Prevalence and incidence of Sjögren's disease: A systematic literature review

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Background

- Sjögren's disease (SjD) is a complex chronic, systemic, autoimmune disease characterized by lymphocytic infiltration of exocrine glands (e.g., salivary and lacrimal glands), leading to oral and ocular dryness that can significantly impact quality of life
  - The disorder has been historically categorized as follows:
    - Primary Sjögren's disease: A standalone autoimmune disease diagnosed when a patient presents with dry eyes and dry mouth (i.e., sicca symptoms), along with confirming tests
    - Secondary Sjögren's disease: Diagnosed when a patient has both SjD and another autoimmune disorder such as rheumatoid arthritis, lupus, or scleroderma, making diagnosis and management more complex
- Recent work has criticized this dichotomy, and instead recommends that SjD be described as a singular disease, with comorbidity (hereafter, Sjögren's-associated disease) or without comorbidity (hereafter, SjD)
- The cause of SjD is not fully understood; the disorder primarily affects women aged 40 to 60. Other potential risk factors are genetic predisposition, family history of autoimmune diseases, coexisting autoimmune conditions, hormonal changes, infections such as Epstein-Barr virus, and geographical location. However, SjD can also occur in individuals without these factors, underscoring its complex origin
- Understanding the prevalence and incidence of SjD is fundamental for effective management and support for patients. However, changing diagnostic criteria for SjD has affected prevalence[1,2] and incidence studies, leading to variations in reported rates and making comparisons between studies challenging

Objective

- To describe and characterize the prevalence and incidence rates of Sjögren's disease, with a particular emphasis on specific geographic locations and unique populations

Methods

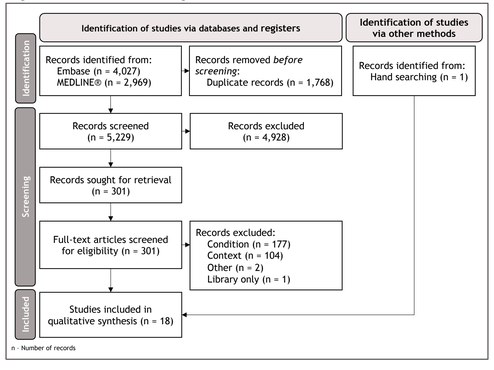
- A systematic literature review was conducted by searching MEDLINE® and Embase from database inception to September 27, 2022. Abstracts from the following conferences were also searched from 2020 to 2022 via Embase:
  - American College of Rheumatology (ACR)
  - European League Against Rheumatism Annual Congress (EULAR)
  - International Symposium on Sjögren's Syndrome
- Two investigators (NG and AA) reviewed all abstracts identified through the searches and assessed eligibility according to the following criteria[3]:
  - **Condition:** SjD
  - **Context:** United States (US), France, Germany, Italy, Spain, the United Kingdom (UK), China, and Japan
  - **Population:** Adults (aged ≥18 years)
  - Records were restricted to those published in English
- Following full-text screening, study and patient characteristics as well as outcomes (prevalence or incidence of SjD) were extracted by two reviewers

Results

Study selection

- Of 6,997 total records identified, 18[4-21] unique studies were included for the qualitative synthesis (**Figure 1**)
  - One record[18] was identified from hand-searching of previously published literature reviews
- Of note, the initial scope of our review was broader, and aimed to identify records on prevalence and incidence as well as burden of illness in SjD. However, for the purposes of this report, only studies reporting the prevalence or incidence of SjD were included

Figure 1. PRISMA flow diagram



Study and patient characteristics

- We identified various designs: 10 studies were cross-sectional, 6 were retrospective cohort studies, and 2 were prospective cohort studies
- Study dates encompassed time periods between 1976 and 2018
- Total sample size (i.e., the denominator from which prevalence or incidence of SjD was estimated) ranged from 341 (sample survey of the UK in 1995) to ~67 million (French population census in 2021)
  - The overall median sample size was 25,885
- Baseline patient characteristics as well as the populations in which prevalence or incidence were measured varied across studies
- Proportion of female SjD patients ranged from 21 to 100% (overall median: 89%)
  - The lower bound of this range was reported by a study that investigated prevalence of systemic autoimmune disease among adults exposed to the September 11, 2001 terrorist attack.[14] All other included studies reported that more than half of their study participants were female

Study and patient characteristics (continued)

- Mean age of SjD patients ranged from 39 to 73 years (overall median: 58 years)
- In terms of the classification of SjD, 10 studies reported on "primary" SjD (i.e., SjD without comorbidity)
  - One study reported only "secondary" SjD (i.e., Sjögren's-associated disease), two studies reported unspecified SjD (i.e., SjD described as neither "primary" nor "secondary" by reporting authors), and the remaining five studies reported a mix of "primary" or "secondary" SjD (i.e., SjD with or without comorbidity) with results stratified by classification
    - Of the five studies reporting a mix of SjD with or without comorbidity, the proportion of cases of SjD without comorbidity ranged from 12 to 87% of the total SjD cases (overall median: 45%)

Prevalence

- Fifteen studies reported prevalence of SjD; nine studies reported the prevalence of SjD within a general population (**Table 1**), while six studies reported prevalence SjD within special populations that were not representative of a general population (**Table 2**)
  - Prevalence of SjD ranged from 0.3 to 180 cases per 10,000 persons in population-based studies across select countries. The study designs and diagnostic criteria employed varied across the studies (**Table 1**)
  - Prevalence rates were more than 100 times higher among patients with other autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (**Table 2**)

Table 1. Population-based prevalence studies of Sjögren's disease in select countries

Study	Country (region)	Study features	Case identification criteria	Prevalence per 10,000 (95% CI)
Zhang 1995	China	Sample survey (response rate not stated); Age >16 years	Modified Fox Criteria Copenhagen Criteria	SjD: 33 SjD: 77
Thomas 1998	UK	Sample survey (<35% response); Age 18-75 years	European Classification Criteria	Unspecified SjD: 180 (110-280)[a]
Sardu 2012	Italy (Sardinia)	Population-based census; National Health Database; Age 15-89 years	ICD-9 code 710.2	SjD: 3.1 (1.3-6.1)
Seror 2021[c]	France (Paris)	Population-based census National Claim Database	Study-specific algorithm	SjD: 2.2-3.2 Sjögren's-associated disease: 1.7-2.2
Maldini 2014	France	Population-based census; Age ≥15 years	AECG Enlarged AECG criteria[b]	SjD: 1.0 (0.9-1.2) SjD: 1.5 (1.3-1.8)
Narvaez 2020	Spain	Sample survey (15% response rate); Age ≥20 years	AECG	SjD: 25 (15-43) Unspecified SjD: 33 (21-51)
Albrecht 2020[c]	Germany	Insurance database; Conference abstract	M35.0 (ICD-10)	SjD: 73 Sjögren's-associated disease: 4.6
Maciel 2017a	US (Minnesota)	Population-based Medical linkage system; Age ≥18 years	AECG or ACR criteria Physician diagnosis Estimates based on 1976-2005 incidence	SjD: 2.2 (1.3-3.1) SjD: 10.3 (8.3-12.2) SjD: 11.0 (9.0-13.8)
Izmirly 2019	US (Manhattan)	Population-based registry of cases of Lupus Surveillance; Age ≥18 years	Physician-diagnosed Rheumatologist diagnosis Modified criteria	SjD: 1.3 (1.1-1.5)[d] SjD: 0.7 (0.6-0.9)[d] SjD: 0.3 (0.2-0.4)[d]

[a]Adjusted for non-response to questionnaire and non-participation to home visit (interview subjects and antibody test performed). [b]Enlarged criteria based on the presence of ≥3 of 4 AECG items among subjective. [c]Data were only available in a conference abstract at the time of this review. [d]Age adjusted rate. ACR - American College of Rheumatology; AECG - American-European Consensus Group; CI - Confidence interval; ICD - International Classification of the Disease; SjD - Referred to as "primary" Sjögren's disease by reporting authors; Sjögren's-associated disease - Referred to as "secondary" Sjögren's disease by reporting authors; UK - United Kingdom; Unspecified SjD - Sjögren's disease described as neither "primary" nor "secondary" by reporting authors; US - United States

Table 2. Prevalence studies of Sjögren's disease among special groups in select countries

Study	Country (region)	Population; study features	Case identification criteria	Prevalence per 10,000 (95% CI)
Bowman 2004	UK (Birmingham)	Caucasian women, age 35-74 years; Sample survey (65% response rate)	AECG	SjD: 20 (3-9) SjD: 40 (4-13)[a]
Hida 2008	Japan	Nagasaki atomic bomb survivors, age 57-93 years; Sample survey (63% response rate)	AECG	SjD: 198 Sjögren's-associated disease: 30
Annunziata 2011	Italy	Multiple sclerosis patients; Multi-centre cohort study	AECG	SjD: 91
Aggarwal 2015	US	Systemic lupus erythematosus patients; Lupus Family Registry and Repository	AECG	SjD: 96 Sjögren's-associated disease: 2,030
Harrold 2020	US	Rheumatoid arthritis patients, age ≥18 years; National population-based cohort	Physician diagnosis	Sjögren's-associated disease: 3,000
Miller-Archie 2020	US (New York)	9/11 survivors, age ≥18 years; Survey of World Trade Center health registry enrollees (51% response rate) followed by physician survey and tests	AECG	Unspecified SjD: 5.9

[a]Authors used two different denominators to calculate prevalence. AECG - American-European Consensus Group; CI - Confidence interval; SjD - Referred to as "primary" Sjögren's disease by reporting authors; Sjögren's-associated disease - Referred to as "secondary" Sjögren's disease by reporting authors; UK - United Kingdom; Unspecified SjD - Sjögren's disease described as neither "primary" nor "secondary" by reporting authors; US - United States

Incidence

- Six studies reported incidence of SjD. Reported annual incidence rates of SjD in the US varied from 1.1 to 5.8 per 100,000 person-years, based on different time periods and diagnostic criteria used (**Table 3**)
  - In Germany and France, reported incidence rates from conference abstracts also differed
  - Incidence rates from 3 studies originated from the same cohort in the US (Minnesota), demonstrating an upward trend in rates from 1976 to 2015

Table 3. Population-based incidence studies of Sjögren's disease in select countries

Study	Country (region); study years	Population; study features	Case identification criteria	Annual incidence per 100,000 PY (95% CI)
Pillemer 2001	US (Minnesota); 1976-1992	Retrospective medical record review, Rochester Epidemiology Project; Age ≥18 years	Physician diagnosis	SjD: 3.9 (2.8-4.9)[a]
Nannini 2013	US (Minnesota); 1976-2005	Retrospective medical record review, Rochester Epidemiology Project; Age ≥18 years	AECG	SjD: 5.1 (4.1-6.1)[a]
Maciel 2017b	US (Minnesota); 1976-2015	Retrospective medical record review, Rochester Epidemiology Project; Age ≥18 years	Physician diagnosis, AECG and ACR	SjD: 5.8
Izmirly 2019	US (Manhattan); 2007-2009	Population-based registry of cases of Lupus Surveillance; Age ≥18 years	Physician diagnosis Rheumatologist diagnosis Modified criteria	SjD: 3.5 (2.9-4.1)[b] SjD: 2.1 (1.7-2.6)[b] SjD: 1.1 (0.8-1.5)
Albrecht 2020	Germany; 2018	Insurance database; Conference abstract	M35.0 (ICD-10)	SjD: 102
Seror 2021	France; 2012-2018	Population-based census National Claim Database; Conference abstract	Study-specific algorithm	SjD: 0.3-4.1 Sjögren's-associated disease: 0.1-2.1

[a]Rate is age- and sex-adjusted annual incidence. Study population was comprised of a 98% White population in 1990. [b]Age adjusted to the United States 2000 Standard Population. ACR - American College of Rheumatology; AECG - American-European Consensus Group; CI - Confidence interval; PY - Person-years; SjD - Referred to as "Primary" Sjögren's disease by reporting authors; Sjögren's-associated disease - Referred to as "secondary" Sjögren's disease by reporting authors; US - United States

Discussion

- Case identification criteria used in the included studies may not accurately reflect the diagnosis of SjD in clinical practice, as some studies used study-specific classification algorithms that may not be typically used by evaluating physicians
  - This may have led to potentially overestimating prevalence compared with more stringent definitions based on validated criteria[11] (**Table 1**)
- Sampling surveys tend to report higher prevalence (10- to 20-fold) due to active screening. However, sampling surveys may include sampling bias and responder bias, while census surveys may underestimate known cases (**Table 1**)
- Genetic factors play a role in the risk of SjD[4]
- Racial/ethnic influences were observed, with higher prevalence rates among non-Europeans[13]

Conclusions

- Global prevalence of Sjögren's disease in the general population ranges from 0.3 to 180 cases per 10,000 persons. Prevalence rates are higher among patients with other autoimmune diseases
- Global incidence of Sjögren's disease ranges from 0.1 to 5.8 cases per 100,000 person-years
- Variations in Sjögren's disease prevalence and incidence estimates among studies may be attributed to differences in study methodologies, diagnostic criteria, genetic backgrounds, environmental factors, and disease classification (e.g., Sjögren's disease with or without comorbidity)
- Despite differences in study design and disease definition, Sjögren's disease is a prevalent autoimmune disorder affecting patients globally, and further research into the burden of illness is needed

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