Sexual dimorphism in the prevalence, manifestation and outcomes of axial spondyloarthritis

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Abstract | Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that predominantly affects the axial skeleton, although it can affect peripheral joints, and extra-musculoskeletal manifestations also occur. Historically, axSpA was thought to be a disease predominantly seen in men, although with the advent of magnetic resonance imaging techniques and advances in research, this dogma has been challenged and refuted. Sex and gender are different concepts, and both can have a role in disease. In axSpA, consideration of the influence of sex and gender on the disease phenotype is necessary to predict outcomes and to enable the development of therapeutic approaches that are best suited to individual patients.

A fascinating interplay exists between sex, gender and disease. Sex and gender refer to different entities, yet often they are conflated in the care of patients and the study of disease[1]. The term sex is used to describe the physiological differences between a male and female body. In addition to the X and Y chromosomes and levels of sex hormones, such as testosterone, oestrogen and progesterone, male and female bodies also differ in organ size and function, height and bodyweight, body composition and physiological processes, such as pain mechanisms[2] and immune processes (TABLE 1). Gender refers to socially constructed characteristics of women and men that include norms, roles and relationships, which vary in different societies and which may be fluid[3]. Gender identity refers to the personal sense of one's own gender and is reflected in a person's pronouns, where gender expression reflects a person's behaviour, mannerisms, interests and appearance associated with femininity or masculinity[4]. A patient's gender can influence how they cope with disease and how they are perceived by health-care providers[5–7], and conversely, the gender of the doctor can also influence the patient–doctor interaction. However, in many studies the word 'gender' is also used to describe (biological) differences between men and women. These sex differences may influence the onset, diagnosis and progression of rheumatological diseases, such as axial spondyloarthritis (axSpA).

Why patients of one sex or gender have a particular disease susceptibility, and why genders within a single disease have different phenotypes, including manifestations, disease activity and severity, are not yet clear. Many rheumatological diseases have a sex predisposition. AxSpA is a chronic inflammatory arthritis of the sacroiliac joints and spine that affects men and women equally. AxSpA defines a spectrum of disease, including the most commonly known form, ankylosing spondylitis (AS), with radiographic damage to the sacroiliac joints (also known as radiographic axSpA). AS with radiographic damage is more prevalent in men than in women[8–10]. With newer Assessment of SpondyloArthritis international Society (ASAS) classification criteria and advanced MRI, we are now able to more broadly define axSpA and classify the disease before significant damage ensues, thus including non-radiographic axSpA (nr-axSpA)[11]. With the inclusion of nr-axSpa, the percentage of women in the axSpA group has increased, because (compared with men) radiographic changes occur less often in women[12]. This advance has resulted in a more gender-equal disease distribution, with more women presenting with nr-axSpA than previously, when fewer women were diagnosed based on the radiographic criteria. Men tend to have more radiographic damage and a higher serological inflammatory burden, whereas women tend to report more symptoms and more severe symptoms, especially at the peripheral joints, with a similar overall burden of disease between the sexes (TABLE 2). As the spectrum of axSpA can be viewed as a single disease, in this Review AS and nr-AxSpA are not interpreted differently in the context of sex and gender except to highlight specific inflammatory and radiographic differences that exist. Women with axSpA report different symptoms from affected men. Factors that might affect disease expression and phenotype can be genetic, anatomical, psychological or societal in nature. Additionally,

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Key points

- Sex and gender have important roles in disease, with differential contributions to axial spondyloarthritis (axSpA) phenotype, response to therapy and outcomes.
- AxSpA has equal prevalence in women and men, contrary to evidence that initially (and falsely) indicated that it is a disease that predominantly affects men.
- Women and men with axSpA have different phenotypes, which is important to keep in mind when assessing for this diagnosis in the clinical setting.
- Anatomical, physiological and hormonal differences might account for axSpA phenotypic heterogeneity.
- More research is needed to better understand the contributions of sex and gender to disease in axSpA.

women experience menses, pregnancy and menopause, which add complexity to this relationship. Interestingly, male and female patients with axSpA tend to differ in their responses to treatment. In this Review, we discuss sex and gender differences and how they might contribute to differences in phenotypes and therapeutic responses in axSpA[13–19].

Differences across sex and gender

Defining sex and gender

As we consider the influence of the biological variable (sex) and the social construct (gender) on disease phenotypes and outcomes, it is essential to understand how they differ from each other. An important point to recognize is that these variables are not binary, even though studies have largely assessed them in a binary manner. Sex is assigned at birth based on male and female attributes and chromosomal differences when known. Intersex is designated when these characteristics fall outside of the binary definitions. Typically, sex will also be associated with anatomical and physiological features. Although hormonal metabolism is physiologically associated with sex, pharmacological hormone therapy might have a role regardless of sex.

Gender refers to an individual's identity, one's roles and expectations in society, and includes the pronouns that a person uses[20]. Like sex, gender is also not a binary term[21], yet it has been interpreted that way in the majority of studies to date. How gender is determined in a study might also be important[20,22,23]. If a study participant fills out a case-report form, they might identify as a specific gender (or not). This identification is truly gender and sex should not replace this definition in most studies[23], unless questions relating to biological sex are also asked, or genetic information is known. Researchers may inappropriately identify a patient's gender by the patient's feminine or masculine expression (resulting in identification as a woman or man, respectively); this is not gender identity and should be separately considered. As we discuss the literature throughout this Review, we use the terms that the authors of the studies used, recognizing that conflation of terms might have occurred and that these variables are not binary, despite their designation.

Physiological and anatomical features

Physical differences between men and women could explain variation in spinal loading. Men have a longer, narrower, heart-shaped sacrum, whereas women have a wider pelvic outlet and a broader, oval-shaped pubic arch (FIG. 1). In a biodynamic study of spinal loading of men and women, men had greater absolute spine compression[24]. However, when analysing these spinal loads under whole-body free-dynamic conditions, women experienced greater spinal loads, implying that women were more likely to experience musculoskeletal injury from heavy lifting over time. In another study, trunk muscle size differed between sexes (men versus women) and within a sex (left side versus right side), with larger loading muscles, including erector spinae, internal and external obliques, psoas major and quadratus lumborum, in men[25]. Latissimus dorsi tended to be larger on the right side than on the left for both men and women. Women had larger psoas major and quadratus lumborum musculature on the right than on the left, whereas men had similar measurements on each side. Although the implications of these findings for axSpA are not known, they demonstrate the anatomical and spinal loading differences that could set patients up for varying clinical presentations.

Drug effects

Sex influences the efficacy and adverse effects associated with medical treatments. Notably, in the case of general drug development, most studies were until recently performed in male rodents and male volunteers, and therefore there is a lack of sufficient data on the effects in females[26]. As a result, some unexpected adverse effects have occurred (with drugs such as cardiovascular drugs, salicylates and anti-coagulants), along with increased risks of hospital admission related to adverse drug reactions in women[27–29]. In general, women have lower liver and renal function than men, because of the smaller volumes of these organs, which results in lower glomerular filtration rates and lower capacity for drug elimination in women. In addition, the gastrointestinal tract transit time is longer and the pH higher in women, which (among other effects) increases the resorption of weak acids, which influences drug resorption. Emerging data also show that there are sex differences in expression of cytochrome enzymes and drug-transporter proteins, which contribute to a potentially higher drug toxicity in women[28].

Body composition

Sex differences are not limited to the gonads, breasts and concentrations of hormones, as men and women also differ in height, bodyweight and body composition. In general, males are taller and have greater bodyweight than females. In addition, there is a sex difference in body composition, as women have approximately 10% higher body fat than men for the same BMI[19]. In addition, women have greater deposits of subcutaneous adipose tissue (80–90% of total body fat)[30], especially in the hips and thighs (which can result in the so-called 'pear shape'), whereas men have higher percentages of intra-abdominal visceral adipose tissue (6–20% of total body fat), which can lead to an 'apple shape'. The fat distribution typically seen in women confers protection against metabolic diseases, but following menopause fat is redistributed to the central phenotype, which is

associated with the metabolic syndrome[31]. Interestingly, the adipose tissue also acts as an endocrine organ, secreting not only adipokines (such as the anti-inflammatory adiponectin and the pro-inflammatory leptin) but also cytokines, such as TNF. Women generally have a higher percentage of body fat than men, with higher levels of circulating leptin at all ages, even before puberty and after menopause. Women also have higher levels of circulating adiponectin, which are reduced in association with elevation of BMI[1,32]. Results published in 2019 revealed an association between a high android-to-gynoid fat ratio and chronic low-back pain, as well a probable link between leptin levels and osteoarthritis[33].

Pain processing

Several sex differences contribute to pain sensitization and transportation of pain signals. First, women have a higher density of pain receptors in the skin than men[34]. In addition, the results of studies in rodents demonstrate differences in expression of genes encoding prostaglandins, which are mediators of pain signalling[35]. Mu opioid receptors have lower activation in women than in men, especially during the follicular phase of the menstrual cycle, and overall, women show less of a response to mu opioids (such as morphine)[36]. By contrast, kappa opioids, such as pentazocine and butorphanol, produce a greater analgesic response in women than in men[37]. Notably, the pain threshold is increased by testosterone, whereas conflicting evidence is associated with the effects of oestrogen and progesterone on pain tolerance. High oestrogen and low progesterone can be associated with high pain sensitivity, whereas low oestradiol concentrations result in low pain sensitivity[38,39].

Hormones and life-cycle effects

Sex hormones have roles in immune modulation. Compared with men, women have stronger immune responses, especially in innate immunity (with higher Toll-like receptor expression and activity and greater efficiency of antigen-presenting cells to initiate a secondary response in primed lymphocytes)[40], but also in adaptive immunity, which is modulated by oestrogen and progesterone concentrations, which both stimulate type 2 T helper (T_H2) cell responses and antibody production by B cells. Therefore, women have a lower burden of bacterial, viral and parasitic infections during their reproductive years and have higher immunoglobulin levels following infection or vaccination[41]. Men are more

Table 1 | **Differences between men and women in the context of axial spondyloarthritis**

Category	Comparison between the sexes		Effects of differences between the sexes
	Women	Men	
Genetics			
Sex chromosomes	XX[a]	XY[a]	Gene expression
Anatomy and physiology			
Pelvic anatomy	Wider pelvic outlet and broader pubic arch (oval-shaped)	Longer, narrower sacrum (heart-shaped)	Effects not determined
Kidneys	Smaller size; lower glomerular filtration rate	Larger size; higher glomerular filtration rate	Lower renal function may result in greater drug adverse-event risk in women
Liver	Smaller size; oestrogens influence the plasma concentrations of enzymes	Larger size	Lower drug elimination may result in greater drug adverse-event risk in women
Gastrointestinal	Longer gut transit time; higher pH	Shorter gut transit time; lower pH	Influence on drug metabolism may result in greater drug adverse-event risk in women
Body composition	Higher fat mass	Higher muscle mass	Influence on drug metabolism
Hormones	Higher oestrogen and progesterone levels; effects of pregnancy and menopause	Higher testosterone levels	Effects not determined
Immune response	Oestrogen stimulates humoral response	Testosterone lowers humoral response	Men are more vulnerable to infections; women have a higher risk of autoimmune diseases
Pain processing			
Cutaneous pain receptors	More sensory pain receptors in the skin	Fewer sensory pain receptors in the skin	Women feel more pain
Opioid-receptor types	Kappa pain receptors	Mu pain receptors	Different responses to different opioids
Hormonal effects	No known effects on pain threshold	Testosterone increases pain threshold	Men feel less pain

[a]XX and XY are not the only possible sex-chromosome compositions.

Table 2 | **Comparison of clinical manifestations of axial spondyloarthritis in women and men**

Manifestation	Women with axial spondyloarthritis	Men with axial spondyloarthritis
Presentation	More widespread and peripheral pain	More classic low-back pain
Median delay to diagnosis (years)	9–14	5–7
Burden of inflammation	Normal C-reactive protein concentrations more common	Elevated C-reactive protein concentrations more common
Peripheral manifestations	More common	Less common
Extra-musculoskeletal manifestations	Similar in men and women	Similar in men and women
Radiographic damage	Less common	More common
Patient-reported outcomes	Worse	Better
Function	Greater functional impairment	Less functional impairment
Comorbidities	Lower cardiovascular morbidity and mortality	Greater cardiovascular morbidity and mortality
Fibromyalgia	More common	Less common

susceptible than women to sepsis and have higher mortality following sepsis. Testosterone downregulates TNF production, but upregulates production of anti-inflammatory IL-10 (REF. [42]). By contrast, cell-mediated immunity and humoral immune responses are enhanced by oestrogen, as is the production of IL-1, IL-6 and TNF.

During the menstrual cycle, the balance between T_H1 and T_H2 pathways fluctuates[43]. During pregnancy, in which oestrogen concentrations increase (prior to a drastic decrease following delivery), there is a T_H2 bias, with a reduction of the T_H1 response and elevation of antibody responses[44,45]. In menopausal women, compared with pre-menopausal women, concentrations of oestrogen are lower, concentrations of pro-inflammatory markers in the serum are higher, and numbers of B cells and T_H1 cells are lower[46]. Autoimmune disease onset or activity might be influenced by menopause through alterations of gonadal hormone concentrations or the androgen-to-oestrogen ratio[47]. In addition, the reduction in oestrogen concentrations associated with menopause can also affect comorbidity, with an increase in the occurrence of cardiovascular manifestations and osteoporosis. The post-menopausal incidence of chronic inflammatory disease approaches or even exceeds the incidence normally observed in men, whereas the post-menopausal incidence of autoimmune disease is lower than or equivalent to the observed rates in men of a similar age[48].

The heightened immune responsiveness in pre-menopausal women also results in a high prevalence of many autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus. By contrast, AS is more common in men (with a 3:1 male:female ratio), whereas nr-axSpA and psoriatic arthritis both have an equal sex distribution.

The axSpA genotype and phenotype

Genetics and hormonal factors in axSpA

Studies of genetic variation to identify possible susceptibility factors have not produced consistent results. In a North American cohort of white families affected by AS, different *ANKH* haplotype variants were associated with AS in men and in women[49]. *ANKH* and *TNAP* gene products interact in ossification, and evidence also exists for a specific association of a *TNAP* haplotype with AS in men, but not in women[27,50]. Sexual dimorphism also exists in immune responses, such as those involving inflammatory cytokines. In a study of 68 men and 19 women with AS, concentrations of TNF, vascular endothelial growth factor and IL-18 were higher in men than in women[51]. All patients were HLA-B27 positive, and age and C-reactive protein (CRP) concentrations were similar in both gender groups, but concentrations of other inflammatory cytokines were higher in men, suggesting that they had a higher inflammatory burden. Although 22% of the study cohort had used immunomodulatory drugs, no breakdown by sex was reported that might have explained the differences in cytokine concentrations.

In SpA, oestrogen might have an anti-inflammatory effect via inhibition of TNF production, although not all available evidence supports this hypothesis[52]. In an SpA mouse model oestrogen inhibited the onset of arthritis[53]. In a study of women with AS, among pre-menopausal women, oestrogen concentrations were lower in those with active AS than in those with inactive disease, or in healthy individuals[54]. Similarly, oestrogen concentrations in postmenopausal women with AS were lower than those in matched healthy individuals. Oral oestrogen therapy was associated with a reduction in arthritis and clinical activity. In this study, premenopausal women received norethindrone 1 mg plus ethynilestradiol 0.035 mg daily for 21 days of the monthly cycle and post-menopausal women received conjugated oestrogens 0.625 mg for 25 days, with the addition of 2 mg of chlormadinone beginning on day 16. By contrast, in a study of 571 women with AS, use of oestrogen-based oral contraception was not associated with any difference in onset or severity of the disease among pre-menopausal women with AS[55]. In the SKG mouse model of SpA, female mice treated with oestrogen have less-severe arthritis and SpA manifestations than either untreated or ovariectomized mice[53], possibly as a result of the anti-inflammatory effect of oestrogen. Expression of TNF, IFNγ and IL-17A is also lower in oestrogen-treated mice. Notably, in a case–control study

involving 50 men with AS, testosterone concentrations were not higher in serum extracts from patients than from matched individuals, and did not seem to influence disease progression[56]. However, dehydroepiandrosterone, which is the precursor of testosterone and oestradiol, enhances the T_H1 immune response and might be involved in AS onset and severity[57]. These results suggest that the factors that are important for disease susceptibility differ from those that are involved in disease activity in axSpA, as disease onset in almost all patients occurs well before menopause, and no difference in incidence is evident in nulliparous versus primiparous or multiparous women, in whom oestrogen concentrations might differ.

Musculoskeletal manifestations

The musculoskeletal manifestations of axSpA include axial inflammatory disease (sacroiliitis, spondylitis and hip arthritis) and peripheral musculoskeletal manifestations (synovitis, enthesitis and dactylitis). Among these manifestations, the percentage of patients affected by enthesitis and the severity of involvement of the entheses are greater in women than in men[58–62]. In addition, compared with men, a greater prevalence of peripheral arthritis occurs in women with AS in the course of the disease (68.9% versus 51.2%), whereas the prevalence of inflammatory back pain is lower (50.6% versus 66.4%)[63]. The greater involvement of peripheral joints and entheses could be an explanation for the same or even greater disease burden in women than in men, despite lower radiological progression. However, in relation to the differences between the sexes in musculoskeletal manifestations of axSpA, conflicting results exist, and results from some studies suggest that there are no differences[59,64,65]. For instance, in a cohort in Iran, women were more likely to have enthesitis, but overall disease severity was comparable in men and women[59]. By contrast, in a cohort in Israel, although both men and women had low-back pain, men had more typical inflammatory back pain, whereas women had more widespread, pelvic and heel pain[64]. In a Turkish cohort, although hip involvement was more common in men, both men and women had similar measurements of spinal mobility, as well as peripheral joint involvement and extra-musculoskeletal manifestations[65].

Extra-musculoskeletal manifestations

Female sex is positively associated with several extra-musculoskeletal manifestations, such as inflammatory bowel disease (IBD)[58,66,67] and psoriasis[66,68]. By contrast, results indicate that a higher percentage of men than women with axSpA experience acute anterior uveitis (AAU)[68,69]. However, other results suggest there are no sex differences relating to AAU[50], and in one systematic review a higher prevalence of uveitis was identified in women (with a male:female prevalence ratio of 28.5%:33.3%)[70,71]. However, in the systematic review, no distinction was made between different types of uveitis, even though intermediate and posterior uveitis are more often associated with other diseases, such as sarcoidosis. In addition to this association with prevalence, men with axSpA have a higher risk than women (multivariate analysis, hazard ratio = 1.76) of a shorter interval between episodes of AAU[72]. Interestingly, AAU, which is associated with AS, might also be influenced by sex hormones. In an endotoxin-induced rat model of uveitis, males seemed to suffer from uveitis with greater severity and prevalence than females. Additionally, oestrogen downregulated expression of inflammatory genes and ameliorated disease manifestations[73].

In around 50% of patients with uveitis, AAU is the cause. AAU is strongly associated with HLA-B27 in Western countries, which in general have a higher HLA-B27 prevalence than the southern parts of the world[74,75]. A higher prevalence of HLA-B27 is seen in North America and Europe, followed by Asia, whereas a lower prevalence is seen in Latin America, followed by Africa[76]. A strong association also exists between HLA-B27 and axSpA[76]. Approximately 10–40% of patients with AS develop the characteristic AAU that is associated with HLA-B27. AAU is often the first reason for seeking medical care. Presentation with AAU is

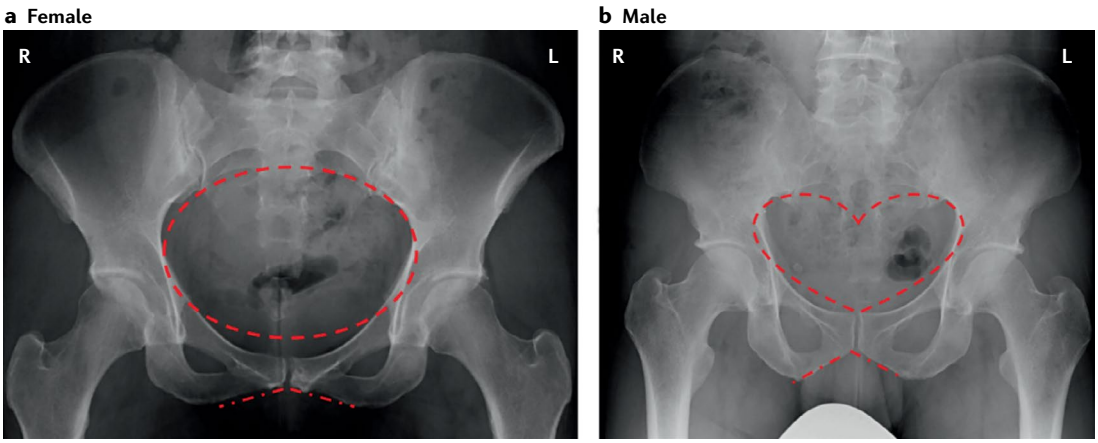

Fig. 1 | **Anatomical differences in pelvic anatomy in men and women with axial spondyloarthritis.** Radiographs of the anterior–posterior pelvis (frontal plane). **a** | The pelvis in a woman with axial spondyloarthritis (axSpA) without radiographic damage (non-radiographic axSpA). **b** | The pelvis in a man with axSpA with radiographic damage (ankylosing spondylitis). Dashed red lines indicate anatomical differences of the pelvis in women and men. 'L' and 'R' indicate the left-hand and right-hand sides of the patients, respectively.

therefore a unique opportunity[77,78] for the identification of undiagnosed axSpA. Evidence indicates that the risk of developing AAU associated with HLA-B27 is higher for men than for women[79]. Results also indicate that there is no sex difference in the risk of developing axSpA following the onset of uveitis, which suggests that AAU can be used for identification of both women and men with undiagnosed axSpA[69]. Notably, in patients with AS but without current AAU, treatment with specific TNF inhibitors, such as adalimumab, infliximab, golimumab and certolizumab, can decrease the rate of occurrence of AAU, as well as AS disease activity[80].

Comorbidities

Several comorbidities commonly occur in axSpA, such as cardiovascular disease (CVD) and osteoporosis[81]. Some of these comorbidities have differential occurrences in relation to axSpA, such as obesity, with women having a higher prevalence than men[82].

Osteoporosis. Osteoporosis and osteopenia in younger patients (<50 years old) occur frequently in axSpA[83,84]; they are especially prevalent in long-standing disease and may be related to more severe radiographic disease with ankylosis and immobilization[85]. The prevalence of osteoporosis in patients with AS is estimated as being between 19% and 50%[86,87], compared with 13% in early axSpA. Among young men with SpA (mean age 37 years), an estimated 15% have at least one osteoporotic vertebral fracture[88]. Most of these fractures are located at the level of the thoracic spine. The thoracic spine is often not included in radiographic evaluation of spinal disease, which is mainly based on cervical and lumbar X-radiography. Interestingly, although treatment with TNF inhibitors improves bone mineral density (BMD) and reduces disease activity in patients with AS, over the treatment period an increase in the number and severity (according to Genant scoring) of vertebral fractures still occurs[89,90]. In a cohort of patients with a short AS disease duration, who were relatively young and predominantly men, 51–54% had decreased BMD (osteopenia or osteoporosis) and 13–16% had osteoporosis[91], even though osteoporosis is generally known as a 'female disease', because its prevalence and the rate of fractures are much higher in postmenopausal women than in older men. The lifetime risk of fracture for a 60-year-old woman is approximately 44%, nearly double the risk of 25% for a man of the same age[92]. Men diagnosed with early axSpA, according to a multivariate regression model, are at four times the risk of having a low BMD compared with women[93–95].

The pathophysiology of osteoporosis is complex. Apart from their contribution to inflammation, monocytes from men with AS have a lower capacity to generate osteoclasts in vitro than cells from healthy individuals; osteoclastogenesis correlates negatively with disease duration[96]. Osteoclasts might therefore have a role in the pathophysiology of bone disease in patients with AS.

Cardiovascular disease. Many reports have demonstrated increased CVD-associated morbidity and mortality in patients with axSpA compared with the general population[97]. Reasons for this high proportion are the high presence of inflammation in axSpA, and also the preponderance of CVD risk factors compared with the general population[98]. Very few studies have focused on sex differences in CVD in the populations with axSpA. In the general population, women seem to be at a similar risk of CVD to men with respect to traditional risk factors such as dyslipidaemia, hypertension, diabetes and smoking, and this risk is heightened after menopause, possibly because of changes in vascular and lipid profiles[99].

Globally, CVD is the leading cause of death in men and women, and the percentage of mortality that results from CVD is higher in women[100]. Research relating to sex differences in CVD in the general population indicates that CVD outcomes associated with elevated blood pressure, obesity and dyslipidaemia are similar in women and men. However, long-term smoking is more hazardous for women than for men[101]. Determination of the cardiovascular risk profile should take into account that there are differences in the effects of major cardiovascular risk factors, such as smoking and diabetes mellitus, that lead to worse outcomes in women[102]. The causes of the greater CVD mortality in women are multifactorial and include a delay in recognition of CVD risk factors, diagnosis and treatment; moreover, women tend to have more microvascular coronary disease, endothelial dysfunction and heart failure with preserved ejection fraction[102]. Regarding female-specific risk factors, associations exist between preeclampsia, preterm delivery, gestational diabetes, polycystic ovarian syndrome and menopause onset and the occurrence of CVD, but no absolute risk data are available[102,103].

Obesity. Among patients with axSpA, overweight and obesity are more common than in the general population, and they are associated with worse clinical outcomes compared with normal bodyweight and underweight[82]. Obese patients with axSpA have higher disease activity scores, worse physical function and worse quality of life than patients with a normal weight[104]. Evidence indicates that BMI correlates with serological inflammation (assessed by the concentration of CRP) in women with axSpA[105]. High disease activity scores (Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)) in women with AS are associated with a high body-fat percentage and fat mass index, whereas men with high disease activity scores have a low body-fat percentage and fat mass index[19]. Results indicate that BMI is inversely associated with TNF-inhibitor treatment response in both women and men. Women generally have a higher body-fat percentage than men, which might partially explain the lesser TNF-inhibitor treatment response in women with axSpA[106]. Compared with normal bodyweight, obesity is associated with a five times higher likelihood of developing new spinal bone lesions, in both men and women with AS[107]. In addition, male sex is associated with an odds ratio of 2.32 (95% CI 1.14–4.72) compared with female sex for new spinal lesions over 5 years in individuals with AS[107]. Serum concentrations of leptin and high-molecular-weight adiponectin are inversely

associated with spinal radiographic progression in AS[108]. Women with AS, who generally have higher serum concentrations of leptin and high-molecular-weight adiponectin than men, might therefore have a lower risk of structural damage of the spine.

Diagnosis of axSpA in women

Patients with axSpA commonly suffer from a delay in diagnosis, which tends to be longer for women than for men. In a meta-analysis, diagnostic delays of approximately 8.8 years for women and 6.5 years for men were identified[109]. Many pitfalls are associated with the diagnosis of axSpA in women compared with in men. First, there can be gender differences in the clinical presentation of axSpA, with women describing different patterns of pain to men. Whereas men are more likely to have low back and buttock pain, women commonly describe middle and upper back pain, peripheral joint pain and even widespread pain, which can be confused with fibromyalgia[64,110]. Second, even when men and women present with similar symptoms, health-care providers might not expect women to have axSpA, and therefore this diagnosis might be dismissed[109]. A contributing factor in this dismissal might be the lower levels of serological inflammation that are found in women. CRP concentrations tend to be lower or normal in women compared with men[111]. Last, the MRI findings in axSpA can vary by sex. The first studies describing MRI findings in patients with axSpA had majority male populations, and when these studies included women, they tended to have severe disease with imaging findings that mirrored those of men[112,113].

Although imaging can be helpful to differentiate axSpA from other, diagnostically similar conditions in women, challenges remain. A woman could have chronic pelvic and/or buttock pain from pregnancy, the post-partum state, osteitis condensans ilii, pelvic stress reaction, pelvic fracture or degenerative sacroiliac joint disease, all of which have MRI features that can mimic axSpA. Radiographic features can distinguish some of these diagnoses, such as osteitis condensans ilii, which is associated with sclerotic bone lesions on the iliac side, and degenerative sacroiliac joint disease, which is associated with osteophytes, subchondral sclerosis and interosseous-space narrowing. Although degenerative sacroiliac joint disease is readily identified by radiography, it is an under-recognized entity[114]. More awareness of this condition is needed to aid in its identification, especially because it is more commonly seen in women than in men. Other axSpA mimics require MRI for diagnosis, for example, to visualize a pelvic stress reaction or post-partum changes. Unfortunately, women with axSpA and those who are post-partum can report similar pain characteristics, have low levels of serological inflammation and have identical patterns of bone-marrow oedema on MRI[115,116]. Although both conditions can show unilateral or bilateral bone-marrow oedema along the sacroiliac joints, only axSpA can show widespread fat lesions unilaterally or bilaterally. However, these fat lesions are not always present. Erosions, when present, are also suggestive of axSpA, although they can (rarely) occur unilaterally in post-partum women. For this reason, post-partum women are often recommended to wait 6–12 months after giving birth to undergo MRI to establish the correct diagnosis. Last, to separate out fibromyalgia from psoriatic arthritis, a subtype of spondyloarthritis, studies with whole-body MRI and ^{18}F-Na PET–CT have shown that patients with active disease will have inflammation in their axial and peripheral joints and entheses, whereas patients with fibromyalgia will not[117].

Outcomes in axSpA

The majority of efficacy outcomes in axSpA are derived from subjective patient-reported data. Unlike other inflammatory arthritides such as RA and psoriatic arthritis, there are rarely obviously assessable objective findings of active joint inflammation on physical examination. Some end points, such as ASDAS, include CRP concentration or the erythrocyte sedimentation rate, and MRI was a secondary end point in several studies. The lack of easily measurable objective inflammation poses a particular challenge for axSpA assessment, particularly in women, who often have a lower serological burden of inflammation and less related damage than men. Patient-reported outcomes (PROs), therefore, need to be interpreted with caution, as symptoms of pain, stiffness and fatigue are associated with a wide range of possibilities, even in individuals with clear disease.

Patient-reported outcomes in axSpA

A number of PRO measures for individuals with axSpA have been developed over the past two decades[118]. These assessment tools are used in clinical settings to describe the disease, to quantify and capture data, and to understand treatment outcomes and effectiveness.

Reasons for sex and/or gender differences in PROs among individuals with axSpA are not well understood, but several hypotheses exist. For sex-based or gender-based differences in symptoms such as pain perception or pain amplification, central pain mechanisms might be more prevalent in women than in men[119]. This sex distribution in the pain conditions characterized by augmented central pain processing occurs in patients with fibromyalgia or RA[120–122]. With respect to sex differences measured by health-related quality of life (HRQoL), assessment tools that are currently used might be measuring domains that do not adequately capture issues germane to inflammatory disease processes, or the questions used in the assessment of HRQoL might not be interpreted similarly in men and women. Other sex and/or gender differences observed in commonly used PROs might be associated with clinical manifestations, such as the involvement of peripheral arthritis, disease activity and/or burden of the disease in patients with axSpA[60,63,123].

Here, we discuss findings for commonly used PRO measures including pain, function, disease activity and HRQoL in relation to sex-based or gender-based differences reported in clinical studies (TABLE 3).

Pain. A systematic review and meta-analysis found that baseline pain scores are generally associated with gender in patients with inflammatory arthritis[63]. Although results have suggested that there is no difference in the reporting of pain using a visual analogue scale for patients

Table 3 | **Baseline gender effects on disease activity, function and quality-of-life scores in axial spondyloarthritis**

Study	AS or axSpA	Participants (male:female)	Study design	Disease activity, function and quality-of-life scores (male:female)				Ref.
				BASDAI	ASDAS-CRP	BASFI	Quality of life[a]	
De Jong et al., 2020	axSpA	182:131	Cross-sectional	4.6:5.2[b]	2.7:2.8	NR	NR	156
Lubrano et al., 2018	axSpA	236:104	Retrospective multicentre study	5.7:6.1	3.7:3.4	5.5:5.5	NR	157
van der Slik et al., 2019	AS	176:78	Prospective cohort	5.9:6.5[b]	3.66:3.93[b]	5.4:6.2[b]	9:12[b]	151
Hebeisen et al., 2018	AS	294:146	Prospective cohort	5.5:5.8	3.6:3.4	4.3:4.4	54.4:54.9	158
Haroon and Gheita, 2018	AS	21:19	Cross-sectional	5.7:6.5	NR	5.8:6.7	NR	159
Law et al., 2018	AS	121:89	Observational cohort	2.9:3.7	2.0:2.2	2.3:2.3	PCS, 43.6:41.8; MCS, 49.2:46.0	160
Ibáñez Vodnizza et al., 2017	AS	25:16	Prospective cohort	5.1: 5.2	NR	NR	NR	106
Lubrano et al., 2017	axSpA	228:93	Retrospective	5.7:6.1	3.7:3.4[b]	5.5:5.5	NR	62
Kilic et al., 2017	axSpA	221:139	Cross-sectional observational cohort	3.3:4.2[b]	2.6:2.7	2.5:2.8	7.1:8.9[b]	125
Landi et al., 2016	AS	817:1,072	Observational cohort	4.1:4.8[b]	NR	4.6:4.8	6.9:8.3[b]	60
Rubio Vargas et al., 2016	axSpA	81:87	Observational cohort	3.6:4.3[b]	2.3:2.5	NR	NR	105
Shahlaee et al., 2015	AS	253:67	Prospective cohort	4.6:5.0	NR	3.8:4.3	7.7:8.5	59
Webers et al., 2016	AS	154:62	Prospective observational cohort	3.2:3.9[b]	2.7:2.8	3.5:3.2	5.8:7.2	70
Gremese et al., 2014	axSpA	118:52	Retrospective	5.5:5.6	NR	NR	NR	161
Tournadre et al., 2013	axSpA	239:236	Prospective cohort	4.0:4.6[b]	2.9:3.0	2.7:3.3[b]	8.0:10.2[b]	58
van der Horst-Bruinsma et al., 2013	AS	957:326	Pooled data clinical controlled trials	58.6:62.7[b]	3.7:3.6	55.8:57.5	NR	127
de Carvalho et al., 2012	axSpA	1,090:415	Observational cohort	4.0:4.6[b]	NR	4.5:4.8	7.5:8.3[b]	61
Ibn Yacoub et al., 2012	AS	87:43	Cross-sectional	43.1:48.8[b]	NR	53:54.2	NR	137
Roussou and Sultana, 2011	axSpA	172:344	Prospective cohort	5.7:6.3	NR	4.9:5.2	NR	111
Cansu et al., 2011	AS	66:36	Prospective cohort	NR	NR	NR	NR	65
Bodur et al., 2012	AS	1,038:343	Prospective observational cohort	3.7:4.2[b]	NR	3.3:3.2	6.8:7.3	162
Jung et al., 2010	AS	434:71	Registry	1:1	NR	NR	NR	163
Lee et al., 2007	AS	302:100	Cross-sectional	NR	NR	43.3:49.0[b]	NR	164

Table adapted from Rusman et al. (2020)[165]. AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functionality Index; CRP, C-reactive protein; EQ-5D, European Quality of Life Five Dimension; ESR, erythrocyte sedimentation rate; MCS, mental component summary; NR, not reported; PCS, physical component summary; SF-36, 36-item short form health survey. [a]Quality-of-life measures include both generic measures such as EQ-5D and SF-36 and disease-specific measures such as ASQoL. [b]Significant difference by gender or sex.

with AS[124], other results indicate that women with AS report higher pain scores than men[125–128]. With further stratification of patients by sex and disease classification of axSpA (radiographic versus non-radiographic), women with nr-axSpA report higher visual analogue scale scores on pain assessment than other groups[123]. With respect to the influence of gender on changes in PROs in response to treatment, results from a study using pooled data from published clinical trials suggest that women have smaller differences between baseline and week 12 of treatment (with etanercept or sulfasalazine) in efficacy and pain assessments[127].

Function

The Bath Ankylosing Spondylitis Functionality Index (BASFI) is a validated measure of functional impairment[129], which is recommended by the ASAS as the formal assessment tool to evaluate functional status in patients with axSpA. Studies examining whether sex and/or gender differences influence BASFI scores in the USA are scarce and results from other countries are inconclusive. Although results from studies with British, French and Brazilian cohorts indicate that women with axSpA report higher BASFI scores (greater functional impairment) than men[58,61,111], studies conducted elsewhere (such as South American countries, Sweden, Denmark, China and Iran) have identified no gender difference in functional status measured by the BASFI[59,60,123,125,126].

Disease activity

To evaluate disease activity in clinical studies, the BASDAI[130] has been developed. The BASDAI is validated in axSpA[131,132], and endorsed by the ASAS[133,134], although a preferred measure of disease activity is the

ASDAS[135,136]. Findings of differences in the BASDAI reporting according to sex and/or gender are generally consistent and demonstrate that women report worse disease activity scores than men[60,61,70,111,125–127,137], although in studies conducted in Iran and Denmark, no sex or gender-based differences were observed in the reporting of the BASDAI[59,123]. In a longitudinal study, women with AS had higher BASDAI scores than men at baseline and 12 years of follow-up[70]. In addition to the BASDAI, the more recently developed ASDAS has been used in clinical settings[138]. The ASDAS excludes questions on fatigue (and both the BASDAI and the ASDAS exclude questions regarding pain on physical examination with palpation, which lack specificity), includes the patient global assessment of disease activity and an objective measure of inflammation (preferably CRP, or erythrocyte sedimentation rate) and is weighted, leading to a more robust measure of disease than the BASDAI. Data on the influence of sex and/or gender on ASDAS scores are limited, but suggest that there are no sex- or gender-related differences at baseline or over time[70,127]. The differences between the BASDAI and the ASDAS in this respect might result from the ASDAS being balanced by the presence of an objective measure of inflammation, which is typically greater in men with axSpA than in women. In addition, the ASDAS does not account for fatigue and entheseal-like pain that might be more commonly reported in women with axSpA.

Health-related quality of life

The Ankylosing Spondylitis Quality of Life (ASQoL) has been the most commonly used disease-specific measure of HRQoL in axSpA studies[139]. Although there is evidence from use of the ASQoL that women with axSpA have a lower quality of life than men[60,61,125], there are also results that show no differences in overall ASQoL scores by sex and/or gender at baseline[59,70]. In addition to disease-specific measures, studies often use generic measures (such as the 36-item short form health survey; SF-36) to assess quality of life in patients with axSpA[140]. Evidence from these studies indicates that there are no gender-based differences in reporting HRQoL using generic measures at baseline[70,123]. With regard to changes in quality of life over time, ASQoL scores (but not scores from the use of generic measures) are worse in women with axSpA than in men[141].

Health status

The ASAS Health Index is a spondyloarthritis-specific PRO measure of health and functioning[142] that has been validated in a global study in both axSpA and peripheral spondyloarthritis[143]. In a single-centre study of 307 patients with AS (of whom 20% were women), who were assessed for gender differences using the ASAS Health Index, a cross-sectional analysis demonstrated that women reported higher ASAS Health Index scores than men, even though women had higher disease activity, as assessed by the ASDAS[144].

Table 4 | **Gender effects in TNF-inhibitor treatment response**

Study	AS or axSpA	Study design	Participants (male:female)	Treatment response (male vs female)	TNF-naive population	Follow-up period	Ref.
Rusman et al., 2021	AS	Prospective cohort study	235:121	ASDAS: 64% vs 47% (RR 1.4, 95% CI 1.1–1.9)[a]	Yes	6 months	17
Sieper et al., 2019	nr-axSpA	Open-label prospective study	295:301	ASDAS partial remission: OR 2.4, 95% CI 1.6–3.6[a]	Yes	12 weeks	166
Laganà et al., 2019	SpA	Retrospective	123:122	No differences	Yes	No specification	167
Lubrano et al., 2018	axSpA	Retrospective multicentre study	236:104	Partial remission: OR 3.0, 95% CI 1.4–3.5[a]; ASAS40: OR 3.16, 95% CI 1.60–6.30[a]; ASDAS MI: OR 1.91, 95% CI 1.13–3.23	Yes	No strict cut-off point. Only data on the inclusion period of 2004–2015	157
Hebeisen et al., 2018	AS	Prospective cohort study	294:146	ASAS20: OR 0.34, 95% CI 0.16–0.71[a]; ASDAS <1.3: OR 0.10, 95% CI 0.03–0.31[a]	Yes	1 year	158
Lubrano et al., 2017	axSpA	Retrospective	228:93	ASAS40: greater response in men than in women[a]	Yes	Every 3 months	62
Lorenzin et al., 2015	AS	Retrospective	52:18	ASAS20: 82.9% vs 65.7%	NR	60 months	169
Gremese et al., 2014	axSpA	Retrospective	118:52	BASDAI 50: 67.8% vs 46.2%[a]	Yes	12 months	161
van der Horst-Bruinsma et al., 2013	AS	Pooled data clinical controlled trials	957:326	ASDAS: 89.4% vs 68.4%[a]	Yes	12 weeks	127
Paccou et al., 2012	AS	Retrospective	121:68	BASDAI 50: 78.5% vs 21.5%[a]	Yes	3 months	168
Arends et al., 2011	AS	Prospective longitudinal observational cohort	152:68	ASAS20 and ASAS40: greater response in men than in women[a]	Yes	ASAS20: 3 months and 6 months; ASAS40: 6 months	170
Glintborg et al., 2010	AS	Observational cohort	364:239	Change in BASDAI: 27 vs 22	Yes	6 months	171

Table adapted from Rusman et al. (2018)[141]. AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; ASAS20/40, ASAS 20%/40% improvement criteria; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASDAS MI, ASDAS major improvement; BASDAI, Bath Ankylosing Spondylitis Disease Activity Score; BASDAI 50, BASDAI 50% improvement; NR, not reported; TNF naive, no prior use of TNF-inhibitor treatment. [a]Significant difference by gender or sex.

Table 5 | **Gender effects on TNF-inhibitor adherence**

Study	AS or axSpA	Study design	Participants (male:female)	Treatment adherence[a] (male:female)	Study time period	Ref.
Hebeisen et al., 2018	AS	Prospective cohort study	294:146	5.2:2.9 years[b]	12 years	158
Flouri et al., 2018	AS	Prospective observational cohort	446:115	Hazard ratio for treatment discontinuation in men vs women: 0.73 (95% CI 0.51–1.04)	10 years	172
Al Arashi et al., 2018	AS	Prospective cohort	205:75	91.6:34.4 months[b]	Mean 6.3 years	173
Yahya et al., 2018	axSpA	Retrospective review of routinely recorded clinical data	386:115	No gender effects observed	1, 5 and 10 years	174
Iannone et al., 2017	SpA	Prospective observational cohort	72:75	23.0:19.6 months[b]	2 years	175
Rusman et al., 2018	AS	Prospective cohort	74:48	44.9:33.4 months[b]	Mean 4.8 years	16
Arends et al., 2011	AS	Prospective longitudinal observational cohort	152:68	Hazard ratio for treatment discontinuation in women vs men: 0.41 (95% CI 0.25–0.66)[b]	6 months	170
Glintborg et al., 2010	AS	Observational cohort	364:239	Hazard ratio for treatment discontinuation in women 1.46 (95% CI 1.07–2.00)[b]	5 years	171
Kristensen et al., 2010	AS	Prospective observational cohort	182:61	Hazard ratio for treatment discontinuation in men 0.36 (95% CI 0.19–0.68)[b]	2 years	176

Table adapted from Rusman et al. (2018)[142]. AS, ankylosing spondylitis; axSpA, axial spondyloarthritis. [a]Treatment adherence refers to time on TNF inhibitor, unless otherwise indicated. [b]Significant difference by gender or sex.

Sex effect on treatment response

At the present time, sex differences in treatment response are an unresolved issue. Despite evidence of lower treatment efficacy and drug adherence to biologic DMARDs in women with axSpA than in men, few studies have considered sex differences in their analyses (TABLE 4 and 5). In most randomized, controlled trials, the results have not demonstrated any sex effects or differences on efficacy, possibly because of the low numbers of women included in the trials, or because the trials were only powered to determine the efficacy of trial drugs, not to detect a difference in response by sex[145–150]. Notably, in a study on pooled data from four clinical trials following stratification for gender, a lower level of response (by ASDAS and BASDAI scores) and treatment adherence was identified in women than in men[127]. In women with AS, TNF-inhibitor adherence was half of that in men across multiple studies, and more women than men switched from TNF-inhibitor treatment to another[16,151,152]. These results suggest that sex differences exist in efficacy and treatment response. Further results have indicated that male sex is a predictor of functional improvement, which was seen in 69.9% of men with axSpA and 50.0% of women during TNF-inhibitor treatment[2]. In observational studies of patients with AS on TNF inhibitors, women were more likely than men to stop or switch therapy earlier, showed a lower response to treatment and had higher disease activity[16,17]. A re-analysis performed for the anti-IL-17A biologic DMARD secukinumab, on the other hand, showed no sex differences in efficacy[153].

The presence of HLA-B27, the absence of enthesitis, short symptom duration and TNF-inhibitor naive status are some of the predictors that are positively associated with treatment response[62,152]. These predictors correlate negatively with female sex, because, compared with men, women with AS are more often HLA-B27 negative, have a higher prevalence of enthesitis and have longer delays in diagnosis. These factors might contribute to the sex differences in TNF-inhibitor adherence and response. Differences in TNF-inhibitor response associated with sex and gender might be related to gene expression, gonadal hormones and body composition (especially higher body fat percentages in women)[106]. Men with axSpA have higher serum TNF concentrations than women[154], which might explain the worse TNF-inhibitor treatment responses in women with axSpA. In the Swiss Clinical Quality Management Cohort, men and women with nr-axSpA initiating TNF-inhibitor therapy were compared for response to treatment[155]. Patients with fibromyalgia were excluded. Notably, women had a longer delay to diagnosis and were less likely than men to achieve a 40% improvement in ASAS criteria at 1 year (17% versus 38%, adjusted odds ratio 0.19; 95% CI 0.05–0.62)[155].

Conclusions

Sexual dimorphism exists in axSpA. Historically, axSpA was a disease predominantly seen in men, in the radiographic form (AS). As the understanding of axSpA has evolved, it is now known that women carry about half of the disease burden. Men and women experience axSpA differently, which might be partly attributed to anatomical and hormonal variation. As male and female bodies have many differences in organ size, pain transmission and body composition, it is important to realize that these differences also influence PROs and

treatment efficacy. Fortunately, most drugs work well in both sexes, but there is still a paucity of data relating to efficacy and adverse effects in the context of sex and gender. Therefore, we would like to set a research agenda to encourage investigators to take sex and gender into account when evaluating diagnostic procedures, disease manifestations and treatment efficacy. Existing data, such as those from large cohorts and from clinical trials could be re-examined to identify sex and/or gender effects. New data will emerge from this research and will provide useful tools for personalized treatment of men and women with axSpA.

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