Comorbidity and health care utilisation in persons with Sjögren's syndrome: a claims data analysis

K. Albrecht[1], T. Dörner[1,2], I. Redeker[1], K. Karberg[3], U. Marschall[4], A. Zink[1,2], J. Callhoff[1]

[1]German Rheumatism Research Centre, Epidemiology Unit, Berlin; [2]Charité University Medicine Berlin; [3]Practice for Rheumatology and Internal Medicine, Berlin; [4]BARMER Statutory Health Insurance Fund, Wuppertal, Germany.

Katinka Albrecht, MD
Thomas Dörner, MD
Imke Redeker, Dr. rer. nat.
Kirsten Karberg, MD
Ursula Marschall, MD
Angela Zink, Dr. rer. pol.
Johanna Callhoff, Dr. rer. medic.

Please address correspondence to:
Katinka Albrecht,
Epidemiology and Health Services Research,
German Rheumatism Research Centre,
Charitéplatz 1,
10117 Berlin, Germany.
E-mail: albrecht@drfz.de

Received on June 8, 2020; accepted in revised form on July 29, 2020.

Clin Exp Rheumatol 2020; 38 (Suppl. 126): S78-S84.

Key words: Sjögren's syndrome, health services research, epidemiologic studies, comorbidity

Funding: the study was supported by the Wolfgang Schulze Foundation of the German Rheuma-Liga and by the Federal Ministry of Education and Research within the network TARISMA [01EC1902A].

Competing interests: none declared.

ABSTRACT

Objective. *To capture comorbidity and medication of persons with Sjögren's syndrome (SS) in a population-based cohort in comparison to matched controls.*

Methods. *Individuals with an outpatient diagnosis of M35.0 (ICD-10) in ≥2 quarters of a year or an inpatient diagnosis of M35.0 were identified in a German statutory health insurance fund covering 7.2 million people. Persons in rheumatologic care were grouped by incident or prevalent diagnosis and by co-existing autoimmune disease (sSS) or primary (p)SS and compared to age- and sex-matched controls regarding comorbidity (ICD-10), medical prescriptions, hospitalisation and inability to work in the previous year.*

Results. *In 2018, 7,283 persons (0.10%) had incident and 54,273 persons (0.75%) prevalent SS diagnosis, and 5,961 (11%) were in rheumatologic care. Of these (90% female, mean age 66 years), 3,457 (58%) had further autoimmune disease (sSS), mostly rheumatoid arthritis (80%) and systemic lupus erythematosus (13%). Compared to controls, frequent comorbid conditions in SS were hypertension (controls: 52%, pSS: 55%, sSS: 63%), osteoarthritis (22%/40%/47%), osteoporosis (10%/26%/38%) and depression (21%/34%/36%). Systemic antirheumatic drugs were prescribed in 31% (pSS) and 66% (sSS) while <5% received topical therapies. Glucocorticoids (8%/34%/59%), NSAIDs (28%/41%/45%), opioids (8%/15%/21%), analgesics (19%/30%/36%) and antidepressants (14%/21%/21%) were frequently prescribed. Compared to controls, hospitalisation (21%/32%/39%) and inability to work in persons <65 years (41%/48%/44%, median days 17/24/30) were more frequent in pSS and sSS than in controls.*

Conclusion. *SS claims diagnosis is associated with substantial comorbidity and frequent prescription of anti-inflammatory drugs, analgesics and antidepressants. The individual and societal burden of SS shows that, in addition to effective treatment strategies, intensive attention to comorbidities is important in this disease.*

Introduction

Sjögren's syndrome (SS) is an autoimmune disease leading to dryness due to chronic inflammation of the lacrimal and salivary glands, called sicca syndrome (1). This can occur independently as primary disease (pSS) or secondary (sSS) in the context of other autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and others. SS is often referred to as the most common connective tissue disease (2). However, both the heterogeneity of the disease itself, which leads to high variation in reported prevalence, and the non-specific symptoms, which may result in an overestimation of SS, need consideration (3). Many people, especially the elderly, suffer from eye and mouth dryness, which in many cases are caused by medication or simply related to age. Therefore, the classification criteria of pSS require the detection of anti-SSA (Ro) autoantibodies or a positive lip biopsy as well as detection of sicca symptoms by Schirmer's test and salivary flow-rate (4). Various extra-glandular manifestations can occur in pSS while another defined autoimmune disease cannot be confirmed (5).

Population-based studies that used case-finding methods and confirmed cases with SS diagnosis by applying the American-European Study Group (AECG) criteria resulted in a lower prevalence of pSS of 39/100,000 (3) compared to other reports (6). Using health insurance

data, the clinically non-validated claims diagnosis is distinctly more frequent (7, 8). In claims data, secondary forms can only be differentiated to a limited extent by means of further autoimmune diagnoses (9). So far, there have been no meaningful data for Germany. The latest estimates from 2010 gave about 0.2% for primary and at least 0.4% for sSS (10). Health care of these patients is also difficult to determine as clinical characteristics range from exclusively dental and eye symptoms to severe systemic organ manifestations. Among European countries, pSS care varies due to different health care systems and current efforts are made to harmonise pSS research in Europe (11). A former assessment of the data from the German National database and from the German Rheumatoid Arthritis Population Survey (GRAPS) led to the assumption that only every tenth patient suffering from pSS is under rheumatologic care (10). Therefore, the first aim of this study was to use current health insurance data to report on the frequency of SS diagnosis, on diagnostic measures and prescriptions and on the proportion of individuals under care by a rheumatologist in a population-related data source. Regarding the consequences of SS in terms of comorbidities, hospital stays and inability to work, available data are also very limited. In the National database, the rheumatologist-reported disease activity of patients with pSS has declined in the last 10 years, accompanied by less frequent use of glucocorticoids, more frequent prescription of antimalarials, increased employment and reduced hospitalisation, sick leave and early retirement (12). These data demonstrate improvements compared to former results of the German Sjögren's cohort (13). However, it remains unclear whether these trends are generalisable. Therefore, the second objective was to compare comorbidity, hospitalisation and sick leave of persons with SS with a matched population cohort as a validation approach.

Methods

Cross-sectional analysis

Data from a large German statutory health insurance ("BARMER") were used for analysis. The main part of the analysis refers to cross-sectional data from 2018. We selected all persons who were at least 18 years old in 2016 and had continuously been insured by the BARMER health insurance from 2016 to 2018. Persons with SS were identified as those with an outpatient diagnosis of M35.0 in at least two quarters of a year according to the German modification of the International Statistical Classification of Diseases (ICD-10 GM) or an inpatient diagnosis of M35.0. We focused the analysis on patients in rheumatologic care. Rheumatologists were identified by using the medical specialist number code "31" in the claims data and by identifying those physicians who used claims codes exclusive to rheumatologists (GOP 13690, 13691, 13692, 13700, 13701, 99012).

Persons with SS diagnosis were further divided into those with another autoimmune disease (AID) and those without. The AIDs considered here comprised rheumatoid arthritis (RA, M05, M06), systemic lupus erythematosus (SLE, M32.1, M32.8, M32.9), mixed-connective tissue disease (MCTD, M35.1), systemic sclerosis (M34), myositis (M33), autoimmune hepatitis (K75.4), and primary biliary cholangitis (K74.3) (14). We also considered conditions that result in pSS-like manifestations (15): acquired immune deficiency (B24), amyloidosis (E85), graft-versus-host-disease (T86), chronic hepatitis C (B18.2), IgG4-related disease (D89.8) and sarcoidosis (D86). For all diagnoses at least two diagnoses in different quarters of 2018 had to be encoded.

Outcomes derived from claims data

Diagnostic procedures performed in any of the years 2016 to 2018 were analysed using the following claims codes from the German evidenced based medicine (EBM) catalogue: SSA/SSB antibody test (32492), sonography of facial/neck soft tissue and/or salivary glands excluding thyroid gland (33011), computed tomography of the lungs (34330). For the lip biopsy, the Schirmer-test and the salivary flow-rate, no specific coding was available.

All diagnoses associated with M35.0+ were included: keratoconjunctivitis sicca (*H19.3), interstitial kidney disease (*N16.4), polyneuropathy (*G63.5), myopathy (*G73.7) and lung involvement (*J99.1). General comorbidities were selected by clinical relevance and by previous reports (9): hypertension, chronic obstructive pulmonary disease (COPD), osteoarthritis, osteoporosis, fibromyalgia, depression, hypothyroidism, solid tumour, metastatic cancer, hyperactive bladder and neuromuscular dysfunction of the bladder. Where applicable, definitions from the Elixhauser comorbidity score were used (16). The referring ICD-codes are reported in Table II.

Medical prescriptions were identified via the anatomical therapeutic chemical classification (ATC). The following substances were analysed: abatacept, antidepressants, azathioprine, belimumab, cyclosporine, glucocorticoids, (hydroxy-) chloroquine, leflunomide, methotrexate, mycophenolate, NSAIDs, opioids, other analgesics, pilocarpine, rituximab, saliva substitute, topic fluoride, tear substitute. The referring ATC-codes are reported in Table III. Cyclophosphamide could not be assessed, because it is administered on an inpatient basis and is not available as a procedure code. For biologic disease-modifying anti-rheumatic drugs (bDMARDs), procedure codes (OPS) for administration in hospital were additionally considered. Glucocorticoid use was calculated by defined daily doses (DDD) (17) and indicated as categories (no, >0 -2, 2 -5, 5 -7.5, 7.5 -10, >10mg), corresponding to prednisolone equivalent per day. The DDD here is a surrogate and does not necessarily reflect the prescribed doses for individual patients. Anticholinergic drugs are reported as they can cause or alleviate sicca symptoms (15) but cases were not excluded from further analyses. The data only contain prescription drugs. Several pain killers, *e.g.* ibuprofen in doses up to 400mg, are also available over the counter. These are not included here.

Hospitalisation was analysed using inpatient data from the hospital claims data. Persons were counted as being hospitalised in 2018 if they had at least one inpatient admission.

Sick leave and days of sick leave were assessed in 2018. To count the days on sick leave in 2018, sick leave periods starting before January 1st 2018 or ending after December 31st 2018 were cropped so that the maximal possible number of days on sick leave was 365 days. The proportion of sick leave attributable to SS/RA was calculated by dividing the number of days of sick leave due to SS by the number of total days on sick leave.

Control group

To compare the frequencies of diagnostic procedures, comorbidities, prescriptions, sick leave and hospitalisation in patients with SS to persons without SS and without any other AID, we randomly selected control groups matched 5:1 for age and sex from the insurance population without any AID defined above. For one person with SS, only one control could be matched. One control group each was matched to all SS patients in 2018 and to those in rheumatologic care, respectively.

Frequency of SS ICD-diagnostic codes over time

We further assessed whether the frequency of the diagnosis had changed over the years. The earliest data available are from 2005. Similar to the cross-sectional analysis, we selected all individuals being continuously insured in three consecutive years and assessed the presence of two diagnoses in different quarters of the third year, corresponding to prevalent SS diagnosis. To be counted as incident, patients had to have no diagnosis in the two preceding years.

We did not statistically test for differences between the groups as the focus of this paper is the description of frequencies and not the comparison between pSS and sSS. Moreover, most comparisons are likely statistically significant due to the large case numbers and reporting them might overstate the relevance of the differences.

Results

General results

A total of 7,204,430 individuals aged ≥18 years in 2016 had continuous health coverage from January 1st, 2016 to December 31st, 2018. Of those, 54,273 (0.75%) had at least two outpatient or one inpatient diagnoses of SS (Fig. 1). A total of 60% were aged above 70 years and 77% were female. Incident diagnosis was present in 7,283 persons (0.10%) and here 47% were aged above 70 years with a 73% female dominance. Among individuals with prevalent SS diagnosis, 5,961 (11%) were under care of a rheumatologist (altogether 645 rheumatologists), with 12% aged ≤50 years, 47% aged 51 to 70, 41% aged >70 years and 90% female.

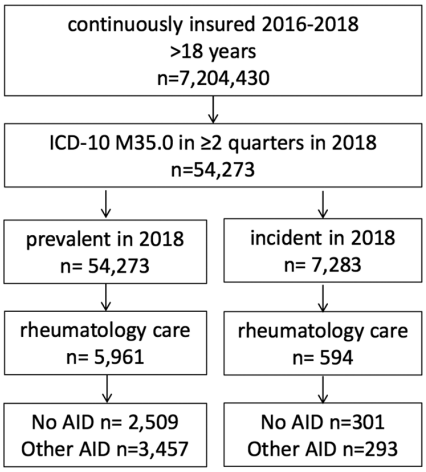

Fig. 1. Flow chart. AID: autoimmune disease.

An ophthalmologist was consulted by 97% of the persons with incident SS diagnosis and by 85% if a rheumatologist also was consulted. Within a period of three years including the year of diagnosis, SSA/SSB antibodies had been tested in 34% of persons with and in 6% of persons without visit to a rheumatologist. Sonography of the facial/neck soft tissue and/or salivary glands and computer tomography of the lungs was rarely performed (Table I).

Due to the age and gender distribution and the low frequency of overall coded diagnostic tests, we limited further analyses to the individuals who consulted a rheumatologist (n=5,961) under the assumption that the SS diagnosis is reliable here.

Primary or secondary Sjögren's syndrome

In the latter cohort, other AIDs were present in n=3,457 patients (58%) so that we categorised them as sSS. The most common AID was RA (80%), followed by systemic lupus erythematosus (13%), mixed connective tissue disease (8%), systemic sclerosis (7%), sarcoidosis (2.3%), primary biliary cholangitis (1.9%), autoimmune active hepatitis (1.7%) and myositis (1.5%). Acquired immune deficiency (n=2), amyloidosis (n=13), graft-versus-host disease (n=1), chronic hepatitis C (n=17) and IgG4-related disease (n=3) all occurred in <0.5% of the rheumatologic patients with AID.

Table I. Distribution of SS diagnosis in claims data.

	Controls	≥2 M35.0 in 2018		Rheumatologist	
		prevalent	incident	prevalent	incident
n.	271,361	54,273	7,283	5,961	594
Age, years (%)					
18-30	1	1	2	1	2
31-50	6	6	10	11	14
51-70	33	33	41	47	53
>70	60	60	47	41	31
Female (%)	77	77	73	90	86
Specialty care (%)					
Rheumatology	1	11	8	100	100
Ophthalmology	44	95	97	82	85
Diagnostics (%)					
SSA/SSB autoantibodies	1	6	5	34	37
Sonography of facial/neck soft tissue and/or salivary glands	4	8	7	16	14
Computer tomography chest	4	6	5	12	12

Controls are 1:5 gender- and age-matched to all persons with M35.0 and without autoimmune diseases. Diagnostics were assessed as at least once during the last three years.

Table II. Organ manifestation and comorbidity in persons with SS diagnosis in rheumatology care and gender and age matched controls.

		Controls	Prevalent		incident	
			pSS	sSS	pSS	sSS
n.		29,801	2,509	3,457	301	293
Age in years, mean		66.0	65.2	66.5	61.3	64.2
Female, %		89.8	89.2	90.2	85.8	86.0
Associated organ manifestation/comorbidity						
Keratokonjunctivitis sicca	*H19.3	0.2	25.8	25.4	20.9	26.6
	H16,H19.3	0.5	28.1	28.4	22.5	28.3
Interstitial kidney disease	*N16.4	0.0	0.3	0.5	0.0	0.0
	N16-19	7.3	12.7	17.0	11.9	11.6
Lung involvement	*J99.1	0.0	1.2	1.4	0.3	1.0
Myopathy	*G73.7	0.0	2.4	3.0	0.31.1	
Polyneuropathy	*G63.5	0.0	0.6	0.8	0.3	0.3
	G60-64	6.0	12.5	15.6	11.3	10.2
Hyperactive bladder	N39	5.4	9.9	11.5	7.3	7.5
Neuromuscular dysfunction of bladder	N31	0.9	1.4	1.9	1.3	1.0
General Comorbidity						
Hypertension	I10-13,15	51.5	54.7	62.7	50.0	58.0
COPD	I27.8-9, J40-47, 60-67, 68.4, 70.1, 70.3	13.8	22.7	24.5	19.2	24.2
Osteoarthritis	M15-17	21.5	39.9	46.9	35.4	42.7
Osteoporosis	M80-82	10.1	26.4	37.9	16.3	28.7
Fibromyalgia	M79.7	1.1	10.8	11.2	8.9	8.2
Depression	F20.4,31.3-5, 32, 33, 34.1, 41.2, 43.2	20.6	33.5	36.4	34.8	38.2
Hypothyroidism	E00-03, E89.0	14.7	22.9	22.5	23.2	23.9
Solid tumour	C00-26, 30-34, 37-41, 43, 45-58, 60-76, 97	8.8	10.4	9.8	8.0	10.2
Metastatic Cancer	C77-80	1.1	1.2	1.8	1.3	1.0

In addition to SS associated codes (*e.g.* +M35.0*J99.1), extended codes for comorbidity are reported.

Table III. Medication in persons with SS diagnosis in rheumatology care, all values are percentages, unless otherwise indicated.

	ATC	Controls	pSS	sSS
n.		29,805	2,509	3,457
Saliva substitute	A01AD72	0.0	1.8	1.5
Tear substitute	S01XA20	0.0	0.3	0.0
Topic fluoride	A01AA	0.0	0.2	0.1
Cyclosporine eye drops	S01XA18	0.0	2.5	2.2
Pilocarpine	N07AX01	0.0	4.4	3.5
Anticholinergic drugs	A03AA,AB,CA,DA,E N04A S01FA	4.0	6.7	6.8
NSAIDs	M01A	27.6	41.2	44.8
Other analgesics	N02B	19.0	29.5	36.3
Opioids	N02A	8.3	14.9	21.4
Antidepressants	N06A	13.9	20.9	21.4
Glucocorticoids	H02AB01-07 H02BX	7.5	33.9	59.0
mean DDD per day of those with glucocorticoids		0.26[#]	0.37	0.42
cs and bDMARDs		0.8	31.2	65.9
csDMARDs	M01C P01BA01,02 A07EC01 L04AA06,13,32, L04AD01, AX01,03 C02KX01 L01AA01	0.7	29.0	59.4
Azathioprine	L04AX01	0.2	2.8	5.9
Cyclosporine, systemic	L04AD01	0.0	0.2	0.4
(Hydroxy-)chloroquine	P01BA02 P01BA01	0.1	18.5	23.4
Leflunomide	L04AA13	0.0	0.8	6.2
Mycofenolate mofetil	L04AA06	0.0	0.3	1.0
Methotrexate	L01BA01 L04AX03 M01CX01	0.3	7.8	30.0
bDMARDs	L04AB L04AA24,26 L01XC02 L04AC03,07,08,10,13-15	0.2	2.9	13.3
Abatacept	L04AA24	0.0	0.0	1.3
Belimumab	L04AA26	0.0	0.0	0.6
Rituximab	L01XC02	0.0	0.0	1.2
TNF-Inhibitors	L04AB	0.1	2.2	8.1

NSAID: non-steroidal antirheumatic drugs; DDD: defined daily dose.
[#]corresponding to an average dose of 2.6 mg prednisolone per day over the year.

All remaining patients were considered to have pSS based on the available claims data and their limitations.

Organ manifestation and comorbidity

Table II shows the frequency of associated and comorbidity ICD-diagnoses for patients with prevalent and incident SS under rheumatologic care and matched controls. The most frequent organ manifestations of SS comprised keratoconjunctivitis (23%-28%), interstitial kidney disease (12%-17%) and polyneuropathy (10%-16%). The last two were mainly reported as general comorbidity but not as SS-associated manifestation. Myopathy and lung involvement were coded in ≤3%.

The most common comorbidities in SS were hypertension (50%-63%), osteoarthritis (35%-47%) and depression (29%-34%). A markedly more frequent occurrence in SS than in controls was found for osteoarthritis (controls 22%, pSS 40%, and sSS 47%), osteoporosis (10%/26%/38%) and depression (21%/34%/36%). Osteoporosis was noticeably more frequent in prevalent compared to incident SS (pSS 26% *vs*. 16%, sSS 38% *vs*. 29%). Interestingly, patients with sSS had consistently more comorbidities than patients with pSS.

Medical prescriptions

Saliva substitutes were prescribed in less than 2% and nearly none of the SS patients had a prescription for tear substitute or topic fluorides. Cyclosporine eye drops were prescribed to about 2% of the pSS patients and pilocarpine for around 4%. Nearly 7% of the SS patients had a prescription for anticholinergic drugs compared to 4% of the controls. Frequent prescriptions were observed for NSAIDs (41–45%) and analgesics (30%–6%), also opioids and antidepressants were prescribed more frequently in pSS and sSS compared to controls (Table III).

Glucocorticoids were prescribed in 34% in pSS and 59% in sSS. The majority of patients had an average daily dose ≤5mg prednisolone equivalent over the year (Fig. 2). The mean DDDs are reported in Table II.

CsDMARDs were more often prescribed in sSS (59%) than in pSS (29%). The most commonly utilised csDMARDs were hydroxychloroquine (19% in pSS, 23% in sSS) and methotrexate (8% in pSS, 30% in sSS). bDMARDs were also prescribed more commonly in sSS (13%) than in pSS (3%).

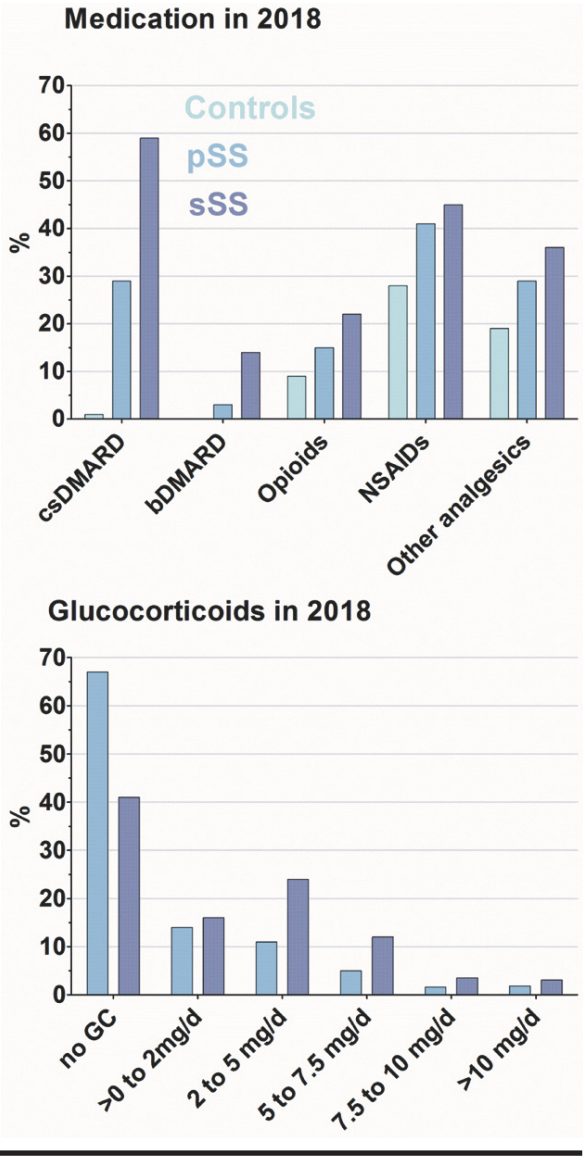

Fig. 2. Medication of patients with SS diagnosis in rheumatologic care.
pSS: persons with SS diagnosis (M35.0, ICD-10) without other autoimmune disease diagnoses; sSS: persons with SS and other autoimmune disease diagnoses; controls: age- and sex-matched persons without any autoimmune disease diagnosis; csDMARD: conventional synthetic disease-modifying antirheumatic drug; bDMARD: biologic disease-modifying antirheumatic drug; NSAIDs: non-steroidal antirheumatic drugs; GC: glucocorticoids.
Glucocorticoid categories are calculated from the defined daily doses (DDD), corresponding to a mean prednisolone equivalent dose per day for the year 2018. The DDD is a unit of measurement and does not necessarily reflect the prescribed doses for individual patients.

Hospitalisation and sick leave

A total of 32% (pSS) and 39% (sSS) were hospitalised (due to all causes) in 2018 compared to 21% of the controls. Notably, hospitalisation in 2007 was comparable: 34% in pSS, 34% in sSS, 16% controls.

Sick leave was assessed in persons aged ≤ 65 years which in Germany corresponded to the retirement age for many years. We had no information about the employment status of the patients. There were no major differences in the frequency of sick leave at least once in 2018 (44% sSS, 48% pSS, 41% controls). However, the mean and median number of days of sick leave was relevantly higher in sSS (mean: 67, median 30) than in pSS (mean 53, median 24) and controls (mean 40, median 17). In sSS, the proportion of patients with very long sick leave periods was highest (Table IV). The proportion of sick leave days due to SS was low. The most common sick leave diagnoses were with 10% acute upper respiratory infections (J06.9), 2.7% disorder of teeth and supporting structures (K08.9), 1.9% gastroenteritis (A09.9) and 1.9% acute bronchitis (J20.9). As sick leave data are only available since 2014, no comparison to previous years is possible.

Table IV. Sick leave in persons aged up to 65 years.

	Controls	pSS	sSS
Persons <=65 years, n	13,215	1,173	1,474
Sick leave (%)	41	48	44
Persons with sick leave, n	5,419	562	642
Sick leave, days (mean)	40	53	67
Sick leave, days (median)	17	24	30
Sick leave because of SS, mean %	NA	4.5	2.6
Sick leave because of RA mean %	NA	0.1	7.1

Days of sick leave are calculated for persons with sick leave only. Mean days of sick leave because of SS is calculated as (sick leave days due to SS)/(total sick leave days).

Frequency of SS ICD-diagnosis 2007-2018

The frequency of prevalent and incident SS diagnosis (M35.0) changed somewhat during this period but there was no trend over time (Supplementary Table S1).

Discussion

The ICD-10 diagnostic code M35.0, called "Sicca syndrome [Sjögren]" is abundantly frequent in the German BARMER health insurance data and without relevant changes over the last 10 years. The age and gender distribution with a disproportionately high proportion of men and elderly persons does not correspond to the expectations for the prevalence of a defined SS. We assume an inaccuracy of the claims diagnosis and narrowed it down further before expecting an SS. Since the SS classification criteria cannot be applied in claims data (3), our first approach was to approximate cases with coding of specific diagnostics and drug prescriptions which worked quite well for RA diagnosis (18). However, SSA/SSB autoantibodies were tested in less than 10% of all persons with SS diagnosis and in less than half of all patients under rheumatologic care. Diagnostics may have been carried out in further cases, but remained hidden in general claims codes. The same applies to the lip biopsy, Schirmer's test and salivary flow-rate which could not be identified at all. A further concern is that the diagnostic measures required in the classification criteria are rarely carried out in general care (6). For these reasons, we could not rule out SS by missing diagnostics. In contrast to RA, anti-inflammatory drugs were also not indicative, as they are not always necessary in SS. Due to these restrictions, we limited the further analyses to persons with SS diagnosis who had seen a rheumatologist. For this group, the age and gender distribution as well as the proportion of persons with other autoimmune diseases, thus with sSS, fits well with what is to be expected (10,14) although the mean age at incident diagnosis is higher compared to the mean age of onset which is usually reported between the 4th to 5th decade (12, 14).

Regarding organ manifestation, specific associated coding was hardly present, so that we additionally reported extended definitions for kidney disease and polyneuropathy. Here the proportions corresponded closer to the expectations as US claims data found hypertension, osteoarthritis and hyperlipidaemia as frequent comorbidity diagnoses in SS (9). Our study also points to depression and osteoporosis as they are diagnosed in at least 3 out of 10 persons with SS. Depression is of major clinical relevance as it is known to be associated with a high disease burden and work disability (13). It was common already in incident SS. The more frequent occurrence of osteoporosis in prevalent SS suggests a connection with the underlying inflammatory activity and glucocorticoids that were used in many patients.

Comparable to US data (9), we observed frequent prescriptions of symptomatic NSAIDs, other analgesics, antidepressants and opioids, all of them being more frequent compared to the gender and age-matched controls. The rare prescription of local symptomatic treatment is most likely related to patients buying it over the counter but is not in accordance with the current EULAR recommendations on the management of SS where local therapy is given a central role (19). Consistent with prior studies (13), depression and depressive mode disorders occur often among patients with SS and as such explain the higher prescription rate of antidepressants. The frequent use of glucocorticoids, especially in sSS but also in one third of pSS patients indicates systemic disease activity in at least one third of patients without other autoimmune diseases. This is in agreement with the proportion of patients with glucocorticoids in the German national database (12).

In the National database, we had observed a decline in hospitalisation and sick leave due to SS over the years (12). In the claims data, the number of persons with inpatient stays, independent of the cause, has not changed. This may be attributed to an increase of the overall case numbers in German hospitals in this time period (12). In line with population-based US data, we observed a higher need of hospitalisation compared to controls (20). In coincidence with the former German Sjögren's cohort, the number of days of absence among persons with SS was also higher compared to controls (13), indicating a higher individual and societal burden.

Limitations and strengths

This study is based on claims data; therefore, the diagnosis of SS could not be confirmed by external clinical validation. Uncertainty about fulfilling pSS classification criteria or not remains a main limitation of the claims data analysis. Our analysis does not include rheumatologic outpatient clinics at university hospitals and rheumatologists who work as general practitioners as these institutions are not entitled to use a specific rheumatologic billing code. Our results are therefore restricted to patients in non-university rheumatologic outpatient care. A major advantage is that the BARMER data capture rheumatologic care nationwide with more than 600 rheumatologists and enable a comparison with population controls of the same age and sex.

This study shows the complexity of claims data analyses. A simple pres-

entation of frequencies of claims diagnoses will not lead to valid prevalence rates. In our data, ICD-10 M35.0 was frequently coded, although it is classified in the ICD catalogue as a disease with systemic involvement of the connective tissue and there are separate accounting figures for unspecific dry mouth or eye symptoms.

In summary, ICD-10 diagnosis of SS is frequently used in German claims data and should not be equated with clinical diagnosis of SS. Patients with SS diagnosis in rheumatologic care are characterised by a high risk of comorbidity and frequent prescriptions of unspecific anti-inflammatory drugs, pain killers and antidepressants. They are at higher risk of hospital stays and work leave compared to persons without autoimmune diseases. The individual and societal burden of SS shows that, in addition to effective treatment strategies, intensive attention to comorbidities is important in this disease.

Acknowledgements

The authors thank the BARMER for providing access to data via their data warehouse for this study.

References

1. STEFANSKI AL, TOMIAK C, PLEYER U, DIETRICH T, BURMESTER GR, DÖRNER T: The diagnosis and treatment of Sjögren's syndrome. *Dtsch Arztebl Int* 2017; 114: 354-361.
2. WITTE T: [Sjögren's syndrome]. *Z Rheumatol* 2019; 78: 511-7.
3. CORNEC D, CHICHE L: Is primary Sjögren's syndrome an orphan disease? A critical appraisal of prevalence studies in Europe. *Ann Rheum Dis* 2015; 74: e25.
4. SHIBOSKI CH, SHIBOSKI SC, SEROR R *et al*.: 2016 American College of Rheumatology/ European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis* 2017; 76: 9-16.
5. SEROR R, RAVAUD P, BOWMAN SJ *et al*.: EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis* 2010; 69: 1103-9.
6. QIN B, WANG J, YANG Z *et al*.: Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis* 2015; 74: 1983-9.
7. MACIEL G, CROWSON CS, MATTESON EL, CORNEC D: Prevalence of Primary Sjögren's Syndrome in a US Population-Based Cohort. *Arthritis Care Res* (Hoboken) 2017; 69: 1612-6.
8. MACIEL G, CROWSON CS, MATTESON EL, CORNEC D: Incidence and mortality of physician-diagnosed primary Sjögren syndrome: time trends over a 40-year period in a population-based US Cohort. *Mayo Clin Proc* 2017; 92: 734-43.
9. BIRT JA, TAN Y, MOZAFFARIAN N: Sjögren's syndrome: managed care data from a large United States population highlight real-world health care burden and lack of treatment options. *Clin Exp Rheumatol* 2017; 35: 98-107.
10. WESTHOFF G, ZINK A: [Epidemiology of primary Sjögren's syndrome]. *Z Rheumatol* 2010; 69: 41-9.
11. SEGHIERI C, LUPI E, EXARCHOS TP, FERRO F, TZIOUFAS AG, BALDINI C: Variation in primary Sjögren's syndrome care among European countries. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S27-8.
12. CALLHOFF J, THIELE K, DORNER T *et al*.: Trends in employment and hospitalisation in patients with Sjögren's syndrome 1996-2016: results from the German National database. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S83-9.
13. WESTHOFF G, DORNER T, ZINK A: Fatigue and depression predict physician visits and work disability in women with primary Sjögren's syndrome: results from a cohort study. *Rheumatology* (Oxford) 2012; 51: 262-9.
14. PATEL R, SHAHANE A: The epidemiology of Sjögren's syndrome. *Clin Epidemiol* 2014; 6: 247-55.
15. CORNEC D, SARAUX A, JOUSSE-JOULIN S *et al*.: The Differential Diagnosis of Dry Eyes, Dry Mouth, and Parotidomegaly: A Comprehensive Review. *Clin Rev Allergy Immunol* 2015; 49: 278-87.
16. QUAN H, SUNDARARAJAN V, HALFON P *et al*.: Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; 43: 1130-9.
17. Methodology WCCfDS: ATC classification index with DDDs, 2019. Oslo, Norway 2018.
18. HENSE S, LUQUE RAMOS A, CALLHOFF J *et al*.: [Prevalence of rheumatoid arthritis in Germany based on health insurance data: Regional differences and first results of the PROCLAIR study]. *Z Rheumatol* 2016; 75: 819-27.
19. RAMOS-CASALS M, BRITO-ZERON P, BOMBARDIERI S *et al*.: EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis* 2020; 79: 3-18.
20. MACIEL G, SERVIOLI L, NANNINI C *et al*.: Hospitalisation rates among patients with primary Sjögren's syndrome: a population-based study, 1995-2016. *RMD Open* 2018; 4: e000575.