

SUPPLEMENTARY TABLES AND FIGURES

eTable 1 Comparison of the scleritis systemic disease associations reported in a selection of eye clinic retrospective cohort studies including at least 100 patients

Country, years, and citation	N	Clinical phenotype of scleritis, patient characteristics and outcome	Percentage % with systemic disease	Most frequent disease associations, % and treatment
UK, 1964-1974. Watson and Hayreh. ¹	207	Diffuse anterior (57.5%), Nodular anterior (64.7%), necrotizing (20.3%), posterior (2.9%). 30% had anterior uveitis. Bilateral (45%). Demographic: Female: Male >1.5:1; women had peak incidence in 3 rd and 6 th decades, men had peak incidence in 4 th decade. OUTCOME: 20.3% lost $\geq$ 2-lines visual acuity during follow-up	46.0%	Rheumatoid arthritis (10.1%), ankylosing spondylitis (1.0%), psoriatic arthritis (3), SLE (1.0%), PAN (1.0%), systemic vasculitis (1.0%), GPA (0.5%), relapsing polychondritis (1.0%), rheumatic heart disease (1.0%), palindromic rheumatoid (1.0%), rosacea (1.0%), gout (2.4%), Cogan's (1.4%), thyrotoxicosis (0.5%) Active TB (1.9%), syphilis (2.9%), herpes zoster (7.7%), herpes simplex (1%). Treatment: systemic corticosteroid (9.7%).
UK, 1974-1996. McCluskey et al. ²	137	All posterior scleritis cases, nil necrotizing. 34% had associated anterior scleritis, 18% had swollen optic discs, 2% had uveitis. Bilateral (35.4%). Demographic: Female 64.6%; mean age 49.3 years. OUTCOME: 31.1% visual loss, of which 10.2% blind, 7.3% 6/24-6/60, 5.1% 6/12-6/18.	28.3%	Rheumatoid arthritis (3.6%), Systemic vasculitis (2.9%),GPA (2.9%), VKH (1.5%), relapsing polychondritis (3), thyroid disease (1.5%), sarcoidosis (1.5%), primary biliary cirrhosis (0.7%), SLE (0.7%), multiple myeloma (0.7%), lymphoma (0.7%), pancreatic carcinoma (0.7%), ankylosing spondylitis (0.7%), PAN (0.7%). Idiopathic in 49.6%. Treatment: 18% on medication for active disease at the time of the study.
UK and India, 2004-2013. Lavric et al. ³	114	All posterior scleritis. 19.3% had anterior scleritis at presentation. Bilateral(15.8%). Demographic: Female 71.7%; mean age 45.9 (sd 16.8) years. 74 patients from UK, 40 from India. 52.7% Asian. OUTCOME: 38.6% VA <6/12 at presentation.	37.7%	Rheumatoid arthritis (12.3%), SLE (4.4%), pANCA+ vasculitis (5.3%), Crohn' disease (2.6%), sarcoidosis (1.8%), ankylosing spondylitis (1.8%), thyroid disease (1.8%), GPA (0.9%), fibromyalgia (0.9%), congenital rubella syndrome (0.9%), psoriatic arthritis (0.9%), polyarteritis nodosa (0.9%), Lyme disease (0.9%), varicella zoster virus (0.9%), necrobiotic xanthogranuloma (0.9%). Idiopathic (62.3%). Treatment: Systemic steroids (38.6%), IV methylprednisolone (8.8%), any immunosuppressants (32.5%), including mycophenolate mofetil (7.0%) and azathioprine (17.5%).
USA and Spain. 2005-2010. Sainz de la Maza et al. ⁴	500	75% diffuse anterior, 14.2% nodular anterior, 4% necrotizing anterior, 0.6% scleromalacia perforans. posterior n=31. Associated anterior uveitis 26.4%, PUK 7.4%. Bilateral (41.2%). Demographic: Female 71.0%; mean age 53.7 (range 12-96) years. OUTCOME: Decreased vision at presentation 15.8%	35.8% overall, 19.3-80% by subtype of scleritis	24.8% connective tissue or vasculitic diseases (rheumatoid arthritis (6.4%), HLAB27-associated (4.8%), GPA (2.8%), relapsing polychondritis (2.2%), IBD associated arthritis (2.2%), SLE (2.0%), anylosing spondylitis (1.2%), psoriatic arthritis (1%), Behçet' (0.4%), TINU (0.4%), GCA (0.2%), JIA (0.2%), mixed connective tissue (0.2%), Cogan disease (0.2%); 9.6% infectious diseases (7.0% viruses, 2.0% bacteria, 0.4% parasites, 0.2% fungi; Miscellaneous diseases (1.0% rosacea and 0.4% foreign body). Treatment: Not reported
USA, 1984-2002. Akpek et al. ⁵	243	Diffuse anterior (66.4%), plus keratitis (18.2%) and uveitis (29.8%).Bilateral (50%). Demographic: Female 70%; median age 52 years, range 5 to 93. OUTCOME: Not reported	44.0%	37% had rheumatic disease: rheumatoid arthritis (15.2%); systemic vasculitis (9.1%) including ANCA+ vasculitis but nil systemic, GPA, PAN, Takayasu's, GCA, Behçet' disease; SLE (4.1%), relapsing polychondritis (1.6%), IBD (3.3%), spondyloarthropathy (1.7%). 7.0% had infectious cause: herpes zoster (4.5%), herpes simplex (1.6%), syphilis (0.4%), Lyme disease (0.4%). Treatment: Not reported
USA, 1978-2010, Multicentre SITE cohort	825	100% non-necrotising anterior scleritis. Bilateral (50.7%). Demographic: Female 60.0%; 49.5% aged 40-59 years.; 60% White, 15% Black, 3.0% Hispanic, 21% other.	38.0%	Rheumatoid arthritis (18%), SLE (5%), GPA (4%). Others included relapsing polychondritis (2%), Crohn' disease (2%), Ulcerative Colitis (1%), Sjogren' Syndrome (2%), spondyloarthropathies (2%).

study. Kempen et al. ⁶		OUTCOME: 36.2% achieved remission during follow-up.		Treatment: Alkylating agents (11%), TNF inhibitor (12%), antimetabolite (38%), rituximab (1%), other immune modulatory therapy (5%).
Japan, 2004-2015. Tanaka et al. ⁷	123	76 diffuse anterior, 17 anterior nodular, 10 anterior necrotizing, 20 posterior. Associated anterior uveitis 38.2%, PUK 8.1%, CMO 6.5%, optic disc swelling 8.9%. Bilateral (41.5%). Demographic: Female 55.3%; mean age 57.8 (sd16.4, range 15-83) years. OUTCOME: Decreased vision (loss of 3 lines of LogMAR chart from baseline to last visit in worse eye) in 16.9%. 54.5% recurrent scleritis.	31.7%	26.0% autoimmune: Rheumatoid arthritis (n=8), ANCA+ vasculitis (n=7), relapsing polychondritis (n=6), psoriasis (n=2), Behçet' disease (n=2), thyroid ophthalmopathy (n=2). 5.7% infectious: herpes zoster viruses (n=5). Treatment: Systemic immunosuppression (52.8%) with corticosteroid (45.5%), methotrexate (11.4%), cyclophosphamide (4.1%), TNF α inhibitor (3.3%), ciclosporine (2.4%), azathioprine (2.4%), mycophenolate mofetil (1.6%), tocilizumab (1.6%), rituximab (0.8%).
Japan, 2011-2015. Yoshida et al. ⁸	128	Diffuse anterior (32.8%), episcleritis (27.3%), nodular anterior (18.0%), necrotizing anterior (17.2%), posterior scleritis (4.7%). Bilateral (33.6%). Demographic: Female 55.5%; mean age at onset 54.3 (sd 17.4) years. OUTCOME: Not reported for the whole cohort.	31.3%	ANCA+ vasculitis (7.8%), rheumatoid arthritis (6.3%), haematological malignancy (3.1%), Herpetic infection (2.3%), Ulcerative colitis (2.3%), SLE (1.2%), Hepatitis C (1.2%), relapsing polychondritis (0.8%), pemphigus (0.8%), interstitial nephritis (0.8%), gout (0.8%), Still's disease (0.8%), psoriasis (0.8%), malignant tumour (0.8%). Treatment: Systemic immunosuppression. (50%, including corticosteroid, cyclophosphamide, ciclosporine, methotrexate, azathioprine, salazosulfapyridine), plus n=3 rituximab, and n=1 adalimumab
Singapore, 11-year cohort. Bin Ismail et al. ⁹	120	Diffuse anterior (62.5%), nodular anterior (20.8%), necrotizing anterior (5.8%), posterior scleritis (10.8%). Anterior uveitis in 42.5%, optic disc swelling in 2.5%, CMO in 2.5%. Bilateral (30.8%). Demographic: Female 56.7%; mean age 48.6 (sd 15.9) years; 69.2% Chinese, 12.5% Indian, 11.7% Malay and 6.7% Other races/ethnicities. OUTCOME: Recurrence in 16.7%.	34.1%	25.8% autoimmune: rheumatoid arthritis (7.5%), GPA (4.2%), relapsing polychondritis (3.3%), Sjogren' syndrome (3.3%), psoriatic arthropathy (1.7%). 8.3% infective (latent TB in 10 patients). Treatment: Corticosteroids (53.3%) including IV methylprednisolone (n=5); 26.7% with second-line, including azathioprine (13.3%), methotrexate (9.2%), MMF (5%), sulphasalazine (5%), hydroxychloroquine (4.2%), cyclophosphamide (3.3%), cyclosporine (3.3%) and biologic (1.7%, all infliximab).
Turkey, 1995-2006. Erkanli et al. ¹⁰	114	Diffuse (42%), nodular (42%), necrotizing (6%), posterior (9%), no scleromalacia perforans. 15% had anterior uveitis, 2% had disc swelling, 4% had CMO. Bilateral (31%). Demographic: Female 71.9%; mean age 48 (sd 17.7) years. OUTCOME: Loss of visual acuity (>2 lines) in 12.3%.	32%	Rheumatoid arthritis (7%), GPA (5%), SLE (3%), Behçet' disease (2%), Ulcerative colitis (2%), Sjogren' syndrome (3%), JIA (2%), sarcoidosis (3%), TB (1%), ankylosing spondylitis (1%), Familial Mediterranean Fever (1%), relapsing polychondritis (1%), monoclonal gammopathy (1%), leukocytoclastic vasculitis (1%), psoriatic arthritis (1%). Treatment: Systemic (96%), of which 47% had first line corticosteroids with or without non-steroidal anti-inflammatories. 39% had second-line immunosuppression, including methotrexate in n=34, cyclophosphamide in n=7 and azathioprine in n=3. One switched to MMF, and n=2 received anti-TNF α biologic therapy.
Egypt, 2013-2017. El Latif et al. ¹¹	303	Anterior (91.4%, including nodular 44.9%, diffuse 25.1%, necrotizing with inflammation 16.8%), scleromalacia perforans(4.6%) and posterior (8.3%). Bilateral (33.6%). Demographic: Female 74.9%; mean age 46.1(sd13.3, range 8-81) years. OUTCOME: 9.6% lost $\geq$ 2 lines visual acuity despite treatment	47.8%	Rheumatoid arthritis (12.9%), GPA (7.6%), SLE (3.6%), Behçet' disease (2.0%), Familial Mediterranean Fever (1.7%), relapsing polychondritis (1.3%), ulcerative colitis (1.3%), sarcoidosis (1.0%), polyarteritis nodosa (1.0%), primary Sjogren' syndrome (1.0%), Ankylosing spondylitis (0.7%), rheumatoid factor positive Juvenile arthritis (0.7%), undifferentiated. Spondyloarthropathy (0.7%), psoriasis (0.3%). In 6.6% scleritis preceded diagnosis. Infectious: Presumed TB (6.9%), varicella zoster virus (2.3%), herpes simplex virus (0.7%), brucellosis (0.3%)

				Prior ocular surgery in 21.7% (most frequently pterygium surgery). Treatment: Systemic corticosteroids (68.0%), second-line (33%), including methotrexate (n=66), cyclophosphamide (n=12), cyclosporine A (n=10), mycophenolate mofetil. (n=10), azathioprine (n=7), and infliximab (n=2).
Brazil, 2001-2006.de Oliveira Machado et al. ¹²	100	Diffuse and nodular anterior (71%), necrotizing anterior (3%), posterior (24%), scleromalacia perforans (2%). Bilateral (21%). Demographic: Female 69%.	35%	No English language breakdown available. Treatment: Systemic immunosuppression (18%).

References

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eTable 2: Clinical ‘Read’ codes included in case definition of scleritis

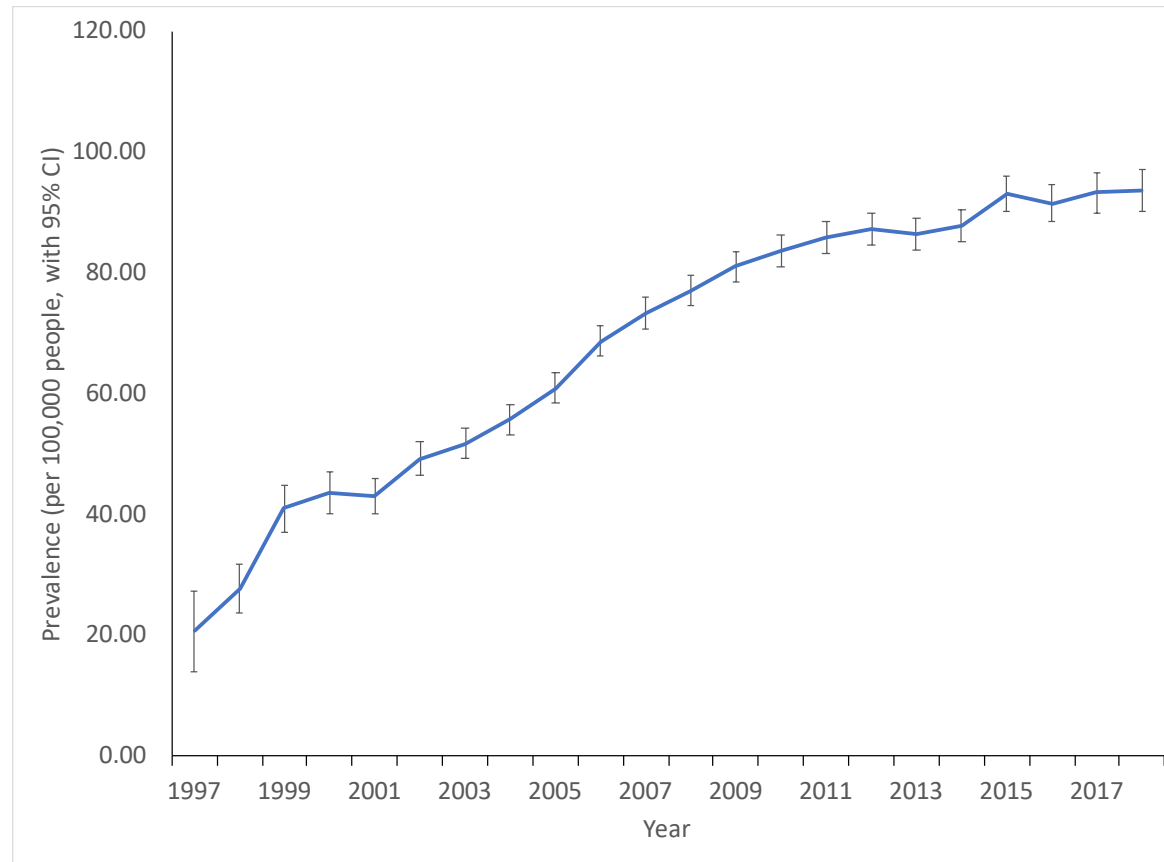
Read code	Read code label	Frequency (n patients)
F4K0.12	Scleritis	2630
F4K0.00	Scleritis and episcleritis	164
F4K0000	Unspecified scleritis	75
F4K0300	Anterior scleritis	63
F4K0400	Scleromalacia perforans	25
F4K0700	Posterior scleritis	24
F4K0500	Sclerokeratitis	23
F4K0600	Brawny scleritis	1
TOTAL		3005

eTable 3: 22-year data on annual incidence (per 100,000 person-years) and point prevalence (per 100,000 people) of scleritis in the UK

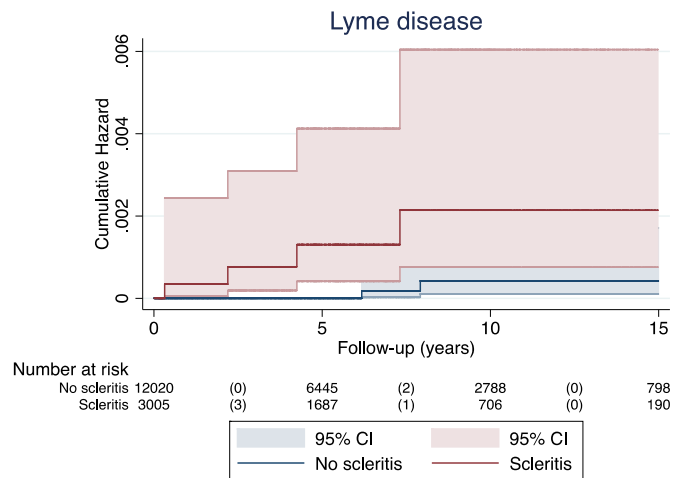
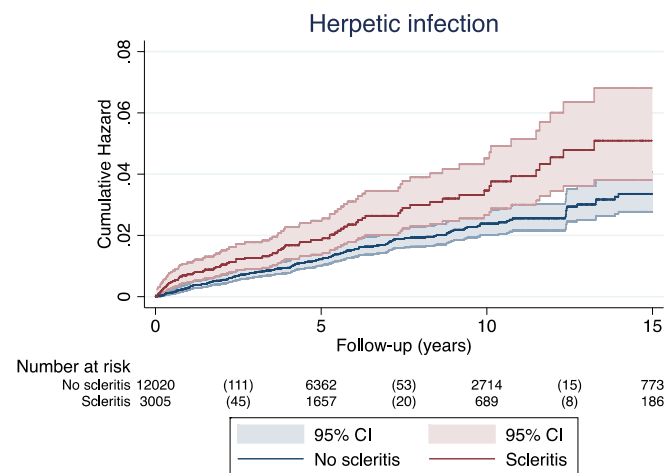
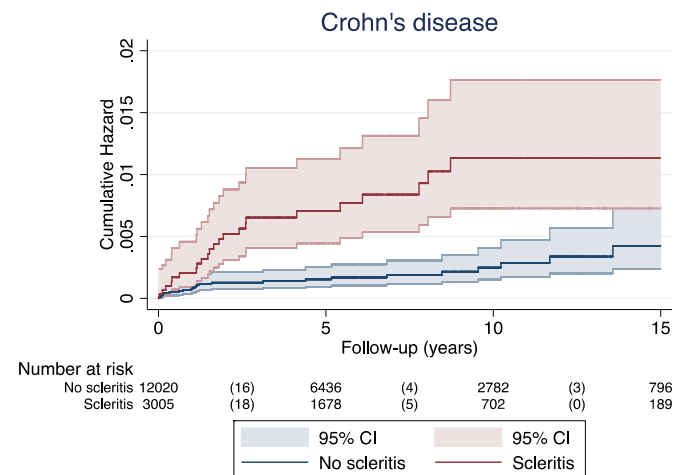
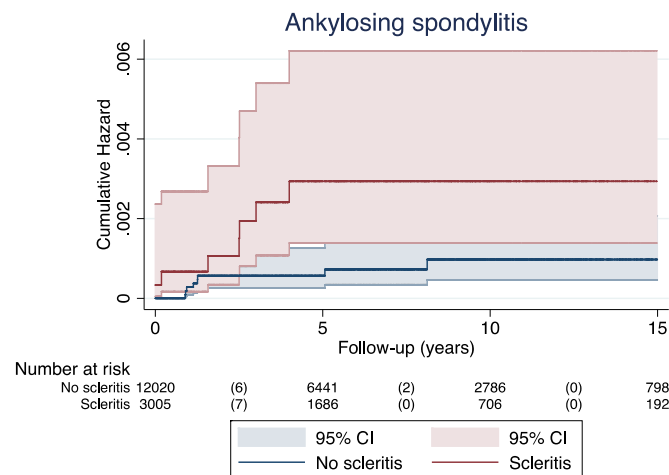
	INCIDENCE			PREVALENCE		
Year	n	Person-years	Incidence (95% CI)	n	N	Prevalence (95% CI)
1997	16	378046	4.23 (2.16-6.31)	38	183385	20.72 (14.13-27.31)
1998	39	825161	4.73 (3.24-6.21)	186	670096	27.76 (23.77-31.75)
1999	70	1163537	6.02 (4.61-7.43)	437	1065766	41.00 (37.16-44.85)
2000	72	1500083	4.80 (3.69-5.91)	582	1333621	43.64 (40.10-47.18)
2001	120	2185051	5.49 (4.51-6.47)	878	2040725	43.02 (40.18-45.87)
2002	130	2751159	4.73 (3.91-5.54)	1221	2479272	49.25 (46.49-52.01)
2003	157	3308013	4.75 (4.00-5.49)	1608	3107019	51.75 (49.23-54.28)
2004	169	3562864	4.74 (4.03-5.46)	1938	3471125	55.83 (53.35-58.32)
2005	164	3901788	4.20 (3.56-4.85)	2268	3724667	60.89 (58.39-63.40)
2006	174	4130162	4.21 (3.59-4.84)	2811	4091387	68.71 (66.17-71.24)
2007	172	4290027	4.01 (3.41-4.61)	3122	4258181	73.32 (70.75-75.89)
2008	165	4544022	3.63 (3.08-4.19)	3410	4423710	77.08 (74.50-79.67)
2009	195	4770972	4.09 (3.51-4.66)	3847	4744400	81.09 (78.52-83.65)
2010	196	4754805	4.12 (3.55-4.70)	4025	4813391	83.62 (81.04-86.20)
2011	195	4799242	4.06 (3.49-4.63)	4115	4795047	85.82 (83.20-88.44)
2012	176	4961364	3.55 (3.02-4.07)	4261	4887926	87.17 (84.56-89.79)
2013	166	4870146	3.41 (2.89-3.93)	4330	5008807	86.45 (83.87-89.02)
2014	145	4591176	3.16 (2.64-3.67)	4150	4727089	87.79 (85.12-90.46)
2015	140	4093402	3.42 (2.85-3.99)	4125	4428419	93.15 (90.31-95.99)
2016	107	3535174	3.03 (2.45-3.60)	3422	3738221	91.54 (88.48-94.61)
2017	96	3171188	3.03 (2.42-3.63)	3160	3387683	93.28 (90.03-96.53)
2018	82	2938304	2.79 (2.19-3.39)	2831	3023960	93.62 (90.17-97.07)

eTable 4: Age group and sex-specific cumulative incidence of scleritis for the period 1997-2018 (per 100,000 person-years, with 95% confidence intervals)

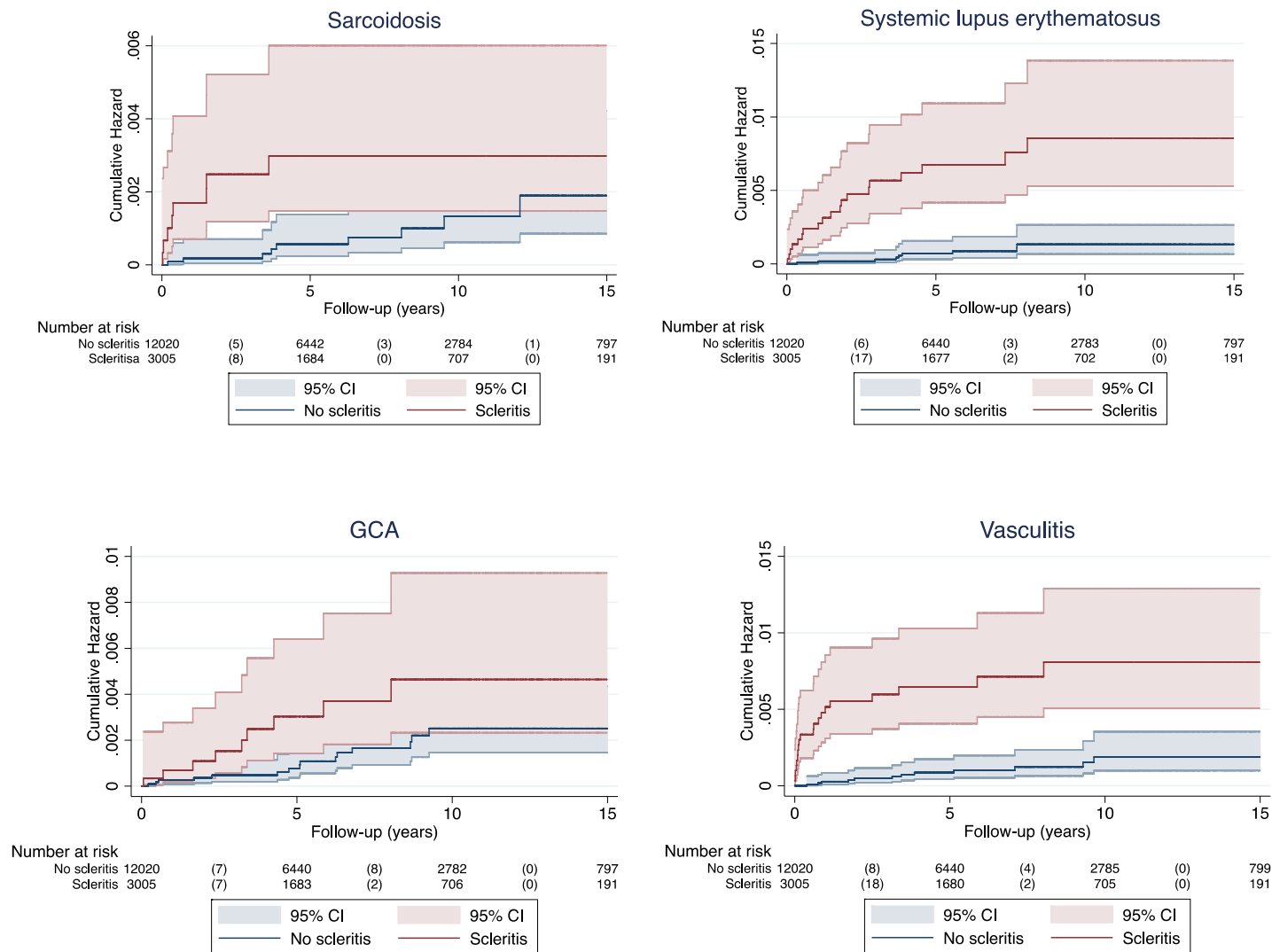
	Male			Female		
Age group (years)	n	N	Cumulative incidence (95% CI)	n	N	Cumulative incidence (95% CI)
0-9	31	39.63	0.78 (0.55-1.11)	23	37.35	0.62 (0.41-0.93)
10-19	47	43.54	1.08 (0.81-1.44)	47	38.51	1.22 (0.92-1.62)
20-29	72	45.16	1.59 (1.27-2.01)	122	42.68	2.86 (2.39-3.41)
30-39	160	53.74	2.98 (2.55-3.48)	279	52.69	5.29 (4.71-5.95)
40-49	201	58.86	3.41 (2.97-3.92)	379	57.15	6.63 (6.00-7.33)
50-59	209	52.64	3.97 (3.47-4.55)	406	51.57	7.87 (7.14-8.68)
60-69	215	41.57	5.17 (4.52-5.91)	306	42.78	7.15 (6.39-8.00)
70-79	129	26.90	4.80 (4.04-5.70)	185	31.75	5.83 (5.04-6.73)
80-89	50	11.53	4.33 (3.29-5.72)	72	18.52	3.89 (3.09-4.90)
90 and above	1	1.49	0.67 (0.09-4.75)	12	4.08	2.94 (1.67-5.18)



eFigure 1: 22-year trend in prevalence of scleritis in the UK (per 100,000 people, with 95% confidence intervals)



eFigure 2: Nelson-Aalen curves comparing the cumulative hazard of developing a sample of significantly associated incident I-IMIDs during 15-year cumulative follow-up, in scleritis cases versus controls (note the variable y-axis scales).



eFigure 2 (Continued): Nelson-Aalen curves comparing the cumulative hazard of developing a sample of significantly associated incident I-IMIDs during 15-year cumulative follow-up, in scleritis cases versus controls (note the variable y-axis scales).