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Systematic review and meta analysis

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

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CLINICAL SCIENCE

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

Rheumatology key messages

- Incidence and prevalence estimates of SSc vary considerably between studies.
- There is a temporal trend towards increased incidence and prevalence over calendar period.
- This increase is likely due to increased awareness and improvement in diagnostic methods and criteria.

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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. In studies reporting estimates stratified by sex, the person-time denominator for each sex, if not provided, was calculated 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

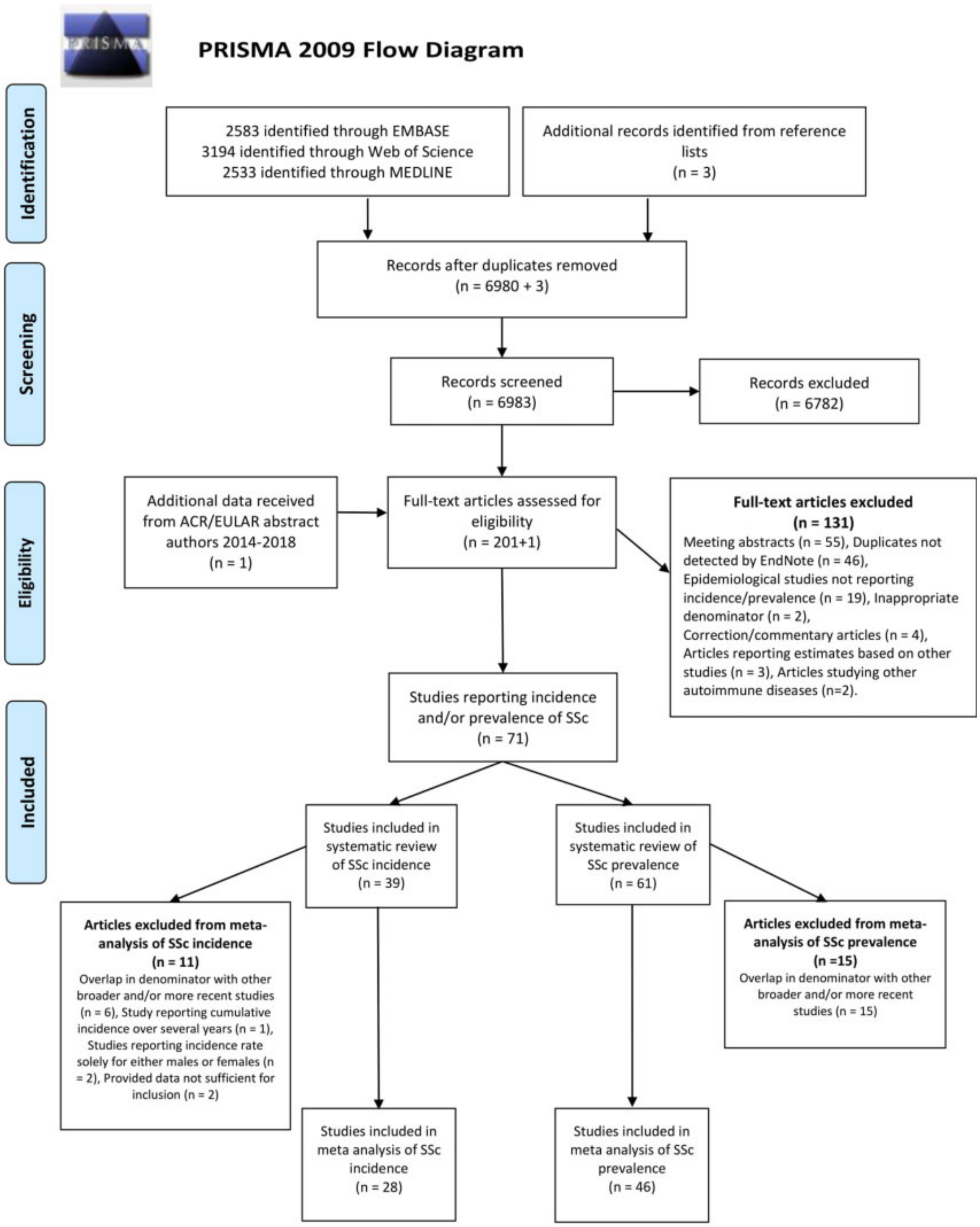
There were 23 studies (30 independent populations) presenting prevalence estimates stratified by sex. The pooled prevalence among men was 6.0 (95% CI 4.8, 7.5) per 100 000, $I^2 = 97\%$ (supplementary Fig. S3, available at *Rheumatology* online) and 28.0 (95% CI 23.1, 33.9) per 100 000, $I^2 = 99\%$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

Fig. 1 PRISMA 2009 flow diagram for process and outcome of the study selection strategy



PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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 [22]	Australia	ACR/EULAR 2013	2018	N/A
Airò 2007 [23]	Italy	ACR 1980 and/or LeRoy and Medsger 2001	[g]	N/A
Airò 2020 [15]	Italy	ACR 1980 or ACR/EULAR 2013	[g]	[g]
Alamanos 2005 [24]	Greece	ACR 1980	2002	1981-2002
Allcock 2004 [25]	UK	ACR 1980 or [a]	2000	N/A
Anagnostopoulos 2010 [26]	Greece	ACR 1980	2007–2008	N/A
Andréasson 2014 [27]	Sweden	ACR/EULAR 2013	2010	2006–2010
Arias-Nuñez 2008 [28]	Spain	ACR 1980 and/or LeRoy and Medsger 2001	2006	1988–2006
Arnett 1996 [17]	USA	ACR 1980	1990–1994	N/A
Bajraktari 2013 [29]	Kosovo	ACR 1980	2010	[g]
Barnabe 2012 [30]	Canada	ICD codes	2007	N/A
Bauer 2013 [31]	USA	LeRoy 1988	2010	1980–2010
Bernatsky 2009 [32]	Canada	ICD codes	2003	N/A
Butt 2018 [33]	Denmark	ICD codes	N/A	1995–2015
Çakır 2012 [34]	Turkey	ACR 1980	?	N/A
Chandran 1995 [35]	Australia	Doctor's opinion	[g]	N/A
Ciaffi 2021 [36]	Italy	Doctor's opinion	2016	2016
Eason 1981 [37]	New Zealand	ACR 1980	N/A	1970–1979
Eaton 2010 [38]	Denmark	ICD codes	[g]	N/A
El Adssi 2013 [39]	France	ACR 1980 and/or LeRoy and Medsger 2001	2006	N/A
Elfving 2016 [12]	Finland	ACR/EULAR 2013	N/A	2010
Englert 2005 [40]	Australia	ACR 1980	1991	N/A
Englert 1999 [41]	Australia	ACR 1980 or [a]	1988	N/A
Fan 2020 [20]	USA	ICD codes	2011–2016	2011–2016
Fernández-Ávila 2020 [42]	Colombia	ICD codes	2012–2016	N/A
Fretheim 2020 [43]	Norway	ACR 1980 and/or ACR/EULAR 2013	2013	N/A
Furst 2012 [16]	USA	ICD codes	2008	2003–2008
García Rodrígues 2019 [44]	UK	Doctor's opinion	2012	2000–2012
Geirsson 1994 [45]	Iceland	ACR 1980	1990	1975–1990
Hoffmann-Vold 2012 [46]	Norway	ACR 1980 and/or LeRoy and Medsger 2001	[g]	N/A
Horimoto 2017 [47]	Brazil	LeRoy and Medsger 2001 or ACR/EULAR 2013	2014	2014
Hvidberg 2020 [48]	Denmark	ICD codes	2013	N/A
Kaipiainen-Seppanen 1996 [11]	Finland	ACR 1980 or CREST	N/A	1990
Kanecki 2017 [49]	Poland	ICD codes	2012	2008–2012
Kang 2018 [13]	South Korea	ACR 1980	[g]	2008–2013
Kim 2020 [14]	South Korea	ACR 1980	2016	N/A
Kuo 2016 [50]	Taiwan	ICD codes	2010	N/A
Kuo 2011 [51]	Taiwan	ICD codes	[g]	2002–2007
Kurland 1969 [52]	USA	Doctor's opinion	[g]	[g]
Laing 1997 [53]	USA	ACR 1980 or [b]	N/A	1985–1991[c]
Le Guern 2004 [54]	France	ACR 1980 and/or LeRoy and Medsger 2001	2001	N/A
Lo Monaco 2011 [55]	Italy	LeRoy and Medsger 2001	1999–2007	1999–2007
Madu 2019 [56]	Botswana	Doctor's opinion	N/A	2008–2015
Maricq 1989 [57]	USA	ACR 1980	1985	N/A
Mayes 2003 [58]	USA	ACR 1980 or [d]	1989–1991	1989–1991
Medsger 1971 [59]	USA	Doctor's opinion	N/A	1947–1968
Medsger 1978 [60]	USA	Doctor's opinion	N/A	1963–1968[c]
Meyer 2016 [61]	France	ACR 1980 and/or LeRoy and Medsger 2001	2008	N/A
Michet 1985 [62]	USA	ACR 1980	[g]	[g]
Peláez-Ballestas 2018 [63]	Latin America	Doctor's opinion	?	N/A
Peláez-Ballestas 2011 [64]	Mexico	Doctor's opinion	?	N/A
Piga 2016 [65]	Italy	ICD codes	[g]	N/A
Quintana 2016 [66]	Argentina	ACR/EULAR 2013	[g]	N/A
Radić 2010 [67]	Croatia	ACR 1980	2008	N/A
Repa[e]	Greece	ACR/EULAR 2013	2015	[g]
Roberts-Thomson 2006 [68]	Australia	ACR 1980 or [a]	2002	1993–2002
Roberts-Thomson 2001 [69]	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
Sardu 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 [76]	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.
[a]One major criterion, sclerodactyly and at least two of the following minor criteria: RP, oesophageal dysmotility, calcinosis, telangiectasia or an elevated ANA titre.
[b]Sclerodactyly and one or more other features of the CREST syndrome.
[c]Included only in the analyses stratified by sex.
[d]A rheumatologist diagnosis of SSc, sclerodactyly and at least two other features of the CREST syndrome.
[e]Argyro Repa, Rheumatology Department, University Hospital Crete, Greece.
[f]RP, sclerodactyly, telangiectasias or calcinosis and one organ involvement characteristic of SSc, including oesophageal hypomotility, small bowel hypomotility, pulmonary arterial hypertension or scleroderma renal crisis.
[g]Reported but not included in the overall meta-analyses. N/A: not available; ICD: International Classification of Diseases; NHS: UK National Health Service; ? Prevalence calendar period was not stated clearly.

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 ($P = 0.18$).

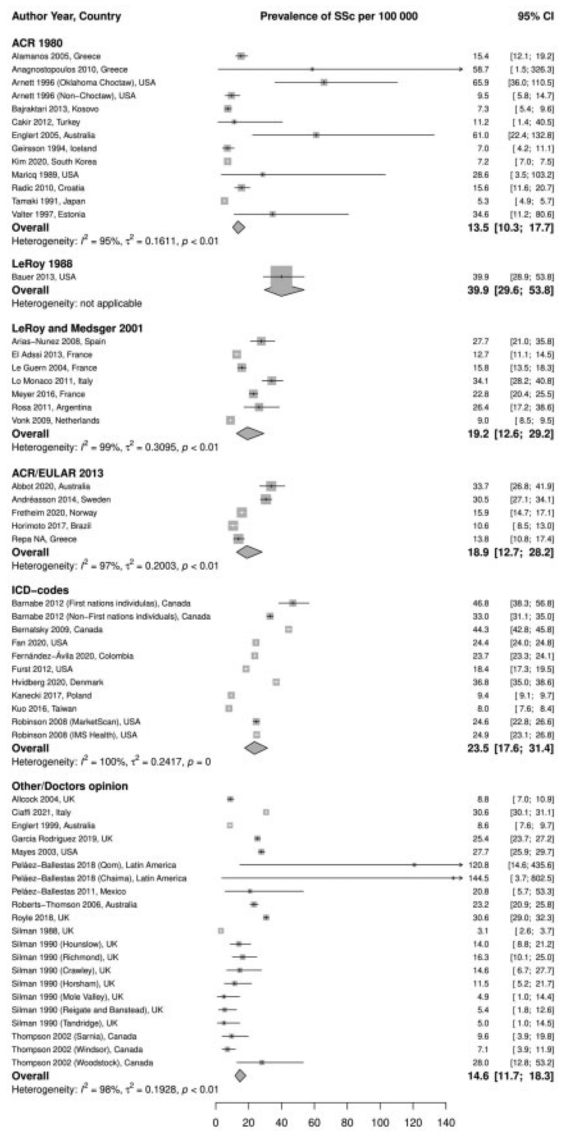
Stratification by sex

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

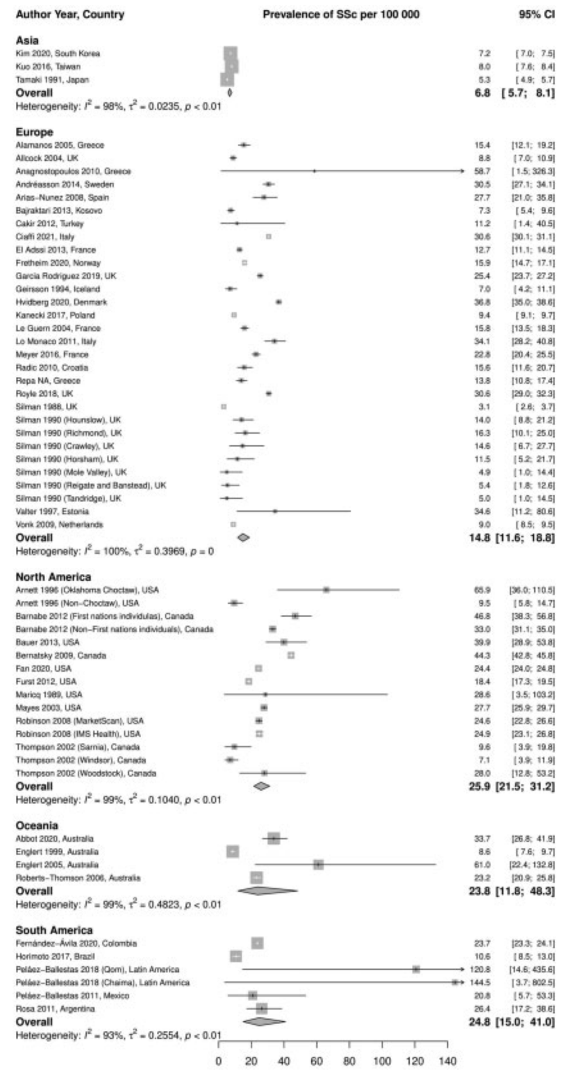
Stratification by case definition. There were four studies using ACR 1980 criteria to define cases; the pooled incidence was 0.7 (95% CI 0.6, 1.0) per 100 000 person-years, $I^2 = 86\%$. Only one study used LeRoy 1988 criteria, and the incidence rate was 2.4 (95% CI 1.9, 3.1) per 100 000 person-years. 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

FIG. 2 Meta-analysis of SSc prevalence per 100 000, stratified by case definition method



ICD: International Classification of Diseases.

FIG. 3 Meta-analysis of SSc prevalence per 100 000, stratified by region



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.

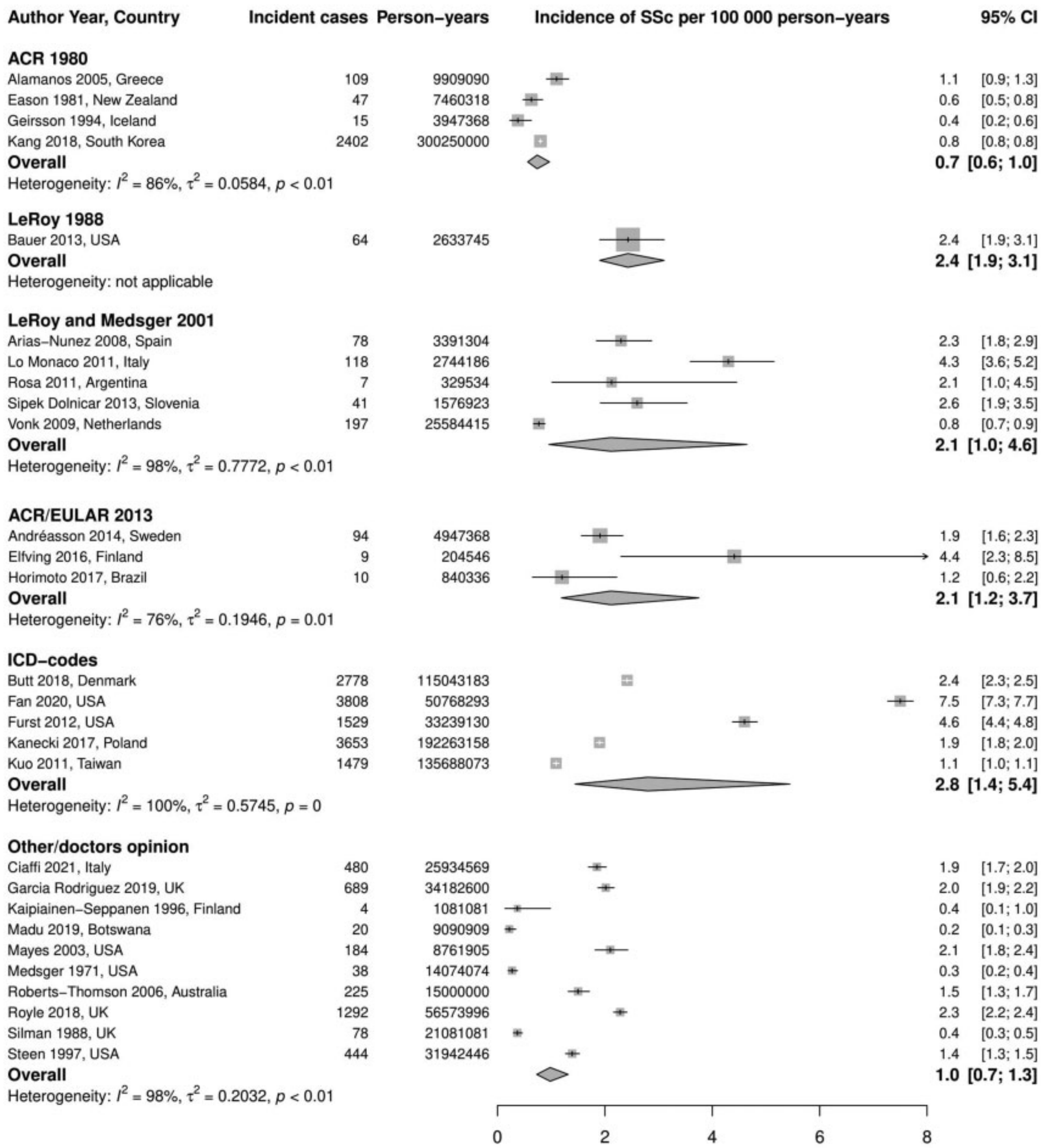
Stratification by geographic region. We found only one study reporting incidence rate of SSc in Africa: 0.2 (95% CI 0.1, 0.3) per 100 000 person-years, which represents the lowest observed incidence rate. In Asia, two studies were found with a pooled incidence of 0.9 (95% CI 0.7, 1.3) per 100 000 person-years, $I^2 = 99\%$. 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-

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

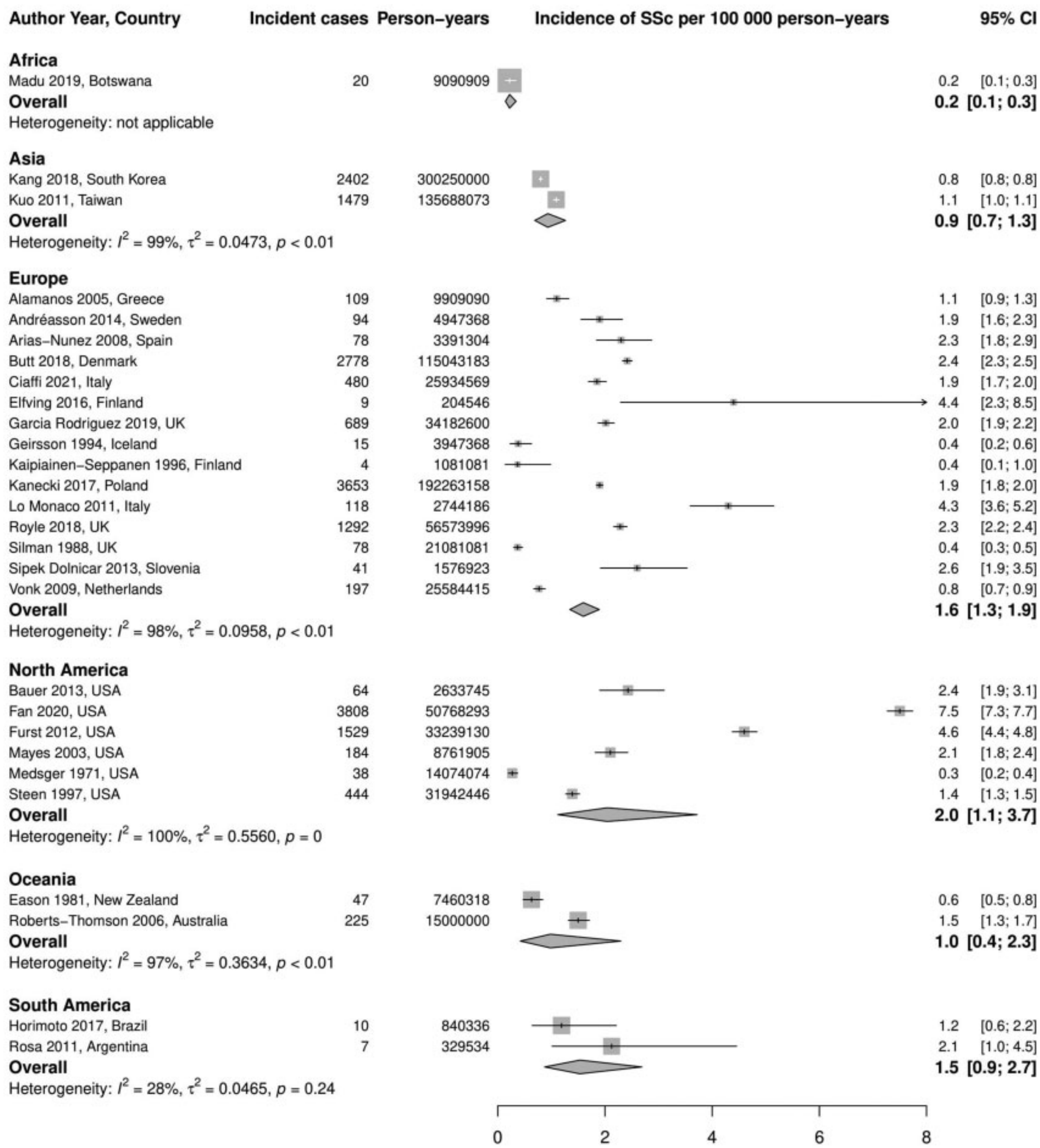


ICD: International Classification of Diseases.

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. 5 Meta-analysis of SSc incidence per 100 000 person-years, stratified by region



[55]. 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 inpatient 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 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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