

Appendix 1**READ Codes:****Ulcerative Colitis:**

Code	Description
J410z00	Ulcerative proctocolitis NOS
N031000	Arthropathy in ulcerative colitis
J41z.00	Idiopathic proctocolitis NOS
J41y.00	Other idiopathic proctocolitis
J412.00	Ulcerative (chronic) ileocolitis
J413.00	Ulcerative pancolitis
Jyu4100	[X]Other ulcerative colitis
N045400	Juvenile arthritis in ulcerative colitis
J410000	Ulcerative ileocolitis
J411.00	Ulcerative (chronic) enterocolitis
J41..00	Idiopathic proctocolitis
J410.00	Ulcerative proctocolitis
J410300	Ulcerative proctitis
J410400	Exacerbation of ulcerative colitis
J41..12	Ulcerative colitis and/or proctitis
J410100	Ulcerative colitis
J410200	Ulcerative rectosigmoiditis
J41yz00	Other idiopathic proctocolitis NOS

Crohn's Disease:

Code	Description
J400.00	Regional enteritis of the small bowel
J400000	Regional enteritis of the duodenum
J400100	Regional enteritis of the jejunum
J40..00	Regional enteritis - Crohn's disease
N031100	Arthropathy in Crohn's disease
ZR3S.11	CDAI - Crohn's disease activity index
J402.00	Regional ileocolitis
J401z11	Crohn's colitis
J400200	Crohn's disease of the terminal ileum
J400300	Crohn's disease of the ileum unspecified
J400400	Crohn's disease of the ileum NOS
J400500	Exacerbation - Crohn's disease - small intestine
J08z900	Orofacial Crohn's disease
J400z00	Crohn's disease of the small bowel NOS
J40z.00	Regional enteritis NOS
J401000	Regional enteritis of the colon
J401100	Regional enteritis of the rectum
J401200	Exacerbation - Crohn's disease - large intestine
J40..12	Granulomatous enteritis
J40..11	Crohn's disease
ZR3S.00	Crohn's disease activity index
J401.00	Regional enteritis of the large bowel
J401z00	Crohn's disease of the large bowel NOS
Jyu4000	[X]Other Crohn's disease
N045300	Juvenile arthritis in Crohn's disease
J40z.11	Crohn's disease NOS

Ophthalmic Extraintestinal Manifestations (IBD associated Ocular Inflammation):

Code	Description
F443.11	Uveitis NOS
F443000	Anterior uveitis
F441200	Chronic anterior uveitis
F443.00	Unspecified iridocyclitis
F443100	Iritis
F440z00	Acute or subacute iritis NOS
F442.00	Certain types of iridocyclitis
F442z00	Certain types of cyclitis NOS
F441z00	Chronic iridocyclitis NOS
F44..12	Iridocyclitis
F441.00	Chronic iridocyclitis
F441.11	Chronic iritis
F441000	Unspecified chronic iridocyclitis
F441100	Chronic iridocyclitis due to disease
F440300	Recurrent iridocyclitis
F440500	Secondary noninfected iridocyclitis
F440000	Unspecified acute iridocyclitis
F440100	Unspecified subacute iridocyclitis
F440200	Primary iridocyclitis
F440.11	Iritis - acute
F440.00	Acute and subacute iridocyclitis
F4K0z00	Scleritis or episcleritis NOS
F4K0.12	Scleritis
F4K0.11	Episcleritis
F4K0.00	Scleritis and episcleritis
FyuD800	Scleritis+episcleritis in diseases
F4K0700	Posterior scleritis
F4K0000	Unspecified scleritis
F4K0200	Nodular episcleritis
F4K0300	Anterior scleritis
F4K0600	Brawny scleritis
F4K0100	Episcleritis periodica fugax

Appendix 2. Multivariable Cox hazard models for IBD associated Ocular Inflammation

	Inflammatory Bowel Disease				Ulcerative colitis			Crohn's Disease				
	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value
All IAOs	2.25	1.89	2.68	<0.001	1.65	1.30	2.09	<0.001	3.37	2.59	4.40	<0.001
Sex (reference) Male	1.00				1.00				1.00			
Female	0.92	0.77	1.09	0.342	0.78	0.62	0.98	0.030	1.17	0.89	1.54	0.264
Age Category (reference) <18 years	1.00				1.00				1.00			
18-30	1.75	1.05	2.92	0.033	1.76	0.83	3.76	0.143	1.62	0.80	3.27	0.181
30-40	1.42	0.86	2.35	0.167	1.93	0.94	3.96	0.072	0.99	0.49	2.01	0.971
40-50	1.02	0.62	1.69	0.933	1.54	0.75	3.15	0.238	0.60	0.29	1.24	0.171
50-60	1.22	0.74	2.01	0.439	1.75	0.86	3.59	0.125	0.78	0.38	1.60	0.504
60-70	1.01	0.60	1.70	0.975	1.46	0.70	3.06	0.312	0.64	0.30	1.36	0.246
>70	0.76	0.44	1.31	0.320	1.02	0.47	2.19	0.968	0.55	0.25	1.19	0.129
Smoking Status (reference) current smoker	1.00				1.00				1.00			
non smoker	0.77	0.63	0.95	0.015	1.16	0.86	1.56	0.334	0.48	0.36	0.64	<0.001
Charlson comorbidity score (reference) 0	1.00				1.00				1.00			
1	1.11	0.90	1.37	0.313	1.14	0.86	1.50	0.363	1.09	0.79	1.50	0.616
>=2	1.06	0.78	1.43	0.709	1.18	0.81	1.73	0.386	0.89	0.54	1.44	0.626
Body mass index (reference) <25kg/m ²	1.00				1.00				1.00			
25-30Kg/m ²	0.95	0.77	1.18	0.658	0.88	0.67	1.17	0.380	1.06	0.75	1.49	0.752
>30Kg/m ²	0.89	0.69	1.14	0.354	0.73	0.52	1.03	0.074	1.14	0.78	1.66	0.508
Missing	0.87	0.67	1.14	0.311	0.78	0.55	1.10	0.162	1.02	0.68	1.54	0.908
Townsend (least deprived – reference) 1	1.00				1.00				1.00			
2	1.08	0.84	1.39	0.545	1.15	0.83	1.60	0.39	0.98	0.65	1.47	0.919
3	1.11	0.86	1.44	0.424	1.20	0.86	1.67	0.276	0.98	0.65	1.48	0.932
4	0.92	0.69	1.22	0.571	0.84	0.57	1.24	0.378	1.02	0.67	1.55	0.929
5	0.94	0.68	1.30	0.689	0.87	0.55	1.36	0.537	1.02	0.63	1.63	0.948
Missing	0.80	0.59	1.09	0.164	0.89	0.60	1.31	0.545	0.69	0.42	1.14	0.146
Anaemia** (reference) no	1.00				1.00				1.00			
yes	1.68	1.17	2.42	0.005	1.20	0.69	2.08	0.519	2.34	1.44	3.81	<0.001
Abdominal pain† (reference) no	1.00				1.00				1.00			
yes	1.56	0.99	2.44	0.054	1.27	0.65	2.47	0.488	1.94	1.05	3.58	0.033
Lower gastrointestinal bleeding† (reference) no	1.00				1.00				1.00			
yes	6.45	4.48	9.29	<0.001	8.13	5.23	12.64	<0.001	4.25	2.23	8.11	<0.001
Loperamide prescription† (reference) no	1.00				1.00				1.00			
yes	2.09	1.34	3.27	0.001	2.44	1.34	4.44	0.004	1.82	0.94	3.52	0.077
Diarrhoea† (reference) no	1.00				1.00				1.00			
yes	4.46	3.25	6.13	<0.001	3.37	2.12	5.34	<0.001	5.99	3.87	9.27	<0.001
Axial arthropathy* (reference) no	1.00				1.00				1.00			
yes	2.77	1.77	4.36	<0.001	2.49	1.32	4.71	0.005	3.15	1.66	5.99	<0.001

† coded within 6 months of Index date; ‡ <11.9g/dL (females); <12.9g/dL (males); *recorded at baseline
EIM: extraintestinal manifestations

Appendix 3. Demographic details of the anterior uveitis and episcleritis & scleritis cohorts and their controls

	Anterior uveitis subjects	Matched subjects without anterior uveitis	Episcleritis & Scleritis subjects	Matched subjects without episcleritis & scleritis
Number of subjects	22,547	89,422	17,439	68,823
Median py of follow-up (IQR)	5.1 (2.3-9.1)	4.9 (2.2-8.9)	5.9 (2.7-9.8)	5.5 (2.4-9.5)
Median age (IQR)	53 (39-68)	52 (38-67)	48 (36-61)	47 (35-59)
Age category (%)				
<18 years	887 (3.9)	3,952 (4.3)	1266 (7.3)	5223 (7.6)
18-30	1,934 (8.5)	8,239 (9.1)	1403 (8.1)	5994 (8.7)
30-40	3171 (13.6)	12,690 (14.0)	2702 (15.5)	11494 (16.7)
40-50	3,071 (17.7)	16,373 (18.2)	3859 (22.1)	15480 (22.5)
50-60	4,020 (17.7)	15,933 (17.8)	3521 (20.2)	13915 (20.2)
60-70	3,587 (15.8)	14,051 (15.7)	2667 (15.3)	10026 (14.6)
>70	5,190 (22.8)	18,341 (21.0)	2021 (11.6)	6691 (9.7)
Female sex (%)	12,145 (53.5)	47,868 (53.4)	10860 (62.3)	42939 (62.4)
Townsend Index (%)				
1 - least deprived	4,822 (21.3)	19,181 (21.4)	4381 (25.1)	16706 (24.3)
2	4,316 (19.0)	17,162 (19.1)	3479 (20.0)	13279 (19.3)
3	4,058 (17.9)	15,946 (17.8)	3181 (18.2)	12636 (18.4)
4	3,577 (15.8)	13,811 (15.4)	2480 (14.2)	10281 (14.9)
5	2,498 (11.0)	9,652 (10.8)	1444 (8.3)	6051 (8.8)
missing	3,428 (15.1)	13,827 (15.4)	2474 (14.2)	9870 (14.3)
Charlson comorbidity score (%)				
0	13,574 (59.8)	60,673 (67.7)	11671 (66.9)	49861 (72.5)
1	5,033 (22.2)	17,263 (19.3)	3697 (21.2)	12641 (18.4)
>/=2	4,092 (18.0)	11,643 (13.0)	2071 (11.9)	6321 (9.2)
Smoking status (%)				
current smoker	4,126 (18.2)	16,754 (18.7)	2738 (15.7)	13079 (19.0)
non- smoker	18,573 (81.8)	72,825 (81.3)	14701 (84.3)	55744 (81.0)
Body mass index (%)				
<25kg/m2	7,344 (32.4)	29,447 (32.9)	5908 (33.9)	23455 (34.1)
25-30Kg/m2	6,709 (29.5)	24,625 (27.4)	4940 (28.3)	17708 (25.7)
>30Kg/m2	4,661 (20.6)	16,187 (18.1)	3322 (19.1)	11885 (17.3)
missing	3,985 (17.6)	19,320 (21.6)	3269 (18.8)	15775 (22.9)
Anaemia^{††} (%)	1,490 (6.5)	3,503 (3.9)	691 (4.0)	2126 (3.1)
Abdominal pain[†] (%)	469 (2.1)	1,421 (1.6)	402 (2.3)	1212 (1.8)
Lower gastrointestinal bleeding[†] (%)	204 (0.9)	642 (0.7)	172 (1.0)	446 (0.7)
Loperamide prescription[†] (%)	367 (1.6)	988 (1.1)	213 (1.2)	555 (0.8)
Diarrohea[†] (%)	552 (2.4)	1,441 (1.6)	459 (2.6)	1073 (1.6)
B27 positive at Index	34 (0.2)	2 (0.0)	3 (0.02)	5 (0.01)
Axial arthropathy at baseline	734 (3.2)	588 (0.7)	221 (1.3)	494 (0.7)

[†] coded within 6 months of Index date

[‡] <11.9g/dL (females); <12.9g/dL (males)

Appendix 4. Multivariable Cox hazard models for anterior uveitis associated with inflammatory bowel disease

	Inflammatory Bowel Disease				Ulcerative colitis				Crohn's Disease			
	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value
Anterior uveitis	3.39	2.70	4.25	<0.001	2.23	1.63	3.04	<0.001	5.77	4.04	8.24	<0.001
Sex (reference) Male	1.00				1.00				1.00			
Female	0.81	0.65	1.02	0.077	0.75	0.56	1.02	0.067	0.89	0.63	1.26	0.500
Age Category (reference) <18 years	1.00				No <18 cases	-	-	-	1.00			
18-30	2.60	1.07	6.35	0.035	1.00 (reference)					1.46	0.56	3.810
30-40	2.25	0.93	5.40	0.07	1.45	0.73	2.92	0.291	0.89	0.34	2.34	0.815
40-50	1.56	0.65	3.77	0.321	1.22	0.61	2.42	0.572	0.48	0.18	1.30	0.148
50-60	1.91	0.79	4.60	0.149	1.38	0.69	2.73	0.361	0.66	0.25	1.76	0.407
60-70	1.36	0.55	3.35	0.501	1.21	0.60	2.46	0.599	0.33	0.11	0.96	0.041
>70	1.05	0.42	2.62	0.909	0.96	0.46	1.99	0.913	0.24	0.08	0.71	0.01
Smoking Status (reference) current smoker	1.00				1.00				1.00			
non smoker	0.86	0.65	1.13	0.282	1.32	0.88	1.99	0.185	0.55	0.38	0.80	0.002
Charlson comorbidity score (reference) 0	1.00				1.00				1.00			
1	0.93	0.70	1.24	0.621	1.02	0.70	1.50	0.914	0.84	0.54	1.30	0.434
>=2	0.99	0.68	1.45	0.955	1.06	0.66	1.73	0.799	0.90	0.49	1.67	0.748
Body mass index (reference) <25kg/m ²	1.00				1.00				1.00			
25-30Kg/m ²	1.11	0.84	1.46	0.48	0.91	0.63	1.31	0.598	1.44	0.94	2.21	0.09
>30Kg/m ²	0.82	0.58	1.16	0.271	0.73	0.47	1.15	0.175	0.95	0.55	1.63	0.853
Missing	0.83	0.58	1.17	0.289	0.81	0.51	1.27	0.357	0.88	0.52	1.52	0.653
Townsend (least deprived – reference) 1	1.00				1.00				1.00			
2	1.05	0.75	1.47	0.786	1.14	0.72	1.82	0.567	0.94	0.57	1.56	0.811
3	1.04	0.73	1.48	0.813	1.17	0.72	1.88	0.525	0.91	0.54	1.54	0.734
4	1.14	0.80	1.62	0.475	1.33	0.82	2.16	0.241	0.95	0.56	1.61	0.86
5	0.78	0.50	1.22	0.273	0.86	0.46	1.62	0.647	0.69	0.37	1.31	0.262
Missing	0.76	0.50	1.15	0.196	1.08	0.65	1.82	0.759	0.44	0.22	0.90	0.024
Anaemia** (reference) no	1.00				1.00				1.00			
yes	1.70	1.07	2.69	0.024	1.36	0.70	2.63	0.364	2.19	1.15	4.17	0.017
Abdominal pain [†] (reference) no	1.00				1.00				1.00			
yes	1.62	0.92	2.86	0.096	1.17	0.47	2.89	0.737	2.16	1.04	4.49	0.039
Lower gastrointestinal bleeding [†] (reference) no	1.00				1.00				1.00			
yes	5.97	3.71	9.62	0<0.001	6.73	3.60	12.57	<0.001	5.29	2.54	11.03	<0.001
Loperamide prescription [†] (reference) no	1.00				1.00				1.00			
yes	2.13	1.22	3.72	0.007	3.19	1.53	6.64	0.002	1.46	0.63	3.35	0.376
Diarrhoea [†] (reference) no	1.00				1.00				1.00			
yes	4.87	3.23	7.36	<0.001	2.72	1.42	5.21	0.003	8.01	4.74	13.55	<0.001
Axial arthropathy* (reference) no	1.00				1.00				1.00			
yes	2.08	0.58	2.64	0.008	1.45	0.59	3.56	0.421	2.75	1.38	5.50	0.004

[†] coded within 6 months of Index date; ‡ <11.9g/dL (females); <12.9g/dL (males); *recorded at baseline

Appendix 5. Multivariable Cox hazard models for episcleritis & scleritis associated with inflammatory bowel disease

	Inflammatory Bowel Disease				Ulcerative colitis				Crohn's Disease			
	aHR	[95% Confidence Interval]	p-value	aHR	[95% Confidence Interval]	p-value	aHR	[95% Confidence Interval]	p-value			
Combined episcleritis & scleritis	1.73	1.31	2.28	<0.001	1.43	0.97	2.11	0.067	2.13	1.42	3.19	<0.001
Sex (reference) Male	1.00				1.00				1.00			
Female	1.05	0.79	1.38	0.749	1.03	0.71	1.49	0.887	1.07	0.71	1.62	0.743
Age Category (reference) <18 years	1.00				1.00	0.23	2.10	0.521	1.00			
18-30	1.11	0.52	2.36	0.786	1.00				0.80	0.28	2.30	0.683
30-40	1.02	0.51	2.03	0.956	1.12	0.49	2.55	0.796	0.60	0.22	1.62	0.317
40-50	1.11	0.57	2.17	0.749	1.43	0.66	3.09	0.369	0.51	0.19	1.36	0.179
50-60	1.12	0.57	2.19	0.749	0.81	0.35	1.87	0.620	0.97	0.38	2.51	0.955
60-70	1.45	0.73	2.87	0.292	1.68	0.75	3.76	0.207	0.79	0.29	2.14	0.637
>70	0.65	0.28	1.49	0.306	0.89	0.33	2.38	0.817	0.26	0.07	0.99	0.049
Smoking Status (reference) current smoker	1.00				1.00				1.00			
non smoker	0.83	0.60	1.16	0.277	0.98	0.62	1.56	0.941	0.70	0.44	1.11	0.129
Charlson comorbidity score (reference) 0	1.00				1.00				1.00			
1	1.15	0.83	1.58	0.402	1.15	0.75	1.78	0.524	1.14	0.71	1.84	0.587
>=2	0.82	0.49	1.38	0.465	0.83	0.42	1.66	0.603	0.82	0.38	1.79	0.626
Body mass index (reference) <25kg/m ²	1.00				1.00				1.00			
25-30Kg/m ²	0.96	0.69	1.33	0.800	0.76	0.48	1.21	0.249	1.21	0.76	1.94	0.418
>30Kg/m ²	0.71	0.47	1.07	0.103	0.86	0.51	1.44	0.561	0.53	0.27	1.05	0.071
Missing	0.98	0.65	1.46	0.912	1.12	0.67	1.86	0.675	0.80	0.42	1.53	0.495
Townsend (least deprived – reference) 1	1.00				1.00				1.00			
2	1.15	0.78	1.71	0.479	1.10	0.67	1.79	0.713	1.26	0.64	2.47	0.497
3	1.78	1.24	2.58	0.002	1.27	0.78	2.07	0.334	2.80	1.56	5.03	0.001
4	1.05	0.67	1.65	0.836	0.58	0.29	1.15	0.117	1.98	1.02	3.84	0.044
5	0.76	0.41	1.41	0.389	0.44	0.17	1.14	0.092	1.38	0.59	3.25	0.459
Missing	0.89	0.55	1.44	0.629	0.89	0.49	1.62	0.710	0.88	0.38	2.04	0.765
Anaemia** (reference) no	1.00				1.00				1.00			
yes	2.02	1.14	3.58	0.016	1.02	0.37	2.81	0.965	3.36	1.66	6.80	0.001
Abdominal pain† (reference) no	1.00				1.00				1.00			
yes	1.08	0.48	2.45	0.846	1.01	0.32	3.21	0.981	1.17	0.37	3.70	0.794
Lower gastrointestinal bleeding† (reference) no	1.00				1.00				1.00			
yes	5.18	2.71	9.93	<0.001	6.71	3.06	14.71	<0.001	3.26	1.01	10.50	0.048
Loperamide prescription† (reference) no	1.00				1.00				1.00			
yes	2.97	1.47	6.02	0.002	2.89	1.11	7.53	0.030	3.19	1.14	8.95	0.027
Diarrhoea† (reference) no	1.00				1.00				1.00			
yes	3.01	1.72	5.26	<0.001	3.19	1.50	6.77	0.003	2.76	1.21	6.32	0.016
Axial arthropathy* (reference) no	1.00				1.00				1.00			
yes	2.96	1.31	6.68	0.009	4.50	1.83	11.08	0.001	1.07	0.15	7.67	0.949

† coded within 6 months of Index date; ‡ <11.9g/dL (females); <12.9g/dL (males); *recorded at baseline

Appendix 6

**Adjusted hazard ratios for risk of inflammatory bowel disease for complete case analysis
(all-case analysis estimates are in brackets)**

	aHR	[95% Confidence Interval]		p-value
Any IBD associated ocular inflammation				
Inflammatory bowel disease	2.29 (2.25)	1.86	2.80	<0.001
Ulcerative colitis	1.43 (1.65)	1.07	1.90	0.015
Crohn's disease	3.95 (3.37)	2.88	5.41	<0.001
Anterior uveitis				
Inflammatory bowel disease	3.49 (3.39)	2.69	4.51	<0.001
Ulcerative colitis	2.05 (2.23)	1.43	2.96	<0.001
Crohn's disease	6.52 (5.77)	4.35	9.79	<0.001
Episcleritis or scleritis				
Inflammatory bowel disease	1.56 (1.73)	1.12	2.18	0.009
Ulcerative colitis	1.20 (1.43)	0.74	1.94	0.459
Crohn's disease	2.04 (2.13)	1.28	3.27	0.003

Adjusted hazard ratio (aHR) – adjustment variables: age at index; sex; Townsend deprivation quintile; Charlson comorbidity score; body mass index; smoking status; anaemia, abdominal pain, lower gastrointestinal bleeding, loperamide prescription, diarrhoea, axial arthropathy.

Complete case numbers (excludes subjects with missing BMI and Townsend level data)

Any IBD associated ocular inflammation	Anterior Uveitis	Episcleritis or Scleritis
Subjects without IAOI 100,826	Subjects without AU 60,835	Subjects without episcleritis or scleritis 45,477
Subjects with any IAOI 26,954	Subjects with AU 16,237	Subjects with episcleritis or scleritis 12,162
Total 127,780	Total 77,072	Total 57,639
<i>BMI; Body Mass Index IAOI; Any IBD associated ocular inflammation</i>		

Appendix 7: Nomogram: prediction of inflammatory bowel disease diagnosis within 3-years of a diagnosis of anterior uveitis



