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REVIEW

# Gender differences in axial spondyloarthritis

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## Abstract

Within the concept of axial spondyloarthritis (axSpA), relevant differences between men and women have been described for patients with the radiographic disease form [ankylosing spondylitis (AS)]. The subjective perception of disease activity (spinal and peripheral pain, fatigue, morning stiffness) has been shown to be higher in female than in male patients. Moreover, women experience more functional limitations and a lower quality of life, despite lower degrees of radiographic spinal damage. Peripheral clinical involvement (arthritis and enthesitis) is, additionally, more predominant in women. On the other hand, a higher level of objective signs of inflammation (C-reactive protein, erythrocyte sedimentation rate, magnetic resonance imaging of sacroiliac joints and spine) has been reported in men. Whether these differences might explain the better response to treatment with anti-tumor necrosis factor agents observed in male patients remains unclear. The underlying causes of the discrepancies are still unknown and genetic, environmental, cultural and/or societal factors may be involved. While AS is still more prevalent in men in a ratio of 2-3:1, the prevalence of males and females in patients with axSpA without radiographic sacroiliac damage is similar. Gender differences in this subgroup of patients have not been adequately addressed, and are particularly needed to further validate the Assessment of SpondyloArthritis international Society classification criteria.



**Key words:** Axial spondyloarthritis; Ankylosing spondylitis; Classification; Gender; Outcome

**Core tip:** In comparison to men, women with ankylosing spondylitis (AS) experience a higher subjective burden of disease despite lower objective signs of systemic inflammation and less spinal radiographic damage. A better response to treatment with tumor necrosis factor inhibitors has been demonstrated in male AS patients.

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## INTRODUCTION

Ankylosing spondylitis (AS) is still considered the prototype disease of a group of inflammatory rheumatic conditions, referred to as spondyloarthritides (SpA), and characterized by inflammation of the sacroiliac joints (SIJ), the spine, as well as peripheral joints and enthesis[1,2]. It was traditionally associated with a long diagnostic delay[3], as the defining radiographic changes of the SIJ, described by the modified New York criteria[4], usually develop gradually over several years. It is now regarded as part of a disease continuum, referred to as axial SpA (axSpA), defined by the 2009 Assessment of SpondyloArthritis international Society (ASAS) classification criteria[5]. Within this concept, AS, also called radiographic axSpA, is opposed to nonradiographic (nr-) axSpA[6,7]. In the absence of definite radiographic SIJ damage, patients can be classified as having nr-axSpA either in the presence of sacroiliitis on magnetic resonance imaging (MRI) plus at least one SpA feature or in the presence of human Leukocyte Antigen (HLA)-B27 plus at least two SpA

features[5]. Relevant differences between men and women have been delineated for the AS subgroup and this review will particularly focus on new data published after the extensive 2008 survey by Lee *et al*[8]. Recent studies have also highlighted differences in sex distribution between AS and nr-axSpA[9-12]. Data on gender differences in the nr-axSpA subgroup are, however, only beginning to emerge[13].

## GENDER DIFFERENCES IN ANKYLOSING SPONDYLITIS

### Distribution

AS was believed to affect predominantly men, with a ratio of 10 males for every female patient[14]. It remained a relevant example of sex biased research for many decades as it was often carried out in military or veteran's hospitals. Underestimation of disease prevalence in the female population might have additionally been due to differences in disease phenotype, reluctance to perform X-rays of the pelvis and lumbar spine in women of child-bearing age, gender differences in the act of seeking a doctor's advice or a faster investigative approach in men with back pain and stiffness in physically demanding jobs. Studies conducted in the last decade reported a much smaller sex distribution difference, still favoring males, in the order of 2-3:1, also reflecting progress in imaging technologies and changing gender roles[9,11,15]. A recent systematic analysis of 13 cross-sectional population studies revealed a mean gender ratio of 3.4:1 and some differences between geographic regions (3.8:1 in Europe and 2.3:1 in Asia)[16].

### Pathogenesis

The strong genetic association of AS with HLA-B27, discovered by Brewerton and Schlosstein in 1973[17,18], was subsequently shown to presumably not be implicated in the unequal sex distribution, as the prevalence of HLA-B27 was similar in women and men[19]. These findings should be confirmed in larger population studies, as the proportion of HLA-B27 positivity was significantly lower in women than in men in recent treatment studies[20,21] and in the Swiss Clinical Quality Management (SCQM) axSpA cohort[22]. While only a quarter of the genetic susceptibility to AS is currently explained by HLA-B27, sex differences have not been addressed in other discovered major histocompatibility complex (MHC)- or non-MHC genetic associations involved in the innate immune stimulation, the interleukin-23 pathway or peptide presentation[23]. Potential sex differences have been described for the *ANKH* gene, coding for a protein regulating the cellular export of inorganic pyrophosphate[24]. The association of *ANKH* with disease susceptibility remains, however, controversial[25,26]. By contrast, no evidence for an involvement of the X-chromosome in the development of AS could be detected[27].

Genetic factors may also have an indirect impact on disease susceptibility by interacting with environmental factors influenced by gender. HLA-B27 is particularly interesting in this regard, as it might interact with bacterial antigens[28]. The triggering role of Chlamydia trachomatis is clearly established for the development of reactive arthritis after urogenital infection with this bacterium and the disease has an important male predominance (up to 20:1)[29]. A significant proportion of HLA-B27-positive patients with Chlamydia-induced SpA will eventually develop AS and Chlamydia trachomatis has also been detected by polymerase chain reaction in synovial tissues from patients with other SpA forms[30].

Smoking represents another environmental and societal factor potentially influencing gender differences in rad-axSpA. Although studies linking smoking with incident AS are lacking, smoking was demonstrated to be associated with increased disease activity, impaired function and poorer quality of life in cross-sectional analyses[31-38]. Furthermore, it was associated with future radiographic spinal progression in longitudinal studies[39,40], probably through an amplifying effect of disease activity on radiographic damage[41]. While the prevalence of smoking is higher in men than in women with AS[38,42], a causal effect between smoking and gender differences in disease outcome, as depicted below, remains to be established.

No differences in gonadal and adrenal sex hormones have been identified in male and female patients with AS in comparison to healthy controls[42]. A recent analysis of 448 women using the oral contraceptive pill in comparison to 123 female non-users failed to demonstrate any effect of the use of exogenous estrogens on the initiation or on the severity of AS[43].

### Disease onset and diagnostic delay

The age at symptom onset was similar in women and men with AS in most of the studies available to date, while a longer duration from disease onset to diagnosis has been detected in women[3,44]. However, HLA-B27 has been shown to have a strong effect not only on the age at symptom onset[9,21], but also on diagnostic delay[15], and was not available in all patients. Additional investigations are therefore needed. We found an earlier disease onset in male patients in a large cohort of 1199 patients with AS (mean age at onset 26.3 years in men *vs* 29.3 years in women, $P < 0.001$)[22]. The documented differences in HLA-B27 prevalence in men and women in this study (see above) may not fully account for the gender difference in disease onset, as women were on average 1.8 years older than men at the beginning of back pain in the subgroup of HLA-B27-positive patients[22].

### Signs and symptoms

A multitude of comparisons of male and female patients with AS have provided data on women having more pain at the level of the cervical spine and in peripheral joints, with the hip joints being more often involved in men[45-56]. The intensity of symptoms (spinal pain, peripheral joint pain and swelling, areas of localized tenderness, fatigue, morning stiffness) was substantiated with the patient-reported Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[57] in the more recent literature. Women

presented with higher BASDAI, global pain, nocturnal pain, joint pain and fatigue scores in comparison to men[58-66]. As these common symptoms overlap with the clinical features of fibromyalgia, which is more prevalent in women with AS than in men[67-69], additional objective parameters to assess disease activity seem advisable. Whether the use of the recently defined Ankylosing Spondylitis Disease Activity Score (ASDAS) will prove helpful in this regard, as its calculation includes acute phase reactants [erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)] in addition to patient-reported parameters[70], remains to be established.

### Clinical findings

The report of women being more often treated with methotrexate, sulfasalazine and prednisone in an North American cohort suggested a higher prevalence of peripheral arthritis in women with AS[56]. When analyzing the presence of current or previous peripheral synovitis, these gender differences with regard to the presence of peripheral arthritis in AS have been substantiated[62,71]. In the Swiss SCQM axSpA Cohort (826 men and 373 women with AS), a significantly higher percentage of women had peripheral synovitis as well as a higher number of swollen joints at inclusion, while no differences have been observed with regard to the percentage of men and women with previous peripheral arthritis (unpublished results). The discrepancies might be explained by longer disease duration in men in this cohort, allowing for more clinical manifestations to accumulate. As demonstrated in another registry, the presence of peripheral arthritis seems to delay spinal radiographic progression (see below), independently of other confounding factors, including gender[72].

Peripheral enthesitis evaluated by the Maastricht Ankylosing Spondylitis Enthesitis Score was also more frequently found in women in comparison to men with AS[62,73]. The finding might be confounded by a potential overlap between enthesitic and fibromyalgia tender points.

Spinal mobility, as assessed by different clinical parameters, such as the tragus-to-wall distance, the Schober' s test or the Bath Ankylosing Spondylitis Metrology Index in more recent studies, was consistently more greatly impaired in women in comparison to men. Spinal mobility cannot be used as a proxy for radiographic damage in an individual patient[74], as both inflammation and structural damage have been shown to contribute to its impairment[75].

With regard to extra-articular manifestations - acute anterior uveitis, psoriasis and inflammatory bowel disease-only bowel inflammation was positively associated with the percentage of women in the evaluated AS studies of a systematic review and meta-analysis of 156 selected articles[76].

### Imaging studies

Radiographic differences between genders in AS have been analyzed in numerous studies[34,45,46,48,49,51-56,62,77]. After adjustment for age and disease duration and using either the Bath Ankylosing Spondylitis Radiography Index or the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) in the more recent literature, men consistently presented with more important spinal changes on X-rays in comparison to women. This was confirmed in a recent 12-year prospective follow-up analysis, especially in the presence of HLA-B27 positivity[78].

Male sex was also associated with MRI inflammation of the SIJ in several studies of patients with axSpA, including patients with AS, while HLA-B27 was an independent predictor of future MRI positivity[21,79,80].

### Laboratory findings

While ESR and CRP levels have been demonstrated to be higher in women in comparison to men in the general population[81-83], acute phase reactants were either similar, or slightly more elevated in male patients with AS in comparison to females, suggesting a higher level of systemic inflammation in men[20,59-61,84,85]. Elevated CRP was shown to be associated with radiographic progression in AS[39]. As smoking is associated with pro-inflammatory effects and may raise CRP levels in a non-specific manner[86], it remains unclear, whether higher acute phase reactant levels in AS might be explained in part by the higher prevalence of smokers in the male AS population.

### Disease activity and radiographic progression

Higher disease activity, as measured by the ASDAS, which includes both patient-reported outcomes and acute-phase reactants, led to more spinal structural damage, especially syndesmophyte formation, in a recent 12-year longitudinal study[78]. The authors highlighted the fact that the ASDAS outperformed all other disease activity measures (BASDAI and CRP, patient-reported global activity and CRP, back pain and CRP) in this analysis. A significant interaction was found between ASDAS and gender: the effect of ASDAS on the change in mSASSS was higher in males versus females (0.98 *vs* -0.06 units per 2 years and per additional unit of ASDAS). Whether an association exists between important mechanical forces acting on the spine (observed in male-dominated more intensive occupational activities) and formation of syndesmophytes, should be confirmed in future studies.

### Functional outcomes

Self-reported functional ability in performing daily activities is usually assessed with the Bath Ankylosing Spondylitis Functional Index. A similar level of functional impairment has been demonstrated in women and men with AS[20,56,61,64]. After adjustment for the level of radiographic spinal damage, however, the disability observed was more pronounced in female in comparison to male patients[56]. The documented higher level of peripheral symptoms (arthritis and enthesitis) in women might be regarded as a confounder in this analysis[87].

### Quality of life

Health-related quality of life encompasses the individual

well-being considering social, emotional and physical aspects, as well as the effect of disease on a patient's well-being, mainly measured by the Short-Form Health Survey (SF-36) and the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL). It is significantly impaired in AS[88]. In unadjusted analyses, women reported a significantly worse quality of life and a greater reduction in vitality than men[88-90]. However, after adjustment for the normal differences in men and women's self-assessment of their health in the general population, the crude effect of AS on the quality of life was greater in men[88].

### Work disability

Analyses of gender differences with regard to work disability in AS led to conflicting results due to differences in economic environment, social security system, disability compensation system in different countries as well as comorbidities, disease duration and proportions of patients with manual jobs in the respective studies[91-100]. The contributing factors to absenteeism (impossibility to attend work, either due to temporary sick leave or permanent worker disability) and presenteeism (reduced performance or productivity at work due to health reasons) in AS patients have been analyzed recently[101]. Female sex, an impaired health-related quality of life and helplessness (a personal factor) were associated with presenteeism, while at-work limitations and lower quality of life contributed to sick leave.

### Family life

In a US analysis, patients with AS were more likely to have never been married and men were more likely to divorce, especially in longstanding disease[102]. In the same study, women with AS were less likely to have children than women in the general population, in contrast to men. The authors postulate that women might be more sensitive to the concern about having children with AS. The quality of marital life was shown to be characterized by a higher global distress and a higher probability of aggression from their partner in female SpA patients from Korea[103]. Furthermore, in comparison to healthy individuals in Europe, a higher proportion of women with SpA was shown to be single or divorced[104]. Disease activity was, moreover, higher in divorced than married female SpA patients. With regard to inheritance, a higher prevalence of AS among children and siblings of female index cases has been demonstrated, suggesting that women may require a higher genetic load to develop the disease[44, 105]. The higher prevalence of a family history of SpA found in female patients with axSpA[13,56,62,64], would be compatible with this hypothesis.

### Response to treatment

Tumor necrosis factor (TNF) inhibitor treatment is recommended in patients with highly active AS and insufficient response to non-steroidal anti-inflammatory drugs[106]. Elevated acute phase reactants have been shown to represent the most important predictor of treatment response[84,107-113]. Gender differences in response to TNF inhibition or treatment survival have also been identified in most studies, which were, however, not adjusted for all known confounding factors. In the Groningen Leeuwarden AS observational cohort, male gender was a predictor of treatment response, while female gender predicted treatment discontinuation independently of other parameters[111]. Female gender was also a predictor of anti-TNF-agent discontinuation in the South Swedish Arthritis Treatment Group Register and in the Danish nationwide DANBIO register[84,113]. In a study of pooled data from four clinical control trials of etanercept, sulfasalazine or placebo in AS, female patients had less improvement in ASDAS than male patients[20]. In contrast, female gender was an independent predictor of improvement in BASDAI and the Bath Ankylosing Spondylitis Functional Index in the British Society of Rheumatology Biologics Register[110], while gender did not influence treatment responses in other studies[107,112,113].

### Mortality

An increased mortality was found in men but not women with AS (standard mortality rate 1.63 *vs* 1.38, $P < 0.001$) in a cohort of 677 patients followed since 1977, with circulatory disease being the most frequent cause of death[114]. A trend towards increased mortality in women was only found after longer disease duration (35-40 years). The authors postulate that a larger study population with a longer time span of observation might be necessary to demonstrate excess mortality in women with AS. The finding that the increased mortality in AS was related to the degree of disease activity, however, points to a really existing gender difference in this regard.

## GENDER DIFFERENCES IN NONRADIOGRAPHIC AXIAL SPONDYLOARTHRITIS

The most striking differences between patients with axSpA fulfilling or not fulfilling the modified New York classification criteria (AS *vs* nr-axSpA) are the unequal gender distribution (1:1 in nr-axSpA and favoring men in a ratio of 2-3:1 in AS) and the higher level of CRP in AS compared to nr-axSpA[9-12]. Women as well as patients with low systemic inflammation might have a lower risk to develop radiographic spinal damage and remain longer in the nonradiographic disease stage. The risk of misdiagnosis in patients with other reasons for back pain in context of HLA-B27 positivity[115] would represent an alternative, mutually not exclusive explanation for the higher prevalence of women in the nr-axSpA group. Comparisons between women and men with nr-axSpA, as well as between women with AS and women with nr-axSpA, along with prospective longitudinal data are therefore needed. Tournadre *et al*[13] have analyzed the differences between female and male patients in the French cohort Devenir des Spondylarthropathies Indifférenciées Récentes of patients classified as having axSpA. Data are also presented in the subgroup of patients classified by the imaging and

the clinical arms of the ASAS classification, respectively. Only patients in the clinical arm are available for analysis of gender differences in nr-axSpA in this study, as both patients with AS and patients with nr-axSpA are present in the imaging arm by definition. Higher self-reported disease activity parameters and functional impairment were found in women. Multivariate regression models confirmed the relationship between higher levels of BASDAI, ASDAS-CRP, fatigue and ASQoL and female gender[13].

## CONCLUSION

Female AS patients experience higher levels of pain and other self-reported disease activity parameters, a greater impairment of health-related quality of life and a reduced treatment response upon TNF inhibition. On the other hand, male AS patients present with higher objective measures of disease activity (acute phase reactants, inflammation of SIJ on MRI) and a more important radiographic spinal damage. The causes underlying these relevant differences remain largely unknown.

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