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REVIEW

Epidemiology of Sjögren's: A Systematic Literature Review

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ABSTRACT

Introduction: Primary Sjögren's is a multi-system autoimmune disease affecting patients' physical, mental, and emotional wellbeing. The epidemiology of Sjögren's is not well understood, and up-to-date epidemiological evidence is needed to improve knowledge and awareness of Sjögren's among patients and healthcare professionals, and to ascertain the global burden of disease. The objective of this research was to conduct a de novo systematic literature review (SLR) to identify and synthesise evidence on global epidemiology of primary Sjögren's.
Methods: This SLR was conducted in May 2021 by searching MEDLINE and Embase databases, relevant conference proceedings, websites of registries, and health technology assessment agencies and databases. Publications were systematically screened for English language articles reporting on the incidence, prevalence, age at symptom onset, and age at diagnosis for people with primary Sjögren's.
Results: Of 3510 records identified, 68 publications were included, representing 62 unique studies. Studies reported on age at symptom onset (16/62; 25.8%) and age at diagnosis (43/62; 69.4%) more frequently than incidence (7/62; 11.3%) and prevalence (9/62; 14.5%). Primary Sjögren's was found to have the highest incidence and prevalence in females and in older age groups (incidence: ≥65 years; prevalence: ≥75 years). Average age at onset and diagnosis of primary Sjögren's ranged between 34–57 years and 40–67 years, respectively.
Conclusions: This SLR identified a paucity of incidence and prevalence data for primary Sjögren's, highlighting a need for further epidemiological studies. The global Sjögren's community must work together to follow the defined classification criteria of primary Sjögren's and reporting guidelines for incidence and prevalence data to allow for meaningful epidemiological comparisons across studies, settings, and countries.

Keywords: Sjögren's Disease; Autoimmune Disease; Epidemiology; Prevalence; Incidence; Diagnosis; Onset

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Key Summary Points

Why carry out this study?

Primary Sjögren's is a multi-system autoimmune disease that affects the salivary and lachrymal glands.

The global burden of primary Sjögren's is poorly understood, which is partly due to a lack of patient and healthcare professional awareness of the disease and limited available epidemiological evidence.

The aim of this research was to conduct a systematic literature review (SLR) to identify and synthesize the most recent evidence on global incidence, prevalence, age of onset, and age of diagnosis of primary Sjögren's.

What was learned from this study?

Sixty-eight relevant publications, corresponding to 62 unique studies, were identified. The SLR found that incidence and prevalence of primary Sjögren's was highest in females and in older age groups (≥65 years), while the average age at onset and diagnosis of primary Sjögren's ranged between 34–57 years and 40–67 years, respectively.

The SLR revealed that there were a limited number of studies reporting on the incidence and prevalence of primary Sjögren's and estimates varied widely between studies, highlighting a key weakness in the epidemiological evidence base.

To address the weaknesses in the epidemiological evidence base, the defined classification criteria for primary Sjögren's should be adopted consistently and studies should adhere to available reporting guidelines for incidence and prevalence data. This would improve the comparability of epidemiological data between studies, settings, and countries and lead to a better understanding of the true burden of primary Sjögren's.

INTRODUCTION

Sjögren's is an autoimmune disease affecting the salivary and lachrymal glands [1], which can occur in both people with no other autoimmune diseases (primary Sjögren's), or people with another autoimmune disease (secondary Sjögren's), most often systemic lupus erythematosus (SLE) or rheumatoid arthritis [2]. While ocular and oral dryness are often cited as hallmark symptoms of Sjögren's, up to 30–50% of people with Sjögren's present with systemic disease that affects multiple organs, including neurological, pulmonary, articular, and kidney involvement [3]. Such widespread disease has a considerable impact on the health-related quality of life of people with Sjögren's [3], who are affected psychologically as well as physically with problems such as depression and fatigue, frequently impacting their daily lives and ability to work [4].

The process of Sjögren's diagnosis involves the assessment of multiple parameters, such as examination of medical history, specific ocular and oral assessments, physical examination, blood tests, and the use of biopsy and ultrasound to assess salivary glands [1]. Due to the systemic nature of Sjögren's, people with Sjögren's may initially present or be referred to a broad range of medical and surgical specialties outside of rheumatology, including internal medicine, gynaecology, ophthalmology, dermatology, otolaryngology, orthopaedic surgery and dentistry, among others [5]. Initial presentation to a specialty outside of rheumatology has been associated with significant delays to diagnosis, emphasizing the need for greater awareness of Sjögren's among healthcare professionals (HCPs) [5].

Several sets of criteria have been developed to aid diagnosis of Sjögren's, such as the 1993 European Community Study Group criteria [6], the 2002 American-European Consensus Group (AECG) criteria [7], the 2012 American College of Rheumatology (ACR) criteria [8], and the 2016 joint ACR and European Alliance of Associations for Rheumatology (EULAR) criteria [9]. The diagnostic approach taken across these criteria is broadly similar, and all allow the use of

objective tests to diagnose Sjögren's. However, granular approaches vary between the different classification criteria, and the fact that there have not been consistently accepted criteria may lead to underdiagnosis of the condition. In addition, Sjögren's is associated with a number of non-specific symptoms, which can further complicate diagnosis [10].

In 2016, another set of Sjögren's classification criteria (the 2016 ACR/EULAR criteria) [9] were developed, increasing the heterogeneity of classification criteria used between epidemiological studies [10]. The 2016 ACR/EULAR criteria differ from the previously used 2012 ACR criteria, as the former recommends the use of antibodies against Sjögren's syndrome-related antigen A (SSA; Ro) for diagnosis, instead of anti-Sjögren's syndrome-related antigen B (SSB; La), or a combination of rheumatoid factor (Rf) and anti-nuclear antibody (ANA) titer [8, 9]. Additionally, the 2016 ACR/EULAR criteria permit the inclusion of results from Schirmer testing and unstimulated whole saliva flow rate, whereas these are not included in the 2012 ACR criteria [8, 9].

Up-to-date epidemiological evidence is needed to improve knowledge and awareness of Sjögren's among patients and HCPs, as well as to ascertain the global burden of the condition on people with Sjögren's, healthcare payers, and providers. The objective of this research was to conduct a de novo SLR to identify and synthesise up-to-date published evidence on the global incidence and prevalence, as well as the age at symptom onset and age at diagnosis of primary Sjögren's.

METHODS

An SLR was performed according to a pre-specified protocol, which was not registered to PROSPERO. An approach consistent with the Cochrane Handbook for Systematic Reviews and Interventions was taken [12]. The SLR was conducted and reported in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [13].

Search Strategy

Online databases including Ovid Medical Literature Analysis and Retrieval System Online (MEDLINE) and Epub Ahead of Print, In-Process, In-Data Review & Other Non-Indexed Citations and Daily 1946 to 12th May, 2021, and Excerpta Medica Database (Embase) 1974 to 12th May, 2021 were searched on 13th May, 2021 using MEDLINE and Embase in accordance with pre-specified search criteria to identify relevant articles. The search strategies used for each information source are summarised in Supplementary Data S1 and S2. For clarity, it should be noted that the SLR was conducted in the English language only using search terms related to the widely used nomenclature of 'Sjögren's syndrome'. However, when discussing the context of the results in this article, the updated terminology of 'Sjögren's' will be used, which has been proposed by patient advocacy groups, including Sjögren's Europe and the Sjögren's Foundation, in an effort to change perceptions of the disease [14]. A plain language terminology table including definitions of the epidemiology terms used throughout this manuscript is provided in Supplementary Data S3.

Conference proceedings from the previous 2 years (2019–2021) from the ACR, British Society for Rheumatology (BSR), Canadian Rheumatology Association (CRA), EULAR, International Society of Pharmacoeconomics and Outcomes Research (ISPOR; International and Europe) were also hand-searched to identify relevant abstracts (Supplementary Data S4). Searches of registry and database websites, as well as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) websites, were conducted to identify further publications of interest (Supplementary Data S5). The bibliographies of relevant SLRs and meta-analyses identified during the search of electronic databases and manual search of congresses were also hand-searched to identify additional relevant studies for inclusion. Information sources searched in this SLR are summarised in Supplementary Data S6.

Study Selection

The SLR aimed to report on the incidence and prevalence, as well as the age at symptom onset and the age at diagnosis of primary Sjögren's in Australia, Brazil, Canada, China, EU5 countries (United Kingdom [UK], Italy, Spain, France, and Germany), Japan, and the United States (US). Inclusion and exclusion criteria used to assess the relevance of abstracts and full texts are presented in Table 1. In particular, studies that reported on people with Sjögren's <18 years of age and those that did not explicitly state that they reported on people with primary Sjögren's, were excluded. Studies reporting on secondary Sjögren's, or combined cohorts of patients with primary and secondary Sjögren's, were not considered, in order to improve the homogeneity and specificity of the findings. Each abstract and full text was reviewed against eligibility criteria by two independent reviewers, followed by consultation with a third independent reviewer if a consensus could not be reached. For both the abstract and full-text review stages, 100% of the included records and 10% of the excluded records were verified by a third independent reviewer. Studies that reported either the incidence or prevalence of primary Sjögren's were assumed to report crude/unadjusted values unless it was specified that the reported values were stratified/adjusted to specific population demographics (e.g., sex, age, or race/ethnicity).

Data Extraction and Analyses

The following data were extracted: study details (including but not limited to study methodology, population eligibility criteria, and setting), population characteristics (e.g., age, sex, race/ethnicity, disease type, disease activity [EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) scores [15], and/or EULAR Sjögren's Syndrome Patient-Reported Index (ESSPRI) scores] [16], treatments for Sjögren's), and epidemiological outcomes (e.g., incidence, prevalence, age at symptom onset, age at diagnosis).

Data extraction was performed in line with guidelines from the University of York Centre for Reviews and Dissemination [17]. Data from each included study were extracted by a single individual into a pre-specified extraction grid (Microsoft Excel®), and independently verified by a second individual. Any discrepancies or missing information identified by the second individual were discussed by both individuals until a consensus was reached on the information that should be presented in the extraction grid. If necessary, a third individual was enlisted to arbitrate the final decision. Articles reporting on the same study were grouped and considered as one unique study for subsequent review stages, with the article reporting the main results of the study considered as the primary article, and additional articles considered as secondary articles; both primary and secondary articles were extracted. Where calculation errors were identified or data were missing, clarification was not sought from study authors. Instead, the correct value was calculated where possible and confirmed by a second independent reviewer.

A formal data synthesis through meta-analysis or other summary methodology could not be performed due to substantial inter-publication heterogeneity in study populations and reported outcomes. A narrative summary was carried out, considering risk of bias from the quality assessment of each study.

Quality Assessment

The quality of included studies was assessed using an adapted version of the Joanna Briggs Institute checklist [18]. The checklist was adapted to include additional questions targeted to address the epidemiological aims of this SLR. The full quality assessment checklist can be found in Supplementary Data S7. One reviewer completed the quality assessment and extracted information that was verified by a second independent reviewer; any discrepancies were discussed until a consensus was reached. A third individual was enlisted, where necessary, to arbitrate the final decision.

Table 1 Eligibility criteria for the SLR (population, intervention, comparison, outcomes and study design framework [PICOS])

Category	Inclusion Criteria	Exclusion Criteria
Population	• Patients with primary Sjögren's[a] who are aged ≥18 years	• Patients with primary Sjögren's[a] who are aged <18 years • Patients with secondary Sjögren's[b] • Population does not include people with Sjögren's
Intervention/ Comparators	• Any or none	• Not applicable
Outcomes	Outcomes of interest: • Prevalence • Incidence • Age at the time of diagnosis • Age at onset of first symptom In the following population: • Primary Sjögren's within a general population	• Studies not reporting on any relevant outcomes • Studies reporting relevant outcomes for a patient population that is not of interest (e.g. people with secondary Sjögren's) • Studies reporting relevant outcomes, but in a mixed population, without reporting data specifically for the patient group of interest
Study design	• All observational and epidemiological study designs • Systematic literature reviews (SLRs) and network meta-analyses (NMAs) of relevant studies were included at the abstract screening stage, then excluded but hand-searched for additional primary studies at the full-text review stage	Any other study design, including: • Editorials, notes, or comments • Case reports/studies/series[c]
Publication type	• Peer-reviewed journal articles • Congress abstracts published since 2019	• Congress abstracts published prior to 2019
Other considerations	• Human subjects • Geographies of interest: Australia, Brazil, Canada, China, EU5 countries (France, Germany, Italy, Spain, United Kingdom), Japan and the United States • No date limit was applied for peer-reviewed journal articles	• Studies not describing human subjects • Abstracts and full-texts in other languages, with no relevant results published in English • Any other geographic location

NMAs network meta-analyses, *PICOS* population, intervention, comparison, outcomes, and study design framework, *SLR* systematic literature review

[a]Primary Sjögren's occurs without any other inflammatory, autoimmune diseases

[b]Secondary Sjögren's occurs in association with another autoimmune diseases

[c]Case studies (and similar study designs) were tagged and excluded at the abstract screening stage

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Characteristics of Included Studies

After deduplication of search results, abstract screening and full-text review, 68 publications were included in the SLR, representing 62 unique studies (Fig. 1). Publications describing included studies were published between 1979 and 2021; 55/62 (88.7%) of included studies were published since 2007. Where reported, the mean study follow-up period ranged from 5–12.4 years across included studies [19, 20]. The majority of studies (56/62, 90.3%) were conducted in a single country and the most represented geographies were Spain (15/62, 24.2%), China (12/62, 19.4%) and the US (8/62, 12.9%).

Out of 62 studies, 28 (45.2%) and 14 (22.6%) were retrospective and prospective cohorts, respectively. A further eight (12.9%) studies were cross-sectional, while ten (16.1%) studies used a case–control study design. Additionally, 29 (46.8%) studies reporting on data from registries or databases were identified. Of the 42 studies that reported on the study setting, the majority (39/42, 92.9%) took place in a hospital setting (inpatients, outpatients, and/or tertiary centre). A summary of included publications is presented in Supplementary Data S8.

Incidence

A total of 7/62 (11.3%) studies reported on the incidence of primary Sjögren's within a sample cohort taken from the general population (Supplementary Data S9) [21–27]. Where reported, overall sample sizes ranged from 113,306 to ~4.5 million people. Most studies examining the incidence of primary Sjögren's (5/7, 71.4%) were conducted in the US [22–26], while one study was conducted in Canada [21] and another in France [27]. Incidence estimates ranged from 3.5–3.9 per 100,000 person-years [23, 26] and 0.3–26.1 per 100,000 persons (Table 2) [21, 22, 24, 25, 27]. A single study, conducted in New York in the US, reported the incidence of primary Sjögren's, stratified by race/ethnicity [23]. The study reported that the incidence of primary Sjögren's was highest in the Asian population, followed by the White population, with lowest incidence rates reported in the Latino and Black populations [23].

Incidence of Sjögren's by age was reported in two studies (2/62, 3.2%; both carried out in Olmsted County, MN, USA) and was found to be highest in people aged ≥65 years [24, 25]. Similarly, the four studies (4/62, 6.5%) reporting incidence of primary Sjögren's by sex were all conducted in the US and showed that females had a higher incidence of the disease than males across all age subgroups [23–26]. Overall, incidence of primary Sjögren's for females was reported as 8.7–9.5 per 100,000 persons (age-adjusted) and 5.7–6.9 per 100,000 person-years (age-adjusted). For males, the reported incidence ranges were 1.1–1.6 per 100,000 persons (age-adjusted) and 0.5–1.0 per 100,000 person-years (age-adjusted) [23–26]. In contrast to the female population, the oldest age group of males (≥75 years) was found to have a dramatically higher incidence of primary Sjögren's than younger age groups across all three studies (3/62, 4.8%) reporting incidence of primary Sjögren's stratified by age and sex [24–26].

A change in incidence of primary Sjögren's over time was described in one study (Olmsted County, MN, USA) [24]. The incidence of primary Sjögren's was noted to increase significantly over a 40-year period (p=0.005) from 4.2 (1976–1985) to 5.9 (2006–2015) per 100,000 persons [24].

Prevalence

A total of 9/62 (14.5%) studies reported on the prevalence of primary Sjögren's (Table 2) [23, 27–34]. Of these, three (33.3%) reported on point prevalence [28, 31, 33], five (55.6%)

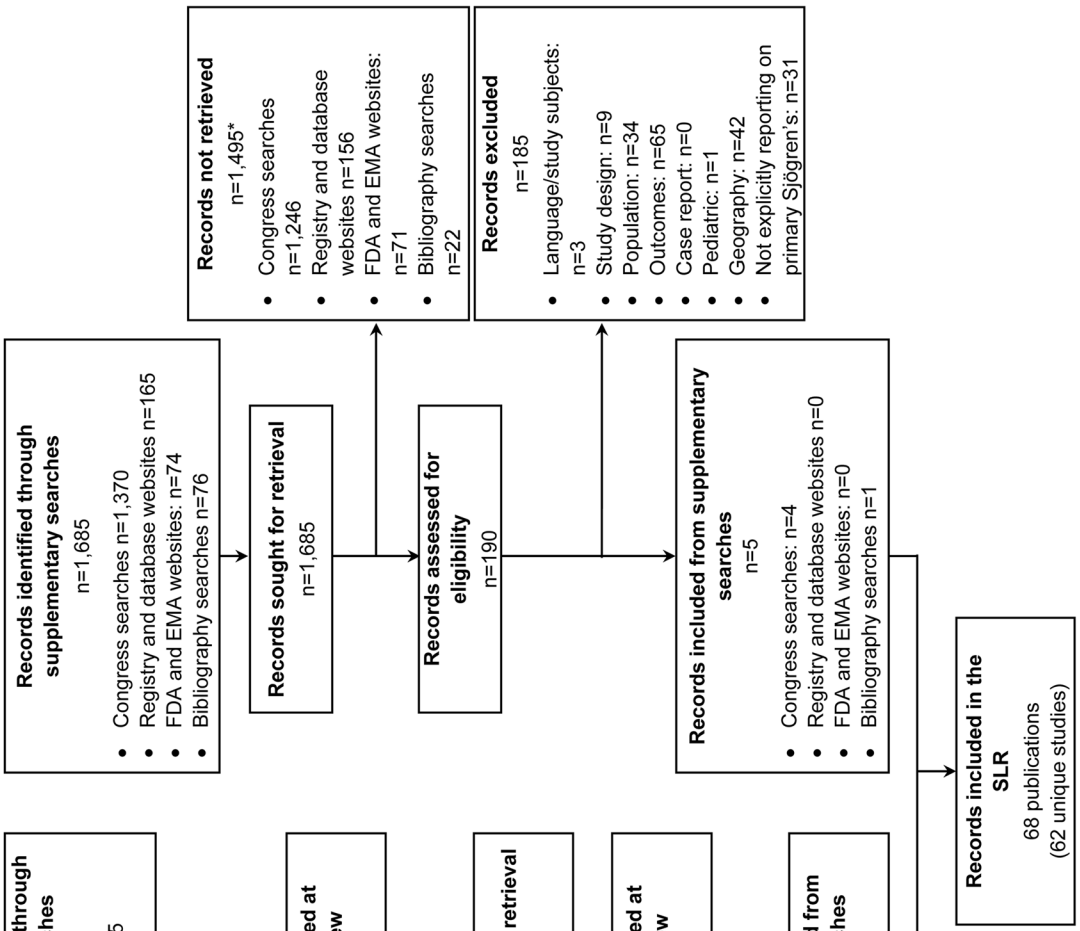

Fig. 1 PRISMA diagram. *Duplicates between supplementary searches and database searches, clearly irrelevant abstracts, and abstracts/full texts that could not be found online were not retrieved and excluded at this stage. *FDA* Food and Drug Administration, *EMA* European Medicines Agency, *Embase* Excerpta Medica Database, *MEDLINE* Medical Literature Analysis and Retrieval System Online, *NMAs* network meta-analyses, *PRISMA* Preferred Reporting Items for Systematic Review and Meta-Analysis, *SLR* systematic literature review

Table 2 Summary of studies reporting on the incidence and prevalence of primary Sjögren's

Incidence

Study	Geography	Incidence	Incidence metric
Izmirly 2019 [23]	United States (US)	3.5	per 100,000 person-years
Pillemer 2001 [26][d]	US	3.9	per 100,000 person-years
Seror 2021 [27]	France	0.3–4.1	per 100,000 persons
Nannini 2013 [25]	US	5.1	per 100,000 persons
Maciel 2017 [24]	US	5.8	per 100,000 persons
Crowson 2011 [22][d]	US	3.9	per 100,000 persons
Avina-Zubieta 2017 [21]	Canada	26.1	per 100,000 persons[a]

Prevalence

Study	Geography	Prevalence	Prevalence metric	Point or period prevalence	Study population size	Female (%)
Cortes 2019 [28]	Spain	55.0	per 100,000 persons[b]	Point	Not reported (NR)	NR
Devauchelle-Pensec 2019 [30]	France	29.5	per 100,000 persons	Period 2005–2016	NR	90%
Izmirly 2019 [23]	US	12.4/13.1[e]	per 100,000 person-years	Period January 2007–December 2007	1,585,873	NR
Maciel 2017 [31]	US	103.0[f]	per 100,000 persons[b]	Point 1st January 2015	113,306	86%
Narvaez 2020 [32]	Spain	250.0	per 100,000 persons[c]	Period November 2016–October 2017	4,916	NR
Seror 2021 [27]	France	22–32	per 100,000 persons	Period 2011–2018	NR	76–89%
Tsuboi 2014 [29]	Japan	30.0	per 100,000 persons[c]	Period January 2010–December2010	NR[g]	NR
Valim 2013 [33]	Brazil	170.0	per 100,000 persons[c]	Point	1,205	51%

Table 2 continued

Prevalence						
Study	**Geography**	**Prevalence**	**Prevalence metric**	**Point or period prevalence**	**Study population size**	**Female (%)**
Zhang 1995 [34]	China	330.0–770.0	per 100,000 persons[c]	NR	NR	NR

NR not reported, *US* United States
To allow for comparison between studies, prevalence estimates were scaled to 100,000 persons:
[a]This study reported 1175 incident cases in a Canadian population of 4,500,000 people and therefore incidence was manually calculated to allow for comparison
[b]These studies reported prevalence per 10,000 population and estimates were multiplied by 10
[c]These studies reported prevalence as a percentage and estimates were multiplied by 1000
[d]Pillemer 2001 and Crowson 2011 both reported on data collected as part of the Rochester Epidemiology Project, during the same time frame, and therefore likely contain some patient overlap
[e]Izmirly 2019 reported a prevalence of 12.4 (unadjusted) and 13.1 (age-adjusted to the US population in 2000)
[f]The prevalence in Maciel 2017 was age- and sex-adjusted to the US White population in 2010
[g]Tsuboi 2014 did not report a total population size from which the authors identified cases of primary Sjögren's. Instead, the authors report the prevalence of primary Sjögren's, extrapolated over the whole population of Japan (October 1, 2021)

reported on period prevalence [23, 27, 29, 30, 32], and one (11.1%) study did not provide details on the type of prevalence reported [34]. Sample sizes for studies reporting point prevalence ranged from 1205 to >100,000 people across two studies [31, 33], with the third study not reporting on the sample size [28]. Across the five studies that reported on period prevalence, two reported on sample sizes, which ranged from 4916 to ~1.5 million people [23, 32]. Of the nine studies that reported on the prevalence of primary Sjögren's, four (44.4%) were carried out in EU5 countries, with two (22.2%) studies each conducted in Spain and France (Table 2) [27, 28, 30, 32]. Prevalence was reported with a variety of metrics and ranged from 0.03%–0.77% [29, 32–34], 5.5–10.3 per 10,000 persons [24, 28], 22–32 per 100,000 persons [27, 30], and 12.4 (unadjusted) or 13.1 (age-adjusted to the US population in 2000) per 100,000 person-years; prevalence estimated scaled to 100,000 persons are reported in Table 2 [23]. The variety of prevalence reporting metrics limited direct comparison between studies.

The single study (1/9, 11.1%) discussed previously that was conducted in New York in the USA, reporting prevalence of primary Sjögren's stratified by race/ethnicity, reported that prevalence was highest in the White population, followed by the Asian, Latino, and Black populations [23]. Prevalence of Sjögren's was generally reported to rise with increasing age in both males and females, and was highest in people aged ≥75 years (32.3 per 10,000 persons) and lowest for those aged 18–44 years (2.2 per 10,000 persons) [31]. Only two studies (22.2%), both conducted in the USA, reported prevalence of primary Sjögren's by sex, with prevalence reported to be substantially higher in females than in males, at 20.5 vs. 3.1 per 100,000 person-years (period prevalence)[21] and 16.3 vs. 3.1 per 10,000 persons (point prevalence) [29]. Prevalence was higher in females across all race/ethnicity and age subgroups [23, 31].

Age at Symptom Onset and Diagnosis

Out of 62 studies, 16 (25.8%) and 43 (69.4%) studies reported on age at symptom onset and age at diagnosis, respectively. In summary, the average age at symptom onset ranged from 34–57 years (excluding results from Botsios 2011 that reported on subgroups stratified by age at symptom onset) [35–37] and the average age at diagnosis ranged from 40–67 years (Supplementary Data S10 and S11) [36, 38]. The mean age at symptom onset was slightly lower in China (34–54 years) in comparison to the mean age at symptom onset reported in European countries (42–57 years). In contrast, the age at diagnosis was broadly similar between geographic locations: European studies: 45–67 years; Asian studies: 40–62 years; North American studies: 53–59 years; Australian studies: 48–60 years.

Only one study (2.3%) reported on age at diagnosis stratified by race/ethnicity and found that white patients tended to be diagnosed with primary Sjögren's at a slightly older age as compared to patients of other races/ethnicities [39]. No studies reported on age at symptom onset stratified by race/ethnicity.

A small number of studies reported age at symptom onset (2/16, 12.5%) and age at diagnosis (5/43, 11.6%) stratified by sex. Overall, these studies suggested that age at symptom onset is slightly higher in males (mean: 55–57 years) than females (mean: 53 years) [35, 40]. Likewise, age at diagnosis was found to be slightly higher in males than females, with means ranging between 53–67 years and 51–64 years across the five studies, for males and females, respectively [23, 27, 38, 41, 42].

Quality Assessment

The domains of the modified version of the Joanna Briggs Institute quality assessment checklist used are outlined in Supplementary Data S7. Overall, included studies were deemed to be at a low risk of bias (Supplementary Data S12). Coverage of data analysis, sampling of participants and condition identification were key domains in which the included studies performed particularly well (i.e., the risk of bias was low). The risk of bias was highest in the study subject description, confounding and study design domains, which may be attributed to the stringent criteria used for the quality assessment. Notably, only a few studies were determined to have a low risk of bias in the sample size domain. This can also be explained by the stringent criteria that were applied to the quality assessment, where only studies with an overall sample size of >100,000 people were considered to satisfy this domain. In addition, many studies did not report the overall sample size.

Five studies (8.1%) included in this SLR reported on a large international database, the Big Data Sjögren Project Consortium [38, 39, 43–45]. Generally, these studies performed well, with 6–9 of the 12 quality assessment domains indicating low risk of bias across all five studies. However, none of the five studies performed well in the study subject description domain. This can be explained by the stringent requirement to describe the age, sex, and race/ethnicity of the overall study population to satisfy this domain (as opposed to just one or two of these characteristics). Therefore, the five studies reporting on the Big Data Sjögren Project Consortium can generally be considered to be at a low risk of bias.

DISCUSSION

This SLR provides an up-to-date summary of the available evidence for the incidence, prevalence, age at symptom onset, and age at diagnosis of primary Sjögren's from a global perspective, following the introduction of the 2016 ACR/EULAR diagnostic criteria. Results from 62 studies suggest that women and those in older age groups have the highest incidence and prevalence of Sjögren's, and that age at symptom onset and diagnosis ranges between 34–57 years and 40–67 years, respectively. Yet, the SLR also identified a paucity of global epidemiology studies on Sjögren's, highlighting an unmet need in this area.

This SLR identified an incidence range of 3.5–3.9 per 100,000 person-years or 0.3–26.1 per

100,000 persons [21–23, 26]. The range of incidence estimates identified in this SLR exceeded the range found in Qin et al. 2015 (6.9–20.1 per 100,000 person-years) [11], with the prevalence estimates identified in both studies proving to be even more variable. The current SLR identified a prevalence range of 12.4–13.1 per 100,000 person-years or 22.0–770.0 per 100,000 persons (once metrics were scaled to 100,000 persons) [27, 34]. Qin et al. 2015 observed even larger variability in prevalence estimates, ranging from 11.3–3790.1 per 100,000 persons [11]. This wide variation affirms the need for robust, population-wide epidemiology studies to further understand the incidence and prevalence of Sjögren's.

Considerable variations in incidence and prevalence estimates are also observed for other autoimmune diseases such as SLE [46], where the overall incidence in Europe varies between 1.5[47, 48] and 7.4 [49] per 100,000 person-years. Even greater variations are seen for SLE prevalence estimates, which range from 29.0 [47] to 210.0 [50] per 100,000 persons in Europe [46]. The variation in epidemiological estimates for SLE and those reported here for Sjögren's may be due to study methodology and the criteria used to define cases. For example, some studies that were identified in the review used robust classification criteria to define cases [27, 51, 52], whereas others considered a diagnosis by a physician, even if not with a standardized method, to be sufficient for case ascertainment [31]. The geographical variation in Sjögren's epidemiology estimates and data availability in this review may also reflect differences in availability of study funding and patient registry data across countries [53]. In addition, varying estimates may be influenced by external, non-measured variables, such as a possible increased awareness of Sjögren's in medical communities; for instance, in 2012, the patient advocacy group Sjögren's Foundation launched an awareness campaign to reduce the diagnostic delay for Sjögren's by 50% in 5 years. In 2018, the goal was reportedly surpassed, reducing the time to diagnosis from approximately 6.0 to 2.8 years [54]. Variable epidemiological estimates may also be impacted by the increased availability of more accurate diagnostic testing over time, such as standardised techniques for diagnosis via salivary gland biopsy [55].

As with other autoimmune conditions such as SLE [46], the incidence and prevalence of primary Sjögren's was reported to be higher in females than in males, which is consistent with the findings of Qin et al. [11]. For instance, the difference in incidence between sexes for Sjögren's is around 6–11 times higher in females than males, respectively, compared to ~5 times for SLE [46]. The reasons for sex differences in autoimmune diseases could include genetic and hormonal differences [56], but may also include differences in presenting symptoms [42], and sex-related differences in healthcare-seeking behavior [57], leading to a possible underdiagnosis in males and greater awareness among HCPs for primary Sjögren's in females. Results from this SLR also suggest that for both sexes, incidence and prevalence increase with age [24]. Given the multi-system involvement and considerable impact of the disease on the physical and mental health of affected patients, this finding is significant as the ageing global population could confer an increase in the overall healthcare burden of primary Sjögren's [58].

The difference between average ages of onset (34–57 years) [35, 36] and diagnosis (40–-67 years)[36, 38] identified by this SLR reflects the known diagnostic delays in Sjögren's [59], thought to be related to the diverse symptomatology and generally poor familiarity of Sjögren's among non-rheumatology HCPs [60]. However, prompt diagnosis is important for treating symptoms and for monitoring the potential life-threatening complication of lymphoma, which is known to occur at far higher rates in people with primary Sjögren's than in the general population [60].

The female predominance and average age at symptom onset of primary Sjögren's have important implications, as both disease manifestations and potential commencement of therapy are likely to overlap with the window of childbearing potential for women. Primary Sjögren's has been associated with a range of gynaecologic and obstetric complications, including: vaginal dryness, increased risk of sub-fertility/infertility, foetal complications

(especially neonatal lupus and congenital heart block) and foetal loss [61–63]. Furthermore, some systemic therapies for primary Sjögren's such as hydroxychloroquine and methotrexate have been shown to carry teratogenic risk [64–66]. Therefore, prompt diagnosis and considered management of primary Sjögren's is especially important for improving pregnancy-related outcomes for women of childbearing potential.

Overall, the findings of this SLR provide key insights into the demographics and epidemiology of primary Sjögren's. In particular, the age at onset of primary Sjögren's overlaps with the ages of childbearing and employment, meaning that poor disease control carries both health-related and economic-burden for society [67, 68]. Additionally, the observed rising prevalence of primary Sjögren's with increasing age, within the context of an ageing global population, means that healthcare providers, payers, and policy-makers must work together to facilitate cost-effective solutions for people with primary Sjögren's that carry sustainable, long-term budget impacts for healthcare systems.

Limitations of the Evidence

This SLR identified a lack of studies reporting on incidence and prevalence of primary Sjögren's, with even fewer studies stratifying the results by demographic factors. It is possible that with the emergence of large registries such as the Big Data Sjögren Consortium, smaller scale epidemiology studies are no longer considered sufficiently robust in comparison. The studies that reported on the incidence and prevalence of primary Sjögren's were conducted across a limited range of countries within the SLR eligibility criteria, with a substantial proportion of studies (5/7, 71.4% of incidence studies; 2/8, 25.0% of prevalence studies) reporting on results from the US. Therefore, conducting a meaningful assessment of geographical differences in the prevalence or incidence of primary Sjögren's was not possible, due to a lack of evidence. Furthermore, differences in study methodologies, metrics for reporting incidence and prevalence, and standardisation techniques made direct comparisons between studies challenging. Therefore, no meta-analysis or other methodologies were possible to provide robust, modeled epidemiological outcomes.

Moreover, a substantial proportion of studies did not provide a detailed description of the clinical setting, creating difficulties in contextualisation of the results. There were also very few population-based studies, potentially leading to bias in reported epidemiological estimates. As previously mentioned, the fact no single classification criteria for Sjögren's has yet been consistently adopted, contributes to the challenge of understanding the true epidemiology of Sjögren's [10]. This is confirmed by the findings of this SLR, where studies reporting on the epidemiology of Sjögren's used a variety of classification criteria for case definition and ascertainment.

Limitations of the SLR

One potential limitation of this SLR was the restriction of studies to those published in the English language. The rationale for the decision was that it was reasonable to assume that the vast majority of relevant evidence is expected to be published in English, especially considering the multinational nature of the large Sjögren's registries and associated publications. In addition, studies that did not explicitly state that they reported on people with primary Sjögren's, and studies that reported on people with Sjögren's <18 years of age, were also excluded from the study. The exclusion of studies not clearly describing people with primary Sjögren's, in particular when study populations combined primary and secondary Sjögren's cohorts, was intended to increase the homogeneity and robustness of resulting data. Similarly, the age restriction was implemented to reduce bias introduced by paediatric cohorts, which frequently represent a distinct clinical entity, in terms of autoimmune diseases, to their adult counterparts [69, 70]. Another potential limitation of this SLR is that when calculation errors were identified or data were missing from the included studies, clarification

was not sought from study authors. Instead, the correct value was calculated when possible and confirmed by a second independent reviewer.

Future research should be conducted to strengthen the limited and heterogenous evidence base for the incidence and prevalence of primary Sjögren's, particularly outside the US, to enable assessment of geographic and cultural factors, and ultimately modeling of the epidemiology of Sjögren's. Although this SLR did not assess the incidence and prevalence of secondary Sjögren's, additional research to better understand and describe the epidemiology of secondary Sjögren's may also be warranted. Some stakeholders advocate for the distinction between primary and secondary Sjögren's to be abandoned due to a lack of evidence supporting a pathological distinction between the subsets and because secondary Sjögren's is much less researched and is often excluded from all-important clinical trials [71, 72]. A comprehensive overview of the published epidemiology literature on all people affected by the disease would also help the field to understand the relative epidemiological burden of Sjögren's compared to other autoimmune diseases and to assess the overall burden of Sjögren's on affected individuals and society.

CONCLUSIONS

This SLR identified an unmet need for studies on the epidemiology of primary Sjögren's, and in particular, a paucity of incidence and prevalence data across a diverse range of geographies. There is a need for the Sjögren's community to align on the methodology used for the classification of Sjögren's and reporting of incidence and prevalence estimates, to allow meaningful epidemiological comparisons across studies.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Eleanor Thurtle: Employee of Costello Medical; Alice Grosjean has nothing to disclose; Monia Steenackers: Employee of Novartis Pharma AG; Katharina

Strege: Employee of Costello Medical at time of study initiation, current employee of AstraZeneca with stock ownership and/or stock options or interests in the company; Giovanna Barcelos: Current employee of Pfizer Inc.; all substantial contributions to this work were made as an employee of Novartis Pharma AG; Pushpendra Goswami: Employee of Novartis Pharma AG.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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