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Epidemiology of scleritis in the United Kingdom from 1997 to 2018: Population-based analysis of 11 million patients and association between scleritis and infectious and immune-mediated inflammatory disease

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Conflicts of Interest

The authors have no conflicts of interest related to this work.

Abstract

Objective: To estimate 22-year trends in scleritis prevalence and incidence and associations with infectious/immune-mediated inflammatory diseases (I-IMIDs) in the United Kingdom (UK).

Methods: Retrospective cross-sectional and population cohort study (1997-2018) included 10,939,823 patients (n=2946 incident scleritis cases) in The Health Improvement Network

(THIN), a nationally-representative primary care records database. Case-control and cohort study (1995-2019) included 3005 incident scleritis cases and 12,020 control patients matched by age, sex, region and Townsend Deprivation Index (TDI). We adjusted Poisson, Logistic and Cox proportional hazard multivariable models by age, sex, TDI, race/ethnicity, smoking, nation and body mass index category. Estimates include 95% confidence intervals.

Results: Scleritis incidence rates declined from 4·23(2·16-6·31) to 2·79(2·19-3·39) per 100,000 person-years between 1997 and 2018. Prevalence was 93·62(90·17-97·07)/100,000 people in 2018 (61,650 UK patients). Amongst 2946 incident scleritis patients, 62·2%(n=1831) were female, mean age was 44·9(SD17·6, range 1-93) years and 88·8%(n=1257) were White. Higher risk of incident scleritis was associated with female sex (adjusted incidence rate ratio [aIRR]=1·54, 1·43-1·66,p<0.001), Black (aIRR=1·52, 1·14-2·01,p=0.004) or South Asian race/ethnicity (aIRR=1·50, 1·19-1·90,p<0.001) versus White, and older age (peak aIRR=4·95, 3·99-6·14,p<0.001 for ages 51-60 years versus <10 years). Compared to controls, scleritis patients had 2-fold increased risk of prior I-IMID diagnosis (p<0.001, 17 I-IMIDs) and significantly increased risk of subsequent diagnosis of 13 I-IMIDs. Strongest associations included granulomatosis with polyangiitis, Behçet's disease, and Sjögren's syndrome.

Conclusion: Over 1997-2018 the UK incidence of scleritis declined from 4·23 to 2·79/100,000 persons/year. Incident scleritis was associated with 19 I-IMIDs, providing data for rational investigation and cross-specialty engagement.

Introduction

Scleritis is a sight-threatening condition, which may be associated with systemic infectious and immune-mediated inflammatory disease (I-IMID). I-IMID results from aberrant immune responses to inciting infectious and non-infectious (autoimmune and autoinflammatory) pathology, and frequently requires systemic immunosuppression to avoid irreversible tissue damage.[1] It has been long-recognised that scleritis (especially if necrotising) may portend worse survival prognosis in patients with certain I-IMIDs, including rheumatoid arthritis (RA).[2,3] A key challenge to advancing evidence-based management of scleritis is the paucity of population-based epidemiological data on incidence internationally, and absence of data on the strength of association with systemic I-IMIDs, and with other sight-threatening ocular inflammatory phenotypes (e.g. uveitis and optic neuritis) with which scleritis and these I-IMIDs may be associated.[1,4] Robust epidemiological data would facilitate increased awareness of scleritis as a cause of ocular symptoms in patients with I-IMIDs, more tailored investigation and risk stratification, health system cost modelling, and allocation of appropriate resources (medicines, infrastructure, equipment and staff) to meet current and future demand.

Our appreciation of the epidemiology of scleritis is currently informed by few studies. Three USA database studies reported scleritis incidence rates of 3·4 (Northern California Epidemiology of Uveitis Study, 1998-1999, n=731,895 patients within Health Maintenance Organisation)[5], 4·1 (Pacific Ocular Inflammation Study, 2006-2007, n=217,061 Kaiser Permanente enrolees)[6,7] and 1.6 (infectious scleritis, Optum private insurance database, 2007-2015, n=21.5 million insured patients)[8] per 100,000 person-years. Similarly, the Rochester Epidemiology Project (2006-2015, n=144,248 population) reported an incidence

of 5.5 per 100,000 person-years.[9] Large retrospective cohort studies from subspecialty practices over the past four decades (n>100 to 825, see Supplementary eTable 1), indicate that scleritis is associated with I-IMIDs in between 31·3% and 47·8% of cases, preceding IMID diagnosis in between 6·6%[10] and 38·7%.[11] Rheumatological diagnoses are most frequent.

The United Kingdom (UK) has an ageing population, but significant advances in therapeutic options for I-IMIDs, including biologic therapies, may have impacted the population burden of scleritis.[12] A National Health Service (NHS) primary care electronic patient record database, The Health Improvement Network (THIN),[13,14] provides a promising opportunity to interrogate scleritis epidemiology more robustly than has been possible in prior studies. Here we estimate the UK incidence and prevalence of scleritis between 1997 and 2018, and evaluate associations with systemic I-IMIDs.[1]

Patients and Methods

Patient and Public Involvement

This study responds directly to the 2013 Sight Loss and Vision Priority Setting Partnership in the UK, overseen by the James Lind Alliance, an authoritative and independent non-profit initiative managed by the National Institute for Health Research (NIHR).[15] This initiative brought patients, carers and health professionals together to identify and prioritise unanswered questions for research. Within ocular inflammatory disease, "*What causes scleritis?*" was identified as a priority research question.

Data Source, data access and ethics

We analysed data from THIN from 01/01/1995 to 01/09/2019. THIN contains longitudinal

information for a cohort of 15 million patients from 808 primary care general practices (GP),

including patient demographics, diagnoses, drug prescriptions, and laboratory test results.

The study was conducted in compliance with the Helsinki Declaration. Use of IQVIA Medical

Research Data was approved by the UK Research Ethics Committee (reference number:

18/LO/0441). In accordance with this approval, the study protocol was reviewed and

approved by an independent Scientific Review Committee (SRC) (reference

number:19THIN086). IQVIA Medical Research Data (IMRD) incorporates data from THIN, A

Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset

licensed by IQVIA. This work used de-identified data provided by patients as a part of their

routine primary care; individual consent was not obtained.

Design

We estimated annual scleritis prevalence by performing sequential cross-sectional studies

on data collected on 1st January annually, from 1997 to 2018, inclusive. We estimated

annual scleritis incidence rates through a series of yearly (1st January to 31st December)

cohort studies. Data for 1995, 1996, and 2019 were excluded as incomplete. Risk factors for

scleritis were explored in a cohort analysis (1997 to 2018). In addition, we performed a

matched case-control and retrospective cohort study using all data (1st January 1995 to 1st

September 2019) to explore odds ratios and hazard ratios of 58 I-IMIDs, in patients

diagnosed with scleritis compared to controls. We did not explore strength of association

between scleritis and medications or scleral injury/foreign body. This study followed the

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Population

General practices were eligible for inclusion one year after commencing electronic medical record use and acceptable mortality rates (a data quality indicator). We included patients aged >1 year, who registered with a participating GP for at least one year before cohort entry (to ensure documentation of important baseline covariates).

In the UK, scleritis and I-IMIDs are diagnosed by hospital specialists. Diagnoses are communicated to GPs, who enter the clinical 'Read' codes into the electronic medical record. We diagnosed scleritis cases (eTable2), and 58 individual I-IMIDs,[1] from relevant Read codes.

For the matched case-control and cohort studies, we matched patients with scleritis (newly diagnosed during study period) each with four controls, randomly selected from a pool of age-, sex-, region- and Townsend Deprivation Index (TDI)-matched patients without scleritis.[16] The TDI is a measure of material deprivation in the population of a given area, and incorporates unemployment rate, and household non-car ownership, non-home ownership and overcrowding.[16] Where TDI was missing, we matched cases with a control in whom it was also missing. We used an established method for randomly selecting matched controls.[17] Matched controls were assigned the same index date (+/-1 year) as the index (diagnosis) date for scleritis patients to avoid immortal time bias.[17] Scleritis patients and controls were followed up from index date until the earliest out of outcome event (incident

I-IMID diagnosis, defined using Read codes for each disease), death, patient leaving GP, GP ceasing database contributions, or study end.

Statistical Analysis

All variables were recorded at cohort entry and were summarized using appropriate descriptive statistics: mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables, and frequency (percentage [%], n) for categorical variables. All statistical analyses were performed with Stata IC, version 15.0 (StataCorp LLC), setting statistical significance at $p<0.05$.

For point prevalence, over the period 1997 to 2018, we calculated the proportion of eligible patients in the dataset on 1st January each year who have at any time prior to that date had a recorded diagnosis of scleritis. We estimated crude annual scleritis incidence rates by dividing the number of patients with new scleritis diagnosis by total person-years at risk. Across the whole study period, we estimated overall incidence rates stratified by age, sex, race/ethnicity, body mass index category, smoking status, TDI, and nations within the UK.

To explore scleritis risk factors, we performed univariable and multivariable Poisson regression analyses to estimate crude and adjusted incidence rate ratios, accounting for person-years of follow-up. The adjustment variables we considered included age category, sex, race/ethnicity, smoking category, BMI category at first registration, nation within the UK, and TDI, all as recorded at index date.[14,15] We created a separate category for missing data to avoid censoring when covariate values were missing. We included variables with significance $p<0.10$ in single variable analyses in multivariable models. In patients with incident scleritis between 1995 and 2019, we performed a case-control and matched cohort

study to evaluate association with I-IMIDs. For patients with scleritis compared to matched

controls, we calculated the odds of prior diagnosis, and hazard of incident diagnosis, of each

I-IMID independently, excluding patients with that outcome at baseline in the latter. We

performed logistic regression analysis to obtain crude and adjusted odds ratios and their

corresponding 95% confidence intervals (CI) for each IMID at/prior to baseline, and all I-

IMIDs combined, comparing patients with and without scleritis. We estimated adjusted

hazard ratios (HR, 95%CI) using Cox proportional hazards regression models for incidence of

each I-IMID after scleritis diagnosis. The adjustment variables were the same as those

selected for the multivariable Poisson model. We confirmed model assumptions using log-

log plots and the Schoenfeld residuals test. We used the Nelson-Aalen cumulative hazard

function to plot cumulative hazard of these outcomes.

Role of funding source

The funding sources had no involvement in study design, collection, analysis or

interpretation of data, writing the report, or decision to submit for publication.

Results

Prevalence and incidence analysis

The cross-sectional and retrospective cohort studies (1st January 1997 to 31st December

2018), included 10,939,823 patients with 75·2 million person-years follow-up, of whom

2946 (0.0039, 95%CI 0·0037-0·0041)%/person-year) developed incident scleritis.

Scleritis incidence rates declined from 4·23 (2·16-6·31) to 2·79 (2·19-3·39) per 100,000

person-years between 1997 and 2018 (Figure 1A, eTable3). In contrast to the incidence rate,

scleritis prevalence (per 100,000) increased from 20·72 (14·13-27·31) in 1997 to 93·62

(90·17-97·07) in 2018 (eFigure 1, eTable 3).This reflects evolving THIN database maturity

over time, with the database more closely approaching a steady state (of patients being

added versus patients being removed) in more recent years. There were an estimated

61,650 (95% CI 59,380-63,919) scleritis patients in the UK in 2018.

Table 1 compares characteristics of the 2946 incident scleritis cases and 10·9 million

patients in the THIN population without scleritis. In brief, incident scleritis cases were

62·2%(n=1831) female, with mean age at cohort entry of 44·9(SD17·6, range 1-93) years,

88·8%(n=1257) were White, median BMI was 25·6(IQR 17·3-44·6)kgm^{-2}, 33·4%(n=984) were

smokers or ex-smokers, 24·8%(n=624) were from TDI category 1 (least deprived) and

71·2%(n=2098) resided in England. Figure 1B illustrates that over this period, more women

than men developed incident scleritis, with peak onset in 50-59 year-old women, compared

to 70-79 year old men; incidence rates for other variable subgroups are presented in Table

2, and by age group in each sex in eTable 4.

In a multivariable Poisson regression model, significant predictors of incident scleritis

included female sex (adjusted incidence rate ratio, [aIRR]=1·53 [1·42-1·66], p<0·001); Black

(aIRR=1·52 [1·14-2·01], p=0·004) or South Asian (aIRR=1·50 [1·19-1·90], p=0·001)

race/ethnicity compared to White; and obesity (BMI>30·0kgm^{-2}) (aIRR=1·16 [1·04-1·30],

p=0·008), compared to normal weight (BMI 18·4-24·9kgm^{-2}). The aIRR also increased with

age, peaking at 4·95 ([3·99-6·14], p<0·001) in those aged 51-60 years compared to 1-10

years. Compared to English residents, Scottish residents were at significantly lower risk

(aIRR=0·85 [0·76-0·95], p=0·005) whereas Welsh residents were at higher risk (aIRR=1·14 [1·02-1·28], p=0·026). There was no significant association with TDI or smoking category.

3005 incident scleritis patients and 12,020 randomly matched controls were included between 01/01/1995 and 01/09/2019. 12 I-IMIDs with no data were excluded from analysis. Scleritis patients (28.4%, n=853/3005) were 2-times more likely than controls (16.0%, n=1923/12020) to have a prior diagnosis of any I-IMID (adjusted OR=2.01, 95% CI 1.83-2.22, p<0.001). In a series of single then adjusted logistic regression analyses, we identified significantly greater odds of a prior diagnosis of 17 individual I-IMIDs in patients with scleritis compared to controls (Table 3, Figure 2): granulomatosis with polyangiitis ([GPA] OR=50·7, p<0.001); Behçet's disease (OR=9·1, p=0.014); Sjögren's syndrome (OR=7·1, p<0.001); reactive arthritis (formerly Reiter's syndrome) (OR=7.0, p=0.002); RA (OR=5·7, p<0.001); other vasculitis (OR=5·4, p<0.001); giant cell arteritis [GCA] (OR=3·8, p=0.001); Crohn's disease (OR=3·6, p<0.001); SLE (OR=3·5, p<0.001); ankylosing spondylitis [AS] (OR=3·4, p<0.001); sarcoidosis (OR=2·6, p<0.001); polymyalgia rheumatica (OR=2·3, p<0.001); ulcerative colitis (OR=2·2, p<0.001); herpes virus infections (simplex and zoster) (OR=1·6, p<0.001); Epstein Barr virus [EBV] infection (OR=1·5, p=0.014); measles (OR=1·5, p=0.047) and psoriasis (OR=1·3, p=0.004). Scleritis cases were also significantly more likely than controls to have previously had uveitis (OR 17·3, p<0.001) or optic neuritis (OR 2·7, p=0.023).

After excluding those with prevalent I-IMID at baseline, there were 8.8% (n=190/2152) scleritis patients and 6.1% (n=619/10,097) controls who developed incident I-IMIDs over median follow-up of 5·8 (IQR 2·6-9·8) and 5.5 (IQR 2·4-9·6) years, respectively. We

compared the hazard of diagnosis with each individual I-IMID in scleritis cases and matched

controls in a series of adjusted Cox proportional hazard regression analyses (Table 3 and

Figures 2 and 3 and eFigure2). Scleritis cases were significantly more likely to develop 13

incident I-IMIDs: GPA (HR=96·4, p<0.001); Behçet's disease (HR=17·5, p=0.011); Mumps

(HR=11·1, p=0.045); Sjögren's syndrome (HR=8·5, p<0.001); SLE (HR=8·5, p<0.001); Lyme

disease (HR=8·4, p=0.018); other vasculitis (OR=6·7, p<0.001); RA (HR=4·2, p<0.001); Crohn's

disease (HR=4·2, p<0.001); AS (HR=3·4, p=0.020); sarcoidosis (HR=3·1, p=0.025); GCA

(HR=2·4, p=0.043); and herpetic infection (HR=1·5, p=0.003). Scleritis patients were also

twenty times more likely than controls to develop incident uveitis (HR 20·1, p<0.001).

Discussion

This large, population-representative national study of the UK epidemiology of scleritis

provides needed prevalence and incidence estimates, and offers insights into the presence

and strength of associations with systemic I-IMIDs. The UK incidence of new cases appears

to have fallen by about one-third over the past 22 years, to 2·8/100,000 person-years. This

trend is likely to reflect improvements in the management of systemic I-IMIDs. Over this

period there has been increasing availability of antimicrobial therapies and

immunosuppressive therapies including biologics.[19] Whilst more variable, the UK incidence

of RA also decreased between 1997 and 2014, from 45·4 to 38·1/100,000 person-years.[20]

Our study finds close agreement with incidence rate estimates from USA database studies in

Northern California (1998-1999, 3·4/100,000 person-years)[5] and Hawaii (2006-2007,

4·1/100,000 person-years).[6] Our study estimated incidence rates in those years of 4·7 and

4·2/100,000 person-years, respectively. The apparent rise in prevalence of patients ever

diagnosed with scleritis likely reflects increasing maturity of the THIN database (see below).

A similar pattern has been observed in this database for optic neuritis,[4] and the latest prevalence estimate of 93·6/100,000 in 2018 reflects the most reliable.

Common to previous scleritis epidemiology studies in the USA,[5-8] we observed higher risk of incident scleritis amongst women. Factors contributing to well-established sex differences in immune-mediated diseases are complex and multiple, with genetic, hormonal, and environmental contributions.[21,22] We observed peak scleritis onset in 50-59 year-old women and 70-79 year old men. This broadly aligns with other scleritis database studies,[6] and with other autoimmune conditions, and in particular, those associated with chronic, fibrotic Th2-mediated pathology.[22] Black and South Asian people in the UK were 1·5 times more likely to develop incident scleritis than White people. Black race/ethnicity has previously been identified as a significant risk factor for both incident scleritis,[6] and other I-IMIDs including sarcoidosis[23] and SLE.[24] Obesity at cohort entry (BMI>30 kgm^{-2}) was also significantly associated with higher scleritis incidence (aIRR 1·2, p=0·008). A growing body of evidence links obesity, with its chronic state of low-grade inflammation and the pleiotropic effects of adipokines on the immune system, to risk and severity of rheumatic conditions.[25] The regional variation observed across the UK, with significantly higher risk in Wales and significantly lower risk in Scotland was interesting, but challenging to explain. It perhaps relates to as yet unidentified environmental differences.

To our knowledge, this is the first population-representative study to systematically explore the strength of association between scleritis, and I-IMIDs of potential relevance.[1] Whilst this study does not infer direct causation, we identified that 28.4% scleritis patients had an associated I-IMID prior to scleritis diagnosis, and 8.8% developed one during subsequent

follow-up. These were only slightly lower than reported by scleritis cohort studies (see Supplementary eTable 1). A likely explanation is that milder scleritis, which may be well-captured in this primary care records database, is less likely to be associated with systemic disease, or referred to tertiary centres for management. We found autoimmune and autoinflammatory disease to be a more frequent association with scleritis than infectious disease in the UK. We identified significant infectious associations preceding/subsequent to scleritis diagnosis, including herpetic infection (OR=1·6 p<0.001, HR=1·5, p=0.003), EBV infection (OR=1·5, p=0.014), and Lyme Disease (HR=8·4, p=0.018), with Mumps (HR=11·1, p=0.045) and Measles (OR 1·5, p=0.047) also just reaching significance. We identified significant associations with 19 I-IMIDs, including strongest associations with both pre-existing and subsequent diagnosis of GPA (OR=50·7 HR=96·4, p<0.001 for both), Behçet's disease (OR=9·1 p=0.014, HR=17·5 p=0.011), Sjögren's syndrome (OR=7·1, HR=8·5, p<0.001 for both), RA (OR=5·7, HR=4·2, p<0.001 for both), other vasculitis (OR=5·4, HR=6·7, p<0.001 for both), Crohn's disease (OR=3·6, HR=4·2, p<0.001 for both), SLE (OR=3·5, HR=8·5, p<0.001 for both), GCA (OR=3·8 p=0.001, HR=2·4 p=0.043), AS (OR=3·4 p<0.001, HR=3·4, p=0.020), and sarcoidosis (OR=2·6 p<0.001, HR=3·1 p=0.025). Epidemiological research in different world regions reveals different patterns (See Supplementary eTable 1), with more infectious causes in India, for example.[26] The systemic associations highlight the potential value of cross-specialty multidisciplinary care to detect preclinical or early disease and optimise management.[27]

There are currently no licensed biologic therapies for scleritis in the UK, despite off-license use of numerous agents reported to be effective in I-IMID-associated scleritis, including infliximab.[12] More widespread use of licensed treatments for I-IMIDs—including RA, IBD, AS,

GPA and psoriasis—with anti-TNFa agents and Rituximab (anti-CD20), has likely contributed to declining UK scleritis incidence. Future benefit may be observed with increasing use of anti-IL-6 and anti-IL-1 agents, small molecule janus kinase inhibitors, and future new treatments. This study confirms that the rarity of scleritis offers challenges for randomized controlled trials, and for scleritis to be captured as a secondary outcome measure in rheumatological disease clinical trials. A more pragmatic, resource-efficient Bayesian adaptive clinical trial design, embedded within routine healthcare, may offer a solution, and has been recently explored in JIA-associated uveitis. [28]

Strengths of the study include its very large sample size, permitting evaluation of associations between scleritis and uncommon I-IMIDs, and time trends over a 22-year period. In addition, THIN is reliably generalizable to the UK population.[13,14] The limitations of this study include insufficient power to identify associations between scleritis and rare I-IMIDs (e.g. relapsing polychondritis), and the possibility that some weakly statistically significant associations were spurious. Read codes did not permit accurate differentiation of scleritis subtypes (eTable 1), which include anterior or posterior, and diffuse, nodular, or necrotizing (including scleromalacia perforans). We included, "F4K0.00 Scleritis and episcleritis" (n=164 patients), but excluded, "F4K0z00 Scleritis or episcleritis not otherwise specified", to limit risk of inclusion of patients with isolated episcleritis. Nevertheless, this might have led to an overestimate of the prevalence of scleritis and an underestimate of associations with I-IMIDs, given that episcleritis is less strongly associated with systemic diseases. Read codes also did not permit differentiation of all subtypes of the associated I-IMIDs of interest (eg primary versus secondary Sjogren's). In addition, within the prevalent cases, we were not able to differentiate patients with single episode, versus relapsing and

remitting, versus chronically active scleritis. Furthermore, individual cases or controls may have had more than one I-IMID or infection of interest, and this study did not explore associations or temporal relationships between these. Finally, retrospective estimates from this database of routinely collected data have potential risks of bias. There is a risk of diagnostic error in the hospital or incorrect coding resulting in misclassification bias, and of data entry error or missing data arising from incomplete investigation or data entry omissions. We were not able to review medical records to validate the Read codes assigned. However, the close agreement in scleritis incidence rate with other large database and epidemiological surveys in the USA was reassuring.[5-9]

The trend of declining incidence of scleritis, with rising prevalence, indicates evolving database maturity. Reasons for this include more adults newly registering for a GP at onset or recurrence of scleritis, or patients newly volunteering medical history of previous scleritis. Over time, electronic data capture is improving as systems become more familiar, easier and faster to use. As more patients are added at birth and followed throughout the life course, with resulting stabilisation of the database's age structure, increasing confidence can be placed in the estimates of prevalence and age at onset. With higher scleritis incidence in older age groups, we anticipate some rise in prevalence over time, if population aging continues.

Future research is needed to establish the population-based incidence of scleritis in relation to temporal trends in incidence of different I-IMIDs,[29] and to identify effective treatments. We recommend that scleritis and episcleritis not be combined in future epidemiological studies, on account of the important differences between them.[30] Compared with

episcleritis, scleritis can be rapidly and directly sight-threatening, is usually more painful, has greater need for systemic therapy, takes longer to resolve, and is associated with developing severe ocular sequellae.[11,31]

This study highlights how the use of routinely collected large-scale data offers unprecedented opportunity to advance understanding of the epidemiology of rare conditions and their associations. Here we report declining UK scleritis burden over 22 years, and multiple significant associations with I-IMIDs which precede or follow scleritis diagnosis, providing guidance for health policy and clinical management. Most strongly associated were GPA, Behcet's Disease, Sjogren's syndrome, RA, SLE, Crohn's disease and sarcoidosis. The interplay between ophthalmologically managed scleritis, and I-IMIDs managed by rheumatology and other specialties, highlights the need for multi-specialty care pathways for patients with this potentially blinding disease.

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TABLES

Table 1 Comparison of the UK population exposed and not exposed to incident scleritis

		No Scleritis % (n)	Scleritis % (n)	Single variable IRR (95% CI), p value	Adjusted IRR (95% CI), p value)
	Characteristic at baseline				
	Total, %(n)	10,936,877	2946		
	Male, % (n)	49·1 (5,365,369)	37·9 (1,115)	1	1
Gender	**Female, % (n)**	50·9 (5,571,508)	62·2 (1,831)	1·63 (1·52-1·76), p<0·001	1·53 (1·42-1·66), p<0·001
	1-10 y	18·9 (2,070,295)	4·3 (126)	1	1
	11-20 y	9·9 (1,081,516)	3·9 (115)	1·77 (1·38-2·29), p<0·001	1·62 (1·25-2·09), p<0·001
	21-30 y	18·2 (1,985,113)	11·3 (332)	3·53 (2·88-4·34), p<0·001	2·56 (2·04-3·20), p<0·001
	31-40 y	16·6 (1,815,638)	20·8 (614)	5·17 (4·27-6·26), p<0·001	3·73 (3·01-4·61), p<0·001
Age Group at cohort entry	**41-50 y**	12·1 (1,325,429)	20·6 (607)	5·96 (4·92-7·22), p<0·001	4·34 (3·50-5·37), p<0·001
	51-60 y	9·6 (1.045,415)	19·7 (579)	6·91 (5·70-8·38), p<0·001	4·95 (3·99-6·14), p<0·001
	61-70 y	7·0 (765, 070)	11·9 (350)	5·95 (4·85-7·29), p<0·001	4·17 (3·33-5·23), p<0·001
	71-80 y	4·8 (526,347)	6·21 (183)	5·47 (4·36-6·86), p<0·001	3·82 (2·98-4·88), p<0·001
	81-90 y	2·5 (270,652)	1·2 (36)	3·48 (2·40-5·04), p<0·001	2·44 (1·67-3·57), p<0·001
	91-100 y **100+ y**	0·5 (50,658) 0·01 (744)	0·14 (4) 0	3·73 (1·38-10·10),p=0·010	2·68 (0·99-7·29), p=0·053
	England	71·3 (7,792,462)	71·2 (2,098)	1	1
Nation	**Scotland**	14·1 (1,538,768)	12·0 (352)	0·88 (0·78-0·98)	0·85 (0·76-0·95), p=0·005
	Wales	11·0 (1,203,070)	12·4 (365)	1·09 (0·97-1·21)	1·14 (1·02-1·28), p=0·026
	Northern Ireland	3·7 (402,577)	4·5 (131)	0·89 (0·74-1·06)	1·02 (0·85-1·22), p=0·854
TDI	**1**	18·2 (1,985,030)	21·2 (624)	1	1

	2	16·5 (1,807,692)	18·1 (534)	0·99 (0·88-1·11), p=0·876	1·00 (0·89-1·12), p=0·950
	3	17·5 (1,910,916)	18·6 (549)	1·04 (0·93-1·16), p=0·528	1·08 (0·96-1·21), p=0·219
	4	16·3 (1,783,513)	16·9 (499)	1·08 (0·96-1·22), p=0·184	1·15 (1·02-1·30), p=0·019
	5	12·0 (1,314,506)	10·4 (307)	0·93 (0·81-1·07), p=0·307	1·03 (0·90-1·19), p=0·644
	Missing	19·5 (2,135,220)	14·7 (433)	0·92 (0·81-1·03), p=0·158	0·93 (0·82-1·05), p=0·258
	White	39·0 (4,263,911)	24·7 (1,257)	1	1
	Black	1·6 (177,868)	1·7 (51)	1·39 (1·05-1·84), p=0·020	1·52 (1·14-2·01), p=0·004
	Mixed	1·2 (131,309)	0·9 (25)	1·15 (0·77-1·71), p=0·494	1·20 (0·81-1·79), p=0·360
Race/ Ethnicity	**Others**	0·6 (70,389)	0·1 (4)	0·31 (0·11-0·82), p=0·018	0·43 (0·16-1·14), p=0·088
	South Asian	2·4 (262,288)	2·7 (78)	1·32 (1·05-1·66), p=0·018	1·50 (1·19-1·90), p<0·001
BMI (kg/m2)	**Missing**	55·1 (6,031,112)	52·0 (1,531)	0·82 (0·77-0·89), p<0·001	0·91 (0·84-0·98), p=0·014
	Underweight (<18·5)	1·7 (182,197)	1·6 (46)	0·93 (0·69-1·25), p=0·634	1·02 (0·76-1·38), p=0·875
	Normal (18·5-24·9)	25·6 (2,796,771)	31·6 (931)	1	1
	Overweight (25-29·9)	17·5 (1,918,346)	24·9 (733)	1·06 (0·96-1·17), p=0·244	1·04 (0·94-1·15), p=0·436
	Obese (>30)	10·0 (1089299)	16·2 (476)	1·26 (1·13-1·41), p<0·001	1·16 (1·04-1·30), p=0·008
	Missing	45·3 (4,950,264)	25·8 (760)	0·43 (0·39-0·48), p<0·001	0·81 (0·71-0·91), p<0·001
	Never smoker	38·7 (4,230,414)	48·7 (1,436)	1	1
Smoker Status	**Ex-smoker**	10·6 (1,159,235)	13·1 (386)	1·03 (0·92-1·16), p=0·576	1·00 (0·89-1·12), p=0·938
	Current smoker	16·9 (1,853,047)	20·3 (598)	0·95 (0·86-1·04), p=0·266	0·98 (0·89-1·08), p=0·663
	Missing	33·8 (3,694,181)	17·9 (526)	0·37 (0·34-0·41), p<0·001	0·86 (0·75-0·99), p=0·036

KEY: BMI Body mass index; TDI Townsend Deprivation Index (1 = least deprived, 5 = most deprived)

Table 2 Cumulative incidence rate (per 100,000 person-years) of scleritis, stratified by key variables

Subgroup	Characteristic at baseline	Incidence rate (per 100,000 person-years)
Gender	Male	2·98 (2·80-3·15)
Age Group at cohort entry	Female	4·85 (4·64-5·08)
	1 to 18 years	0·88 (0·74-1·04)
	18 years+	4·63 (4·47-4·81)
Country	England	3·97 (3·80-4·14)
	Scotland	3·48 (3·14-3·87)
	Wales	4·30 (3·88-4·77)
	Northern Ireland	3·52 (2·97-4·18)
Townsend Deprivation Index	1 (least deprived)	3·93 (3·63-4·25)
	2	3·89 (3·58-4·24)
	3	4·08 (3·75-4·43)
	4	4·26 (3·90-4·65)
	5 (most deprived)	3·66 (3·27-4·09)
	Missing	3·60 (3·27-3·95)
Race/ethnicity	Black	6·01 (4·57-7·91)
	White	4·31 (4·08-4·56)
	Mixed	4·95 (3·34-7·33)
	Others	1·32 (0·50-3·52)
	South Asian	5·69 (4·56-7·10)
	Missing	3·56 (3·38-3·74)
Body Mass Index (kg/m2)	Underweight (<18·5)	5·36 (4·98-5·76)
	Normal (18·5-24·9)	5·06 (4·74-5·39)
	Overweight (25-29·9)	5·36 (4·98-5·76)
	Obese (>30-34·9)	6·36 (5·71-7·10)
	Morbidly obese (>35)	6·46 (5·51-7·57)
	Missing BMI	2·19 (2·04-2·35)
Smoking Status	Never smoker	5·13 (4·86-5·39)
	Ex-smoker	5·29 (4·79-5·84)
	Current smoker	4·85 (4·48-5·26)
	Missing	1·91 (1·75-2·08)

Table 3: Comparison of 3005 scleritis patients and 12020 matched controls, exploring association with 58 infectious and immune-mediated inflammatory diseases, highlighting the adjusted odds of baseline (prior) diagnosis and adjusted hazard of incident diagnosis during follow-up, with the latter excluding baseline diagnoses of the outcome

	Case-control analysis			Retrospective matched cohort analysis[a]		
Diagnosed comorbidities at baseline/ during follow-up[b]	**Cases n (%)**	**Controls n (%)**	**aOR (95%CI)[c], p value**	**Cases n (%)**	**Controls n (%)**	**aIRR (95% CI)[c], p value**
TOTAL	3005	12020		<3005[a]	<12020[a]	
Clinical Phenotypes						
Optic neuritis	9 (0·30)	14 (0·12)	2·71 (1·15-6·38), p=0·023	5 (0·17)	0	Not estimable
Uveitis	294 (9·78)	73 (0·61)	17·3 (13·29-22·60), p<0·001	92 (3·39)	32 (0·27)	20·08 (14·02-28·76), p<0·001
Immune-mediated inflammatory disease associations, non-infectious						
Ankylosing spondylitis	18 (0·60)	22 (0·18)	3·39 (1·78-6·42), p<0·001	4 (0·13)	2 (0·02)	3·44 (1·21-9·76), p=0·020
Behçet's Disease	4 (0·13)	2 (0·02)	9·09 (1·57-52·53), p=0·014	3 (0·10)	0	17·45 (1·94-156·74), p=0·011
Coeliac disease	16 (0·53)	36 (0·30)	1·62 (0·89-2·95), p=0·118	4 (0·13)	14 (0·12)	1·07 (0·43-2·69), p=0·883
Cogan's syndrome	1 (0·03)	0	Not estimable	0	0	Not estimable
CREST syndrome	1 (0·03)	0	Not estimable	0	1 (0·01)	Not estimable
Crohn's disease	38 (1·26)	43 (0·36)	3·60 (2·28-5·67), p<0·001	7 (0·24)	10 (0·08)	4·16 (2·90-7·58), p<0·001
Dermato- or polymyositis	2 (0·07)	1 (0·01)	5·44 (0·43-68·09), p=0·189	0	1 (0·01)	5·38 (0·33-88·57), p=0·239
Giant cell arteritis	14 (0·47)	13 (0·11)	3·83 (1·74-8·44), p=0·001	7 (0·23)	14 (0·12)	2·36 (1·03-5·44), p=0·043
Gout	95 (3·16)	300 (2·50)	1·20 (0·94-1·54), p=0·152	52 (1·79)	181 (1·54)	0·96 (0·73-1·24), p=0·737
Granulomatosis with polyangiitis	28 (0·93)	2 (0·02)	50·66 (11·94-214·93), p<0·001	17 (0·57)	0	96·36 (12·99-715·00), p<0·001
IgA nephropathy	2 (0·07)	0	Not estimable	4 (0·13)	0	Not estimable
Juvenile idiopathic arthritis (JIA)	5 (0·17)	0	Not estimable	0	0	Not estimable
Lymphoma	8 (0·27)	13 (0·11)	2·40 (0·97-5·97), p=0·059	4 (0·13)	0	Not estimable
Multiple Sclerosis	11 (0·37)	34 (0·28)	1·29 (0·64-2·58), p=0·473	0	13 (0·11)	1·12 (0·41-3·08), p=0·825
Polyarteritis nodosa	3 (0·10)	0	Not estimable	1 (0·03)	0	Not estimable
Polymyalgia rheumatica	45 (1·50)	78 (0·65)	2·31 (1·57-3·40), p<0·001	15 (0·51)	72 (0·60)	1·11 (0·70-1·75), p=0·670
Porphyria	0	2 (0·02)	Not estimable	0	1 (0·01)	Not estimable
Psoriasis	147 (4·89)	420 (3·49)	1·34 (1·10-1·63), p=0·004	39 (1·36)	116 (1·00)	1·22 (0·92-1·60), p=0·163
Reactive arthritis	7 (0·23)	4 (0·03)	6·96 (1·99-24·36), p=0·002	0	0	Not estimable
Relapsing polychondritis	5 (0·17)	0	Not estimable	2 (0·07)	0	Not estimable
Rheumatoid arthritis	150 (4·99)	114 (0·95)	5·70 (4·40-7·39), p<0·001	40 (1·40)	67 (0·56)	4·22 (3·32-5·39), p<0·001

Sarcoidosis	25 (0·83)	35 (0·29)	2·61 (1·53-4·46), p<0·001	3 (0·10)	7 (0·06)	3·09 (1·15-8·27), p=0·025
Sjogren's syndrome	22 (0·73)	13 (0·11)	7·14 (3·50-14·57), p<0·001	9 (0·30)	7(0·06)	8·53 (3·35-21·67), p<0·001
Systemic lupus erythematosus	20 (0·67)	26 (0·22)	3·47 (1·90-6·33), p<0·001	10 (0·34)	5 (0·04)	8·49 (3·35-21·74), p<0·001
Stevens Johnson Syndrome	0	2 (0·02)	Not estimable	0	0	Not estimable
SWEET syndrome	1 (0·03)	2 (0·02)	1·36 (0·12-15·50), p=0·803	0	0	Not estimable
Systemic sclerosis	0	1 (0·01)	Not estimable	0	0	Not estimable
Thyroid disease, autoimmune	14 (0·47)	42 (0·35)	1·11 (0·60-2·06), p=0·783	4 (0·13)	18 (0·15)	1·16 (0·45-2·94), p=0·761
Ulcerative colitis	43 (1·43)	68 (0·57)	2·20 (1·49-3·27), p<0·001	1 (0·03)	25 (0·21)	1·77 (0·99-3·16), p=0·054
Vasculitis, other	26 (0·87)	17 (0·14)	5·37 (2·87-10·05), p<0·001	14 (0·47)	12 (0·10)	6·68 (3·22-13·86), p<0·001
Vitiligo	12 (0·40)	44 (0·37)	1·04 (0·54-2·00), p=0·901	6 (0·20)	16 (0·13)	1·33 (0·55-3·22), p=0·524
Vogt Koyanagi Harada	0	0	Not estimable	1 (0·03)	0	Not estimable
Waldenstrom's macroglobulinaemia	0	2 (0·02)	Not estimable	1 (0·03)	4 (0·03)	0·69 (0·08-6·35), p=0·747
Immune-mediated inflammatory disease associations, infectious						
Aspergillosis	2 (0·07)	3 (0·02)	2·56 (0·37-17·62), p=0·340	1 (0·03)	3 (0·02)	1·72 (0·17-17·46), p=0·648
Brucellosis	1 (0·03)	0	Not estimable	0	0	Not estimable
Cytomegalovirus infection	1 (0·03)	0	Not estimable	0	1 (0·01)	Not estimable
Epstein Barr virus infection	53 (1·76)	144 (1·20)	1·50 (1·09-2·08), p=0·014	1 (0·03)	4 (0·03)	0·72 (0·08-6·68),p=0·772
Herpes simplex or zoster virus infection	171 (5·69)	417 (3·47)	1·61 (1·34-1·94), p<0·001	49 (1·73)	158 (1·36)	1·53 (1·16-2·02), p=0·003
Human immunodeficiency virus infection	0	8 (0·07)	Not estimable	0	1 (0·01)	Not estimable
Lyme disease	2 (0·07)	2 (0·02)	4·12 (0·56-30·33), p=0·164	4 (0·13)	2 (0·02)	8·41 (1·43-49·39), p=0·018
Measles	33 (1·10)	95 (0·79)	1·51 (1·00-2·27), p=0·047	0	0	Not estimable
Mumps	0	0	Not estimable	3 (0·10)	2 (0·02)	11·11 (1·05-117·16), p=0·045
Syphilis	2 (0·07)	12 (0·10)	0·63 (0·14-2·88), p=0·551	0	0	Not estimable
Tuberculosis	24 (0·80)	67 (0·56)	1·35 (0·83-2·19), p=0·223	4 (0·13)	4 (0·03)	3·37 (0·82-13·78), p=0·091
Toxocariasis	0	1 (0·01)	Not estimable	0	0	Not estimable
Toxoplasmosis	2 (0·07)	2 (0·02)	3·76 (0·45-31·49), p=0·223	0	0	Not estimable

[a] Patients with a record of the comorbidity at baseline were excluded for the corresponding follow-up analysis estimating aIRRs.

[b] Diseases (12) for which Read codes were available in THIN but no data present in scleritis patients or controls (and thus excluded from analysis): Churg-Strauss, acanthamoeba, chikungunya, dengue, familial Mediterranean fever, Graft-versus-host, Kawasaki disease, microscopic polyangiitis, Takayasu's arteritis, West Nile virus, Yaws, Zika virus.

Diseases for which no Read codes were recorded in the THIN dataset (4): Blau syndrome, Bartonella or cat scratch disease, human herpes 6 virus and human coronavirus. There was also no specific Read code for c or p ANCA positivity, but these were likely captured under a combination of Read codes, grouped here as 'Vasculitis, other'.

[c] All models adjusted for gender, age category, race/ethnicity, BMI category, smoking category, country and Townsend Deprivation Index

FIGURE LEGENDS

Figure 1A: 22-year trend in incidence of scleritis in the UK (per 100,000 person-years, with 95% confidence intervals). See Supplementary eTable 3 for data. **Figure 1B**: Age group and sex-specific cumulative incidence of scleritis for the period 1997-2018 (per 100,000 person-years, with 95% confidence intervals). See Supplementary eTable 4 for data.

Figure 2: Forest plots displaying the adjusted odds ratio (left) of a prevalent diagnosis of an I-IMID at baseline, and adjusted hazard ratio (right) of an incident diagnosis of an I-IMID during follow-up, comparing 3005 patients diagnosed with scleritis and 12020 control patients. See Table 3 for data.

Figure 3: Nelson-Aalen curves comparing scleritis cases versus controls for the cumulative hazard during 15-year cumulative follow-up of developing A) Granulomatosis with polyangiitis; B) Behcet's Disease; C) Sjogren's syndrome; D) Rheumatoid arthritis. Example interpretation: By 5 years follow-up, an estimated 3·86% (n=116/3005) scleritis patients are diagnosed with rheumatoid arthritis, compared to 0·79% (n=95/12020) without scleritis. Note the variable y-axis scales.

A

Incidence (per 100,000 person-years, with 95% CI)

8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00

1997 1999 2001 2003 2005 2007 2009 2011 2013 2015 2017

Year

B

Incidence (per 100,000 person-years, with 95% CI)

6
5
4
3
2
0

— Male — Female

1-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89 90-99

Age group (years)

Adjusted Odds Ratio (95% CI)	Immune-mediated inflammatory diseases	Adjusted Hazard Ratio (95% CI)
	IMIDs, NON-INFECTIOUS	
50.66 (11.94, 214.93)	Granulomatosis with polyangiitis	96.36 (12.99, 715.00)
9.09 (1.57, 52.53)	Behcet's Disease	17.45 (1.94, 156.74)
7.14 (3.50, 14.57)	Sjogren' syndrome	8.53 (3.35, 21.67)
6.96 (1.99, 24.38)	Reiter's syndrome	
5.70 (4.40, 7.39)	Rheumatoid arthritis	4.22 (3.32, 5.39)
5.44 (0.43, 68.09)	Dermato- or polymyositis	5.38 (0.33, 88.57)
5.37 (2.87, 10.05)	Vasculitis, other	6.68 (3.22, 13.86)
3.83 (1.74, 8.44)	Giant cell arteritis (GCA)	2.36 (1.03, 5.44)
3.60 (2.28, 5.67)	Crohn's disease	4.16 (2.90, 7.58)
3.47 (1.90, 6.33)	Systemic lupus erythematosus	8.49 (3.35, 21.74)
3.39 (1.78, 6.42)	Ankylosing spondylitis	3.44 (1.21, 9.76)
2.61 (1.53, 4.46)	Sarcoidosis	3.09 (1.15, 8.27)
2.40 (0.97, 5.97)	Lymphoma	
2.31 (1.57, 3.40)	Polymyalgia rheumatica	1.11 (0.70, 1.75)
2.20 (1.49, 3.27)	Ulcerative colitis	1.77 (0.99, 3.16)
1.62 (0.89, 2.95)	Coeliac disease	1.07 (0.43, 2.69)
1.36 (0.12, 15.50)	SWEET syndrome	
1.34 (1.10, 1.63)	Psoriasis	1.22 (0.92, 1.60)
1.29 (0.64, 2.58)	Multiple Sclerosis	1.12 (0.41, 3.06)
1.20 (0.94, 1.54)	Gout	0.96 (0.73, 1.24)
1.11 (0.60, 2.06)	Thyroid disease, autoimmune	1.16 (0.45, 2.94)
1.04 (0.54, 2.00)	Vitiligo	1.33 (0.55, 3.22)
	Waldenstrom's macroglobulinaemia	0.69 (0.08, 6.35)
	IMIDs, INFECTIOUS	
4.12 (0.50, 30.33)	Lyme disease	8.41 (1.43, 49.39)
3.76 (0.45, 31.45)	Toxoplasmosis	
2.56 (0.37, 17.62)	Aspergillus	1.72 (0.17, 17.40)
1.61 (1.34, 1.94)	Herpetic infection	1.53 (1.16, 2.02)
1.51 (1.00, 2.27)	Measles	
1.50 (1.09, 2.08)	Epstein Barr virus	0.72 (0.08, 6.68)
1.35 (0.83, 2.19)	Tuberculosis	3.37 (0.82, 13.78)
0.63 (0.14, 2.88)	Mumps	11.11 (1.05, 117.16)
	Syphilis	
	CLINICAL PHENOTYPES	
2.71 (1.15, 6.38)	Optic neuritis	
17.30 (13.29, 22.80)	Uveitis	20.08 (14.02, 28.76)

.1   1   100
Decreased Risk   Increased Risk

.1   1   10   100 300
Decreased Risk   Increased Risk