Rheumatology Advances in Practice, 2024, **8(3)**, rkae086
https://doi.org/10.1093/rap/rkae086
Advance access publication 27 July 2024
Systematic Review and Meta-Analysis

Clinical science

Prevalence, incidence, and mortality of Raynaud's phenomenon, Sjögren's syndrome and scleroderma: an umbrella review of systematic reviews

Anthony Chen [1], Stephanie J. Lax[1], Matthew J. Grainge [1], Peter C. Lanyon[1,2], Fiona A. Pearce [1,2,*]

[1]Lifespan and Population Health, School of Medicine, University of Nottingham, Nottingham, UK
[2]Department of Rheumatology, Nottingham University Hospitals NHS Trust, Nottingham, UK

*Correspondence to: Fiona Pearce, Nottingham City Hospital, B63 Clinical Sciences Building, Hucknall Rd, Nottingham NG5 1PB, UK.
E-mail: Fiona.Pearce@nottingham.ac.uk

Abstract

Objectives: To comprehensively review systematic reviews of prevalence, incidence, and mortality of Raynaud's, Sjögren's and Scleroderma, and to identify any research gaps.

Methods: An umbrella review of English language systematic reviews was undertaken using PubMed and Embase (OVID) covering the period 2000–2023 (PROSPERO CRD42023434865). The estimate and its corresponding 95% confidence interval were reported when available from each systematic review. The quality of systematic reviews was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) tool. A narrative synthesis was undertaken.

Results: Seventeen systematic reviews were identified, of which 1 was for RP, 5 for Sjögren's and 11 for Scleroderma. There were some high-quality systematic reviews for Sjögren's and mortality of Scleroderma. However, there were only low-quality systematic reviews of prevalence and incidence of RP and Scleroderma. Furthermore, there were no systematic reviews for the mortality of RP. For RP, the pooled prevalence was 4850 per 100 000; pooled annual incidence was 250 per 100 000. For Sjögren's, prevalence was 60–70 per 100 000; annual incidence was 6.92 per 100 000 and the pooled standardized mortality ratio ranged from 1.38 to 1.48. For Scleroderma, pooled prevalence ranged from 17.6 to 23 per 100 000; annual incidence was 1.4 per 100 000; and the pooled standardized mortality ratio ranged from 2.72 to 3.53.

Conclusion: The outcomes of RP were less well described compared with Sjögren's and Scleroderma. There was a lack of high-quality systematic reviews for the prevalence and incidence of RP and Scleroderma. Therefore, further studies and systematic reviews with rigorous case definitions, assessing different ethnic groups are warranted in this area.

Lay Summary

What does this mean for patients?

RP, SS and Scleroderma are rare conditions, which can be distressing for those affected. RP affects blood flow to parts of the body such as the fingers and toes. Sjogren's occurs when the immune system mistakenly targets the tear or saliva glands leading to symptoms including dry eyes and mouth. Scleroderma is a disease that causes hard and thickened skin. These diseases can impact quality of life and increase the risk of other health problems including earlier death. Our knowledge of these conditions, such as how common they are and their health outcomes, is lacking. Previous studies that have reviewed the prevalence (number of existing cases) and incidence (number of new cases) of these conditions and if they increase the risk of early death have reached different conclusions. This paper reviews and assesses the quality of these studies (known as systematic reviews) to identify what further research is needed. Our review found 17 English language research reviews conducted between 2000 and 2023. There was a lack of information on risk of early death in RP and lack of high-quality studies on prevalence and incidence of RP and Scleroderma, suggesting more studies should be conducted on these topics.

Keywords: umbrella review, prevalence, incidence, mortality, Raynaud's, Sjögren's, and scleroderma.

Key messages

- There were no systematic reviews for the mortality of Raynaud's.
- There were only low-quality systematic reviews for the prevalence and incidence of Raynaud's and Scleroderma.
- There were high-quality systematic reviews for Sjögren's and mortality of Scleroderma.

Received: 19 March 2024. **Accepted:** 1 July 2024

Introduction

Raynaud's Phenomenon, Sjögren's Syndrome and Scleroderma are diseases of unknown aetiology that share some common features and risk factors [1–3]. Over the past two decades, a number of studies were conducted to investigate the prevalence, incidence and mortality of these conditions. These studies also examined the severity and prognosis of conditions which in turn would help plan healthcare resources in the populations, improve healthcare and mean economic costing. There have also been several systematic reviews on the conditions. However, there have not been good-quality, recent, systematic reviews of all aspects of the epidemiology of these conditions. Where there have been several previous systematic reviews, these contained variations in findings relating to prevalence, incidence and mortality [4, 5]. It is unknown why they varied; whether these differences were due to their methodology and study quality, databases searched or criteria of including primary studies. This has created a confusing landscape. There have been no reviews of reviews that have sought to explain these variations or to identify potential gaps in the literature. Therefore, this umbrella review aims to comprehensively review existing systematic reviews on the prevalence, incidence and mortality of Raynaud's, Sjögren's and scleroderma and to identify any gaps in the current literature. This will help to identify priorities for future research.

Methods

This umbrella review was prospectively registered in PROSPERO (CRD42023434865) [6] on 15 June 2023. It was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and recommendations for umbrella reviews. No revisions were made to the protocol registered in PROSPERO during the study period. Ethical approval was not required because this study retrieved and synthesized data from previously published studies.

Search strategy and selection criteria

A comprehensive systematic literature search was undertaken in PubMed (this includes Medline and PubMed Central databases) and Embase (OVID) from 1 January 2000 to 1 June 2023. We searched using MeSH terms and keywords for 'RP', 'SS' or 'Scleroderma' or 'SSc' and terms such as 'prevalence', 'incidence' or 'mortality' (see Supplementary Tables S1–S3, available at *Rheumatology Advances in Practice* online, for full details of the search strategy). For mortality, we included systematic reviews investigating all-cause or cause-specific mortality. We limited our search to systematic reviews published in English and excluded conference abstracts. We included systematic reviews of patients of any age, sex and geographical area, based in the general population. Occupational cohorts, indigenous populations, critically ill patients and cohorts identified from specialist centres were excluded. We excluded systematic reviews which focused on a specific sub-condition (such as scleroderma renal crisis, scleroderma overlap syndrome or scleroderma-associated digital-ulcers; see Supplementary Table S6, available at *Rheumatology Advances in Practice* online for the list of excluded studies). We searched PROSPERO for any systematic review protocols on topic [7–10]. We emailed the authors of four protocols [7–10] for further information and received one reply [10]. On screening the full text, it was found to be out of scope. Duplicate systematic reviews were removed manually. Two reviewers (AC and SL) independently screened titles and abstracts for relevance using Rayyan [11], and full-text papers for eligibility using AirTable. Discrepancies were resolved through discussion with a third reviewer (FP or PL) where required.

Data extraction and quality assessment

AC independently extracted the following data from each eligible systematic review: first author; publication year and affiliation; number of primary studies included in the systematic review (databases searched and eligibility criteria); study characteristics; main outcome estimates with assessments of heterogeneity (e.g. I^2); whether risk of bias was reported (see Tables 1–3) and SIGN quality assessment (SIGN checklist in Supplementary Table S4, available at *Rheumatology Advances in Practice* online). This was then checked by SL. For each systematic review, we recorded either a narrative statement summarizing the authors' main findings or extracted a pooled estimate and its corresponding confidence interval (95% unless stated otherwise). Rates were converted to a per 100 000 denominator where required. The methodological quality of each systematic review was assessed by AC and SL using the Scottish Intercollegiate Guidelines Network (SIGN), a 12-question tool appropriate for systematic reviews of observational studies [12]. Any discrepancies in quality assessment were resolved through a discussion between AC and SL. Systematic reviews were reported to be of high quality if most of the SIGN criteria (i.e. had their own quality assessment) were met and had little to no risk of bias. Systematic reviews that met most of the SIGN criteria with only minor flaws (i.e. did not consider publication bias or state conflicts of interests) were deemed to be of acceptable quality. Systematic reviews were rated low quality if they had major flaws such as a lack of quality assessment of their included studies and/or lack of relevant characteristics in the tables. Any discrepancies were resolved through a discussion between the two reviewers (AC and SL). If an agreement could not be reached, a third reviewer (FP or PL) was contacted.

Results

Literature search and selection process

PubMed and Embase yielded 63 studies for Raynaud's (Fig. 1), 158 for Sjögren's (Fig. 2) and 178 for scleroderma (Fig. 3). After title and abstract screening, 6 studies remained for Raynaud's, 15 for Sjögren's and 23 for scleroderma. After full-text screening, 1 systematic review was included for Raynaud's [1], 5 for Sjögren's [4, 5, 13–15] and 11 for scleroderma [14–24]. The earliest included systematic review was published in 2008, with an increasing frequency over time: one systematic review was published in 2005–2009, four in 2010–2014, seven in 2015–2019 and five in 2020–2023. According to the SIGN quality assessment, six systematic reviews were of high quality, four were of acceptable quality and seven were of low quality.

Raynaud's Phenomenon (RP)

One systematic review by Garner *et al.* [1] met the inclusion criteria, reporting the prevalence and incidence but not mortality of Raynaud's. It included studies of the general population from high-income countries. According to the SIGN

Table 1. Synthesis of RP systematic reviews

First authors (publication year) and affiliation	Number of primary studies identified, searched database and inclusion/exclusion criteria	Study characteristics	Main findings and I^2 statistics	Risk of bias reported or mitigated	SIGN quality assessment and score
Prevalence					
Garner *et al.* (2015) [1] *Department of Rheumatology, University of Nottingham, UK*	17 studies *Databases searched:* Searched database: MEDLINE, EMBASE, CINAHL, AMED and PubMed Literature search in June 2011 and rerun in October 2014 Studies from 1991 to 2011 *Inclusion criteria:* 'Studies reporting the prevalence and/or incidence of primary Raynaud's (PRP), potential risk factors of PRP, human data of PRP people of any age; studies in any language'. *Exclusion criteria:* 'Studies assessing treatment of PRP, secondary RP to other diseases, RP in a specific occupation (i.e. people using vibration tools). Unpublished material, editorials, letters, case reports or reviews'.	*Systematic review* General population of high-income countries (3 studies from North America, 14 Europe, 1 New Zealand, 2 Asia). In total, 33 733 participants in review Raynaud's by case definitions, possible and definite. Age mean (range) 15–84 years *Performed a meta-analysis with random effects model to pool data.*	*Pooled estimate* Pooled prevalence from five studies was 4.85% (95% CI 2.08, 8.71). *4850 cases per 100 000* Females 5.74% (2.74–9.75) Males 4.12% (1.60–7.74) I^2 = 98.2% for pooled prevalence definite PRP	Authors stated they mitigated no numeric value reported	**Low quality**
Incidence					
Garner *et al.* (2015) [1] *Department of Rheumatology, University of Nottingham, UK*	Two studies Databases searched and inclusion/exclusion criteria same as above	*Performed meta-analysis with a random effects model to pool data* In total, 33 733 participants in the review 1 France—296 subjects, 1 USA, 717 women and 641 men over a 7-year period.	*Pooled estimate* Pooled annual incidence was 0.25% (95% CI 0.19, 0.32). *250 cases per 100 000* Females: 0.24% Males: 0.26% I^2 = not reported	Same as above	**Low quality**

quality assessment checklist, it was reported to be of low quality due to a lack of quality assessment of their included studies. The authors included 17 studies of prevalence from 4 of the 6 World Health Organisation (WHO) world regions (the Americas, Southeast Asia, Europe, Western Pacific; but not Africa nor the Eastern Mediterranean region). The pooled estimate of prevalence (pooled prevalence from the five studies of definite Raynaud's in the general adult population) was 4850 per 100 000 (95% CI 2080, 8710), with the pooled prevalence for females being 5740 per 100 000 (2740–9750) and for males 4120 per 100 000 (95% CI 1600, 7740). This review identified only two studies of incidence, which came from Europe and North America. The pooled annual incidence from two studies of incidence was 250 per 100 000 (95% CI 190, 320). There were no systematic reviews of mortality among people with Raynaud's.

Sjogren's Syndrome (SS)

Five systematic reviews were included for SS: one systematic review examined both prevalence and incidence [16], one examined prevalence [17], and three examined mortality [4, 5, 15]. Of the five systematic reviews, three were of high quality [4, 5, 13] and two was acceptable [14, 15]. Two systematic reviews reported the prevalence of Sjögren's. Qin *et al.* [13] conducted a systematic literature search of PubMed and Embase and included 18 studies conducted worldwide, published in English, between 1995 and 2013. The pooled prevalence of primary Sjögren's was 60.82 (95% CI 43.69, 77.94) per 100 000. The authors found the prevalence rate (per 100 000) of Sjögren's in women was higher than in men and a higher rate Sjögren's prevalence in Europe compared with Taiwan. Albrecht *et al.* [14] included 20 studies published from 2014 to 2022, conducted

Table 2. Synthesis of SS systematic reviews

First authors (publication year) *and affiliation*	Number of primary studies identified, searched database and inclusion/exclusion criteria	Study characteristics	Main findings and I^2 statistics	Risk of bias reported or mitigated	SIGN quality assessment and score
Prevalence					
Qin *et al.* (2015) [13] *Department of Laboratory Diagnostics, Second Military Medical University, Shanghai, China*	18 studies *Databases searched:* PubMed and EMBASE Updated search on 22 October 2013. *Inclusion criteria:* 'Population-based studies and surveys examining a geographic region or clearly defined random or clustered sampling procedure'. *Exclusion criteria:* Hospital or clinic reports including survey or audits.	*Systematic review* 21 overall systematic reviews (15 reported prevalence and incidence in the EU, 2 in America, and 4 in Asia) Subgroup analyses by case definitions. *Performed a meta-analysis with random effects model to pool data.*	Overall prevalence: 60.82 (43.69–77.94) per 100 000. Female: 116.72 (70.39–163.05). Male: 5.53 (2.49–8.58) 11 studies from Europe pooled prevalence rate: 71.22 (95% CI 48.7, 93.7) per 100 000. Studies from Asia 44.85 (3.51–86.2) $I^2 = 98.95$	No significant publication bias. Egger's test $P = 0.566$	**High quality**
Albrecht *et al.* (2023) [14] *Programme Area Epidemiology and Health Services Research, German Rheumatism Research Centre Berlin, Germany*	20 studies *Databases searched:* PubMed and Web of Science Search period (2014–8 November 2022). *Inclusion criteria:* German or English language. Prevalence of inflammatory rheumatic disease (i.e. connective tissue diseases) Adults or children and adolescents in Germany were included.	*Systematic review a narrative synthesis was reported.* Individuals in Germany with inflammatory Rheumatic Diseases. *Did not perform a meta-analysis*	680–770 cases per 100 000 population from 2007 to 2018. German prevalence, 40 cases per 100 000 assumed so far. SS including sicca syndrome 70–770 cases per 100 000. Primary Sjögren's—70 per 100 000. Global prevalence 60.8 (95% CI 43.7, 77.9/100 000)	All studies have a moderate to high risk of bias	**Acceptable**
Incidence					
Qin *et al.* (2015) [13] *Department of Laboratory Diagnostics, Second Military Medical University, Shanghai, China*	Six studies *Databases searched* and *inclusion criteria/exclusion criteria:* Same as above in reference [2]	*Systematic review* Six studies describing incidence rates for primary SS. Three from Taiwan, two from Europe. One from the USA. *Performed a meta-analysis with random effects model to pool data.*	*Pooled estimate* Pooled incidence rate: 6.92 (95% CI 4.98, 8.86) per 100 000. Female: 12.30 (9.07–15.53) Male: 1.47 (0.81–2.12) Female/Male: 9.29 (6.61–13.04). Studies from Asia reported an incidence rate ranging from 6.0 to 11.8 per 100 000. EU ranges from 3.9 to 5.3 per 100 000 person-years. USA prospective population-based study 1976–1992 reported an incidence rate of 3.9 per 100 000 person-years. I^2=98.51	No significant publication bias. Egger's test $P = 0.566$	**High quality**

(continued)

Table 2. (continued)

First authors (publication year) *and affiliation*	Number of primary studies identified, searched database and inclusion/exclusion criteria	Study characteristics	Main findings and I^2 statistics	Risk of bias reported or mitigated	SIGN quality assessment and score
Mortality					
Singh *et al.* (2016) [4] *Division of Rheumatology and Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA*	10 studies *Databases searched:* Ovid Medline In-Process, OVID EMBASE Search: each databases inception to 27 October 2014. *Inclusion criteria:* 'Population-based or representative of the community rheumatology practice or multicentre studies. Mortality rate in primary Sjögren's patients (with or without risk factors and causes of mortality) and compared the mortality rate with the general population or matched control population, reported as SMR or RR, respectively'. *Exclusion criteria:* 'single-centre studies with high attrition rate (<80% follow-up); lack of comparison of mortality rate to a control, non-SS population; and studies with insufficient information to allow estimation of SMR with 95% CI'	*Systematic review* Cohort studies of primary SS patients. Population based rheumatology practice or multicentre studies. Mortality rate vs general population. In total, 7888 patients and 682 died. Median follow-up of 9 years. 91% female. *Performed a meta-analysis with random effects model to pool data.*	*Pooled estimate* Pooled SMR: 1.38 (95% CI 0.94, 2.01). Leading causes of death were cardiovascular diseases, solid-organ and lymphoid malignancies and infections. Unclear whether over-representation in the Sjögren's population than general population. *Subgroup analyses:* Advanced age of diagnosis RR 1.09 (1.07–1.12) Male sex RR 2.18 (1.45–2.37) Vasculitis RR 7.27 (2.70, 19.57) anti-SSB positivity [RR 1.45 (95% CI 1.03, 2.04)] cryoglobulinemia [RR 2.62 (95% CI 1.77, 3.90)] Examined other risk factors parotid enlargement. Primary SS was not associated with an increase in all-cause mortality compared with the general population. $I^2 = 94\%$	No publication bias was found.	**High quality**
Beltai *et al.* (2020) [15] *Department of Rheumatology, University of Montpellier Montpellier, France*	Two cohort studies *Databases searched:* Medline and Cochrane Library. Search: up to March 2018 *Inclusion criteria:* systematic reviews included 'case-control, cohort, and cross-sectional studies. Index cases age >18 years. Primary SS diagnosis based on several definitions. Control group of healthy individuals'. *Exclusion criteria:* 'Patients with secondary Sjögren's or another immune mediated inflammatory disease'.	*Systematic review* Cardiovascular mortality. *'Risk of cardiovascular mortality'* 745 subjects and 25 cardiac-related deaths. *Performed a meta-analysis with random effects model to pool data.*	No statistically significant association between Primary SS and cardiovascular mortality RR 1.48 (0.77–2.85, $P = 0.24$). An association between cardiovascular morbidity. Control group: Yes $I^2 = 44\%$	No publication bias was found	**Acceptable**

(continued)

Table 2. (continued)

First authors (publication year) *and affiliation*	Number of primary studies identified, searched database and inclusion/exclusion criteria	Study characteristics	Main findings and I^2 statistics	Risk of bias reported or mitigated	SIGN quality assessment and score
Huang *et al.* (2021) [5] *Department of Rheumatology and Clinical Immunology, University of Peking* *Peking, China*	14 studies *Databases searched:* PubMed, Cochrane Library and EMBASE—23 October 2020. *Inclusion criteria:* 'Population-based, single-centre or multicentre cohort studies. The all-cause mortality rate was assessed through a comparison with the general population or a matched control group, or by directly reporting the Standardized Mortality Ratio (SMR)'.	*Systematic review* All-cause mortality rate *vs* general population. 14 584 patients. 902 deaths observed. *Performed a meta-analysis with random effects model to pool data.*	*Pooled estimate* Primary SS SMR 1.46-fold (95% CI 1.10, 1.93) greater than general population. Risk higher in European countries: 1.55 (1.04–2.33). Primary SS was associated with mortality in the general population. 46% increase in death. Subgroup analyses Age (per one year) RR 1.09 (1.06–1.12) Male gender RR 1.95 (1.15–3.31), $I^2 = 26.2$ Vasculitis RR 7.27 (2.70–19.57) Anti-La/SS-B+ RR 1.45 (1.03–2.04) Cryoglobulinaemia RR 2.62 (1.77–3.90) $I^2 = 92.4\%$	No publication bias was found	**High quality**

Table 3. Synthesis of Scleroderma systematic reviews

First authors (publication year) *and affiliation*	Number of primary studies identified, searched database and inclusion/exclusion criteria	Study characteristics	Main findings and I^2 statistics	Risk of bias reported or mitigated	SIGN quality assessment and score
Prevalence					
Chifflot *et al.* (2008) [16] *Department of Rheumatology, Teaching Hospital Hautpierre, Strasbourg, France*	32 studies (total) *Databases searched:* PubMed (1 December 2006) Studies from 1969–1 December 2006 *Inclusion criteria:* 'Original studies in English or French concerning the prevalence and incidence of Scleroderma in adults'. *Exclusion criteria:* 'SLE in childhood or localized forms of Scleroderma (morphea) reports'.	*Systematic review* Worldwide prevalence of Scleroderma in adults. *Not perform a meta-analysis*	Prevalence of Scleroderma ranged from 0.7/100 000 to 48.9/100 000. Japan: 0.7 per 100 000 in 1974–6 USA: 27.6/100 000 in 1990. Italy: 48.9 per 100 000 in 1992. Australia: 23.3/100 000 in 1999. France: 15.8/100 000 in 2001 England: 8.8/100 000 in 2000	Risk of bias not reported	**Low quality**
Morrisroe *et al.* (2017) [19] *Department of Medicine & Rheumatology, Melbourne and Adelaide, Australia*	54 studies (total) *Databases searched:* MEDLINE (through PUBMED and OVID), EMBASE and the Cochrane Library were searched on 14 September 2016) *Inclusion criteria* 'Studies in Australia regarding prevalence and mortality'. *Exclusion criteria:* 'Review articles, conference abstracts, non-human trials, paediatric studies, case reports and small case series. Not available full-text studies limited to Scleroderma pathogenesis were excluded'.	*Systematic review* Studies from Australian region. Investigated trend of Scleroderma prevalence over time. *Not perform a meta-analysis*	Australia prevalence 0.46/100 000 in 1974, 20.0/100 000 in 1993, 23.3 to 86/100 000 (most recently). I^2 = Not reported	Evaluated the potential for bias, but could not see results of bias	**Low quality**
Zhong *et al.* (2019) [18] *Irma Lerma Rangel College of Pharmacy Texas, USA.*	18 studies *Databases searched:* Articles published from 2006 to 2016. PubMed/MEDLINE and Embase. Studies from EU, NA and Asia. *Inclusion criteria:* 'Only articles published in English were included'.	*Systematic review* People with SSc (Scleroderma) *Performed a meta-analysis with random effects model to pool data.*	*Pooled estimate* The pooled prevalence was 23 per 100 000 (95% CI 16, 29 per 100 000; 18 studies) in a total sample of 11 574 individuals, from 18 studies. Taiwan prevalence (3.8 per 100 000), USA (50 per 100 000), European studies reported a Scleroderma prevalence between 10 and 35 per 100 000. *High I^2 statistic between-study heterogeneity*	Risk of bias not reported	**Low quality**
Bairkdar *et al.* (2021) [15] *Division of Clinical Epidemiology and Rheumatology, Stockholm, Sweden*	46 studies *Databases searched:* MEDLINE, Web of Science and EMBASE searched and last updated on 20 October 2020	*Systematic review* People with SSc. Studies from Asia, EU, Oceania and North America.	*Pooled estimate* The overall pooled prevalence of Scleroderma was 17.6 (95% CI 15.1, 20.5) per 100 000. Prevalence ranged from 3.1 to 144.5 per 100 000 individuals.	Some publication bias examined funnel plot visually. Egger's test otherwise ($P = 0.19$)	**Low quality**

(continued)

Table 3. (continued)

First authors (publication year) *and affiliation*	Number of primary studies identified, searched database and inclusion/exclusion criteria	Study characteristics	Main findings and I^2 statistics	Risk of bias reported or mitigated	SIGN quality assessment and score
	Inclusion criteria 'The methods of diagnosing Scleroderma 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 Scleroderma (point prevalence and/or period prevalence)'. Published in English with no restriction on publication year.	*Performed a meta-analysis with random effects model to pool data.*	Stratification 23 studies examining sex differences. Male 6.0 (4.8–7.5) per 100 000, $I^2 = 97\%$ Female 28.0 (23.1–33.9) per 100 000 Three studies (Asia): 6.8 (95% CI 5.7, 8.1) 24 studies (European): 14.8 (11.6–18.8) 10 studies (North America): 25.9 (21.5–31.2) Four studies (Oceania): 23.8 (11.8–48.3) Five studies (South America): 24.8 (15–41) $I^2 = 100\%$		
Incidence					
Chifflot *et al.* (2008) [16] *Department of Rheumatology, Teaching Hospital Hautpierre, Strasbourg, France*	32 studies (total) *Databases searched* and *inclusion criteria/Exclusion criteria:* Same as those in its prevalence reference above.	*Systematic review* Worldwide incidence of Scleroderma in adults. *Not perform a meta-analysis*	Incidence of Scleroderma ranges from 0.06/thousand/year to 12.2/thousand/year.	Risk of bias not reported	**Low quality**
Zhong *et al.* (2019) [18] *Irma Lerma Rangel College of Pharmacy Texas, USA*	12 studies *Databases searched* and *Inclusion criteria/Exclusion criteria:* Same as those in its prevalence reference above	*Systematic review* People with SSc (Scleroderma) *not perform a meta-analysis of incidence.*	*Pooled estimates were not reported for incidence* Scleroderma incidence rates (0.77 per 100 000) Netherlands. 5.6 per 100 000 person-years in the USA. *High I^2 statistic between-study heterogeneity*	Risk of bias not reported	**Low quality**
Bairkdar *et al.* (2021) [17] *Division of Clinical Epidemiology and Rheumatology, Stockholm, Sweden*	28 studies *Databases searched* and *Inclusion criteria/Exclusion criteria:* Same as those in its prevalence reference above	*Systematic review* People with SSc. Studies from Asia, EU, Oceania, and North America. *Performed a meta-analysis with random effects model to pool data.*	*Pooled estimate* Overall pooled incidence rate = 1.4 (95% CI 1.1, 1.9) per 100 000 PYAR. Stratification Male 0.5 (0.4–0.7) per 100 000 PYAR from 14 studies, Female 2.3 (1.8–2.9) per 100 000 PYAR, from 13 studies $I^2 = 100\%$	Probable publication bias—funnel plot. Not confirmed by Egger's test ($P = 0.18$)	**Low quality**
Mortality					
Elhai *et al.* (2012) [21] *Rheumatology A Department, Descartes University, Paris, France*	Nine studies *Databases searched:* MEDLINE and Embase databases from January 1960 to June 2010. *Inclusion criteria:* 'Studies reported either SMR or enough data to calculate it (observed deaths in	*Systematic review* Mortality rate in Scleroderma patients over the past 40 years. *Performed a meta-analysis with random effects model to pool data.*	*Pooled estimate* The pooled SMR for SSc was 3.53 (95% CI 3.03, 4.11) 732 deaths, heart involvement was the most common followed by lung involvement. $I^2 = 93\%$	Publication bias unlikely.	**High quality**

(continued)

Table 3. (continued)

First authors (publication year) *and affiliation*	Number of primary studies identified, searched database and inclusion/exclusion criteria	Study characteristics	Main findings and I^2 statistics	Risk of bias reported or mitigated	SIGN quality assessment and score
	Scleroderma patients, expected deaths general population same age and gender)'	$N = 2691$ patients from nine studies. Cause-specific mortality findings Included studies were cohort or case-control studies.			
Komocsi *et al.* (2012) [22] *Department of Interventional Cardiology, Heart Institute, University of Pecs, Hungary*	18 studies *Databases searched:* PubMed, Web of Science with Conference Proceedings and the Cochrane Central Register of Controlled Trials databases searched in July 2010. *Inclusion criteria:* 'Studies recruited scleroderma patients regardless of organ manifestations. Prospective or retrospective cohorts allow assessment of the impact of organ manifestations on mortality'.	*Systematic review* $N = 12\,829$ patients *Performed a meta-analysis with random effects model to pool data.*	Hazard ratio (HR) of mortality Scleroderma Cardiac involvement, HR 3.15, $I^2 = 68\%$ Pulmonary interstitial disease, HR 2.58 $I^2 = 68\%$ Pulmonary hypertension, HR 3.50, $I^2 = 82\%$ Renal manifestations, HR 2.76 $I^2 = 75\%$ Cardiac, lung and kidney involvement highlighted as the main causes of death. Control population included.	Risk of bias not reported	**High quality**
Toledano *et al.* (2012) [20] *Rheumatology Department, Hospital Clinico San Carlos, Madrid, Spain*	Seven studies *Databases searched:* MEDLINE (1950–June 2009), EMBASE (1980–June 2009). *Inclusion criteria:* '(1) Study population with rheumatoid arthritis, SLE, Scleroderma, vasculitis, osteoarthritis, osteoporosis, dermatomyositis or spondyloarthritis; (2) outcome of interest was mortality, and should be reported as an SMR, or this could be calculated and (3) cohorts or longitudinal observational studies of moderate to high quality'. *Exclusion criteria:* 'Studies on cancers, trauma, or infections related to the musculoskeletal system, as well as on congenital malformations, pregnancy or neonatal complications, or studies dealing solely with predictors of mortality but not reporting rates were excluded for this review'.	*Systematic review* Mortality of rheumatic diseases including Scleroderma. *Performed a meta-analysis with random effects model to pool data.* *N = 1700 patients*	*Pooled estimate* Scleroderma SMRs subtotal 3.51 (95% CI 2.74, 4.50) I^2='*Heterogeneity was large*'.	Only moderate to high quality studies were included.	**High Quality**
Rubio-Rivas M *et al.* (2014) [23] *Autoimmune Diseases Unit, Bellvitge University Hospital, Barcelona, Spain*	17 studies *Databases searched:* MEDLINE and SCOPUS databases searched in July 2013. Included studies ranged from January 1960- July 2013.	*Systematic review with a meta-analysis. Initially fixed effects model was used, and then confirmation through random effects model used* $N = 9239$ patients	Scleroderma SMR 2.72 (1.93-3.83) > general population Scleroderma diagnosis cumulative survival estimated at 74.9% at 5 years and 62.5% at 10 years.	Risk of bias not reported	**Acceptable**

(continued)

Table 3. (continued)

First authors (publication year) *and affiliation*	Number of primary studies identified, searched database and inclusion/exclusion criteria	Study characteristics	Main findings and I^2 statistics	Risk of bias reported or mitigated	SIGN quality assessment and score
	Exclusion Criteria: 'Studies without SMR or raw data not enough to estimate were ruled out'.	Separate analysis of survival and cause-specific mortality analyses. No language restriction.	Pulmonary involvement represented the main cause of death. I^2= Not reported		
Morrisroe *et al.* (2017) [19] *Department of Medicine & Rheumatology, Melbourne and Adelaide, Australia*	54 studies (total) *Databases used:* MEDLINE (through PUBMED and OVID), EMBASE, Cochrane Library searched in September, 2016 *Inclusion criteria/Exclusion criteria:* Same as its prevalence above	*Systematic review* Studies from Australian region. *Not perform a meta-analysis*	Overall (SMR) of 3.4 and a 10-year survival of 84% in a newly diagnosed patient. Cardiopulmonary involvement highlighted as the primary cause of death in Scleroderma. Control group included.	Evaluated the potential for bias, but could not see results of bias	**Low Quality**
Pokeerbux *et al.* (2018) [25] *Lille Inflammation Research International, University of Lille, Lille, France*	18 studies *Databases used:* MEDLINE and EMBASE up to July 2017. *Inclusion criteria:* '(i) Participants aged over 18, (ii) ACR 1980 preliminary classification criteria or ACR/EULAR 2013 classification criteria for Scleroderma, (iii) have at least one additional visit after the inclusion visit, and (iv) be incident cases, defined as patients having disease duration from time of diagnosis to enrolment in the study of less than 3 years'.	*Systematic review* *Performed a meta-analysis with random effects model to pool data.* $N = 11\,719$ patients Language restriction—English or French.	*Pooled estimate* Overall pooled SMR was 3.45 (95% CI 3.03, 3.94). Cardiac, pulmonary, and renal involvement. Age of disease onset. $I^2 = 88.8\%$	Publication bias unlikely	**Low Quality**
Lee YH et. al. (2019) [28] *Department of Rheumatology, Korea University College of Medicine, Seoul, Korea*	22 studies *Databases used:* MEDLINE, EMBASE, and Cochrane database from their earliest date to January 2018. *Inclusion criteria:* '(1) cohort study predefined Scleroderma definition and (2) overall, sex and/or disease subtype specific SMR data available with 95% CI'.	*Systematic review* Studies examining mortality in patients with Scleroderma. $N = 13\,214$ patients with Scleroderma with $N = 4218$ deaths *Performed a meta-analysis with random effects model to pool data.*	*Pooled estimate* Overall SMR Scleroderma (SMR 2.823, 95% CI 2.219, 3.591, $P < 0.001$) Sex-specific meta-analysis overall SMR Female SMR: 2.929, 95% CI 2.504, 3.427, $P < 0.001$. Male SMR: 3.523, 95% CI 2.933, 4.232, $P < 0.001$. I^2= Not reported	Risk of bias not reported	**Acceptable**
Erzer *et al.* (2020) [26] *Switzerland, Germany, and South Africa* *Department of Rheumatology, Basel, Switzerland.*	91 studies *Databases searched:* Embase, PubMed and African Health Sciences databases for literature published until March 2018. *Inclusion criteria:* 'Patients were eligible for the analysis, Scleroderma diagnosis by a physician and lived in Sub-Saharan Africa'.	*African studies—South Africa, Nigeria and Senegal.* *Systematic review* $N = 1884$ participants *Not perform a meta-analysis*	160 Scleroderma deaths out of 1884 patients Scleroderma mortality was 8.49%	Risk of bias not reported	**Low Quality**

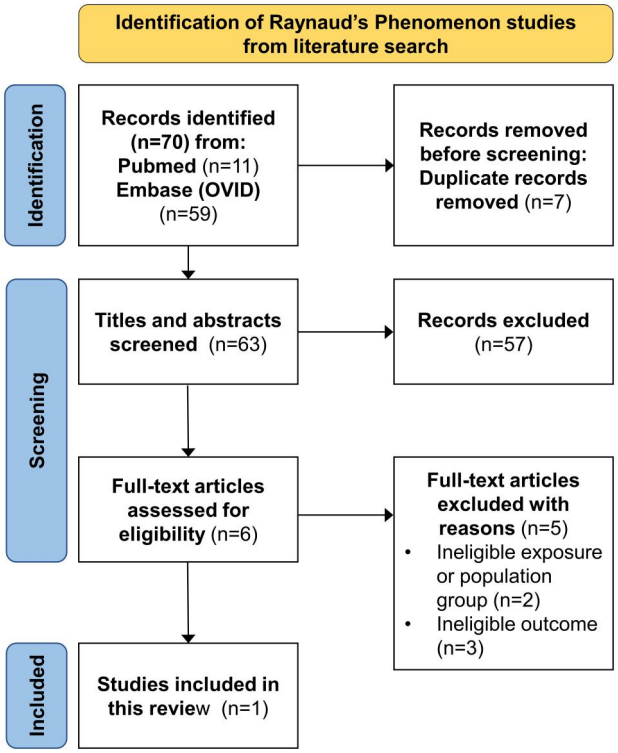

Figure 1. PRISMA diagram of identification and screening of RP studies

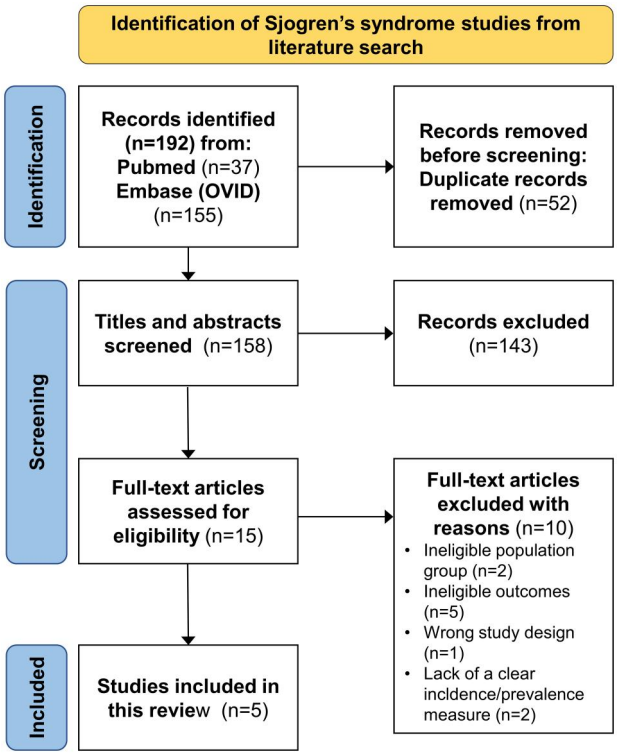

Figure 2. PRISMA diagram of identification and screening of SS studies

in the German population only and including sicca syndrome as well as SS. The authors [14] found a pooled prevalence of primary Sjögren's including sicca syndrome of 70 per 100 000 people in Germany.

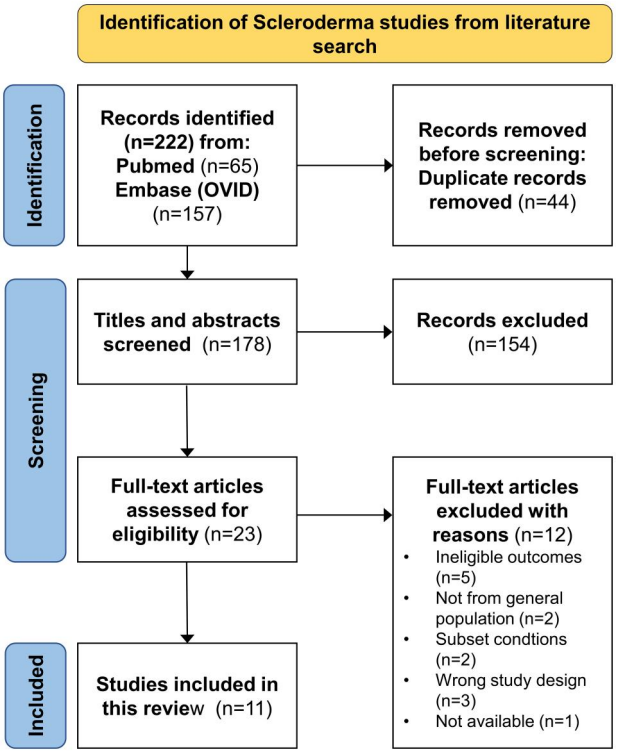

Figure 3. PRISMA diagram of identification and screening of Scleroderma studies

One systematic review of Sjögren's incidence, by Qin *et al.* [13] who included six studies of incidence reported a pooled annual incidence rate of 6.92 (4.98–8.86) per 100 000. The authors found a higher incidence rate of primary Sjögren's in females (12.30, 9.07–15.53) than males (1.47, 0.81–2.12), and there tended to be a higher incidence rate in Asia (Taiwan) than in other regions (EU and North America).

There were three systematic reviews of mortality in Sjögren's including two studies [4, 5] of all-cause mortality and one of only cardiovascular mortality [15]. Singh *et al.* [4] reviewed 10 studies of 7888 primary Sjögren's patients with 682 deaths over a median follow-up of 9 years, which reported a pooled standardized mortality ratio of 1.38 (0.94–2.01), suggesting a possible association of primary Sjögren's with increased all-cause mortality. Huang *et al.* [5] performed a systematic review of 14 studies (14 584 primary Sjögren's patients and 902 deaths observed) and found a 1.46-fold (95% CI 1.10, 1.93) increased risk of death in primary Sjögren's. The authors further showed the risk of mortality was highest among Sjögren's individuals with vasculitis. The results for the one study of cardiovascular mortality were similar to the findings for all-cause mortality. Beltai *et al.* [15] reviewed 14 studies of 67 124 patients with primary Sjögren's found that the patients had a raised risk of mortality compared with the general population cardiovascular mortality (RR = 1.48, 0.77–2.85), which did not reach statistical significance.

Scleroderma

Eleven systematic reviews were included for scleroderma: three systematic reviews [16–18] reported both prevalence and incidence, one systematic review [19] reported both prevalence and mortality and seven systematic reviews [18–24]

reported mortality only. Of the 11 systematic reviews, four were of high quality [20–23], one was acceptable [24] and six were of low quality [16–19, 25, 26]. The papers reported showed wide ranges of estimates of prevalence with Chifflot *et al.* [16] reviewed 32 studies reporting prevalence ranging from 0.7 in Japan in 1974–6 to 48.9 in Italy in 1992. Morrisroe *et al.* [19] reviewing 54 studies from Australia reporting that the prevalence of scleroderma increased over time from 0.46 per 100 000 in 1974 to 20.0 per 100 000 in 1993 to 86.0 per 100 000, most recently. The prevalence was found to be similar between the general and the Aboriginal populations in the country. The two meta-analyses by Zhong [18] and Bairkdar [17] reported similar pooled estimates. Zhong *et al.* [18] pooled the data of 18 studies of 11 574 individuals and estimated a scleroderma prevalence of 23 per 100 000 (16–29 per 100 000). The prevalence of scleroderma varied across countries, ranging from 3.8 per 100 000 in Taiwan to 50 per 100 000 in the USA. Bairkdar *et al.* [17] reviewed 46 studies published up to October 2020 and reported a pooled prevalence of 17.6 (15.1–20.5) per 100 000, with a prevalence of 28.0 (23.1–33.9) per 100 000 in women, and 6.0 per 100 000 (4.8–7.5) in men. The highest prevalence of scleroderma was found to be in North America 25.9 per 100 000 (21.5–31.2).

Three systematic reviews [16–18] also examined the incidence rates of scleroderma, with two reporting narrative results and only one meta-analysis. In the narrative results, Chifflot *et al.* [16] reported incidence rates ranging from 0.06 to 12.2 per 100 000 person-years. Zhong *et al.* [18] reviewed 12 studies and reported incidence rates of scleroderma ranging from 0.77 per 100 000 person-years in the Netherlands to 5.6 per 100 000 person-years in the USA. Bairkdar *et al.* [17] performed a meta-analysis of the data from 28 studies published up to October 2020, finding the pooled incidence rate of scleroderma in the population was 1.4 (1.1–1.9) per 100 000 person-years and there was a higher incidence in women (2.3, 1.8–2.9) than in men (0.5, 0.4–0.7).

Eight systematic reviews [19–26] reviewed mortality in people with scleroderma, with six presenting results of a meta-analysis and two were systematic reviews [19, 26]. Of the six meta-analyses, three were rated high quality but the latest paper included was published in 2012 and three later systematic reviews including papers up to 2019 were rated acceptable or low quality. The results of the six meta-analyses were similar (irrespective of quality rating) reporting a pooled SMR for scleroderma of around 3.5, which is substantially higher than for Sjögren's. Three high-quality studies including papers published in 2013 or earlier: Elhai *et al.* [21] who reviewed nine studies and pooled the data of scleroderma SMR as 3.53 (95% CI 3.03, 4.11). Komosci *et al.* [22] reviewed 18 studies and found the risk of death was significantly increased among patients with cardiac involvement HR (3.15, 2.33–4.26), pulmonary interstitial disease (HR 2.58, 1.98–3.37), with pulmonary hypertension (HR 3.50, 1.94–6.30) and with renal manifestations (HR 2.76, 1.91–4.00). Toledano *et al.* [20] reviewed seven studies and reported a pooled SMR of 3.51 (2.74–4.50).

There were five low or acceptable quality scleroderma systematic reviews. Morrisroe *et al.* [19], a systematic review of 54 studies, found that despite improvements in Australian healthcare, the mortality remained high with an SMR of 3.4 (no confidence interval was given). Reviewing 18 studies of 11 719 patients with scleroderma, Pokeerbux *et al.* [25] reported a pooled SMR of 3.45 (3.03–3.94). Reviewing 22 studies of 13 214 patients and 4218 deaths, Lee *et al.* [24] found an overall SMR of 2.82 (2.22–3.59). Reviewing 91 studies including 1884 patients, Erzer *et al.* [26] reported a scleroderma mortality of 8.49% of all patients (160 out of 1884 total patients from 1945 to 2018). Rubio-Rivas *et al.* [23] in their systematic review of 17 studies found that scleroderma patients had an increased risk of mortality (SMR =2.72, 1.93–3.83) compared with the general population.

Discussion

In our umbrella review, the outcomes of Raynaud's were less well-described compared with the other conditions. We identified that there were no systematic reviews for the mortality of Raynaud's and no high-quality systematic reviews covering the prevalence and incidence of Raynaud's and scleroderma (prevalence and incidence) (see Supplementary Fig. S1, available at *Rheumatology Advances in Practice* online). A common theme among the low-quality systematic reviews ($n=7$) was a lack of quality assessment or investigation for publication bias among the included studies. Some of these systematic reviews lacked information on whether two authors selected and extracted data and relevant characteristics in their main finding tables. None of the systematic reviews included a list of excluded studies (see Supplementary Table S5 and Supplementary Data S1, available at *Rheumatology Advances in Practice* online).

There was little evidence about the epidemiology of Raynaud's, identifying only one systematic review, which was rated low quality. The pooled prevalence was reported as 4850 per 100 000, and incidence was reported as 250 per 100 000 per year. However, the heterogeneity in the prevalence estimate was extremely high ($I^2 = 98.2\%$) and the incidence findings were based only on two papers, making it difficult to draw firm conclusions. There were no systematic reviews of mortality in Raynaud's, probably because of a lack of primary research studies to include.

There was more evidence about Sjögren's. Our umbrella review identified four high or acceptable quality systematic reviews for prevalence, incidence and mortality of Sjögren's. Most of these systematic reviews reported their own quality assessment or acknowledged publication bias. Overall, the prevalence was found by two systematic reviews [13, 14] to be between 60 and 70 per 100 000; the incidence was reported by one acceptable quality study to be around 7 per 100 000 per year. The incidence of Sjögren's was eight times higher among females than males; it was higher in studies from Asia (Taiwan) than Europe or North America. The mortality was found in two systematic reviews [4, 5] to be 1.4 times higher than the general population. Two Sjögren's systematic reviews [4, 5] reported a variation in the significance of Sjögren's with all-cause mortality. This variations between these findings could be owing to the Huang *et al.* [5] later publication date including four additional studies that were not in Singh *et al.* [4] systematic review. Although the largest number of the systematic reviews were about scleroderma, there were no high-quality systematic reviews of prevalence or incidence. Two low-quality systematic reviews [17, 18] reported a pooled prevalence around 20 per 100 000, and the most recent study of incidence reported it around 1.4 per 100 000 per year. Heterogeneity in these studies was very high (>90%) again making it difficult to draw firm

conclusions. There were several high-quality studies of mortality, which reported similar pooled estimates of mortality around 3.5 times higher than the general population, which is substantially (about 2.5 times) higher than in Sjögren's. In scleroderma, the main causes of deaths were highlighted as having cardiovascular, renal and pulmonary involvement [19, 21–23, 25].

Our umbrella review reported a higher proportion of women than men suffering from each condition [5, 17, 18]. This is expected as previous studies demonstrated that high levels of oestrogen were associated with the high prevalence of Raynaud's in pre- and post-menopausal women [27, 28]. A systematic review [13] found that studies from Europe showed a higher prevalence of primary Sjögren's compared with Asian counterparts, but the incidence was higher in Taiwan (Asia) compared with European and American studies. However, note that this difference should be interpreted cautiously due to difference in the number of studies from each region. There was a higher prevalence and incidence of scleroderma [18] in America compared with Taiwan and Netherlands, respectively. These geographical differences could be due to differences in genetic make-up, environment, lifestyle and cultural factors, diagnostic criteria and research methods between countries and healthcare resources [13, 22]. Furthermore, methodological differences such as the number of studies examined and differences in publication period of the original study can be contributing factors to the difference in findings.

A recent study [29] published in May 2023 using linked data from the Clinical Practice Research Datalink (CPRD) investigated the prevalence and incidence of autoimmune diseases in a cohort study of 22 million people in the UK. The authors had found that the incidence of Sjögren's out of 12 292 individuals changed from 6.0 per 100 000 in 2000–02 to 10.7 per 100 000 in 2017–19; SSc 4880 patients 2.6 per 100 000 in 2000–02 to 3.3 per 100 000 in 2017–19. Therefore, the incidence rate ratio (95% CI) for these two auto-immune diseases were 2.09 (1.84–2.37) and 1.23 (1.06–1.43), respectively. However, this study did not include any information regarding on the prevalence, incidence and mortality of Raynaud's. This study was not included in any of the systematic reviews because their search dates were before November 2022.

Strengths and limitations

To our knowledge, our umbrella review is the first to examine the prevalence, incidence and mortality of Raynaud's, Sjögren's and Scleroderma. We captured various forms of measuring outcomes such as trend in time and differences in sex and geography. The umbrella review provides a comprehensive overview of available evidence of the diseases of interests, and the contradictions and consistencies between the systematic reviews. This will help clinicians and researchers to easily understand the depth and breadth of systematic reviews available on the diseases of interest's outcomes. We assessed the quality of the systematic reviews in our umbrella review using the SIGN guidelines. This will help to identify areas for improvement.

This study has some limitations. First, we limited our search to 2000–2023. Second, only English-language texts were included. Therefore, there remains a potential we have missed studies that are relevant studies to our research question. Third, there were a few systematic reviews available for Raynaud's. This indicates further research is needed. Finally, due to the number of systematic reviews rated low quality the implications for clinical practise and healthcare planning are limited.

Conclusion

In our umbrella review, gaps in available high-quality systematic reviews of epidemiology were found in Raynaud's and scleroderma. Furthermore, there were little to no systematic reviews investigating the prevalence, incidence and mortality of Raynaud's in comparison to Sjogren's and scleroderma. Therefore, further studies with rigorous case definitions, assessing different ethnic groups and updated systematic reviews are warranted in this area.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

The data and associated materials used in this study will be made available upon request.

Funding

This work was supported by a PhD studentship to Anthony Chen from a benefactor donation to the University of Nottingham. F.P. is funded by an NIHR Advanced Fellowship (NIHR300863). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Disclosure statement: The authors have declared no conflicts of interest.

References

1. Garner R, Kumari R, Lanyon P, Doherty M, Zhang W. Prevalence, risk factors and associations of primary Raynaud's phenomenon: systematic review and meta-analysis of observational studies. BMJ Open 2015;5:e006389.
2. Bjork A, Mofors J, Wahren-Herlenius M. Environmental factors in the pathogenesis of primary Sjogren's syndrome. J Intern Med 2020;287:475–92.
3. Ramos PS. Epigenetics of scleroderma: integrating genetic, ethnic, age, and environmental effects. J Scleroderma Relat Disord 2019; 4:238–50.
4. Singh AG, Singh S, Matteson EL. Rate, risk factors and causes of mortality in patients with Sjögren's syndrome: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2016;55:450–60.
5. Huang H, Xie W, Geng Y, Fan Y, Zhang Z. Mortality in patients with primary Sjogren's syndrome: a systematic review and meta-analysis. Rheumatology (Bulgaria) 2021;60:4029–38.
6. Chen A, Lax S, Grainge M, Pearce F, Lanyon P. Incidence, prevalence, and mortality of Raynaud's Phenomenon, Scleroderma, Sjogren's Syndrome and Systemic Lupus Erythematosus: an overview of systematic reviews. [Online]. 2023. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=434865 (20 October 2023, date last accessed).
7. Abbot S. Risk factors for the development of systemic sclerosis: a systematic review of observational studies. [Online]. 2017. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017067304 (30 October 2023, date last accessed).

8. Belbasis L, Dosis V, Evangelou E. Environmental risk factors for rheumatic diseases: an umbrella review of meta-analyses. [Online]. 2017. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017069086 (20 October 2023, date last accessed).
9. Nune A, Kouranloo K, Dey M. Incidence and clinical outcomes of new-onset autoimmune connective tissue diseases after COVID-19 infection: a systematic review. [Online]. 2022. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022358750 (20 October 2023, date last accessed).
10. Kang S, Tian J. Global epidemiology of systemic sclerosis (SSc): a comprehensive systematic analysis and modelling study. 2022. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022368186 (20 October 2023, date last accessed).
11. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan – a web and mobile app for systematic reviews. Syst Rev 2016;5:210.
12. SIGN. Methodology checklist 1: systematic reviews and meta-analyses. [Online]. 2023. https://www.sign.ac.uk/what-we-do/methodology/checklists/ (6 July 2023, date last accessed).
13. Qin B, Wang J, Yang Z *et al.* Epidemiology of primary Sjogren's syndrome: a systematic review and meta-analysis. Annals of the Rheumatic Diseases 2015;74:1983–9.
14. Albrecht K, Binder S, Minden K *et al.* Systematic review to estimate the prevalence of inflammatory rheumatic diseases in Germany. Z Rheumatol 2023;83:20–30.
15. Beltai A, Barnetche T, Daien C *et al.* Cardiovascular morbidity and mortality in primary Sjogren's syndrome: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2020;72:131–9.
16. Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. Semin Arthritis Rheum 2008;37:223–35.
17. Bairkdar M, Rossides M, Westerlind H *et al.* Incidence and prevalence of systemic sclerosis globally: a comprehensive systematic review and meta-analysis. Rheumatology (Oxford) 2021;60:3121–33.
18. Zhong L, Pope M, Shen Y, Hernandez JJ, Wu L. Prevalence and incidence of systemic sclerosis: a systematic review and meta-analysis. Int J Rheum Dis 2019;22:2096–107.
19. Morrisroe K, Stevens W, Proudman S, Nikpour M. A systematic review of the epidemiology, disease characteristics and management of systemic sclerosis in Australian adults. Int J Rheum Dis 2017;20:1728–50.
20. Toledano E, Candelas G, Rosales Z *et al.* A meta-analysis of mortality in rheumatic diseases. Reumatol Clin 2012;8:334–41.
21. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2012;51:1017–26.
22. Komocsi A, Vorobcsuk A, Faludi R *et al.* The impact of cardiopulmonary manifestations on the mortality of SSc: a systematic review and meta-analysis of observational studies. Rheumatology (Oxford) 2012;51:1027–36.
23. Rubio-Rivas M, Royo C, Simeón CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Semin Arthritis Rheum 2014;44:208–19.
24. Lee YH. Overall and sex- and disease subtype-specific mortality in patients with systemic sclerosis: an updated meta-analysis. Zeitschrift fur Rheumatologie 2019;78:195–201.
25. Pokeerbux MR, Giovannelli J, Dauchet L *et al.* Survival and prognosis factors in systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. Arthritis Res Ther 2019;21:86.
26. Erzer JN, Jaeger VK, Tikly M, Walker UA. Systemic sclerosis in sub-Saharan Africa: a systematic review. Pan Afr Med J 2020;37:176.
27. Greenstein D, Jeffcote N, Ilsley D, Kester RC. The menstrual cycle and Raynaud's phenomenon. Angiology 1996;47:427–36.
28. Fraenkel L, Zhang Y, Chaisson CE *et al.* The association of estrogen replacement therapy and the Raynaud phenomenon in postmenopausal women. Ann Intern Med 1998;129:208–11.
29. Conrad N, Misra S, Verbakel JY *et al.* Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. Lancet 2023;401:1878–90.

Rheumatology Advances in Practice, 2024, 8, 1–14
https://doi.org/10.1093/rap/rkae086
Systematic Review and Meta-Analysis

This promotional material has been created and funded by Novartis Pharmaceuticals UK Ltd. for UK healthcare professionals only.

Are you using a treatment that addresses all 6 key manifestations of PsA?

The key clinical manifestations of PsA are joints, axial, skin, enthesitis, dactylitis and nails.[1]

Joint relief in PsA:

68% of patients achieved **ACR50** with Cosentyx® (secukinumab) at **Year 1** (observed data)[2]

Results from ULTIMATE (N=166). The primary endpoint of GLOESS mean change from baseline vs placebo at Week 12 was met (−9 vs −6, p=0.004)[2,3]

Click here to visit our HCP portal and learn more

Skin clearance in PsO:

55% of patients achieved **PASI100** at **Week 52** with Cosentyx 300 mg AI (secondary endpoint, observed data, N=41)[4]

Results from MATURE. The co-primary endpoints PASI 75 and IGA mod 2011 0/1 at Week 12 were met for Cosentyx 300 mg (N=41) vs placebo (N=40), (95% vs 10% and 76% vs 8% respectively, p<0.0001)[4]

Axial joint relief in PsA:

69% of patients achieved **ASAS40** at **Week 52** with Cosentyx 300 mg (secondary endpoint, observed data, N=139)[1]

Results from MAXIMISE. The primary endpoint of ASAS20 with Cosentyx 300 mg (N=164) vs placebo (N=164) at Week 12 was met (63% vs 31% respectively, p<0.0001)[1]

Cosentyx is the first and only, fully human biologic that directly blocks IL-17A regardless of its source[5–10]

8 years

A **consistent safety profile** with **over 8 years** of real-world experience[5,6,11]

The most frequently reported adverse reactions are upper respiratory tract infections (17.1%) (most frequently nasopharyngitis, rhinitis).[5,6]

Cosentyx licensed indications in rheumatology: Cosentyx is indicated for the treatment of active psoriatic arthritis in adult patients (alone or in combination with methotrexate) when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; moderate to severe plaque psoriasis in children and adolescents from the age of 6 years, and adults who are candidates for systemic therapy; active enthesitis-related arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate conventional therapy; active juvenile psoriatic arthritis in patients 6 years or older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.[5,6]

ULTIMATE (N=166), a multicentre, randomised, double-blind, placebo-controlled, 52-week Phase III trial in patients with PsA. Patients were randomly assigned to receive either weekly subcutaneous Cosentyx (300 mg or 150 mg according to the severity of psoriasis) or placebo followed by 4-weekly dosing thereafter. The primary outcome of mean change in the ultrasound GLOESS from baseline to Week 12 was met (−9 vs −6; p=0.004).[2,3]
MATURE (N=122), a 52-week, multicentre, double-blind, randomised, placebo-controlled, Phase III trial in patients with PsO. Eligible patients were randomised to Cosentyx 300 mg or placebo. The co-primary endpoints were PASI75 and IGA mod 2011 0/1 responses at Week 12. The study met the co-primary endpoints: PASI75 and IGA mod 2011 0/1 response at Week 12 were met for Cosentyx 300 mg vs placebo (95% vs 10% and 76% vs 8% respectively, p<0.0001).[4]
MAXIMISE (N=498) a double blind, placebo-controlled, multicentre, Phase IIIb study in patients with PsA. Patients were randomised in a 1:1:1 ratio to receive Cosentyx 300 mg, 150 mg or placebo. The primary endpoint of the proportion of patients achieving and ASAS20 response with Cosentyx 300 mg at Week 12 vs placebo was met (63% vs 31% respectively, p<0.0001).[1]

ACR, American College of Rheumatology; AI, auto-injector; ASAS, Assessment of SpondyloArthritis International Society; BASDAI, Bath; ankylosing spondylitis disease activity index; EULAR, European Alliance of Associations for Rheumatology; GLOESS, Global EULAR and OMERACT synovitis score; IGA mod 2011 0/1, investigator global assessment modified 2011 0/1; OMERACT, outcome measures in rheumatology; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; PsO, plaque psoriasis.

References: 1. Baraliakos X, et al. *RMD open* 2019;5:e001005; **2.** Conaghan PG, et al. Poster 253. *Rheumatology* 2022;61(Suppl1). DOI:10.1093/rheumatology/keac133.252; **3.** D'Agostino MA, et al. *Rheumatology* 2022;61:1867–1876; **4.** Sigurgeirsson B, et al. *Dermatol Ther* 2022;35(3):e15285; **5.** Cosentyx® (secukinumab) GB Summary of Product Characteristics; **6.** Cosentyx® (secukinumab) NI Summary of Product Characteristics; **7.** Lynde CW, et al. *J Am Acad Dermatol* 2014;71(1):141–150; **8.** Fala L. *Am Health Drug Benefits* 2016;9(Special Feature):60–63; **9.** Schön M & Erpenbeck L. *Front Immunol* 2018;9:1323; **10.** Gorelick J, et al. *Practical Dermatol* 2016;12:35–50; **11.** European Medicines Agency. European public assessment report. Medicine overview. Cosentyx (secukinumab). Available at: https://www.ema.europa.eu/en/documents/overview/cosentyx-epar-medicine-overview_en.pdf [Accessed May 2024].

NOVARTIS

Prescribing information, adverse event reporting and full indication can be found on the next page.

UK | May 2024 | 425034

Cosentyx® (secukinumab) Great Britain Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 75 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 75 mg dose is given as one injection of 75 mg. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 75mg and 150 mg pre-filled syringe and 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common (≥1/10):* Upper respiratory tract infection. *Common (≥1/100 to <1/10):* Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions:* Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** PLGB 00101/1205 – 75 mg pre-filled syringe x 1 - £304.70; PLGB 00101/1029 - 150 mg pre-filled pen x2 £1,218.78; PLGB 00101/1030 - 150 mg pre-filled syringe x2 £1,218.78; PLGB 00101/1198 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** June 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

UK | 290802 | June 2023

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report.

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg monthly. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common* (≥1/10): Upper respiratory tract infection. *Common* (≥1/100 to <1/10): Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions:* Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity*: Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** EU/1/14/980/005 - 150 mg pre-filled pen x2 £1,218.78; EU/1/14/980/010 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** May 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

UK | 284832 | May 2023

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com