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The risk of a subsequent diagnosis of inflammatory bowel disease in subjects with ophthalmic disorders associated with inflammatory bowel disease

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5 1 Title Page
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8 2 The risk of a subsequent diagnosis of inflammatory bowel disease in
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10 3 subjects with ophthalmic disorders associated with inflammatory bowel
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12 4 disease
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16 6 **Short title:** Inflammatory Bowel Disease risk in associated eye disease
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6 45 **Ethics**
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8 46 Use of IQVIA Medical Research Data* is approved by the UK Research Ethics Committee (reference number:
9 47 18/LO/0441). In accordance with this approval, the study protocol was reviewed and approved by an
10 48 independent Scientific Review Committee (SRC) in September and 2019 (reference number: 19THIN066).

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13 49 *IQVIA Medical Research Data (IMRD-UK) incorporates data from THIN, A Cegedim Database. Reference
14 50 made to THIN is intended to be descriptive of the data asset licensed by IQVIA. This work used de-identified
15 51 data provided by patients as a part of their routine primary care.
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23 53 **Abbreviations:**

24 54 Extra-Intestinal Manifestation (EIM), anterior uveitis (AU), inflammatory bowel disease (IBD); Crohn's
25 55 disease (CD); ulcerative colitis (UC); Hazard ratio (HR); The Health Improvement Network (THIN); IQVIA
26 56 Medical Research Data (IMRD-UK).
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Abstract:

Introduction

Ophthalmic conditions including anterior uveitis (AU), episcleritis and scleritis may occur in association with the inflammatory bowel diseases (IBD) as ophthalmic extraintestinal manifestations (O-EIM). They may predate an IBD diagnosis, but the risk is not well described.

Methods

A retrospective cohort study examined the risk of a subsequent diagnosis of IBD in subjects with O-EIMs compared to age/sex matched subjects without O-EIMs. Hazard ratios (HR) were adjusted for age, sex, body mass index, deprivation, comorbidity, smoking, and baseline axial arthropathy, diarrhoea, loperamide prescription, anaemia, lower gastrointestinal bleeding and abdominal pain.

Logistic regression was used to produce a prediction model for the diagnosis of IBD within 3 years of an AU diagnosis.

Results

38,805 subjects with an O-EIM were identified (median age 51 (38-65), 57% female) and matched to 153,018 subjects without O-EIMs. 213 (0.6%) subsequent IBD diagnoses (102 ulcerative colitis (UC) and 111 Crohn's disease (CD)) were recorded in those with O-EIMs and 329 (0.2%) (215 UC and 114 CD) in those without. Median time to IBD diagnosis was 882 (IQR 365-2,043) days in those with O-EIMs and 1,403 (623-2,516) in those without. The adjusted HR for a subsequent diagnosis of IBD was 2.25 (95%CI 1.89-2.68), $p < 0.001$; for ulcerative colitis 1.65 (1.30-2.09), $p < 0.001$; and for Crohn's disease 3.37 (2.59-4.40), $p < 0.001$ in subjects with O-EIMs compared to those without.

Within 3 years of an AU diagnosis, 84 (0.5%) subjects had a recorded diagnosis of IBD. The prediction model performed well with a C-statistic of 0.75 (0.69-0.80).

Conclusions

Subjects with O-EIMs have a two-fold increased risk of a subsequent IBD diagnosis. Healthcare professionals should be alert for potential signs and symptoms of IBD in those presenting with ophthalmic conditions associated with IBD.

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89 Article Summary

90 Strengths and limitations of this study

- 91 • Large sample size from a nationally representative primary care database.
- 92 • Routinely gathered data gives a “real-life” view of the reporting of eye and inflammatory bowel diseases in a community setting.
- 93
- 94 • Prediction model development to help clinicians become aware of the risks of inflammatory
- 95 bowel disease in patients presenting with eye diseases.
- 96 • Risk of under recording where eye manifestations do not reach a threshold for presentation to
- 97 health care professionals.
- 98 • Database is not linked to secondary care database and therefore cross validation of secondary
- 99 care diagnoses was not possible.

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102 Introduction

103 Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a
104 relapsing, inflammatory, autoimmune condition of unknown aetiology. Thought to be the
105 consequence of dysregulation of the immune system at the interface between the microbiome and
106 the bowel wall, IBD shares many of the disturbed pathways observed in other autoimmune
107 conditions^{1,2}.

108 A number of conditions are commonly observed in those suffering with IBD and are therefore known
109 as extraintestinal manifestations (EIMs) of IBD. EIMs can be classified as: *IBD-specific* (e.g. metastatic
110 CD); *drug-related* (e.g. anti-TNF associated skin lesions or steroid-induced cataract development);
111 *associated* - signalling a predisposition to autoimmunity (e.g. ankylosing spondylitis); or *reactive* -
112 implying common pathophysiological pathways without histopathological similarity (e.g. pyoderma
113 gangrenosum)^{3,4}. Certain conditions belonging to the reactive and associated EIM subtypes have been
114 accepted as *classical* EIMs and include ophthalmic, dermatological, musculoskeletal and hepatobiliary
115 diseases^{5,6}.

116 A link between IBD and ophthalmic conditions has long been recognised. The cell surface immune
117 regulation protein Human Leucocyte Antigen B27 (HLA B27) is more common in IBD and uveitis which
118 also links uveitis with the musculoskeletal EIMs, in particular the axial arthropathies (ankylosing
119 spondylitis and sacroiliitis)⁷⁻¹⁰. The *classical* EIMs in the ophthalmic group include anterior uveitis
120 (AU), episcleritis and scleritis. These complications may occur in up to 13% of IBD patients, with the
121 potential for significant morbidity including blindness^{11,12}.

122 Ophthalmic EIMs range from mild and benign to severe, requiring urgent intervention to preserve the
123 eye. Uveitis is a sight-threatening condition and is more commonly bilateral and anterior in the context
124 of IBD; it may run in parallel or independently of IBD activity¹²⁻¹⁴. Treatment for uveitis depends on
125 the severity and the specific location of inflammation, and commonly includes topical, intraocular and
126 systemic corticosteroids, with second-line immunosuppressants and biologics where needed¹².

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3 127 Episcleritis is a benign condition that is not sight threatening and presents with eye redness and mild
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5 128 to moderate discomfort. It is caused by inflammation of the episcleral tissue which lies above the
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7 129 sclera and below the conjunctiva. It runs a parallel course when associated with IBD and often does
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10 130 not require specific treatment ^{12,15}. Scleritis on the other hand is a serious, destructive, inflammatory
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12 131 condition and can be sight threatening. It presents with redness of the sclera, deep 'boring' pain and
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14 132 may cause tissue destruction leading to visual impairment. Treatment is essential and may include
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16 133 systemic anti-inflammatory agents, corticosteroids and immunosuppressants ¹². Unlike episcleritis, it
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18 134 may appear independently of IBD activity and is uncommon compared to episcleritis ¹⁶.
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21 135 *Classical* EIMs may occur prior to a diagnosis of IBD and may occur in isolation in those who never
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23 136 develop IBD ^{17,18}. The aim of this study was to examine the risk of and time to a subsequent diagnosis
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26 137 of IBD in those with a new diagnosis of a *classical* ophthalmic EIM.
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138 Materials and Methods

139 Data Source

140 Data in the IQVIA Medical Research Data (IMRD-UK) database are obtained from over 800 primary
141 care practices across the United Kingdom (UK). IMRD-UK contains data on 15.8 million subjects and is
142 considered representative of the UK population¹⁹. Data on included subjects is longitudinally captured
143 including primary and secondary care diagnostics, drug prescriptions, symptoms and diagnoses, and
144 demographic information. Data are uploaded using a hierarchical system of (Read) codes²⁰. To be
145 eligible for the study, IMRD-UK primary care practices required at least one year since the installation
146 of the computerised medical record system and achievement of an acceptable mortality recording
147 (AMR) level²¹. These criteria help to ensure data reliability and reduce the risk of under-recording
148 baseline data.

149 Study Design

150 *Cohort study*

151 A retrospective matched cohort study was undertaken between 1st January 1995 and 25th September
152 2019 to investigate the association between IBD outcome and all studied O-EIM exposures (anterior
153 uveitis (AU), scleritis and episcleritis), with secondary studies of anterior uveitis alone and combined
154 episcleritis and scleritis. Those subjects with an incident O-EIM diagnosis of interest (recorded through
155 Read codes – Appendix 1)²² were compared to subjects without the specific O-EIMs of interest for
156 each analysis, matched by age at cohort entry (± 2 years) and sex in a ratio of 1:4. Index date was
157 defined as the start of follow up and was the date of O-EIM diagnosis for the O-EIM group. The same
158 date was assigned to matched subjects without an O-EIM in order to mitigate for immortality time
159 bias²³. Only subjects without a co-existing IBD diagnosis at index date were included in the study.
160 Individuals were eligible for inclusion from either the date of eligibility of their primary care practice
161 or one year after they were registered, whichever was later.

162 Subjects were followed from their index date until the first of the following events (exit date): death;
163 subject left the practice; last data collection from their practice; study end date (25th September 2019);

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3 164 diagnosed with IBD (CD or UC) as identified through Read codes. Subjects coded for both UC and CD
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5 165 were assigned to one condition based on frequency of coding. For those with equal coding, the earliest
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7 166 diagnosis date and the latest diagnosis of IBD subtype was used.
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10 167 In this retrospective cohort study using IMDR-UK patients are anonymous and were not identified or
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13 168 involved in the study.
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16 169 *Prediction model*

17 170 Subjects with an incident diagnosis of AU over the same study period were investigated to identify
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19 171 predictors for a diagnosis of IBD within the following 3-years. Case examples were used to determine
20
21 172 the probability of diagnosis of IBD in subjects presenting with anterior uveitis.
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25 173 *Validation*

26 174 Primary care coding to identify patients with IBD has been previously validated^{24,25}. O-EIM codes were
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28 175 reviewed by two clinicians, having been first sourced from other published primary care database
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30 176 studies²⁶⁻²⁸. Ophthalmology expert advice was sought for ophthalmic EIM coding decisions. AU codes,
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32 177 excluding uveitis associated with other pathologies (e.g. infective), were selected for inclusion along
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34 178 with episcleritis and scleritis. Clinical codes used to identify UC, CD and ophthalmic EIMs are listed in
35
36 179 Appendix 1.
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43 181 **Statistical Analysis**

44 182 *Cohort study*

45 183 The time from index date to a later diagnosis of IBD in those with and without a baseline O-EIM were
46
47 184 presented as median time to IBD and UC or CD diagnoses with accompanying interquartile ranges
48
49 185 (IQR). Log-rank tests were used to compare time to IBD diagnosis between those with and without O-
50
51 186 EIMs. Cox proportional hazard models, with time to subsequent diagnosis of IBD as the time-metric,
52
53 187 were produced to assess the adjusted hazard ratio (aHR) of IBD diagnoses in participants with an O-
54
55 188 EIM compared to matched subjects without O-EIMs. For all O-EIMs and when AU was examined alone,
56
57 189 aHRs were produced for all IBD, UC and CD outcomes. However, for the combined episcleritis and
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3 190 scleritis study, due to IBD diagnoses being less commonly observed, only an aHR for all IBD was
4
5 191 modelled. Hazard ratios were adjusted for age at index; sex; smoking status; body mass index (BMI);
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7 192 Townsend level of deprivation (quintiles); Charlson comorbidity score; baseline axial arthropathy
8
9 193 diagnosis; and within 6-months of O-EIM diagnosis (prior to an IBD diagnosis) coding of anaemia
10
11 194 (<11.9g/dL for females and <12.9g/dL for males), abdominal pain, loperamide prescription, diarrhoea
12
13 195 or lower gastrointestinal bleeding. Smoking status was dichotomised into current smokers and non-
14
15 196 smokers with missing data for smoking status considered non-smokers; a method that has been
16
17 197 previously validated²⁹. Missing data for Townsend deprivation quintile were considered a separate
18
19 198 category. Proportional hazards were assessed using log-log plots. Cumulative incidence plots were
20
21 199 produced to illustrate the cumulative risk of IBD over time.
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201 *Prediction model*

202 Multivariable logistic regression was used to establish a prediction model for IBD diagnosis in subjects
203 presenting with a new diagnosis of anterior uveitis. Only those with an IBD diagnosis within 3-years or
204 those who had a minimum of 3-years follow up were included in the development cohort. Backwards
205 stepwise elimination was used to examine variables with an elimination alpha-to-remove p-value of
206 0.20. Sex, age (categorical) and smoking status were included due to their clinical importance. Further
207 candidate variables including baseline axial arthropathy, BMI (categorical) and within 6-months coding
208 of anaemia, abdominal pain, lower gastrointestinal bleeding, loperamide prescription and diarrhoea
209 (prior to an IBD diagnosis) were assessed. A receiver operating characteristic (ROC) curve and C-
210 statistic was used to assess model discrimination; calibration was assessed using the Hosmer-
211 Lemeshow test for goodness of fit. Internal validation of the prediction model was performed through
212 bootstrapping by resampling the dataset (with replacement) 200 times and comparing the resulting
213 average of the area under the ROC curve from the bootstrap samples to the original model.

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3 215 Analyses were performed using Stata version 16.0 and p-values <0.05 were considered statistically
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5 216 significant³⁰.
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8 217 **Patient and public involvement**
9 218 Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination
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11 219 plans of this research.
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220 Results

221 Study Subjects

222 Following exclusions (Figure 1), 38,805 subjects with an O-EIM were identified (median age 51 (38-65)
223 and 57% female). O-EIM cases included those coded as AU: 22,098 (57%); episcleritis: 13,955 (36%);
224 scleritis: 2,482 (0.6%); episcleritis or scleritis (a non-specific code where it was not possible to
225 determine whether subjects were episcleritis or scleritis): 270 (0.01%). O-EIM subjects were age and
226 sex matched to 153,018 subjects without an O-EIM. The median follow-up period was five years with
227 a total of 244,503 person years (py) of follow-up time in O-EIM subjects and 934,847 py in those
228 without O-EIMs.

229 In those with an O-EIM, 2.9% (1,116) had another, non-ophthalmic EIM at index date compared to
230 0.9% (1,433) in subjects without O-EIMs. Subject characteristics are shown in Table 1.

232 Risk of Inflammatory Bowel Disease Diagnosis in Associated Ophthalmic Conditions

233 During the study period 213 (0.6%) IBD diagnoses (103 UC and 111 CD) were observed in subjects with
234 O-EIMs compared to 329 (0.2%) (215 UC and 114 CD) in the matched control group. 893 (2.3%)
235 subjects with O-EIMs had an axial arthropathy recorded at baseline and 35 (0.1%) had the HLA-B27
236 genotype coded, compared to 1,013 (0.7%) controls with an axial arthropathy and 7 (0.005%) with the
237 HLA-B27 genotype. From index date (O-EIM diagnosis date for exposed subjects, with matched
238 controls assigned the same index date as their corresponding exposed subjects), the median time to
239 IBD diagnosis was 882 (IQR 365-2,043) days in subjects with O-EIMs compared to 1,403 (623-2,516)
240 days in those without O-EIMs. For UC the median time to diagnosis was 922 (410-1,910) days
241 compared to 1,360 (547-2,406) days, while median time to CD diagnosis was 738 (269-2,011) days
242 compared to 1,625 (641-2,779) days, in subjects with and without O-EIMs respectively. For all IBD, UC
243 and CD the log-rank test p-value was <0.001. Following adjustment, the aHR for a diagnosis of IBD in
244 O-EIM subjects compared to those without O-EIMs was 2.25 (95%CI 1.89-2.68), with an aHR of 1.65

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3 245 (1.30-2.09) for UC and 3.37 (2.59-4.40) for CD, p-values <0.001 (Table 2; full models are shown in
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5 246 Appendix 2). Figure 2 shows the cumulative incidence plot for IBD diagnoses in subjects with O-EIMs
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7 247 compared to those without.
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14 249 Risk of Inflammatory Bowel Disease Diagnosis in Anterior Uveitis, Episcleritis and 15 16 250 Scleritis

17 251 Subject characteristics of O-EIM and matched subjects without O-EIMs in these secondary analyses
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19 252 together with the full Cox models are shown in Appendices 3, 4 and 5. Subject numbers for individual
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21 253 O-EIMs differ slightly to those in the combined O-EIM study above because only the first diagnosed
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23 254 incident O-EIM was considered in the combined study, but a subject might be subsequently diagnosed
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25 255 with other O-EIMs and therefore be eligible for inclusion in more than one analysis for the individual
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27 256 O-EIMs presented in this section. In the AU study, 22,547 subjects with a new diagnosis of AU (median
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29 257 age 53 (39-68) years, 54% female) were matched to 89,422 subjects without AU. AU subjects and their
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31 258 matched subjects provided 137,878 and 531,653 py of follow-up, respectively. 152 (0.7%) IBD
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33 259 diagnoses (67 UC and 85 CD) were observed in AU subjects during the study period and 157 (0.2%)
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35 260 IBD diagnoses (107 UC and 50 CD) among subjects without AU. The median time to an IBD diagnosis
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37 261 was 898 (373-2,027) days in the AU subjects compared to 1,457 (539-2,700) in those without AU (log-
38
39 262 rank test p<0.001). The median time to UC diagnosis was 1,117 (489-2,008) days compared to 1,490
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41 263 (553-2,553) days and the median time to a CD diagnosis was 687 (286-2,006) days compared to 1,160
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43 264 (516-2,892) days for AU subjects compared matched subjects without AU, respectively (log-rank tests
44
45 265 p<0.001 for both CD and UC). The aHR for a subsequent IBD diagnosis in subjects with AU compared
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47 266 to matched subjects without AU was 3.39 (2.70-4.25); for UC aHR was 2.23 (1.63-3.04) and for CD 5.77
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49 267 (4.04-8.24), all p-values <0.001 (Table 2 (full models are shown in Appendix 4)).
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56 268 In the analysis of episcleritis and scleritis combined, 17,439 subjects (14,752 (85%) episcleritis and
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58 269 2,976 scleritis; median age 48 (36-61) and 62% female) were identified and matched to 68,823
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3 270 controls. Episcleritis and scleritis subjects and matched participants contributed 36,324 and 136,304
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5 271 py follow-up, respectively. 104 (0.6%) IBD cases (23 UC and 81 CD) were observed among episcleritis
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7 272 and scleritis subjects and 53 (0.1%) (30 UC and 23 CD) among those without these O-EIMs. The median
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9 273 time to an IBD diagnosis in episcleritis and scleritis subjects was 848 (348-2,239) days compared to
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11 274 1,522 (577-2,838) days in controls, log-rank test $p < 0.001$. The aHR for the diagnosis of IBD in those
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13 275 subjects with an incident diagnosis of episcleritis or scleritis compared to matched subjects without
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15 276 these O-EIMs was 1.73 for IBD (1.31-2.28), $p < 0.001$ (Table 2 (full models are shown in Appendix 5)).
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20 277 Prediction Model

21 278 22,547 AU subjects were identified with 15,458 eligible for inclusion in the prediction model
22
23 279 development cohort based on sufficient follow-up time or an IBD diagnosis within 3 years of the AU
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25 280 diagnosis. 84 (0.53%) subjects had a recorded diagnosis of IBD (63% CD) within 3 years of follow-up.
26
27 281 The characteristics of those with and without an IBD diagnosis are shown in Table 3. Those with an
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29 282 IBD diagnosis were younger (median age 44 (IQR 35-56) and 53 (39-68) years respectively, $p < 0.001$)
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31 283 but there was no difference in sex, smoking status or body mass index category.
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35 284 Following backwards stepwise regression, female sex, smoking status, BMI and abdominal pain within
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37 285 6 months of an AU diagnosis exceeded the alpha-to-remove threshold. However, female sex and
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39 286 smoking status were retained in the model due to their clinical importance. Weight loss within 6
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41 287 months of an AU diagnosis and HLA-B27 genotype were coded in only 5 and 19 cases respectively and
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43 288 were therefore not included in the analysis. The multivariable logistic regression model to assess the
44
45 289 risk of being diagnosed with IBD within a 3-year period following AU diagnosis is presented in Table 4.
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47 290 The Hosmer-Lemeshow χ^2 test for goodness of fit was applied to the prediction model development
48
49 291 data set and was not significant at 0.093, suggesting reasonable model fit. The receiver operating
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51 292 characteristic (ROC) curve, shown in Figure 3, produced an area under the curve (AUC) C-statistic of
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53 293 0.75 (95%CI 0.69-0.80). Following internal validation by bootstrapping, resampling the dataset 200
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55 294 times, the mean difference between the original AUC and AUC in each bootstrap sample was 0.021.
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57 295 This produced a bias-corrected C-statistic value of 0.71 (0.67-0.77).
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3 296 A probability calculator was produced to determine the likelihood of an IBD diagnosis within the
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5 297 anterior uveitis cohort using the following examples: 1) a female, 34-year-old, current smoker and a
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7 298 within 6-month history of anaemia would have a 2% risk of IBD being diagnosed within 3 years of an
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9 299 anterior uveitis diagnosis; 2) a male, 18-year-old, non-smoker and a history of axial arthropathy,
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11 300 diarrhoea and loperamide use would have a 25% 3-year IBD diagnosis risk; 3) a female, 49-year-old,
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13 301 current smoker with a history of anaemia, diarrhoea and lower gastrointestinal bleeding would have
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15 302 a 55% risk of an IBD diagnosis within 3 years. A nomogram for the prediction model is shown in
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17 303 Appendix 6.
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305 Discussion

306 In this study, we have shown that subjects with an O-EIM, but without a recorded diagnosis of IBD,
307 are at a two-fold greater risk (by an average of 5 years follow-up) of subsequently being diagnosed
308 with IBD than matched subjects without an O-EIM. The risk was highest in those who later had a CD
309 diagnosis. A wide time scale was observed between an O-EIM diagnosis and a subsequent IBD
310 diagnosis with a median time to IBD diagnosis of greater than two years. When AU was examined
311 alone, subjects had a 3-fold greater risk of a later IBD diagnosis compared to matched subjects without
312 AU and again the risk was highest for a subsequent CD diagnosis at almost 6-fold.

313 Ophthalmic conditions are among the most common extraintestinal manifestations of IBD and are
314 commonly diagnosed at the time or following a diagnosis of IBD ¹⁸. This study, however, has
315 established that subjects with a diagnosis of an O-EIM associated with IBD, either in combination or
316 as separate entities (anterior uveitis or episcleritis and scleritis), were at increased risk of developing
317 a subsequent diagnosis of IBD over time (combined O-EIM aHR 2.25 (1.89-2.68), p<0.001). The time
318 to a diagnosis of IBD was shorter in those with ophthalmic conditions compared to matched controls
319 (median time 2.4 years versus 3.8 years, respectively). However, the time from O-EIM diagnosis to IBD
320 was often greater than two years. This was a significant time lag which may reflect a lack of symptoms
321 to indicate IBD. Relatively few subjects were coded with anaemia, abdominal pain, lower
322 gastrointestinal bleeding, weight loss, diarrhoea or loperamide prescriptions around the time of the
323 diagnosis of the ophthalmic condition. However, given that many EIMs parallel the course of IBD, it is
324 possible that IBD may be present earlier and pauci-symptomatic and as such they may represent a
325 missed opportunity and a delayed diagnosis.

326 The aetiology of ophthalmic EIMs is not well understood. They are thought to be more common in
327 those with CD rather than UC ¹², and our findings support this. A limitation of the IMRD-UK database
328 is that it does not allow for the discrimination of IBD severity, activity or gastrointestinal location. This
329 is pertinent because those with colonic or ileocolonic disease have been shown to have an increased

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3 330 risk of ophthalmic EIMs ^{16,31,32}. Several studies have suggested that certain peptide targets for the
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5 331 immune system are found in both joints, eyes and the colon ^{33,34}. It may be that immune dysregulation
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7 332 in relation to the enteric flora and subsequent cross-reactive antigens play a role in some EIM
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9 333 presentations. Moreover, the HLA-B27 antigen appears to play an important role in some mouse
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11 334 models where colitis and arthritis only developed in those where gut flora was present ³⁴. HLA-B27
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13 335 positivity was not commonly coded in the IMRD-UK database and is highly likely to be under-recorded
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15 336 given its specialist nature. However, previous reports that this genotype is observed in greater
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17 337 numbers in those with EIMs and its association with arthropathies and ophthalmic conditions makes
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19 338 this an important consideration in such a study ^{7,16,35}. Arthropathies and the HLA-B27 haplotype were
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21 339 seen in larger numbers at baseline in ophthalmic conditions associated with IBD than in controls in
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23 340 the present study. Previously, it has been found that HLA-B27 is present in 90% of those with
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25 341 ankylosing spondylitis, but just under half of those with CD and sacroiliitis are positive for this allele ⁸.
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27 342 IBD is known to have a genetic link with increased risk seen in the offspring of those with IBD, and this
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29 343 is also the case with uveitis in those with IBD. The HLA region of Chromosome 6 contains both major
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31 344 histocompatibility complex genes (HLAs) as well as other important IBD related genes (TNF- α). The
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33 345 vicinity of these genes increases the likelihood of inheriting several important genetic variations (a
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35 346 phenomenon known as linkage disequilibrium) and may help to explain familial traits and the
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37 347 relationship between some EIMs and the IBDs ³². Other HLA types (HLA-B58) have also been associated
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39 348 with IBD and uveitis, however it is unclear how the interplay between genetic and environmental
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41 349 factors apply, given that most of those who are HLA-B27 positive will not suffer any ill effect from this
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43 350 phenotypic variant and HLA-B27 does not itself appear to increase the risk of IBD ³². A limitation of
44
45 351 this study is the lack of family history data and as a result an assessment of the risk in those with a
46
47 352 family history of EIMs or IBD could not be made.
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49 353 Vavricka et al have reported that multiple EIMs were not uncommon in IBD subjects, with CD and UC
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51 354 subjects studied having more than one EIM in 16% and 8% of cases respectively ³⁶. Axial arthropathies
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53 355 in the present study were included at baseline given evidence that ophthalmic and joint

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3 356 manifestations may be seen more frequently together in IBD⁹. More than 2% of cases had a pre-
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5 357 existing axial arthropathy compared to less than one percent of matched controls. Other investigators
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7 358 have examined IBD and arthritis in UK primary care databases, however, type 1 and 2 EIM
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9 359 arthropathies are challenging to identify given a lack of specific coding, and, seropositive and negative
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11 360 inflammatory arthritides, although associated, are not classical EIMs and as such were not examined
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14 361 in this study²⁶. The presence of an axial arthropathy increased the risk of IBD more than two-fold and
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16 362 was found to be associated with later IBD in anterior uveitis. Although not specifically examined in this
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18 363 study, an increased number of other EIMs in those who develop a new diagnosis of an ophthalmic
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20 364 condition associated with IBD compared to controls has been demonstrated previously. This has been
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22 365 shown to be particularly true among those with arthritic as well as ophthalmic conditions³⁷.

366 Prediction Model

367 The prediction model for IBD diagnosis in subjects with anterior uveitis found associations with several
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30 368 variables. Anaemia, diarrhoea, and lower gastrointestinal bleeding heralded an IBD diagnosis,
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32 369 highlighting the need for careful history taking in ophthalmic care settings and investigation for IBD if
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34 370 such symptoms are revealed. Other inflammatory and autoimmune conditions associated with uveitis
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36 371 can lead to anaemia, including sarcoidosis. Some of these conditions will produce an anaemia of
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38 372 chronic disease, and others a haemolytic anaemia^{38,39}. In the context of ophthalmic conditions
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40 373 associated with IBD, iron deficiency anaemia should be investigated to prevent an IBD diagnostic
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42 374 delay. Age was strongly associated with IBD in our model. Those in the age group 18-30 had the highest
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44 375 risk compared to under 18 year-olds, however all ages up to 70 had an increased IBD risk compared
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46 376 to the reference group (under 18 years). Ottaviano et al. reviewed the published literature on
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48 377 ophthalmic EIMs in children and found that there was little data available. They suggested that this
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50 378 may be related to asymptomatic uveitis, as well as a lower prevalence of these EIMs in childhood
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52 379 compared to adults⁴⁰. In the present study, less than 6% of the cohort were aged under 18 and only
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54 380 0.2% of subjects in this age category developed IBD during the study period, with a slight
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56 381 preponderance towards CD, as has been previously shown in paediatric series⁴⁰.

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3 382 The use of primary care databases has both strengths in terms of subject numbers and subject level
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5 383 data, but also limitations. Perhaps most relevant to the present study are the risk of under-recording
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7 384 and validation. The accuracy of coding in IMRD-UK is related to the primary care practitioner's ability
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9 385 to record diagnoses accurately. Several EIMs (especially episcleritis, which is self-limiting and typically
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11 386 causes only mild discomfort) and IBD symptoms, especially early on in the disease process, may not
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13 387 lead to healthcare-seeking behaviour in primary care and may therefore not be coded in the database
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15 388 in a timely fashion. Although IBD in primary care has previously been validated ²⁴ and in the present
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17 389 study at least 50% of those with an IBD diagnosis had more than one IBD code recorded, to our
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19 390 knowledge a validation study of the ophthalmic conditions used in the present study has not been
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21 391 previously undertaken. Given the lack of external validation, an often-prohibitive task in terms of cost
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23 392 and time, there is a risk of bias. Episcleritis is the most common ophthalmic condition associated with
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25 393 IBD ¹⁸, however, given its benign course it may potentially be under-recorded in the IMRD-UK
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27 394 database. For uveitis and scleritis, however, these diagnoses would be made in a secondary care eye
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29 395 service. For this reason, they may be more reliably recorded when the information reaches primary
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31 396 care. There may also be delays in the recording of data making time-to-event analysis challenging to
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33 397 interpret. IBD is more commonly associated with anterior uveitis and this was therefore the focus of
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35 398 this study, however, IBD can rarely be associated with intermediate, posterior or panuveitis, and so
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37 399 our estimates could be considered to be conservative. Offsetting this were limitations in the way
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39 400 uveitis was coded with a few "unspecified" uveitis Read codes risking the inclusion of some non-
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41 401 anterior phenotypes, although AU is the most common type of uveitis.

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45 403 Ophthalmic conditions associated with IBD which present prior to an IBD diagnosis are not common.
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47 404 However, an increasing prevalence of IBD both in the UK and around the world has been
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49 405 demonstrated ⁴¹⁻⁴³. Given the increasing numbers of patients with IBD, the need for clinicians from
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51 406 many disciplines outside gastroenterology to be aware of IBD is important. Those who care for
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3 407 patients presenting with ophthalmic conditions associated with IBD should be attentive to features
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5 408 which may increase the likelihood of an IBD diagnosis, in order that appropriate investigation and
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7 409 referral can be made in those patients with suggestive clinical features.
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19 413 **Contribution statement:** All authors contributed to the conception and design of the work, DK, NT,
20 414 TT, JS, KN, NJ and RR contributed to the acquisition of the data. DK, NT, TT, JS and NJ contributed to
21 415 the analysis of the data and all authors contributed to the interpretation of data. DK drafted the
22 416 manuscript and all authors contributed to the revision and critical review of the manuscript. All
23 417 authors gave final approval of the version published and agree to be accountable for all aspects of the
24 418 work.
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48 427 under licence and are not available for open access. No additional data available.
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546 **Table 1. Demographics details of study subjects**

	Subjects with ophthalmic extraintestinal manifestations n (%)	Matched subjects without ophthalmic extraintestinal manifestations n (%)
Number of subjects	38,805	153,018
Median person years of follow-up (IQR)	5.4 (2.3-9.4)	5.2 (2.3-9.2)
Median age (IQR)	51 (38-65)	49 (37-63)
Age category n		
<18 years	2,142 (5.5)	9086 (5.9)
18-30	3,264 (8.4)	13,924 (9.1)
30-40	5620 (14.5)	23,644 (15.5)
40-50	7,589 (19.5)	30,586 (20.0)
50-60	7,221 (18.6)	28,622 (18.7)
60-70	5,989 (15.4)	22,990 (15.0)
>70	6,980 (18.0)	24,166 (15.8)
Female sex	22,249 (57.3)	87,694 (57.3)
Townsend Quintile		
1 - least deprived	8,880 (22.9)	34,368 (22.4)
2	7,520 (19.4)	29,210 (19.1)
3	6,989 (18.0)	27,726 (18.1)
4	5,873 (15.1)	23,272 (15.2)
5	3,814 (9.8)	15,312 (10.0)
Missing	5,729 (14.8)	23,130 (15.1)
Charlson comorbidity score		
0	24,457 (63.0)	106,735 (69.8)
1	8,414 (21.7)	28,888 (18.9)
>=2	5,934 (15.3)	17,395 (11.4)
Smoking status		
current smoker	6,632 (17.1)	28,586 (18.7)
non-smoker	32,173 (82.9)	124,432 (81.3)
Body mass index		
<25kg/m ²	12,799 (33.0)	51,136 (33.4)
25-30Kg/m ²	11,200 (28.8)	40,782 (26.6)
>30Kg/m ²	7,683 (19.8)	26,849 (17.6)
Missing	7,123 (18.4)	34,251 (22.4)
Anaemia^{†‡}	2,102 (5.4)	5,469 (3.4)
Abdominal pain[†]	837 (2.2)	2,574 (1.7)
Lower gastrointestinal bleeding[†]	363 (0.9)	1,042 (0.7)
Loperamide prescription[†]	558(1.4)	1,506 (1.0)
Diarrhoea[†]	974 (2.5)	2,424 (1.6)
HLA-B27 positive at baseline	35 (0.1)	7 (0.0)
Axial arthropathy at baseline	893 (2.3)	1,013 (0.7)
EIM at baseline (other than ophthalmic)[§]	1,116 (2.9)	1433 (0.9)

[†] coded within 6 months of Index date
[‡] <11.9g/dL (females); <12.9g/dL (males)
[§] EIM: Extraintestinal manifestations: axial arthropathies, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, aphthous stomatitis

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548 **Table 2. Adjusted hazard ratios for risk of inflammatory bowel disease**

	aHR	[95% Confidence Interval]		p-value
Any associated ophthalmic condition				
Inflammatory bowel disease	2.25	1.89	2.68	<0.001
Ulcerative colitis	1.65	1.30	2.09	<0.001
Crohn's disease	3.37	2.59	4.40	<0.001
Anterior uveitis				
Inflammatory bowel disease	3.39	2.7	4.25	<0.001
Ulcerative colitis	2.23	1.63	3.04	<0.001
Crohn's disease	5.77	4.04	8.24	<0.001
Episcleritis or scleritis				
Inflammatory bowel disease	1.73	1.31	2.28	<0.001

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.

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551 **Table 3. Characteristics of anterior uveitis subjects with and without an inflammatory bowel disease**
 552 **diagnosis by 3 years**

	IBD diagnosis (n=84)	No IBD diagnosis (n=15,906)
Median age (IQR)	44 (35-56)	53 (39-68)
Age category (%)		
<18 years	0 (0)	604 (4)
18-30	17 (20)	1,173 (8)
30-40	18 (21)	2,092 (14)
40-50	18 (21)	2,912 (19)
50-60	14 (17)	2,861 (19)
60-70	12 (14)	2,531 (16)
>70	5 (6)	3,285 (21)
Female sex (%)	45 (54)	8,365 (54)
Smoking status (%)		
current smoker	21 (25)	2,893 (19)
non- smoker	63 (75)	12,565 (81)
Body mass index (%)		
<25kg/m ²	37 (44)	4,999 (33)
25-30Kg/m ²	23 (27)	4,588 (30)
>30Kg/m ²	14 (17)	3,111(20)
missing	10 (12)	2,760 (18)
Anaemia^{†‡} (%)	12 (14)	828 (5)
Abdominal pain[†] (%)	4 (5)	351 (2)
Loperamide prescription[†] (%)	8 (10)	238 (2)
Diarrhoea[†] (%)	20 (24)	349 (2)
Lower gastrointestinal bleeding[†] (%)	9 (11)	145 (1)
HLA-B27 positive at baseline (%)	0 (0)	19 (0.1)
Axial arthropathy at baseline (%)	6 (7)	510 (3)

† coded within 6 months of Index date

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

IBD: Inflammatory Bowel Disease

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555 **Table 4. Multivariable logistic regression prediction model of factors associated with developing**
 556 **inflammatory bowel disease within 3 years of an anterior uveitis diagnosis**

	β -Coefficient	Odds Ratio	[95% Conf. Interval]		P value
Sex					
Male (reference)		1.00			
Female	0.001	1.00	0.64	1.56	0.995
Age Category					
<18 years (reference)		1.00			
18-30	2.56	12.88	4.57	36.30	<0.001
30-40	2.05	7.75	2.79	21.59	<0.001
40-50	1.69	5.41	1.94	15.05	0.001
50-60	1.40	4.04	1.41	11.52	0.009
60-70	1.30	3.65	1.26	10.54	0.017
>70	0.00	1.00			
Smoking Status					
current smoker (reference)		1.00			
non smoker	-0.17	0.85	0.51	1.42	0.528
Anaemia[†]					
no (reference)		1.00			
yes	1.13	3.11	1.61	6.00	0.001
Diarrhoea[†]					
no (reference)		1.00			
yes	2.38	10.76	5.99	19.33	<0.001
Loperamide					
no (reference)		1.00			
yes	0.74	2.10	0.86	5.12	0.102
Lower gastrointestinal bleed					
no (reference)		1.00			
yes	2.27	9.69	4.54	20.70	<0.001
Axial arthropathy*					
no (reference)		1.00			
yes	0.67	1.95	0.83	4.60	0.128
Intercept	-7.08	0.0008	0.0003	0.0024	<0.001

[†] coded within 6 months of Index date

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

* Coded at baseline

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3 563 FIGURE legends
4

5
6 564 *Figure 1 Study flow chart.*

7 565 *Extraintestinal Manifestation (EIM); Inflammatory bowel disease (IBD).*

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10 567 *Figure 2. Cumulative incidence of IBD (inflammatory bowel diseases) in subjects with*
11 568 *ophthalmic conditions (black line) and those without (grey line) with 95% confidence*
12 569 *intervals (dashed lines).*

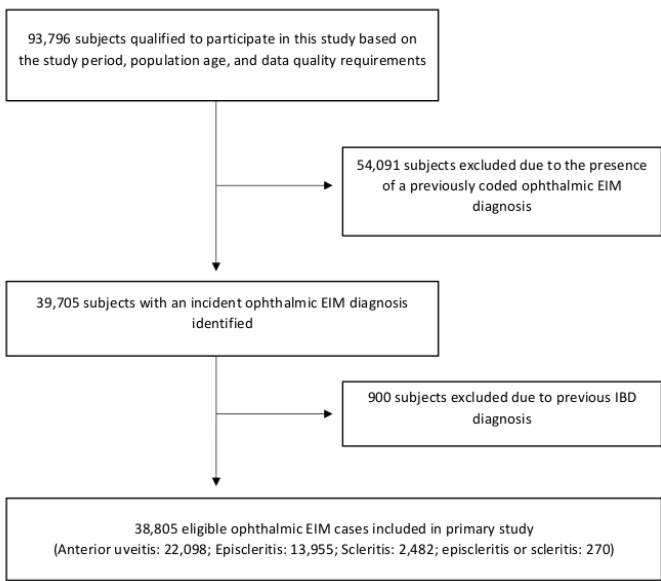
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14 570 *Figure 3. Receiver operating characteristic curve of ability of prediction model to detect an*
15 571 *inflammatory bowel disease diagnosis within three years of an anterior uveitis diagnosis.*

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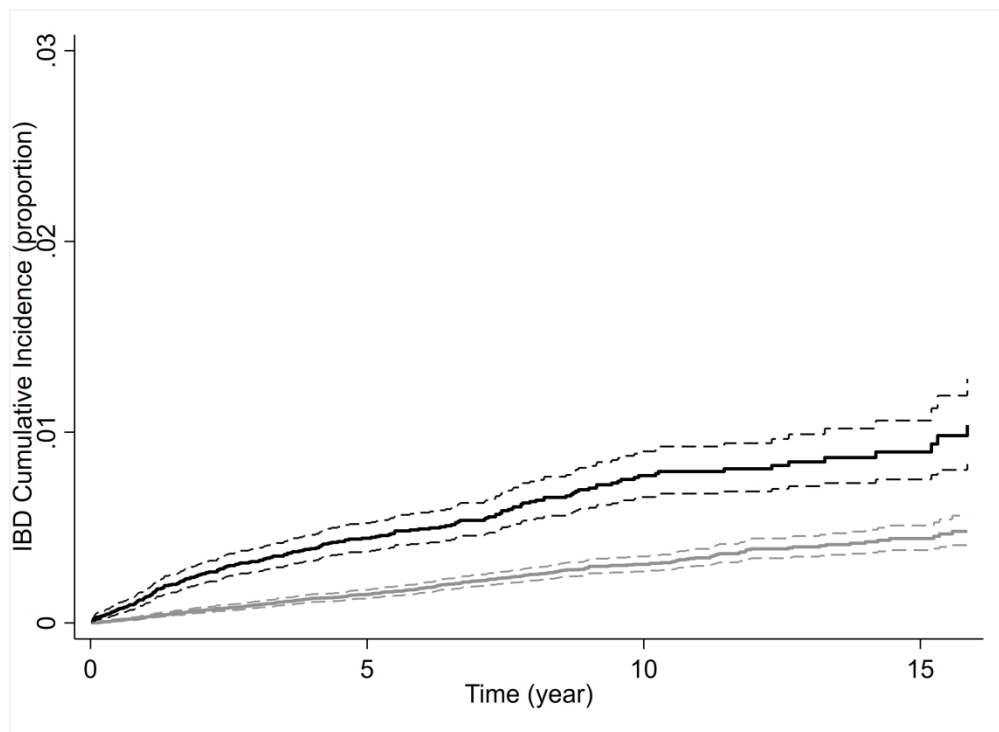
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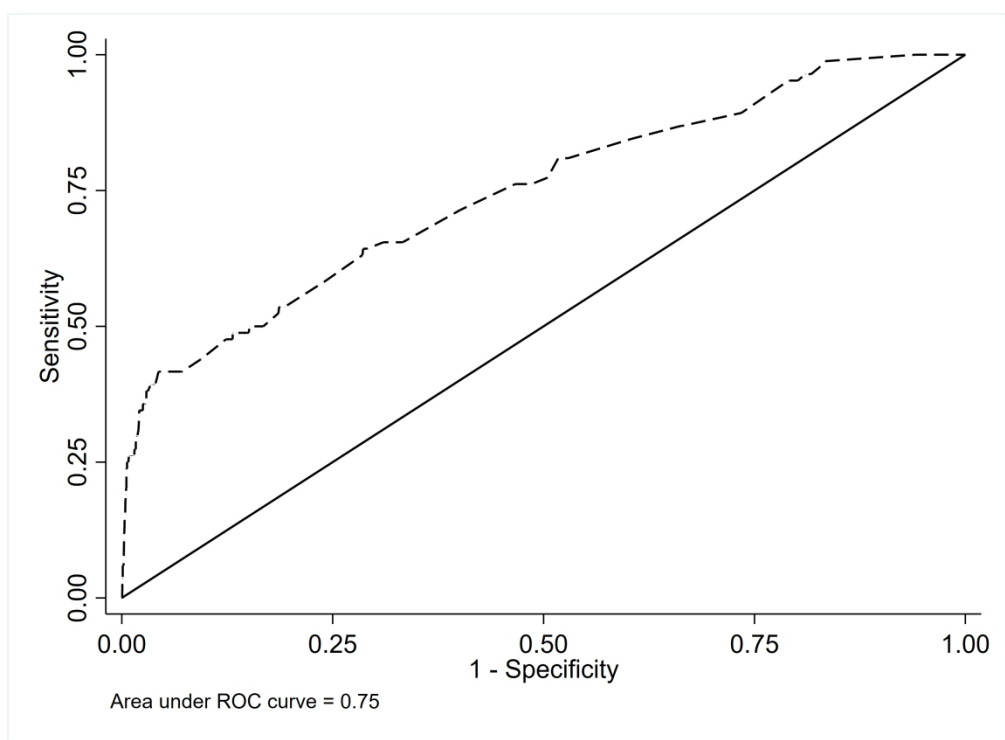
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Appendix 1

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:

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 ophthalmic extraintestinal manifestations 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
All ophthalmic EIMs	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/m²	1.00				1.00				1.00			
25-30Kg/m²	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/m²	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

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1	Lower gastrointestinal bleeding† (reference)													
2	no	1.00				1.00					1.00			
3	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	
4	Loperamide prescription† (reference) no													
5	no	1.00				1.00					1.00			
6	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	
7	Diarrhoea† (reference) no													
8	no	1.00				1.00					1.00			
9	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	
10	Axial arthropathy* (reference) no													
11	no	1.00				1.00					1.00			
12	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	
13	† coded within 6 months of Index date; ‡ <11.9g/dL (females); <12.9g/dL (males); *recorded at baseline													
14	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/m ²	7,344 (32.4)	29,447 (32.9)	5908 (33.9)	23455 (34.1)
25-30Kg/m ²	6,709 (29.5)	24,625 (27.4)	4940 (28.3)	17708 (25.7)
>30Kg/m ²	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[†] (%)			172 (1.0)	446 (0.7)
Loperamide prescription[†] (%)	204 (0.9)	642 (0.7)		
Diarrohea[†] (%)	367 (1.6)	988 (1.1)	213 (1.2)	555 (0.8)
B27 positive at Index	552 (2.4)	1,441 (1.6)	459 (2.6)	1073 (1.6)
Axial arthropathy at baseline	34 (0.2)	2 (0.0)	3 (0.02)	5 (0.01)
	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	0.06	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	0.29	0.89	0.34	2.34	0.815
40-50	1.56	0.65	3.77	0.321	1.22	0.61	2.42	0.57	0.48	0.18	1.30	0.148
50-60	1.91	0.79	4.60	0.149	1.38	0.69	2.73	0.36	0.66	0.25	1.76	0.407
60-70	1.36	0.55	3.35	0.501	1.21	0.60	2.46	0.59	0.33	0.11	0.96	0.041
>70	1.05	0.42	2.62	0.909	0.96	0.46	1.99	0.91	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	0.18	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	0.91	0.84	0.54	1.30	0.434
>=2	0.99	0.68	1.45	0.955	1.06	0.66	1.73	0.79	0.90	0.49	1.67	0.748
Body mass index (reference) <25kg/m²	1.00				1.00				1.00			
25-30Kg/m²	1.11	0.84	1.46	0.48	0.91	0.63	1.31	0.59	1.44	0.94	2.21	0.09
>30Kg/m²	0.82	0.58	1.16	0.271	0.73	0.47	1.15	0.17	0.95	0.55	1.63	0.853
Missing	0.83	0.58	1.17	0.289	0.81	0.51	1.27	0.35	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	0.56	0.94	0.57	1.56	0.811
3	1.04	0.73	1.48	0.813	1.17	0.72	1.88	0.52	0.91	0.54	1.54	0.734
4	1.14	0.80	1.62	0.475	1.33	0.82	2.16	0.24	0.95	0.56	1.61	0.86
5	0.78	0.50	1.22	0.273	0.86	0.46	1.62	0.64	0.69	0.37	1.31	0.262
Missing	0.76	0.50	1.15	0.196	1.08	0.65	1.82	0.75	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	0.33	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													
no	1.00					1.00					1.00		
yes	2.13	1.22	3.72	0.007	3.19	1.53	6.64	0.007	1.46	0.63	3.35	0.376	
Diarrhoea[†] (reference) no													
no	1.00					1.00					1.00		
yes	4.87	3.23	7.36	<0.001	2.72	1.42	5.21	0.001	8.01	4.74	13.55	<0.001	
Axial arthropathy* (reference) no													
no	1.00					1.00					1.00		
yes	2.08	0.58	2.64	0.008	1.45	0.59	3.56	0.42	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				0.70	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/m²	1.00				1.00				1.00			
25-30Kg/m²	0.96	0.69	1.33	0.800	0.76	0.48	1.21	0.249	1.21	0.76	1.94	0.418

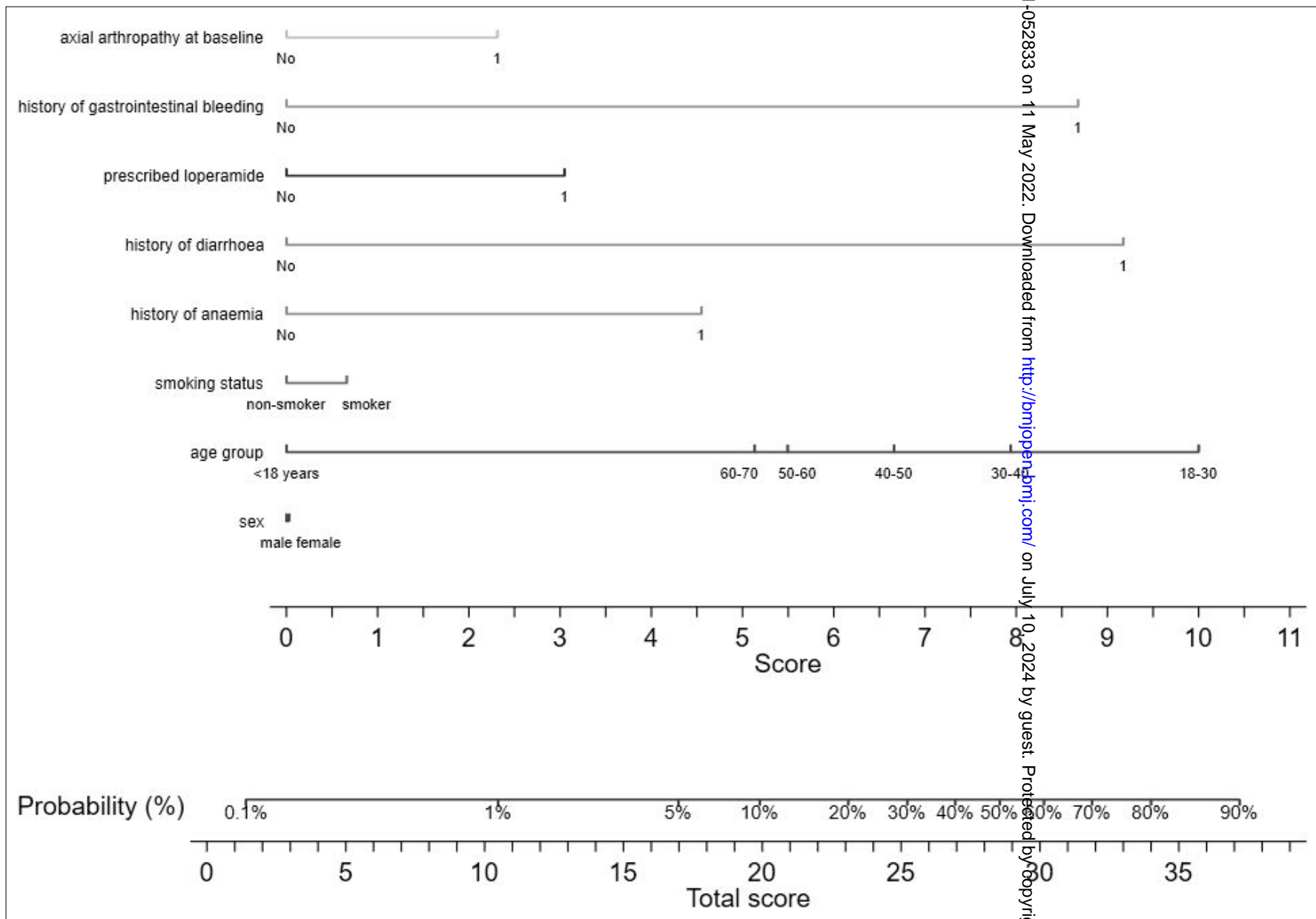
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	>30Kg/m ²	0.71	0.47	1.07	0.103	0.86	0.51	1.44	0.561	0.53	0.27	1.05	0.071
	Missing	0.98	0.65	1.46	0.912	1.12	0.67	1.86	0.675	0.80	0.42	1.53	0.495
	Townsend (least deprived – reference) 1	1.00				1.00				1.00			
	2	1.15	0.78	1.71	0.479	1.10	0.67	1.79	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: Nomogram: prediction of inflammatory bowel disease diagnosis within 3-years of a diagnosis of anterior uveitis



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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

		Item No	Recommendation	Page number
✓	Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1 & 3
✓			(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
	Introduction			
✓	Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5 & 6
✓	Objectives	3	State specific objectives, including any prespecified hypotheses	5 & 6
	Methods			
✓	Study design	4	Present key elements of study design early in the paper	7 & 8
✓	Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7 & 8
✓	Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7, 8 & 9
✓			(b) For matched studies, give matching criteria and number of exposed and unexposed	
✓	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8 & 9
✓	Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
✓	Bias	9	Describe any efforts to address potential sources of bias	7 & 8
✓	Study size	10	Explain how the study size was arrived at	7 & 11
✓	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8 & 9
✓	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8 & 9
			(b) Describe any methods used to examine subgroups and interactions	8 & 9
			(c) Explain how missing data were addressed	9
			(d) If applicable, explain how loss to follow-up was addressed	N/A
			(e) Describe any sensitivity analyses	N/A
	Results			
✓	Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, 11, Figure 1
			(b) Give reasons for non-participation at each stage	7, 11, Figure 1
			(c) Consider use of a flow diagram	Figure 1

✓	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
			(b) Indicate number of participants with missing data for each variable of interest	11, Table 1
			(c) Summarise follow-up time (eg, average and total amount)	11, Table 1
✓	Outcome data	15*	Report numbers of outcome events or summary measures over time	11, 12,13
✓	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12,13
			(b) Report category boundaries when continuous variables were categorized	
			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
✓	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12,13 (appendices)
	Discussion			
✓	Key results	18	Summarise key results with reference to study objectives	15
✓	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
✓	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18 & 19
✓	Generalisability	21	Discuss the generalisability (external validity) of the study results	17, 19
	Other information			
✓	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

BMJ Open

The risk of a subsequent diagnosis of inflammatory bowel disease in subjects with ophthalmic disorders associated with inflammatory bowel disease: a retrospective cohort analysis of UK primary care data

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5 1 Title Page
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8 2 The risk of a subsequent diagnosis of inflammatory bowel disease in
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10 3 subjects with ophthalmic disorders associated with inflammatory bowel
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12 4 disease: a retrospective cohort analysis of UK primary care data
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14 5

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16 6 **Short title:** Inflammatory Bowel Disease risk in associated eye disease
17

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3 44 Word Count: 4350
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6 45 **Ethics**
7

8 46 Use of IQVIA Medical Research Data* is approved by the UK Research Ethics Committee (reference number:
9 47 18/LO/0441). In accordance with this approval, the study protocol was reviewed and approved by an
10 48 independent Scientific Review Committee (SRC) in September 2019 (reference number: 19THIN066).

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13 49 *IQVIA Medical Research Data (IMRD-UK) incorporates data from THIN, A Cegedim Database. Reference
14 50 made to THIN is intended to be descriptive of the data asset licensed by IQVIA. This work used de-identified
15 51 data provided by patients as a part of their routine primary care.
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21 52

22 53 **Abbreviations:**
23

24 54 Extra-Intestinal Manifestation (EIM), anterior uveitis (AU), inflammatory bowel disease (IBD);
25 55 Crohn's disease (CD); ulcerative colitis (UC); Hazard ratio (HR); The Health Improvement Network
26 56 (THIN); IQVIA Medical Research Data (IMRD-UK).
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Abstract:

Objectives Ophthalmic conditions including anterior uveitis (AU), episcleritis and scleritis may occur in association with the inflammatory bowel diseases (IBD) as ophthalmic extraintestinal manifestations. This aim of this study was to assess the risk of a later IBD diagnosis in those presenting with IBD associated ocular inflammation (IAOI).

Design Retrospective Cohort study

Setting Primary care UK database

Participants 38,805 subjects with an IAOI were identified (median age 51 (38-65), 57% female) and matched to 153,018 subjects without IAOI.

Measures The risk of a subsequent diagnosis of IBD in subjects with IAOIs compared to age/sex matched subjects without IAOI. Hazard ratios (HR) were adjusted for age, sex, body mass index, deprivation, comorbidity, smoking, and baseline axial arthropathy, diarrhoea, loperamide prescription, anaemia, lower gastrointestinal bleeding and abdominal pain.

Logistic regression was used to produce a prediction model for a diagnosis of IBD within 3 years of an AU diagnosis.

Results 213 (0.6%) subsequent IBD diagnoses (102 ulcerative colitis (UC) and 111 Crohn's disease (CD)) were recorded in those with IAOIs and 329 (0.2%) (215 UC and 114 CD) in those without. Median time to IBD diagnosis was 882 (IQR 365-2,043) days in those with IAOI and 1,403 (623-2,516) in those without. The adjusted HR for a subsequent diagnosis of IBD was 2.25 (95%CI 1.89-2.68), $p < 0.001$; for UC 1.65 (1.30-2.09), $p < 0.001$; and for CD 3.37 (2.59-4.40), $p < 0.001$ in subjects with IAOI compared to those without.

Within 3 years of an AU diagnosis, 84 (0.5%) subjects had a recorded diagnosis of IBD. The prediction model performed well with a C-statistic of 0.75 (0.69-0.80).

Conclusions Subjects with IAOI have a two-fold increased risk of a subsequent IBD diagnosis. Healthcare professionals should be alert for potential signs and symptoms of IBD in those presenting with ophthalmic conditions associated with IBD.

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90 Article Summary

91 Strengths and limitations of this study

- 92 • Large sample size from a nationally representative primary care database.
- 93 • Routinely gathered data gives a “real-life” view of the reporting of eye and inflammatory bowel
94 diseases in a community setting.
- 95 • Prediction model development to help clinicians become aware of the risks of inflammatory
96 bowel disease in patients presenting with eye diseases.
- 97 • Risk of under recording where eye manifestations do not reach a threshold for presentation to
98 health care professionals.
- 99 • Database is not linked to secondary care database and therefore cross validation of secondary
100 care diagnoses was not possible.

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103 Introduction

104 Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a
105 relapsing, inflammatory, autoimmune condition of unknown aetiology. Thought to be the
106 consequence of dysregulation of the immune system at the interface between the microbiome and
107 the bowel wall, IBD shares many of the disturbed pathways observed in other autoimmune
108 conditions^{1,2}.

109 A number of conditions are commonly observed in those suffering with IBD and are therefore known
110 as extraintestinal manifestations (EIMs) of IBD. EIMs can be classified as: *IBD-specific* (e.g. metastatic
111 CD); *drug-related* (e.g. anti-TNF associated skin lesions or steroid-induced cataract development);
112 *associated* - signalling a predisposition to autoimmunity (e.g. ankylosing spondylitis); or *reactive* -
113 implying common pathophysiological pathways without histopathological similarity (e.g. pyoderma
114 gangrenosum)^{3,4}. Certain conditions belonging to the reactive and associated EIM subtypes have
115 been accepted as *classical* EIMs and include ophthalmic, dermatological, musculoskeletal and
116 hepatobiliary diseases^{5,6}.

117 A link between IBD and ophthalmic conditions has long been recognised. The cell surface immune
118 regulation protein Human Leucocyte Antigen B27 (HLA B27) is more common in IBD and uveitis
119 which also links uveitis with the musculoskeletal EIMs, in particular the axial arthropathies
120 (ankylosing spondylitis and sacroiliitis)⁷⁻¹⁰. The *classical* EIMs in the ophthalmic group include
121 anterior uveitis (AU), episcleritis and scleritis. These complications may occur in up to 13% of IBD
122 patients, with the potential for significant morbidity including blindness^{11,12}.

123 Ophthalmic EIMs range from mild and benign to severe, requiring urgent intervention to preserve
124 the eye. Uveitis is a sight-threatening condition and is more commonly bilateral and anterior in the
125 context of IBD; it may run in parallel or independently of IBD activity¹²⁻¹⁴. Treatment for uveitis
126 depends on the severity and the specific location of inflammation, and commonly includes topical,
127 intraocular and systemic corticosteroids, with second-line immunosuppressants and biologics where

1
2
3 128 needed¹². Episcleritis is a benign condition that is not sight threatening and presents with eye
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5 129 redness and mild to moderate discomfort. It is caused by inflammation of the episcleral tissue which
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7 130 lies above the sclera and below the conjunctiva. It runs a parallel course when associated with IBD
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9
10 131 and often does not require specific treatment ^{12,15}. Scleritis on the other hand is a serious,
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12 132 destructive, inflammatory condition and can be sight threatening. It presents with redness of the
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14 133 sclera, deep 'boring' pain and may cause tissue destruction leading to visual impairment. Treatment
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16 134 is essential and may include systemic anti-inflammatory agents, corticosteroids and
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18 135 immunosuppressants ¹². Unlike episcleritis, it may appear independently of IBD activity and is
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21 136 uncommon compared to episcleritis ¹⁶.

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24 137 *Classical* EIMs may occur prior to a diagnosis of IBD and may occur in isolation in those who never
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26 138 develop IBD ^{17,18}, here we term these conditions IBD associated ocular inflammation (IAOI). The aim
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28 139 of this study was to examine the risk of and time to a subsequent diagnosis of IBD in those with a
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30
31 140 new diagnosis of IAOI.

141 Materials and Methods

142 Data Source

143 Data in the IQVIA Medical Research Data (IMRD-UK) database are obtained from over 800 primary
144 care practices across the United Kingdom (UK). IMRD-UK contains data on 15.8 million subjects and
145 is considered representative of the UK population ¹⁹. Data on included subjects is longitudinally
146 captured including primary and secondary care diagnostics, drug prescriptions, symptoms and
147 diagnoses, and demographic information. Data are uploaded using a hierarchical system of (Read)
148 codes ²⁰. To be eligible for the study, IMRD-UK primary care practices required at least one year since
149 the installation of the computerised medical record system and achievement of an acceptable
150 mortality recording (AMR) level ²¹. These criteria help to ensure data reliability and reduce the risk of
151 under-recording baseline data.

152 In this retrospective cohort study using IMDR-UK patients are anonymous and were not identified or
153 involved in the study.

154 Study Design

155 *Cohort study*

156 A retrospective matched cohort study was undertaken between 1st January 1995 and 25th September
157 2019 to investigate the association between IBD outcome and all studied IAOI exposures (anterior
158 uveitis (AU), scleritis and episcleritis), with secondary studies of anterior uveitis alone and combined
159 episcleritis and scleritis. Individuals were eligible for inclusion from either the date of eligibility of
160 their primary care practice or one year after they were registered, whichever was later. Those
161 subjects with an incident IAOI diagnosis of interest (recorded through Read codes – Appendix 1)²²
162 and without an established IBD diagnosis (exposed) were compared to subjects without the specific
163 IAOI diagnosis of interest and without an established IBD diagnosis (unexposed) for each analysis.
164 Exposed participants were matched to unexposed participants by age at cohort entry (± 2 years) and
165 sex in a ratio of 1:4. Index date was defined as the start of follow up and was the date of IAOI
166 diagnosis for the IAOI group. The same date was assigned to matched subjects without an IAOI in

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3 167 order to mitigate for immortal time bias²³. Only subjects without a co-existing IBD diagnosis at index
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5 168 date were included in the study.

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8 169 Subjects were followed from their index date until the first of the following events (exit date): death;
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10 170 subject left the practice; last data collection from their practice; study end date (25th September
11
12 171 2019); diagnosed with IBD (CD or UC) as identified through Read codes. Subjects coded for both UC
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14 172 and CD were assigned to one condition based on frequency of coding. For those with equal coding,
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16 173 the earliest diagnosis date and the latest diagnosis of IBD subtype was used.

174 *Prediction model*

175 Subjects with an incident diagnosis of AU over the same study period were investigated to identify
176 predictors for a diagnosis of IBD within the following 3-years. Case examples were used to determine
177 the probability of diagnosis of IBD in subjects presenting with anterior uveitis.

178 *Validation*

179 Primary care coding to identify patients with IBD has been previously validated^{24,25}. IAOI codes were
180 reviewed by two clinicians, having been first sourced from other published primary care database
181 studies²⁶⁻²⁸. Ophthalmology expert advice was sought for IAOI coding decisions. AU codes, excluding
182 uveitis associated with other pathologies (e.g. infective), were selected for inclusion along with
183 episcleritis and scleritis. Clinical codes used to identify UC, CD and IAOI are listed in Appendix 1.

185 **Statistical Analysis**

186 *Cohort study*

187 The time from index date to a later diagnosis of IBD in those with and without a baseline IAOI were
188 presented as median time to IBD and UC or CD diagnoses with accompanying interquartile ranges
189 (IQR). Log-rank tests were used to compare time to IBD diagnosis between those with and without
190 IAOIs. Cox proportional hazard models, with time to subsequent diagnosis of IBD as the time-metric,
191 were produced to assess the adjusted hazard ratio (aHR) of IBD diagnoses in participants with an
192 IAOI compared to matched subjects without IAOIs. For all IAOIs and when AU was examined alone,

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2
3 193 aHRs were produced for all IBD, UC and CD outcomes. However, for the combined episcleritis and
4
5 194 scleritis study, due to IBD diagnoses being less commonly observed, only an aHR for all IBD was
6
7
8 195 modelled.

10 196 **Covariates**

11 197 Hazard ratios were adjusted for age at index; sex; smoking status; body mass index (BMI); Townsend
12
13
14 198 level of deprivation (quintiles); Charlson comorbidity score; baseline axial arthropathy diagnosis; and
15
16 199 within 6-months of IAOI diagnosis (prior to an IBD diagnosis) coding of anaemia (<11.9g/dL for
17
18 200 females and <12.9g/dL for males), abdominal pain, loperamide prescription, diarrhoea, or lower
19
20
21 201 gastrointestinal bleeding. Smoking status was dichotomised into current smokers and non-smokers
22
23 202 with missing data for smoking status considered non-smokers; a method that has been previously
24
25 203 validated²⁹.

28 204 **Missing data**

29 205 Missing data for Townsend deprivation quintile and BMI were considered as separate categories and
30
31 206 a complete case analysis, where subjects with missing data were excluded, was undertaken.
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33
34 207 Proportional hazards were assessed using log-log plots. Cumulative incidence plots were produced
35
36 208 to illustrate the cumulative risk of IBD over time.

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41 210 ***Prediction model***

42 211 Only participants with an IBD diagnosis within 3-years or those who had a minimum of 3-years follow
43
44 212 up were included in the development cohort. Multivariable logistic regression was used to establish
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46
47 213 a prediction model for IBD diagnosis in subjects presenting with a new diagnosis of anterior uveitis.
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49 214 Backwards stepwise elimination was used to select predictor variables with an elimination alpha-to-
50
51 215 remove p-value of 0.20.

54 216 **Candidate predictor variables**

55 217 Sex, age (categorical) and smoking status were included due to their clinical importance. Further
56
57
58 218 candidate variables including baseline axial arthropathy, BMI (categorical) and within 6-months
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3 219 coding of anaemia, abdominal pain, lower gastrointestinal bleeding, loperamide prescription and
4
5 220 diarrhoea (prior to an IBD diagnosis) were assessed. Some potential candidate predictors such as
6
7 221 Townsend deprivation and co-morbidity score were not included, due to the small number of
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10 222 outcome events.
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13 223 **Model performance**

14 224 A receiver operating characteristic (ROC) curve and C-statistic was used to assess model
15
16 225 discrimination; calibration was assessed using the Hosmer-Lemeshow test for goodness of fit.
17
18 226 Internal validation of the prediction model was performed through bootstrapping by resampling the
19
20 227 dataset (with replacement) 200 times and comparing the resulting average of the area under the
21
22 228 ROC curve from the bootstrap samples to the original model.
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26 229 Analyses were performed using Stata version 16.0 and p-values <0.05 were considered statistically
27
28 230 significant³⁰.
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31 231

32 33 232 **Patient and public involvement**

34 233 Patients and/or the public were not involved in the design, or conduct, or reporting, or
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36 234 dissemination plans of this research.
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235 Results

236 Study Subjects

237 Following exclusions (Figure 1), 38,805 subjects with an IAOI were identified (median age 51 (38-65)
238 and 57% female). IAOI cases included those coded as AU: 22,098 (57%); episcleritis: 13,955 (36%);
239 scleritis: 2,482 (0.6%); episcleritis or scleritis (a non-specific code where it was not possible to
240 determine whether subjects were episcleritis or scleritis): 270 (0.01%). The age distribution of AU
241 (with a higher frequency in the elderly) and episcleritis or scleritis (with a higher frequency in the 40-
242 50 age group) was in keeping with previous findings.^{31,32} IAOI subjects were age and sex matched to
243 153,018 subjects without an IAOI. The median follow-up period was five years with a total of
244 244,503 person years (py) of follow-up time in IAOI subjects and 934,847 py in those without IAOIs.
245 In those with an IAOI, 2.9% (1,116) had another, non-ophthalmic EIM at index date compared to
246 0.9% (1,433) in subjects without IAOIs. Subject characteristics are shown in Table 1.

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248 Risk of Inflammatory Bowel Disease Diagnosis in Associated Ophthalmic Conditions

249 During the study period 213 (0.6%) IBD diagnoses (103 UC and 111 CD) were observed in subjects
250 with IAOIs compared to 329 (0.2%) (215 UC and 114 CD) in the matched control group. 893 (2.3%)
251 subjects with IAOIs had an axial arthropathy recorded at baseline and 35 (0.1%) had the HLA-B27
252 genotype coded, compared to 1,013 (0.7%) controls with an axial arthropathy and 7 (0.005%) with
253 the HLA-B27 genotype. From index date (IAOI diagnosis date for exposed subjects, with matched
254 controls assigned the same index date as their corresponding exposed subjects), the median time to
255 IBD diagnosis was 882 (IQR 365-2,043) days in subjects with IAOIs vs 1,403 (623-2,516) days in those
256 without IAOIs. For a UC diagnosis 922 (410-1,910) vs 1,360 (547-2,406) days and for a CD diagnosis
257 738 (269-2,011) vs 1,625 (641-2,779) days, in subjects with and without IAOIs respectively. For all
258 IBD, UC and CD the log-rank test p-value was <0.001. Following adjustment, the aHR for a diagnosis
259 of IBD in IAOI subjects compared to those without IAOIs was 2.25 (95%CI 1.89-2.68), with an aHR of

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3 260 1.65 (1.30-2.09) for UC and 3.37 (2.59-4.40) for CD, p-values <0.001 (Table 2; full models are shown
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5 261 in Appendix 2). Figure 2 shows the cumulative incidence plot for IBD diagnoses in subjects with IAOIs
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7 262 compared to those without.
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14 264 Risk of Inflammatory Bowel Disease Diagnosis in Anterior Uveitis, Episcleritis and 15 265 Scleritis

16 266 Subject characteristics of IAOI and matched subjects without IAOIs in these secondary analyses
17 267 together with the full Cox models are shown in Appendices 3, 4 and 5. Subject numbers for
18 268 individual IAOIs differ slightly to those in the combined IAOI study above because only the first
19 269 diagnosed incident IAOI was considered in the combined study, but a subject might be subsequently
20 270 diagnosed with other IAOIs and therefore be eligible for inclusion in more than one analysis for the
21 271 individual IAOIs presented in this section. In the AU study, 22,547 subjects with a new diagnosis of
22 272 AU (median age 53 (39-68) years, 54% female) were matched to 89,422 subjects without AU. AU
23 273 subjects and their matched subjects provided 137,878 and 531,653 py of follow-up, respectively. 152
24 274 (0.7%) IBD diagnoses (67 UC and 85 CD) were observed in AU subjects during the study period and
25 275 157 (0.2%) IBD diagnoses (107 UC and 50 CD) among subjects without AU. The median time to an
26 276 IBD diagnosis was 898 (373-2,027) days in the AU subjects compared to 1,457 (539-2,700) in those
27 277 without AU (log-rank test p<0.001). For a UC diagnosis 1,117 (489-2,008) days vs 1,490 (553-2,553)
28 278 days and for a CD diagnosis 687 (286-2,006) vs 1,160 (516-2,892) days for AU subjects compared to
29 279 subjects without AU, respectively (log-rank tests p<0.001 for both CD and UC). The aHR for a
30 280 subsequent IBD diagnosis in subjects with AU compared to matched subjects without AU was 3.39
31 281 (2.70-4.25); for UC aHR was 2.23 (1.63-3.04) and for CD 5.77 (4.04-8.24), all p-values <0.001 (Table 2
32 282 (full models are shown in Appendix 4)).
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56 283 In the analysis of episcleritis and scleritis combined, 17,439 subjects (14,752 (85%) episcleritis and
57 284 2,976 scleritis; median age 48 (36-61) and 62% female) were identified and matched to 68,823
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3 285 controls. Episcleritis and scleritis subjects and matched participants contributed 36,324 and 136,304
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5 286 py follow-up, respectively. 104 (0.6%) IBD cases (23 UC and 81 CD) were observed among episcleritis
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7 287 and scleritis subjects and 53 (0.1%) (30 UC and 23 CD) among those without these IAOIs. The median
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9 288 time to an IBD diagnosis in episcleritis and scleritis subjects was 848 (348-2,239) days compared to
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11 289 1,522 (577-2,838) days in controls, log-rank test $p < 0.001$. The aHR for the diagnosis of IBD in those
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13 290 subjects with an incident diagnosis of episcleritis or scleritis compared to matched subjects without
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15 291 these IAOIs was 1.73 for IBD (1.31-2.28), $p < 0.001$ (Table 2 (full models are shown in Appendix 5)).
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18 292 Complete case analyses were performed where subjects with missing variables were dropped from
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20 293 the Cox models. There was minimal change in estimates and significance remained unchanged.
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22 294 Adjusted HRs for the complete-case analyses are found in Appendix 6.
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27 295 Prediction Model

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29 296 22,547 AU subjects were identified with 15,458 eligible for inclusion in the prediction model
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31 297 development cohort based on sufficient follow-up time or an IBD diagnosis within 3 years of the AU
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33 298 diagnosis. 84 (0.53%) subjects had a recorded diagnosis of IBD (63% CD) within 3 years of follow-up.
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35 299 The characteristics of those with and without an IBD diagnosis are shown in Table 3. Those with an
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37 300 IBD diagnosis were younger (median age 44 (IQR 35-56) and 53 (39-68) years respectively, $p < 0.001$)
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39 301 but there was no difference in sex, smoking status or body mass index category.
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41
42 302 Following backwards stepwise regression, female sex, smoking status, BMI and abdominal pain
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44 303 within 6 months of an AU diagnosis exceeded the alpha-to-remove threshold. However, female sex
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46 304 and smoking status were retained in the model due to their clinical importance while weight loss
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48 305 within 6 months of an AU diagnosis and HLA-B27 genotype were coded in only 5 and 19 cases
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50 306 respectively and were therefore not included in the analysis. The multivariable logistic regression
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52 307 model to assess the risk of being diagnosed with IBD within a 3-year period following AU diagnosis is
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54 308 presented in Table 4. The Hosmer-Lemeshow χ^2 test for goodness of fit was applied to the
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56 309 prediction model development data set and was not significant at 0.093, suggesting reasonable
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3 310 model fit. The receiver operating characteristic (ROC) curve, shown in Figure 3, produced an area
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5 311 under the curve (AUC) C-statistic of 0.75 (95%CI 0.69-0.80). Following internal validation by
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7 312 bootstrapping, resampling the dataset 200 times, the mean difference between the original AUC and
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9 313 AUC in each bootstrap sample was 0.021. This produced a bias-corrected C-statistic value of 0.71
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12 314 (0.67-0.77).

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15 315 A probability calculator was produced to determine the likelihood of an IBD diagnosis within the
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17 316 anterior uveitis cohort using the following examples: 1) a female, 34-year-old, current smoker and a
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19 317 within 6-month history of anaemia would have a 2% risk of IBD being diagnosed within 3 years of an
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21 318 anterior uveitis diagnosis; 2) a male, 18-year-old, non-smoker and a history of axial arthropathy,
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23 319 diarrhoea and loperamide use would have a 25% 3-year IBD diagnosis risk; 3) a female, 49-year-old,
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25 320 current smoker with a history of anaemia, diarrhoea and lower gastrointestinal bleeding would have
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27 321 a 55% risk of an IBD diagnosis within 3 years. A nomogram for the prediction model is shown in
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31 322 Appendix 7.

323 Discussion

324 In this study, we have shown that subjects with an IAOI, but without a recorded diagnosis of IBD, are
325 at a two-fold greater risk (by an average of 5 years follow-up) of subsequently being diagnosed with
326 IBD than matched subjects without an IAOI. The risk was highest in those who later had a CD
327 diagnosis. A wide time scale was observed between an IAOI diagnosis and a subsequent IBD
328 diagnosis with a median time to IBD diagnosis of greater than two years. When AU was examined
329 alone, subjects had a 3-fold greater risk of a later IBD diagnosis compared to matched subjects
330 without AU and again the risk was highest for a subsequent CD diagnosis at almost 6-fold.

331 Ophthalmic conditions are among the most common extraintestinal manifestations of IBD and are
332 commonly diagnosed at the time or following a diagnosis of IBD ¹⁸. This study, however, has
333 established that subjects with a diagnosis of an IAOI, either in combination or as separate entities
334 (anterior uveitis or episcleritis and scleritis), were at increased risk of developing a subsequent
335 diagnosis of IBD over time (combined IAOI aHR 2.25 (1.89-2.68), $p < 0.001$). The time to a diagnosis of
336 IBD was shorter in those with ophthalmic conditions compared to matched controls (median time
337 2.4 years versus 3.8 years, respectively). However, the time from IAOI diagnosis to IBD was often
338 greater than two years. This was a significant time lag which may reflect a lack of symptoms to
339 indicate IBD. Relatively few subjects were coded with anaemia, abdominal pain, lower
340 gastrointestinal bleeding, weight loss, diarrhoea or loperamide prescriptions around the time of the
341 diagnosis of the ophthalmic condition. However, given that many EIMs parallel the course of IBD, it
342 is possible that IBD may be present earlier and pauci-symptomatic and as such they may represent a
343 missed opportunity and a delayed diagnosis.

344 The aetiology of ophthalmic EIMs is not well understood. They are thought to be more common in
345 those with CD rather than UC ¹², and our findings support this. A limitation of the IMRD-UK database
346 is that it does not allow for the discrimination of IBD severity, activity or gastrointestinal location.
347 This is pertinent because those with colonic or ileocolonic disease have been shown to have an

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3 348 increased risk of ophthalmic EIMs ^{16,33,34}. Several studies have suggested that certain peptide targets
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5 349 for the immune system are found in both joints, eyes and the colon ^{35,36}. It may be that immune
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7 350 dysregulation in relation to the enteric flora and subsequent cross-reactive antigens play a role in
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9 351 some EIM presentations. Moreover, the HLA-B27 antigen appears to play an important role in some
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11 352 mouse models where colitis and arthritis only developed in those where gut flora was present ³⁶.
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13 353 HLA-B27 positivity was not commonly coded in the IMRD-UK database and is highly likely to be
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15 354 under-recorded given its specialist nature. However, previous reports that this genotype is observed
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17 355 in greater numbers in those with EIMs and its association with arthropathies and ophthalmic
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19 356 conditions makes this an important consideration in such a study ^{7,16,37}. Arthropathies and the HLA-
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21 357 B27 haplotype were seen in larger numbers at baseline in ophthalmic conditions associated with IBD
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23 358 than in controls in the present study. Previously, it has been found that HLA-B27 is present in 90% of
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25 359 those with ankylosing spondylitis, but just under half of those with CD and sacroiliitis are positive for
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27 360 this allele ⁸. IBD is known to have a genetic link with increased risk seen in the offspring of those with
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29 361 IBD, and this is also the case with uveitis in those with IBD. The HLA region of Chromosome 6
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31 362 contains both major histocompatibility complex genes (HLAs) as well as other important IBD related
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33 363 genes (TNF- α). The vicinity of these genes increases the likelihood of inheriting several important
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35 364 genetic variations (a phenomenon known as linkage disequilibrium) and may help to explain familial
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37 365 traits and the relationship between some EIMs and the IBDs ³⁴. Other HLA types (HLA-B58) have also
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39 366 been associated with IBD and uveitis but it is unclear how the interplay between genetic and
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41 367 environmental factors apply, given that most of those who are HLA-B27 positive will not suffer any ill
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43 368 effect from this phenotypic variant and HLA-B27 does not itself appear to increase the risk of IBD ³⁴.
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45 369 A limitation of this study is the lack of family history data and as a result an assessment of the risk in
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47 370 those with a family history of EIMs or IBD could not be made.
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49
50 371 Vavricka et al have reported that multiple EIMs were not uncommon in IBD subjects, with CD and UC
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52 372 subjects studied having more than one EIM in 16% and 8% of cases respectively ³⁸. Axial
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54 373 arthropathies in the present study were included at baseline given evidence that ophthalmic and

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3 374 joint manifestations may be seen more frequently together in IBD⁹. More than 2% of cases had a
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5 375 pre-existing axial arthropathy compared to less than one percent of matched controls. Other
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7 376 investigators have examined IBD and arthritis in UK primary care databases. However, type 1 and 2
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9 377 EIM arthropathies are challenging to identify given a lack of specific coding, and, seropositive and
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11 378 negative inflammatory arthritides, although associated, are not classical EIMs and as such were not
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13 379 examined in this study²⁶. The presence of an axial arthropathy increased the risk of IBD more than
14
15 380 two-fold and was found to be associated with later IBD in anterior uveitis. Although not specifically
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17 381 examined in this study, an increased number of other EIMs in those who develop a new diagnosis of
18
19 382 an ophthalmic condition associated with IBD compared to controls has been demonstrated
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21 383 previously. This has been shown to be particularly true among those with arthritic as well as
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23 384 ophthalmic conditions³⁹.

28 385 Prediction Model

29 386 The prediction model for IBD diagnosis in subjects with anterior uveitis found associations with
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31 387 several variables. Anaemia, diarrhoea, and lower gastrointestinal bleeding heralded an IBD
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33 388 diagnosis, highlighting the need for careful history taking in ophthalmic care settings and
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35 389 investigation for IBD if such symptoms are revealed. Other inflammatory and autoimmune
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37 390 conditions associated with uveitis can lead to anaemia, including sarcoidosis. Some of these
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39 391 conditions will produce an anaemia of chronic disease, and others a haemolytic anaemia^{40,41}. In the
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41 392 context of ophthalmic conditions associated with IBD, iron deficiency anaemia should be
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43 393 investigated to prevent an IBD diagnostic delay. Age was strongly associated with IBD in our model.
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45 394 Those in the age group 18-30 had the highest risk compared to under 18 year-olds, however all ages
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47 395 up to 70 had an increased IBD risk compared to the reference group (under 18 years). Ottaviano et
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49 396 al. reviewed the published literature on ophthalmic EIMs in children and found that there was little
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51 397 data available. They suggested that this may be related to asymptomatic uveitis, as well as a lower
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53 398 prevalence of these EIMs in childhood compared to adults⁴². In the present study, less than 6% of
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55 399 the cohort were aged under 18 and only 0.2% of subjects in this age category developed IBD during
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3 400 the study period, with a slight preponderance towards CD, as has been previously shown in
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5 401 paediatric series ⁴².

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8 402 The use of primary care databases has both strengths in terms of subject numbers and subject level
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10 403 data, but also limitations. Perhaps most relevant to the present study are the risk of under-recording
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12 404 and validation. The accuracy of coding in IMRD-UK is related to the primary care practitioner's ability
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14 405 to record diagnoses accurately. Several EIMs (especially episcleritis, which is self-limiting and
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16 406 typically causes only mild discomfort) and IBD symptoms, especially early on in the disease process,
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18 407 may not lead to healthcare-seeking behaviour in primary care and may therefore not be coded in the
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20 408 database in a timely fashion. Although IBD in primary care has previously been validated ²⁴ and in
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22 409 the present study at least 50% of those with an IBD diagnosis had more than one IBD code recorded,
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24 410 to our knowledge a validation study of the ophthalmic conditions used in the present study has not
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26 411 been previously undertaken. Given the lack of external validation, an often-prohibitive task in terms
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28 412 of cost and time, there is a risk of bias. Episcleritis is the most common ophthalmic condition
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30 413 associated with IBD ¹⁸, however, given its benign course it may be under-recorded in the IMRD-UK
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32 414 database. For uveitis and scleritis, however, these diagnoses would be made in a secondary care eye
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34 415 service. For this reason, they may be more reliably recorded when the information reaches primary
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36 416 care. There may also be delays in the recording of data making time-to-event analysis challenging to
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38 417 interpret. IBD is more commonly associated with anterior uveitis, and this was therefore the focus of
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40 418 this study. However, IBD can rarely be associated with intermediate, posterior or panuveitis, and so
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42 419 our estimates could be considered to be conservative. Offsetting this were limitations in the way
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44 420 uveitis was coded with a few "unspecified" uveitis Read codes risking the inclusion of some non-
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46 421 anterior phenotypes, although AU is the most common type of uveitis.

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56 423 Ophthalmic conditions associated with IBD which present prior to an IBD diagnosis are not common.

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58 424 However, an increasing prevalence of IBD both in the UK and around the world has been
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3 425 demonstrated^{43–45}. Given the increasing numbers of patients with IBD, the need for clinicians from
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5 426 many disciplines outside gastroenterology to be aware of IBD is important. Those who care for
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7 427 patients presenting with ophthalmic conditions associated with IBD should be attentive to features
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9 428 which may increase the likelihood of an IBD diagnosis, in order that appropriate investigation and
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11 429 referral can be made in those patients with suggestive clinical features.
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24 433 **Contribution statement:** All authors contributed to the conception and design of the work, DK, NT,
25 434 TT, JSC, KN, NJA and RCR contributed to the acquisition of the data. DK NT, TT, JSC and NJA
26 435 contributed to the analysis of the data and all authors including AKD and TB contributed to the
27 436 interpretation of data. DK drafted the manuscript and all authors contributed to the revision and
28 437 critical review of the manuscript. All authors gave final approval of the version published and agree
29 438 to be accountable for all aspects of the work.
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36 440 **Competing interests:** KN reports grant from AstraZeneca, Sanofi and Boehringer Ingelheim, outside
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47 444 **Funding Declaration:** Nothing to declare.
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52 447 under licence and are not available for open access. No additional data available.
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571 **Table 1. Demographics details of study subjects**

	Subjects with IBD associated ocular inflammation	Matched subjects without IBD associated ocular inflammation
	n (%)	n (%)
Number of subjects	38,805	153,018
Median person years of follow-up (IQR)	5.4 (2.3-9.4)	5.2 (2.3-9.2)
Median age (IQR)	51 (38-65)	49 (37-63)
Age category n		
<18 years	2,142 (5.5)	9086 (5.9)
18-30	3,264 (8.4)	13,924 (9.1)
30-40	5620 (14.5)	23,644 (15.5)
40-50	7,589 (19.5)	30,586 (20.0)
50-60	7,221 (18.6)	28,622 (18.7)
60-70	5,989 (15.4)	22,990 (15.0)
>70	6,980 (18.0)	24,166 (15.8)
Female sex	22,249 (57.3)	87,694 (57.3)
Townsend Quintile		
1 - least deprived	8,880 (22.9)	34,368 (22.4)
2	7,520 (19.4)	29,210 (19.1)
3	6,989 (18.0)	27,726 (18.1)
4	5,873 (15.1)	23,272 (15.2)
5	3,814 (9.8)	15,312 (10.0)
Missing	5,729 (14.8)	23,130 (15.1)
Charlson comorbidity score		
0	24,457 (63.0)	106,735 (69.8)
1	8,414 (21.7)	28,888 (18.9)
>=2	5,934 (15.3)	17,395 (11.4)
Smoking status		
current smoker	6,632 (17.1)	28,586 (18.7)
non-smoker	32,173 (82.9)	124,432 (81.3)
Body mass index		
<25kg/m ²	12,799 (33.0)	51,136 (33.4)
25-30Kg/m ²	11,200 (28.8)	40,782 (26.6)
>30Kg/m ²	7,683 (19.8)	26,849 (17.6)
Missing	7,123 (18.4)	34,251 (22.4)
Anaemia^{†‡}	2,102 (5.4)	5,469 (3.4)
Abdominal pain[†]	837 (2.2)	2,574 (1.7)
Lower gastrointestinal bleeding[†]	363 (0.9)	1,042 (0.7)
Loperamide prescription[†]	558(1.4)	1,506 (1.0)
Diarrhoea[†]	974 (2.5)	2,424 (1.6)
HLA-B27 positive at baseline	35 (0.1)	7 (0.0)
Axial arthropathy at baseline	893 (2.3)	1,013 (0.7)
IAC at baseline (other than ophthalmic)[§]	1,116 (2.9)	1433 (0.9)

[†] coded within 6 months of Index date

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

[§] IAC: IBD associated condition: axial arthropathies, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, aphthous stomatitis

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573 **Table 2. Adjusted hazard ratios for risk of inflammatory bowel disease**

	aHR	[95% Confidence Interval]		p-value
Any IBD associated ocular inflammation				
Inflammatory bowel disease	2.25	1.89	2.68	<0.001
Ulcerative colitis	1.65	1.30	2.09	<0.001
Crohn's disease	3.37	2.59	4.40	<0.001
Anterior uveitis				
Inflammatory bowel disease	3.39	2.7	4.25	<0.001
Ulcerative colitis	2.23	1.63	3.04	<0.001
Crohn's disease	5.77	4.04	8.24	<0.001
Episcleritis or scleritis				
Inflammatory bowel disease	1.73	1.31	2.28	<0.001

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.

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576 **Table 3. Characteristics of anterior uveitis subjects with and without an inflammatory bowel disease**
 577 **diagnosis by 3 years**

	IBD diagnosis (n=84)	No IBD diagnosis (n=15,906)
Median age (IQR)	44 (35-56)	53 (39-68)
Age category (%)		
<18 years	0 (0)	604 (4)
18-30	17 (20)	1,173 (8)
30-40	18 (21)	2,092 (14)
40-50	18 (21)	2,912 (19)
50-60	14 (17)	2,861 (19)
60-70	12 (14)	2,531 (16)
>70	5 (6)	3,285 (21)
Female sex (%)	45 (54)	8,365 (54)
Smoking status (%)		
current smoker	21 (25)	2,893 (19)
non- smoker	63 (75)	12,565 (81)
Body mass index (%)		
<25kg/m ²	37 (44)	4,999 (33)
25-30Kg/m ²	23 (27)	4,588 (30)
>30Kg/m ²	14 (17)	3,111(20)
missing	10 (12)	2,760 (18)
Anaemia^{†‡} (%)	12 (14)	828 (5)
Abdominal pain[†] (%)	4 (5)	351 (2)
Loperamide prescription[†] (%)	8 (10)	238 (2)
Diarrhoea[†] (%)	20 (24)	349 (2)
Lower gastrointestinal bleeding[†] (%)	9 (11)	145 (1)
HLA-B27 positive at baseline (%)	0 (0)	19 (0.1)
Axial arthropathy at baseline (%)	6 (7)	510 (3)

[†] coded within 6 months of Index date

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

IBD: Inflammatory Bowel Disease

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580 **Table 4. Multivariable logistic regression prediction model of factors associated with developing**
 581 **inflammatory bowel disease within 3 years of an anterior uveitis diagnosis**

	β -Coefficient	Odds Ratio	[95% Conf. Interval]		P value
Sex					
Male (reference)		1.00			
Female	0.001	1.00	0.64	1.56	0.995
Age Category					
<18 years (reference)		1.00			
18-30	2.56	12.88	4.57	36.30	<0.001
30-40	2.05	7.75	2.79	21.59	<0.001
40-50	1.69	5.41	1.94	15.05	0.001
50-60	1.40	4.04	1.41	11.52	0.009
60-70	1.30	3.65	1.26	10.54	0.017
>70	0.00	1.00			
Smoking Status					
current smoker (reference)		1.00			
non smoker	-0.17	0.85	0.51	1.42	0.528
Anaemia[†]					
no (reference)		1.00			
yes	1.13	3.11	1.61	6.00	0.001
Diarrhoea[†]					
no (reference)		1.00			
yes	2.38	10.76	5.99	19.33	<0.001
Loperamide					
no (reference)		1.00			
yes	0.74	2.10	0.86	5.12	0.102
Lower gastrointestinal bleed					
no (reference)		1.00			
yes	2.27	9.69	4.54	20.70	<0.001
Axial arthropathy*					
no (reference)		1.00			
yes	0.67	1.95	0.83	4.60	0.128
Intercept	-7.08	0.0008	0.0003	0.0024	<0.001

[†] coded within 6 months of Index date

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

* Coded at baseline

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6 589 *Figure 1 Study flow chart.*
7 590 *Inflammatory bowel disease (IBD).*
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10 592 *Figure 2. Cumulative incidence of IBD (inflammatory bowel diseases) in subjects with*
11 593 *ophthalmic conditions (black line) and those without (grey line) with 95% confidence*
12 594 *intervals (dashed lines).*
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14 595 *Figure 3. Receiver operating characteristic curve of ability of prediction model to detect an*
15 596 *inflammatory bowel disease diagnosis within three years of an anterior uveitis diagnosis.*
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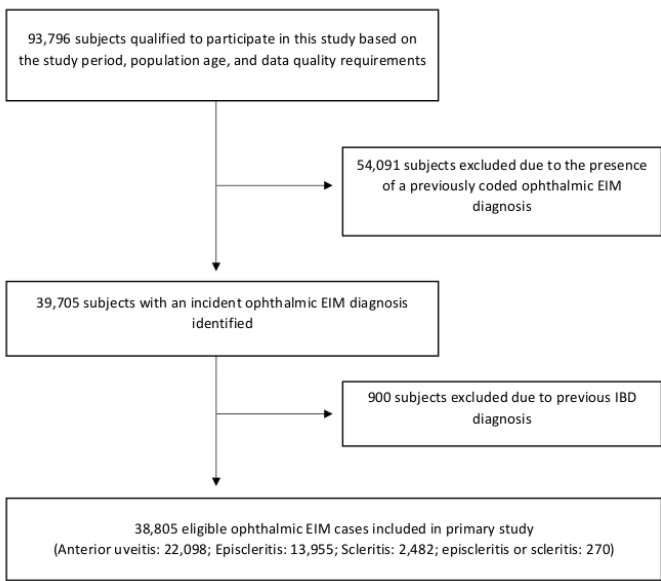
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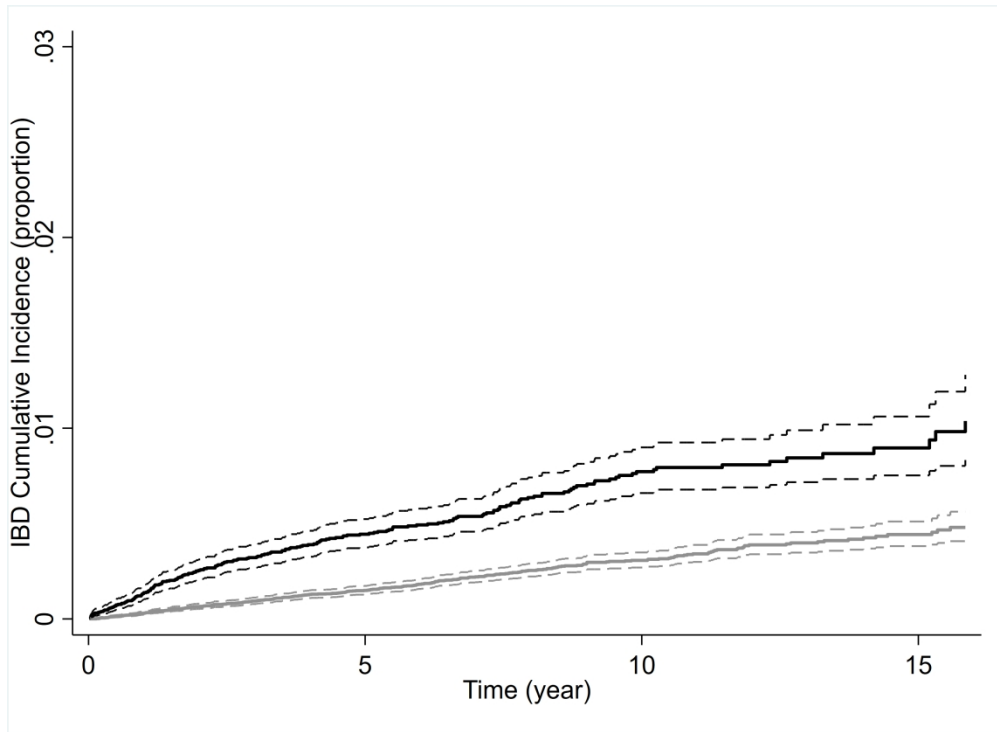
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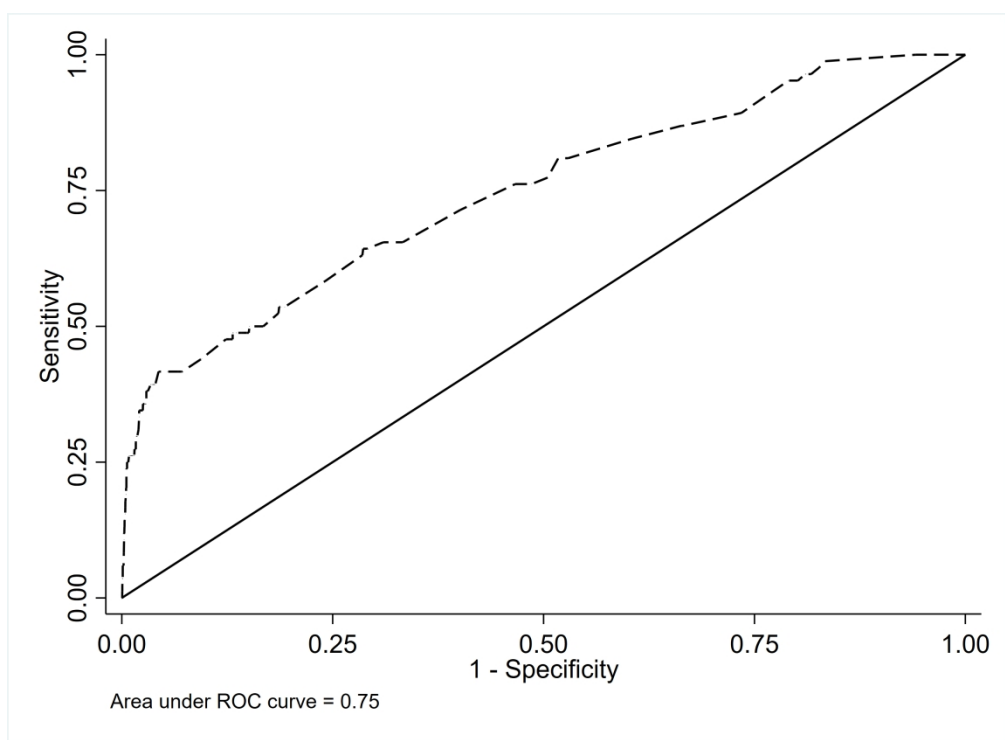
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Appendix 1

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

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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/m ²	7,344 (32.4)	29,447 (32.9)	5908 (33.9)	23455 (34.1)
25-30Kg/m ²	6,709 (29.5)	24,625 (27.4)	4940 (28.3)	17708 (25.7)
>30Kg/m ²	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[†] (%)			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	0.06	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	0.29	0.89	0.34	2.34	0.815
40-50	1.56	0.65	3.77	0.321	1.22	0.61	2.42	0.57	0.48	0.18	1.30	0.148
50-60	1.91	0.79	4.60	0.149	1.38	0.69	2.73	0.36	0.66	0.25	1.76	0.407
60-70	1.36	0.55	3.35	0.501	1.21	0.60	2.46	0.59	0.33	0.11	0.96	0.041
>70	1.05	0.42	2.62	0.909	0.96	0.46	1.99	0.9	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	0.18	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	0.91	0.84	0.54	1.30	0.434
>/=2	0.99	0.68	1.45	0.955	1.06	0.66	1.73	0.79	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	0.59	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	0.17	0.95	0.55	1.63	0.853
Missing	0.83	0.58	1.17	0.289	0.81	0.51	1.27	0.35	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	0.5	0.94	0.57	1.56	0.811
3	1.04	0.73	1.48	0.813	1.17	0.72	1.88	0.52	0.91	0.54	1.54	0.734
4	1.14	0.80	1.62	0.475	1.33	0.82	2.16	0.24	0.95	0.56	1.61	0.86
5	0.78	0.50	1.22	0.273	0.86	0.46	1.62	0.64	0.69	0.37	1.31	0.262
Missing	0.76	0.50	1.15	0.196	1.08	0.65	1.82	0.75	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	0.36	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	0.73	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	0.00	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	0.00	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	0.4	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*

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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				0.70	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.

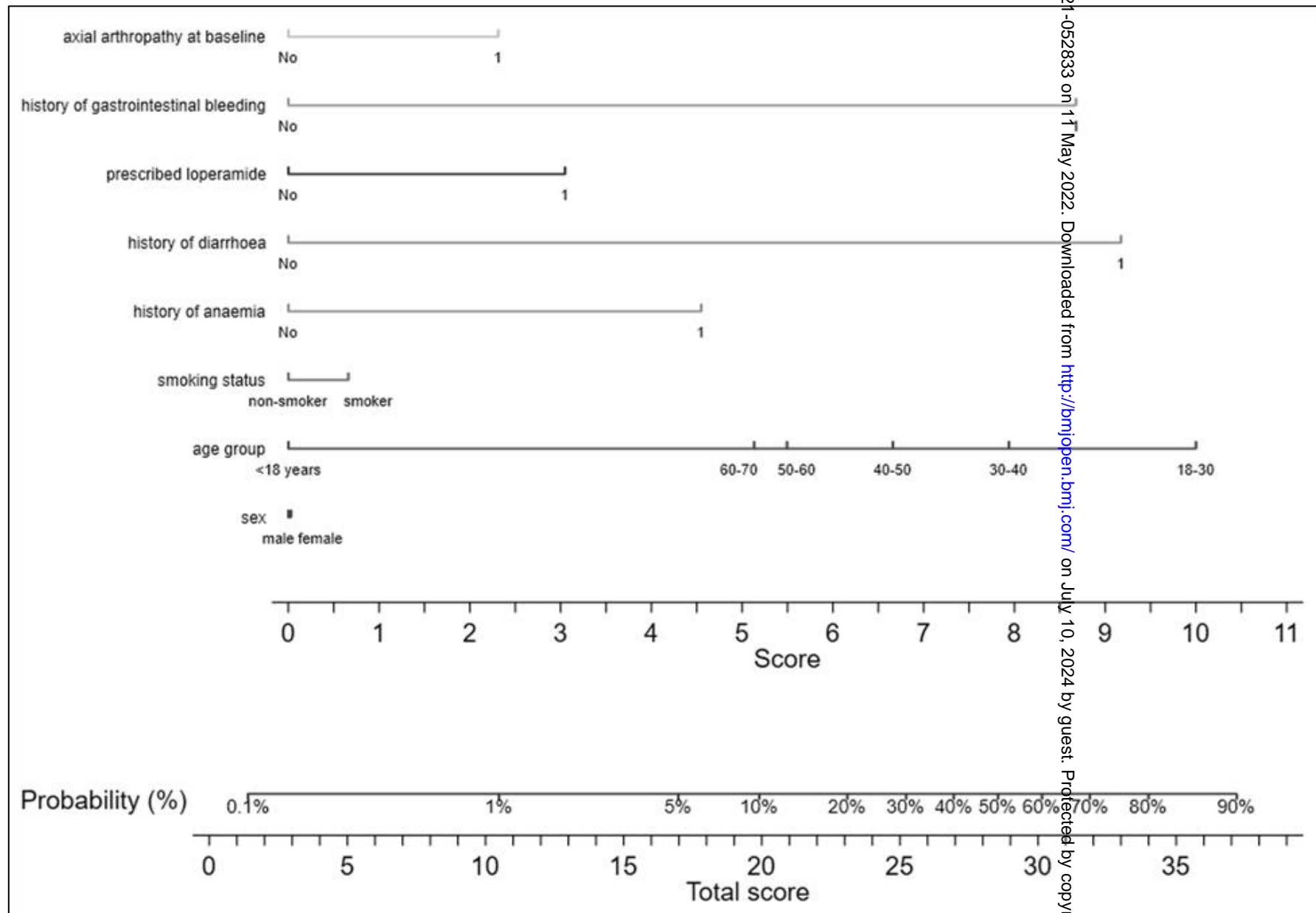
Complete case numbers (excludes subjects with missing BMI and Townsend level data)

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

BMI; Body Mass Index
IAOI; Any IBD associated ocular inflammation

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



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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

		Item No	Recommendation	Page number
✓	Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1 & 3
✓			(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
	Introduction			
✓	Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5 & 6
✓	Objectives	3	State specific objectives, including any prespecified hypotheses	5 & 6
	Methods			
✓	Study design	4	Present key elements of study design early in the paper	7 & 8
✓	Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7 & 8
✓	Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7, 8 & 9
✓			(b) For matched studies, give matching criteria and number of exposed and unexposed	
✓	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8 & 9
✓	Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
✓	Bias	9	Describe any efforts to address potential sources of bias	7 & 8
✓	Study size	10	Explain how the study size was arrived at	7 & 11
✓	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8 & 9
✓	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8 & 9
			(b) Describe any methods used to examine subgroups and interactions	8 & 9
			(c) Explain how missing data were addressed	9
			(d) If applicable, explain how loss to follow-up was addressed	N/A
			(e) Describe any sensitivity analyses	N/A
	Results			
✓	Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, 11, Figure 1
			(b) Give reasons for non-participation at each stage	7, 11, Figure 1
			(c) Consider use of a flow diagram	Figure 1

✓	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
			(b) Indicate number of participants with missing data for each variable of interest	11, Table 1
			(c) Summarise follow-up time (eg, average and total amount)	11, Table 1
✓	Outcome data	15*	Report numbers of outcome events or summary measures over time	11, 12,13
✓	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12,13
			(b) Report category boundaries when continuous variables were categorized	
			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
✓	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12,13 (appendices)
	Discussion			
✓	Key results	18	Summarise key results with reference to study objectives	15
✓	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
✓	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18 & 19
✓	Generalisability	21	Discuss the generalisability (external validity) of the study results	17, 19
	Other information			
✓	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

BMJ Open

The risk of a subsequent diagnosis of inflammatory bowel disease in subjects with ophthalmic disorders associated with inflammatory bowel disease: a retrospective cohort analysis of UK primary care data

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Keywords:	GASTROENTEROLOGY, OPHTHALMOLOGY, Inflammatory bowel disease < GASTROENTEROLOGY, EPIDEMIOLOGY

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5 1 Title Page
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8 2 The risk of a subsequent diagnosis of inflammatory bowel disease in
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10 3 subjects with ophthalmic disorders associated with inflammatory bowel
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12 4 disease: a retrospective cohort analysis of UK primary care data
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16 6 **Short title:** Inflammatory Bowel Disease risk in associated eye disease
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6 45 **Ethics**
7

8 46 Use of IQVIA Medical Research Data* is approved by the UK Research Ethics Committee (reference number:
9 47 18/LO/0441). In accordance with this approval, the study protocol was reviewed and approved by an
10 48 independent Scientific Review Committee (SRC) in September 2019 (reference number: 19THIN066).

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13 49 *IQVIA Medical Research Data (IMRD-UK) incorporates data from THIN, A Cegedim Database. Reference
14 50 made to THIN is intended to be descriptive of the data asset licensed by IQVIA. This work used de-identified
15 51 data provided by patients as a part of their routine primary care.
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22 53 **Abbreviations:**
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24 54 Extra-Intestinal Manifestation (EIM), anterior uveitis (AU), inflammatory bowel disease (IBD);
25 55 Crohn's disease (CD); ulcerative colitis (UC); Hazard ratio (HR); The Health Improvement Network
26 56 (THIN); IQVIA Medical Research Data (IMRD-UK).
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Abstract:

Objectives Ophthalmic conditions including anterior uveitis (AU), episcleritis and scleritis may occur in association with the inflammatory bowel diseases (IBD) as ophthalmic extraintestinal manifestations. This aim of this study was to assess the risk of a later IBD diagnosis in those presenting with IBD associated ocular inflammation (IAOI).

Design Retrospective Cohort study

Setting Primary care UK database

Participants 38,805 subjects with an IAOI were identified (median age 51 (38-65), 57% female) and matched to 153,018 subjects without IAOI.

Measures The risk of a subsequent diagnosis of IBD in subjects with IAOIs compared to age/sex matched subjects without IAOI. Hazard ratios (HR) were adjusted for age, sex, body mass index, deprivation, comorbidity, smoking, and baseline axial arthropathy, diarrhoea, loperamide prescription, anaemia, lower gastrointestinal bleeding and abdominal pain.

Logistic regression was used to produce a prediction model for a diagnosis of IBD within 3 years of an AU diagnosis.

Results 213 (0.6%) subsequent IBD diagnoses (102 ulcerative colitis (UC) and 111 Crohn's disease (CD)) were recorded in those with IAOIs and 329 (0.2%) (215 UC and 114 CD) in those without. Median time to IBD diagnosis was 882 (IQR 365-2,043) days in those with IAOI and 1,403 (623-2,516) in those without. The adjusted HR for a subsequent diagnosis of IBD was 2.25 (95%CI 1.89-2.68), $p < 0.001$; for UC 1.65 (1.30-2.09), $p < 0.001$; and for CD 3.37 (2.59-4.40), $p < 0.001$ in subjects with IAOI compared to those without.

Within 3 years of an AU diagnosis, 84 (0.5%) subjects had a recorded diagnosis of IBD. The prediction model performed well with a C-statistic of 0.75 (0.69-0.80).

Conclusions Subjects with IAOI have a two-fold increased risk of a subsequent IBD diagnosis. Healthcare professionals should be alert for potential signs and symptoms of IBD in those presenting with ophthalmic conditions associated with IBD.

87 Article Summary

88 Strengths and limitations of this study

- 89 • Included a large sample size from a nationally representative primary care database.
- 90 • Used routinely gathered data to give a “real-life” view of the reporting of eye and inflammatory
91 bowel diseases in a community setting.
- 92 • Undertook prediction model development to help clinicians become aware of the risks of
93 inflammatory bowel disease in patients presenting with eye diseases.
- 94 • There are risks of under recording of eye manifestations when they do not reach a threshold for
95 presentation to healthcare professionals.
- 96 • Linked data to secondary care were not available and therefore cross validation of secondary
97 care diagnoses was not possible.

100 Introduction

101 Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a
102 relapsing, inflammatory, autoimmune condition of unknown aetiology. Thought to be the
103 consequence of dysregulation of the immune system at the interface between the microbiome and
104 the bowel wall, IBD shares many of the disturbed pathways observed in other autoimmune
105 conditions^{1,2}.

106 A number of conditions are commonly observed in those suffering with IBD and are therefore known
107 as extraintestinal manifestations (EIMs) of IBD. EIMs can be classified as: *IBD-specific* (e.g. metastatic
108 CD); *drug-related* (e.g. anti-TNF associated skin lesions or steroid-induced cataract development);
109 *associated* - signalling a predisposition to autoimmunity (e.g. ankylosing spondylitis); or *reactive* -
110 implying common pathophysiological pathways without histopathological similarity (e.g. pyoderma
111 gangrenosum)^{3,4}. Certain conditions belonging to the reactive and associated EIM subtypes have
112 been accepted as *classical* EIMs and include ophthalmic, dermatological, musculoskeletal and
113 hepatobiliary diseases^{5,6}.

114 A link between IBD and ophthalmic conditions has long been recognised. The cell surface immune
115 regulation protein Human Leucocyte Antigen B27 (HLA B27) is more common in IBD and uveitis
116 which also links uveitis with the musculoskeletal EIMs, in particular the axial arthropathies
117 (ankylosing spondylitis and sacroiliitis)⁷⁻¹⁰. The *classical* EIMs in the ophthalmic group include
118 anterior uveitis (AU), episcleritis and scleritis. These complications may occur in up to 13% of IBD
119 patients, with the potential for significant morbidity including blindness^{11,12}.

120 Ophthalmic EIMs range from mild and benign to severe, requiring urgent intervention to preserve
121 the eye. Uveitis is a sight-threatening condition and is more commonly bilateral and anterior in the
122 context of IBD; it may run in parallel or independently of IBD activity¹²⁻¹⁴. Treatment for uveitis
123 depends on the severity and the specific location of inflammation, and commonly includes topical,
124 intraocular and systemic corticosteroids, with second-line immunosuppressants and biologics where

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3 125 needed¹². Episcleritis is a benign condition that is not sight threatening and presents with eye
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5 126 redness and mild to moderate discomfort. It is caused by inflammation of the episcleral tissue which
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7 127 lies above the sclera and below the conjunctiva. It runs a parallel course when associated with IBD
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10 128 and often does not require specific treatment ^{12,15}. Scleritis on the other hand is a serious,
11
12 129 destructive, inflammatory condition and can be sight threatening. It presents with redness of the
13
14 130 sclera, deep 'boring' pain and may cause tissue destruction leading to visual impairment. Treatment
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16 131 is essential and may include systemic anti-inflammatory agents, corticosteroids and
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18 132 immunosuppressants ¹². Unlike episcleritis, it may appear independently of IBD activity and is
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21 133 uncommon compared to episcleritis ¹⁶.

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24 134 *Classical* EIMs may occur prior to a diagnosis of IBD and may occur in isolation in those who never
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26 135 develop IBD ^{17,18}, here we term these conditions IBD associated ocular inflammation (IAOI). The aim
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28 136 of this study was to examine the risk of and time to a subsequent diagnosis of IBD in those with a
29
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31 137 new diagnosis of IAOI.

138 Materials and Methods

139 Data Source

140 Data in the IQVIA Medical Research Data (IMRD-UK) database are obtained from over 800 primary
141 care practices across the United Kingdom (UK). IMRD-UK contains data on 15.8 million subjects and
142 is considered representative of the UK population¹⁹. Data on included subjects is longitudinally
143 captured including primary and secondary care diagnostics, drug prescriptions, symptoms and
144 diagnoses, and demographic information. Data are uploaded using a hierarchical system of (Read)
145 codes²⁰. To be eligible for the study, IMRD-UK primary care practices required at least one year since
146 the installation of the computerised medical record system and achievement of an acceptable
147 mortality recording (AMR) level²¹. These criteria help to ensure data reliability and reduce the risk of
148 under-recording baseline data.

149 In this retrospective cohort study using IMDR-UK patients are anonymous and were not identified or
150 involved in the study.

151 Study Design

152 *Cohort study*

153 A retrospective matched cohort study following patients from 1st January 1995 to 25th September
154 2019 was undertaken to investigate the association between IBD outcome and all studied IAOI
155 exposures (anterior uveitis (AU), scleritis and episcleritis), with secondary studies of anterior uveitis
156 alone and combined episcleritis and scleritis. Individuals were eligible for inclusion from either the
157 date of eligibility of their primary care practice or one year after they were registered, whichever
158 was later. Those subjects with an incident IAOI diagnosis of interest (recorded through Read codes –
159 Appendix 1)²² and without an established IBD diagnosis (exposed) were compared to subjects
160 without the specific IAOI diagnosis of interest and without an established IBD diagnosis (unexposed)
161 for each analysis. Exposed participants were matched to unexposed participants by age at cohort
162 entry (± 2 years) and sex in a ratio of 1:4. Index date was defined as the start of follow up and was
163 the date of IAOI diagnosis for the IAOI group. The same date was assigned to matched subjects

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3 164 without an IAOI in order to mitigate for immortal time bias²³. Only subjects without a co-existing IBD
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5 165 diagnosis at index date were included in the study.
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8 166 Subjects were followed from their index date until the first of the following events (exit date): death;
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10 167 subject left the practice; last data collection from their practice; study end date (25th September
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12 168 2019); diagnosed with IBD (CD or UC) as identified through Read codes. Subjects coded for both UC
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14 169 and CD were assigned to one condition based on frequency of coding. For those with equal coding,
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16 170 the earliest diagnosis date and the latest diagnosis of IBD subtype was used.
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19 20 171 *Prediction model*

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22 172 Subjects with an incident diagnosis of AU over the same study period were investigated to identify
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24 173 predictors for a diagnosis of IBD within the following 3-years. Case examples were used to determine
25
26 174 the probability of diagnosis of IBD in subjects presenting with anterior uveitis.
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29 175 *Validation*

30 176 Primary care coding to identify patients with IBD has been previously validated^{24,25}. IAOI codes were
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32 177 reviewed by two clinicians, having been first sourced from other published primary care database
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34 178 studies²⁶⁻²⁸. Ophthalmology expert advice was sought for IAOI coding decisions. AU codes, excluding
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36 179 uveitis associated with other pathologies (e.g. infective), were selected for inclusion along with
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38 180 episcleritis and scleritis. Clinical codes used to identify UC, CD and IAOI are listed in Appendix 1.
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43 44 45 182 **Statistical Analysis**

46 183 *Cohort study*

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48 184 The time from index date to a later diagnosis of IBD in those with and without a baseline IAOI were
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50 185 presented as median time to IBD and UC or CD diagnoses with accompanying interquartile ranges
51
52 186 (IQR). Log-rank tests were used to compare time to IBD diagnosis between those with and without
53
54 187 IAOIs. Cox proportional hazard models, with time to subsequent diagnosis of IBD as the time-metric,
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56 188 were produced to assess the adjusted hazard ratio (aHR) of IBD diagnoses in participants with an
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58 189 IAOI compared to matched subjects without IAOIs. For all IAOIs and when AU was examined alone,
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3 190 aHRs were produced for all IBD, UC and CD outcomes. However, for the combined episcleritis and
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5 191 scleritis study, due to IBD diagnoses being less commonly observed, only an aHR for all IBD was
6
7 192 modelled.
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10 193 *Covariates*

11 194 Hazard ratios were adjusted for age at index; sex; smoking status; body mass index (BMI); Townsend
12
13 195 level of deprivation (quintiles); Charlson comorbidity score; baseline axial arthropathy diagnosis; and
14
15 196 within 6-months of IAOI diagnosis (prior to an IBD diagnosis) coding of anaemia (<11.9g/dL for
16
17 197 females and <12.9g/dL for males), abdominal pain, loperamide prescription, diarrhoea, or lower
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19 198 gastrointestinal bleeding. Smoking status was dichotomised into current smokers and non-smokers
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21 199 with missing data for smoking status considered non-smokers; a method that has been previously
22
23 200 validated²⁹.
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28 201 *Missing data*

29 202 Missing data for Townsend deprivation quintile and BMI were considered as separate categories and
30
31 203 a complete case analysis, where subjects with missing data were excluded, was undertaken.
32
33 204 Proportional hazards were assessed using log-log plots. Cumulative incidence plots were produced
34
35 205 to illustrate the cumulative risk of IBD over time.
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41 207 *Prediction model*

42 208 Only participants with an IBD diagnosis within 3-years or those who had a minimum of 3-years follow
43
44 209 up were included in the development cohort. Multivariable logistic regression was used to establish
45
46 210 a prediction model for IBD diagnosis in subjects presenting with a new diagnosis of anterior uveitis.
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48 211 Backwards stepwise elimination was used to select predictor variables with an elimination alpha-to-
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50 212 remove p-value of 0.20.
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55 213 *Candidate predictor variables*

56 214 Sex, age (categorical) and smoking status were included due to their clinical importance. Further
57
58 215 candidate variables including baseline axial arthropathy, BMI (categorical) and within 6-months
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3 216 coding of anaemia, abdominal pain, lower gastrointestinal bleeding, loperamide prescription and
4
5 217 diarrhoea (prior to an IBD diagnosis) were assessed. Some potential candidate predictors such as
6
7 218 Townsend deprivation and co-morbidity score were not included, due to the small number of
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10 219 outcome events.

220 **Model performance**

14 221 A receiver operating characteristic (ROC) curve and C-statistic was used to assess model
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17 222 discrimination; calibration was assessed using the Hosmer-Lemeshow test for goodness of fit.
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19 223 Internal validation of the prediction model was performed through bootstrapping by resampling the
20
21 224 dataset (with replacement) 200 times and comparing the resulting average of the area under the
22
23 225 ROC curve from the bootstrap samples to the original model.

26 226 Analyses were performed using Stata version 16.0 and p-values <0.05 were considered statistically
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28
29 227 significant³⁰.

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33 229 **Patient and public involvement**

34 230 Patients and/or the public were not involved in the design, or conduct, or reporting, or
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37 231 dissemination plans of this research.

232 Results

233 Study Subjects

234 Following exclusions (Figure 1), 38,805 subjects with an IAOI were identified (median age 51 (38-65)
235 and 57% female). IAOI cases included those coded as AU: 22,098 (57%); episcleritis: 13,955 (36%);
236 scleritis: 2,482 (0.6%); episcleritis or scleritis (a non-specific code where it was not possible to
237 determine whether subjects were episcleritis or scleritis): 270 (0.01%). The age distribution of AU
238 (with a higher frequency in the elderly) and episcleritis or scleritis (with a higher frequency in the 40-
239 50 age group) was in keeping with previous findings.^{31,32} IAOI subjects were age and sex matched to
240 153,018 subjects without an IAOI. The median follow-up period was five years with a total of
241 244,503 person years (py) of follow-up time in IAOI subjects and 934,847 py in those without IAOIs.
242 In those with an IAOI, 2.9% (1,116) had another, non-ophthalmic EIM at index date compared to
243 0.9% (1,433) in subjects without IAOIs. Subject characteristics are shown in Table 1.

244

245 Risk of Inflammatory Bowel Disease Diagnosis in Associated Ophthalmic Conditions

246 During the study period 213 (0.6%) IBD diagnoses (103 UC and 111 CD) were observed in subjects
247 with IAOIs compared to 329 (0.2%) (215 UC and 114 CD) in the matched control group. 893 (2.3%)
248 subjects with IAOIs had an axial arthropathy recorded at baseline and 35 (0.1%) had the HLA-B27
249 genotype coded, compared to 1,013 (0.7%) controls with an axial arthropathy and 7 (0.005%) with
250 the HLA-B27 genotype. From index date (IAOI diagnosis date for exposed subjects, with matched
251 controls assigned the same index date as their corresponding exposed subjects), the median time to
252 IBD diagnosis was 882 (IQR 365-2,043) days in subjects with IAOIs vs 1,403 (623-2,516) days in those
253 without IAOIs. For a UC diagnosis 922 (410-1,910) vs 1,360 (547-2,406) days and for a CD diagnosis
254 738 (269-2,011) vs 1,625 (641-2,779) days, in subjects with and without IAOIs respectively. For all
255 IBD, UC and CD the log-rank test p-value was <0.001. Following adjustment, the aHR for a diagnosis
256 of IBD in IAOI subjects compared to those without IAOIs was 2.25 (95%CI 1.89-2.68), with an aHR of

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3 257 1.65 (1.30-2.09) for UC and 3.37 (2.59-4.40) for CD, p-values <0.001 (Table 2; full models are shown
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5 258 in Appendix 2). Figure 2 shows the cumulative incidence plot for IBD diagnoses in subjects with IAOIs
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7 259 compared to those without.
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14 261 Risk of Inflammatory Bowel Disease Diagnosis in Anterior Uveitis, Episcleritis and 15 16 262 Scleritis

17 263 Subject characteristics of IAOI and matched subjects without IAOIs in these secondary analyses
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19 264 together with the full Cox models are shown in Appendices 3, 4 and 5. Subject numbers for
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21 265 individual IAOIs differ slightly to those in the combined IAOI study above because only the first
22
23 266 diagnosed incident IAOI was considered in the combined study, but a subject might be subsequently
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25 267 diagnosed with other IAOIs and therefore be eligible for inclusion in more than one analysis for the
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27 268 individual IAOIs presented in this section. In the AU study, 22,547 subjects with a new diagnosis of
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29 269 AU (median age 53 (39-68) years, 54% female) were matched to 89,422 subjects without AU. AU
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31 270 subjects and their matched subjects provided 137,878 and 531,653 py of follow-up, respectively. 152
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33 271 (0.7%) IBD diagnoses (67 UC and 85 CD) were observed in AU subjects during the study period and
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35 272 157 (0.2%) IBD diagnoses (107 UC and 50 CD) among subjects without AU. The median time to an
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37 273 IBD diagnosis was 898 (373-2,027) days in the AU subjects compared to 1,457 (539-2,700) in those
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39 274 without AU (log-rank test p<0.001). The median time to a UC diagnosis was 1,117 (489-2,008) days in
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41 275 AU subjects and 1,490 (553-2,553) days in subjects without AU. For a CD diagnosis, the median time
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43 276 to diagnosis was 687 (286-2,006) days in AU subjects and 1,160 (516-2,892) days in subjects without
44
45 277 AU. Log-rank tests gave p<0.001 for both CD and UC. The aHR for a subsequent IBD diagnosis in
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47 278 subjects with AU compared to matched subjects without AU was 3.39 (2.70-4.25); for UC aHR was
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49 279 2.23 (1.63-3.04) and for CD 5.77 (4.04-8.24), all p-values <0.001 (Table 2 (full models are shown in
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51 280 Appendix 4)).
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3 281 In the analysis of episcleritis and scleritis combined, 17,439 subjects (14,752 (85%) episcleritis and
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5 282 2,976 scleritis; median age 48 (36-61) and 62% female) were identified and matched to 68,823
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7 283 controls. Episcleritis and scleritis subjects and matched participants contributed 36,324 and 136,304
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9 284 py follow-up, respectively. 104 (0.6%) IBD cases (23 UC and 81 CD) were observed among episcleritis
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11 285 and scleritis subjects and 53 (0.1%) (30 UC and 23 CD) among those without these IAOIs. The median
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13 286 time to an IBD diagnosis in episcleritis and scleritis subjects was 848 (348-2,239) days compared to
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15 287 1,522 (577-2,838) days in controls, log-rank test $p < 0.001$. The aHR for the diagnosis of IBD in those
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17 288 subjects with an incident diagnosis of episcleritis or scleritis compared to matched subjects without
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19 289 these IAOIs was 1.73 for IBD (1.31-2.28), $p < 0.001$ (Table 2 (full models are shown in Appendix 5)).
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24 290 Complete case analyses were performed where subjects with missing variables were dropped from
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26 291 the Cox models. There was minimal change in estimates and significance remained unchanged.
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28 292 Adjusted HRs for the complete-case analyses are found in Appendix 6.

293 Prediction Model

294 22,547 AU subjects were identified with 15,458 eligible for inclusion in the prediction model
295 development cohort based on sufficient follow-up time or an IBD diagnosis within 3 years of the AU
296 diagnosis. 84 (0.53%) subjects had a recorded diagnosis of IBD (63% CD) within 3 years of follow-up.
297 The characteristics of those with and without an IBD diagnosis are shown in Table 3. Those with an
298 IBD diagnosis were younger (median age 44 (IQR 35-56) and 53 (39-68) years respectively, $p < 0.001$)
299 but there was no difference in sex, smoking status or body mass index category.

300 Following backwards stepwise regression, female sex, smoking status, BMI and abdominal pain
301 within 6 months of an AU diagnosis exceeded the alpha-to-remove threshold. However, female sex
302 and smoking status were retained in the model due to their clinical importance while weight loss
303 within 6 months of an AU diagnosis and HLA-B27 genotype were coded in only 5 and 19 cases
304 respectively and were therefore not included in the analysis. The multivariable logistic regression
305 model to assess the risk of being diagnosed with IBD within a 3-year period following AU diagnosis is

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3 306 presented in Table 4. The Hosmer-Lemeshow χ^2 test for goodness of fit was applied to the
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5 307 prediction model development data set and was not significant at 0.093, suggesting reasonable
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7 308 model fit. The receiver operating characteristic (ROC) curve, shown in Figure 3, produced an area
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10 309 under the curve (AUC) C-statistic of 0.75 (95%CI 0.69-0.80). Following internal validation by
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12 310 bootstrapping, resampling the dataset 200 times, the mean difference between the original AUC and
13
14 311 AUC in each bootstrap sample was 0.021. This produced a bias-corrected C-statistic value of 0.71
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16 312 (0.67-0.77).

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19 313 A probability calculator was produced to determine the likelihood of an IBD diagnosis within the
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21 314 anterior uveitis cohort using the following examples: 1) a female, 34-year-old, current smoker and a
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23 315 within 6-month history of anaemia would have a 2% risk of IBD being diagnosed within 3 years of an
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25 316 anterior uveitis diagnosis; 2) a male, 18-year-old, non-smoker and a history of axial arthropathy,
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27 317 diarrhoea and loperamide use would have a 25% 3-year IBD diagnosis risk; 3) a female, 49-year-old,
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29 318 current smoker with a history of anaemia, diarrhoea and lower gastrointestinal bleeding would have
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31 319 a 55% risk of an IBD diagnosis within 3 years. A nomogram for the prediction model is shown in
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33 320 Appendix 7.
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321 Discussion

322 In this study, we have shown that subjects with an IAOI, but without a recorded diagnosis of IBD, are
323 at a two-fold greater risk (by an average of 5 years follow-up) of subsequently being diagnosed with
324 IBD than matched subjects without an IAOI. The risk was highest in those who later had a CD
325 diagnosis. A wide time scale was observed between an IAOI diagnosis and a subsequent IBD
326 diagnosis with a median time to IBD diagnosis of greater than two years. When AU was examined
327 alone, subjects had a 3-fold greater risk of a later IBD diagnosis compared to matched subjects
328 without AU and again the risk was highest for a subsequent CD diagnosis at almost 6-fold.

329 Ophthalmic conditions are among the most common extraintestinal manifestations of IBD and are
330 commonly diagnosed at the time or following a diagnosis of IBD ¹⁸. This study, however, has
331 established that subjects with a diagnosis of an IAOI, either in combination or as separate entities
332 (anterior uveitis or episcleritis and scleritis), were at increased risk of developing a subsequent
333 diagnosis of IBD over time (combined IAOI aHR 2.25 (1.89-2.68), $p < 0.001$). The time to a diagnosis of
334 IBD was shorter in those with ophthalmic conditions compared to matched controls (median time
335 2.4 years versus 3.8 years, respectively). However, the time from IAOI diagnosis to IBD was often
336 greater than two years. This was a significant time lag which may reflect a lack of symptoms to
337 indicate IBD. Relatively few subjects were coded with anaemia, abdominal pain, lower
338 gastrointestinal bleeding, weight loss, diarrhoea or loperamide prescriptions around the time of the
339 diagnosis of the ophthalmic condition. However, given that many EIMs parallel the course of IBD, it
340 is possible that IBD may be present earlier and pauci-symptomatic and as such they may represent a
341 missed opportunity and a delayed diagnosis.

342 The aetiology of ophthalmic EIMs is not well understood. They are thought to be more common in
343 those with CD rather than UC ¹², and our findings support this. A limitation of the IMRD-UK database
344 is that it does not allow for the discrimination of IBD severity, activity or gastrointestinal location.
345 This is pertinent because those with colonic or ileocolonic disease have been shown to have an

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3 346 increased risk of ophthalmic EIMs ^{16,33,34}. Several studies have suggested that certain peptide targets
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5 347 for the immune system are found in both joints, eyes and the colon ^{35,36}. It may be that immune
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7 348 dysregulation in relation to the enteric flora and subsequent cross-reactive antigens play a role in
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9 349 some EIM presentations. Moreover, the HLA-B27 antigen appears to play an important role in some
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11 350 mouse models where colitis and arthritis only developed in those where gut flora was present ³⁶.
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13 351 HLA-B27 positivity was not commonly coded in the IMRD-UK database and is highly likely to be
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15 352 under-recorded given its specialist nature. However, previous reports that this genotype is observed
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17 353 in greater numbers in those with EIMs and its association with arthropathies and ophthalmic
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19 354 conditions makes this an important consideration in such a study ^{7,16,37}. Arthropathies and the HLA-
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21 355 B27 haplotype were seen in larger numbers at baseline in ophthalmic conditions associated with IBD
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23 356 than in controls in the present study. Previously, it has been found that HLA-B27 is present in 90% of
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25 357 those with ankylosing spondylitis, but just under half of those with CD and sacroiliitis are positive for
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27 358 this allele ⁸. IBD is known to have a genetic link with increased risk seen in the offspring of those with
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29 359 IBD, and this is also the case with uveitis in those with IBD. The HLA region of Chromosome 6
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31 360 contains both major histocompatibility complex genes (HLAs) as well as other important IBD related
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33 361 genes (TNF- α). The vicinity of these genes increases the likelihood of inheriting several important
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35 362 genetic variations (a phenomenon known as linkage disequilibrium) and may help to explain familial
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37 363 traits and the relationship between some EIMs and the IBDs ³⁴. Other HLA types (HLA-B58) have also
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39 364 been associated with IBD and uveitis but it is unclear how the interplay between genetic and
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41 365 environmental factors apply, given that most of those who are HLA-B27 positive will not suffer any ill
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43 366 effect from this phenotypic variant and HLA-B27 does not itself appear to increase the risk of IBD ³⁴.
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45 367 A limitation of this study is the lack of family history data and as a result an assessment of the risk in
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47 368 those with a family history of EIMs or IBD could not be made.
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50 369 Vavricka et al have reported that multiple EIMs were not uncommon in IBD subjects, with CD and UC
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52 370 subjects studied having more than one EIM in 16% and 8% of cases respectively ³⁸. Axial
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54 371 arthropathies in the present study were included at baseline given evidence that ophthalmic and

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3 372 joint manifestations may be seen more frequently together in IBD⁹. More than 2% of cases had a
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5 373 pre-existing axial arthropathy compared to less than one percent of matched controls. Other
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7 374 investigators have examined IBD and arthritis in UK primary care databases. However, type 1 and 2
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9 375 EIM arthropathies are challenging to identify given a lack of specific coding, and, seropositive and
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11 376 negative inflammatory arthritides, although associated, are not classical EIMs and as such were not
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13 377 examined in this study²⁶. The presence of an axial arthropathy increased the risk of IBD more than
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15 378 two-fold and was found to be associated with later IBD in anterior uveitis. Although not specifically
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17 379 examined in this study, an increased number of other EIMs in those who develop a new diagnosis of
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19 380 an ophthalmic condition associated with IBD compared to controls has been demonstrated
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21 381 previously. This has been shown to be particularly true among those with arthritic as well as
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23 382 ophthalmic conditions³⁹.

383 Prediction Model

384 The prediction model for IBD diagnosis in subjects with anterior uveitis found associations with
385 several variables. Anaemia, diarrhoea, and lower gastrointestinal bleeding heralded an IBD
386 diagnosis, highlighting the need for careful history taking in ophthalmic care settings and
387 investigation for IBD if such symptoms are revealed. Other inflammatory and autoimmune
388 conditions associated with uveitis can lead to anaemia, including sarcoidosis. Some of these
389 conditions will produce an anaemia of chronic disease, and others a haemolytic anaemia^{40,41}. In the
390 context of ophthalmic conditions associated with IBD, iron deficiency anaemia should be
391 investigated to prevent an IBD diagnostic delay. Age was strongly associated with IBD in our model.
392 Those in the age group 18-30 had the highest risk compared to under 18 year-olds, however all ages
393 up to 70 had an increased IBD risk compared to the reference group (under 18 years). Ottaviano et
394 al. reviewed the published literature on ophthalmic EIMs in children and found that there was little
395 data available. They suggested that this may be related to asymptomatic uveitis, as well as a lower
396 prevalence of these EIMs in childhood compared to adults⁴². In the present study, less than 6% of
397 the cohort were aged under 18 and only 0.2% of subjects in this age category developed IBD during

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3 398 the study period, with a slight preponderance towards CD, as has been previously shown in
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5 399 paediatric series ⁴².

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8 400 The use of primary care databases has both strengths in terms of subject numbers and subject level
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10 401 data, but also limitations. Perhaps most relevant to the present study are the risk of under-recording
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12 402 and validation. The accuracy of coding in IMRD-UK is related to the primary care practitioner's ability
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14 403 to record diagnoses accurately. Several EIMs (especially episcleritis, which is self-limiting and
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16 404 typically causes only mild discomfort) and IBD symptoms, especially early on in the disease process,
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18 405 may not lead to healthcare-seeking behaviour in primary care and may therefore not be coded in the
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20 406 database in a timely fashion. Although IBD in primary care has previously been validated ²⁴ and in
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22 407 the present study at least 50% of those with an IBD diagnosis had more than one IBD code recorded,
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24 408 to our knowledge a validation study of the ophthalmic conditions used in the present study has not
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26 409 been previously undertaken. Given the lack of external validation, an often-prohibitive task in terms
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28 410 of cost and time, there is a risk of bias. Episcleritis is the most common ophthalmic condition
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30 411 associated with IBD ¹⁸, however, given its benign course it may be under-recorded in the IMRD-UK
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32 412 database. For uveitis and scleritis, however, these diagnoses would be made in a secondary care eye
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34 413 service. For this reason, they may be more reliably recorded when the information reaches primary
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36 414 care. There may also be delays in the recording of data making time-to-event analysis challenging to
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38 415 interpret. IBD is more commonly associated with anterior uveitis, and this was therefore the focus of
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40 416 this study. However, IBD can rarely be associated with intermediate, posterior or panuveitis, and so
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42 417 our estimates could be considered to be conservative. Offsetting this were limitations in the way
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44 418 uveitis was coded with a few "unspecified" uveitis Read codes risking the inclusion of some non-
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46 419 anterior phenotypes, although AU is the most common type of uveitis.

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49 420 The Charlson comorbidity score and Townsend deprivation levels were included as variables in the
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51 421 Cox regression models as important aspects of a patient's medical and socioeconomic background.
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53 422 However, due to concerns around overfitting, these variables were not included in the prediction
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3 423 model. Overall there was a preponderance of higher comorbidity scores in those with eye conditions
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5 424 compared to those without, and this may reflect the clustering of disease seen in these patients.
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12 Ophthalmic conditions associated with IBD which present prior to an IBD diagnosis are not common.
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14 427 However, an increasing prevalence of IBD both in the UK and around the world has been
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16 428 demonstrated^{43–45}. Given the increasing numbers of patients with IBD, the need for clinicians from
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18 429 many disciplines outside gastroenterology to be aware of IBD is important. Those who care for
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20 430 patients presenting with ophthalmic conditions associated with IBD should be attentive to features
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22 431 which may increase the likelihood of an IBD diagnosis, in order that appropriate investigation and
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24 432 referral can be made in those patients with suggestive clinical features.
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32 434 **Contribution statement:** All authors contributed to the conception and design of the work, DK, NT,
33
34 435 TT, JSC, KN, NJA and RCR contributed to the acquisition of the data. DK, NT, TT, JSC and NJA
35
36 436 contributed to the analysis of the data and all authors including AKD and TB contributed to the
37
38 437 interpretation of data. DK drafted the manuscript and all authors contributed to the revision and
39
40 438 critical review of the manuscript. All authors gave final approval of the version published and agree
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42 439 to be accountable for all aspects of the work.
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56
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59 443 submitted work. Other authors have no conflicts of interest to declare.
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63 445 **Funding Declaration:** Nothing to declare.
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73 447 **Data sharing statement:** The data underlying this article were provided by IQVIA Medical Research Data
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75 448 under licence and are not available for open access. No additional data available.

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569 **Table 1. Demographics details of study subjects**

	Subjects with IBD associated ocular inflammation n (%)	Matched subjects without IBD associated ocular inflammation n (%)
Number of subjects	38,805	153,018
Median person years of follow-up (IQR)	5.4 (2.3-9.4)	5.2 (2.3-9.2)
Median age (IQR)	51 (38-65)	49 (37-63)
Age category n		
<18 years	2,142 (5.5)	9086 (5.9)
18-30	3,264 (8.4)	13,924 (9.1)
30-40	5620 (14.5)	23,644 (15.5)
40-50	7,589 (19.5)	30,586 (20.0)
50-60	7,221 (18.6)	28,622 (18.7)
60-70	5,989 (15.4)	22,990 (15.0)
>70	6,980 (18.0)	24,166 (15.8)
Female sex	22,249 (57.3)	87,694 (57.3)
Townsend Quintile		
1 - least deprived	8,880 (22.9)	34,368 (22.4)
2	7,520 (19.4)	29,210 (19.1)
3	6,989 (18.0)	27,726 (18.1)
4	5,873 (15.1)	23,272 (15.2)
5	3,814 (9.8)	15,312 (10.0)
Missing	5,729 (14.8)	23,130 (15.1)
Charlson comorbidity score		
0	24,457 (63.0)	106,735 (69.8)
1	8,414 (21.7)	28,888 (18.9)
>=2	5,934 (15.3)	17,395 (11.4)
Smoking status		
current smoker	6,632 (17.1)	28,586 (18.7)
non-smoker	32,173 (82.9)	124,432 (81.3)
Body mass index		
<25kg/m ²	12,799 (33.0)	51,136 (33.4)
25-30Kg/m ²	11,200 (28.8)	40,782 (26.6)
>30Kg/m ²	7,683 (19.8)	26,849 (17.6)
Missing	7,123 (18.4)	34,251 (22.4)
Anaemia^{†‡}	2,102 (5.4)	5,469 (3.4)
Abdominal pain[†]	837 (2.2)	2,574 (1.7)
Lower gastrointestinal bleeding[†]	363 (0.9)	1,042 (0.7)
Loperamide prescription[†]	558(1.4)	1,506 (1.0)
Diarrhoea[†]	974 (2.5)	2,424 (1.6)
HLA-B27 positive at baseline	35 (0.1)	7 (0.0)
Axial arthropathy at baseline	893 (2.3)	1,013 (0.7)
IAC at baseline (other than ophthalmic)[§]	1,116 (2.9)	1433 (0.9)

[†] coded within 6 months of Index date

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

[§] IAC: IBD associated condition: axial arthropathies, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, aphthous stomatitis

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571 **Table 2. Adjusted hazard ratios for risk of inflammatory bowel disease**

	aHR	[95% Confidence Interval]		p-value
Any IBD associated ocular inflammation				
Inflammatory bowel disease	2.25	1.89	2.68	<0.001
Ulcerative colitis	1.65	1.30	2.09	<0.001
Crohn's disease	3.37	2.59	4.40	<0.001
Anterior uveitis				
Inflammatory bowel disease	3.39	2.7	4.25	<0.001
Ulcerative colitis	2.23	1.63	3.04	<0.001
Crohn's disease	5.77	4.04	8.24	<0.001
Episcleritis or scleritis				
Inflammatory bowel disease	1.73	1.31	2.28	<0.001

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.

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574 **Table 3. Characteristics of anterior uveitis subjects with and without an inflammatory bowel disease**
 575 **diagnosis by 3 years**

	IBD diagnosis (n=84)	No IBD diagnosis (n=15,906)
Median age (IQR)	44 (35-56)	53 (39-68)
Age category (%)		
<18 years	0 (0)	604 (4)
18-30	17 (20)	1,173 (8)
30-40	18 (21)	2,092 (14)
40-50	18 (21)	2,912 (19)
50-60	14 (17)	2,861 (19)
60-70	12 (14)	2,531 (16)
>70	5 (6)	3,285 (21)
Female sex (%)	45 (54)	8,365 (54)
Smoking status (%)		
current smoker	21 (25)	2,893 (19)
non- smoker	63 (75)	12,565 (81)
Body mass index (%)		
<25kg/m ²	37 (44)	4,999 (33)
25-30Kg/m ²	23 (27)	4,588 (30)
>30Kg/m ²	14 (17)	3,111(20)
missing	10 (12)	2,760 (18)
Anaemia^{†‡} (%)	12 (14)	828 (5)
Abdominal pain[†] (%)	4 (5)	351 (2)
Loperamide prescription[†] (%)	8 (10)	238 (2)
Diarrhoea[†] (%)	20 (24)	349 (2)
Lower gastrointestinal bleeding[†] (%)	9 (11)	145 (1)
HLA-B27 positive at baseline (%)	0 (0)	19 (0.1)
Axial arthropathy at baseline (%)	6 (7)	510 (3)

[†] coded within 6 months of Index date

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

IBD: Inflammatory Bowel Disease

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578 **Table 4. Multivariable logistic regression prediction model of factors associated with developing**
 579 **inflammatory bowel disease within 3 years of an anterior uveitis diagnosis**

	β -Coefficient	Odds Ratio	[95% Conf. Interval]		P value
Sex					
Male (reference)		1.00			
Female	0.001	1.00	0.64	1.56	0.995
Age Category					
<18 years (reference)		1.00			
18-30	2.56	12.88	4.57	36.30	<0.001
30-40	2.05	7.75	2.79	21.59	<0.001
40-50	1.69	5.41	1.94	15.05	0.001
50-60	1.40	4.04	1.41	11.52	0.009
60-70	1.30	3.65	1.26	10.54	0.017
>70	0.00	1.00			
Smoking Status					
current smoker (reference)		1.00			
non smoker	-0.17	0.85	0.51	1.42	0.528
Anaemia[†]					
no (reference)		1.00			
yes	1.13	3.11	1.61	6.00	0.001
Diarrhoea[†]					
no (reference)		1.00			
yes	2.38	10.76	5.99	19.33	<0.001
Loperamide					
no (reference)		1.00			
yes	0.74	2.10	0.86	5.12	0.102
Lower gastrointestinal bleed					
no (reference)		1.00			
yes	2.27	9.69	4.54	20.70	<0.001
Axial arthropathy*					
no (reference)		1.00			
yes	0.67	1.95	0.83	4.60	0.128
Intercept	-7.08	0.0008	0.0003	0.0024	<0.001

[†] coded within 6 months of Index date

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

* Coded at baseline

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6 587 *Figure 1 Study flow chart.*

7 588 *Inflammatory bowel disease (IBD).*

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10 590 *Figure 2. Cumulative incidence of IBD (inflammatory bowel diseases) in subjects with*
11 *ophthalmic conditions (black line) and those without (grey line) with 95% confidence*
12 *intervals (dashed lines).*

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14 593 *Figure 3. Receiver operating characteristic curve of ability of prediction model to detect an*
15 *inflammatory bowel disease diagnosis within three years of an anterior uveitis diagnosis.*

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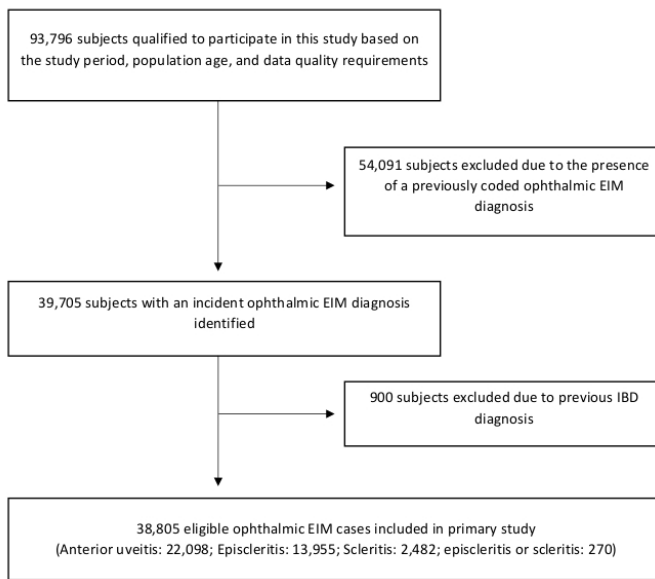
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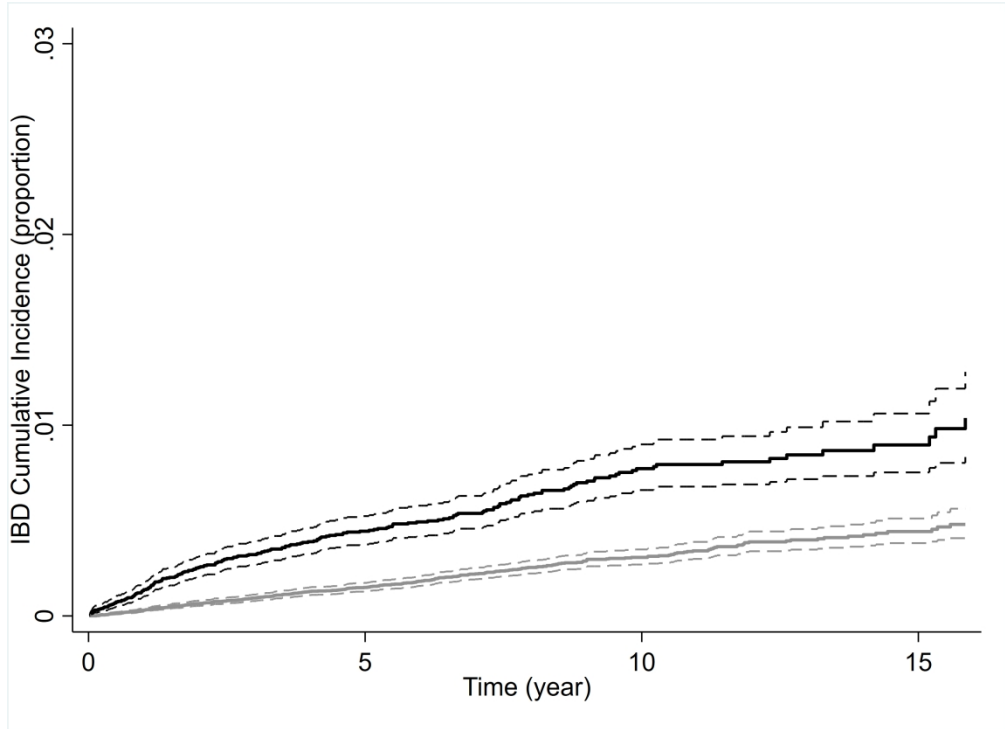
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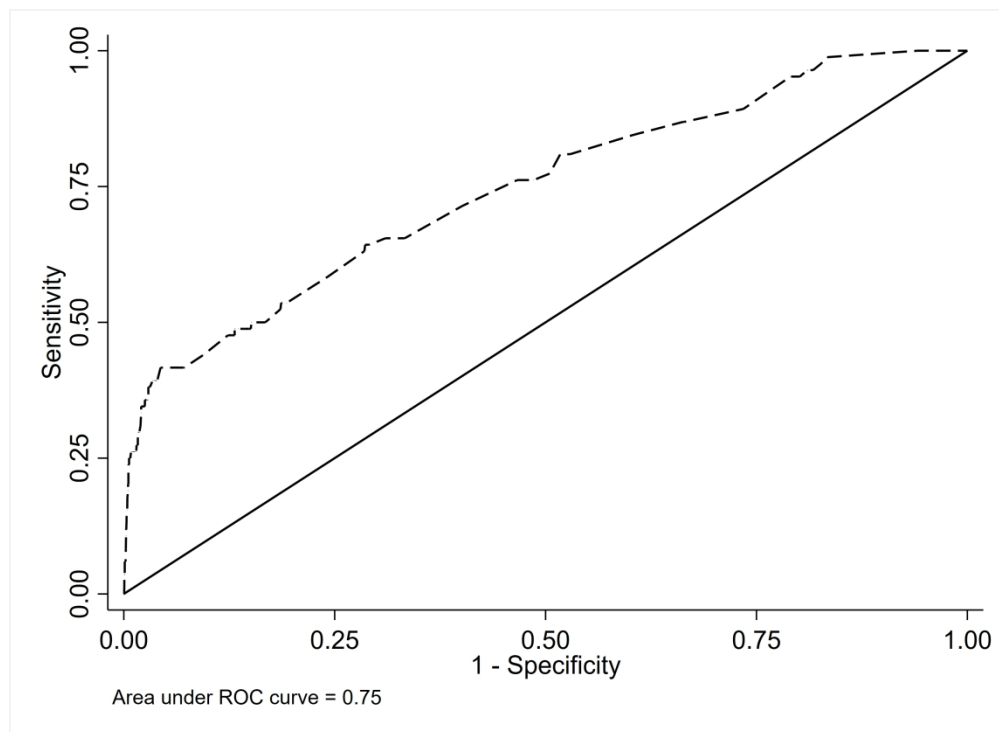
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Appendix 1

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/m ²	7,344 (32.4)	29,447 (32.9)	5908 (33.9)	23455 (34.1)
25-30Kg/m ²	6,709 (29.5)	24,625 (27.4)	4940 (28.3)	17708 (25.7)
>30Kg/m ²	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[†] (%)			172 (1.0)	446 (0.7)
204 (0.9)	642 (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	0.06	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	0.29	0.89	0.34	2.34	0.815
40-50	1.56	0.65	3.77	0.321	1.22	0.61	2.42	0.57	0.48	0.18	1.30	0.148
50-60	1.91	0.79	4.60	0.149	1.38	0.69	2.73	0.36	0.66	0.25	1.76	0.407
60-70	1.36	0.55	3.35	0.501	1.21	0.60	2.46	0.59	0.33	0.11	0.96	0.041
>70	1.05	0.42	2.62	0.909	0.96	0.46	1.99	0.96	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	0.18	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	0.91	0.84	0.54	1.30	0.434
>/=2	0.99	0.68	1.45	0.955	1.06	0.66	1.73	0.79	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	0.59	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	0.17	0.95	0.55	1.63	0.853
Missing	0.83	0.58	1.17	0.289	0.81	0.51	1.27	0.35	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	0.56	0.94	0.57	1.56	0.811
3	1.04	0.73	1.48	0.813	1.17	0.72	1.88	0.52	0.91	0.54	1.54	0.734
4	1.14	0.80	1.62	0.475	1.33	0.82	2.16	0.24	0.95	0.56	1.61	0.86
5	0.78	0.50	1.22	0.273	0.86	0.46	1.62	0.64	0.69	0.37	1.31	0.262
Missing	0.76	0.50	1.15	0.196	1.08	0.65	1.82	0.75	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	0.36	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	0.73	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	0.00	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	0.00	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	0.4	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				0.70	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

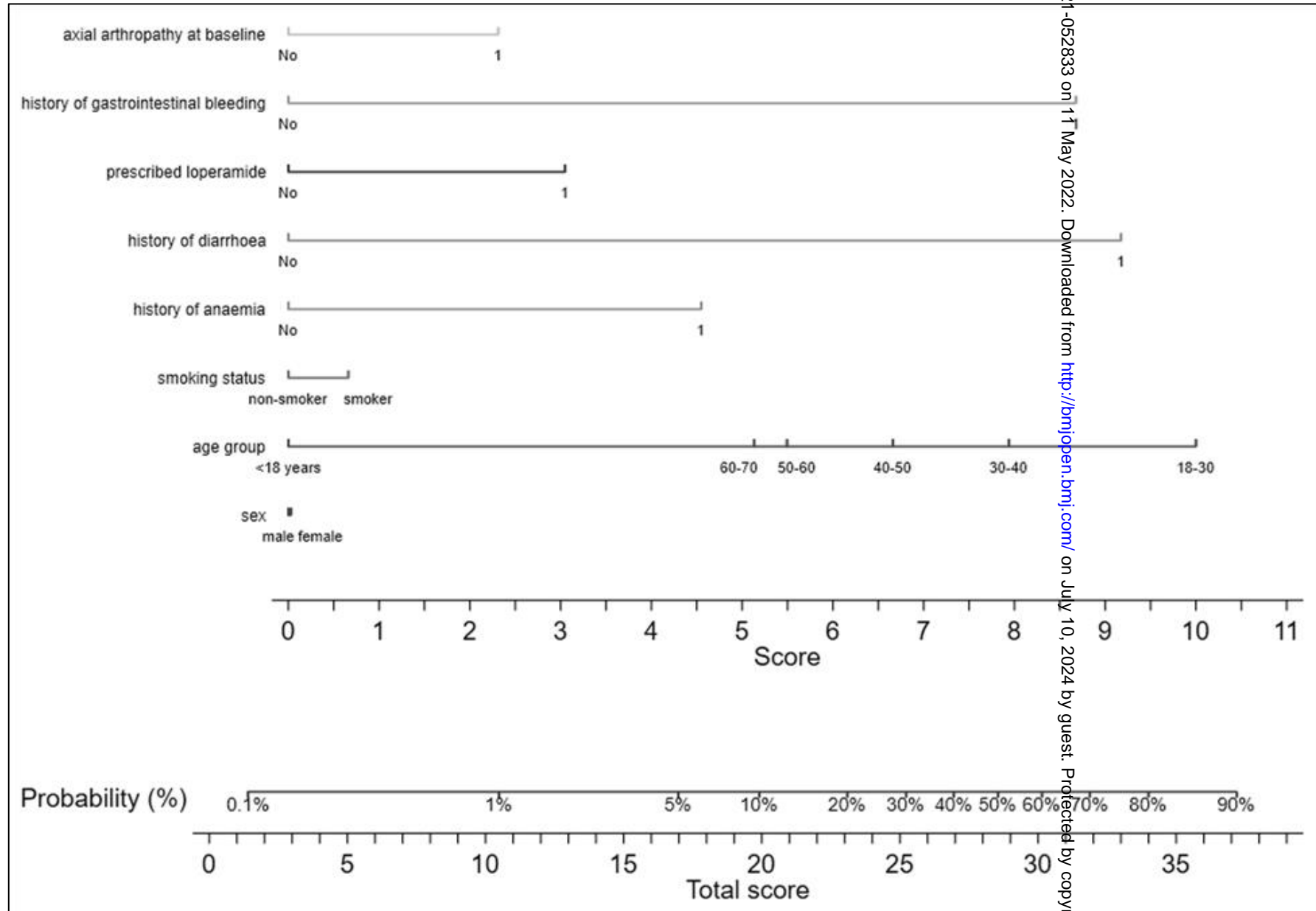
Adjusted hazard ratio (aHR) – adjustment variables: age at index; sex; Townsend deprivation quintile; Charlson comorbidity score; body mass index; smoking status; anaemia, abdominal pain, lower gastrointestinal bleeding, loperamide prescription, diarrhoea, axial arthropathy.

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

BMI; Body Mass Index
IAOI; Any IBD associated ocular inflammation

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



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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

		Item No	Recommendation	Page number
✓	Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1 & 3
✓			(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
	Introduction			
✓	Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5 & 6
✓	Objectives	3	State specific objectives, including any prespecified hypotheses	5 & 6
	Methods			
✓	Study design	4	Present key elements of study design early in the paper	7 & 8
✓	Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7 & 8
✓	Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7, 8 & 9
✓			(b) For matched studies, give matching criteria and number of exposed and unexposed	
✓	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8 & 9
✓	Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
✓	Bias	9	Describe any efforts to address potential sources of bias	7 & 8
✓	Study size	10	Explain how the study size was arrived at	7 & 11
✓	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8 & 9
✓	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8 & 9
			(b) Describe any methods used to examine subgroups and interactions	8 & 9
			(c) Explain how missing data were addressed	9
			(d) If applicable, explain how loss to follow-up was addressed	N/A
			(e) Describe any sensitivity analyses	N/A
	Results			
✓	Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, 11, Figure 1
			(b) Give reasons for non-participation at each stage	7, 11, Figure 1
			(c) Consider use of a flow diagram	Figure 1

✓	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
			(b) Indicate number of participants with missing data for each variable of interest	11, Table 1
			(c) Summarise follow-up time (eg, average and total amount)	11, Table 1
✓	Outcome data	15*	Report numbers of outcome events or summary measures over time	11, 12,13
✓	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12,13
			(b) Report category boundaries when continuous variables were categorized	
			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
✓	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12,13 (appendices)
	Discussion			
✓	Key results	18	Summarise key results with reference to study objectives	15
✓	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
✓	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18 & 19
✓	Generalisability	21	Discuss the generalisability (external validity) of the study results	17, 19
	Other information			
✓	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.