Systematic review and meta analysis

Incidence and prevalence of systemic sclerosis globally: a comprehensive systematic review and meta-analysis

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Abstract

Objectives. We aimed to conduct a systematic review and meta-analysis on the incidence and prevalence of SSc covering the entire literature.

Methods. This study followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement of 2009. We conducted a systematic search in MEDLINE, Web of Science and Embase to identify articles reporting incidence and/or prevalence of SSc. Two authors conducted the search, reviewed articles for inclusion and extracted relevant data. We used random-effects models to estimate the pooled prevalence and incidence of SSc and performed subgroup analyses by sex, case definition and region to investigate heterogeneity. We explored the association between calendar period and reported estimates using meta-regression.

Results. Among 6983 unique records identified, we included 61 studies of prevalence and 39 studies of incidence in the systematic review. The overall pooled prevalence of SSc was 17.6 (95% CI 15.1, 20.5) per 100 000 and the overall pooled incidence rate of SSc was 1.4 (95% CI 1.1, 1.9) per 100 000 person-years. We observed significant regional variations in reported estimates; studies conducted in North America reported considerably higher estimates than other regions. The pooled incidence and prevalence in women were five times higher than in men. More recent studies reported higher estimates than older ones.

Conclusion. In this comprehensive review of the incidence and prevalence of SSc across the world, there was large heterogeneity among estimates, which should be taken into consideration when interpreting the results.

Key words: systemic sclerosis, systematic review, meta-analysis, incidence, prevalence

Introduction

SSc is an autoimmune rheumatic disease characterized by microvascular damage and generalized fibrosis in the skin and visceral organs. SSc has a broad spectrum of clinical manifestations, varying from RP and fatigue to more serious complications such as pulmonary arterial hypertension and lung fibrosis [1–4]. SSc, like other autoimmune diseases, is overrepresented in women...
compared with men [5]. Due to the multidimensional nature of its pathophysiology and manifestations, the diagnostic criteria of SSc have significantly evolved over time. In 1980, the ARA proposed preliminary criteria for the classification of SSc known as the ACR 1980 criteria [6]. They were followed by a new set proposed by LeRoy in 1988 [7], which were revised in 2001 by LeRoy and Medsger and divided the disease into three subsets: diffuse cutaneous, limited cutaneous and limited [8]. A collaboration between the ACR and the EULAR in 2013 yielded new classification criteria that proved to be superior to ACR’s 1980 criteria in terms of sensitivity and specificity [9]. The ACR/EULAR 2013 criteria considered new knowledge and techniques in autoimmunity and nailfold capillaroscopy, and new insights on the importance of vascular abnormalities as opposed to the previous focus on the presence of fibrosis.

SSc has throughout the literature been described as a rare disease. Reports on its occurrence differ greatly with respect to geographic region, the criteria the diagnosis was based on, population size and study design. A systematic review and meta-analysis on SSc incidence and prevalence has recently been published [10]. Because only studies published between 2006 and 2016 were included, any potential temporal trends and the impact of changes in diagnostic criteria over time on SSc incidence and prevalence could not be assessed. More recent studies tend to report higher estimates than older ones; SSc incidence in Finland was 0.4 per 100 000 person-years in 1990 [11] and 4.4 in 2010 [12]. Significant regional variations have also been reported where studies in Europe and the USA reported incidence and prevalence estimates 5–10 times higher than in Asia [13–17]. Moreover, no meta-analysis on the incidence of SSc exists.

Herein, we conducted a systematic review and meta-analysis to estimate the incidence and prevalence of SSc, overall and by sex, SSc case definition and geographic region, without imposing any restriction on calendar period of published studies.

Methods

This study followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement of 2009 [18].

Eligibility criteria

We considered studies that reported (i) the methods of diagnosing SSc [International Classification of Diseases (ICD) codes, calendar period relevant classification criteria or doctor’s opinion], (ii) a clearly defined denominator (population-based, hospital-based or outpatient clinic-based) and (iii) the incidence rate and/or prevalence of SSc (point prevalence and/or period prevalence).

Information sources

We conducted a systematic search in three databases, MEDLINE, Web of Science and Embase, for articles published in English with no restriction on publication year. Our search was last updated on 20 October 2020.

Search

We used keywords for SSc, incidence, prevalence and epidemiology in each database, in addition to corresponding MeSH terms and Emtree terms in MEDLINE and Embase, respectively. Our search strategy is presented in Supplementary Data S1, available at Rheumatology online. In addition, reference lists of review articles were screened to find studies that our search may have missed. Furthermore, we screened abstracts submitted to the two main rheumatology conferences between 2014 and 2018, the EULAR Congress and ACR Meeting. We contacted the first authors of relevant abstracts by e-mail to request additional data.

Study selection

We imported records retrieved through our search to the EndNote software where duplicates were removed. Two authors (M.B., M.H.) screened the titles and abstracts of the remaining records. Full texts of remaining relevant studies were assessed for eligibility, as well as additional data received from ACR/EULAR abstract authors. With regard to the meta-analyses, for studies reporting multiple prevalence estimates for several time periods or years, we included the most recent estimate, or the one covering the whole study period in the meta-analysis of incidence. If multiple estimates corresponding to different criteria were reported, we considered the estimate corresponding to the most recent criteria. For studies overlapping with one another in terms of denominator, the most recent study with the broadest denominator was considered. We considered estimates using capture–recapture when reported, and crude estimates before adjusting for sex and/or age when reported. We considered estimates using the adult population as a denominator when reported. If multiple estimates for different, independent populations, such as different cities or native groups, were reported, we regarded them as separate studies. For the study by Robinson et al. [19], we considered prevalence estimates requiring at least one inpatient stay or at least two ambulatory encounters. For the study by Fan et al. [20], we considered prevalence and incidence estimates requiring at least two medical claims for SSc.

Data items

We extracted the following information from eligible articles:

- Study design, country, calendar period, publication year, percentage of women, denominator size, person-years, the number of prevalent and/or incident cases, and case definition.
- Overall prevalence and incidence estimates as well as estimates stratified by sex.
Synthesis of results
We used random-effects models to pool incidence rates (using log transformation) and prevalence proportions (using logit transformation) across studies. We used the $I^2$ statistic to assess heterogeneity among studies. When denominator size or number of prevalent cases were not reported in primary studies, we calculated them using other reported measures or contacted authors for additional information. If incidence studies reported mean annual incidence without providing person-time denominator, we calculated the person-time denominator using other reported measures. We examined publication bias using funnel plots and Egger’s test. We performed the statistical analyses using the package ‘meta’ [21] in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Additional analyses
We performed subgroup analyses by case definition and geographic region to explore heterogeneity of pooled incidence and prevalence. In terms of case definition, we grouped studies into ACR 1980, LeRoy 1988, LeRoy and Medsger 2001, ACR/EULAR 2013, ICD codes and Other/Doctor’s opinion. Other/Doctor’s opinion included studies using different scoring systems to identify SSc cases or other inclusion criteria specific for each study as well as studies where SSc diagnosis was made based on doctor’s opinion without specifying the criteria used. Studies identifying SSc patients as those fulfilling multiple classification criteria were grouped under the most recent criteria. For the subgroup analysis of geographic region, we grouped studies according to continent: Africa, Asia, Europe, North America, Oceania and South America. We evaluated the impact of calendar period on prevalence and incidence by random-effects meta-regression. To test the impact of studies with small denominator size on the pooled prevalence estimates, we performed a sensitivity analysis where studies with a denominator smaller than 10,000 were excluded.

Results
The PRISMA 2009 flow diagram (Fig. 1) summarizes the screening and study selection process. Of the 6983 unique records identified in the three databases, we excluded 6721 based on abstract and title. The full text of the remaining records ($n = 201$), as well as additional data received from one ACR/EULAR abstract author, were read and assessed for eligibility. We excluded 131 articles due to the following: meeting abstracts ($n = 55$), duplicates not previously detected by EndNote ($n = 46$), studies not reporting incidence/prevalence ($n = 19$), inappropriate denominator ($n = 2$), correction/commentary articles ($n = 4$), articles reporting estimates based on other studies ($n = 3$) and articles studying other autoimmune diseases ($n = 2$). The exclusion of the 55 meeting abstracts was mainly due to duplicates and later published full-length articles already included. Thus, we identified 71 studies reporting incidence and/or prevalence estimates of SSc. SSc prevalence was reported in 61 studies while incidence was reported in 39 studies. Table 1 summarizes the characteristics of the studies.

SSc prevalence
Of the 61 studies reporting prevalence of SSc, we included 46 studies (58 independent populations) in the overall meta-analysis. Fifteen studies were excluded due to overlap in denominator with other broader and/or more recent studies. Prevalence ranged from 3.1 to 144.5 per 100,000 individuals. The pooled prevalence was 17.6 (95% CI 15.1, 20.5) per 100,000, $I^2 = 100\%$ (supplementary Fig. S1, available at Rheumatology online). There were signs of publication bias when the funnel plot was examined visually (supplementary Fig. S2, available at Rheumatology online), but Egger’s test indicated otherwise ($P = 0.19$).

Stratification by sex
There were 23 studies (30 independent populations) presenting prevalence estimates stratified by sex. The pooled prevalence among men was 6.0 (95% CI 4.8, 7.5) per 100,000, $I^2 = 97\%$ (supplementary Fig. S3, available at Rheumatology online) and 28.0 (95% CI 23.1, 33.9) per 100,000, $I^2 = 99\%$ among women (supplementary Fig. S4, available at Rheumatology online).

Subgroup analyses
Stratification by case definition. A pooled prevalence of 13.5 (95% CI 10.3, 17.7) per 100,000, $I^2 = 95\%$, the lowest among case definitions, was estimated from 12 studies (13 independent populations) that used ACR 1980 criteria. One study used LeRoy 1988 criteria and reported a prevalence of 39.9 (95% CI 29.6, 53.8) per 100,000. The pooled prevalence of studies using LeRoy and Medsger 2001 criteria (seven studies) was 19.2 (95% CI 12.6, 29.2) per 100,000, $I^2 = 99\%$. The most recent criteria, ACR/EULAR 2013, were used in five studies; the pooled prevalence was 18.9 (95% CI 12.7, 28.2) per 100,000, $I^2 = 97\%$. The highest pooled prevalence was observed in the nine studies (11 independent populations) using ICD codes to identify SSc patients: 23.5 (95% CI 17.6, 31.4) per 100,000, $I^2 = 100\%$. The remaining 12 studies (21 independent subgroups) were grouped under Other/Doctor’s opinion, and the pooled prevalence was 14.6 (95% CI 11.7, 18.3) per 100,000, $I^2 = 98\%$. Fig. 2 illustrates these results.

Stratification by geographic region. We found three studies conducted in Asia, with a pooled prevalence estimate of 6.8 (95% CI 5.7, 8.1) per 100,000, $I^2 = 98\%$. In Europe, there were 24 studies (30 independent populations) varying in size, design and case definition. The pooled prevalence was 14.8 (95% CI 11.6, 18.8) per 100,000, $I^2 = 100\%$. The pooled prevalence estimates of studies conducted in North America (10 studies, 15
independent populations) and Oceania (4 studies) were comparable, 25.9 (95% CI 21.5, 31.2) per 100 000, $I^2 = 99\%$, and 23.8 (95% CI 11.8, 48.3) per 100 000, $I^2 = 99\%$, respectively. Five studies were conducted in South America (six independent populations), two of them had the highest prevalence estimates observed. The pooled prevalence in South America was also comparable to other regions: 24.8 (95% CI 15.0, 41.0) per 100 000, $I^2 = 93\%$. We found no study conducted in Africa reporting SSc prevalence. These results are illustrated in Fig. 3.

Meta-regression. Results from the meta-regression of prevalence against calendar period indicates that more recent studies report higher prevalence estimates ($P = 0.006$) (supplementary Fig. S5, available at Rheumatology online).
### Table 1 Summary of characteristics of studies reporting incidence and/or prevalence of SSc

| Author year | Country     | Case definition method | Prevalence calendar period | Incidence calendar period |
|-------------|-------------|-------------------------|----------------------------|----------------------------|
| Abbot 2020  | Australia   | ACR/EULAR 2013          | 2018                       | N/A                        |
| Airo 2007   | Italy       | ACR 1980 and/or LeRoy and Medsger 2001 | g                          | N/A                        |
| Airo 2020   | Italy       | ACR 1980 or ACR/EULAR 2013 | g                          | g                          |
| Alamanos 2005 | Greece     | ACR 1980                  | 2002                       | 1981-2002                  |
| Alcock 2004 | UK          | ACR 1980 or a            | 2000                       | N/A                        |
| Anagnostopoulou 2010 | Greece | ACR 1980          | 2007–2008                  | N/A                        |
| Andréasson 2014 | Sweden   | ACR/EULAR 2013          | 2010                       | 2006–2010                  |
| Arias-Nuñez 2008 | Spain      | ACR 1980 and/or LeRoy and Medsger 2001 | 2006                      | 1988–2006                  |
| Arnett 1996 | USA         | ACR 1980                  | 1990–1994                  | N/A                        |
| Bajraktar 2013 | Kosovo      | ACR 1980                 | 2010                       | g                          |
| Barnabe 2012 | Canada      | ICD codes                | 2007                       | N/A                        |
| Bauer 2013  | USA         | LeRoy 1988               | 2010                       | 1980-2010                  |
| Bernatsky 2009 | Canada      | ICD codes                | 2003                       | N/A                        |
| Butt 2018   | Denmark     | ICD codes                | N/A                        | 1995–2015                  |
| Çakır 2012  | Turkey       | ACR 1980                 | ?                          | N/A                        |
| Chandran 1995 | Australia   | Doctor’s opinion         | g                          | N/A                        |
| Ciaffi 2021 | Italy       | Doctor’s opinion         | 2016                       | 2016                       |
| Eason 1981  | New Zealand | ACR 1980                 | N/A                        | 1970–1979                  |
| Eaton 2010  | Denmark     | ICD codes                | g                          | N/A                        |
| El Adassi 2013 | France    | ACR 1980 and/or LeRoy and Medsger 2001 | 2006                      | N/A                        |
| Elving 2016 | Finland     | ACR/EULAR 2013          | N/A                        | 2010                       |
| Englert 2005 | USA        | ACR 1980                 | 1991                       | N/A                        |
| Englert 1999 | Australia   | ACR 1980 or a            | 1988                       | N/A                        |
| Fan 2020   | USA         | ICD codes                | 2011–2016                  | 2011–2016                  |
| Fernández-Ávila 2020 | Colombia | ICD codes                | 2012–2016                  | N/A                        |
| Fretheim 2020 | Norway      | ACR 1980 and/or ACR/EULAR 2013 | 2013                      | N/A                        |
| Furst 2012  | USA         | ICD codes                | 2008                       | 2003-2008                  |
| García Rodríguez 2019 | UK | Doctor’s opinion         | 2012                       | 2000-2012                  |
| Geirsson 1994 | Iceland    | ACR 1980                 | 1990                       | 1975–1990                  |
| Hoffmann-Vold 2012 | Norway | ACR 1980 and/or LeRoy and Medsger 2001 | g                          | N/A                        |
| Horimoto 2017 | Brazil      | LeRoy and Medsger 2001 or ACR/EULAR 2013 | 2014                      | 2014                       |
| Hvidberg 2020 | Denmark    | ICD codes                | 2013                       | N/A                        |
| Kaipiainen-Seppanen 1996 | Finland | ACR 1980 or CREST       | N/A                        | 1990                       |
| Kosecki 2017 | Poland      | ICD codes                | 2012                       | 2008-2012                  |
| Kang 2018   | South Korea | ACR 1980                 | g                          | 2008-2013                  |
| Kim 2020   | South Korea | ACR 1980                 | 2016                       | N/A                        |
| Kuo 2016   | Taiwan      | ICD codes                | 2010                       | N/A                        |
| Kuo 2011   | Taiwan      | ICD codes                | g                          | 2002-2007                  |
| Kurland 1969 | USA         | Doctor’s opinion         | g                          | g                          |
| Laing 1997  | USA         | ACR 1980 or b            | N/A                        | 1985–1991$^{c}$            |
| Le Guern 2004 | France      | ACR 1980 and/or LeRoy and Medsger 2001 | 2001                      | N/A                        |
| Lo Monaco 2011 | Italy     | LeRoy and Medsger 2001   | 1999–2007                  | 1999–2007                  |
| Madu 2019  | Botswana    | Doctor’s opinion         | N/A                        | 2008-2015                  |
| Maricq 1989 | USA         | ACR 1980                 | 1985                       | N/A                        |
| Mayes 2003  | USA         | ACR 1980 or d            | 1989–1991                  | 1989–1991                  |
| Medsger 1971 | USA         | Doctor’s opinion         | N/A                        | 1947–1968                  |
| Medsger 1978 | USA         | Doctor’s opinion         | N/A                        | 1963–1968$^{a}$            |
| Meyer 2016  | France      | ACR 1980 and/or LeRoy and Medsger 2001 | 2008                      | N/A                        |
| Michel 1985 | USA         | ACR 1980                 | g                          | g                          |
| Peláz-Ballestas 2018 | Latin America | Doctor’s opinion     | ?                          | N/A                        |
| Peláz-Ballestas 2011 | Mexico | Doctor’s opinion         | ?                          | N/A                        |
| Piga 2016   | Italy       | ICD codes                | g                          | N/A                        |
| Quintana 2016 | Argentina | ACR/EULAR 2013          | g                          | N/A                        |
| Ratić 2010 | Croatia     | ACR 1980                 | 2008                       | N/A                        |
| Repa$^{a}$ | Greece      | ACR/EULAR 2013          | 2015                       | g                          |
| Roberts-Thomson 2006 | Australia | ACR 1980 or a          | 2002                       | 1993-2002                  |
| Roberts-Thomson 2001 | Australia | ACR 1980 or a          | g                          | g                          |

(continued)
Table 1 Continued

| Author year          | Country | Case definition method       | Prevalence calendar period | Incidence calendar period |
|----------------------|---------|------------------------------|---------------------------|--------------------------|
| Robinson 2008 [19]   | USA     | ICD codes                    | 2001–2002                 | N/A                      |
| Rosa 2011 [70]       | Argentina | ACR 1980 and/or LeRoy and Medsger 2001 | 2004                      | 1999–2004                |
| Royle 2018 [71]      | UK      | Read codes (NHS)             | 2013                      | 1994–2013                |
| Sandu 2012 [72]      | Italy   | ICD codes                    | g                        | N/A                      |
| See 2013 [73]        | Taiwan  | ICD codes                    | g                        | g                        |
| Silman 1988 [74]     | UK      | Doctor’s opinion             | 1986                      | 1980–1985                |
| Silman 1990 [75]     | UK      | Doctor’s opinion             | 1987                      | N/A                      |
| Sipek Dolnicar 2013  | Slovenia | LeRoy and Medsger 2001      | N/A                       | 2007–2009                |
| Steen 1997 [77]      | USA     | ACR 1980 or f                | N/A                       | 1963–1982                |
| Tamaki 1991 [78]     | Japan   | ACR 1980                    | 1988                      | N/A                      |
| Thompson 2002 [79]  | Canada  | ACR 1980 or CREST           | 1996                      | N/A                      |
| Valter 1997 [80]     | Estonia | ACR 1980                    | ?                        | N/A                      |
| Vonk 2009 [81]       | Netherlands | ACR 1980 and LeRoy and Medsger 2001 | 2007                     | 2005–2006                |
| Yu 2013 [82]         | Taiwan  | ICD codes                    | g                        | g                        |

Prevalence calendar period and incidence calendar period refer to the estimates used in the meta-analyses.

Sensitivity analysis. There were four studies (five independent populations) [26, 40, 57, 63] with a denominator smaller than 10 000. All of them reported a prevalence higher than the overall pooled prevalence mentioned above, and they were grouped under ACR 1980 or Other/Doctor’s opinion. After exclusion of them, the overall pooled estimate declined slightly to 16.7 (95% CI 14.3, 19.5) per 100 000, \( I^2 = 100% \). The pooled estimate in Europe was hardly affected, while there was no change in North America and Asia. In South America, however, there was a considerable decrease in the pooled estimate to 18.9 (95% CI 11.2, 31.9) per 100 000, \( I^2 = 95% \), when the two populations with highest prevalence estimates were excluded. A similar change was noticed in Oceania, 18.8 (95% CI 8.6, 41.1) per 100 000, \( I^2 = 99% \) (supplementary Figs S6–8, available at Rheumatology online).

SSc incidence

Of the 39 studies reporting incidence of SSc, we included 28 studies in the overall meta-analysis. The exclusion of 11 studies was due to overlap in denominator with other broader and/or more recent studies (\( n = 6 \)), report of cumulative incidence over several years (\( n = 1 \)), incidence rate solely for either men or women (\( n = 2 \)) or insufficient data (\( n = 2 \)). The pooled incidence rate was 1.4 (95% CI 1.1, 1.9) per 100 000 person-years, \( I^2 = 100% \) (supplementary Fig. S9, available at Rheumatology online). The funnel plot (supplementary Fig. S10, available at Rheumatology online) indicates a probable publication bias. This visual impression was not confirmed by Egger’s test (\( P = 0.18 \)).

Stratification by sex

There were 14 studies reporting SSc incidence in men with a pooled incidence of 0.5 (95% CI 0.4, 0.7) per 100 000 person-years, \( I^2 = 96% \) (supplementary Fig. S11, available at Rheumatology online). Thirteen studies reported SSc incidence in women with a pooled incidence of 2.3 (95% CI 1.8, 2.9) per 100 000 person-years, \( I^2 = 98% \) (supplementary Fig. S12, available at Rheumatology online).

Subgroup analyses

Stratification by case definition. There were four studies using ACR 1980 criteria to define cases; the pooled incidence was 0.7 (95% CI 0.6, 1.0) per 100 000 person-years, \( I^2 = 86% \). Only one study used LeRoy 1988 criteria, and the incidence rate was 2.4 (95% CI 1.9, 3.1) per 100 000 person-years. LeRoy and Medsger 2001 criteria were used in five studies giving a pooled incidence of 2.1 (95% CI 1.0, 4.6) per 100 000 person-years, \( I^2 = 98% \). A comparable pooled incidence rate was observed in studies using ACR/EULAR 2013 criteria (three studies): 2.1 (95% CI 1.2, 3.7) per 100 000 person-years, \( I^2 = 76% \). Five studies used ICD codes to identify SSc cases, the pooled incidence was 2.8 (95% CI 1.4, 5.4) per 100 000 person-years, \( I^2 = 100% \), which is the highest rate in this analysis. Ten studies were...
grouped under Other/Doctor's opinion and the pooled incidence was 1.0 (95% CI 0.7, 1.3) per 100 000 person-years, $I^2 = 98\%$. Fig. 4 demonstrates these results.

**Stratification by geographic region.** We found only one study reporting incidence rate of SSc in Africa: 0.2 (95% CI 0.1, 0.3) per 100 000 person-years, which represents the lowest observed incidence rate. In Asia, two studies were found with a pooled incidence of 0.9 (95% CI 0.7, 1.3) per 100 000 person-years, $I^2 = 99\%$. Studies in Europe (15 studies) and North America (6 studies) had comparable pooled rates: 1.6 (95% CI 1.3, 1.9) per 100 000 person-years, $I^2 = 98\%$, and 2.0 (95% CI 1.1, 3.7) per 100 000 person-years, $I^2 = 100\%$, respectively. There were two studies from Oceania, and the pooled incidence was 1.0 (95% CI 0.4, 2.3) per 100 000 person-years, $I^2 = 97\%$. Two studies were also conducted in South America with a pooled incidence of 1.5 (95% CI 0.9, 2.7) per 100 000 person-years, $I^2 = 28\%$. These results are demonstrated in Fig. 5.

**Meta-regression.** Meta-regression of incidence against calendar period suggests that more recent studies report higher incidence rates ($P = 0.002$) (supplementary Fig. S13, available at *Rheumatology* online).

**Discussion**

In this report, we present the first ever meta-analysis on the incidence of SSc globally, in addition to a meta-
analysis on the prevalence of SSc covering the whole available literature in English. The pooled prevalence is 17.6 per 100,000 and the pooled incidence rate is 1.4 per 100,000 person-years. When we excluded studies with small denominator size, the overall pooled prevalence and estimates of the majority of subgroups were hardly affected. These sensitivity analyses proved our results to be robust. This report revealed high $I^2$ values indicating large heterogeneity among included studies due to differences in study design, case definition, geographic region and calendar period.

More recent studies reported higher estimates than older ones. We could attribute this temporal trend to the wider availability of modern diagnostic methods in addition to increased awareness of SSc and more sensitive criteria, rather than a true increase in SSc occurrence. Our subgroup analyses revealed that pooled estimates in the ACR 1980 group were lower than other groups while pooled estimates of LeRoy and Medsger 2001 and ACR/EULAR 2013 were comparable. This observation was confirmed in studies reporting prevalence or incidence estimates using different sets of criteria; estimates corresponding to more recent criteria were higher than estimates corresponding to older ones. In Italy, the prevalence and incidence using ACR 1980 criteria were 25.4 per 100,000 and 3.2 per 100,000 person-years, respectively, while they were 34 and 4.3, respectively, using LeRoy and Medsger 2001 criteria.

### FIG. 4 Meta-analysis of SSc incidence per 100,000 person-years, stratified by case definition method

| Author/Year, Country | Incident cases | Person-years | Incidence of SSc per 100,000 person-years | 95% CI |
|----------------------|---------------|--------------|------------------------------------------|-------|
| **ACR 1980**         |               |              |                                          |       |
| Alamargos 2005, Greece | 169           | 9909890      | 1.1 (0.9, 1.3)                           |       |
| Easton 1981, New Zealand | 47          | 7469218      | 0.6 (0.5, 0.9)                           |       |
| Geirsson 1994, Iceland | 15           | 3947368      | 0.4 (0.2, 0.6)                           |       |
| Kang 2018, South Korea | 2402         | 300259000    | 0.8 (0.6, 0.8)                           |       |
| **Overall**          |               |              |                                          | 0.7 (0.6, 1.0) |
| Heterogeneity: $I^2 = 86\%, \hat{t}^2 = 0.0584$, p < 0.01 |
| **LeRoy 1988**       |               |              |                                          |       |
| Bauz 2013, USA       | 64            | 2933745      | 2.4 (1.9, 3.1)                           |       |
| **Overall**          |               |              |                                          | 2.4 (1.9, 3.1) |
| Heterogeneity: not applicable |
| **LeRoy and Medsger 2001** |           |              |                                          |       |
| Aras-Juncos 2008, Spain | 78         | 3931304      | 2.3 (1.8, 2.9)                           |       |
| Le Monac 2011, Italy | 118           | 2744186      | 4.3 (3.6, 5.2)                           |       |
| Rosa 2011, Argentina | 7             | 329534       | 2.1 (1.0, 4.5)                           |       |
| Spek-Dolinar 2013, Slovenia | 41     | 1597623      | 2.6 (1.9, 3.3)                           |       |
| Veerk 2009, Netherlands | 197         | 255542415    | 0.8 (0.7, 0.9)                           |       |
| **Overall**          |               |              |                                          | 2.1 (1.0, 4.6) |
| Heterogeneity: $I^2 = 98\%, \hat{t}^2 = 0.7772$, p < 0.01 |
| **ACR/EULAR 2013**   |               |              |                                          |       |
| Andriason 2014, Sweden | 94         | 4947368      | 1.9 (1.6, 2.3)                           |       |
| Elling 2016, Finland | 9             | 204546       | 4.4 (2.3, 6.5)                           |       |
| Horimoto 2017, Brazil | 10          | 840336       | 1.2 (0.6, 2.2)                           |       |
| **Overall**          |               |              |                                          | 2.1 (1.2, 3.7) |
| Heterogeneity: $I^2 = 76\%, \hat{t}^2 = 0.1946$, p = 0.01 |
| **ICD-codes**        |               |              |                                          |       |
| Batt 2016, Denmark   | 2778          | 115043183    |                                          |       |
| Fan 2020, USA        | 3868          | 50762932     | 7.5 (7.2, 7.7)                           |       |
| Furst 2012, USA      | 4229         | 36001350     | 4.6 (4.4, 4.8)                           |       |
| Kaneschi 2017, Poland | 2693        | 19203158     | 1.9 (1.8, 2.0)                           |       |
| Kao 2011, Taiwan     | 1479          | 135668073    | 1.1 (1.0, 1.1)                           |       |
| **Overall**          |               |              |                                          | 2.8 (1.4, 5.4) |
| Heterogeneity: $I^2 = 100\%, \hat{t}^2 = 0.5745$, p = 0 |

| Other/doctors opinion |               |              |                                          |       |
| Ciavari 2021, Italy  | 480           | 25934569     | 1.9 (1.7, 2.0)                           |       |
| Garcia-Rodriguez 2019, UK | 885      | 34183600     | 2.0 (1.9, 2.2)                           |       |
| Kajalainen-Seppasen 1996, Finland | 4 | 108161 | 0.4 (0.1, 1.0) |
| Muck 2019, Botswana   | 20            | 9049609      | 0.2 (0.1, 0.3)                           |       |
| Mayes 2003, USA       | 184           | 8761665      | 2.1 (1.8, 2.4)                           |       |
| Medsgen 1971, USA    | 38            | 14074174     | 0.3 (0.2, 0.4)                           |       |
| Roberts-Thomson 2006, Australia | 225 | 150253000     | 1.5 (1.3, 1.7)                           |       |
| Royle 2018, UK       | 1292          | 5637396      | 2.3 (2.2, 2.4)                           |       |
| Silman 1988, UK      | 78            | 21031081     | 0.4 (0.3, 0.5)                           |       |
| Steen 1997, USA      | 444           | 31942446     | 1.4 (1.3, 1.5)                           |       |
| **Overall**          |               |              |                                          | 1.0 (0.7, 1.3) |
| Heterogeneity: $I^2 = 98\%, \hat{t}^2 = 0.2032$, p < 0.01 |

ICD: International Classification of Diseases.
In Sweden, the incidence of SSc increased from 1.4–1.9 per 100 000 person-years when using ACR/EULAR 2013 criteria instead of ACR 1980 criteria, and the prevalence increased from 23.5–30.5 per 100 000 [27]. We found no study comparing LeRoy and Medsger 2001 with ACR/EULAR 2013 criteria.

Pooled estimates from studies that used ICD codes to ascertain SSc were comparable to the ones in which ACR/EULAR 2013 criteria were used. Butt et al. showed that identification of incident SSc cases through ICD-10 codes in Denmark had a positive predictive value of 94% using ACR/EULAR 2013 criteria as reference [33]. The definition of SSc cases using ICD codes differed among included studies with some studies used rather strict definitions of SSc leading to higher specificity and thus lower prevalence/incidence. Robinson et al. [19] reported considerably lower prevalence when requiring at least one in-patient claim or two or more office or emergency room visits compared with requiring at least one medical claim. Similarly, Fan et al. [20] reported an incidence of 16.4 per 100 000 person-years and a prevalence of 44.1 per 100 000 requiring one medical claim of SSc using ICD codes. These estimates declined to 7.5 and 24.4, respectively, when two medical claims were required.

Stratification by region showed significant variation between different parts of the world. The pooled

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### Table: Incidence and Prevalence of SSc

| Author Year, Country | Incident cases | Person-years | Incidence of SSc per 100 000 person-years | 95% CI |
|---------------------|----------------|--------------|------------------------------------------|-------|
| **Africa**          |                |              |                                          |       |
| Maldonado 2019, Botswana | 20            | 909809       | 0.2 (0.1; 0.3)                           |       |
| Overall             |                |              | 0.2 (0.1; 0.3)                           |       |
| Heterogeneity: not applicable |              |              |                                          |       |
| **Asia**            |                |              |                                          |       |
| Kang 2018, South Korea | 2402          | 300259000    | 0.8 (0.6; 0.9)                           |       |
| Kuo 2011, Taiwan    | 1479           | 13588703     | 1.1 (1.0; 1.1)                           |       |
| Overall             |                |              | 0.9 (0.7; 1.3)                           |       |
| Heterogeneity: $\hat{p}^2 = 99\%$, $\hat{C}^2 = 0.0473$, $p < 0.01$ |              |              |                                          |       |
| **Europe**          |                |              |                                          |       |
| Alamanos 2005, Greece | 169           | 990690       | 1.1 (0.9; 1.3)                           |       |
| Andriessen 2014, Sweden | 94            | 4947268      | 1.8 (1.6; 2.3)                           |       |
| Arias-Nunez 2008, Spain | 78            | 3391304      | 2.3 (1.8; 2.8)                           |       |
| Butt 2018, Denmark  | 2778           | 11503183     | 2.4 (2.3; 2.5)                           |       |
| Ciaffi 2021, Italy  | 480            | 25006669     | 1.9 (1.7; 2.0)                           |       |
| Elving 2016, Finland| 8              | 204646       | 4.4 (2.0; 8.5)                           |       |
| Garcia Rodriguez 2019, UK | 669           | 34183000     | 2.6 (1.9; 3.2)                           |       |
| Gissinsson 1994, Iceland | 15            | 9047986      | 0.4 (0.2; 6.6)                           |       |
| Kallioinen–Seppanen 1995, Finland | 4  | 1010181 | *                                      |       |
| Karlsen 2017, Poland | 3853           | 19028158     | 1.9 (1.2; 3.2)                           |       |
| Le Menace 2011, Italy | 118           | 2744186      | 4.3 (3.0; 5.2)                           |       |
| Rylai 2018, UK      | 1292           | 5573896      | 2.3 (2.2; 2.4)                           |       |
| Silman 1988, UK     | 78             | 21081681     | 0.4 (0.3; 0.5)                           |       |
| Sipek Dominer 2013, Slovenia | 41          | 1579823     | 2.6 (1.9; 3.2)                           |       |
| Vuk 2009, Netherlands | 197           | 25584415     | 0.8 (0.7; 0.9)                           |       |
| **Overall**         |                |              | 1.6 (1.3; 1.9)                           |       |
| Heterogeneity: $\hat{p}^2 = 98\%$, $\hat{C}^2 = 0.0958$, $p < 0.01$ |              |              |                                          |       |
| **North America**   |                |              |                                          |       |
| Bauer 2013, USA     | 64             | 263745       | 2.4 (1.9; 2.1)                           |       |
| Fan 2020, USA       | 3388           | 50788293     | 7.5 (7.3; 7.7)                           |       |
| Furt 2012, USA      | 1529           | 30329130     | 4.6 (4.4; 4.8)                           |       |
| Meyers 2003, USA    | 184            | 5701805      | 2.1 (1.9; 2.3)                           |       |
| Medsger 1971, USA   | 58             | 1407474      | 0.3 (0.2; 0.4)                           |       |
| Steen 1997, USA     | 444            | 3194246      | 1.4 (1.3; 1.5)                           |       |
| **Overall**         |                |              | 2.0 (1.1; 3.7)                           |       |
| Heterogeneity: $\hat{p}^2 = 100\%$, $\hat{C}^2 = 0.5560$, $p = 0$ |              |              |                                          |       |
| **Oceania**         |                |              |                                          |       |
| Eason 1991, New Zealand | 47           | 7460318      | 0.6 (0.5; 0.8)                           |       |
| Rober–Thomson 2006, Australia | 225 | 15003600 | 1.5 (1.3; 1.7)                           |       |
| **Overall**         |                |              | 1.0 (0.4; 2.3)                           |       |
| Heterogeneity: $\hat{p}^2 = 97\%$, $\hat{C}^2 = 0.3634$, $p < 0.01$ |              |              |                                          |       |
| **South America**   |                |              |                                          |       |
| Horimoto 2017, Brazil | 10            | 849326       | 1.2 (0.6; 2.2)                           |       |
| Rosa 2011, Argentina | 7             | 309634       | 2.1 (1.4; 4.5)                           |       |
| **Overall**         |                |              | 1.5 (0.9; 2.7)                           |       |
| Heterogeneity: $\hat{p}^2 = 28\%$, $\hat{C}^2 = 0.0465$, $p = 0.24$ |              |              |                                          |       |
prevalence in studies from Asia was the lowest as relatively low estimates were consistently reported. For example, SSc prevalence in Taiwan was 8 per 100 000, while it was 34.8 in Sardinia, Italy despite similarities in design, calendar period and case definition method [50, 65]. Likewise, the incidence rate was 1.1 and 4.6 per 100 000 person-years in Taiwan and the USA, respectively [16, 51]. We may therefore conclude that the lower occurrence of SSc in Asia, can not only be explained by methodological differences, and a true difference may be present. In North America, high estimates were seen in the majority of studies despite considerable methodological variations among them, which indicates the occurrence of SSc there may be the highest worldwide. Scarce data from Africa did not allow us to provide estimates of incidence and prevalence for the continent. Interestingly, a higher incidence of SSc was reported in African American women compared with European American women (2.25 vs 1.28 per 100 000 person-years) in the USA [53], and a recent genetic study has identified two African ancestry-predominant HLA alleles that were associated with increased frequency of SSc among African Americans [83].

In Europe, the previously proposed north-to-south gradient [84] where higher latitude indicates lower occurrence seems to be rather present in our analysis despite a few exceptions. Prevalence estimates in Italy (34.8 and 58.6 per 100 000 [15, 65]) and Spain (27.7 per 100 000 [28]) were markedly higher than France (13.2 and 15.8 per 100 000 [39, 54]), the Netherlands (8.9 per 100 000 [81]) and Norway (15.9 per 100 000 [43]). On the contrary, prevalence in Sweden (30.5 per 100 000) seems to not adhere to this gradient despite using similar methodology to the Norwegian study [27]. The prevalence in Denmark was also higher than in Norway: 36.8 per 100 000. Similar results were also observed regarding incidence rates: Italy (4.6 per 100 000 person-years [15]), Spain (2.3 per 100 000 person-years [28]), the Netherlands (0.8 per 100 000 person-years [81]), Sweden (1.9 per 100 000 person-years [27]) and Denmark (2.4 per 100 000 person-years [33]).

As expected, the pooled incidence and prevalence estimates for Europe were similar to the overall pooled estimates as more European than studies from other regions were included in our analyses. The pooled prevalence estimates in both South America and Oceania after exclusion of studies with small denominator size were also comparable to the overall pooled estimate. SSc has consistently been described to be more common in women compared with men. A women-to-men ratio of almost 5:1 was noticed in the majority of studies. Our analyses stratified by sex seem to be in line with that. The pooled prevalence and incidence in women were almost five times higher than the pooled estimates in men (prevalence 28 vs 6.1 per 100 000; incidence 2.3 vs 0.5 per 100 000 person-years).

This report has some limitations. It was restricted to studies published in English, excluding potentially relevant studies in other languages. If incidence and prevalence estimates from some parts of the world were missed, pooled overall and regional estimates may not reflect the true picture of SSc epidemiology. Furthermore, reported estimates from developing regions may be lower than other regions due to the limited accessibility to the modern diagnostic methods. We were unable to account for the broad and overlapping spectrum of methods used to identify patients in primary studies, ranging from primary care practice- to tertiary centre- and register-based studies, differing in their coverage of the studied population. Large heterogeneity was observed among studies as indicated by high $I^2$ values due to variations in design, case definition, calendar period and region. Also, inclusion of studies with large denominators and thus small standard errors led to an overestimation of the $I^2$ statistic [85]. We believe pooled estimates and measures of heterogeneity should be interpreted with caution. A major strength of our study is the comprehensive and broad search strategy, and that we present the first ever meta-analysis of SSc incidence. Compared with a previous systematic review [10], considerably more studies were included in our meta-analysis of SSc prevalence (46 vs 18). This allowed us to conduct sensitivity analyses, subgroup analyses and analyses stratified by sex to explore the impact of different factors on prevalence and incidence estimates.

In conclusion, the incidence and prevalence of SSc vary significantly depending on study settings, acquisition routes, region and calendar period, in addition to the considerably higher occurrence of SSc in women in comparison to men. Our results should therefore be interpreted taking these issues into consideration.

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**Data availability statement**

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

**Supplementary data**

Supplementary data are available at Rheumatology online.

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