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Invited Review Article

Cardiovascular phenotypes in women with Sjögren disease: hormonal, immune, and clinical perspectives

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ABSTRACT

Background: Sjögren disease (SjD) is a systemic autoimmune disorder with a marked female predominance and an increasingly recognised, although incompletely characterised, cardiovascular (CV) burden. This review examines the biological, clinical, and gender-related determinants of CV involvement in women with SjD.
Methods: We conducted a structured narrative review of PubMed/MEDLINE covering the period from January 2010 to July 2026, supplemented by backward citation searching to identify relevant earlier studies. Original SjD-specific studies were prioritised, while systematic reviews, meta-analyses, consensus statements, and evidence from related autoimmune or cardiovascular

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populations were used to provide clinical and mechanistic context. Evidence was interpreted according to study design, population specificity, and recognised methodological limitations.
Results: SjD-specific observational evidence supports an association with systemic immune activation, endothelial dysfunction, subclinical vascular injury, and selected cardiopulmonary manifestations. Sex-hormone signalling, menopausal changes, and X-linked immune mechanisms may contribute to female susceptibility, although their relationship with CV outcomes remains largely hypothetical. Evidence concerning coronary microvascular dysfunction, heart failure with preserved ejection fraction, arrhythmias, autonomic dysfunction, and pulmonary hypertension is heterogeneous and frequently derived from small cohorts or indirect evidence. In women, fatigue, dyspnoea, pain, palpitations, and autonomic symptoms may overlap with systemic manifestations of SjD and complicate recognition of concomitant CV disease.
Conclusions: Cardiovascular care in women with SjD may benefit from combining established prevention and symptom-driven diagnostic pathways with attention to interstitial lung disease, systemic organ involvement, treatment exposure, and reproductive and hormonal history. The proposed assessment framework is intended to provide practical clinical orientation and to support individualised decision-making, rather than to define a standardised SjD-specific screening pathway. Prospective, sex-disaggregated studies are needed to clarify the prognostic relevance of these factors and to inform future recommendations regarding cardiovascular assessment and follow-up.

Introduction

Cardiovascular relevance of SjD and sex- and gender-specific determinants

Sjögren disease (SjD) is a systemic autoimmune disease characterised by lymphocytic infiltration of the exocrine glands, sicca symptoms, and possible multiorgan involvement. From a cardiovascular (CV) perspective, SjD is increasingly recognised as a condition associated with endothelial dysfunction, subclinical atherosclerosis, possible coronary microvascular involvement, pulmonary hypertension (PH), and clinically overt atherosclerotic or cardiopulmonary disease, all of which may contribute to long-term morbidity.[1–3] Nevertheless, current evidence is derived predominantly from single-centre observational studies, retrospective analyses, and relatively small cohorts, limiting its generalisability across populations and geographical settings.[4]

In women, particularly during the peri- and postmenopausal period, nonspecific CV symptoms may overlap with systemic inflammation, fatigue, pain, autonomic manifestations, and cardiometabolic comorbidities, potentially contributing to delayed recognition of cardiovascular disease.[5] More broadly, sex- and gender-related differences may influence disease susceptibility, age at onset, symptom presentation, diagnostic pathways, and access to preventive or therapeutic interventions. These considerations are particularly relevant because SjD is a markedly female-predominant disease.[6]

Hormonal, immunological, and genetic factors may contribute both to the female predominance of SjD and to its cardiovascular manifestations. In particular, declining oestrogen levels during the menopausal transition may impair endothelial function, promote pro-inflammatory signalling, and adversely affect vascular and metabolic homeostasis, thereby increasing cardiovascular vulnerability in midlife and beyond.[7] However, despite the marked female predominance of SjD, cardiovascular risk assessment and management remain largely extrapolated from general cardiovascular models, with limited evidence derived from adequately powered sex-disaggregated analyses.

Among cardiopulmonary complications, PH is uncommon but clinically important, particularly when associated with interstitial lung disease (ILD). Its onset may be insidious, and symptoms such as dyspnoea, fatigue, and reduced exercise tolerance can be difficult to distinguish from other systemic manifestations of SjD.[8,9] Although women account for most reported cases because of the underlying epidemiology of SjD, some cohorts suggest that men may develop more severe extraglandular or cardiopulmonary involvement and poorer outcomes.[9–11] These observations remain preliminary and require confirmation in larger prospective studies.

In this review, the term “sex” refers to biological attributes, including chromosomes, reproductive anatomy, and hormonal pathways, whereas “gender” refers to sociocultural roles, norms, behaviours, and structural determinants that may influence symptom attribution, access to care, and clinical outcomes.[12] This review examines the biological and gender-related determinants of cardiovascular involvement in SjD, with particular attention to women, and discusses their potential implications for risk assessment, diagnosis, and clinical management. Given the limitations of the available evidence, the proposed management considerations should be interpreted as individualised, pragmatic suggestions rather than formal guideline recommendations.

Structured literature search, eligibility, and evidence appraisal

This structured narrative review focused on sex- and gender-related cardiovascular phenotypes in primary Sjögren disease. PubMed/MEDLINE was searched for English-language publications from 1 January 2010 to 30 july 2026. This interval was selected to capture the contemporary literature on SjD classification, systemic manifestations, cardiovascular phenotypes, and sex- and gender-related mechanisms. The reference lists of eligible studies, systematic reviews, and relevant consensus or guideline documents were also examined to identify additional pertinent publications, including earlier studies considered important for epidemiological,

mechanistic, or historical context. Search concepts combined terms for Sjögren disease with cardiovascular disease, endothelial or microvascular dysfunction, atherosclerosis, heart failure, arrhythmia, autonomic dysfunction, pulmonary hypertension, interstitial lung disease, sex, gender, hormones, menopause, X chromosome, quality of life, and psychosocial outcomes.

Eligible sources included adult human studies of primary SjD reporting cardiovascular outcomes, subclinical vascular or myocardial measures, cardiopulmonary manifestations, autonomic findings, sex-disaggregated results, or relevant patient-reported outcomes; directly relevant mechanistic studies; systematic reviews and meta-analyses; and consensus or guideline documents used to contextualise general cardiovascular pathways. Paediatric studies, studies focused exclusively on secondary Sjögren syndrome, and publications without direct relevance to the prespecified domains were not prioritised. Case reports were used only to contextualise rare manifestations and not to estimate prevalence or treatment effects. Evidence was appraised qualitatively according to study design, sample size, population specificity, endpoint type, consistency, and directness to women with primary SjD. No protocol registration, duplicate screening, formal risk-of-bias instrument, or certainty-grading framework was used; therefore, the methods and conclusions should not be interpreted as those of a systematic review.

Pathophysiology and sex-specific cardiovascular mechanisms in Sjögren's disease

Sex hormones across the female lifespan and cardiovascular risk

Sex hormones regulate both immune responses and cardiovascular homeostasis, providing an important biological link between the marked female predominance of SjD and its vascular manifestations. In genetically susceptible women, alterations in oestrogen, progesterone, and androgen signalling may contribute to the coexistence of autoimmune activation, endothelial dysfunction, and vascular injury.[13]

Among oestrogens, 17β-oestradiol influences humoral immunity by promoting B-cell survival and differentiation and modulating the balance among Th1, Th2, and Th17 responses.[14] These effects may contribute to autoantibody production and autoimmune susceptibility in women with SjD. Oestrogen receptors, including ERα, ERβ, and the G-protein-coupled oestrogen receptor GPER1, are expressed in immune cells, endothelial cells, vascular smooth muscle cells, and cardiomyocytes. Through these receptors, oestrogens regulate inflammation, oxidative stress, nitric oxide production, vascular tone, cellular survival, and vascular remodelling.[14,15]

The cardiovascular effects of oestrogens are nevertheless context-dependent. Reduced oestrogen activity or an altered balance among receptor-mediated pathways may impair nitric oxide bioavailability, increase the endothelial expression of adhesion molecules, including ICAM-1 and VCAM-1, and promote endothelin-1 expression and reactive oxygen species production. These changes may contribute to endothelial activation, vascular inflammation, and arterial remodelling in women with SjD.[13,14] Progesterone generally exerts anti-inflammatory and vasodilatory effects, partly by attenuating the expression of cytokines such as TNF-α and IL-6, whereas androgens have immunomodulatory, antioxidant, and vascular actions. Reduced androgen availability in women with SjD may therefore further contribute to endothelial dysfunction and increased arterial stiffness, although the available clinical evidence remains limited.[15–19]

The influence of these hormonal pathways varies across the female lifespan. During the reproductive years, cyclic fluctuations in oestrogen and progesterone may modulate endothelial function and immune activity.[20] Pregnancy represents a distinct immunoendocrine state in which autoimmune symptoms may improve in some patients because of pregnancy-related immune adaptation, whereas the rapid postpartum decline in oestrogen and progesterone may favour disease flares. Women with SjD may also experience an increased risk of adverse pregnancy outcomes, including hypertensive disorders of pregnancy and pre-eclampsia, potentially reflecting underlying endothelial vulnerability.[19]

The menopausal transition may represent a particularly relevant period of cardiovascular vulnerability. Declining endogenous oestrogen levels are associated with adverse changes in vascular function, body composition, lipid and glucose metabolism, and inflammatory activity. In women with SjD, these changes may interact with chronic autoimmune inflammation and accelerate endothelial and microvascular dysfunction. Reduced cumulative lifetime exposure to endogenous oestrogens, including earlier menopause or a shorter reproductive lifespan, has also been associated with SjD, although its direct contribution to subsequent cardiovascular events remains uncertain.[2,18] Reproductive and hormonal history may therefore provide additional clinical context when assessing cardiovascular risk, but prospective studies are needed to determine whether these variables improve risk prediction beyond conventional risk factors and SjD-related disease characteristics.

Chronic inflammation and immunovascular context in SjD

SjD is characterised by focal lymphocytic infiltration of the exocrine glands together with heterogeneous systemic immune activation. B-cell hyperactivity, anti-Ro/SSA and anti-La/SSB autoantibodies, hypergammaglobulinaemia, BAFF upregulation, and type I and type II interferon signatures identify partly overlapping biological subsets rather than a uniform inflammatory phenotype. Original studies demonstrated increased circulating and glandular BAFF expression associated with altered B-cell differentiation, as well as interferon signatures in a substantial proportion of patients. In one cohort, a type I interferon signature was detected in 55% of patients with primary SjD compared with 4.5% of healthy controls and was associated with greater biological disease activity.[21–23]

Routine laboratory findings do not provide a single reliable measure of systemic or vascular inflammation in SjD. Erythrocyte sedimentation rate may be increased, partly in association with hypergammaglobulinaemia, whereas C-reactive protein can remain within the normal range despite clinically relevant systemic disease. Disease activity should therefore be interpreted in the context of organ manifestations, ESSDAI domains, immunoglobulin levels, complement, blood counts, renal and hepatic indices, and

autoantibody profiles. However, none of these variables has been prospectively validated as a SjD-specific cardiovascular risk biomarker.[23,24]

This immune milieu may contribute to endothelial activation through interferon signalling, IL-6, BAFF-related B-cell activity, oxidative stress, and immune-complex pathways. These mechanisms provide biological plausibility for a relationship between chronic immune activation and vascular dysfunction; however, direct longitudinal evidence linking individual inflammatory pathways or biomarkers to cardiovascular events in SjD remains limited. Chronic inflammation should therefore be regarded as a potential contributor and risk modifier rather than proof of a causal cardiovascular pathway or an indication for cardiovascular-directed immunosuppression.[2,3,23,25]

Sex-specific immune, genetic, and epigenetic mechanisms in SjD

Beyond circulating hormone levels, sex-specific immune regulation may contribute to the female predominance of SjD and to its cardiovascular phenotype. Oestrogen receptor signalling interacts with transcriptional pathways such as NF-κB, AP-1, and STATs, which regulate cytokine production and inflammatory activation. In SjD, chronic elevation of IL-6, BAFF, and type I interferon pathways may lower the threshold for immune activation and amplify vascular inflammation.[23,25] Progesterone- and androgen-receptor signalling may counteract some inflammatory pathways; however, whether reduced hormone availability or receptor dysregulation materially contributes to systemic inflammation in SjD remains uncertain.[19]

MicroRNAs (miRNAs) represent an additional layer of regulation linking sex hormones, immune activation, and vascular remodelling. Oestrogen-sensitive miRNAs, including miR-146a and miR-155, have been implicated in SjD-related immune signalling and B-cell activation, whereas their direct contribution to endothelial dysfunction in SjD remains uncertain. Experimental evidence also suggests that oestradiol-dependent modulation of vascular miRNAs may influence smooth muscle cell proliferation and vascular remodelling.[26,27] Rigassi et al. demonstrated that oestradiol suppresses miR-193a in human coronary smooth muscle cells, reducing cell proliferation via PI3K/MAPK pathways and thereby providing anti-mitogenic vascular protection.[27]

Sex chromosome dosage provides a plausible additional explanation for female-biased autoimmunity. In primary human immune cells, TLR7 can escape X-chromosome inactivation in a proportion of B cells, monocytes, and plasmacytoid dendritic cells; biallelic cells show greater TLR7 expression and responsiveness. TLR8 escape has also been demonstrated in human monocytes and CD4+ T cells. These are important original observations, but they were not established specifically in women with SjD and should therefore be interpreted as a general autoimmune mechanism rather than proof of SjD-specific causality. SjD-relevant X-linked candidates also include CD40LG and BTK, while altered XIST localisation and skewed X-inactivation remain investigational. The current evidence supports biological plausibility for enhanced nucleic-acid sensing and type I interferon activation in women, but it does not establish that X-inactivation escape independently predicts cardiovascular disease in SjD.[28,29]

Epidemiology and sex- and gender-related clinical patterns

Epidemiology, age at diagnosis, and the menopausal transition

Sjögren disease shows a marked female predominance, but prevalence estimates vary substantially with case definition and ascertainment. Population-based studies reported primary SjD prevalence ranging from approximately 0.02% to 0.25%, while a Manhattan surveillance study estimated a physician-diagnosed prevalence of 13.1 per 100,000 adults and a roughly sixfold higher rate in women than men. A US geographically defined cohort estimated 2–10 cases per 10,000 inhabitants. These differences preclude a single universally applicable prevalence estimate.[24,30–35]

SjD is commonly diagnosed between 50 and 60 years of age, frequently during or after the menopausal transition. In a cohort of more than 13,000 patients, the mean age at diagnosis was 57 years in women and 60 years in men, and more than 70% of female patients were older than 50 years at diagnosis.[10] Although this distribution does not demonstrate a causal relationship with menopause, it supports a possible interaction among reproductive ageing, immune dysregulation, and the clinical emergence of SjD. Postmenopausal hormonal changes may influence both autoimmune activity and cardiovascular vulnerability, while higher autoantibody frequency and reduced dehydroepiandrosterone levels have been associated with more active disease in women older than 50 years.[6]

Age at diagnosis and menopausal status may therefore provide relevant clinical context for cardiovascular assessment. Only approximately one-third of patients present before the age of 50 years, whereas the highest disease frequency is observed during the fifth and sixth decades of life, in parallel with the endocrine and cardiometabolic changes accompanying menopause.[6,32,36] During this period, declining endogenous oestrogen levels, vascular ageing, and the increasing prevalence of hypertension, dyslipidaemia, diabetes, and adiposity may interact with chronic systemic inflammation and SjD-related organ involvement.

The peri- and postmenopausal period may consequently represent a window of increased cardiovascular vulnerability. Closer assessment of blood pressure, lipid and glucose profiles, and new exertional or cardiopulmonary symptoms may be appropriate, particularly in women with multiple cardiometabolic risk factors, extraglandular disease, interstitial lung disease (ILD), or other indicators of cardiopulmonary involvement.[17,37] However, prospective studies are required to determine whether reproductive and hormonal variables improve cardiovascular risk prediction beyond conventional risk factors and SjD-related clinical characteristics. [38]

Cardiovascular clinical patterns, diagnostic bias, and access to care

Cardiovascular involvement in SjD ranges from subclinical endothelial and microvascular abnormalities to clinically overt ischaemic, myocardial, arrhythmic, thromboembolic, and cardiopulmonary disease. Acute cardiac manifestations such as pericarditis and myocarditis are uncommon and have generally been reported in fewer than 1–2% of patients, which historically contributed to the perception that cardiac involvement was marginal in SjD.[39] Nevertheless, a systematic review and meta-analysis including more than 67,000 patients documented an increased burden of cardiovascular morbidity, including ischaemic heart disease, cerebrovascular events, heart failure, and venous thromboembolism, although no significant increase in cardiovascular mortality was observed.[40]

Traditional cardiovascular risk factors coexist with immune-inflammatory mechanisms that may promote endothelial dysfunction, arterial stiffness, and accelerated atherogenesis.[41,42] Consistent with this hypothesis, studies have demonstrated increased carotid intima–media thickness and arterial stiffness in patients with SjD compared with healthy controls, supporting the presence of subclinical vascular injury before the development of overt cardiovascular events.[43,44] Echocardiographic abnormalities, including left ventricular remodelling, diastolic dysfunction, and small pericardial effusions, have also been reported.[39,45] In addition, Raynaud phenomenon, small-vessel vasculitis, and immune-mediated endothelial dysfunction may contribute to coronary microvascular impairment and ischaemia in the absence of obstructive epicardial coronary artery disease.[41,45,46] These manifestations are examined in greater detail in Section 4.

Recognition of cardiovascular involvement may be particularly challenging in women with SjD because dyspnoea, fatigue, palpitations, pain, presyncope, and reduced exercise tolerance can overlap with systemic disease manifestations, autonomic dysfunction, or postural orthostatic tachycardia syndrome.[47–49] More broadly, cardiovascular disease has historically been perceived as predominantly affecting men, contributing to underestimation of cardiovascular risk and delayed recognition of ischaemic symptoms in women.[17,50,51] In SjD, this problem may be amplified by the clinical focus on sicca symptoms and rheumatological disease activity, allowing hypertension, dyslipidaemia, and early manifestations of vascular or myocardial involvement to receive insufficient attention during routine follow-up.[52]

Gender-related diagnostic bias may further influence symptom interpretation and clinical decision-making. Women's cardiovascular symptoms are more frequently minimised or attributed to functional, psychological, or non-cardiac causes. In patients with SjD, fatigue, musculoskeletal pain, and dysautonomia may obscure cardiac warning signs and contribute to diagnostic delay.[48,53–56] Women with myocardial infarction may also be more likely to attribute their symptoms to benign causes and delay seeking emergency care.[57,58] Similar patterns of under-recognition have been described in other female-predominant or historically underdiagnosed

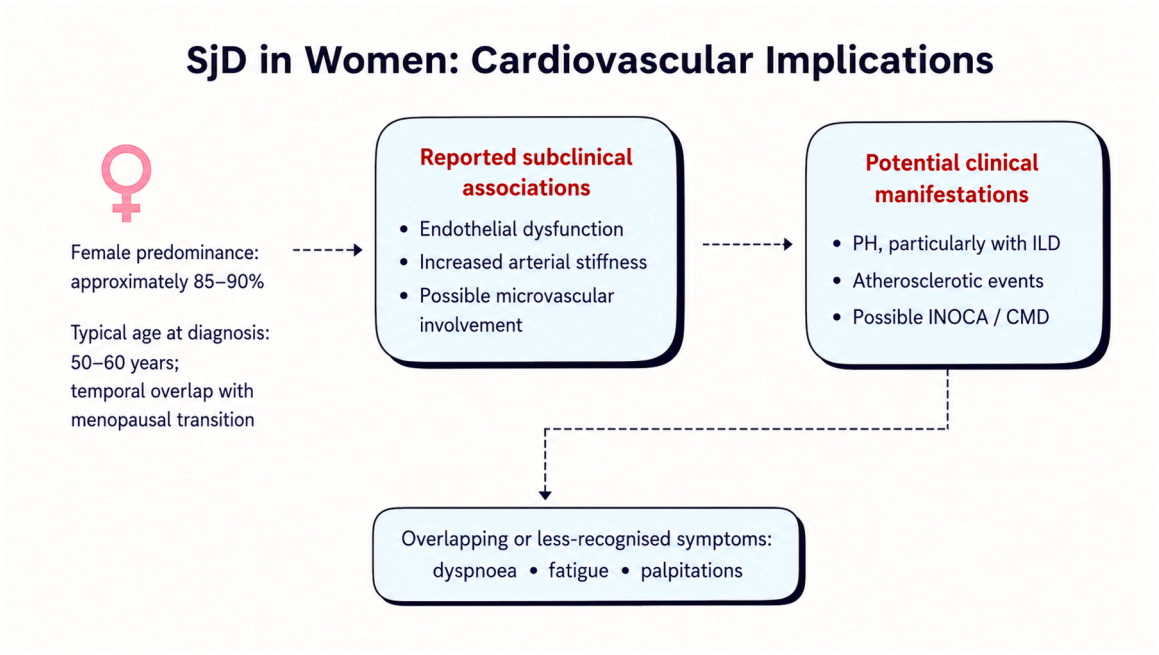


Fig. 1. Cardiovascular implications of Sjögren disease in women. Sjögren disease (SjD) predominantly affects women and is frequently diagnosed between 50 and 60 years of age, overlapping with the menopausal transition. Reported subclinical cardiovascular associations include endothelial dysfunction, increased arterial stiffness, and possible microvascular involvement. Potential clinical manifestations include pulmonary hypertension, particularly in patients with interstitial lung disease, atherosclerotic cardiovascular events, and possible ischemia with non-obstructive coronary arteries or coronary microvascular dysfunction. Dyspnoea, fatigue, and palpitations may overlap with systemic SjD symptoms and contribute to delayed cardiovascular recognition. The figure provides a conceptual overview and does not imply established causal relationships. Abbreviations: CMD, coronary microvascular dysfunction; ILD, interstitial lung disease; INOCA, ischemia with non-obstructive coronary arteries; PH, pulmonary hypertension; SjD, Sjögren disease.

conditions, including obstructive sleep apnoea, reinforcing the need for a gender-sensitive diagnostic approach.[53] Fig. 1 shows CV implications of SjD in women

Diagnostic disparities are accompanied by inequalities in testing and treatment. For a similar level of cardiovascular risk or clinical suspicion, women may undergo fewer diagnostic investigations and receive preventive therapies less frequently than men.[52] Older risk-prediction models, including the Framingham Risk Score, may underestimate cardiovascular risk in some women, whereas more recent instruments such as SCORE2 incorporate sex-specific risk estimates.[59–61] Nevertheless, conventional scores do not specifically account for SjD-related inflammation, microvascular dysfunction, autonomic manifestations, or cardiopulmonary organ involvement (Fig. 2).

Therapeutic disparities have also been documented after acute coronary syndromes, with women being less likely to undergo revascularisation or receive optimally dosed evidence-based therapies, including beta-blockers and lipid-lowering treatment.[62–65] In SjD, cardiovascular prevention should therefore address conventional risk factors while also considering systemic inflammation, ILD, possible antiphospholipid antibodies, and other disease-related risk modifiers. Antihypertensive, lipid-lowering, antiplatelet, or anticoagulant therapies should be prescribed according to established clinical indications, without sex, reproductive status, or ongoing rheumatological treatment contributing to therapeutic inertia.[65]

In patients with arterial hypertension or suspected hypertension-mediated cardiac damage, echocardiography may provide additional information on left ventricular geometry, systolic and diastolic function, and left atrial involvement, in accordance with general cardiovascular practice. This should not be interpreted as support for routine echocardiographic screening in all patients with SjD.[66]

Reducing these disparities requires greater awareness of sex-specific clinical patterns, systematic assessment of conventional and disease-related cardiovascular risk factors, and closer integration between rheumatology and cardiology. A low threshold for cardiovascular evaluation may be appropriate in patients with persistent or unexplained cardiopulmonary symptoms, particularly when these symptoms are disproportionate to rheumatological disease activity.[52,65]

Cardiovascular manifestations and therapeutic responses in women

CV manifestations in women with SjD cover a broad clinical spectrum, ranging from endothelial dysfunction and subclinical vascular injury to clinically overt ischaemic, myocardial, arrhythmic, and cardiopulmonary disease. These manifestations may reflect interactions among systemic autoimmunity, conventional risk factors, hormonal transitions, and immune–vascular mechanisms; however, dedicated sex-disaggregated evidence remains limited.[3,40,41,45]

Ischemic and microvascular disease

Meta-analytic and population-based evidence suggests an increased risk of ischaemic and cerebrovascular events in SjD, although effect estimates vary across designs and residual confounding cannot be excluded.[3,40] Coronary microvascular dysfunction and INOCA

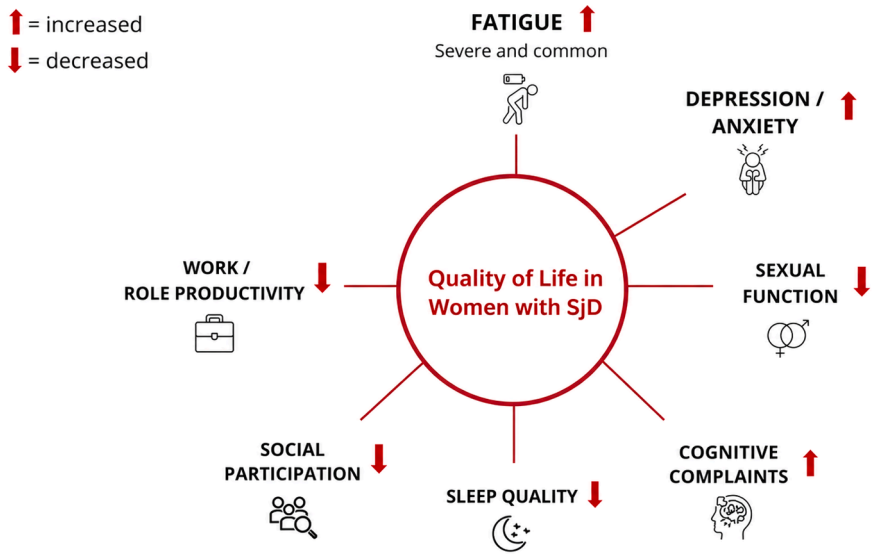


Fig. 2. Multidimensional impact of Sjögren disease on quality of life in women. Sjögren disease can adversely affect multiple dimensions of quality of life, including fatigue, psychological well-being, cognitive function, sleep quality, sexual function, social participation, and work or role productivity. Red arrows indicate the direction of change commonly reported in observational studies: upward arrows denote an increased burden, whereas downward arrows denote reduced function, participation, or quality. These interrelated domains support a patient-centred and multidisciplinary approach to assessment and management. Abbreviations: QoL, quality of life; SjD, Sjögren disease.

are biologically plausible in the setting of immune-mediated endothelial dysfunction and are common considerations in symptomatic women generally; however, direct SjD-specific coronary functional data are limited. Therefore, CMD should not be presented as the principal explanation for excess ischaemic risk in women with SjD. Persistent symptoms should instead be evaluated according to established chest-pain pathways, with coronary functional testing considered when clinically indicated.

Arrhythmias and autonomic dysfunction

Small studies and case-based literature have described QTc or repolarisation abnormalities and occasional ectopy in SjD, but their prevalence and prognostic significance are uncertain.[67] Autonomic symptoms and small-fibre neuropathy may occur, whereas direct evidence linking anti-adrenergic or anti-muscarinic antibodies to clinically important arrhythmia in SjD remains limited.[68] In patients with palpitations, presyncope/syncope, or orthostatic intolerance, standard symptom-driven evaluation—including ECG, orthostatic vital signs, ambulatory monitoring, or autonomic testing when indicated—may clarify the mechanism. These investigations are not proposed as routine screening in asymptomatic patients.

Heart failure and myocardial involvement

HFpEF is a relevant differential diagnosis in older women with dyspnoea and multimorbidity, but it has not been established as a SjD-specific "key clinical endpoint". Limited SjD echocardiographic studies report remodelling or diastolic abnormalities, with heterogeneous definitions and uncertain prognostic significance.[39,45] Chronic inflammation and microvascular dysfunction provide a mechanistic hypothesis derived largely from broader HFpEF literature.[46,69] Accordingly, natriuretic peptides and echocardiography should be used for unexplained symptoms according to general heart-failure guidance rather than for routine SjD screening. Acute myocarditis and pericarditis appear rare; evidence for treatment is based mainly on case reports and general myocarditis practice (Table 1).

Pulmonary hypertension

Pulmonary hypertension (PH) is an uncommon but clinically important complication reported in SjD, particularly with interstitial lung disease (ILD). Available estimates are heterogeneous and often originate from selected referral cohorts.[8,9] In patients with ILD or otherwise unexplained dyspnoea, exercise limitation, desaturation, or signs of right-heart strain, echocardiography is an appropriate probability-assessment tool, with definitive classification following established PH pathways.[85] SjD-specific evidence does not support routine echocardiographic screening of every asymptomatic patient. Treatment should be determined by PH group and specialist

Table 1
Sex- and gender-related clinical patterns in Sjögren disease: cardiovascular phenotype, evidence gaps, and clinical implications.

Domain	Women with SjD	Men with SjD / evidence gap	Clinical implications
Epidemiology and life course	Women represent approximately 85–90% of patients. Diagnosis commonly occurs at 50–60 years, frequently during or after the menopausal transition.[6,10,30–36]	Men represent approximately 10–15% of patients and may be diagnosed slightly later. Direct sex comparisons remain underpowered.[6,10,11]	Include age, menopausal status, and reproductive history as clinical context, without assuming a causal relationship with cardiovascular disease.
Vascular and ischaemic phenotype	Subclinical endothelial injury and increased arterial stiffness have been reported, while possible coronary microvascular involvement may contribute to ischaemia with non-obstructive coronary arteries. Symptoms may be nonspecific.[3,40–46]	Male-specific estimates are limited because of small sample sizes; comparative coronary microvascular data are particularly scarce.	Assess persistent chest pain, dyspnoea, or exercise intolerance even when obstructive coronary disease is absent.
Cardiopulmonary involvement	Most reported cases occur in women because of the female predominance of SjD. Pulmonary hypertension, particularly with interstitial lung disease, is uncommon but clinically important.[8,9]	Some cohorts suggest more severe extraglandular or cardiopulmonary involvement and poorer outcomes in men, but confirmation is needed.[9–11]	Maintain a low threshold for cardiopulmonary evaluation in patients with unexplained dyspnoea, reduced exercise tolerance, or interstitial lung disease.
Risk factors and comorbidities	Conventional cardiometabolic risk factors coexist with systemic inflammation, endothelial dysfunction, and SjD-related organ involvement.[2,4,30,38,41,45]	Traditional cardiovascular comorbidities may be proportionally more frequent in men, although absolute case numbers are small.[30]	Combine guideline-based risk-factor management with assessment of inflammation and relevant organ involvement.
Symptoms, diagnosis, and access to care	Fatigue, pain, dysautonomia, and atypical cardiovascular symptoms may complicate symptom attribution; broader sex- and gender-related diagnostic bias may contribute to delayed diagnosis and lower use of testing or preventive treatment.[47–59]	Gender-related diagnostic pathways in men with SjD are insufficiently characterised.	Use a gender-sensitive approach and avoid attributing persistent cardiovascular symptoms solely to systemic disease or psychological causes.
Psychosocial burden and quality of life	Fatigue, pain, anxiety, depression, sleep disturbance, and reduced participation contribute substantially to impaired quality of life.[70–81]	The psychosocial burden is less extensively characterised; comparative cohorts suggest a lower prevalence of depression than in women.[30]	Use validated patient-reported outcomes and psychological screening; integrate exercise and rehabilitation support when appropriate.[82–84]

Abbreviations: SjD, Sjögren disease; cardiovascular terms are written in full within the table.

assessment; evidence for pulmonary arterial hypertension-targeted therapy specifically in SjD is limited and not sex-disaggregated.

Therapeutic considerations and clinical outcomes

Menopausal hormone therapy (MHT) requires individualised consideration and should not be prescribed specifically for cardiovascular prevention. In symptomatic women younger than 60 years or within 10 years of menopause onset, the benefit–risk ratio may be favourable in the absence of contraindications after individual assessment. Cardiovascular and thrombotic risks vary according to formulation, route of administration, timing of initiation, and baseline risk.[7,86,87] Evidence specific to women with SjD remains lacking.

Associations between immunomodulatory treatments and cardiometabolic outcomes have been reported mainly in other autoimmune populations, whereas SjD-specific cardiovascular outcome data are insufficient. Hydroxychloroquine has favourable metabolic or antithrombotic associations in some autoimmune populations, while cumulative glucocorticoid exposure may adversely affect blood pressure, lipids, glucose metabolism, and adiposity. Cardiovascular benefit from rituximab, belimumab, or other B-cell-directed therapies has not been demonstrated in SjD.[2,38,65] Treatment should therefore be guided by rheumatological indications, with conventional cardiovascular risk factors monitored according to general standards.[65]

The magnitude of cardiovascular mortality and nonfatal cardiovascular burden specifically in women with SjD remains uncertain because most cohorts are not adequately sex-disaggregated. The available evidence supports vigilance rather than disease-specific universal screening. Table 2 therefore presents a pragmatic, symptom- and risk-triggered assessment framework based on general cardiovascular guidance and limited SjD evidence; it should not be interpreted as a validated algorithm or formal SIC recommendation.

Quality of life and psychosocial implications in women

Women with SjD frequently experience substantial impairment in quality of life (QoL), primarily driven by sicca symptoms, pain, fatigue, sleep disturbance, and systemic disease burden. Observational studies and meta-analyses have documented lower SF-36 scores across physical, emotional, vitality, social functioning, bodily pain, and general health domains compared with healthy controls.[70–73] Generic utility measures, such as the EQ-5D, also show significantly lower values in patients with SjD than in the general population, while disease-specific instruments such as the EULAR Sjögren's Syndrome Patient-Reported Index (ESSPRI) correlate closely with overall QoL.[72,73] Psychological distress further contributes to this burden: anxiety and depression may amplify fatigue, pain perception, sleep disturbance, and functional limitations, thereby reducing exercise tolerance and social or occupational participation.[74,75]

Women appear to experience a particularly pronounced psychosocial burden. Comparative studies indicate a higher prevalence of fibromyalgia, chronic pain, myopathies, and depression in women than in men with SjD, whereas cardiovascular comorbidities may be

Table 2
Proposed cardiovascular assessment framework for women with Sjögren disease.

Clinical setting	Suggested initial assessment	When to consider further testing	Potential referral
At SjD diagnosis or first comprehensive review	CV history and examination; blood pressure; smoking, BMI/waist, lipids, glucose/HbA1c; medication exposure; cardiopulmonary symptoms; ILD/organ involvement	ECG if symptoms, relevant drug exposure, or established CVD/risk; additional testing only when clinically indicated	Primary care/rheumatology; cardiology according to findings
Stable, asymptomatic follow-up	Reassess conventional risk factors at intervals recommended for the general population; an annual clinical review is a pragmatic option in patients with multiple risk factors or systemic organ involvement	No SjD evidence supports routine serial ECG, echocardiography, biomarkers, or vascular imaging in all patients	Risk-based prevention pathway
Chest pain or exertional symptoms	ECG and standard chest-pain/ischaemia assessment	Persistent symptoms without obstructive CAD: consider an INOCA/CMD pathway according to general guidance	Cardiology/centre with coronary functional expertise
Dyspnoea, ILD, desaturation, or right-heart signs	ECG, oxygen saturation, natriuretic peptides and echocardiography as clinically appropriate	Suspected PH: specialist work-up and definitive classification according to established PH pathways	Cardiology/pulmonology/ PH centre
Palpitations, presyncope/ syncope, orthostatic intolerance	ECG and orthostatic vital signs	Ambulatory ECG or autonomic testing when symptom pattern and initial findings justify it	Cardiology/ electrophysiology/ autonomic clinic
Possible heart failure or myocardial involvement	Natriuretic peptides, ECG and echocardiography according to symptoms/signs	CMR or other advanced testing for unresolved myocardial disease, following general guidance	Heart-failure/imaging specialist
Re-evaluation triggers	New or worsening cardiopulmonary symptoms; new ILD/organ involvement; major change in glucocorticoid exposure or cardiometabolic profile; pregnancy/menopause-related clinical change when relevant	Escalate testing according to the presenting syndrome; no fixed SjD-specific re-screening interval is validated	Multidisciplinary care as indicated

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CMD, coronary microvascular dysfunction; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; HbA1c, glycated haemoglobin; ILD, interstitial lung disease; INOCA, ischaemia with non-obstructive coronary arteries; PH, pulmonary hypertension; SjD, Sjögren disease.

proportionally more frequent among male patients.[30] Within female cohorts, physical QoL is predominantly associated with symptom and disease burden, while depression is a major determinant of mental well-being.[70,76] Consequently, QoL assessment should combine generic and disease-specific patient-reported outcomes with validated screening for anxiety and depression. In women with cardiovascular involvement, these assessments may improve symptom attribution, treatment personalization, and recovery following cardiopulmonary events.

Gender-related and socio-cultural factors may further influence clinical outcomes. Family caregiving responsibilities, delayed diagnosis, symptom underestimation, and limited social support may restrict access to care, reduce the time available for self-management, increase psychological stress, and undermine treatment adherence and participation in cardiovascular prevention or rehabilitation programmes. Conversely, supportive family, psychological, and healthcare networks may strengthen coping strategies, facilitate disease adaptation, and improve QoL.[70,77–79] Integrated rheumatology–cardiology care should therefore incorporate psychosocial assessment, therapeutic education, sleep hygiene, pacing strategies, and tailored support for women with a high symptom burden or cardiovascular involvement. This is particularly relevant because anxiety and depression may adversely affect prognosis and reduce adherence to cardiovascular rehabilitation.[78–81]

Physical activity represents an additional component of comprehensive care. Although inactivity may worsen fatigue, psychological distress, functional limitation, and cardiovascular risk, structured exercise—particularly supervised walking and aerobic programmes—has been associated with improvements in cardiorespiratory fitness, exercise tolerance, and fatigue in women with SjD.[82–84] Resistance exercise may be incorporated according to general cardiovascular and functional recommendations, but SjD-specific trial evidence is limited. Individualised exercise programmes, integrated with psychological and social support, may therefore promote long-term participation, functional recovery, and cardiovascular prevention.

Knowledge gaps and future perspectives

The current evidence base on cardiovascular risk in SjD is still dominated by observational studies, mostly single-centre or administrative-database studies, with heterogeneous endpoints and limited assessment of hard CV outcomes. This markedly limits the definition of sex-specific risk curves and truly personalised prevention strategies.[2,3,41]

Even when women represent the majority of the study population, sex- and gender-based analyses are often post hoc or purely descriptive: few studies systematically evaluate differences in clinical presentation, comorbidities, and treatment response between women and men with SjD, and even fewer incorporate this information into predictive models or clinical algorithms. Recent SjD cohorts addressing pulmonary hypertension demonstrate the feasibility of a sex-specific approach but remain limited in sample size and follow-up duration.[6,8,9]

Another key gap is the lack of prospective data linking reproductive life-course hormone exposure to autoimmune phenotype and cardiovascular burden in women with SjD, despite case–control evidence suggesting lower cumulative oestrogen exposure. [6,20]

Large longitudinal studies should include prespecified sex- and gender-based analyses, reproductive and hormonal variables, clinically meaningful cardiovascular outcomes, validated patient-reported outcomes, and mechanistic endpoints. These may include microvascular imaging and cardiopulmonary indices derived from related connective-tissue diseases, but such measures require prospective validation in SjD.[3,10,88]

Finally, the underrepresentation of women in cardiology registries and in trials on prevention, revascularization and lipid-lowering therapies, combined with documented biases in the use of procedures and drugs, makes it difficult to translate general cardiovascular evidence to women with SjD. Future studies should incorporate minimum enrolment targets, stratified analyses and dedicated strategies to overcome these disparities.[55,60]

Conclusion

Available evidence supports an association of SjD with systemic immune activation, endothelial dysfunction, subclinical vascular injury, and selected cardiopulmonary manifestations. Evidence specifically establishing excess CMD, HFpEF, arrhythmia, or PH phenotypes in women with SjD is limited, heterogeneous, and predominantly observational. The marked female predominance of SjD also makes comparisons with men imprecise.

These patterns may partly reflect endocrine–immune interactions, including menopausal hormonal changes, altered sex-hormone receptor signalling, and chronic inflammatory activation, which together may promote vascular vulnerability and shape the female cardiovascular risk trajectory.

From a clinical perspective, these considerations support a pragmatic integration of cardiovascular risk assessment into SjD follow-up, prioritizing patients with cardiopulmonary symptoms, SjD-related organ involvement (especially ILD/PH), or multiple traditional cardiovascular risk factors. In these settings, timely cardiology referral and selected use of advanced diagnostic testing may help reduce under-recognition of non-obstructive and cardiopulmonary phenotypes. Given current evidence gaps, such approaches should be individualised and validated in prospective, sex-disaggregated studies.

A personalised approach may combine hormonal variables, clinical profile, and comorbidities with psychosocial dimensions, including quality of life, anxiety and depressive symptoms, caregiving burden, and barriers to accessing care. Multidisciplinary pathways involving rheumatology, cardiology, and, when appropriate, endocrinology, supported by patient-reported outcomes, could promote more coherent risk assessment, therapeutic decision-making, and patient participation; however, their effect on cardiovascular outcomes in SjD remains to be established.

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Data availability

Data sharing is not applicable to this article, as no new data were created or analysed in this study.

Ethical statement

Not applicable. This narrative review did not involve human participants, identifiable personal data, or animal experiments.

Author contributions

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Declaration of competing interest

Authors declare no conflict of interest

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cpcardiol.2026.103481.

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