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Abstract

Health-related quality of life (HRQoL) has an increasing role in medical decision-making. This review of the literature aims to provide an overview on HRQoL, costs, and work disability in Sjögren's syndrome (SS), a disease characterized by focal lymphocytic infiltration of exocrine glands with no therapeutics of proven immunomodulatory potential. HRQoL is markedly reduced in SS in multiple studies across many countries when compared with healthy controls. The reduction in HRQoL is similar to that observed in other chronic diseases such as rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia and, interestingly, non-SS sicca syndrome. Impaired HRQoL in SS has been found to be associated with fatigue, pain/articular involvement, ocular and oral involvement, pruritus, sexual dysfunction, impaired sleep, pulmonary manifestations, psychological dysfunction and impaired physical function. Until now no therapeutic has been shown to improve HRQoL in an adequately powered double-blind, placebo-controlled randomized controlled trial. Although pSS does not, in general, impair life expectancy and is often inappropriately considered a benign 'nuisance' disease for those patients without systemic manifestations, the associated costs and work disability are striking. This, together with the significant reduction in HRQoL, strongly argues for the development of new therapeutic approaches to manage this neglected disease.

Key words

Sjögren's syndrome, quality of life, health-related quality of life, cost, work disability, SF-36, EQ-5D

Key Messages

- SS is associated with a similar reduction in HRQoL when compared with other systemic autoimmune diseases
- Pharmacological treatments have so far failed to demonstrate improved HRQoL in SS
- SS is associated with substantial direct and indirect costs

INTRODUCTION

Health has been defined as a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity. Health-related quality of life (HRQoL) is a closely-related concept with varying definitions including how an individual functions and their perceived well-being in relation to these physical, mental and social domains, and also as the impact of all health-related factors upon an individual's life(1). Increasing emphasis is being placed on HRQoL in medical decision making as data on mortality and biological functioning inadequately capture the potential merits or demerits of therapeutic interventions. HRQoL data can also be used to judge the relative value of interventions across different diseases and so facilitate cost-effective allocation of healthcare resources.

Sjögren's syndrome (SS) is characterized by focal lymphocytic infiltration of exocrine glands leading to profound dryness. It is associated with high levels of fatigue and with systemic manifestations, but not with a general increase in all-cause mortality(2). SS has been divided into primary (pSS) or secondary (sSS) better termed 'associated with', according the absence or presence of another defined connective tissue disease such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or systemic sclerosis. Although this distinction may be arbitrary, most research studies have focused on pSS, to avoid the perceived complexities of studying multiple systemic diseases simultaneously. SS is an area of large unmet medical need with no interventions of proven immunomodulatory potential. Determining HRQoL for SS, as well as the direct and indirect costs of disease, are vital to encourage drug development, to provide a rationale for regulators and funders to license and approve any resulting therapies, and to justify the set-up of specialist multidisciplinary clinics to optimize care for patients with SS.

This review of the literature aims to provide an overview on HRQoL, costs, and work disability in Sjögren's syndrome (SS).

METHODOLOGY The following databases were searched: Medline, PubMed, LILACS and Web of Science; and thespecific terms used were: 'Sjögren's syndrome' AND 'quality of life', 'health-related quality of life', 'health status measurement', 'subjective health status', 'quality of life questionnaire', 'cost', cost-effectiveness', 'economic', 'health economics' and 'work disability'. Limitations imposed were publications relating to adults, in the English, Spanish or Portuguese language and published since 2000 until 2018. Validation studies of assessment instruments were not included.

All retrieved references were screened on the basis of title and abstract for possible inclusion. Full articles were retrieved for assessment if the abstract fulfilled the following criteria: (a) it was indicated that quality of life, costs or work disability were assessed; and (b) the sample included SS patients. Studies found on HRQoL were observational (qualitative and quantitative), interventional (controlled and uncontrolled trials), and reviews (systematic and meta-analysis). The majority of studies relating to costs were observational. To give a comprehensive overview of the available literature, this review reports data from all methodologies. We first report the HRQoL studies (observational qualitative, observational quantitative and interventional), followed by studies of costs. The quantitative observational studies on HRQoL were categorized according to the individual SS symptom domains that were identified in the systematic literature search.

In total 297 articles were found, of which 74 fulfilled the inclusion criteria of the review. The most common reasons for exclusion were not reporting on Sjögren's syndrome, costs, work disability, or measures of quality of life (Figure 1).

HEALTH-RELATED QUALITY OF LIFE IN SS

Observational qualitative studies

Lackner et al reported that whilst most 'concepts' affecting quality of life were related to the physical domain, these impacted upon the psychological/emotional and social domains because of a perceived lack of understanding by relatives as well as difficulties at work, limitation of nutrition and impaired social life. Notably, physical domain concepts included some symptoms not routinely assessed by clinicians. Many patients felt dependent upon relatives as, for example, they were unable to drive a car due to the effects or ocular dryness and had difficulty with housework due to pain. Difficulties with computer use and long conversation brought additional challenges to working(3). In another qualitative study patients reported their quality of life was affected by the long journey to diagnosis, the quality of interaction with healthcare professionals, the complex variety of disease manifestations and their ability to cope positively with chronic disease(4). Other qualitative studies show that fatigue in SS is complex and includes not only standard physical and cognitive components but also ocular fatigue, with Stack et al showing an interrelationship between ocular symptoms and fatigue(5).

Observational quantitative studies

The two most commonly used generic measures of HRQoL are the Short-Form Health Survey (SF-36) and the EQ-5D (Figure 2).

However, HRQoL was reduced in pSS patients in all studies reviewed regardless of the tool used (Table 1).

PSS patients from Sweden(6), Spain(7), Netherlands(8,9), United States(10,11), Turkey(12,13), United Kingdom(14), Korea(15), China(16), Italy(17,18) and Brazil(19) have significantly lower HRQoL when compared with healthy controls or with normative data of the general population (Figure 3).

Belenguer et al showed that patients with extraglandular involvement had lower SF-36 scores for the vitality, social functioning, bodily pain and general health scales than those without, and there was a significant correlation between age and physical functioning and bodily pain scales(7). Meijer et al concluded that predictors for reduced HRQoL were fatigue, tendomyalgia, articular involvement, use of artificial saliva, use of anti-depressants, comorbidity, male sex and eligibility for disability compensation(8). Segal et al demonstrated that pain severity and depression were the only unique predictors of emotional well-being, and physical functioning was predicted by age, pain severity and somatic fatigue(10). Lendrem et al also found that pain and depression were the key determinants of EQ-5D utility values(14) while the European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Outcome (ESSPRI), which assesses dryness, pain and fatigue, was the only independent predictor of the HRQoL on a multiple regression analysis in a Korean cohort(15).

The meta-analysis of Zhang et al showed that patients with pSS had a lower score on each SF-36 scale when compared with healthy controls, with the largest difference seen in the Role Physical. The mean difference in Physical Component Summary (PCS) was −12.34 (95% CI: −18.42, −6.26) and Mental Component Summary (MCS) was −6.18 (95% CI: −9.58, −2.78)(20).

Interestingly, although HRQoL is reduced in pSS patients when compared with healthy controls, no difference is seen when compared with non-SS sicca patients(21–23). In Champey et al the only SF-36 subscale to show any statistically significant difference between these groups was general health, which was significantly lower for patients with pSS. However, it is possible that the determinants of poor HRQoL may be different, with depression and ESSPRI being major determinants of HRQoL in pSS patients in one study, whereas anxiety and xerostomia significantly correlated with HRQoL in non-SS sicca patients (21).

The decrease in HRQoL associated with pSS is also similar to RA(24,25), fibromyalgia(24) and SLE(25). However, Strömbeck et al found pSS to have higher (i.e. better) physical function SF-36 scores than the RA and fibromyalgia patients while most psychological domains were comparable(24) and whilst Hyphantis et al showed lower scores on physical and social relations domains of the World Health Organisation Quality of Life Instrument Short Form (WHOQOL-BREF) in pSS than SLE patients, these differences seemed to be weakened after controlling for age and education(26). Furthermore, Kotsis et al reported that worries about the consequences of illness was a stronger correlate of physical HRQoL than pain in pSS(25).

HRQoL and systemic disease activity in pSS

Baturone et al. showed higher concentrations of IL-6 were associated with lower values of PCS, suggesting that this could be explained by the pro-inflammatory effects of this cytokine and its role in the pathophysiology of pain(27).

Cornec et al reported that SF-36 MCS scores were similar in low, moderate and high ESSDAI activity groups, whereas PCS scores were significantly lower in patients with moderate and high systemic activity. Multivariate analyses indicated that this observation was explained by the more intense symptoms seen in the moderate and high disease activity groups(28). Regarding the ESSDAI domains Lendrem et al showed a negative correlation between the articular domain and an unexpected positive correlation between the biological domain of the ESSDAI and HRQoL(29).

The extraglandular systemic manifestation that had the greatest impact on HRQoL in the study by Belenguer et al was pulmonary involvement, predominantly associated with reduction in the physical scales(7). Palm et al also found that pSS patients with lung disease had a reduction in SF-36 physical function, which remained statistically significant after adjusting for age at diagnosis, gender and current smoking status(30).

HRQoL in studies of individual SS symptom domains

Fatigue and pain

Fatigue is negatively correlated with HRQoL in pSS(31) and with both lower PCS(16,23) and MCS scores(16). Pain is also associated with lower PCS scores (16,23) Champey et al failed to find associations between dryness symptoms, when measured by a simple visual analogue scale, and HRQoL(23). In a small Moroccan

study, levels of both fatigue and HRQoL were adversely associated with joint involvement, xerostomia and educational and socioeconomic levels, and beneficially with use of Methotrexate and antidepressants(32). Studies of fatigue over time show this to remain stable alongside an expected age-related decline in SF-36(33), although one study found an improvement in vitality that might have been due to patients acquiring effective coping strategies(6).

Ocular disorders

As dry eye symptoms increase, more aspects of life are affected on a clinically meaningful level, including perceptions of health, physical functioning, social functioning, and role-emotional limitations. However, mental health appears unaffected by dry eye symptoms, regardless of severity level(34).

Zhang et al used the NEI-VFQ to evaluate vision-related quality of life (VR-QoL)(35), and found more severe corneal epithelial damage and lower VR-QoL in women with SS compared with dry eye due to other causes, especially in the domains of general health, general vision and long-distance vision activities. Lower VR-QoL in SS negatively correlated with levels of anxiety and depression(36).

Oral disorders

The Oral Health Impact Profile (OHIP) has been used to assess oral health-related quality of life (OHRQoL)(37) in patients with SS. The tool measures aspects of quality of life directly related to oral health and function independent of the other problems associated with SS. Many studies have indicated that oral health and function have an independent influence on general quality of life in these patients, demonstrating that dentists and physicians must work collaboratively(38).

Patients with pSS have lower scores for both oral and general quality of life when compared with healthy controls. However, both pSS and xerostomia patients have lower mean scores across all 8 domains of the SF-36 when compared with normative community data(39).

Xerostomia and hyposalivation have a considerable negative impact upon activities of daily living and social relationships(38), and lower salivary flow rates correlate with poorer oral health. Although lower salivary flow rates were also associated with more numerous autoimmune symptoms in a small study of 39 pSS patients, oral health was an independent predictor of HRQoL in multivariate analysis showing this has a

significant effect on patients' perceptions of their overall health and well-being beyond any effects attributable to other symptoms or damage associated with the disease (40). Poorer OHRQoL in patients with pSS is associated with dysgeusia, burning sensations in the tongue, and halitosis(41). Indeed, 70% of pSS patients in one study had clinical hypogeusia, uninfluenced by age, and taste threshold was significantly correlated with both the physical and the mental components of SF-12(42).

The role emotional was the SF-36 domain most strongly associated with oral distress in the study by Enger et al, suggesting that oral distress greatly impacts patients' confidence and self-esteem in social, role dependent, and emotional relationships(43).

Lower scores on the MD Anderson Dysphagia Inventory (MDADI), a specific questionnaire for swallowing function and quality of life(44), have been shown in patients with SS(45,46). Pierce et al demonstrated that swallowing disorders in SS produced mild to moderate reductions in swallowing-related quality of life. Food sticking in throat was a predictive factor for SF-36 PCS scores, whilst difficulty swallowing medication, wheezing while eating, and mucous/phlegm were independent predictors for MCS. However, only 27 of the 64 participants(42%) who reported a current swallowing disorder had ever sought professional help for this(45).

Patients with SS who reported a voice disorder, such as frequent throat-clearing, throat soreness, difficulty projecting, and vocal discomfort, experienced a greater burden on general quality of life as compared to those without voice disorders. However, a regression analysis showed that only frequent throat clearing was associated with PCS, and vocal discomfort with MCS. Despite the added burden of a voice disorder on quality of life in SS, voice-related treatment seeking was low (15.8%) The majority of patients who received voice treatment reported improvement(47).

Pruritus

In a cross-sectional study of 19 pSS patients, 53% reported chronic itch, with the shins, backs and forearms being most affected(48). The ItchyQoL evaluates how itch affects quality of life by analyzing 3 domains: symptoms, functional limitations, and emotions relating to itch(49). The emotional domain was the most impaired, with the poorest scores being "aggravated by temperature or seasonal changes" and "need to scratch"(48).

Sexual disorders

Vaginal dryness is common in pSS and patients report a poorer quality of sexual life(9,18). Priori et al found a lower scores on the Female Sexual Function Index (FSFI) in both pre- and post-menopausal women with pSS compared with healthy controls with the affected domains being pain, lubrication, desire, and arousal. Anxiety levels were inversely correlated with sexual function but causality was not tested. Interestingly, no correlation was observed between FSFI and SF-36, disease duration, ESSDAI and damage indexes(18). On the contrary, Van Nimwegen et al found a significant correlation between FSFI scores and lower mental quality of life (RAND-36 item Health Survey), patient-reported symptoms (ESSPRI), fatigue, depressive symptoms and relationship dissatisfaction, but also not with ESSDAI. They also showed that pSS patients experienced more sexual distress and were sexually active less frequently than controls(9). Exclusion of patients not having sexual intercourse in these studies may lead to underestimation of the effects of pSS on sexual function and HRQoL. Indeed, sexual activity is lower in pSS compared with healthy controls with 83% of patients reporting a reduction in frequency since disease onset(17). Notably, PCS scores were lower in pSS patients not having a sexual relationship and not feeling pleasure during sexual activity(17)

Sleep disorders

Compared to healthy controls, patients with pSS have a significant reduction in global sleep quality as well as changes in perceived sleep quality, daily disturbances and sleep efficiency. Poor sleep quality correlates with physical and mental domains of the SF-36 and mood disturbances(50). Lendrem et al also demonstrated that daytime sleepiness correlates with reduced quality of life(14).

Autonomic dysfunction

Two studies found patients with pSS to have significant autonomic dysfunction compared to healthy controls(51,52) and patients with primary biliary cirrhosis (PBC) (51). They also experienced increased heart rate at rest associated with greater fatigue and poorer HRQoL as measured by EQ-5D VAS(51).

Psychological disorders

Higher levels of anxiety and depression in pSS patients are associated with lower HRQoL(10,12–14,16,21). In a large study of emotion processing and regulation in

patients with pSS and representative population controls, pSS was associated with worse mental well-being (RAND-36), the levels of which correlated with high affect intensity (the strength with which emotions are experienced) and alexithymia (specifically difficulty identifying feelings) in both groups. Only clinical alexithymia was more common in pSS (22% vs 12%)(53). Hyphantis et al found that general psychological distress was higher in pSS compared with SLE and healthy controls, and correlated with HRQoL (WHOQOL-BREF). PSS patients had more symptoms of interpersonal sensitivity than SLE patients, and less use of humour defense and more help-rejecting complaints and delusional guilt compared to both SLE and healthy participants. Less use of humour and more delusional guilt were associated with physical HRQoL independent of psychological distress. These results indicate that pSS patients may exhibit some difficulties in adaptation to life stressors and in interpersonal relationships, suggesting that early recognition and treatment of psychological distress might improve HRQoL(26).

Symptoms of cognitive dysfunction, reflected by impaired memory and concentration, were reported by 60% of pSS patients using the Gothenburg Quality of Life instrument(54). Although such symptoms have been reported in a number of studies, Epstein et al were unable to find objective evidence of a reduction in cognition, psychomotor function or memory when compared with controls(19).

Interestingly, in the large Sjögren's International Collaborative Clinical Alliance (SICCA) registry pSS patients had better PCS and MCS and a lower adjusted odds of depression ($p<0.001$, OR 0.67, 95% CI 0.55 to 0.81) when compared with non-SS patients with symptomatic dryness. The authors suggest that having a definitive diagnosis allows a patient a better understanding of their disease and to develop coping mechanisms(55), although it is also plausible that depression-related comorbidities or treatments may themselves be associated with dryness symptoms

Physical function impairments

Self-reported physical function using the Improved Health Assessment Questionnaire (HAQ) is strongly associated with symptoms (pain, fatigue, and depression), disease activity and reduced HRQoL as measured by the EQ-5D, although this may be expected given that mobility is also an EQ-5D domain(56). Furthermore, another study from the same cohort showed that the total physical activity score of the International Physical Activity Questionnaire-short form (IPAQ-SF) showed a weak inverse correlation with the EQ-5D ($r = -0.200$) implying that less physical activity was

associated with better HRQoL, although this did not retain statistical significance on multivariate analysis(57). However, when compared with a healthy control group with similar habitual physical activity levels measured objectively by accelerometry, pSS patients showed reduced aerobic capacity (VO_{2peak}), muscle strength and physical function. Timed up and go test scores correlated negatively with multiple SF-36 domains(19).

Interventional studies

Two uncontrolled studies demonstrated that HRQoL improved following rituximab and corticosteroid in patients with either mucosa-associated lymphoid tissue (MALT) lymphoma or recent-onset pSS without lymphoma(58), and also with rituximab infusions in the absence of corticosteroid(59,60). One phase 2 randomized controlled trial (RCT) reported improvements in MCS following rituximab whereas patients who received placebo had deterioration(61), whilst another showed statistically significant improvement in the SF-36 vitality domain from baseline to week 36(62). However, two phase 3 RCTs of rituximab compared to placebo failed to show statistically significant improvements in their primary outcomes based upon symptoms or in SF-36 scores(63,64).

Abatacept treatment in an uncontrolled pilot study was demonstrated to be effective, safe and well tolerated, and resulted in improved disease activity, laboratory parameters, fatigue and HRQoL (SF-36 vitality, social functioning and mental health domains) in 15 patients with early and active pSS(65). The results of phase 3 abatacept studies are awaited.

Although the muscarinic agonist cevimeline improved symptoms of xerostomia in Chinese patients with SS, there was no improvement in salivary flow rates, dry eye symptoms or HRQoL(66). A pilot study of low-dose cyclosporine A in pSS patients with articular involvement found a reduction in the number of tender and/or swollen joints and improvement of disease activity measured by DAS28, but not in HRQoL(67).

In regard to non-pharmacological treatments, a Chinese herbal medicine said to strengthen qi, nourish yin, and remove stasis, given in combination with hydroxychloroquine, improved total SF-36 scores and all subscales except social function, when compared with hydroxychloroquine alone(68), however there was no placebo control. Aerobic exercise in the form of Nordic walking improved aerobic capacity and fatigue VAS over 12 weeks when compared to a control group but SF-36 scores did not change, although the number of participants was small(69).

A systematic review showed an improvement in quality of life of patients with partial or total edentulous SS who were rehabilitated through dental implants(70). The masticatory function, oral comfort and satisfaction were evaluated after implants in three studies(71–73) through completed questionnaires.

Primary Sjögren's Syndrome Quality of Life questionnaire

Recently, the pSS Quality of Life questionnaire (PSS-QoL) was developed. This is the first specific tool for the assessment of patients' HRQoL in pSS. PSS-QoL consists of 25 questions and can be divided into two main categories: physical (discomfort and dryness) and psychosocial. The internal consistency of the PSS-QoL revealed a Crohnbach's α of 0.892. Strong and moderate correlations were found between the PSS-QoL and ESSPRI (r=0.755) and EQ5D-pain/discomfort (r=0.531). Reproducibility of the PSS-QoL was high, yielding an ICC of 0.958 (95% CI 0.926 to 0.981). (74). There are some potential limitations however. In particular many of the patients evaluating the questionnaire appeared to have had relatively mild disease. Therefore there is a case for not only assessing sensitivity to change as the authors suggest, but also refining and validating the tool in a larger number of patients from different countries and with a wider range of disease manifestations and activity.

COSTS IN SS PATIENTS

Direct costs are related to the value of resources used in diagnosis, treatment, and rehabilitation, and the mean annual total direct cost per pSS patient in the United Kingdom was calculated to be 81% of those of RA at 2004-2005 prices, before the widespread introduction of biologics for RA. The SF-36 physical function subscale was the best predictor of costs in pSS patients as well as controls, and the mental health subscale in RA patients(75). The estimated total annual indirect costs, which include value of economic productivity lost due to the disease, including both labor and other activities such as housework and childcare, were £7677 (95% CI: £5560, £9794) for pSS, £10,444 (95% CI: £8206, £12,681) for RA, and £892 (95% CI: £307, £1478) for controls. Using a model that maximizes the estimates, the equivalent figures were £13,502 (£9542, £17,463), £17,070 (£13,112, £21,028), and £3382 (£2187, £4578), respectively(76).

Segal et al in 2009 also showed that health care utilization was higher in patients than controls in a 5 year retrospective analysis, including out of pocket dental expenses (mean: pSS = $1473.3, controls = $503.6), dental visits (mean: pSS = 4.0, controls =

2.3), current treatments (mean: pSS = 6.6, controls = 2.5), and hospitalizations (53% pSS, vs. 40% controls)(10). Similarly to the UK study, pSS patients were less likely to be in employment due to disability. Fox et al also demonstrated increased oral health care costs and reduced employment in pSS, with an annual out-of-pocket dental care spending two to three times higher than controls. Patients also reported a significantly greater number of dental visits, more decayed teeth and more dental restorations in the preceding year(77).

In a more recent US study, all-cause health care costs were 40% higher for patients in the 12 months after diagnosis when compared with 12 months before with costs averaging U$20,416 per patient. Outpatient visits were required by nearly 100% of SS patients to various providers, averaging nearly 4 visits per patient in a 1-year period(78).

In Germany, the prevalence of physician visits for pSS patients is higher and gainful employment lower for pSS patients compared with controls and these findings were associated with depression, fatigue and lack of stamina(79).

By linking data from a Sjögren's register with that from the Swedish Social Insurance Agency, Mandl et al were able to show that work disability increased significantly during the first 2 years after diagnosis of pSS, initially driven by an increase in sick leave and subsequently by an increase in patients receiving a disability pension. At diagnosis, 26% of patients were work-disabled, while 37% and 41% were disabled at 12 and 24 months after diagnosis, respectively. Work disability at diagnosis, concomitant fibromyalgia, and increasing age were associated with work disability after 24 months(80).

Similarly, a significantly higher percentage of SS patients received disease compensation (47%) when compared with the general Dutch population (2%). Patients were less often employed, worked fewer hours and were less frequently full time employed. No differences were found between pSS and sSS patients regarding employment variables and disease compensation. A high level of education was associated with a greater likelihood of being in work, whereas the opposite was true for bladder involvement, use of oral moisturising gel, NSAIDs and oral corticosteroids, comorbidity and older age at diagnosis. Receipt of disease compensation was associated with a higher number of extraglandular manifestations, use of artificial saliva and anti-malarial drugs, comorbidity, high level of education, male sex and younger age at diagnosis(8).

In East China, medical expenses for the treatment of SS dry eye (SSDE) leads to a heavy economic burden on both patients themselves and the health-care system, with an annual total expenditure on the treatment of SSDE of Chinese Yuan 7637.2 (approximately US$1173.8) and the expense paid by SSDE patients themselves of Chinese Yuan 2627.8 (approximately US$403.9), which is 5.5 and 4.5 times higher than non-SSDE patients. The medical expense had a significant correlation with psychological status in SSDE patients(81).

Regarding rituximab, the results of the UK TRACTISS study found this to be neither clinically nor therefore cost-effective for the management of pSS(63).

CONCLUSION

PSS patients have significantly decreased HRQoL on a par with other chronic inflammatory diseases such as RA. Impaired HRQoL has been associated not only with the main symptoms, such as dryness, pain and fatigue, but also with autonomic response, physical function and activity level, pruritus and psychological, oral, ocular, sexual and sleep disorders. However most studies have not comprehensively evaluated all these domains, meaning that some reported associations may be due to confounding e.g. taste associations may theoretically be due to a reduction in salivary flow. Studies that have focused upon oral and ocular involvement have found these to have had a significant impact upon HRQoL. However a number of other more general studies which have used multivariate analysis have found that dryness is less predictive of HRQoL than pain or fatigue. It is possible this may reflect an inadequacy of single VAS scales, as often used in these studies, to capture the breadth and impact of oral and ocular involvement, which might require more comprehensive tools. Another limitation of the studies reviewed is that studies have included only a small number of patients which may impact upon their reliability and the extent to which their findings may be generalized. More longitudinal data is also desirable, as most studies are cross-sectional and unable to dissect cause and effect, as for example in the relationship of psychological disorders and impaired HRQoL in pSS. In general little association was observed between systemic disease activity, as measured by ESSDAI, and HRQoL, despite ESSDAI being the commonest primary outcome in current clinical trials. However, pulmonary involvement does appear to be associated with impairment in HRQoL. Interestingly, the extent of HRQoL impairment in pSS does not seem to differ from non-SS sicca syndrome, and more work is required to understand how the predictors differ between these two syndromes, and indeed to understand the varying

pathologies underlying non-SS sicca. Studies of HRQoL have tended to use generic measures such as SF-36 and EQ-5D. The advantage of these tools is that they are well understood and allow comparison across diseases. Yet the complex multifaceted nature of SS symptomatology does argue the need for a disease-specific tool such as the PSS-QoL(74) and more work in this direction is warranted, and in particular to ensure we have tools that are sensitive to change.

Although pSS does not, in general, impair life expectancy and is often inappropriately considered a benign 'nuisance' disease, the costs and work disability associated with it, as assessed across multiple countries and continents, is striking. This, together with the significant reduction in HRQoL, strongly argues for the development of new therapeutic approaches to manage this neglected disease.

Conflicts of interest

BAF has received consultancy fees from Novartis, Roche, Medimmune and BMS.

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Table 1. Observational studies on health-related quality of life (HRQoL) in Sjögren's syndrome (SS).

Study	Country	Participants	HRQoL	Main results
pSS patients vs. healthy control (HC) or general population (GP)				
Theander et al, 2005 (6)	Sweeden	58 pSS, GP	SF-36	pSS patients have lower HRQoL than HC or GP
Belenguer et al, 2005 (7)	Spain	110 pSS, GP	SF-36	
Meijer et al, 2009 (8)	Netherlands	154 pSS, 41 sSS, GP	SF-36	
Segal et al, 2009 (10)	United States	277 pSS, 606 HC	SF-36	
Inal et al 2010 (12)	Turkey	107 pSS,109 HC	SF-36 WHOQOL-BREF	
Bongi et al, 2013 (17)	Italy	62 pSS, 33 sicca syndrome, 50 HC	SF-36	
Epstein et al, 2014 (11)	United States	37 pSS, 37 HC	SF-36	
Lendrem et al, 2014 (14)	United Kingdom	639 pSS, GP	EQ-5D	
Priori et al, 2015 (18)	Italy	24 pSS, 24 HC	SF-36	
Van Nimwegen et al, 2015 (9)	Netherlands	46 pSS, 43 HC	RAND-36	
Koçer et al, 2016 (13)	Turkey	32 pSS, 19 HC	SF-36 EQ-5D	
Lee et al 2016 (15)	Korea	178 pSS, GP	EQ-5D	
Liu et al, 2017 (16)	China	304 pSS, GP	SF-36	
Dassouki et al, 2017 (19)	Brazil	29 pSS, 20 HC	SF-36	
pSS vs. non-Sjögren sicca patients or other diseases				
Champey et al, 2006 (23)	France	111 pSS, 65 SAPS, GP	SF-36	HRQoL is reduced in pSS patients and non-SS sicca patients.
Cho et al, 2013 (21)	Korea	104 pSS, 42 non-SS sicca	SF-36	
Milin et al, 2016 (22)	France	55 pSS, 40 non-SS sicca	SF-36	
Strömbeck et al, 2000 (24)	Sweden	42 pSS, 59 RA, 44 fibromyalgia,	SF-36	The pSS group scored higher than the RA and fibromyalgia patients in physical function scale while in most psychological domains were

		GP		comparable.
Kotsis et al, 2014 (25)	Greece	57 pSS, 75 SLE, 199 RA	WHOQOL -BREF	pSS patients' worries about the consequences of their illness was a stronger correlate of physical HRQoL than pain.
Hyphantis et al, 2011 (26)	Greece	40 pSS, 56 SLE, 80 HC	WHOQOL -BREF	Physical and social relations are lower in pSS than SLE patients, but these differences seem to be weakened after controlling for age and education.
HRQoL and systemic disease activity				
Baturone et al, 2009 (27)	Spain	30 pSS	SF-36	pSS patients with the higher concentration of IL- 6 have a significantly lower value in PCS than those with a lower concentration.
Lendrem et al, 2015 (29)	United Kingdom	639 pSS	EQ-5D	There is a negative correlation between the articular domain and a positive correlation between the biological domain of the ESSDAI and HRQoL.
Cornec et al, 2017 (28)	France	120pSS (active)	SF-36	MCS scores is similar in low, moderate and high ESSDAI activity groups, whereas PCS score is significantly lower in patients with moderate and high systemic activity.
Belenguer et al, 2005 (7)	Spain	110 pSS , GP	SF-36	Pulmonary involvement is the extraglandular systemic manifestation that has the greatest impact on the HRQoL.
Palm et al, 2013 (30)	Norway	117 pSS	SF-36	Patients with lung disease have reduced physical function HRQoL.
HRQoL and fatigue and pain				
Theander et al, 2005 (6)	Sweden	58 pSS	SF-36	Fatigue remained stable over 5 years, however there is an age related in decline most SF-36 scores and an improvement in vitality score.
Haldorsen et al, 2011 (33)	Norway	141 pSS	SF-36	Fatigue did not change and SF-36 vitality showed a weak but not clinically significant worsening in 5 years.
Champey et al, 2006 (23)	France	111 pSS, 65 SAPS, GP	SF-36	Fatigue and pain, but not dryness, were correlated with HRQoL.
Yacoub et al, 2012 (32)	Morocco	57 pSS	SF-36	Severe fatigue and reduced HRQoL seemed to be related to the severity of joint involvement, xerostomia, treatment with methotrexate and antidepressant and both educational and socioeconomic levels.
Koh et al, 2017 (31)	South Korea	257 pSS	EQ-5D	Fatigue is negatively correlated with HRQoL and significantly lower in patients with a ESSPRI fatigue score > 5.
Liu et al, 2017 (16)	China	304 pSS	SF-36	Pain and fatigue are primary factors for lower HRQoL.

HRQoL and ocular disorders				
Mertzanis et al, 2005 (34)	United States	130 non- KCS, 32 SS, 48 HC	SF-36	As dry eye symptoms become more severe, more aspects of HRQoL with exception of mental health, are affected.
Zhang et al, 2016 (36)	China	22pSS, 8 sSS, 30 HC	NEI-VFQ	SS patients have lower vision related quality of life than HC, especially in general health, general vision and long-distance vision activities.
HRQoL and oral disorders				
Rostron et al, 2002 (39)	United Kingdom	43 pSS , 40 xerostomia	SF-36	pSS and xerostomia patients have lower mean scores across all 8 domains of SF-36 compared with normative community data.
Stewart et al, 2008 (40)	United States	39 pSS	SF-36 OHIP-14	A poor oral health associated with xerostomia has a significant effect on patients' perceptions of their overall health and well-being.
Kamel et al, 2009 (42)	United Kingdom	28 SS, 37 HC	SF-12	Taste threshold is significantly correlated with both the physical and the mental components.
Enger et l, 2011 (43)	Norway	177 pSS	SF-36 OHIP-14	Patients with high levels of oral distress scored significantly lower than patients with low levels of oral distress on general HRQoL.
Tanner et al, 2015 (47)	United States	101 SS	SF-36	Only frequent throat clearing is associated with PCS, and discomfort while using voice is associated with MCS.
Pierce et al, 2016 (45)	United States	101 SS	SF-36 MDADI	Swallowing disorders in SS produce mild to moderate reductions in swallowing-related quality of life.
Eyigör et al, 2017 (46)	Turkey	69 SS, 40 HC	MDADI	Swallowing dysfunction reduce the quality of life in patients with SS.
Rusthen et al, 2017 (41)	Norway	31 pSS and 33 HC	OHIP-14	A poorer OHRQoL is positively correlated with dysgeusia, burning sensations of the tongue and halitosis.
HRQoL and pruritus				
Valdes-Rodriguez et al, 2017 (48)	United States	10 pruritic, 9 non-pruritic pSS	ItchyQoL	The emotional domain of the total ItchyQoL score is the most noteworthy.
HRQoL and sexual disorders				
Bongi et al, 2013 (17)	Italy	62 pSS, 33 sicca syndrome, 50 HC	SF-36	pSS and sicca syndrome patients have an impaired and reduced physical and mental quality of life with respect to controls.
Priori et al, 2015 (18)	Italy	24 pSS, 24 HC	SF-36	Age, menopause and anxiety seemed are associated with the quality of sexual life of the patients, however there is no correlation with SF-

				36.
Van Nimwegen et al, 2015 (9)	Netherlands	46 pSS, 43 HC	RAND-36	There is a significant correlation between sexual disfunction and lower mental quality of life.
HRQoL and sleep disorders				
Priori et al, 2016 (50)	Italy	29 pSS, 29 HC	SF-36	Bad sleep quality correlates with physical and mental domains of the SF-36 and mood disturbances.
Lendrem et al, 2014(14)	United Kingdom	639 pSS, GP	EQ-5D	Daytime sleepiness correlates with reduced quality of life.
HRQoL and autonomic dysfunction				
Ng et al, 2012 (51)	United Kingdom	21 pSS, 21 GP, 21 PBC	EQ-5D	Dysautonomia correlates with PSS-associated symptoms and quality of life.
Newton et al, 2012 (52)	United Kingdom	317 pSS, 317 HC	EQ-5D	Autonomic symptoms is associated with reduced quality of life.
HRQoL and psychological disorders				
Segal et al, 2009 (10)	United States	277 pSS, 606 HC	SF-36	Pain severity and depression are the only unique predictors of emotional well-being.
Inal et al, 2010 (12)	Turkey	107 pSS, 109 HC	SF-36 WHOQOL-BREF	Anxiety and/or depression show a negative effect on HRQoL.
Liu et al, 2017 (16)	China	304 pSS	SF-36	PCS and MCS correlated negatively with anxiety and depression.
Cho et al, 2013 (21)	Korea	104 pSS, 42 non-SS sicca	SF-36	Depression and ESSPRI are major determinants of HRQoL in pSS patients, whereas anxiety and xerostomia significantly correlates with HRQoL in non-pSS sicca patients.
Lendrem et al, 2014 (14)	United Kingdom	639 pSS GP	EQ-5D	Pain and depression are the two most important predictors of EQ-5D utility values, accounting for 48% of the variability.
Koçer et al, 2016 (13)	Turkey	32 pSS, 19 HC	SF-36 EQ-5D	Depression, fatigue severity, and quality of life tests show a significant positive correlation with each other.
Hyphantis et al, 2011 (26)	Greece	40 pSS, 56 LES, 80 HC	WHOQOL-BREF	General psychological distress is higher in pSS compared with SLE and healthy controls, and correlates with HRQoL.
van Leeuwen et al, 2012 (53)	The Netherlands	300 pSS, 100 HC	RAND-36	Patients have worse mental well-being than healthy control participants.
Epstein et al, 2014 (11)	United States	37 pSS, 37 HC	SF-36	Patients have significantly lower ratings on the total mental component score.

Chou et al, 2017 (55)	Argentina, China, Denmark, India, Japan, UK and the USA	1051 SS, 1350 non-Sjögren sicca.	SF-12	pSS patients have better PCS and MCS and a lower adjusted odds of depression when compared with non-SS patients with symptomatic dryness.
HRQoL and physical function impairment				
Hackett et al, 2012 (56)	United Kingdom	69 pSS, 69 HC	EQ-5D	Impaired function is associated with reduced quality of life.
Ng et al, 2016 (57)	United Kingdom	273 pSS, 273 HC	EQ-5D	There is an inversed correlation between physical activity and quality of life, however this did not retain statistical significance on multivariate analysis.
Dassouki et al, 2017 (19)	Brazil	29 pSS, 20 HC	SF-36	Timed up and go test scores correlate negatively with multiple SF-36 domains.

EQ-5D: EuroQoL-5 dimension; GP: general population; HC: health control; MDADI: MD Anderson Dysphagia Inventory; MCS: Mental Component Summary NEI-VFQ: National Eye Institute Visual Function Questionnaire; non- KCS: non-Sjögren's keratoconjunctivitis sicca; OHIP-14: Oral Health Impact Profile; OHRQoL: oral health-related quality of life; PBC: autoimmune liver disease primary biliary cirrhosis; PCS: Physical Component Summary; pSS: primary Sjögren's syndrome; PSS-QoL: Primary Sjögren's Syndrome Quality of Life questionnaire; RA: rheumatoid arthritis; RAND-36: RAND 36-item Health Survey; SS: Sjögren's syndrome; SAPS - sicca asthenia polyalgia syndrome patients; SF-36: Medical Outcomes Study Short-Form; SLE: systemic lupus erythematosus; sSS: secondary Sjögren's syndrome; WHOQOL-BREF: World Health Organization Quality of Life Instrument, Short- Form.

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Figure Legends

Figure 1. Flow chart of the literature search.

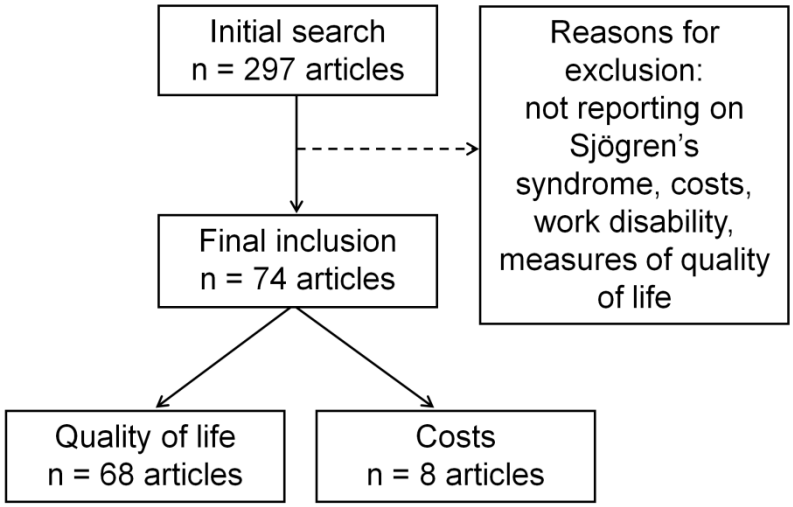
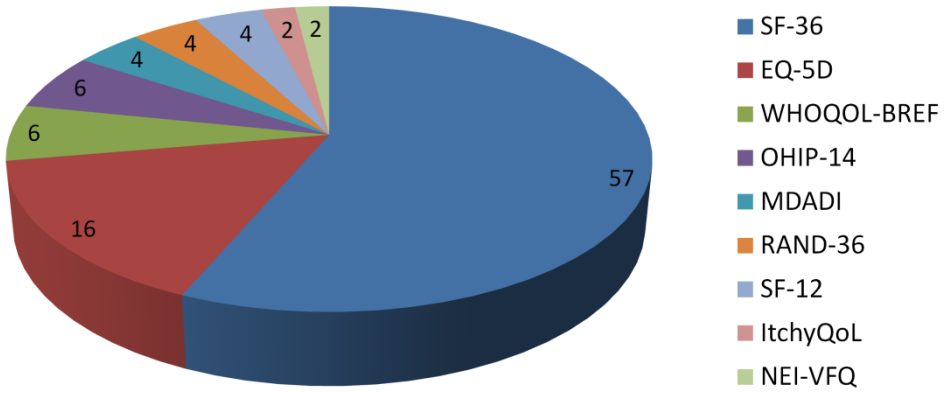


Figure 2. Percentage of observational studies according the health-related quality of life instrument used.



EQ-5D: EuroQoL-5 dimension; MDADI: MD Anderson Dysphagia Inventory; NEI-VFQ: National Eye Institute Visual Function Questionnaire; OHIP-14: Oral Health Impact Profile; OHRQoL: oral health-related quality of life; RAND-36: RAND 36-item Health Survey; SF-36: Medical Outcomes Study Short-Form; WHOQOL-BREF: World Health Organization Quality of Life Instrument, Short- Form.

Figure 3. Numbers of reviewed observational and interventional studies in SS that incorporate HRQoL by country.