies. Recent transcriptomic studies have further shown distinct sex-based differences in gene expression within IL-17-producing cells, with male patients exhibiting upregulation of pro-inflammatory pathways, including TGF- β and PGE2 signaling [25]. As this observation derives from a single study, it should be considered preliminary until independently replicated.

Sex hormones play a key modulatory role. Testosterone suppresses TNF- α production while

promoting anti-inflammatory IL-10, whereas estrogens enhance production of IL-1, IL-6 and TNF- α [3,19,26]. They also influence bone metabolism differently: estrogens reduce osteoclastogenesis and bone resorption, while androgens promote bone formation and osteoproliferation, potentially contributing to greater structural progression in men [27]. However, this proposed connection is primarily supported by experimental evidence and has not been causally established within human axSpA cohorts. These immunological and hormonal differences may partly explain how inflammation translates into clinical symptoms and structural damage across sexes. Although the precise mechanisms remain incompletely understood, current evidence supports sex as a biological determinant shaping disease expression in axSpA.

The patient experience in axSpA is affected by factors beyond inflammation. Although not sex-stratified, recent research shows that coping strategies are tied more to stable traits like education and remain consistent over time. PROs are important but should be interpreted with biomarkers, imaging, and clinical exams in a sex-informed approach [28].

Diagnostic delay and its determinants

Diagnostic delay remains one of the most relevant consequences. Women experience longer delays than men (8.8 vs 6.5 years in earlier meta-analyses) [9]. Recent international data confirm persistent female disadvantage linked to atypical presentations, imaging limitations and diagnostic bias [11,12,29]. Women are less likely to present with the classic combination of elevated CRP, HLA-B27 positivity, and clear radiographic sacroiliitis, and more likely to have symptoms overlapping with mechanical back pain, widespread pain, or fibromyalgia [3,6,9,11,12,29]. The European Map of Axial Spondyloarthritis showed that women had more healthcare contacts before diagnosis, including more frequent visits to general practitioners, physiotherapists and osteopaths [30].

Although the average diagnostic delay in SpA has shortened in recent decades due to greater awareness, wider availability of MRI, and recognition of non-radiographic disease [31], women with atypical presentations remain vulnerable to misclassification, particularly when normal CRP or limited radiographic damage is interpreted as ruling out axSpA. This is clinically relevant because diagnostic delay is associated with worse structural damage and disability in radiographic axSpA [32].

Longitudinal registry data further highlight the dynamic nature of SpA phenotypes. Over-extended follow-up, substantial diagnostic transitions have been observed, particularly from undifferentiated SpA to axSpA or psoriatic arthritis (PsA) [33]. This reinforces the value of viewing SpA as an evolving spectrum rather than a fixed label, especially when initial presentations are less classical.

Imaging, sacroiliac joint anatomy and structural progression

Imaging is central to the diagnosis and monitoring of axSpA, but its interpretation depends on sex-related anatomical and biomechanical factors. MRI has enabled early detection of inflammation before radiographic sacroiliitis becomes visible, yet it introduces challenges because bone marrow oedema (BMO), sclerosis and other structural lesions are not specific to inflammatory sacroiliitis and may also occur in mechanical, degenerative or postpartum contexts [34,35].

Sex differences in sacroiliac joint (SIJ) anatomy contribute to these challenges. The SIJ differs between women and men in morphology, mobility, and load transmission. Women generally exhibit greater SIJ mobility and a higher prevalence of anatomical variants, whereas men tend to have a larger joint surface area and features that may confer greater tolerance to biomechanical stress [36]. These differences are clinically relevant because altered load distribution can produce mechanical BMO, sclerosis, or degenerative changes that mimic inflammatory sacroiliitis [36–38].

Anatomical variants of the SIJ (accessory joints, iliosacral complexes, bipartite plates, semicircular defects) are common (>80% on synthetic CT) and associate with sex, age and BMI [39]. They primarily affect imaging interpretation rather than defining distinct phenotypes [40].

Studies evaluating sex-specific MRI performance support a contextual approach. Ulas et al. demonstrated that while BMO performed similarly in both sexes, structural lesions such as fat metaplasia, erosions, and sclerosis showed lower specificity in women, challenging a uniform “one-size-fits-all” approach to MRI interpretation in axSpA [41]. Because this observation derives from a single sex-stratified study, it requires confirmation in larger independent cohorts. Meanwhile, individual MRI lesions should be interpreted alongside lesion pattern, anatomical context, and pre-test probability.

Sex differences are also evident in structural damage and spinal radiographic progression. Men with axSpA are more likely to develop syndesmophytes and accumulate radiographic spinal damage over time, as shown in longitudinal studies using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) [14,42]. Long-term data from the OASIS cohort showed that radiographic damage in AS progresses slowly but cumulatively, and that existing syndesmophytes or baseline structural damage are among the strongest predictors of further progression [14]. More recent analyses from the Swiss Clinical Quality Management cohort demonstrated that male sex is associated with greater spinal radiographic progression, partly mediated through higher baseline damage [42]. Across studies, the most consistent predictors of progression remain baseline structural damage, elevated

acute-phase reactants, and smoking, while the independent contribution of HLA-B27 and male sex varies by cohort and disease stage [14,42–44].

The mechanisms behind the greater burden of radiographic progression in men are not fully understood and should not be viewed as a simple sex-specific pathway. In axSpA, new bone formation is thought to arise from a complex interaction between inflammation, tissue repair, mechanical stress and osteoproliferative signaling. Longitudinal MRI–radiography studies have shown that spinal inflammatory lesions and, particularly, subsequent fatty lesions are associated with later syndesmophyte formation, supporting an inflammation–repair–new bone formation sequence in at least a subset of lesions [45–47]. Mechanistic reviews emphasize the non-linear relationship between inflammation and new bone formation [48,49]. The higher progression observed in men is therefore best interpreted in relation to their greater frequency of established risk factors, including baseline damage, elevated inflammatory markers, and smoking, rather than as proof of a male-specific osteoproliferative mechanism.

Almoussa et al. found higher overall radiological severity in men but more cervical syndesmophytes in women, suggesting that regional patterns may be obscured by global indices. A larger study by Berbel-Arcobé et al. found cervical involvement to be frequent and associated with male sex, older age, higher disease activity, worse mobility and greater structural damage [3,50,51].

These differences have therapeutic implications. TNFi may slow progression when started early, although effect size remains debated [52,53]. Men at higher risk of progression may benefit from closer radiographic monitoring, particularly in the presence of elevated CRP, smoking, or existing syndesmophytes. Women require careful contextual MRI interpretation and attention to non-inflammatory contributors.

Treatment response and drug persistence

Sex differences in axSpA affect therapy outcomes, but interpreting these differences needs caution. Treatment response is often measured using composite endpoints, including symptoms, global assessment, function, and biomarkers. Because men and women often differ at baseline in pain, fatigue, CRP, imaging findings, and structural damage, they may also differ in how readily they meet response thresholds, even when the same inflammatory pathway is targeted.

A recent systematic review and meta-analysis of 79 randomized trials, including 23 748 patients, found that only a minority of studies reported baseline characteristics, efficacy outcomes, or safety outcomes stratified by sex [54]. Among trials with available sex-disaggregated efficacy data, male patients were significantly more likely to achieve ASAS40 response and ASDAS low disease activity or inactive disease. This pattern was observed

across both TNFi and IL-17 inhibitors, indicating that the difference is not limited to one therapeutic class [54].

Real-world registry data show similar trends but require careful interpretation. In the DANBIO registry, male sex and markers of a more objective inflammatory phenotype (such as elevated CRP) were associated with better continuation of TNFi and response in axSpA [55]. Consequently, men may be more likely to meet response criteria reflecting reductions in objective inflammation, whereas women may continue to report symptoms due to residual enthesitis, peripheral disease, mechanical pain, fibromyalgia overlap, or central sensitization.

Data from the EuroSpA Research Collaboration have been particularly informative. In patients starting their first TNFi, sex differences in treatment effectiveness and retention were observed, with less favorable outcomes in women [56]. A subsequent EuroSpA analysis of more than 13 000 axSpA patients treated with TNFi showed that women had worse BASDAI and BASFI scores at baseline; these differences increased after six months and persisted over follow-up, and could not be fully explained by baseline clinical characteristics [22]. These findings do not mean biologics are intrinsically less effective in women. Conventional criteria capture different domains across phenotypes. Persistent BASDAI/BASFI elevation despite CRP/MRI improvement often reflects residual enthesitis, peripheral disease, mechanical pain, fibromyalgia or central sensitization rather than uncontrolled axial inflammation [22,54,56].

Drug persistence provides a complementary outcome because it captures long-term effectiveness, tolerability and treatment decision-making beyond early response thresholds. In the 17-year REGISPON-3 follow-up study, the timing of bDMARD initiation was similar in women and men, whether measured from symptom onset or from diagnosis. However, women had significantly shorter persistence on both first and second bDMARDs [57].

Overall, sex differences in treatment response arise from biological, clinical and measurement factors. The goal is multi-domain assessment (symptoms, function, biomarkers, imaging, comorbidities, tolerability, patient priorities) rather than sex-specific algorithms or single composite thresholds [58].

Clinical implications and future directions

Implications for current clinical practice

Current evidence does not justify separate diagnostic or therapeutic algorithms for women and men with axSpA. Rather, sex may influence how disease is expressed and interpreted. This aligns with ASAS-EULAR recommendations, which advocate for personalized management based on disease activity, clinical signs, prognostic factors, comorbidities, and patient preferences, rather than treatment decisions based on one characteristic [58]. A sex-informed approach should therefore refine

clinical reasoning, not replace it.

One practical consequence is the need to interpret disease activity by domain rather than by score alone. BASDAI and ASDAS remain useful tools, but they do not measure identical constructs: BASDAI is entirely patient-reported, whereas ASDAS incorporates an inflammatory biomarker, usually CRP [59,60]. When symptoms and objective inflammation are discordant, the question should not simply be whether the patient has “active disease”, but rather which domain is driving the burden: axial inflammation, enthesitis, peripheral disease, pain amplification, fatigue, function, structural damage or comorbidity. This domain-based interpretation is consistent with the ASAS-OMERACT core domain set and is particularly relevant when symptoms, biomarkers, and imaging findings do not evolve in parallel [61–63]. In a sex-informed framework, persistent disease activity warrants reassessment before treatment escalation. Persistent symptoms should be evaluated for residual axial or peripheral inflammation, enthesitis, structural or mechanical contributors, fibromyalgia, fatigue, sleep disturbance, comorbidities, and treatment-related adverse events, as these domains may require different management strategies.

Priorities for future research

Future studies should prioritize well-phenotyped longitudinal cohorts combining standardized imaging, validated PROs, comorbidity assessment, and long-term outcomes. Multi-omics approaches may help clarify sex-related pathways linking immune activation, pain processing, bone remodeling, and treatment response. Clinical trials and registries should also routinely report efficacy and safety outcomes stratified by sex and, where possible, collect relevant sex-related variables. The aim is not to define separate male and female forms of axSpA, but to understand why disease expression and outcomes may differ between sexes and to use this knowledge to refine individualized care.

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Author contributions

Diana Maria Margareta Moldovan: visualization, writing – original draft, writing – review and editing. Fodor Daniela: writing – review and editing, supervision.

Clementina López-Medina: writing – review and editing.

All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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