

Sex and gender differences in rheumatology: clinical impact and future directions

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Abstract

Sex and gender shape disease presentation, diagnostic accuracy, treatment response and clinical outcomes in rheumatology, yet these dimensions remain insufficiently embedded in clinical practice. Owing to the markedly unbalanced sex prevalence ratios across many rheumatic diseases, the ‘minority’ sex is consistently under-represented in clinical studies, limiting the interpretation of long-term outcomes and treatment effectiveness. Sex-related differences in pain perception, inflammatory biomarkers and imaging patterns further complicate disease assessment, and treatment allocation and drug persistence also differ between women and men. Gender-related factors – including disparities in care-seeking behaviours, social roles and lifestyle factors – additionally modulate symptom burden and disease trajectories. Evidence remains particularly scarce for transgender, gender-diverse and intersex individuals, who are rarely captured in clinical cohorts, restricting the development of inclusive and generalizable evidence. Embedding sex-aware and gender-aware approaches into diagnostic reasoning, risk assessment and therapeutic decision-making is therefore essential for advancing precision, equity and truly personalized rheumatological care. Such integration enables clinicians to interpret disease signals more accurately, anticipate divergent multimorbidity trajectories and tailor treatment strategies to the biological and sociocultural contexts of each patient.

Sections

Introduction

Rheumatoid arthritis

Systemic lupus erythematosus

Axial spondyloarthritis

Sjögren disease

Gout

Future directions

Conclusions

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Key points

- Sex and gender contribute to systematic variation in rheumatic disease trajectories, influencing how these conditions emerge, evolve and impact daily functioning.
- Under-representation of the minority sex in clinical studies restricts interpretation of disease outcomes and undermines the robustness of comparative evidence.
- Diagnostic accuracy is reduced when sex-related differences in symptom patterns, imaging features and inflammatory markers are overlooked.
- Treatment patterns and therapeutic responses diverge by sex, contributing to differential drug persistence and achievement of treatment goals.
- Comorbidity profiles differ between sexes, affecting risk stratification and shaping long-term prognosis.
- Current rheumatology guidelines rarely incorporate sex-sensitive or gender-sensitive recommendations, highlighting an urgent need for structured integration into clinical pathways.

Introduction

In rheumatology, biological sex and gender remain among the most powerful yet underutilized determinants of clinical diversity^{1,2}. Each dimension shapes disease onset, progression and therapeutic response, but the explanatory potential of sex-related and gender-related factors is still constrained by conceptual ambiguity and fragmented implementation. Instead of being integrated into diagnostic reasoning or therapeutic algorithms, sex and gender are too often treated as background descriptors – acknowledged in principle yet peripheral in clinical practice. A major conceptual barrier is the persistent conflation of sex, defined by biological attributes such as genetic, epigenetic and hormonal factors, and gender, which encompasses sociocultural norms, identities and lived experiences (Table 1). Although interrelated, these dimensions are not interchangeable. Nevertheless, much of the rheumatology literature continues to misuse gender to describe biological differences, obscuring the distinct biological and sociocultural mechanisms that shape disease expression and outcomes. This conceptual ambiguity ultimately undermines the precision and equity of disease characterization and management.

Importantly, gender extends beyond gender identity and comprises several interrelated domains. These dimensions include gender roles, which reflect social expectations that influence behaviours such as symptom reporting and health-seeking; gender relations, which include caregiving responsibilities, power dynamics and social positioning; and institutionalized gender, which refers to structural factors such as access to care, economic resources and clinical decision-making. Each domain operates across the entire population and could influence disease onset, severity and therapeutic response, meaning that categorizing individuals solely by gender identity does not capture the broader gender-related determinants of health.

This article uses ‘men’ or ‘male’ and ‘women’ or ‘female’ to reflect the language used in specific cited studies, but recognizes that it is

rarely clear how such information was collected or defined (for example, on the basis of endocrine or chromosomal analysis or assignment of sex at birth in medical records or health registry data). Moreover, even if data collection methods are specified, sex and gender information could still be inaccurate or incomplete; for example, when only binary categories such as ‘male’ and ‘female’ are available. *Nature Reviews Rheumatology* also acknowledges that sex and gender both exist on a spectrum, are not necessarily aligned and that people with rheumatic diseases might not identify as either women or men. Whereas sex-related differences are widely reported across rheumatology, gender-related determinants are far less consistently captured in clinical datasets, meaning that discussions within individual disease sections reflect the uneven availability of evidence.

Notably, several rheumatic diseases exhibit pronounced imbalances in prevalence between the sexes, and this unequal distribution contributes to persistent knowledge gaps because the minority sex (that is, the sex in which the disease is comparatively less common) remains consistently under-represented in clinical and therapeutic research^{1,2}. Consequently, sex-related differences are often regarded as secondary observations rather than fundamental determinants of disease heterogeneity and management.

The complexity of sex-related and gender-related determinants becomes particularly evident in populations whose biological characteristics or gender experiences fall outside traditional binary frameworks. Transgender and gender-diverse individuals are estimated to represent approximately 0.5–4.5% of the adult population³. Although this population is numerically small, transgender and gender-diverse individuals are clinically relevant in rheumatology because chronic psychosocial stress, barriers to care and gender-affirming hormone therapy can influence immune and metabolic pathways, with potential implications for disease susceptibility, disease activity and treatment response^{4,5} (Box 1). In parallel, individuals born with variations in sex characteristics (often referred to as intersex conditions or differences of sex development) represent another population rarely considered in rheumatology. These variations, estimated to occur in approximately 0.02–1.7% of the population⁶, involve differences in chromosomal, gonadal or hormonal profiles that are biologically relevant to immune function. Despite this relevance, implications for rheumatic disease remain largely unexplored⁷.

In this Review, we provide a clinically oriented synthesis of sex-related and gender-related differences across selected rheumatic diseases. Rather than offering an exhaustive overview of all conditions, we focus on a set of representative disease models that capture distinct inflammatory paradigms encountered in rheumatology practice. Specifically, we discuss rheumatoid arthritis (RA), a prototypical chronic inflammatory arthritis; systemic lupus erythematosus (SLE) and Sjögren disease, representing systemic autoimmune diseases with marked female predominance; axial spondyloarthritis (axSpA) as a representative model of the spondyloarthritis spectrum; and gout, a prototypical crystal-induced inflammatory arthritis. Together, these conditions illustrate complementary patterns of sex-related and gender-related differences across epidemiology, clinical phenotype, comorbidities and therapeutic response. Where relevant, selected clinical evidence from psoriatic arthritis (PsA) is incorporated to contextualize sex-related and gender-related differences across the spondyloarthritis spectrum.

Despite a growing body of evidence, current rheumatology guidelines seldom translate sex-related and gender-related findings into clinical recommendations, perpetuating inconsistencies in care and

Table 1 | Sex and gender terms relevant to rheumatology

Term	Definition	Clinical relevance in rheumatology
Sex	Biological and physiological characteristics of women, men and intersex individuals, including genetic, epigenetic and hormonal factors	Influences immune dimorphism and differential pharmacokinetics, disease prevalence, progression and treatment outcomes
Gender	Socially constructed norms, roles, behaviours and power structures that shape expectations, opportunities and lived experiences across the lifespan; gender is a multidimensional and dynamic construct that cannot be fully captured by binary classifications	Shapes exposure to risk factors, health-seeking behaviour and access to care; influences treatment adherence and disease perception
Gender identity	An individual's deeply felt internal sense of gender, regardless of genetic factors and sex assigned at birth	Relevant to patient experience, exposure to stigma and barriers to gender-responsive health care
Transgender and gender-diverse people	Individuals whose gender identity or expression differs from the sex assigned at birth; irrespective of whether they receive gender-affirming hormone therapy or surgery	Chronic stress and gender-affirming hormone therapy might influence immune and metabolic profiles; binary research frameworks have contributed to the under-representation of non-binary individuals, highlighting the need for their inclusion to improve clinical evidence and equity of care
Intersex people and differences of sex development	Individuals born with natural variations in sex characteristics (chromosomal, gonadal or hormonal characteristics) that do not fit typical binary notions of male or female bodies	Variations in genetic and hormone profiles might affect immune pathways; this population remains under-represented in rheumatology research
Minority stress	Chronic psychosocial stress related to stigma, discrimination and social marginalization experienced by sexual and gender minority populations	Potential contributor to inflammation, comorbidity burden and barriers to health care access

Definitions of key terms describing biological and sociocultural dimensions relevant to sex, gender and diversity in rheumatology research and care are adapted from the World Health Organization¹⁷⁵, the Istituto Superiore di Sanità (the [Infotrans](#) and [Infolntersex](#) portals) and from Coleman and colleagues¹⁷⁶.

reinforcing diagnostic and therapeutic bias (Table 2). By highlighting shared clinical patterns and persistent knowledge gaps, this Review provides actionable insights to support the integration of sex and gender perspectives into everyday rheumatology practice, a critical step towards equity, precision and patient-centred care.

Rheumatoid arthritis

RA is a chronic inflammatory form of arthritis characterized by persistent synovial inflammation that can lead to progressive joint damage and disability. RA also exemplifies how sex-related and gender-related differences can influence disease activity assessment, treatment response and functional outcomes in routine clinical practice.

Epidemiology and clinical presentation

RA affects approximately 0.5–1% of the population and shows a clear female predominance, with a female-to-male ratio of roughly 2–3:1 (refs. 8,9). Several epidemiological datasets indicate that the incidence of RA has increased over the past 30 years¹⁰. The underlying causes remain unclear and could involve environmental factors¹⁰.

Sex-related and gender-related factors influence diagnostic pathways and disease presentation. Women have historically experienced longer diagnostic delays, although this gap has narrowed over time^{11–15}. Patterns of health care utilization also differ: women more frequently consult primary care physicians and rheumatologists before diagnosis, whereas men more often present to emergency services¹⁶. Across multiple cohorts, women consistently report higher disease activity and greater disability than men¹⁷. In a UK early RA cohort, female sex was identified as an independent predictor of persistent fatigue, a core symptom of RA, together with higher pain levels, poorer mental health and greater baseline disability¹⁸. Such differences reinforce the need to integrate sex-related and gender-related considerations into early diagnostic assessment of RA.

Life-course hormonal factors

Across the life course, hormonal transitions seem to influence RA risk and disease activity. Approximately half of people with RA who become

pregnant experience clinical improvement during pregnancy, whereas postpartum flares occur in up to 30–50% of cases, underscoring the need for close monitoring after delivery¹⁹.

The menopausal transition represents another biologically relevant phase. Early menopause is associated with an increased incidence of RA and higher levels of disease activity and structural progression²⁰. A meta-analysis comprising over 22 million person-years reported a modest increase in incident RA risk among hormone replacement therapy users, particularly among current and long-term users²¹. Researchers have also examined hormonal contraceptive use, with meta-analytical evidence suggesting a modest association between ever-use and reduced RA risk; however, substantial heterogeneity across studies and uncertainty regarding timing, formulation and residual confounding limit definitive conclusions²².

Overall, the available evidence points to modest and heterogeneous associations between hormonal exposures and RA risk. Rather than indicating a uniformly protective or harmful effect of exogenous oestrogens, these findings highlight the complexity of hormonal modulation in RA and reinforce the need for an individualized risk-benefit approach when considering hormonal therapies in those with autoimmune susceptibility.

Therapeutic considerations

Sex influences treatment allocation in RA, although the magnitude of sex-related differences varies across drug classes. In a large German nationwide cohort²³, women had slightly lower odds of receiving conventional synthetic DMARDs (csDMARDs) and glucocorticoids within the first year after diagnosis, although the observed differences were small and of uncertain clinical relevance. More pronounced differences emerged for biological DMARDs (bDMARDs), with women showing lower odds of bDMARD initiation during the first year than men (OR 0.62; 95% CI 0.57–0.69)²³. Data from the Spanish BIOBADASER registry²⁴ did not identify major overall sex differences in time to initiation of bDMARDs or targeted synthetic DMARDs, although women diagnosed in the later years of the registry (2017–2023) initiated therapy slightly later than men.

Box 1 | Transgender and gender-diverse people in rheumatology

Transgender and gender-diverse individuals remain virtually absent from rheumatology research, despite increasing awareness that gender-affirming hormone therapy and psychosocial factors might influence immune, inflammatory and metabolic pathways relevant to rheumatic diseases^{4,5,191}. Existing data are limited to small case series and cross-sectional studies, often derived from non-rheumatological populations, yet these data highlight potentially important implications for disease expression, treatment response and comorbidity risk^{4,5}.

Oestrogen and testosterone — central components of gender-affirming hormone therapy — exert pleiotropic effects on immune regulation^{192,193}. Longitudinal studies in transgender men demonstrate that masculinizing hormonal treatment regimens can attenuate type I interferon responses and enhance TNF-driven and NF- κ B-driven, T_H1-skewed inflammatory pathways^{194,195}. By contrast, the immunological effects of feminizing hormonal treatment regimens remain largely unstudied. Available prospective data, including longitudinal autoantibody profiling, do not show a clear increase in autoimmunity during gender-affirming hormone therapy¹⁹⁶, highlighting the need for robust, long-term studies to determine whether hormonal modulation influences disease onset or clinical presentation in susceptible individuals. Evidence from

other clinical contexts that involve hormone suppression, such as endocrine therapies for breast and prostate cancer, further supports the concept that modulation of sex steroids can exert systemic effects on multiple physiological systems, including immune regulation and bone metabolism, although direct extrapolation to transgender populations requires caution^{197–199}. Data on gender-diverse people, who might receive individualized, partial or no hormonal interventions according to their gender-affirmation goals, remain extremely limited¹⁷⁶.

Beyond hormonal mechanisms, gender-related factors, such as minority-specific stressors, barriers to care and reduced uptake of preventive services, further shape disease experience and outcomes in transgender and gender-diverse populations^{176,200}. Moreover, gender-affirming hormone therapy can interact with conventional antirheumatic drugs, affecting pharmacokinetics, cardiovascular and thrombotic risk, and bone metabolism, underscoring the need for individualized therapeutic monitoring¹⁷⁶.

Closing these knowledge gaps will require systematic inclusion of gender identity and sex assigned at birth in clinical registries, equitable participation of transgender and gender-diverse individuals in clinical trials and the development of multidisciplinary, gender-affirming care pathways.

Beyond differences in treatment allocation, sex also seems to influence therapeutic outcomes. Female sex, higher baseline disease activity and delay in treatment initiation have been identified as predictors of refractory disease, defined as failure to achieve low disease activity after ≥ 3 DMARDs, including at least one biologic. In multivariable analysis, female sex was associated with approximately threefold higher odds of refractory disease²⁵. Consistent with this pattern, analyses of clinical trial datasets indicate that male sex, lower baseline disease activity and shorter disease duration are associated with a greater likelihood of achieving treatment targets²⁶. However, evidence remains mixed. A meta-analysis of phase II–III randomized controlled trials evaluating multiple biologic agents did not detect clear sex-related differences in American College of Rheumatology (ACR)20 response rates²⁷. Similarly, post hoc analyses of the NORD-STAR trial in early RA did not identify meaningful sex-related differences in remission rates across treatment groups²⁸. By contrast, data from the DANBIO registry show that women receiving TNF inhibitors exhibit smaller reductions in Disease Activity Score in 28 joints (DAS28) scores, lower rates of good treatment response according to European Alliance of Associations for Rheumatology (EULAR) criteria and shorter treatment persistence than men²⁹.

Sex differences in the components of composite disease activity indices might partly explain these observations. In the BARFOT early RA cohort, women had higher DAS28 scores than men, primarily driven by patient-reported components such as pain and global assessment, whereas swollen joint counts and inflammatory markers were similar³⁰. Well-documented sex differences in pain perception and pain thresholds — influenced by hormonal, neurobiological and immunoregulatory mechanisms — provide additional context. Although these differences are not specific to RA, they can affect patient-reported components of composite disease activity indices without necessarily reflecting greater inflammatory burden. Supporting this interpretation, meta-analytic evidence indicates that women with RA report

higher pain scores across the disease course, even when receiving similar DMARD therapies³¹. Such differences can influence clinical assessment of disease severity and the likelihood of reaching composite treatment targets, including those based on DAS28 or EULAR criteria. Sex-related differences in inflammatory markers could further influence evaluation of treatment response. For example, lower erythrocyte sedimentation rate (ESR) values in men can increase the probability of meeting remission thresholds according to DAS28-ESR³². After correction for sex-related differences in ESR, approximately 12% of men were reclassified, indicating that DAS28-ESR might overestimate remission rates in male patients.

Despite these differences in disease activity measures and treatment targets, long-term structural outcomes seem broadly similar in women and men. In a Dutch treat-to-target cohort, women presented with higher disease activity over time and required more frequent treatment adjustments, yet radiographic outcomes of the sexes remained comparable³³. This pattern suggests a partial dissociation between composite disease activity indices and structural progression.

Sex could also influence treatment persistence. Meta-analytical evidence indicates that female sex is associated with slightly higher rates of biologic discontinuation³⁴, although the magnitude of this effect is modest. Discontinuation is most often related to lack or loss of efficacy or safety concerns, but sex-specific patterns of comorbidities and extra-articular manifestations might also contribute. Similar findings emerged from the PROPER study, which reported higher discontinuation risk among women following treatment transition to a biosimilar (HR 3.53; 95% CI 1.07–11.67)³⁵, although given the wide confidence intervals, these findings should be interpreted with caution. Such findings suggest that sex-related and gender-related differences can influence multiple aspects of RA treatment, from treatment allocation and response assessment to treatment persistence, whereas long-term structural outcomes seem broadly comparable.

Review article

Comorbidities and clinical outcomes

Comorbidity patterns also differ by sex, influencing overall disease burden and prognosis. In a cohort of ~150,000 individuals with RA, women had a higher prevalence of multimorbidity – defined as the coexistence of two or more chronic conditions – and more frequent mood, neurological and diffuse musculoskeletal disorders, whereas men were more prone to cardiovascular disease³⁶. Although cardiovascular disease represents the leading comorbidity in RA for both sexes, cardiovascular risk could be underestimated in women. In a Dutch cohort of 863 individuals with RA, 36% of women who experienced a cardiovascular event had been classified as low risk by the Systematic Coronary Risk Evaluation algorithm, compared with 10% of men³⁷. Reduced performance of conventional cardiovascular risk-prediction tools in women has also been documented in the general population and might reflect sex-related differences in atherosclerotic biology, clinical presentation and calibration of existing algorithms.

Cardiometabolic outcomes provide another area where sex shapes disease trajectories. RA-associated cardiometabolic risk is further influenced by the well-described ‘lipid paradox’, in which active systemic inflammation is associated with lower total cholesterol and LDL

concentrations yet confers higher cardiovascular risk³⁸. Sex-related and menopause-related differences in lipid profiles add further complexity: postmenopausal women often exhibit a more atherogenic pattern, suggesting that hormonal status modulates cardiovascular risk trajectories³⁹.

Body composition represents another important sex-specific modifier of cardiometabolic risk and RA outcomes⁴⁰, with higher BMI associated with greater RA disease activity in women, but not in men⁴¹. Beyond biological factors, gender-related determinants also influence functional outcomes. Women with RA are at a higher risk of work disability than men, influenced by socioeconomic and psychosocial determinants such as educational attainment, employment conditions and mental health status⁴².

Despite these sex-related and gender-related differences in morbidity, effects on mortality are less consistent. Although all-cause mortality is increased in patients with RA compared with the general population, available evidence does not indicate consistent sex differences in cause-specific mortality⁴³.

Overall, sex seems to shape multiple clinical dimensions of RA. Women show higher prevalence and generally greater disease activity,

Table 2 | Integration of sex and gender considerations across prevention, diagnosis and management in major rheumatology guidelines

Disease	Guidelines and recommendations	Prevention and risk stratification	Diagnosis and classification	Clinical trials: conducting and reporting	Treatment and management
Rheumatoid arthritis	EULAR (2021 (refs. 177,178) and 2018 (ref. 179)) guidelines	None; no sex-specific or gender-specific prevention strategies or risk stratification approaches	None; no sex-specific or gender-specific diagnostic recommendations or classification criteria; no reference to sex-specific or gender-specific symptom profiles	Minimal; sex and gender are included in the core dataset for clinical trials and observational studies	None. No sex-specific or gender-specific treatment or management recommendations
Systemic lupus erythematosus	EULAR (2025 (refs. 180,181), 2024 (refs. 182,183), 2022 (ref. 184) and 2017 (ref. 185)) and ACR (2025 (refs. 186,187), 2020 (ref. 63)) guidelines	Minimal; predominance in reproductive-aged women is acknowledged; male sex is mentioned as a risk factor for lupus nephritis and chronic kidney disease, end-stage kidney disease and kidney flares; incorporating gender in cardiovascular risk stratification is highlighted as a future challenge	None; no sex-specific or gender-specific diagnostic recommendations or classification criteria; no reference to sex-specific or gender-specific symptom profiles	Minimal; sex (but not gender) is included in the core dataset recommended for clinical trials and observational studies	Limited. Recommendations explicitly address drug safety in relation to reproductive health (including contraception, pregnancy, fertility preservation and menopause). Transgender reproductive health noted as a research need
Axial spondyloarthritis	ASAS-EULAR (2023 (ref. 188)) and ACR (2016 (ref. 189)) guidelines	None; men are recognized as having a higher propensity for progressive spinal fusion	None; no sex-specific or gender-specific diagnostic recommendations or classification criteria; no reference to sex-specific or gender-specific symptom profiles	None; no sex-specific or gender-specific recommendations for conducting or reporting clinical trials	Minimal. The guidelines highlight the need to investigate drug efficacy stratified by gender as a research priorities
Sjögren disease	n.a.	None; no sex-specific or gender-specific prevention strategies or risk stratification strategies	None; no sex-specific or gender-specific diagnostic recommendations or classification criteria; no reference to sex-specific or gender-specific symptom profiles	None; no sex-specific or gender-specific recommendations for conducting or reporting clinical trials	None. No sex-specific or gender-specific treatment or management recommendations
Gout	EULAR (2020 (ref. 190)) guidelines	None; no sex-specific or gender-specific prevention strategies or risk stratification strategies	Minimal; male sex is recognized as a clinical feature supporting diagnosis, although both sex-informed and gender-informed diagnostic guidance remain limited	None; no sex-specific or gender-specific recommendations for conducting or reporting clinical trials	None. No sex-specific or gender-specific treatment or management recommendations

We limited our review to European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) guidelines (published from 2015 to 2025), which consistently apply standardized evidence-grading frameworks (for example, GRADE) and provide internationally adopted clinical recommendations in rheumatology. This table is not aimed at providing an exhaustive list of all available guidelines for each rheumatic disease. Only guidelines that explicitly mention or incorporate sex and/or gender differences in their recommendations or discussion were included. General disease management guidelines without specific reference to sex and/or gender considerations were excluded. ‘None’ indicates no mention of sex or gender; ‘Minimal’ indicates acknowledgement without specific recommendations; ‘Limited’ indicates recommendations restricted to specific subpopulations (such as pregnancy). Use of the terms ‘sex’ and ‘gender’ in the table reflects the terminology adopted in the original guideline documents. Use of the terms ‘men’ and ‘women’ in this table reflects the terminology adopted in the original published research; however, *Nature Reviews Rheumatology* recognizes that not everyone affected by rheumatic disease is a woman or man. ASAS, Assessment of Spondyloarthritis International Society; n.a., not available.

with a higher burden of pain and fatigue and, on average, less favourable treatment responses, as well as higher rates of treatment discontinuation and work disability, despite similar or less structural damage. Men, by contrast, more often exhibit an erosive phenotype and faster radiographic progression and show a higher burden of cardiovascular comorbidities. Gender-related factors, such as health care engagement and lifestyle, together with sex-related and gender-related influences on pain perception, could further modulate functional outcomes.

Systemic lupus erythematosus

SLE is a systemic autoimmune disease characterized by heterogeneous clinical manifestations and multisystem involvement. SLE provides one of the clearest examples of how sex-related and gender-related factors shape autoimmune disease. This disease is characterized by marked sex imbalances, distinctive age-related patterns of disease onset and notable differences in clinical expression, serological profiles and outcomes.

Epidemiology and clinical presentation

SLE is one of the most female-predominant autoimmune diseases, particularly during the reproductive years, with a female-to-male ratio of approximately 8–15:1 that decreases to 2–8:1 in prepubertal and late-onset disease^{44,45}. These age-related and sex-related patterns have long suggested a role for hormonal factors in disease susceptibility^{46,47}, although current evidence also implicates X-linked genetic mechanisms and abnormalities in X chromosome inactivation as contributing factors^{48,49}.

Sex-related differences in age at disease onset have been reported. In a large Italian multicentre cohort, women developed SLE at a younger age than men (28 versus 35 years) and received a diagnosis earlier (30 versus 38 years), although diagnostic delay of the sexes remained similar (2.8 ± 5.2 versus 2.2 ± 4.2 years)⁵⁰. Despite these differences, the 2019 EULAR–ACR classification criteria perform comparably across sexes, with sensitivity of 97% and 93% and specificity of 94% and 96%, respectively⁵¹.

Distinct sex-specific clinical phenotypes are evident at disease onset. Men more often present with major organ involvement, including serositis, discoid lupus, thrombocytopenia and lupus nephritis, whereas women more commonly develop malar rash, alopecia, arthritis and leukopenia^{44,50,52–57}. In the Attikon Lupus Cohort, male sex, younger age and higher serological activity were independent predictors of renal involvement⁵⁸, although the relatively small number of male participants warrants cautious interpretation. Despite the higher prevalence of nephritis among men, renal biopsy class distributions of the sexes seem comparable⁵⁸.

Sex-related differences are also evident in serological profiles. Men with SLE more frequently have lupus anticoagulant and anticardiolipin antibodies, whereas women show higher prevalence of anti-Ro/SSA and other extractable nuclear antigen antibodies, including anti-SSB, anti-RNP and anti-Sm antibodies⁵⁹. Such findings highlight how sex-related and gender-related differences shape the epidemiology and clinical expression of SLE.

Life-course hormonal factors

Hormonal exposures across the life course, including pregnancy, hormonal contraception and postmenopausal hormone therapy, have been extensively investigated in SLE because of the potential implications for disease activity and clinical management. During pregnancy, most studies report predominantly mild flares, typically

cutaneous, musculoskeletal or haematological, occurring in approximately 25–65% of pregnancies depending on baseline disease activity and study population⁶⁰. Debate around hormonal contraception has persisted for decades. Although early observational studies suggested an increased risk of flares or thrombosis, two randomized controlled trials showed no increase in disease activity among individuals using hormonal contraceptives, regardless of formulation^{61,62}. Because these trials included only women with inactive or stable disease, the 2020 ACR guideline recommends avoiding oestrogen-containing contraceptives in those with active SLE or antiphospholipid antibodies, while supporting their use in women with stable disease⁶³. Notably, although some women report subjective symptom fluctuations, such as fatigue or pain, across the menstrual cycle, hormonal contraceptive use does not seem to trigger clinically meaningful flares⁶⁴.

Debate around the use of hormone replacement therapy in postmenopausal women with SLE has also persisted for decades. Some observational studies reported no increase in disease activity, whereas the SELENA trial identified a modest rise in mild-to-moderate flares without changes in severe flares⁶⁵. Thrombotic risk remains the primary concern, particularly among women who test positive for antiphospholipid antibodies, although hormone replacement therapy seems safe in well-selected patients with stable disease⁴⁷.

Collectively, these findings indicate that hormonal exposures across the life course can have important implications for SLE management, particularly in relation to flare risk and thrombotic complications.

Therapeutic considerations

Therapeutic management in SLE shows several sex-related differences⁵⁹. Across observational cohorts and registry studies, men receive cyclophosphamide more often than women, a pattern that probably reflects the higher prevalence of severe organ involvement, particularly lupus nephritis, among male patients^{55,66}. Conversely, antimalarial drugs, particularly hydroxychloroquine, seem to be prescribed less frequently in men^{67,68}. For most other therapies, including glucocorticoids and commonly used immunosuppressive drugs such as azathioprine, mycophenolate mofetil and biologic drugs, prescription patterns of the sexes remain broadly similar, although findings vary across studies^{55,67}. Evidence of sex-related differences in treatment adherence remains limited and inconsistent: most studies report comparable adherence to antimalarial drugs, whereas some administrative datasets suggest slightly lower adherence to immunosuppressive therapies among women^{67,69,70}.

Whether biological sex modifies treatment efficacy remains insufficiently explored. Because SLE predominantly affects women, most pivotal randomized controlled trials enrol overwhelmingly female populations, limiting the feasibility of robust sex-stratified analyses and reducing the generalizability of treatment-effect estimates to male patients. In a pooled post hoc analysis of five phase III belimumab trials, male patients showed a higher risk of neuropsychiatric flares (HR 3.26, 95% CI 1.51–7.04), although the small number of men warrants cautious interpretation⁷¹. In the phase III trial of obinutuzumab for lupus nephritis, women seemed more likely to achieve a complete renal response, although this difference largely reflected a higher placebo response among men and again probably reflects the small number of male participants⁷². Such available evidence suggests that observed sex-related differences in SLE treatment largely reflect differences in disease severity, whereas limited representation of men in clinical trials constrains conclusions on sex-specific treatment response.

Comorbidities and clinical outcomes

Sex-related and gender-related differences extend to comorbidities and long-term clinical outcomes in SLE. Several studies report that men with SLE accumulate greater overall organ damage than women^{50,57–59,73–78}. A scoping review found higher rates of chronic kidney disease and progression to end-stage renal disease among men across multiple cohorts, consistent with evidence that damage accrues more rapidly in men than in women⁵⁹. Notably, in a large Chinese cohort, serologically active but clinically quiescent phenotypes were also associated with cumulative organ damage, with the highest burden occurring among antiphospholipid-positive men⁷⁸.

Despite accumulating less objective organ damage, women with SLE frequently report poorer health-related quality of life than men. In a multiethnic cohort of 1083 individuals with SLE, men scored lower in social support domains, whereas women reported worse SLE-specific symptoms, cognitive function, physical health and pain-visibility domains, particularly during reproductive years⁷⁹. Functional consequences are also substantial: work disability affects approximately 20–40% of patients with SLE and frequently leads to reduced productivity or early withdrawal from the workforce, particularly among women⁸⁰.

Cardiovascular disease remains a major sex-related determinant of prognosis in SLE⁸¹. In the general population, men have a higher baseline risk of cardiovascular disease, which partly explains the higher absolute cardiovascular disease rates observed among men with SLE. However, the sex gap seems larger within the SLE population than in the general population, suggesting amplification by disease-related mechanisms. SLE also markedly attenuates the usual female cardiovascular advantage: women aged 35–44 years with SLE have up to a 50-fold higher risk of myocardial infarction than age-matched women in the general population⁸². Accordingly, women with SLE often have an altered lipid profile, including dysfunctional, pro-inflammatory HDL particles associated with increased carotid intima-media thickness^{83,84}.

Despite therapeutic progress, sex-specific mortality patterns persist in SLE. Mortality remains markedly higher in women than in men. In a US population-based analysis covering 1999–2020, age-adjusted mortality rates reached 6.21 per million in women and 1.20 per million in men – an approximately fivefold difference – although both sexes showed declining trends over time⁸⁵. A separate cross-sectional analysis based on the US national death certificate data found that women with SLE died on average approximately 22 years earlier than women without SLE, whereas men died approximately 12 years earlier than their counterparts in the general population⁸⁶. Causes of death also differ by sex: sepsis and hypertension are more frequent among women, whereas cardiovascular disease and diabetes-related complications predominate in men⁸⁶. Notably, among patients with lupus nephritis, mortality is nearly twice as high in men as in women (24.2% versus 13.4%), with infection-related causes contributing substantially to this excess risk⁸⁷.

Overall, sex shapes the clinical spectrum and outcomes of SLE. Men more frequently develop severe organ involvement and accumulate greater organ damage, whereas women experience a substantial disease burden characterized by poorer health-related quality of life and greater functional impact. SLE also substantially reduces the typical cardiovascular protection associated with female sex, thereby increasing cardiometabolic risk.

Axial spondyloarthritis

Axial spondyloarthritis (axSpA), a prototypical condition within the spondyloarthritis spectrum, is a chronic inflammatory disease of the

axial skeleton characterized by inflammatory back pain and variable peripheral and extra-musculoskeletal manifestations^{88,89}. Patients are classified as having radiographic axSpA or non-radiographic axSpA on the basis of structural changes detected on imaging⁹⁰. AxSpA provides a useful clinical model for examining sex-related and gender-related differences across the spondyloarthritis spectrum, particularly regarding diagnostic pathways, disease burden and treatment outcomes. Similar patterns have also been described in PsA, supporting the role of sex and gender as important clinical modifiers across these conditions. A comparative overview of shared and distinct sex-related and gender-related clinical features between axSpA and PsA is provided in Box 2.

Epidemiology and clinical presentation

Historically, clinicians regarded axSpA as more prevalent and more severe in men; however, contemporary epidemiological evidence shows an almost equal overall sex distribution. This apparent balance reflects differing subtype patterns: men develop radiographic axSpA more often, with an approximate female-to-male ratio of 1:3, whereas non-radiographic axSpA has a more even sex distribution. Men are also at a higher risk of structural progression and severe disease, with a male-to-female ratio of approximately 2:1 among individuals with radiographic axSpA⁹¹.

Prevalence strongly aligns with *HLA-B*27* positivity, which occurs more frequently in men, particularly in radiographic axSpA, whereas women, especially women with non-radiographic axSpA, less often carry *HLA-B*27* (refs. 92–94). Genetic differences between sexes extend beyond *HLA-B*27* (ref. 94). In a large longitudinal cohort, other *HLA-B* alleles, including *HLA-B*15* and *HLA-B*37*, were associated with peripheral musculoskeletal manifestations, and women showed a higher burden of enthesitis and peripheral arthritis, highlighting sex-related variation in genetic-phenotypic associations⁹⁵. Transcriptomic analyses further reveal sex-specific gene expression signatures⁹⁶, with differentially expressed genes enriched in immune and inflammatory pathways. These findings support sex-specific immune activation profiles⁹⁷ and could contribute to sex-related heterogeneity in clinical presentation, treatment response and outcomes^{91,98}.

These biological differences align with distinct clinical presentation patterns in women and men. Men more often present with inflammatory back pain and limited peripheral or enthesal involvement, whereas women more often report diffuse or widespread pain patterns that might overlap with fibromyalgia, potentially complicating clinical assessment^{99,100}. Women with axSpA are also more likely to develop cervical spine disease, although estimates vary substantially across cohorts¹⁰¹.

Diagnostic delay in axSpA remains substantial and tends to be longer in women than in men^{89,101}. Several factors could contribute to this disparity. Women more frequently present with less specific imaging findings, which can complicate diagnostic interpretation^{101,102}. Assessment of bone marrow oedema on MRI can be particularly challenging in women, as physiological and mechanical factors, including postpartum changes, can produce sacroiliac signal alterations that mimic inflammatory lesions¹⁰³. Such findings highlight how sex-related and gender-related differences contribute to distinct clinical phenotypes and diagnostic challenges in axSpA.

Life-course hormonal factors

Reproductive life stages also intersect with disease expression in axSpA, although available evidence remains limited. Contemporary prospective data indicate that overall obstetric outcomes in women with axSpA are largely comparable with those in the general population. In a French national prospective matched study of women with SpA,

Box 2 | Comparative sex-related and gender-related features in axial and psoriatic spondyloarthritis

Sex-related and gender-related differences described in axial spondyloarthritis (axSpA) show important similarities to those observed in psoriatic arthritis (PsA), particularly in clinical presentation, disease burden and treatment outcomes, supporting the relevance of sex and gender as clinical modifiers across the spondyloarthritis spectrum^{201–204}.

Shared clinical patterns

Across both axSpA and PsA, women consistently report higher disease activity, greater functional limitation and worse patient-reported outcomes, including pain, fatigue and reduced health-related quality of life, despite similar levels of objective inflammatory activity^{99,201–204}. In PsA, clinical trial data show a comparable pattern, with higher pain scores, functional impairment and patient global assessment in women, compared with higher inflammatory markers and more severe skin involvement in men²⁰². This discordance between higher patient-reported disease burden in women and higher objective inflammatory measures in men seems to be a consistent feature across the spondyloarthritis spectrum.

Sex differences in treatment outcomes also show similar trends. In both axSpA and PsA, men generally achieve higher response rates and maintain longer persistence with biologic therapies, whereas women more frequently discontinue treatment or report suboptimal clinical responses^{202,204}. Real-world studies in PsA further suggest

lower rates of minimal disease activity and less favourable treatment outcomes in women^{205,206}.

Distinct clinical features

Important differences between the two diseases should also be considered. AxSpA remains more strongly associated with male sex, particularly with respect to structural damage and radiographic progression, whereas PsA shows a more balanced sex distribution, with emerging data suggesting a higher proportion of women than historically reported^{201,202}. PsA is also characterized by multidomain disease involvement, including peripheral and polyarticular disease patterns and differences in skin involvement, with sex differences largely reflecting the distribution of clinical domains. By contrast, sex differences in axSpA are more strongly reflected in structural damage, radiographic progression and diagnostic delay^{201,202}.

Implications for clinical practice

Taken together, these observations highlight the importance of incorporating sex and gender into the interpretation of symptoms, the evaluation of treatment response and the assessment of disease impact across the spondyloarthritis spectrum. Differences in disease expression between axSpA and PsA underscore the need for disease-specific interpretation of sex-related and gender-related differences when planning management strategies.

rates of preterm birth, hypertensive disorders, congenital anomalies and caesarean delivery were similar to those observed among matched women in the general population¹⁰⁴.

Data regarding hormonal contraception remain limited but are generally reassuring¹⁰⁵. Available data indicate that combined oral contraceptives do not worsen disease activity in axSpA, and no consistent association with disease onset or severity has emerged¹⁰⁶. Evidence regarding menopause remains indirect. Both axSpA and the menopausal transition are independently associated with increased cardiovascular risk. However, current data do not conclusively show that menopause itself specifically increases cardiovascular risk or accelerates structural disease progression in women with axSpA¹⁰⁷.

Such findings suggest that reproductive and hormonal factors influence disease expression in axSpA, although their clinical relevance remains uncertain owing to limited data.

Therapeutic considerations

Treatment patterns and response to therapy show consistent sex-related differences in axSpA. In a large US claims-based study, women were more likely to continue NSAIDs after diagnosis and initiated bDMARDs later than men (adjusted HR 0.61; 95% CI 0.52–0.72)¹⁰⁸. Observational data further indicate that women are less likely to receive biologic therapies despite reporting a greater disease burden¹⁰⁹.

Men generally achieve higher remission rates and greater improvements in disease activity with TNF inhibitors, whereas women tend to show less favourable responses and shorter treatment persistence^{110–115}. Evidence from large observational cohorts reinforce these differences. In an analysis drawing on multiple European registries within the European Spondyloarthritis Research Collaboration Network¹¹⁶, women

had higher disease activity and functional impairment at baseline – reflected in higher Bath Ankylosing Spondylitis Disease Activity Index and Bath Ankylosing Spondylitis Functional Index scores – and these differences persisted after TNF inhibitor therapy. Similarly, in the Swiss Clinical Quality Management cohort, men with non-radiographic axSpA were more likely to achieve an Assessment of Spondyloarthritis international Society 40 response after 1 year of treatment with a first TNF inhibitor (38% versus 17% in women)⁹³. Data from the Swedish registry also show lower discontinuation rates of TNF inhibitors in men than in women (HR for discontinuation 0.36, 95% CI 0.19–0.68)¹¹⁷, a pattern replicated in the Rheumatology Informatics System for Effectiveness registry, where women discontinue TNF and IL-17 inhibitors more frequently, whereas JAK inhibitor discontinuation shows no sex difference¹¹⁸.

In randomized controlled trials of IL-17 inhibition, clinical responses seem to occur earlier in men, whereas women more often show a slower but progressive improvement, with broadly comparable outcomes at longer follow-up^{119,120}. Importantly, the higher discontinuation rates observed in women across different cohorts and therapeutic classes do not seem to arise from differences in patient behaviour alone, suggesting that a combination of biological factors, differences in disease phenotype and variations in treatment allocation or clinical decision-making could contribute to these disparities.

Comorbidities and clinical outcomes

Sex influences several dimensions of long-term disease burden in axSpA, including structural progression, comorbidity patterns and overall clinical outcomes. Men more frequently develop structural damage, including bilateral sacroiliitis and spinal syndesmophytes¹²¹, than women. In a Swiss longitudinal cohort, syndesmophytes occurred

in 40% of men compared with 15% of women¹²². Radiographic progression is also more pronounced in men, whereas women generally show slower or minimal structural progression over time; over 2 years, mean progression reached 1.0 ± 2.8 units in men compared with 0.3 ± 1.1 in women ($P < 0.001$)¹²².

Sex-related differences extend beyond structural damage and include systemic manifestations and cardiovascular risk. In a Spanish cohort, women showed a lower prevalence of carotid atherosclerosis overall, but among those at a high cardiovascular risk, greater disease activity correlated more strongly with subclinical atherosclerosis in women than in men, suggesting sex-related differences in the interaction between inflammation and cardiovascular risk¹²³.

Metabolic factors could further contribute to sex differences in clinical outcomes. Although BMI does not consistently differ between sexes, women tend to have higher fat mass and a greater prevalence of central obesity, both of which have been associated with worse functional outcomes and poorer quality of life^{124,125}. Consistently across multiple cohorts, women report higher disease activity scores and worse patient-reported outcomes than men, including greater fatigue, reduced physical function, poorer health-related quality of life, a higher level of psychological distress and greater impairment in work productivity and daily activities^{91,97,99,126–130}.

Sex differences are also evident in the distribution and impact of comorbidities. Data from the international COMOSPA cohort indicate that cardiovascular comorbidities occur more frequently in men, whereas fibromyalgia is more prevalent in women, and these comorbid conditions influence disease activity and functional outcomes in sex-specific ways¹³¹.

Mortality also differs by sex. Available data suggest that excess mortality occurs primarily in men with axSpA, whereas no consistent increase has been reported in women¹³². In retrospective cohort analyses, male sex, older age and elevated C-reactive protein levels were associated with increased mortality¹³³, highlighting the contribution of persistent systemic inflammation to long-term risk.

In summary, sex shapes the clinical spectrum and disease trajectory of axSpA. Men more frequently develop radiographic disease with faster structural progression, whereas women more often present with non-radiographic disease, greater symptom burden and longer diagnostic delay. Differences in body composition, comorbidity patterns and treatment response could further contribute to sex-related variation in clinical outcomes.

Sjögren disease

Sjögren disease is a systemic autoimmune disease characterized by exocrine gland dysfunction and a wide spectrum of systemic manifestations^{134,135}. Being one of the most female-predominant autoimmune diseases, this disease provides a compelling clinical model for examining how sex-related and gender-related factors influence disease susceptibility, clinical phenotype and long-term outcomes.

Epidemiology and clinical presentation

Sjögren disease predominantly affects middle-aged women, with a female-to-male ratio of approximately 9:1 (ref. 136). Men with Sjögren disease often display a more systemic disease phenotype than women^{137–140}. In a large Swedish population-based cohort, men were diagnosed at a younger age than women and exhibited a higher frequency of extra-glandular manifestations, particularly interstitial lung disease, cutaneous vasculitis and lymphadenopathy¹³⁸. Similar patterns have been reported in Korean cohorts^{139,140}, where male sex

was associated with more frequent systemic involvement and fewer sicca symptoms; interstitial lung disease is particularly common among men and most frequently shows a non-specific interstitial pneumonia pattern on imaging. Cardiopulmonary involvement also seems more pronounced in men; in an Italian cohort, men had poorer pulmonary function (reduced forced vital capacity and first second of forced expiration) together with earlier echocardiographic signs of right-sided and diastolic dysfunction¹⁴¹.

Life-course hormonal factors

Hormonal transitions across the life course influence disease expression and clinical management in Sjögren disease. Meta-analytic evidence indicates that pregnancy increases the risk of adverse obstetric outcomes, including preterm birth, hypertensive disorders and fetal growth restriction¹⁴². The most severe complication is autoimmune congenital heart block in approximately 2% of foetuses exposed in utero to maternal anti-Ro/SSA or anti-La/SSB-positive antibodies, with substantially higher recurrence risk in women with a previously affected child¹⁴³. Use of hydroxychloroquine during pregnancy has been associated with reduced recurrence of congenital heart block.

Data on the impact of hormonal contraception on disease activity in Sjögren disease remain limited¹⁴⁴. The menopausal transition represents another biologically relevant phase. Sjögren disease frequently manifests around midlife, and the decline in oestrogen has been implicated in exocrine gland dysfunction and immune dysregulation¹⁴⁵. Observational data suggest possible associations between hormone replacement therapy and autoimmune conditions, including Sjögren disease, but reported effect sizes are modest and findings remain inconsistent¹⁴⁶.

Overall, life-course hormonal changes could modulate disease expression and complication risk, although the precise impact on the long-term disease trajectory remains incompletely understood.

Therapeutic considerations

Although several novel agents targeting pathways such as type I interferon signalling, B cell activation and signalling, co-stimulation pathways and FcRn-mediated IgG recycling have undergone evaluation over the past decade¹³⁵, the management of important symptoms such as fatigue, dryness and pain – symptoms that disproportionately affect women¹³⁶ – remains challenging with currently available therapies. A systematic review of biologic and targeted synthetic agents reported modest or inconsistent clinical benefits overall¹⁴⁷, with limited evidence of differential efficacy between sexes. Interpretation of the existing evidence is further constrained by the under-representation of men in clinical trials. Men account for only ~6% of participants in randomized controlled trials, and sex-disaggregated analyses are rarely predefined. These observations highlight the need for more sex-balanced clinical trials to better inform personalized therapeutic strategies in Sjögren disease.

Comorbidities and clinical outcomes

Sex-related and gender-related differences in comorbidities and long-term outcomes are prominent in Sjögren disease. Evidence indicates a higher risk of lymphoproliferative disorders among men. In a multicentre study, the prevalence of lymphoma was higher in men than in women (18% versus 5.2%; $P = 0.0014$), despite similar distributions of conventional lymphoproliferative risk factors between sexes¹⁴⁸.

Cardiopulmonary complications might also contribute to adverse outcomes. In a large Chinese cohort of patients with Sjögren disease-associated interstitial lung disease, rates of pulmonary

hypertension were higher in men than in women¹⁴⁹. In a large retrospective cohort study, the prevalence of cardiovascular conditions was also higher in men, including myocardial infarction, atherosclerosis, cardiomyopathy, stroke and congestive heart failure¹⁵⁰. Environmental exposures might contribute to these differences; notably, smoking, which is still more prevalent among men than among women worldwide¹⁵¹, represents an independent risk factor for interstitial lung disease¹⁵².

These patterns are also reflected in survival. A systematic review and meta-analysis reported a 1.46-fold increase in mortality risk among individuals with Sjögren disease compared with the general population, with male sex, older age, vasculitis, hypocomplementaemia, anti-La/SSB positivity and cryoglobulinaemia emerging as independent predictors of mortality¹⁵³.

By contrast, women with Sjögren disease more commonly experience a substantial chronic disease burden driven by comorbid conditions and patient-reported symptoms. In a large retrospective analysis, the prevalence of fibromyalgia, depression, chronic pain, migraine, fatigue-related symptom burden, hypermobility syndromes (including Ehlers–Danlos syndrome) and other rheumatic autoimmune diseases were reported more frequently among women than among men with Sjögren disease¹⁵⁰. Mucosal and sexual health complications are also common yet remain under-recognized in routine clinical care. Vulvovaginal dryness and genital atrophy – manifestations of exocrine dysfunction – are often associated with sexual dysfunction and psychological distress¹⁵⁴. Consistent with this broader symptom burden, women with Sjögren disease show substantial impairment in work productivity and daily activities, with reduced work performance and high overall disability independently associated with xerostomia, arthritis and depression¹⁵⁵.

In summary, Sjögren disease displays marked sex-related differences in clinical expression and outcomes. Most affected individuals are women, who typically present with classical glandular dysfunction and a substantial symptom burden, including fatigue and pain. By contrast, men, although less frequently affected, more often present at a younger age and display a more systemic disease phenotype, particularly pulmonary and lymphoproliferative involvement, which could contribute to poorer outcomes. Hormonal transitions across the life course and gender-related factors, such as smoking patterns and psychosocial burden, could further influence clinical presentation and disease management.

Gout

Gout is a prototypical crystal-induced inflammatory form of arthritis and results from chronic hyperuricaemia with deposition of monosodium urate crystals in and around joints. Unlike many autoimmune rheumatic diseases, gout shows a marked male predominance and distinct sex differences in age at onset, clinical presentation and comorbidity profiles. These features make gout a useful clinical model for examining how sex-related and gender-related factors influence disease presentation and management in inflammatory arthritis.

Epidemiology and clinical presentation

The reported prevalence of gout varies globally from <1% to nearly 7%, with a marked male predominance¹⁵⁶. This difference is most evident in middle age, when gout occurs up to ten times more frequently in men, but narrows in later life owing to rising prevalence among postmenopausal women¹⁵⁷. Women are diagnosed with gout approximately 8 years later than men on average¹⁵⁸.

Clinical presentation also differs between sexes. Men typically develop acute monoarthritis of the first metatarsophalangeal joint, whereas women more often present with polyarticular involvement

or with disease affecting other joints, including the ankles, knees or upper limb joints such as the wrists, elbows and small joints of the hands^{158–160}. Tophi occur more frequently in men and tend to present later in women, often at atypical sites such as the hands or elbows^{158–160}. These sex-specific clinical patterns might contribute to diagnostic uncertainty or misclassification of gout as RA or osteoarthritis.

Life-course hormonal factors

Unlike other inflammatory rheumatic diseases, gout is uncommon in women of reproductive age and typically develops after menopause. Pregnancy-related modulation of gout has therefore not been systematically investigated, and available evidence remains limited. After menopause, loss of oestrogen-mediated uricosuric effects leads to rising serum urate concentrations and increased risk of gout^{158,161}. Accordingly, in the Nurses' Health Study, postmenopausal women had a modestly higher risk of gout than premenopausal women¹⁶², whereas hormone replacement therapy was associated with a moderate reduction in risk¹⁶². However, findings are inconsistent across cohorts. In a nationwide Korean study of more than one million postmenopausal women, exogenous hormone exposure, including hormone replacement therapy, was associated with a small but statistically significant increase in incident gout¹⁶³.

These observations suggest that hormonal factors contribute to gout risk in women, although further studies are needed to clarify their clinical impact.

Therapeutic considerations

Treatment strategies for gout are broadly similar in men and women, although sex-related differences in comorbidity burden, renal function and drug safety profiles can influence therapeutic decisions. For acute flares, standard options (NSAIDs, colchicine and glucocorticoids) are effective in both sexes; however, treatment choices in women are often constrained by a higher prevalence of chronic kidney disease and polypharmacy. In these settings, clinicians generally favour glucocorticoids because these drugs provide comparable efficacy with a lower risk of renal and gastrointestinal toxicity¹⁶⁴.

Long-term urate-lowering therapy with xanthine oxidase inhibitors such as allopurinol or febuxostat remains the cornerstone of chronic management. Severe hypersensitivity reactions to allopurinol occur more frequently in women, a pattern that probably reflects the higher prevalence of chronic kidney disease and multiple drug exposures¹⁶⁵. The *HLA-B*5801* allele is a recognized genetic predictor of allopurinol hypersensitivity, and international guidelines recommend testing individuals of East Asian or African American ancestry before starting allopurinol¹⁶⁶. Despite this rare but serious adverse event, post hoc analyses suggest broadly comparable efficacy and overall safety of urate-lowering therapies in women and men¹⁶⁷.

Together, these data support broadly similar treatment approaches in women and men, with attention to sex-specific comorbidities and safety considerations.

Comorbidities and clinical outcomes

Patients with gout frequently present with a substantial comorbidity burden, with distinct patterns in the sexes. Women more commonly show cardiometabolic and renal comorbidities – including obesity, diabetes, dyslipidaemia, heart failure and chronic kidney disease – together with other conditions such as urinary tract infections, malignancies and concurrent rheumatic diseases. By contrast, men more frequently present with chronic respiratory disease, coronary artery disease and peripheral vascular disease^{159,168,169}. Additionally, women experience

Review article

greater disease impact and higher disability scores than men, even after adjustment for age, disease duration and comorbidity burden^{170,171}.

Beyond the comorbidity burden, hyperuricaemia itself could contribute to adverse outcomes. In a large Chinese case-control study, hyperuricaemia was independently associated with idiopathic deep venous thrombosis, with a markedly stronger effect in women than in men (OR 7.48 versus 2.64)¹⁷².

Gout and hyperuricaemia are associated with increased mortality risk, although this relationship seems largely influenced by age and

comorbidity burden. Observational studies have reported sex-specific patterns, with higher serum uric acid concentrations predicting increased mortality in women but not consistently in men. Accordingly, in a large prospective cohort of older adults, elevated serum uric acid concentrations were associated with increased all-cause mortality among women, whereas no such association was observed in men¹⁷³. Consistent with these observations, studies conducted specifically in patients with gout also suggest sex differences in mortality patterns. In a nationwide Korean cohort of patients with gout receiving

Table 3 | Important sex-related and gender-related gaps in clinical features and management of rheumatic diseases

Clinical domain	Rheumatoid arthritis	Systemic lupus erythematosus	Axial spondyloarthritis	Sjögren disease	Gout
Epidemiology	Many large datasets lack harmonized, life-course-sensitive measures (including menopausal status, reproductive history and hormone exposures), limiting causal inference on risk modifiers	Severe under-representation of men restricts the reliability of sex-stratified incidence and prevalence data	Misclassification of non-radiographic axSpA as chronic back pain or fibromyalgia in women contributes to underestimation of prevalence in women	Epidemiological data in men remain scarce owing to very low case numbers	Epidemiological data in women, particularly women of reproductive age, remain limited and heterogeneous
Disease presentation and activity	Drivers of higher pain and fatigue in women remain unclear; mechanisms underlying similar radiographic damage in women and men — despite higher disease activity in women — are insufficiently characterized	Evidence of sex differences in disease activity remains inconsistent. Sex-related differences in organ involvement (for example, more renal and serosal disease in men, and more cutaneous and articular disease in women) remains inadequately characterized in longitudinal datasets	Characteristic female phenotypes (such as more diffuse pain, lower inflammatory markers and lower frequencies of imaging positivity) are under-recognized; contributors to higher BASDAI and BASFI scores in women remain poorly understood	Male-associated features (including earlier onset of disease, interstitial lung disease, lymphoma and cardiopulmonary involvement) are incompletely characterized; in women, mucosal and vaginal dryness is under-recognized	Sex-specific contributors to female-predominant polyarticular and atypical joint involvement patterns remain insufficiently studied
Access to care and diagnostic delay	Unclear whether diagnostic delay in women primarily reflects health care-provider factors or differences in symptom reporting and care-seeking behaviour	Sex-stratified data on diagnostic delay remain scarce, particularly for men owing to low representation	Misclassification of axSpA as fibromyalgia or chronic back pain, and difficulty in interpreting sacroiliac MRI findings (including postpartum changes) contribute to diagnostic delay in women	Sparse data preclude robust assessment of sex differences in diagnostic delay	Limited sex-stratified data on diagnostic delay; atypical presentations in women are often misattributed to osteoarthritis or RA, contributing to delayed diagnosis
Comorbidities	Cardiovascular risk in women is frequently underestimated; and life-stage influences and sex-specific comorbidity trajectories remain poorly defined	Sex-specific renal, cardiovascular and thrombotic contributors to damage and mortality remain poorly characterized; and the impact of reproductive life stages on flare risk and long-term outcomes remains insufficiently defined	Sex differences in inflammation-driven cardiovascular risk remain insufficiently characterized, including across reproductive life stages	Drivers of male-predominant interstitial lung disease and lymphoma remain unclear; and female symptom burden and reproductive life-stage effects are insufficiently characterized	Sex differences in multimorbidity (including higher rates of chronic kidney disease and cardiometabolic disease in women; and more respiratory and peripheral vascular disease in men) are insufficiently integrated in gout management and outcomes
Treatment and management	Women receive fewer DMARDs and glucocorticoids; and contributors to poorer response and shorter drug survival in women remain unclear. The under-representation of men limits sex-stratified outcome analyses	Very limited sex-stratified evidence exists regarding treatment efficacy and safety beyond reproductive-health considerations	Mechanisms underlying poorer response and higher TNF inhibitor discontinuation in women remain undefined; and data on sex differences beyond TNF inhibitors are scarce	Sex-stratified therapeutic evidence remains very limited	Higher multimorbidity and chronic kidney disease in women complicate pharmacological management, and under-representation of women in gout clinical trials limits evidence of sex-specific treatment responses and safety
Cross-disease gaps	Systematic under-representation of the minority sex (that is, the sex in which the disease is comparatively less common); limited sex-stratified and gender-stratified longitudinal data; inadequate integration of gender-related variables; and scarce sex-stratified evidence of diagnostic delay, multimorbidity trajectories, life-stage risk modifiers and treatment outcomes				

Use of the terms ‘men’ or ‘male’ and ‘women’ or ‘female’ in this table reflects the terminology adopted in the original published research; however, *Nature Reviews Rheumatology* recognizes that not everyone affected by rheumatic disease is a woman or man. axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; RA, rheumatoid arthritis.

Box 3 | Clinical priorities for sex-sensitive and gender-sensitive rheumatology

Strengthen sex-stratified evidence

Ensure balanced recruitment and systematic sex-stratified analyses in cohorts and clinical trials to generate interpretable data on disease activity, progression and therapeutic outcomes. Adopt a life-course framework by incorporating reproductive transitions, including puberty, pregnancy and menopausal transition, into study design and data interpretation.

Refine diagnostic pathways

Incorporate sex-specific and gender-specific clinical patterns into early assessment. Consider the influence of reproductive ageing and hormonal therapies on symptom expression, inflammatory biomarkers and musculoskeletal manifestations. Artificial intelligence (AI)-assisted diagnostic tools should be trained and validated on sex-balanced datasets to minimize algorithmic bias.

Optimize therapeutic decision-making

Advance sex-stratified pharmacokinetic, pharmacodynamic and immunological research to support personalized treat-to-target strategies. Evaluate how endogenous and exogenous hormonal milieu across the lifespan modify therapeutic response and adverse-event profiles. Integrate sex and gender variables into prediction models, including AI-based tools for treatment response.

Address sex-specific comorbidity risk

Incorporate sex-related differences in multimorbidity trajectories into routine screening and prevention strategies to ensure accurate risk assessment and timely intervention. Integrate reproductive ageing into long-term risk stratification models.

Integrate gender-related determinants

Routinely evaluate behavioural and social factors (such as gender-related care-seeking patterns, pain appraisal, physical activity and treatment adherence) that shape disease burden independently of biological sex.

Improve outcome measurement

Refine composite indices to account for sex-related variation in subjective components, such as patient global assessment, that can distort disease activity estimates and target achievement. Develop digital and AI-supported outcome systems using sex-balanced training datasets.

Ensure inclusion of transgender, gender-diverse and intersex populations

Collect sex assigned at birth, gender identity and hormonal status in clinical datasets; evaluate how gender-affirming hormone therapy and variations in sex characteristics influence immune function, disease expression and treatment response.

Enhance guideline integration

Promote the systematic incorporation of sex and gender considerations into international rheumatology guidelines. Future European Alliance of Associations for Rheumatology–American College of Rheumatology recommendations should include sex-aware diagnostic criteria, sex-stratified interpretation of disease activity and biomarkers, and guidance on screening and management pathways reflecting sex-specific and gender-specific risks.

urate-lowering therapy¹⁶⁸, mortality was higher among women than among men, largely reflecting older age and greater multimorbidity at diagnosis. Causes of death also differed by sex, with chronic kidney disease representing the leading cause of death among women and lung cancer the leading cause among men. In multivariable analyses, older age, chronic kidney disease, malignancy, low haemoglobin and low BMI were independent predictors of mortality in both sexes, whereas smoking was associated with mortality only in men.

In summary, gout exhibits clear sex-related differences in epidemiology, clinical presentation and comorbidity burden. Men develop the disease earlier and more frequently, typically presenting with acute monoarticular flares and earlier tophus formation. By contrast, women are diagnosed later in life, often after menopause, and more frequently present with polyarticular disease, greater disease impact and a higher burden of cardiometabolic and renal comorbidities. Despite these variations in disease expression and multimorbidity profiles, therapeutic strategies remain largely similar in the sexes and women remain under-represented in clinical trials.

Future directions

Sex and gender shape the clinical trajectory of rheumatic diseases in ways that directly affect diagnostic accuracy, therapeutic effectiveness and clinical outcomes. The evidence synthesized in this Review supports the view that these dimensions are core contributors to disease biology, symptom interpretation, comorbidity development

and treatment response. Failure to account for these factors leads to delayed diagnosis, suboptimal drug selection, inappropriate risk stratification and missed treatment targets.

Persistent gaps in the characterization of sex-related and gender-related differences across clinical features and therapeutic responses (Table 3) reflect the consequences of not systematically integrating these variables into research and clinical decision-making. Closing this gap requires moving beyond descriptive epidemiology and treating sex and gender as operational variables embedded within routine clinical decision-making. This paradigm shift requires integrating sex-specific clinical patterns into early diagnostic reasoning, applying sex-informed treat-to-target strategies, refining outcome indices to prevent sex-related misclassification and recognizing multimorbidity trajectories that differ in women and men (Box 3). A life-course perspective is essential within this framework. Reproductive ageing, particularly the menopausal transition, introduces substantial hormonal changes that can influence disease activity, symptom burden and cardiometabolic risk. Integrating this dimension into routine assessment should therefore be considered a priority in sex-informed rheumatology practice.

The systematic integration of sex-informed and life-course-informed clinical reasoning into routine care requires clinical datasets that adequately capture biological and sociocultural diversity across the population. Decision-support systems, including digital and artificial intelligence-assisted tools, must be trained and

validated on representative data to minimize bias and support sex-aware diagnostic and therapeutic decisions. At the same time, operationalizing gender remains methodologically complex. Gender is a multidimensional sociocultural construct, and variables capturing gender-related behaviours, such as caregiving responsibilities, work strain or risk-taking¹⁷⁴, should be assessed using standardized and validated tools.

Ultimately, achieving precision and equity in rheumatology demands that clinicians interpret biomarkers, imaging findings, treatment responses and patient-reported outcomes through a sex-sensitive and gender-sensitive lens. Embedding these dimensions into guidelines, risk assessment algorithms and therapeutic pathways is an important step towards delivering high-quality, personalized care for all people living with rheumatic diseases.

Conclusions

Sex and gender are fundamental determinants of clinical heterogeneity across rheumatic diseases, influencing disease susceptibility, clinical expression, diagnostic pathways, treatment response and long-term outcomes. As illustrated across the disease models discussed in this Review, these dimensions function as cross-cutting modifiers of disease trajectories and should be considered core components of clinical reasoning rather than descriptive variables.

A consistent theme emerging from the available evidence is the persistent under-representation of the minority sex in clinical studies, which limits the interpretation of therapeutic effectiveness and long-term outcomes. At the same time, sex-related differences in pain perception, inflammatory biomarkers and imaging findings can influence the interpretation of disease activity indices, with potential consequences for diagnostic accuracy and treatment optimization. Differences in treatment allocation, drug persistence and safety profiles further highlight how sex can shape therapeutic pathways, whereas distinct comorbidity patterns – particularly cardiovascular, metabolic and psychosocial conditions – contribute to sex-specific risk trajectories.

Beyond biological factors, gender-related determinants, including health care-seeking behaviours, occupational exposures, caregiving roles and structural barriers to care, further modulate disease burden and functional outcomes. Despite growing awareness of these influences, sex-related and gender-related variables remain insufficiently integrated into clinical trials, registries and practice guidelines, limiting the translation of this knowledge into routine care.

Addressing these gaps requires a shift from descriptive recognition to systematic implementation. Integrating sex-disaggregated analyses into research, ensuring more representative clinical cohorts and embedding sex-aware and gender-aware considerations into guidelines and decision-support tools will be essential steps towards this goal. Ultimately, recognizing sex and gender as integral dimensions of disease heterogeneity represents not only a scientific priority but also a necessary step towards improving diagnostic precision, therapeutic effectiveness and equity in rheumatology care.

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Author contributions

M.P., M.B. and E.O. researched data for the article. M.P. and E.O. contributed substantially to discussion of content. All authors wrote the article. M.P., F.R.S., F.C., H.W., K.W.M., U.K. and E.O. reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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