Trends in employment and hospitalisation in patients with Sjögren's syndrome 1996–2016: results from the German National database

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ABSTRACT

Objective. *To assess trends in treatments and outcomes in patients with primary Sjögren's syndrome (pSS), focusing on employment, hospitalisation and medical treatment in the past two decades.*

Methods. *From 1996 to 2016, approximately 300 patients with pSS were annually documented in the National Database of the German Collaborative Arthritis Centres. Data on treatment, physicians' assessments of disease activity, patient-reported outcomes, hospitalisation and employment were collected and compared to patients with rheumatoid arthritis (RA), matched 1:1 for age, sex and disease duration for each calendar year.*

Results. *Patients with pSS (>90% female, age 44 years at disease onset, disease duration 10 years) were more frequently assessed to be in low disease activity in 2016 (93%) than in 1996 (62%), p<0.01. Treatment with antimalarials increased from 1996 to 2016 (31 to 50%, p<0.01) and less patients were on glucocorticosteroids (50 to 34%, p<0.01) but <5% were treated with biologics. Employment (<65 years) increased by 21 percentage points (43 to 64%, p<0.001), exceeding the increase observed for RA patients (+15 percentage points). Early retirement (22 to 10%, p=0.01), hospitalisation/year (13 to 7%, p=0.08) and sick leave (39% in 1997 to 27%, p=0.09) decreased comparably to RA patients.*

Conclusion. *Overall, similar trends were observed for RA and pSS cohorts despite minor changes in pSS therapy. Work participation has improved significantly over two decades in pSS. A greater perception of pSS without systemic manifestations may have caused a shift towards less severely affected patient cohorts today.*

Introduction

The typical patient with primary Sjögren's syndrome (pSS) is a middle-aged female, suffering from classical sicca symptoms of oral and ocular dryness as well as from general conditions, such as fatigue, pain or sleeping disturbances. Severe organ manifestations occur in around 10% of patients and require anti-inflammatory therapy (1). While the overall prognosis of pSS is favourable, quality of life can be severely affected by sicca symptoms and fatigue, and by a variety of additional symptoms. The disease burden in pSS impacts on working ability (2-5). Results from a German pSS cohort displayed that only half of the patients at working age were employed. Compared to healthy females, patients with pSS had also stopped working earlier and had more days on sick leave (2). International studies report that pSS patients are at an increased risk of work disability, in comparison with the general population. This is accompanied by health-related unemployment and work productivity loss (3-5). Clinical presentation of fatigue, depression, and fibromyalgia have separately been identified as predictors of an impaired working status (2, 3).

In order to maintain the working ability, a challenging aim is to improve sicca, fatigue and depressive symptoms in patients with pSS, while disease-modifying therapy is restricted to patients with organ involvement. In this regard, patient education and symptomatic topical therapy are of equal importance. In contrast to rheumatoid arthritis (RA) and other inflammatory rheumatic diseases, no substantial improvement has been identified for systemic treatment of pSS. While patients with RA and spondyloarthritis benefit from biologic therapies, these mechanisms of action

do not specifically intervene with the pathogenesis of pSS, characterised by lymphocytic infiltration of the exocrine glands. New targeted pathways are under development (6) and may result in more successful treatment approaches in the future.

In the 1990s, employment rates in inflammatory rheumatic diseases were lower than in the general population (7). As considerable improvements in employment and healthcare utilisation have been observed in patients with RA, spondyloarthritis and systemic lupus erythematosus in the past years (8-11), the objective of the study was to assess employment rates and hospitalisation in patients with pSS in the past two decades, compared to patients with RA. Due to less treatment options, we expected lower improvements compared to RA. But considering that Germany's employment rate currently is the second highest in the EU and has continuously increased since 2005 (12), our hypothesis was that in patients with pSS, employment rates had also increased.

Methods

Database. Data was derived from the National Database of the German Collaborative Arthritis Centers (NDB). This is an ongoing prospective study that started data collection in 1993 as a long-term monitoring system for rheumatology in Germany (13). Participating rheumatologists from 15 centres consecutively included unselected outpatients with inflammatory rheumatic diseases. Centres comprise both private practices and tertiary outpatient clinics. Physician and patient-reported data is collected once a year for new and returning patients using electronic patient documentation systems. Returning patients can be identified using a unique patient identification number (pseudonym). The NDB was specifically conceptualised to provide data on health care for all patients with rheumatic diseases. As RA and spondyloarthritis are the most frequently reported disease entities, documentation is tailored to these patients, but connective tissue diseases are also collected. For this reason, specific data on pSS symptoms/organ manifestations, treatment and outcomes, such as sicca symptoms, serology, biopsy data, tear substitutes, topical therapy, EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indices (ESSPRI) (14) are not captured. Since the NDB has been continued over two decades, several variables have been added at certain time points. If applicable, we report the year in which a new variable has been added.

Clinical patient characteristics

PSS patients were identified by primary ICD-10 diagnosis of M35.0 (International Classification of Diseases, 10th Ed). Patients with secondary diagnosis of SS were excluded. Data on patient characteristics such as age, gender, education (≤9, 10-13, ≥14 years), body mass index (BMI in kg/m^2, since 2003) and smoking (currently/former/never, since 2005), are collected. Clinical data include symptom onset, disease duration, laboratory markers (erythrocyte sedimentation rate (ESR, since 1997), positive rheumatoid factor (RF, since 2009), among others. Age at symptom onset has been calculated as the difference between age at documentation and the duration of symptoms. From all documented visits available for each patient, it was assessed if the ESR had ever been above 50mm/h and/or if RF was ever positive. Physician-reported disease activity is recorded on a numerical rating scale (NRS) with values ranging from 0 (no activity) to 10 (worst outcome). The numbers of tender and swollen joints are collected using the 28 joints from the DAS-28 (15). A set of 20 comorbidities was reported (yes/no) by the rheumatologist.

Treatment

For each year, treatment was reported including the following agents: antimalarials (chloroquine/hydroxychloroquine), methotrexate, azathioprine, biologics (belimumab since 2012, rituximab since 2007), non-selective non-steroidal anti-rheumatic drugs (NSAIDs), Cox2-inhibitors, glucocorticosteroids (GC, low dose ≤7.5 mg prednisone equivalent/day, high dose >7.5 mg/day), other analgesics and opioids (since 2005).

Patient-reported outcomes

Patient-reported items include global health, fatigue, pain and sleeping disorder on NRS (0–10) with low values indicating good outcomes. Symptoms of anxiety/depression were documented within the EuroQuol (16). Patients were asked about their employment status (Are you full-time employed/part-time employed/unemployed/retired/in early retirement?), about their sick leave (Have you been on sick leave due to your inflammatory disease during the past 12 months?) and hospitalisation (Have you been treated as an inpatient due to your inflammatory rheumatic disease during the last 12 months?).

Statistical analyses

Descriptive statistics (mean, standard deviation (SD) and percentages) were used to summarise patients' characteristics, treatments and outcomes for each calendar year. For the reason of clarity, results are only presented for every fourth year (1996, 2000, 2004, 2008, 2012, 2016).

To test the hypothesis of the study, employment rates in 1996 and 2016 were compared with a chi-square test of proportions. As there is no pSS patient who was observed in 1996 was also observed in 2016 the samples are independent.

Patients of the pSS cohort were compared to RA patients from the NDB. RA patients were identified by primary M05/M06 ICD-10 diagnosis. For comparison with RA, we matched pSS patients to RA patients 1:1 by age (±2 years), sex, disease duration (±3 years) and calendar year. Seven pSS patients could not be matched with an RA patient and were excluded from the analysis.

To examine if alterations over time were biased by differences in the patient case mix, a sub-analysis was performed which included only the first visit of each patient. This analysis was performed to examine if the characteristics of newly included patients in the NDB changed over time. Characteristics of pSS and RA patients at their first study visit are presented. Because the numbers of newly presenting pSS patients per year were low, we cumulated data for the years 1993-1996, 2003-

2006 and 2013-2016. For this analysis, no matching with RA patients was performed.

Ethics approval

The database received study approval from the ethics committee of the Charité – University Medicine Berlin (EA1/196/06).

Results

From 1996 to 2016, a total of 3,000 patients (6,300 visits) with pSS were documented in the NDB. Annually, the visits of 154 (in 2006) to 512 patients (in 2002) were recorded.

Patient characteristics

More than 90% of the patients were female (Table I). Their mean age increased slightly from 53±13 years in 1996 to 57±15 years in 2016. The age at disease onset remained relatively constant considering the large standard deviations and changes between 43±14 years in 1996 and 2000 and 46±15 years in 2012. The median symptom duration increased from 7.5 years in 1996 to 10.1 years in 2016. In 2016, more patients were smokers (former and current) than in 2008 (45% *vs*. 37%) and there were more patients in 2016 with ≥14 years of education than in 1996.

The BMI, the proportion of rheumatoid factor positive patients and the proportion of patients who ever had an ESR of >50mm/h remained relatively constant.

Table I. Characteristics of the pSS patients.

	1996	2000	2004	2008	2012	2016
N	326	475	419	185	191	229
Female, %	94	93	94	94	92	90
Age, mean (SD) in years	53 (13)	54 (13)	55 (14)	56 (13)	57 (14)	57 (15)
Age at disease onset, mean (SD) in years	43 (14)	43 (14)	44 (15)	46 (14)	46 (15)	43 (15)
Symptom duration, mean (SD) in years	10 (9)	10 (10)	11 (10)	10 (9)	10 (8)	12 (9)
Smoking, ever, %				37	35	45
BMI, mean, kg/m² (SD)			25 (5)	25 (5)	25 (5)	25 (5)
Education ≤9 years	18	14	- *	16	17	10
10-13 years	59	64	-	56	53	50
≥14 years	23	22	-	28	30	40
Ever RF positive, %	-	-	-	50	57	60
ESR >50mm/h, %	-	13	14	15	16	14
Comorbidities, physician reported						
Lung disease (since 2005), %				10	8	10
Depression (since 2005), %				10	8	5
Degenerative joint disease (since 2002), %			33	17	15	13
Renal disease (since 2002), %			6	4	4	5

BMI: Body mass index; ESR: erythrocyte sedimentation rate; RF: Rheumatoid factor; SD: standard deviation. *in 2004, education was not collected.

Table II. Treatments for extraglandular (systemic) manifestations (%).

	1996	2000	2004	2008	2012	2016
Antimalarials	31	37	46	36	39	51
Methotrexate	10	9	10	11	8	10
Azathioprine	8	10	11	8	7	5
Biologics	-	0.2	0.0	0.9	0.7	4.3
Belimumab	-	-	-	-	-	0.6
Rituximab	-	-	0.0	0.0	0.7	3.0
Glucocorticosteroids	50	46	45	33	34	34
GCs ≥7.5mg/d	20	15	10	17	9	12
GCs < 7.5mg/d	80	85	90	83	91	88
Non-selective NSAIDs	24	24	18	26	24	23
Cox2-Inhibitors	-	7	14	7	7	11
Other analgetics	6	6	10	7	15	14
Opioids	-	-	-	8	8	5
None of those treatments	21	16	14	19	24	16

Cyclosporine A, cyclophosphamide, leflunomide and mycofenolate were ≤3% in all years.

Systemic treatments

Overall, systemic treatment for pSS patients in the NDB has not changed substantially (Table II). Notably, more patients were treated with antimalarials (50%) in 2016 than 1996 (31%). Treatment with methotrexate (~10%) and azathioprine (~8%) remained stable over the observation periods. Cyclosporine, cyclophosphamide, leflunomide and mycofenolate were used in ≤3% of all patients throughout the years. In 2016, 4.3% were treated with biologics, mainly rituximab. Less patients were treated with GC in 2016 than 20 years earlier (34 vs. 50%) with a decrease in patients with high GC doses (>7.5mg prednisone equivalent/day). The use of nonselective NAIDs (~25%) and Cox-2 inhibitors (~10%) has not changed over the years while analgesics including opioids were slightly more frequently used in recent years.

Physician's and patient's disease assessment

While two thirds of the patients reached low disease activity according to physicians' assessments in 1996, nearly all of them reached this target in 2016 (Table III). Around 90% of the patients had no swollen joints, and about three quarters of the patients had no tender joints throughout the years.

Around 40% of the patients reported good global health with no major changes from 2000 to 2016. Good outcomes for pain, fatigue, sleeping disorder and anxiety/depression were documented by 50–61% of the patients in 2016 with improved outcomes from 2008 to 2016.

Hospitalisation and work participation

Of particular note, fewer patients were hospitalised due to pSS in 2016 than in 1996 (Table IV), including a decrease of the median number of hospital days from 21 in 1996 to 7 in 2016.

Employment of patients <65 years increased from 43% in 1996 to 64% in 2016 (*p*-value from Chi-Square-Test 0.001). Employment increased in all age groups and independently of gender. For employed patients, sick leave due to pSS during the last 12 months decreased from 34% in 2000 to 27% in

Table III. Physician- and patient-reported outcomes (%).

	1996	2000	2004	2008	2012	2016
Physician						
Disease severity: asymptomatic	4	4	2	5	4	3
mild	37	46	43	51	46	60
moderate	49	43	45	38	48	36
severe	10	7	9	5	2	1
very severe		0	0	1		1
Low disease activity, 0-3	62	68	69	85	92	93
No swollen joints	-	89	84	69	89	91
No tender joints	-	73	68	67	64	75
Patient						
Good Global Health, 0-3	-	40	38	35	39	44
Low pain, 0-3	41	44	48	45	42	56
Little fatigue, 0-3	-	-	-	38	40	50
Little sleeping disorder, 0-3	-	-	-	43	47	51
No anxiety/depression	-	-	-	53	58	61

Disease activity, joint counts, global health, pain, fatigue and sleeping disorders are all reported on numeric rating scales from 0–10. Anxiety/depression are reported by EQ-5D.

Table IV. Hospitalisation and work participation, %.

	1996	2000	2004	2008	2012	2016
Hospitalised due to pSS, past year	13	14	15	9	6	7
Patients ≤65 years						
Number of patients	278	403	309	127	130	157
Employed, 41-50 years	44	66	63	48	70	87
Employed, 51-60 years	43	41	43	80	61	66
Employed, 61-65 years	6	2	8	27	14	21
Employed women	42	48	48	57	64	62
Employed men	63	48	47	71	67	80
Employed part-time	9	10	15	14	17	21
Sick leave due to pSS, past year, % of employed	-	34	29	20	24	27
Early retirement	22	16	17	17	11	10

2016. The median number of sick leave days decreased from 21 to 14 days in this period. The proportion of patients with early retirement decreased from 22% to 10% (patients ≤65 years).

Comparison to rheumatoid arthritis

Between 1996 and 2016, a total of 85,300 RA patients were documented in the NDB. Annually, the visits of around 10,000 patients were recorded. In patients with RA, matched for sex, age and disease duration, the hospitalisation rate was higher in 1996 (29%) as compared to pSS, and decreased to 11% in 2016 (Fig. 1).

Employment rates for patients with RA ≤65 years increased from 41% in 1996 to 59% in 2016 as also found for pSS. RA patients were more frequently on sick leave in 1997 (46%) and sick leave decreased to 25% in 2016, again similar as observed for pSS patients.

The proportion of RA patients with early retirement was also higher in earlier years and decreased to similar levels (36% in 1996 to 14% in 2016).

Characteristics of patients at their first visit in the NDB

Characteristics of patients with pSS and RA at their first documented visit in the NDB are reported in Table V. While symptom duration has declined continuously in RA, it remained high for pSS (4.5 years). Physician-rated disease activity showed the same trend for pSS patients with nearly all patients in low disease activity in recent years. However, the level of patient-reported pain and the percentage of patients with joint symptoms and lacking comorbidities did not change in pSS patients. In contrast to RA, ever smoking was recorded on a low level in 2013–2016. Employment rates also increased over the decades for pSS as well as RA patients at their first visit.

Discussion

The NDB is an observational, longitudinal database in daily clinical practice which allows identification of trends over time in patients with rheumatic diseases. This is the first report on patients with pSS from the NDB. The evaluation over two decades shows trends in that average disease activity has decreased, patient-reported outcomes and work participation improved. Employment rates have increased by one fifth, approximating the rates of the general population. Two-thirds of patients with pSS at working age were employed in 2016. Meanwhile, hospitalisation rates, sick leave and early retirement decreased. This data suggest improved healthcare of patients with pSS that can only be partly attributed to reduced GC and increased DMARD usage. Nevertheless, the extent of the improvements is somewhat surprising. In contrast to RA, treatment strategies for pSS have not changed substantially, except for a substantial increase of antimalarials and decrease of high dose GC. This approach is adapted from related connective tissue diseases and is considered the therapy of choice in patients with mild to moderate manifestations (1). Despite the use of rituximab for a small proportion of pSS patients, the biologic era has not yet arrived in pSS (6). The main challenge of pSS treatment remains to provide efficacy for the heterogeneous symptoms regarding sicca symptoms (glandular), fatigue and extraglandular manifestations (1). It is noteworthy that the amount of GC use was reduced over time. This is consistent with a decrease of disease activity as assessed by the rheumatologists in just over half of all patients in 1993–1996 but in almost all patients in 2013–2016 at their initial visit. It is also possible that the awareness of the disease in primary care has increased. As a result, patients with mild forms of the disease would more frequently be presented to rheumatologists today. Then we would have a shift in the patient mix towards a less severely affected collective today. However, in contrast to RA, we could not observe a trend towards an earlier referral after symptom onset in pSS. Lower proportions of patients with a smoking history

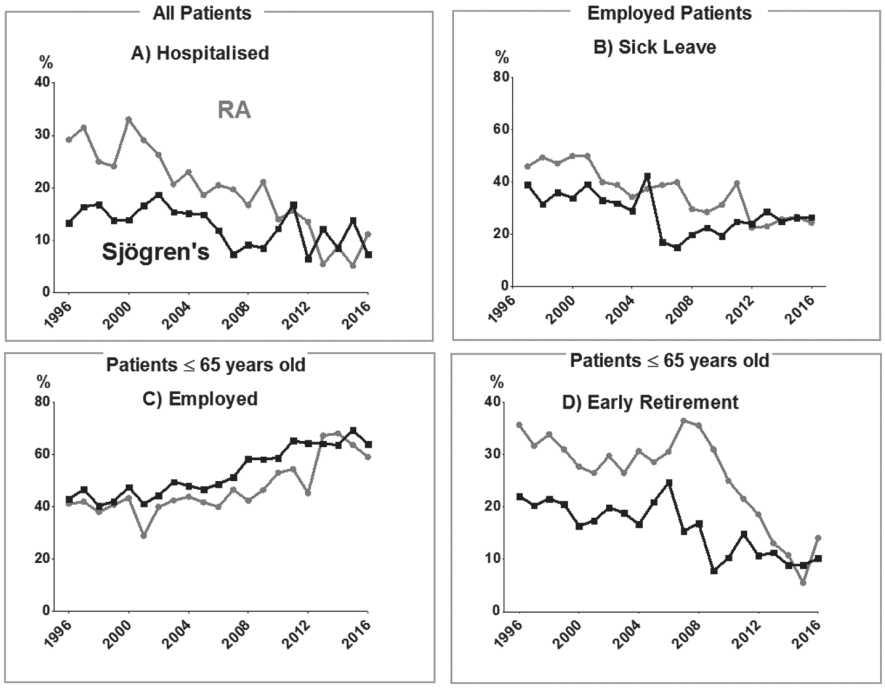

Fig. 1. Hospitalisation and work participation in patients with pSS compared to RA within the same NDB. Displayed are the proportion of patients of all patients ≤65 years between 1996 and 2016, regarding **A**) hospitalisation during the past 12 months, **B**) temporary sick leave, **C**) employment, **D**) early retirement.

Table V. Comparison between pSS and RA patients at first referral by the treating rheumatologist.

	PSS			RA		
	1993-1996	2003-2006	2013-2016	1993-1996	2003-2006	2013-2016
n.	193	117	54	7998	2381	895
Female (%)	91	93	91	77	75	70
Age, mean (SD) in years	51 (14)	54 (13)	48(16)	58 (14)	58 (14)	58 (16)
Age at disease onset, mean (SD) in years	43 (15)	48 (14)	40 (14)	50 (16)	50 (16)	53 (18)
Symptom duration (median), in years	4.1	2.3	4.5	3.7	3.1	1.3
Smoking, ever (%)	-	55	26	-	46	59
BMI, mean (SD)	-	25 (5)	24 (4)	-	26 (5)	26 (5)
Treatment with antimalarials (%)	15	20	23	7	8	6
Disease severity (%): asymptomatic	6	2	2	1	1	1
mild	49	45	86	25	27	51
moderate	37	47	9	52	53	42
severe	8	6	2	20	16	5
very severe	1			3	2	1
Disease activity (Physician) (0–3) (%)	56	60	95	37	40	62
Pain (0–3) (%)	50	38	53	21	26	37
Comorbidities (%)	-	77	77	-	78	66
Employed (%)	51	61	69	46	57	65

at their first referral may indicate positive changes in lifestyle and could also contribute to less severe symptoms in patients in the later observation periods. With regard to work ability, the percentage of employed women among females aged 15 to 65 years in the general population also improved from 55% in 1996 to 71% in 2016 (17). This overall positive national trend is an important factor contributing to an increase in all employment rates that we also observed in other rheumatic diseases (8, 10, 11). The fact that patients with pSS are also participating in this increase, supports that pSS patients are able to benefit from this countrywide trend. In this context, education is known to be associated with employment rates (7) and also increased across the years.

The overall case numbers in German hospitals increased in the period from 1996 to 2016, while the total population remained stable (18). While markedly less pSS and RA patients retired early, the proportion of persons in the general population ≤65 years with early retirement stayed constant with 3.3% in 1992 and 3.4% in 2016 (19). The proportion of patients with musculoskeletal diseases of the total persons with early retirement in Germany decreased during this period (20), confirming that this development also affected patients with pSS and RA. Analyses from the Sjögren and from an early arthritis cohort indicate depression to be a strong predictor of considering early retirement (21). Greater attention to signs of depression may contribute to positive trends and within the NDB, patients with pSS are less frequently affected from depressive symptoms today.

Other patient-reported outcomes are also indicating improvements since 2008 even if those are not as impressive as the improvements in the rheumatologists' assessment. This applies to pain, fatigue and to anxiety/depressive symptoms, respectively. Previous evaluations from the NDB in patients with RA and spondyloarthritis have constantly shown a discrepancy between physician and patient-assessments (10, 22). In pSS, this difference is understandable as patients are rather affected by sicca, fatigue and arthralgia while rheumatologists may focus on the assessment of organ involvement to avoid further damage.

In 2009, ESSDAI was introduced and validated as a specific assessment tool in pSS (14). By this instrument, disease activity is merely measured by organ manifestations. This may have influenced the overall physician assessment in the way that sicca, fatigue and pain have a lower impact on the rheumatologist's assessment of disease activity in recent years. We cannot further verify this possibility since our database does not capture ESSDAI and ESSPRI scores. Complete assessment of disease activity in pSS is only possible with consideration of both instruments and the same applies to the general assessments by patients and physicians from our database.

Comparing the employment and disease status of patients with pSS from the NDB with the German Sjögren cohort that was established in 2009, patients from the inception cohort were less frequently employed, more frequently early retired and remained longer on sick leave (2). The patients of this Sjögren cohort were of comparable age and disease duration but reported more frequently pain, fatigue and depressive symptoms. Disease activity was not reported. The comparison supports the assumption that less severe cases of pSS have been documented within the NDB in recent years.

In the Sjögren's International Collaborative Clinical Alliance (SICCA), 50% of all worldwide participants with pSS were employed and full-time employment was associated with a lower probability of depression (23). Work disability increased from 26 to 41% in the first two years after pSS diagnosis in a Swedish cohort (3). Employment (3, 4) and hospitalisation rates (24, 25) are reported higher in patients with pSS compared to controls across several international cohorts. Trends on these observations are not reported.

Limitations and strengths

Based on the constitution of the NDB, no data are available on specific pSS items. Today, subsets of pSS are distinguished by the specific determination of disease activity (14). Our data lack the distinction between the glandular and extraglandular as well as mild to moderate or severe systemic subsets. The approach to classify subentities according to phenotypes may further help to stratify patients according to a distinct disease status (26, 27). We did not attempt to assess the causal relationship of treatment and disease severity, because the overlap of patients between two years differed between 12% and 76%. About 5.9% of the pSS patients were observed for 5 consecutive years or more during the whole observation period but none over the complete period. This does not allow for meaningful longitudinal analyses. A further limitation is the decreasing number of first referral patients in recent years. The strength of the NDB is the long-term monitoring with a rather general but very continuous documentation of outcomes. Continuous primary data over two decades are scarce and trends on employment rates and healthcare utilisation are of importance for healthcare providers. Documentation of all entities within inflammatory rheumatologic diseases enables the comparison of outcomes between rare connective tissue disease and frequently reported RA. With an approximated prevalence of 0.2% (28), pSS belongs to the group of rare diseases. However, since patients develop pSS already at the age around 40, on average over 20 years of working age remain. Thus, the preservation of their earning capacity has economic relevance.

In conclusion, employment increased in patients with pSS across the last two decades while disease activity and healthcare utilisation decreased. We observed a shift towards less severely affected patients in recent years. A better perception of this rare disease among patients and general practitioners may contribute to earlier recognition of pSS.

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