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Incidence and Mortality of Physician-Diagnosed Primary Sjögren's Syndrome: Time Trends Over a 40-year Period in a Population-based Cohort in the United States

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Abstract

Objective—To estimate the incidence and mortality rates of physician-diagnosed primary Sjögren's syndrome (pSS) among residents of Olmsted County, Minnesota, and their evolution over time.

Patients and Methods—All medical records of patients with a diagnosis or suspicion of SS in Olmsted County, MN, from January 1, 2006 to December 31, 2015 were reviewed to identify incident cases of pSS (defined according to physician diagnosis). These cases were combined with a previous 1976–2005 incident cohort from the same population. Incidence rates were age and sex adjusted to the US white 2010 population. Survival rates were compared with the expected rates in the population of Minnesota.

Results—With 61 incident cases of pSS diagnosed in Olmsted County in 2006–2015, the total cohort included 172 patients with incident pSS in 1976–2015. Of the 172 patients, 151 (88%) were women and 161 (94%) were white, with a mean (SD) age at diagnosis of 58.3 (16.7) years. The average age- and sex- adjusted annual incidence for 2006–2015 was 5.9 per 100,000 population (95%CI 4.4–7.4), and overall incidence for the entire period was 5.8 (95% CI: 4.9–6.6) per

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100,000. The incidence increased with calendar time over the 40-year period (*P*=.005). There was no difference in mortality in the pSS cohort compared to expected (standardized mortality ratio 1.15, 95%CI 0.86–1.50).

Conclusions—The average annual incidence of pSS in this population based-cohort was 5.8/100,000, with a progressive increase over the 40 years covered by the study. Overall survival of pSS patients was not different from the general population.

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disorder characterized by an inflammatory infiltrate and progressive dysfunction of exocrine glands, particularly the lachrymal and salivary glands [1]. Cardinal symptoms include mouth and eye dryness, marked fatigue and wide-spread pain, which have a profound effect on the quality of life of patients with pSS [2]. These symptoms are non-specific and can occur with many other conditions [3, 4]. Up to one third of patients also experience extraglandular inflammatory involvement including polysynovitis, neuropathy and inflammatory lung disease [5–7].

The etiology of pSS is not well understood [8], and probably includes environmental triggers in genetically predisposed subjects, as illustrated by its familial aggregation [9] and predisposing genetic variants [10]. It mainly affects middle-aged females, with a strong sex bias potentially explained by an X chromosome dose effect [11]. pSS occurs as a primary disorder, and secondary SS may occur with other systemic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus [12, 13]. pSS may be associated with malignancies, especially non-Hodgkin lymphoma [14].

There are no specific diagnostic tests for pSS. To facilitate study of the disease and improve uniformity of the patient populations in clinical studies, researchers have developed classification criteria based upon the signs and symptoms and diagnostic tests used in evaluating patients with suspected SS. The coexistence of two different sets of classification criteria for pSS (the 2002 American European Consensus Group (AECG) [15] and the 2012 American College of Rheumatology (ACR) classification criteria [16]) justified new consensual criteria[17–19], which have been developed through an ACR-European League Against Rheumatism (EULAR) collaboration and were recently published [20, 21].

The epidemiology of pSS is poorly defined [22, 23]. We recently reported that the 2015 prevalence of pSS in Olmsted County was 10.3/10,000 inhabitants according to the physician diagnosis, but only 2.2/10,000 according to classification criteria [24]. Estimates of pSS incidence also vary considerably depending on population studied and methods used for case detection and ascertainment, with published incidence rates ranging from 3.1 to 10.7 cases per 100,000 [2526]. The only incidence data available in the US were published by our group, which reported an average incidence of 3.9 per 100,000 for the 1976–1992 period [27] and 5.1 per 100,000 for the 1976–2005 period [28], suggesting a progressive increase of the incidence of the disease over time. It is unclear whether patients with pSS have an increased risk of mortality compared to the general population [29]. The objectives of this study were to estimate the evolution over time of incidence of pSS among residents of Olmsted County, Minnesota and examine its effect on mortality.

Methods

Case identification and ascertainment

The study population included patients with incident pSS diagnosed in Olmsted County, Minnesota, a county with 113,306 adult (age ≥ 18 years) inhabitants as of January 1, 2015. This population is well suited for investigation of the epidemiology of pSS because of the availability of comprehensive medical record information for the entire population [30, 31]. The potential cases were selected based on diagnostic codes for Sjögren's syndrome, auto-antibody positivity (anti-SSA and/or – SSB), sicca syndrome and keratoconjunctivitis sicca (KCS) using the resources of the Rochester Epidemiology Project (REP). This is a medical records linkage system that allows ready access to the complete (inpatient and outpatient) records from all healthcare providers for the local population, including the Mayo Clinic and its affiliated hospital, the Olmsted Medical Center and its affiliated community hospital, local nursing homes and a few private practitioners [32]. This system ensures virtually complete clinical information on all clinically recognized cases of pSS among Olmsted County residents. For the current update of pSS incidence, potential cases were all residents of Olmsted County, Minnesota at the time of their diagnosis, made between January 1, 2006 and December 31, 2015. These new cases were analyzed together with a previously reported incident pSS cohort including patients first diagnosed in 1976–2005 from the same population [28].

In addition to screening by diagnostic codes for Sjögren's syndrome and relevant autoantibodies, 50 randomly selected patient records with diagnostic codes of xerostomia and 50 with KCS but without diagnosis of Sjögren's syndrome or relevant autoantibodies were also screened to assess whether any additional cases of pSS case were missed using the other codes. As no patients with incident pSS were identified in these samples, the probability of missed cases is very low.

All individual clinical charts from patients selected during the first screening phase were reviewed. All patients with a definite physician diagnosis of pSS were included. Almost all diagnoses were made or confirmed by rheumatologists. Cases of uncertain diagnosis and those with secondary SS were excluded. Collected data included date of first pSS diagnosis, age, sex, ethnicity, smoking status, presence of dry eyes and dry mouth, serologic tests (anti-SSA, anti-SSB and antinuclear antibodies, rheumatoid factor), presence of hypergammaglobulinemia and results of diagnostic tests if performed such as Schirmer's test, ocular surface staining, salivary scintigraphy, parotid sialography, unstimulated salivary flow measurement and minor salivary gland biopsy.

The 2002 AECG and 2012 ACR classification criteria were applied to all physician diagnosed cases. Systemic involvement was analyzed at the time of the diagnosis in patients diagnosed between 2006 and 2015 according to the EULAR Sjögren's syndrome disease activity index (ESSDAI) [33–35], with no or low systemic activity category defined as an ESSDAI of less than 5, moderate activity as an ESSDAI comprised between 5 and 13, and high activity as an ESSDAI of 14 or more [36].

Statistical analyses

Descriptive statistics (means, percentages, etc.) were used to summarize the data. Comparisons of patient characteristics between time periods were performed using Chi-square and rank sum tests. Age- and sex-specific incidence rates for adults (age ≥ 18 years) were calculated using the number of incidence cases as the numerator and population estimates based on decennial census counts as the denominator, with linear interpolation to estimate population size for intercensal years. Annual incidence rates were illustrated using a 3 year centered moving average. Overall rates were age and sex adjusted to the 2010 United States white population. Ninety-five percent confidence intervals were computed for incidence rates assuming that the observed number of cases follows a Poisson distribution. Poisson regression models with smoothing splines to allow for non-linear effects were used to evaluate time trends in incidence rates.

Survival following the diagnosis of pSS was estimated using Kaplan-Meier methods. Observed and expected survival rates were compared using the log-rank test, where expected survival was based on the sex and age of the study population and on death rates from the Minnesota Caucasian life tables. The standardized mortality ratio (SMR), the ratio of observed number of deaths to the expected number, was estimated and a 95% CI obtained assuming that the observed number of deaths follows a Poisson distribution. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of the cohort

Between 2006 and 2015, 61 new patients were diagnosed with incident pSS in Olmsted County, and analyzed together with the incident cases diagnosed between 1976 and 2005. One patient age 17 years at diagnosis was excluded from incidence calculations but was included for survival analysis. Among these 172 patients (Table 1), 151 (88%) were women and 161 (94%) were white. The mean (SD) age at diagnosis was 58.3 (16.7) years. A majority (n=94, 58%) were never smokers. More patients reported dry eye symptoms (n=156, 91%) than dry mouth symptoms (n=144, 84%). There were no significant differences concerning these general characteristics between patients diagnosed before or after 2005. Features of systemic involvement at diagnosis were retrospectively collected for patients diagnosed between 2006 and 2015 using the ESSDAI (Table 2). The majority of patients (70%) had no or low systemic activity at incidence, 21% had moderate and 8% had high systemic disease activity. The median (range) ESSDAI score was 1 (0, 23). Among the different ESSDAI domains, most of the systemic activity was scored for the biological domain (in 26 patients), with only 12 patients scored for the glandular, 6 for the peripheral nerve, and 3 for the articular domains, respectively.

Among the objective tests used by physicians to make a pSS diagnosis, serologic studies were the most frequently performed (Table 1). When performed, rheumatoid factor was positive in 53% of cases, antinuclear antibodies in 71%, anti-SSA in 74% and anti-SSB antibodies in 56%. Hypergammaglobulinemia was present in 50% of patients with available

data. Objective tests to assess for sicca complaints were rarely performed. Ocular objective procedures (Schirmer's test or ocular surface staining) were performed in 61 patients and were positive in 53 (87%). Salivary gland morphologic or functional tests (salivary scintigraphy, parotid sialography or unstimulated salivary flow) were performed in 65 patients and were positive in 15 (23%). Minor salivary gland lip biopsy was obtained in only 21 patients and was positive in 12 (57%). Comparing the two periods, physicians more often used serologic tests, especially anti-SSA/SSB antibodies, to diagnose the disease after 2005. Accordingly, only 32 (19%) patients met AECG criteria for classification of pSS, and 36 (21%) fulfilled ACR criteria.

Analysis of pSS incidence over time and impact of seasonality

The overall age and sex adjusted annual incidence of pSS was 5.8 per 100,000 population age ≥ 18 years over the 40-year period covered by the study (Table 3). Incidence was 2 to 7 times higher in females compared to males in the different age classes (5.9 times higher on average), and increased progressively with age, culminating at 19.6 per 100,000 in females aged 65–74 years, with a slight decline thereafter to 15.9 per 100,000 among females aged 75 years and more.

There was some fluctuation in annual incidence of pSS with higher values around 1990, 2005 and 2015. Overall, however, there was a progressive increase of pSS incidence over time (Figure 1A, P=.005). The overall age and sex adjusted incidence rate was 4.2 (95% CI: 2.3, 6.1) for the period 1976–1985, 5.2 (95% CI: 3.4, 7.1) for the period 1986–1995, 7.0 (95% CI: 5.1, 8.9) for the period 1996–2005,and 5.9 (95% CI: 4.4, 7.4) per 100,000 population for the period 2006–2015.

No effect of seasonality on disease incidence was observed (figure 1B), with an age and sex adjusted incidence rate (95% CI) of 1.6 (1.1, 2.1) during winter, 1.1 (0.7, 1.5) during spring, 1.6 (1.1, 2.1) during summer and 1.5 (1.0, 1.9) per 100,000 population during fall (P=.38 for the four season comparison).

Mortality of pSS patients compared to the general population

There were 52 deaths in the 172 patients. Compared to the general population, in which about 45 deaths would be expected, the standardized mortality for patients with pSS incident 1976–2015 was 1.15 (95% CI: 0.86, 1.50) (Figure 1C). No evidence of a time trend in survival according to year of diagnosis was found (P=.90, data not shown). Overall, 5, 10, and 20 year survival rates were 56.7 (95% CI: 46.6–68.9%), 93.7% (95% CI: 90.0–97.6%), 81.8 (95% CI: 75.5–88.6%), and 71.8 (95% CI: 63.8–80.8%), respectively.

Discussion

This study reports estimates of the incidence and mortality rates of pSS patients in a geographically well-defined region in the U.S., and their evolution over a period of 40 years. The estimated incidence of pSS in Olmsted County in 1976–2015 was 5.8/100,000, with a significant progressive increase of pSS incidence over time. Mortality rates of pSS patients were similar to expected rates in the general population.

Better description of the epidemiology of pSS is important for public health stakeholders, regulating agencies and drug companies. To date, no disease-modifying drug has been proven effective to improve pSS symptoms and change disease natural course, as all published large randomized controlled trials are negative [37–39]. These trial failures could be explained by design issues and outcome definitions [40, 41]. Treatment algorithms are currently based on expert opinion, usually by analogy to other systemic autoimmune diseases [42–44]. However, recent years have witnessed an increase in interest of pharmaceutical companies for developing new drugs in the disease, and more than 10 industry-sponsored randomized controlled studies are currently ongoing [45]. Hopefully, some of these innovative drugs tested in the disease will demonstrate their efficacy, and better knowledge of the number and characteristics of patients in the general population who could potentially benefit from these drugs will be of major importance at the time of their commercialization.

All previous studies reporting pSS incidence worldwide are summarized in table 4. Our incidence rate is in the range of what was described in those previous studies, despite study design differences and case definitions. Strengths of the current study include the broad screening methodology, using the REP, allowing complete full access to a performant coding system and to all individual medical records of the screened patients, which resulted in an exhaustive case detection and ascertainment in the general population living in Olmsted County. Most of these other studies used hospital-based medical record search [25, 26, 46, 47], but it is likely that some patients with mild presentation not requiring specific therapies are diagnosed and followed outside of the hospital setting, and are therefore missed by such case-detection strategies. The study by Weng et al in Taiwan used administrative database search with no case ascertainment, which could be biased by coding errors and therefore false diagnoses [48].

The case-ascertainment method in this study was based on definite physician diagnosis of pSS. Even if not standardized, this reflects how the disease is actually diagnosed, and therefore treated, in routine practice in a community setting. Using only administrative coding systems without analyzing actual medical data from the clinical charts may lead to both inclusion of cases that do not have the diagnoses and failure to detect actual cases.

As demonstrated in our study, current classification criteria for pSS are not applicable to epidemiologic studies in a community-based setting, since physicians in Olmsted County do not use several of the tests included in the different versions of the classification criteria (mainly functional salivary and ocular tests and salivary gland biopsy) to diagnose the disease. In our study, the main explanation for not fulfilling the criteria was that the required tests were not performed, and not that they were negative. Of note, a similar observation was made in previous population-based pSS studies. In the prevalence study by Maldini et al, a substantial proportion of patients received a clinical diagnosis of pSS but did not fulfil AECG criteria because oral/ocular tests were not performed, and the authors used “enlarged” criteria to define pSS cases [49].

The low number of patients who underwent a salivary gland biopsy in our cohort probably indicates that treating physicians consider that patients without autoantibodies (anti-SSA,

anti-SSB, but also ANA or RF) do not actually have pSS. The main therapies offered to patients with sicca symptoms with or without pSS are directed toward management of dryness, including tear and saliva substitutes. Therefore, physicians may not consider it clinically useful to perform invasive diagnostic tests such as salivary gland biopsy if results of these tests would not affect clinical decisions regarding diagnosis and management. However, even if "seronegative" pSS patients probably have a lower risk of lymphoma development [50], they have symptoms severe enough to require medical attention [51]. Besides its diagnostic value, salivary gland biopsy also gives important prognostic information, as patients with higher focus scores or ectopic germinal centers have a higher risk of systemic complications and lymphoma development [52–54]. Therefore, minor salivary gland biopsy should be considered in every patient with suspected pSS.

Several reasons could explain the progressive increase of pSS incidence over time seen in this study. Aging of the general population is not a factor, since all incidence estimates are age and sex adjusted to the general population. Interestingly, general characteristics of patients diagnosed with pSS in Olmsted County did not change over time. Physicians could be more aware of the diagnosis in the recent years compared to the early years (1970s–1980s) of the study period. The greater availability of anti-SSA and anti-SSB antibody testing over the 40 years of our study could also have contributed to the increased incidence over time, facilitating a diagnosis in those with milder disease. Patients may seek more often medical care for subjective symptoms that impair their quality of life but may still be considered benign. Changes in lifestyle and environmental exposures could also lead to a real increase of the number of individuals developing this autoimmune disease.

The mortality in patients with incident pSS in Olmsted County is not higher that the general population. Previous studies have shown that subgroups of pSS patients have a decreased survival, especially patients with high systemic disease activity [55], and notably patients who develop severe systemic involvement such as cryoglobulinemic vasculitis [56] or who develop lymphoma [57]. However, those severe presentations are rare among patient with incident pSS, and do not affect the overall survival. Systemic involvement in our cohort was analyzed at the time of diagnosis based on retrospective chart review, which could lead to an under-evaluation of the ESSDAI score, especially its biological domain, if tests required for the scoring were not performed (such as cryoglobulin, IgG or complement levels).

Conclusion

To conclude, the average annual incidence of physician-diagnosed pSS in Olmsted County was 5.8/100,000, with a progressive increase over the 40 years covered by the study. Current classification criteria do not perform well to study the epidemiology of pSS in a community setting. Overall survival of pSS patients was not different from the general population.

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List of abbreviations

pSS	Primary Sjögren's syndrome
AECG	American European Consensus Group
ACR	American College of Rheumatology
EULAR	European League Against Rheumatism
KCS	keratoconjunctivitis sicca
REP	Rochester Epidemiology Project
SMR	standardized mortality ratio

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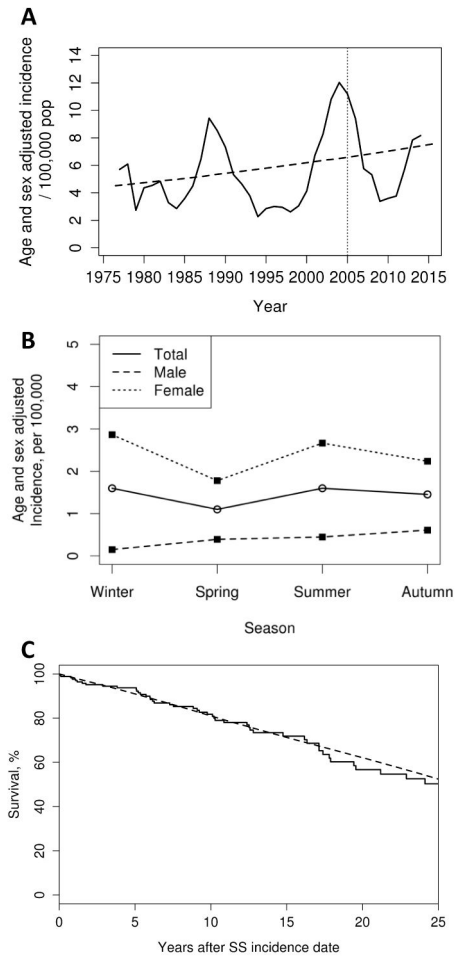

Figure 1.

Incidence over time (A), seasonality (B) and survival (C) in Olmsted County, Minnesota residents with incident primary Sjögren's syndrome (SS) in 1976–2015 (n=172).

Table 1

Characteristics of the patients with incident primary Sjögren's syndrome diagnosed in Olmsted County, Minnesota between 1976 and 2015

Table 1. Characteristics of patients with incident primary Sjögren's syndrome by time period [c]

	1976–2005 (N=111)	2006–2015 (N=61)	Total (N=172)	*P* value[b]
Age, years, mean (SD)	58.0 (16.6)	58.9 (17.0)	58.3 (16.7)	.73
Sex (female)	100 (90%)	51 (84%)	151 (88%)	.21
Ethnicity, White	105 (95%)	56 (92%)	161 (94%)	.06
Smoking status at diagnosis of pSS (never smoked)	58/102 (57%)	36/60 (60%)	94/162 (58%)	.13
Ocular Symptoms	101/111 (91%)	55/61 (90%)	156/172 (91%)	.86
Oral symptoms	94/111 (85%)	50/61 (82%)	144/172 (84%)	.64
Rheumatoid factor				
Not done	23 (21%)	10 (16%)	33 (19%)	.49
Positive	51/88 (58%)	23/51 (45%)	74/139 (53%)	.14
Anti-nuclear antibody				
Not done	14 (13%)	2 (3%)	16 (9%)	.04
Positive	67/97 (69%)	43/59 (73%)	110/156 (71%)	.61
Anti-SSA (anti-Ro)				
Not done	37 (33%)	1 (2%)	38 (22%)	<.001
Positive	51/74 (69%)	48/60 (80%)	99/134 (74%)	.15
Anti-SSB (anti-La)				
Not done	35 (32%)	2 (3%)	37 (22%)	<.001
Positive	42/76 (55%)	34/59 (58%)	76/135 (56%)	.78
Hypergammaglobulinemia				
Not done	24 (22%)	11 (18%)	35 (20%)	.58
Present	45/87 (52%)	24/50 (48%)	69/137 (50%)	.68
Ocular objective tests				
Not done	72 (65%)	39 (64%)	111 (65%)	.90
Abnormal	38/39 (97%)	15/22 (68%)	53/61 (87%)	.001
Oral objective tests				
Not done	56 (50%)	51 (84%)	107 (62%)	<.001
Abnormal	6/55 (11%)	9/10 (90%)	15/65 (23%)	<.001
Salivary gland biopsy				
Not done	100 (90%)	51 (84%)	151 (88%)	.21
Abnormal	3/11 (27%)	9/10 (90%)	12/21 (57%)	.004
Met AECG criteria [a]	15 (14%)	17 (28%)	32 (19%)	.02
Met ACR criteria	20 (18%)	16 (26%)	36 (21%)	.20

[a] Abbreviations: AECG, 2002 American-European Consensus Group; ACR, 2012 American College of Rheumatology

[b] *P* value for comparison between patients diagnosed during the 1976–2005 period vs the 2006–2015 period.

[c] Values in table are n (%) or n present / n available (%) unless otherwise specified.

Table 2

Systemic involvement in 61 patients with primary Sjögren's syndrome diagnosed between 2006 and 2015 according to ESSDAI [a] criteria

Domain	N (%)
Constitutional domain	
0	59 (97%)
1	1 (2%)
2	1 (2%)
Lymphadenopathy domain	
0	59 (97%)
1	2 (3%)
Glandular domain	
0	49 (80%)
1	8 (13%)
2	4 (7%)
Articular domain	
0	58 (95%)
1	1 (2%)
2	2 (3%)
Cutaneous domain	
0	60 (98%)
2	1 (2%)
Respiratory domain	
0	59 (97%)
1	1 (2%)
2	1 (2%)
Renal domain	
0	59 (97%)
3	2 (3%)
Muscular domain	
0	59 (97%)
2	1 (2%)
3	1 (2%)
Peripheral nervous domain	
0	55 (90%)
1	2 (3%)
2	3 (5%)
3	1 (2%)
Central nervous domain	
0	61 (100%)
Hematological domain	
0	59 (98%)

Domain	N (%)
1	1 (2%)
Biological domain	
0	35 (57%)
1	25 (41%)
2	1 (2%)
ESSDAI score, median (range)	1.0 (0.0–23.0)
ESSDAI categories	
Low activity (<5)	43 (70%)
Moderate activity (5–13)	13 (21%)
High activity (≥14)	5 (8%)

[a]ESSDAI, EULAR Sjögren's syndrome disease activity index

Table 3

Incidence of primary Sjögren's syndrome among residents of Olmsted County, Minnesota in 1976–2015 by sex and age group, per 100,000 population age ≥ 18 years.

	Male		Female		Total	
Age group	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**
18–44	6	0.6	30	3.1	36	1.9
45–54	3	1.0	36	12.0	39	6.6
55–64	4	2.0	30	14.1	34	8.2
65–74	3	2.5	29	19.6	32	11.9
75+	5	5.7	25	15.9	30	12.3
Overall[c]	21	1.6[a] (0.9, 2.3)	150	9.5 [a] (8.0, 11.1)	171	5.8[b] (4.9, 6.6)

[a] Age adjusted to US white 2010 population

[b] Age and sex adjusted to US white 2010 population

[c] One patient age 17 years at diagnosis was excluded from incidence calculations.

Table 4

Comparison of published incidence studies of primary Sjögren's syndrome worldwide

Reference	Region	Study Period	Source of cases	Case definition	pSS cases	Background population	Reported incidence rate (95%CI)/100,000
Plesivcnik Novljan et al., 2004[46]	Slovenia	2000–2002	Hospital-based case screening (Rheumatology department)	1996 European criteria	71	599,895	3.9 (1.1, 10.2)
Alamanos et al., 2006[47]	Greece	1982–2003	Medical record search (hospital + private rheumatologists)	AECG [a] criteria	422	488,435	5.3 4.5, 6.1)
Weng et al., 2011[48] *b*	Taiwan	2005–2007	National Health Insurance database"	Catastrophic Illness Certificate", no case review	3352	22,823,550	6.0 (5.8, 6.2)
Kvarnstrom et al., 2015[25]	Sweden	2007–2011	Hospital-based case screening (Rheumatology department)	AECG	199	≈1,300,000	3.1 (2.3, 4.3)
Elfving et al., 2016[26]	Finland	2010	Hospital-based case screening (Rheumatology department)	Physician diagnosis	22	206,441	10.7 (6.7–16.1)
Present study	USA (Minnesota)	1976–2015	Rochester Epidemiology Project: coding system screening for the whole population, and medical records review	Physician diagnosis	172	113,306	5.8 (4.9, 6.6)

[a] Abbreviations: AECG, American-European Consensus Group classification criteria; ICD, International Classification of the Diseases; ACR, American College of Rheumatology; ND, not done; pSS, primary Sjögren's syndrome.

[b] Two other studies from Taiwan were excluded from this table because they used a random sample of the same population, including the same years than the study by Weng et al. [58, 59]