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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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Complete List of Authors:	King, Dominic; Sandwell and West Birmingham Hospitals NHS Trust, Gastroenterology; University of Birmingham, Institute of Applied Health Research Chandan, Joht; University of Birmingham, Institute of Applied Health Research Thomas, Tom; Oxford University, Translational Gastroenterology Unit and Kennedy Institute of Rheumatology Denniston, Alastair; University Hospitals Birmingham NHSFT, Department of Ophthalmology Braithwaite, Tasanee; University of Birmingham, Institute of Applied Health Research; Guy's and St Thomas' Hospitals NHS Trust, The Medical Eye Unit Niranthrankumar, Krishnarajah ; University of Birmingham, Institute of Applied Health Research Reulen, Raoul; University of Birmingham, Institute of Applied Health Research Adderley, Nicola; University of Birmingham, Institute of Applied Health Research Trudgill, Nigel; Sandwell and West Birmingham Hospitals NHS Trust, Gastroenterology
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Title Page

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

Short title: Inflammatory Bowel Disease risk in associated eye disease

Author List:

[1,2]Dominic King MBChB, dominic.king@nhs.net
[2]Joht Singh Chandan PhD, joht.chandan@nhs.net
[3]Tom Thomas MBBS, tom.thomas@nhs.net
[4,5,6,7]Alastair K Denniston PhD, a.denniston@bham.ac.uk
[2,8]Tasanee Braithwaite MPH DM, tasanee.braithwaite@gstt.nhs.uk
[2,7]Krishnarajah Nirantharakumar MD, K.Nirantharan@bham.ac.uk
[2]Raoul C Reulen PhD, R.C.Reulen@bham.ac.uk
[2]Nicola J Adderley* PhD, n.j.adderley@bham.ac.uk
[1]Nigel Trudgill* MD, nigel.trudgill@nhs.net

Affiliations:

[1]Sandwell and West Birmingham Hospitals NHS Trust, West Bromwich, UK
[2]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[3]Translational Gastroenterology Unit and Kennedy Institute of Rheumatology, University of Oxford, Oxford, UK
[4]Department of Ophthalmology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[5]Institute of Inflammation & Ageing, University of Birmingham, Birmingham, UK
[6]NIHR Biomedical Research Centre (Moorfields Eye Hospitals NHS Foundation Trust/University College London)
[7]Health Data Research UK, London
[8]The Medical Eye Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK

*Joint senior authors

Corresponding Author:
Dr Nicola J Adderley
Institute of Applied Health Research
The University of Birmingham
Edgbaston,
Birmingham,
B15 2TT
Tel 0121 414 5643
Email n.j.adderley@bham.ac.uk

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Ethics

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

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

Abbreviations:

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

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.

Article Summary

Strengths and limitations of this study

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

Introduction

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

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

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

Ophthalmic EIMs range from mild and benign to severe, requiring urgent intervention to preserve the eye. Uveitis is a sight-threatening condition and is more commonly bilateral and anterior in the context of IBD; it may run in parallel or independently of IBD activity [12–14]. Treatment for uveitis depends on the severity and the specific location of inflammation, and commonly includes topical, intraocular and systemic corticosteroids, with second-line immunosuppressants and biologics where needed[12].

Episcleritis is a benign condition that is not sight threatening and presents with eye redness and mild to moderate discomfort. It is caused by inflammation of the episcleral tissue which lies above the sclera and below the conjunctiva. It runs a parallel course when associated with IBD and often does not require specific treatment [12,15]. Scleritis on the other hand is a serious, destructive, inflammatory condition and can be sight threatening. It presents with redness of the sclera, deep 'boring' pain and may cause tissue destruction leading to visual impairment. Treatment is essential and may include systemic anti-inflammatory agents, corticosteroids and immunosuppressants [12]. Unlike episcleritis, it may appear independently of IBD activity and is uncommon compared to episcleritis [16].

Classical EIMs may occur prior to a diagnosis of IBD and may occur in isolation in those who never develop IBD [17,18]. The aim of this study was to examine the risk of and time to a subsequent diagnosis of IBD in those with a new diagnosis of a *classical* ophthalmic EIM.

Materials and Methods

Data Source

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

Study Design

Cohort study

A retrospective matched cohort study was undertaken between 1st January 1995 and 25th September 2019 to investigate the association between IBD outcome and all studied O-EIM exposures (anterior uveitis (AU), scleritis and episcleritis), with secondary studies of anterior uveitis alone and combined episcleritis and scleritis. Those subjects with an incident O-EIM diagnosis of interest (recorded through Read codes – Appendix 1)[22] were compared to subjects without the specific O-EIMs of interest for each analysis, matched by age at cohort entry (±2 years) and sex in a ratio of 1:4. Index date was defined as the start of follow up and was the date of O-EIM diagnosis for the O-EIM group. The same date was assigned to matched subjects without an O-EIM in order to mitigate for immortality time bias [23]. Only subjects without a co-existing IBD diagnosis at index date were included in the study. Individuals were eligible for inclusion from either the date of eligibility of their primary care practice or one year after they were registered, whichever was later.

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

diagnosed with IBD (CD or UC) as identified through Read codes. Subjects coded for both UC and CD were assigned to one condition based on frequency of coding. For those with equal coding, the earliest diagnosis date and the latest diagnosis of IBD subtype was used.

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

Prediction model

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

Validation

Primary care coding to identify patients with IBD has been previously validated [24,25]. O-EIM codes were reviewed by two clinicians, having been first sourced from other published primary care database studies [26–28]. Ophthalmology expert advice was sought for ophthalmic EIM coding decisions. AU codes, excluding uveitis associated with other pathologies (e.g. infective), were selected for inclusion along with episcleritis and scleritis. Clinical codes used to identify UC, CD and ophthalmic EIMs are listed in Appendix 1.

Statistical Analysis

Cohort study

The time from index date to a later diagnosis of IBD in those with and without a baseline O-EIM were presented as median time to IBD and UC or CD diagnoses with accompanying interquartile ranges (IQR). Log-rank tests were used to compare time to IBD diagnosis between those with and without O-EIMs. Cox proportional hazard models, with time to subsequent diagnosis of IBD as the time-metric, were produced to assess the adjusted hazard ratio (aHR) of IBD diagnoses in participants with an O-EIM compared to matched subjects without O-EIMs. For all O-EIMs and when AU was examined alone, aHRs were produced for all IBD, UC and CD outcomes. However, for the combined episcleritis and

scleritis study, due to IBD diagnoses being less commonly observed, only an aHR for all IBD was modelled. Hazard ratios were adjusted for age at index; sex; smoking status; body mass index (BMI); Townsend level of deprivation (quintiles); Charlson comorbidity score; baseline axial arthropathy diagnosis; and within 6-months of O-EIM diagnosis (prior to an IBD diagnosis) coding of anaemia (<11.9g/dL for females and <12.9g/dL for males), abdominal pain, loperamide prescription, diarrhoea or lower gastrointestinal bleeding. Smoking status was dichotomised into current smokers and non-smokers with missing data for smoking status considered non-smokers; a method that has been previously validated [29]. Missing data for Townsend deprivation quintile were considered a separate category. Proportional hazards were assessed using log-log plots. Cumulative incidence plots were produced to illustrate the cumulative risk of IBD over time.

Prediction model

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

Analyses were performed using Stata version 16.0 and p-values <0.05 were considered statistically significant [30].

Patient and public involvement

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

Results

Study Subjects

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

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

Risk of Inflammatory Bowel Disease Diagnosis in Associated Ophthalmic Conditions

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

Risk of Inflammatory Bowel Disease Diagnosis in Anterior Uveitis, Episcleritis and Scleritis

Subject characteristics of O-EIM and matched subjects without O-EIMs in these secondary analyses together with the full Cox models are shown in Appendices 3, 4 and 5. Subject numbers for individual O-EIMs differ slightly to those in the combined O-EIM study above because only the first diagnosed incident O-EIM was considered in the combined study, but a subject might be subsequently diagnosed with other O-EIMs and therefore be eligible for inclusion in more than one analysis for the individual O-EIMs presented in this section. In the AU study, 22,547 subjects with a new diagnosis of AU (median age 53 (39-68) years, 54% female) were matched to 89,422 subjects without AU. AU subjects and their matched subjects provided 137,878 and 531,653 py of follow-up, respectively. 152 (0.7%) IBD diagnoses (67 UC and 85 CD) were observed in AU subjects during the study period and 157 (0.2%) IBD diagnoses (107 UC and 50 CD) among subjects without AU. The median time to an IBD diagnosis was 898 (373-2,027) days in the AU subjects compared to 1,457 (539-2,700) in those without AU (log-rank test p<0.001). The median time to UC diagnosis was 1,117 (489-2,008) days compared to 1,490 (553-2,553) days and the median time to a CD diagnosis was 687 (286-2,006) days compared to 1,160 (516-2,892) days for AU subjects compared matched subjects without AU, respectively (log-rank tests p<0.001 for both CD and UC). The aHR for a subsequent IBD diagnosis in subjects with AU compared 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 (4.04-8.24), all p-values <0.001 (Table 2 (full models are shown in Appendix 4)).

In the analysis of episcleritis and scleritis combined, 17,439 subjects (14,752 (85%) episcleritis and 2,976 scleritis; median age 48 (36-61) and 62% female) were identified and matched to 68,823

controls. Episcleritis and scleritis subjects and matched participants contributed 36,324 and 136,304 py follow-up, respectively. 104 (0.6%) IBD cases (23 UC and 81 CD) were observed among episcleritis and scleritis subjects and 53 (0.1%) (30 UC and 23 CD) among those without these O-EIMs. The median time to an IBD diagnosis in episcleritis and scleritis subjects was 848 (348-2,239) days compared to 1,522 (577-2,838) days in controls, log-rank test p<0.001. The aHR for the diagnosis of IBD in those subjects with an incident diagnosis of episcleritis or scleritis compared to matched subjects without these O-EIMs was 1.73 for IBD (1.31-2.28), p<0.001 (Table 2 (full models are shown in Appendix 5)).

Prediction Model

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

Following backwards stepwise regression, female sex, smoking status, BMI and abdominal pain within 6 months of an AU diagnosis exceeded the alpha-to-remove threshold. However, female sex and smoking status were retained in the model due to their clinical importance. Weight loss within 6 months of an AU diagnosis and HLA-B27 genotype were coded in only 5 and 19 cases respectively and were therefore not included in the analysis. The multivariable logistic regression model to assess the risk of being diagnosed with IBD within a 3-year period following AU diagnosis is presented in Table 4. The Hosmer-Lemeshow chi^2 test for goodness of fit was applied to the prediction model development data set and was not significant at 0.093, suggesting reasonable model fit. The receiver operating characteristic (ROC) curve, shown in Figure 3, produced an area under the curve (AUC) C-statistic of 0.75 (95%CI 0.69-0.80). Following internal validation by bootstrapping, resampling the dataset 200 times, the mean difference between the original AUC and AUC in each bootstrap sample was 0.021. This produced a bias-corrected C-statistic value of 0.71 (0.67-0.77).

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

Discussion

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

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

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

risk of ophthalmic EIMs [16,31,32]. Several studies have suggested that certain peptide targets for the immune system are found in both joints, eyes and the colon [33,34]. It may be that immune dysregulation in relation to the enteric flora and subsequent cross-reactive antigens play a role in some EIM presentations. Moreover, the HLA-B27 antigen appears to play an important role in some mouse models where colitis and arthritis only developed in those where gut flora was present [34]. HLA-B27 positivity was not commonly coded in the IMRD-UK database and is highly likely to be under-recorded given its specialist nature. However, previous reports that this genotype is observed in greater numbers in those with EIMs and its association with arthropathies and ophthalmic conditions makes this an important consideration in such a study [7,16,35]. Arthropathies and the HLA-B27 haplotype were seen in larger numbers at baseline in ophthalmic conditions associated with IBD than in controls in the present study. Previously, it has been found that HLA-B27 is present in 90% of those with ankylosing spondylitis, but just under half of those with CD and sacroiliitis are positive for this allele [8]. IBD is known to have a genetic link with increased risk seen in the offspring of those with IBD, and this is also the case with uveitis in those with IBD. The HLA region of Chromosome 6 contains both major histocompatibility complex genes (HLAs) as well as other important IBD related genes (TNF-α). The vicinity of these genes increases the likelihood of inheriting several important genetic variations (a phenomenon known as linkage disequilibrium) and may help to explain familial traits and the relationship between some EIMs and the IBDs [32]. Other HLA types (HLA-B58) have also been associated with IBD and uveitis, however it is unclear how the interplay between genetic and environmental factors apply, given that most of those who are HLA-B27 positive will not suffer any ill effect from this phenotypic variant and HLA-B27 does not itself appear to increase the risk of IBD [32]. A limitation of this study is the lack of family history data and as a result an assessment of the risk in those with a family history of EIMs or IBD could not be made.

Vavricka et al have reported that multiple EIMs were not uncommon in IBD subjects, with CD and UC subjects studied having more than one EIM in 16% and 8% of cases respectively [36]. Axial arthropathies in the present study were included at baseline given evidence that ophthalmic and joint

manifestations may be seen more frequently together in IBD [9]. More than 2% of cases had a pre-existing axial arthropathy compared to less than one percent of matched controls. Other investigators have examined IBD and arthritis in UK primary care databases, however, type 1 and 2 EIM arthropathies are challenging to identify given a lack of specific coding, and, seropositive and negative inflammatory arthritides, although associated, are not classical EIMs and as such were not examined in this study [26]. The presence of an axial arthropathy increased the risk of IBD more than two-fold and was found to be associated with later IBD in anterior uveitis. Although not specifically examined in this study, an increased number of other EIMs in those who develop a new diagnosis of an ophthalmic condition associated with IBD compared to controls has been demonstrated previously. This has been shown to be particularly true among those with arthritic as well as ophthalmic conditions [37].

Prediction Model

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

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

Ophthalmic conditions associated with IBD which present prior to an IBD diagnosis are not common. However, an increasing prevalence of IBD both in the UK and around the world has been demonstrated [41–43]. Given the increasing numbers of patients with IBD, the need for clinicians from many disciplines outside gastroenterology to be aware of IBD is important. Those who care for

patients presenting with ophthalmic conditions associated with IBD should be attentive to features which may increase the likelihood of an IBD diagnosis, in order that appropriate investigation and referral can be made in those patients with suggestive clinical features.

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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/m2	12,799 (33.0)	51,136 (33.4)
25-30Kg/m2	11,200 (28.8)	40,782 (26.6)
>30Kg/m2	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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Table 3. Characteristics of anterior uveitis subjects with and without an inflammatory bowel disease 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/m2	37 (44)	4,999 (33)
25-30Kg/m2	23 (27)	4,588 (30)
>30Kg/m2	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

Table 4. Multivariable logistic regression prediction model of factors associated with developing 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

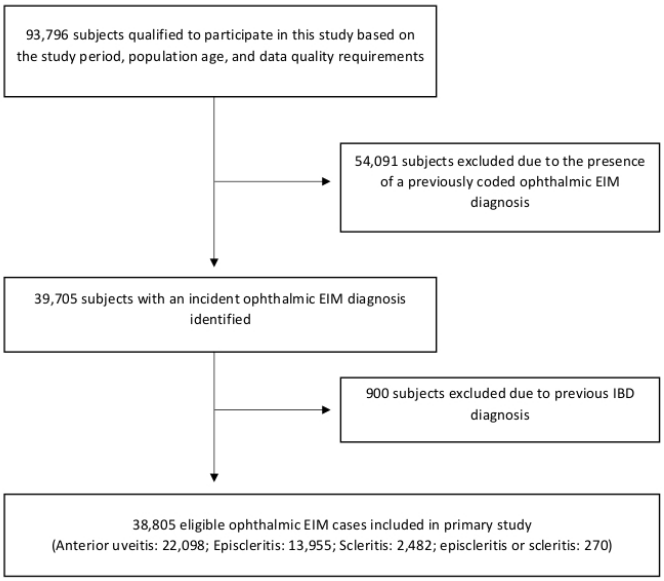
† coded within 6 months of Index date
‡ <11.9g/dL (females); <12.9g/dL (males)
** Coded at baseline*

FIGURE legends

Figure 1 Study flow chart.
Extraintestinal Manifestation (EIM); Inflammatory bowel disease (IBD).

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

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



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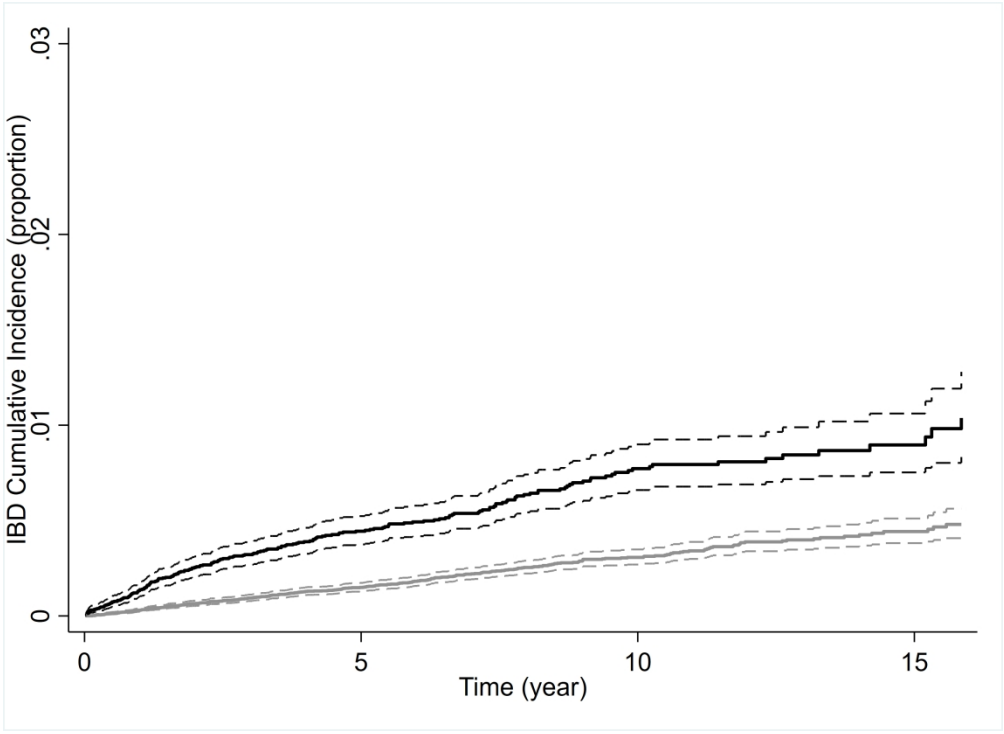
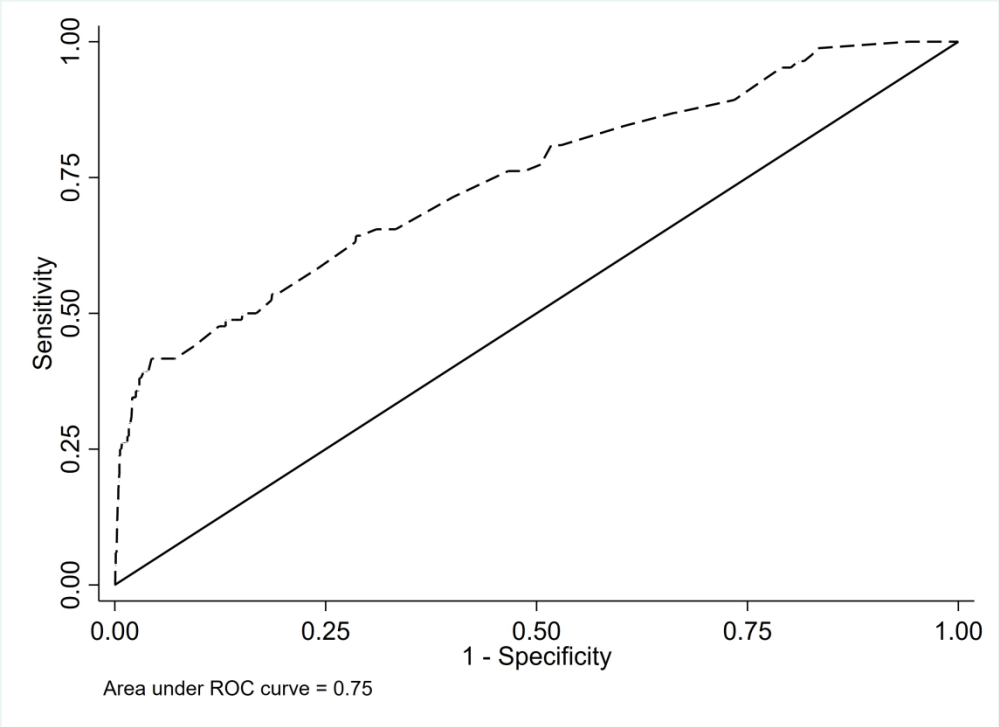


1058x769mm (72 x 72 DPI)



1058x769mm (72 x 72 DPI)

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/m^2	1.00				1.00				1.00			
25-30Kg/m^2	0.95	0.77	1.18	0.658	0.88	0.67	1.17	0.380	1.06	0.75	1.49	0.752
>30Kg/m^2	0.89	0.69	1.14	0.354	0.73	0.52	1.03	0.074	1.14	0.78	1.66	0.508
Missing	0.87	0.67	1.14	0.311	0.78	0.55	1.10	0.162	1.02	0.68	1.54	0.908
Townsend (least deprived – reference) 1	1.00				1.00				1.00			
2	1.08	0.84	1.39	0.545	1.15	0.83	1.60	0.39	0.98	0.65	1.47	0.919
3	1.11	0.86	1.44	0.424	1.20	0.86	1.67	0.276	0.98	0.65	1.48	0.932
4	0.92	0.69	1.22	0.571	0.84	0.57	1.24	0.378	1.02	0.67	1.55	0.929
5	0.94	0.68	1.30	0.689	0.87	0.55	1.36	0.537	1.02	0.63	1.63	0.948
Missing	0.80	0.59	1.09	0.164	0.89	0.60	1.31	0.545	0.69	0.42	1.14	0.146
Anaemia†‡ (reference) no	1.00				1.00				1.00			
yes	1.68	1.17	2.42	0.005	1.20	0.69	2.08	0.519	2.34	1.44	3.81	<0.001
Abdominal pain† (reference) no	1.00				1.00				1.00			
yes	1.56	0.99	2.44	0.054	1.27	0.65	2.47	0.488	1.94	1.05	3.58	0.033

Lower gastrointestinal bleeding† (reference)												
no	1.00				1.00				1.00			
yes	6.45	4.48	9.29	<0.001	8.13	5.23	12.64	<0.001	4.25	2.23	8.11	<0.001
Loperamide prescription† (reference) no	1.00				1.00				1.00			
yes	2.09	1.34	3.27	0.001	2.44	1.34	4.44	0.004	1.82	0.94	3.52	0.077
Diarrhoea† (reference) no	1.00				1.00				1.00			
yes	4.46	3.25	6.13	<0.001	3.37	2.12	5.34	<0.001	5.99	3.87	9.27	<0.001
Axial arthropathy* (reference) no	1.00				1.00				1.00			
yes	2.77	1.77	4.36	<0.001	2.49	1.32	4.71	0.005	3.15	1.66	5.99	<0.001

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

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

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

† coded within 6 months of Index date

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

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

	Inflammatory Bowel Disease				Ulcerative colitis				Crohn's Disease			
	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value
Anterior uveitis	3.39	2.70	4.25	<0.001	2.23	1.63	3.04	<0.001	5.77	4.04	8.24	<0.001
Sex (reference) Male	1.00				1.00				1.00			
Female	0.81	0.65	1.02	0.077	0.75	0.56	1.02	0.067	0.89	0.63	1.26	0.500
Age Category (reference) <18 years	1.00				No <18 cases	-	-	-	1.00			
18-30	2.60	1.07	6.35	0.035	1.00 (reference)					1.46	0.56	3.810
30-40	2.25	0.93	5.40	0.07	1.45	0.73	2.92	0.29	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/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	0.737	2.16	1.04	4.49	0.039

Lower gastrointestinal bleeding† (reference)												
no	1.00				1.00				1.00			
yes	5.97	3.71	9.62	0<0.001	6.73	3.60	12.57	<0.001	5.29	2.54	11.03	<0.001
Loperamide prescription† (reference) no	1.00				1.00				1.00			
yes	2.13	1.22	3.72	0.007	3.19	1.53	6.64	0.002	1.46	0.63	3.35	0.376
Diarrhoea† (reference) no	1.00				1.00				1.00			
yes	4.87	3.23	7.36	<0.001	2.72	1.42	5.21	0.002	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	0.42	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*

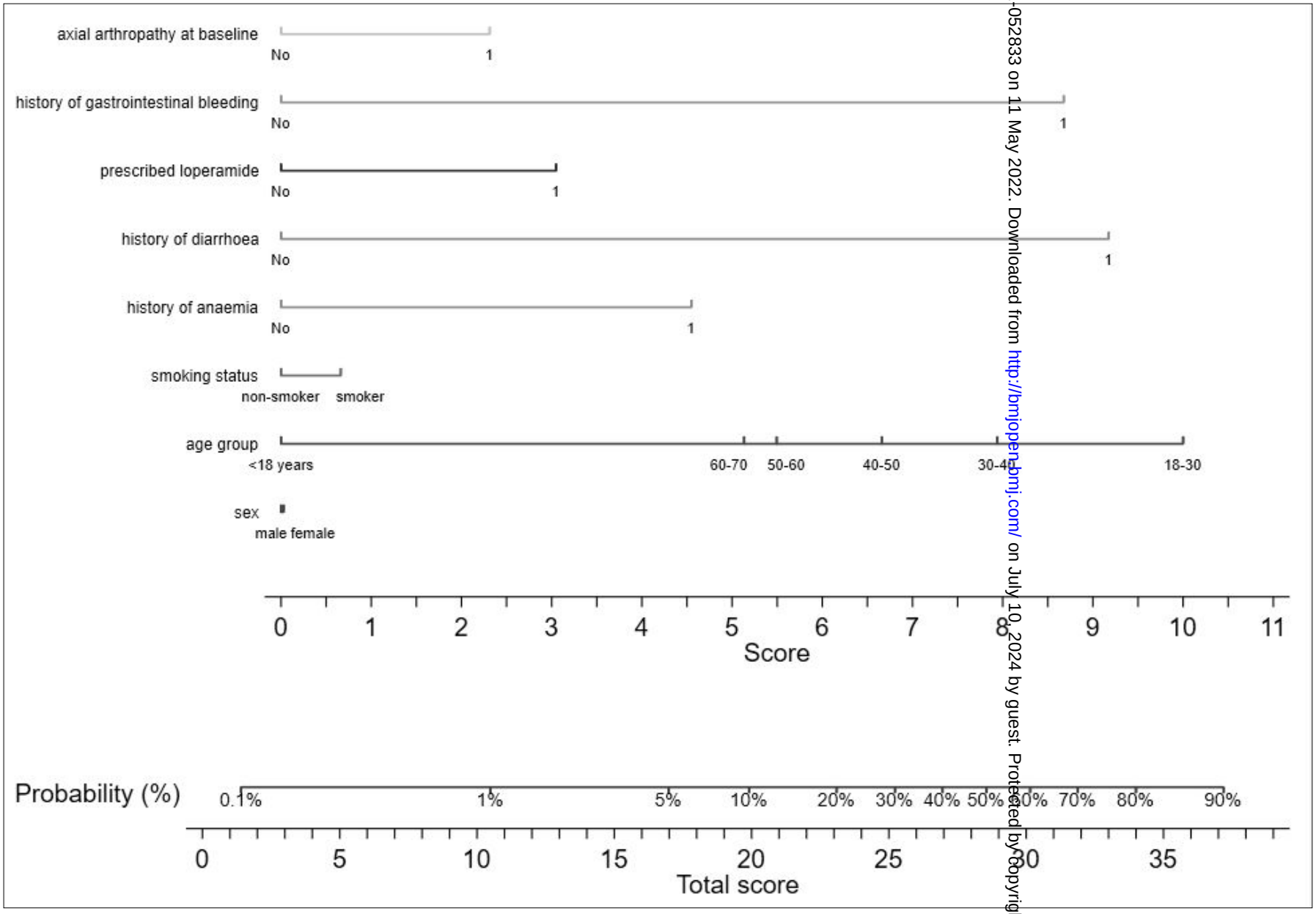
Appendix 5. Multivariable Cox hazard models for episcleritis & scleritis associated with inflammatory bowel disease

	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

>30Kg/m²	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



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	7, 8 & 9
✓	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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Title Page

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

Short title: Inflammatory Bowel Disease risk in associated eye disease

Author List:

[1,2]Dominic King MBChB, dominic.king@nhs.net
[2]Joht Singh Chandan PhD, joht.chandan@nhs.net
[3]Tom Thomas MBBS, tom.thomas@nhs.net
[4,5,6,7]Alastair K Denniston PhD, a.denniston@bham.ac.uk
[2,8]Tasanee Braithwaite MPH DM, tasanee.braithwaite@gstt.nhs.uk
[2,7]Krishnarajah Nirantharakumar MD, K.Nirantharan@bham.ac.uk
[2]Raoul C Reulen PhD, R.C.Reulen@bham.ac.uk
[2]Nicola J Adderley* PhD, n.j.adderley@bham.ac.uk
[1]Nigel Trudgill* MD, nigel.trudgill@nhs.net

Affiliations:

[1]Sandwell and West Birmingham NHS Trust, West Bromwich, UK
[2]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[3]Translational Gastroenterology Unit and Kennedy Institute of Rheumatology, University of Oxford, Oxford, UK
[4]Department of Ophthalmology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[5]Institute of Inflammation & Ageing, University of Birmingham, Birmingham, UK
[6]NIHR Biomedical Research Centre (Moorfields Eye Hospitals NHS Foundation Trust/University College London)
[7]Health Data Research UK, London
[8]The Medical Eye Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK

*Joint senior authors

Corresponding Author:
Dr Nicola J Adderley
Institute of Applied Health Research
The University of Birmingham
Edgbaston,
Birmingham,
B15 2TT
Tel 0121 414 5643
Email n.j.adderley@bham.ac.uk

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Ethics

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

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

Abbreviations:

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

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.

Article Summary

Strengths and limitations of this study

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

Introduction

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

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

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

Ophthalmic EIMs range from mild and benign to severe, requiring urgent intervention to preserve the eye. Uveitis is a sight-threatening condition and is more commonly bilateral and anterior in the context of IBD; it may run in parallel or independently of IBD activity [12–14]. Treatment for uveitis depends on the severity and the specific location of inflammation, and commonly includes topical, intraocular and systemic corticosteroids, with second-line immunosuppressants and biologics where

needed[12]. Episcleritis is a benign condition that is not sight threatening and presents with eye redness and mild to moderate discomfort. It is caused by inflammation of the episcleral tissue which lies above the sclera and below the conjunctiva. It runs a parallel course when associated with IBD and often does not require specific treatment [12,15]. Scleritis on the other hand is a serious, destructive, inflammatory condition and can be sight threatening. It presents with redness of the sclera, deep 'boring' pain and may cause tissue destruction leading to visual impairment. Treatment is essential and may include systemic anti-inflammatory agents, corticosteroids and immunosuppressants [12]. Unlike episcleritis, it may appear independently of IBD activity and is uncommon compared to episcleritis [16].

Classical EIMs may occur prior to a diagnosis of IBD and may occur in isolation in those who never develop IBD [17,18], here we term these conditions IBD associated ocular inflammation (IAOI). The aim of this study was to examine the risk of and time to a subsequent diagnosis of IBD in those with a new diagnosis of IAOI.

Materials and Methods

Data Source

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

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

Study Design

Cohort study

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

order to mitigate for immortal time bias [23]. Only subjects without a co-existing IBD diagnosis at index date were included in the study.

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

Prediction model

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

Validation

Primary care coding to identify patients with IBD has been previously validated [24,25]. IAOI codes were reviewed by two clinicians, having been first sourced from other published primary care database studies [26–28]. Ophthalmology expert advice was sought for IAOI coding decisions. AU codes, excluding uveitis associated with other pathologies (e.g. infective), were selected for inclusion along with episcleritis and scleritis. Clinical codes used to identify UC, CD and IAOI are listed in Appendix 1.

Statistical Analysis

Cohort study

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

aHRs were produced for all IBD, UC and CD outcomes. However, for the combined episcleritis and scleritis study, due to IBD diagnoses being less commonly observed, only an aHR for all IBD was modelled.

Covariates

Hazard ratios were adjusted for age at index; sex; smoking status; body mass index (BMI); Townsend level of deprivation (quintiles); Charlson comorbidity score; baseline axial arthropathy diagnosis; and within 6-months of IAOI diagnosis (prior to an IBD diagnosis) coding of anaemia (<11.9g/dL for females and <12.9g/dL for males), abdominal pain, loperamide prescription, diarrhoea, or lower gastrointestinal bleeding. Smoking status was dichotomised into current smokers and non-smokers with missing data for smoking status considered non-smokers; a method that has been previously validated [29].

Missing data

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

Prediction model

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

Candidate predictor variables

Sex, age (categorical) and smoking status were included due to their clinical importance. Further candidate variables including baseline axial arthropathy, BMI (categorical) and within 6-months

coding of anaemia, abdominal pain, lower gastrointestinal bleeding, loperamide prescription and diarrhoea (prior to an IBD diagnosis) were assessed. Some potential candidate predictors such as Townsend deprivation and co-morbidity score were not included, due to the small number of outcome events.

Model performance

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

Analyses were performed using Stata version 16.0 and p-values <0.05 were considered statistically significant [30].

Patient and public involvement

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

Results

Study Subjects

Following exclusions (Figure 1), 38,805 subjects with an IAOI were identified (median age 51 (38-65) and 57% female). IAOI cases included those coded as AU: 22,098 (57%); episcleritis: 13,955 (36%); scleritis: 2,482 (0.6%); episcleritis or scleritis (a non-specific code where it was not possible to determine whether subjects were episcleritis or scleritis): 270 (0.01%). The age distribution of AU (with a higher frequency in the elderly) and episcleritis or scleritis (with a higher frequency in the 40-50 age group) was in keeping with previous findings.[31,32] IAOI subjects were age and sex matched to 153,018 subjects without an IAOI. The median follow-up period was five years with a total of 244,503 person years (py) of follow-up time in IAOI subjects and 934,847 py in those without IAOIs.

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

Risk of Inflammatory Bowel Disease Diagnosis in Associated Ophthalmic Conditions

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

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 in Appendix 2). Figure 2 shows the cumulative incidence plot for IBD diagnoses in subjects with IAOIs compared to those without.

Risk of Inflammatory Bowel Disease Diagnosis in Anterior Uveitis, Episcleritis and Scleritis

Subject characteristics of IAOI and matched subjects without IAOIs in these secondary analyses together with the full Cox models are shown in Appendices 3, 4 and 5. Subject numbers for individual IAOIs differ slightly to those in the combined IAOI study above because only the first diagnosed incident IAOI was considered in the combined study, but a subject might be subsequently diagnosed with other IAOIs and therefore be eligible for inclusion in more than one analysis for the individual IAOIs presented in this section. In the AU study, 22,547 subjects with a new diagnosis of AU (median age 53 (39-68) years, 54% female) were matched to 89,422 subjects without AU. AU subjects and their matched subjects provided 137,878 and 531,653 py of follow-up, respectively. 152 (0.7%) IBD diagnoses (67 UC and 85 CD) were observed in AU subjects during the study period and 157 (0.2%) IBD diagnoses (107 UC and 50 CD) among subjects without AU. The median time to an IBD diagnosis was 898 (373-2,027) days in the AU subjects compared to 1,457 (539-2,700) in those without AU (log-rank test p<0.001). For a UC diagnosis 1,117 (489-2,008) days vs 1,490 (553-2,553) days and for a CD diagnosis 687 (286-2,006) vs 1,160 (516-2,892) days for AU subjects compared to subjects without AU, respectively (log-rank tests p<0.001 for both CD and UC). The aHR for a subsequent IBD diagnosis in subjects with AU compared 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 (4.04-8.24), all p-values <0.001 (Table 2 (full models are shown in Appendix 4)).

In the analysis of episcleritis and scleritis combined, 17,439 subjects (14,752 (85%) episcleritis and 2,976 scleritis; median age 48 (36-61) and 62% female) were identified and matched to 68,823

controls. Episcleritis and scleritis subjects and matched participants contributed 36,324 and 136,304 py follow-up, respectively. 104 (0.6%) IBD cases (23 UC and 81 CD) were observed among episcleritis and scleritis subjects and 53 (0.1%) (30 UC and 23 CD) among those without these IAOIs. The median time to an IBD diagnosis in episcleritis and scleritis subjects was 848 (348-2,239) days compared to 1,522 (577-2,838) days in controls, log-rank test p<0.001. The aHR for the diagnosis of IBD in those subjects with an incident diagnosis of episcleritis or scleritis compared to matched subjects without these IAOIs was 1.73 for IBD (1.31-2.28), p<0.001 (Table 2 (full models are shown in Appendix 5)).

Complete case analyses were performed where subjects with missing variables were dropped from the Cox models. There was minimal change in estimates and significance remained unchanged. Adjusted HRs for the complete-case analyses are found in Appendix 6.

Prediction Model

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

Following backwards stepwise regression, female sex, smoking status, BMI and abdominal pain within 6 months of an AU diagnosis exceeded the alpha-to-remove threshold. However, female sex and smoking status were retained in the model due to their clinical importance while weight loss within 6 months of an AU diagnosis and HLA-B27 genotype were coded in only 5 and 19 cases respectively and were therefore not included in the analysis. The multivariable logistic regression model to assess the risk of being diagnosed with IBD within a 3-year period following AU diagnosis is presented in Table 4. The Hosmer-Lemeshow chi^2 test for goodness of fit was applied to the prediction model development data set and was not significant at 0.093, suggesting reasonable

model fit. The receiver operating characteristic (ROC) curve, shown in Figure 3, produced an area under the curve (AUC) C-statistic of 0.75 (95%CI 0.69-0.80). Following internal validation by bootstrapping, resampling the dataset 200 times, the mean difference between the original AUC and AUC in each bootstrap sample was 0.021. This produced a bias-corrected C-statistic value of 0.71 (0.67-0.77).

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

Discussion

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

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

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

increased risk of ophthalmic EIMs [16,33,34]. Several studies have suggested that certain peptide targets for the immune system are found in both joints, eyes and the colon [35,36]. It may be that immune dysregulation in relation to the enteric flora and subsequent cross-reactive antigens play a role in some EIM presentations. Moreover, the HLA-B27 antigen appears to play an important role in some mouse models where colitis and arthritis only developed in those where gut flora was present [36]. HLA-B27 positivity was not commonly coded in the IMRD-UK database and is highly likely to be under-recorded given its specialist nature. However, previous reports that this genotype is observed in greater numbers in those with EIMs and its association with arthropathies and ophthalmic conditions makes this an important consideration in such a study [7,16,37]. Arthropathies and the HLA-B27 haplotype were seen in larger numbers at baseline in ophthalmic conditions associated with IBD than in controls in the present study. Previously, it has been found that HLA-B27 is present in 90% of those with ankylosing spondylitis, but just under half of those with CD and sacroiliitis are positive for this allele [8]. IBD is known to have a genetic link with increased risk seen in the offspring of those with IBD, and this is also the case with uveitis in those with IBD. The HLA region of Chromosome 6 contains both major histocompatibility complex genes (HLAs) as well as other important IBD related genes (TNF-α). The vicinity of these genes increases the likelihood of inheriting several important genetic variations (a phenomenon known as linkage disequilibrium) and may help to explain familial traits and the relationship between some EIMs and the IBDs [34]. Other HLA types (HLA-B58) have also been associated with IBD and uveitis but it is unclear how the interplay between genetic and environmental factors apply, given that most of those who are HLA-B27 positive will not suffer any ill effect from this phenotypic variant and HLA-B27 does not itself appear to increase the risk of IBD [34]. A limitation of this study is the lack of family history data and as a result an assessment of the risk in those with a family history of EIMs or IBD could not be made.

Vavricka et al have reported that multiple EIMs were not uncommon in IBD subjects, with CD and UC subjects studied having more than one EIM in 16% and 8% of cases respectively [38]. Axial arthropathies in the present study were included at baseline given evidence that ophthalmic and

joint manifestations may be seen more frequently together in IBD [9]. More than 2% of cases had a pre-existing axial arthropathy compared to less than one percent of matched controls. Other investigators have examined IBD and arthritis in UK primary care databases. However, type 1 and 2 EIM arthropathies are challenging to identify given a lack of specific coding, and, seropositive and negative inflammatory arthritides, although associated, are not classical EIMs and as such were not examined in this study [26]. The presence of an axial arthropathy increased the risk of IBD more than two-fold and was found to be associated with later IBD in anterior uveitis. Although not specifically examined in this study, an increased number of other EIMs in those who develop a new diagnosis of an ophthalmic condition associated with IBD compared to controls has been demonstrated previously. This has been shown to be particularly true among those with arthritic as well as ophthalmic conditions [39].

Prediction Model

The prediction model for IBD diagnosis in subjects with anterior uveitis found associations with several variables. Anaemia, diarrhoea, and lower gastrointestinal bleeding heralded an IBD diagnosis, highlighting the need for careful history taking in ophthalmic care settings and investigation for IBD if such symptoms are revealed. Other inflammatory and autoimmune conditions associated with uveitis can lead to anaemia, including sarcoidosis. Some of these conditions will produce an anaemia of chronic disease, and others a haemolytic anaemia [40,41]. In the context of ophthalmic conditions associated with IBD, iron deficiency anaemia should be investigated to prevent an IBD diagnostic delay. Age was strongly associated with IBD in our model. Those in the age group 18-30 had the highest risk compared to under 18 year-olds, however all ages up to 70 had an increased IBD risk compared to the reference group (under 18 years). Ottaviano et al. reviewed the published literature on ophthalmic EIMs in children and found that there was little data available. They suggested that this may be related to asymptomatic uveitis, as well as a lower prevalence of these EIMs in childhood compared to adults [42]. In the present study, less than 6% of the cohort were aged under 18 and only 0.2% of subjects in this age category developed IBD during

the study period, with a slight preponderance towards CD, as has been previously shown in paediatric series [42].

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

Ophthalmic conditions associated with IBD which present prior to an IBD diagnosis are not common. However, an increasing prevalence of IBD both in the UK and around the world has been

demonstrated [43–45]. Given the increasing numbers of patients with IBD, the need for clinicians from many disciplines outside gastroenterology to be aware of IBD is important. Those who care for patients presenting with ophthalmic conditions associated with IBD should be attentive to features which may increase the likelihood of an IBD diagnosis, in order that appropriate investigation and referral can be made in those patients with suggestive clinical features.

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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/m2	12,799 (33.0)	51,136 (33.4)
25-30Kg/m2	11,200 (28.8)	40,782 (26.6)
>30Kg/m2	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

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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Table 3. Characteristics of anterior uveitis subjects with and without an inflammatory bowel disease 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/m2	37 (44)	4,999 (33)
25-30Kg/m2	23 (27)	4,588 (30)
>30Kg/m2	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

Table 4. Multivariable logistic regression prediction model of factors associated with developing 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

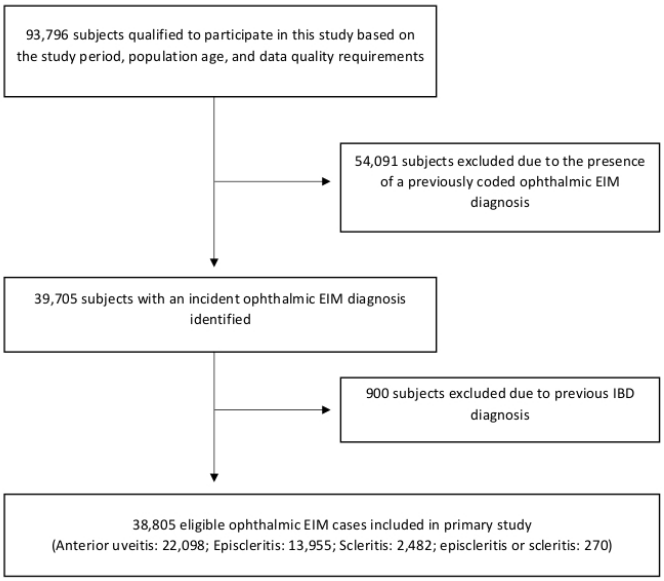
† coded within 6 months of Index date
‡ <11.9g/dL (females); <12.9g/dL (males)
** Coded at baseline*

FIGURE legends

Figure 1 Study flow chart.
Inflammatory bowel disease (IBD).

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

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



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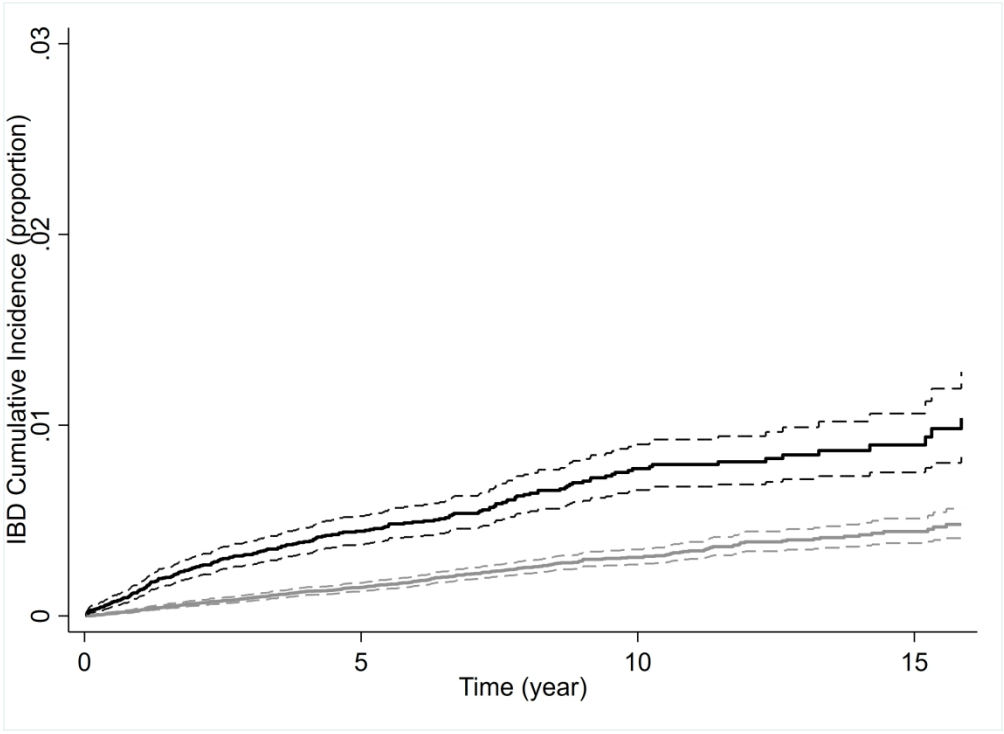
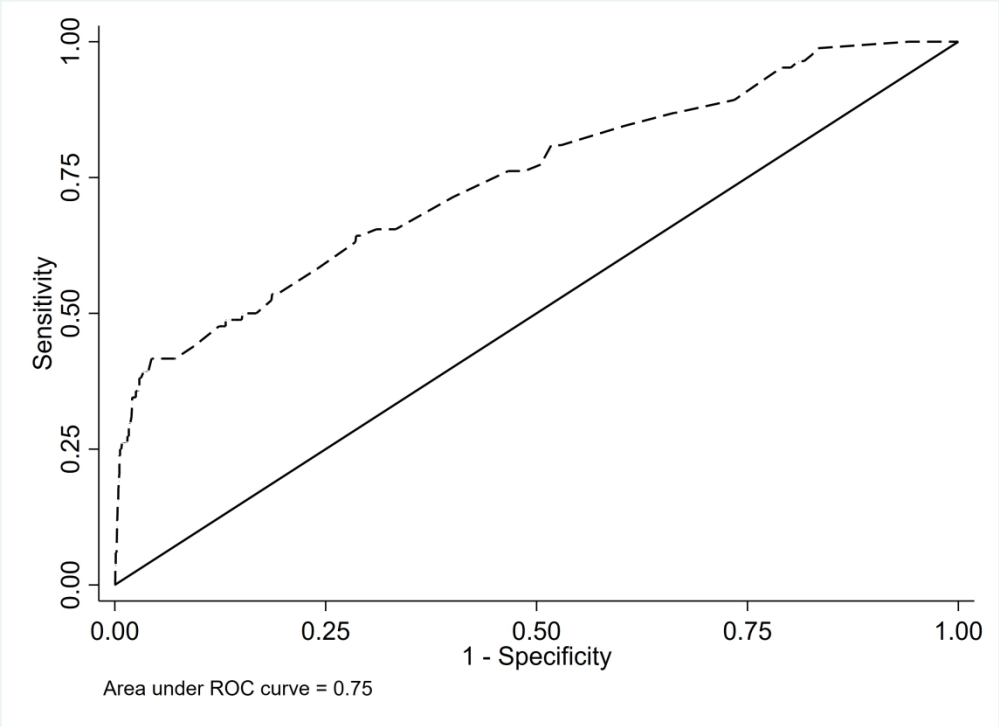


1058x769mm (72 x 72 DPI)



1058x769mm (72 x 72 DPI)

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 IAOIs	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
Lower gastrointestinal bleeding† (reference) no	1.00				1.00				1.00			
yes	6.45	4.48	9.29	<0.001	8.13	5.23	12.64	<0.001	4.25	2.23	8.11	<0.001
Loperamide prescription† (reference) no	1.00				1.00				1.00			
yes	2.09	1.34	3.27	0.001	2.44	1.34	4.44	0.004	1.82	0.94	3.52	0.077
Diarrhoea† (reference) no	1.00				1.00				1.00			
yes	4.46	3.25	6.13	<0.001	3.37	2.12	5.34	<0.001	5.99	3.87	9.27	<0.001
Axial arthropathy* (reference) no	1.00				1.00				1.00			
yes	2.77	1.77	4.36	<0.001	2.49	1.32	4.71	0.005	3.15	1.66	5.99	<0.001

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

EIM: extraintestinal manifestations

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

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

† coded within 6 months of Index date

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

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

	Inflammatory Bowel Disease				Ulcerative colitis				Crohn's Disease			
	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value
Anterior uveitis	3.39	2.70	4.25	<0.001	2.23	1.63	3.04	<0.001	5.77	4.04	8.24	<0.001
Sex (reference) Male	1.00				1.00				1.00			
Female	0.81	0.65	1.02	0.077	0.75	0.56	1.02	0.06	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	0.93	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	0.36	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	0.002	1.46	0.63	3.35	0.376
Diarrhoea† (reference) no	1.00				1.00				1.00			
yes	4.87	3.23	7.36	<0.001	2.72	1.42	5.21	0.003	8.01	4.74	13.55	<0.001
Axial arthropathy* (reference) no	1.00				1.00				1.00			
yes	2.08	0.58	2.64	0.008	1.45	0.59	3.56	0.42	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
>30Kg/m²	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)

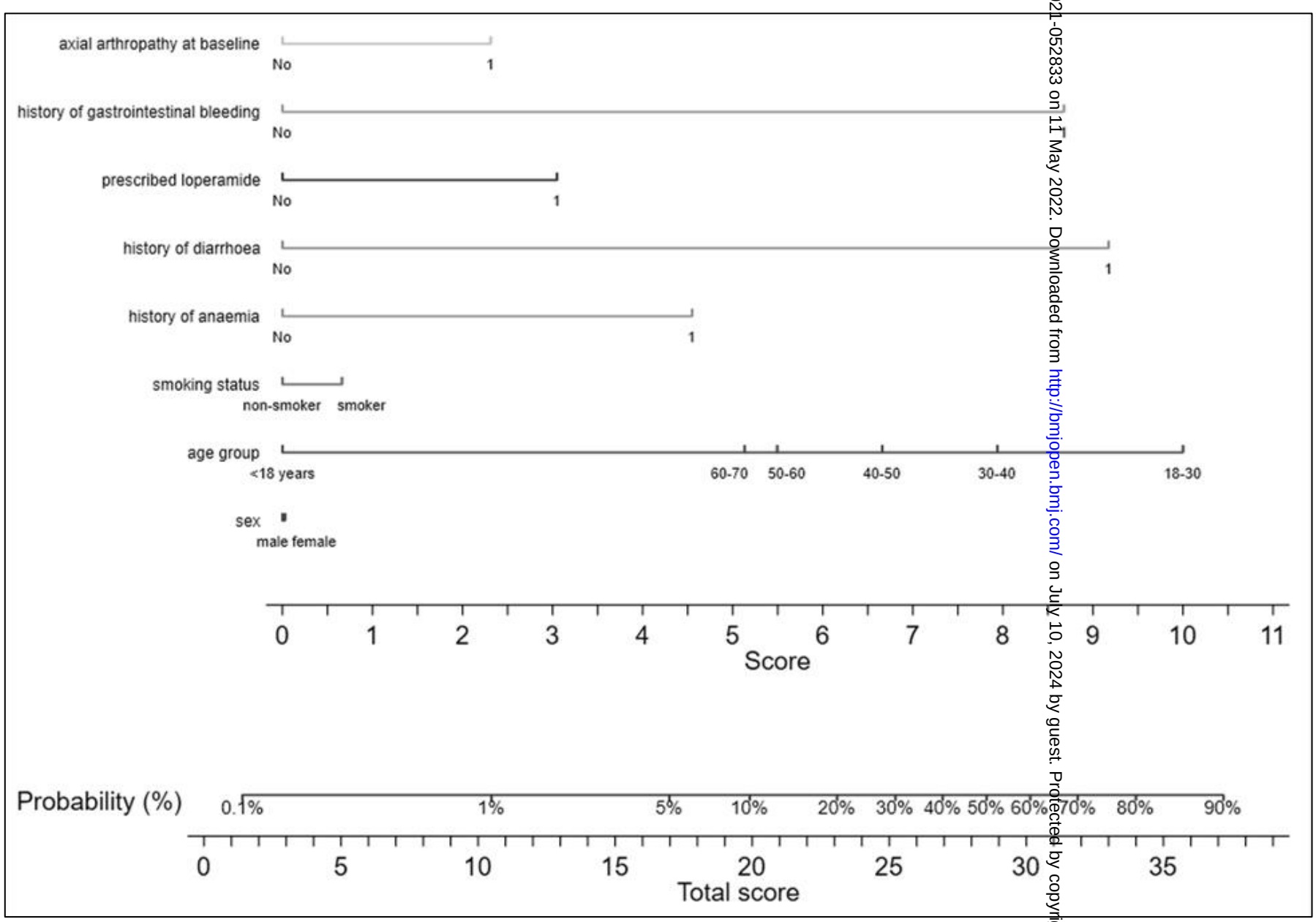
	aHR	[95% Confidence Interval]		p-value
Any IBD associated ocular inflammation				
Inflammatory bowel disease	2.29 (2.25)	1.86	2.80	<0.001
Ulcerative colitis	1.43 (1.65)	1.07	1.90	0.015
Crohn's disease	3.95 (3.37)	2.88	5.41	<0.001
Anterior uveitis				
Inflammatory bowel disease	3.49 (3.39)	2.69	4.51	<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



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	7, 8 & 9
✓	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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Title Page

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

Short title: Inflammatory Bowel Disease risk in associated eye disease

Author List:

[1,2]Dominic King MBChB, dominic.king@nhs.net
[2]Joht Singh Chandan PhD, joht.chandan@nhs.net
[3]Tom Thomas MBBS, tom.thomas@nhs.net
[4,5,6,7]Alastair K Denniston PhD, a.denniston@bham.ac.uk
[2,8]Tasanee Braithwaite MPH DM, tasanee.braithwaite@gstt.nhs.uk
[2,7]Krishnarajah Nirantharakumar MD, K.Nirantharan@bham.ac.uk
[2]Raoul C Reulen PhD, R.C.Reulen@bham.ac.uk
[2]Nicola J Adderley* PhD, n.j.adderley@bham.ac.uk
[1]Nigel Trudgill* MD, nigel.trudgill@nhs.net

Affiliations:

[1]Sandwell and West Birmingham NHS Trust, West Bromwich, UK
[2]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[3]Translational Gastroenterology Unit and Kennedy Institute of Rheumatology, University of Oxford, Oxford, UK
[4]Department of Ophthalmology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[5]Institute of Inflammation & Ageing, University of Birmingham, Birmingham, UK
[6]NIHR Biomedical Research Centre (Moorfields Eye Hospitals NHS Foundation Trust/University College London)
[7]Health Data Research UK, London
[8]The Medical Eye Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK

*Joint senior authors

Corresponding Author:
Dr Nicola J Adderley
Institute of Applied Health Research
The University of Birmingham
Edgbaston,
Birmingham,
B15 2TT
Tel 0121 414 5643
Email n.j.adderley@bham.ac.uk

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Ethics

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

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

Abbreviations:

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

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.

Article Summary

Strengths and limitations of this study

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

Introduction

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

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

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

Ophthalmic EIMs range from mild and benign to severe, requiring urgent intervention to preserve the eye. Uveitis is a sight-threatening condition and is more commonly bilateral and anterior in the context of IBD; it may run in parallel or independently of IBD activity [12–14]. Treatment for uveitis depends on the severity and the specific location of inflammation, and commonly includes topical, intraocular and systemic corticosteroids, with second-line immunosuppressants and biologics where

needed[12]. Episcleritis is a benign condition that is not sight threatening and presents with eye redness and mild to moderate discomfort. It is caused by inflammation of the episcleral tissue which lies above the sclera and below the conjunctiva. It runs a parallel course when associated with IBD and often does not require specific treatment [12,15]. Scleritis on the other hand is a serious, destructive, inflammatory condition and can be sight threatening. It presents with redness of the sclera, deep 'boring' pain and may cause tissue destruction leading to visual impairment. Treatment is essential and may include systemic anti-inflammatory agents, corticosteroids and immunosuppressants [12]. Unlike episcleritis, it may appear independently of IBD activity and is uncommon compared to episcleritis [16].

Classical EIMs may occur prior to a diagnosis of IBD and may occur in isolation in those who never develop IBD [17,18], here we term these conditions IBD associated ocular inflammation (IAOI). The aim of this study was to examine the risk of and time to a subsequent diagnosis of IBD in those with a new diagnosis of IAOI.

Materials and Methods

Data Source

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

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

Study Design

Cohort study

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

without an IAOI in order to mitigate for immortal time bias [23]. Only subjects without a co-existing IBD diagnosis at index date were included in the study.

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

Prediction model

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

Validation

Primary care coding to identify patients with IBD has been previously validated [24,25]. IAOI codes were reviewed by two clinicians, having been first sourced from other published primary care database studies [26–28]. Ophthalmology expert advice was sought for IAOI coding decisions. AU codes, excluding uveitis associated with other pathologies (e.g. infective), were selected for inclusion along with episcleritis and scleritis. Clinical codes used to identify UC, CD and IAOI are listed in Appendix 1.

Statistical Analysis

Cohort study

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

aHRs were produced for all IBD, UC and CD outcomes. However, for the combined episcleritis and scleritis study, due to IBD diagnoses being less commonly observed, only an aHR for all IBD was modelled.

Covariates

Hazard ratios were adjusted for age at index; sex; smoking status; body mass index (BMI); Townsend level of deprivation (quintiles); Charlson comorbidity score; baseline axial arthropathy diagnosis; and within 6-months of IAOI diagnosis (prior to an IBD diagnosis) coding of anaemia (<11.9g/dL for females and <12.9g/dL for males), abdominal pain, loperamide prescription, diarrhoea, or lower gastrointestinal bleeding. Smoking status was dichotomised into current smokers and non-smokers with missing data for smoking status considered non-smokers; a method that has been previously validated [29].

Missing data

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

Prediction model

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

Candidate predictor variables

Sex, age (categorical) and smoking status were included due to their clinical importance. Further candidate variables including baseline axial arthropathy, BMI (categorical) and within 6-months

coding of anaemia, abdominal pain, lower gastrointestinal bleeding, loperamide prescription and diarrhoea (prior to an IBD diagnosis) were assessed. Some potential candidate predictors such as Townsend deprivation and co-morbidity score were not included, due to the small number of outcome events.

Model performance

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

Analyses were performed using Stata version 16.0 and p-values <0.05 were considered statistically significant [30].

Patient and public involvement

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

Results

Study Subjects

Following exclusions (Figure 1), 38,805 subjects with an IAOI were identified (median age 51 (38-65) and 57% female). IAOI cases included those coded as AU: 22,098 (57%); episcleritis: 13,955 (36%); scleritis: 2,482 (0.6%); episcleritis or scleritis (a non-specific code where it was not possible to determine whether subjects were episcleritis or scleritis): 270 (0.01%). The age distribution of AU (with a higher frequency in the elderly) and episcleritis or scleritis (with a higher frequency in the 40-50 age group) was in keeping with previous findings.[31,32] IAOI subjects were age and sex matched to 153,018 subjects without an IAOI. The median follow-up period was five years with a total of 244,503 person years (py) of follow-up time in IAOI subjects and 934,847 py in those without IAOIs.

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

Risk of Inflammatory Bowel Disease Diagnosis in Associated Ophthalmic Conditions

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

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 in Appendix 2). Figure 2 shows the cumulative incidence plot for IBD diagnoses in subjects with IAOIs compared to those without.

Risk of Inflammatory Bowel Disease Diagnosis in Anterior Uveitis, Episcleritis and Scleritis

Subject characteristics of IAOI and matched subjects without IAOIs in these secondary analyses together with the full Cox models are shown in Appendices 3, 4 and 5. Subject numbers for individual IAOIs differ slightly to those in the combined IAOI study above because only the first diagnosed incident IAOI was considered in the combined study, but a subject might be subsequently diagnosed with other IAOIs and therefore be eligible for inclusion in more than one analysis for the individual IAOIs presented in this section. In the AU study, 22,547 subjects with a new diagnosis of AU (median age 53 (39-68) years, 54% female) were matched to 89,422 subjects without AU. AU subjects and their matched subjects provided 137,878 and 531,653 py of follow-up, respectively. 152 (0.7%) IBD diagnoses (67 UC and 85 CD) were observed in AU subjects during the study period and 157 (0.2%) IBD diagnoses (107 UC and 50 CD) among subjects without AU. The median time to an IBD diagnosis was 898 (373-2,027) days in the AU subjects compared to 1,457 (539-2,700) in those without AU (log-rank test p<0.001). The median time to a UC diagnosis was 1,117 (489-2,008) days in AU subjects and 1,490 (553-2,553) days in subjects without AU. For a CD diagnosis, the median time to diagnosis was 687 (286-2,006) days in AU subjects and 1,160 (516-2,892) days in subjects without AU. Log-rank tests gave p<0.001 for both CD and UC. The aHR for a subsequent IBD diagnosis in subjects with AU compared 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 (4.04-8.24), all p-values <0.001 (Table 2 (full models are shown in Appendix 4)).

In the analysis of episcleritis and scleritis combined, 17,439 subjects (14,752 (85%) episcleritis and 2,976 scleritis; median age 48 (36-61) and 62% female) were identified and matched to 68,823 controls. Episcleritis and scleritis subjects and matched participants contributed 36,324 and 136,304 py follow-up, respectively. 104 (0.6%) IBD cases (23 UC and 81 CD) were observed among episcleritis and scleritis subjects and 53 (0.1%) (30 UC and 23 CD) among those without these IAOIs. The median time to an IBD diagnosis in episcleritis and scleritis subjects was 848 (348-2,239) days compared to 1,522 (577-2,838) days in controls, log-rank test p<0.001. The aHR for the diagnosis of IBD in those subjects with an incident diagnosis of episcleritis or scleritis compared to matched subjects without these IAOIs was 1.73 for IBD (1.31-2.28), p<0.001 (Table 2 (full models are shown in Appendix 5)).

Complete case analyses were performed where subjects with missing variables were dropped from the Cox models. There was minimal change in estimates and significance remained unchanged. Adjusted HRs for the complete-case analyses are found in Appendix 6.

Prediction Model

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

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

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

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

Discussion

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

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

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

increased risk of ophthalmic EIMs [16,33,34]. Several studies have suggested that certain peptide targets for the immune system are found in both joints, eyes and the colon [35,36]. It may be that immune dysregulation in relation to the enteric flora and subsequent cross-reactive antigens play a role in some EIM presentations. Moreover, the HLA-B27 antigen appears to play an important role in some mouse models where colitis and arthritis only developed in those where gut flora was present [36]. HLA-B27 positivity was not commonly coded in the IMRD-UK database and is highly likely to be under-recorded given its specialist nature. However, previous reports that this genotype is observed in greater numbers in those with EIMs and its association with arthropathies and ophthalmic conditions makes this an important consideration in such a study [7,16,37]. Arthropathies and the HLA-B27 haplotype were seen in larger numbers at baseline in ophthalmic conditions associated with IBD than in controls in the present study. Previously, it has been found that HLA-B27 is present in 90% of those with ankylosing spondylitis, but just under half of those with CD and sacroiliitis are positive for this allele [8]. IBD is known to have a genetic link with increased risk seen in the offspring of those with IBD, and this is also the case with uveitis in those with IBD. The HLA region of Chromosome 6 contains both major histocompatibility complex genes (HLAs) as well as other important IBD related genes (TNF-α). The vicinity of these genes increases the likelihood of inheriting several important genetic variations (a phenomenon known as linkage disequilibrium) and may help to explain familial traits and the relationship between some EIMs and the IBDs [34]. Other HLA types (HLA-B58) have also been associated with IBD and uveitis but it is unclear how the interplay between genetic and environmental factors apply, given that most of those who are HLA-B27 positive will not suffer any ill effect from this phenotypic variant and HLA-B27 does not itself appear to increase the risk of IBD [34]. A limitation of this study is the lack of family history data and as a result an assessment of the risk in those with a family history of EIMs or IBD could not be made.

Vavricka et al have reported that multiple EIMs were not uncommon in IBD subjects, with CD and UC subjects studied having more than one EIM in 16% and 8% of cases respectively [38]. Axial arthropathies in the present study were included at baseline given evidence that ophthalmic and

joint manifestations may be seen more frequently together in IBD [9]. More than 2% of cases had a pre-existing axial arthropathy compared to less than one percent of matched controls. Other investigators have examined IBD and arthritis in UK primary care databases. However, type 1 and 2 EIM arthropathies are challenging to identify given a lack of specific coding, and, seropositive and negative inflammatory arthritides, although associated, are not classical EIMs and as such were not examined in this study [26]. The presence of an axial arthropathy increased the risk of IBD more than two-fold and was found to be associated with later IBD in anterior uveitis. Although not specifically examined in this study, an increased number of other EIMs in those who develop a new diagnosis of an ophthalmic condition associated with IBD compared to controls has been demonstrated previously. This has been shown to be particularly true among those with arthritic as well as ophthalmic conditions [39].

Prediction Model

The prediction model for IBD diagnosis in subjects with anterior uveitis found associations with several variables. Anaemia, diarrhoea, and lower gastrointestinal bleeding heralded an IBD diagnosis, highlighting the need for careful history taking in ophthalmic care settings and investigation for IBD if such symptoms are revealed. Other inflammatory and autoimmune conditions associated with uveitis can lead to anaemia, including sarcoidosis. Some of these conditions will produce an anaemia of chronic disease, and others a haemolytic anaemia [40,41]. In the context of ophthalmic conditions associated with IBD, iron deficiency anaemia should be investigated to prevent an IBD diagnostic delay. Age was strongly associated with IBD in our model. Those in the age group 18-30 had the highest risk compared to under 18 year-olds, however all ages up to 70 had an increased IBD risk compared to the reference group (under 18 years). Ottaviano et al. reviewed the published literature on ophthalmic EIMs in children and found that there was little data available. They suggested that this may be related to asymptomatic uveitis, as well as a lower prevalence of these EIMs in childhood compared to adults [42]. In the present study, less than 6% of the cohort were aged under 18 and only 0.2% of subjects in this age category developed IBD during

the study period, with a slight preponderance towards CD, as has been previously shown in paediatric series [42].

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

The Charlson comorbidity score and Townsend deprivation levels were included as variables in the Cox regression models as important aspects of a patient's medical and socioeconomic background. However, due to concerns around overfitting, these variables were not included in the prediction

model. Overall there was a preponderance of higher comorbidity scores in those with eye conditions compared to those without, and this may reflect the clustering of disease seen in these patients.

Ophthalmic conditions associated with IBD which present prior to an IBD diagnosis are not common. However, an increasing prevalence of IBD both in the UK and around the world has been demonstrated [43–45]. Given the increasing numbers of patients with IBD, the need for clinicians from many disciplines outside gastroenterology to be aware of IBD is important. Those who care for patients presenting with ophthalmic conditions associated with IBD should be attentive to features which may increase the likelihood of an IBD diagnosis, in order that appropriate investigation and referral can be made in those patients with suggestive clinical features.

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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/m2	12,799 (33.0)	51,136 (33.4)
25-30Kg/m2	11,200 (28.8)	40,782 (26.6)
>30Kg/m2	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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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.

Table 3. Characteristics of anterior uveitis subjects with and without an inflammatory bowel disease 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/m2	37 (44)	4,999 (33)
25-30Kg/m2	23 (27)	4,588 (30)
>30Kg/m2	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

Table 4. Multivariable logistic regression prediction model of factors associated with developing 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

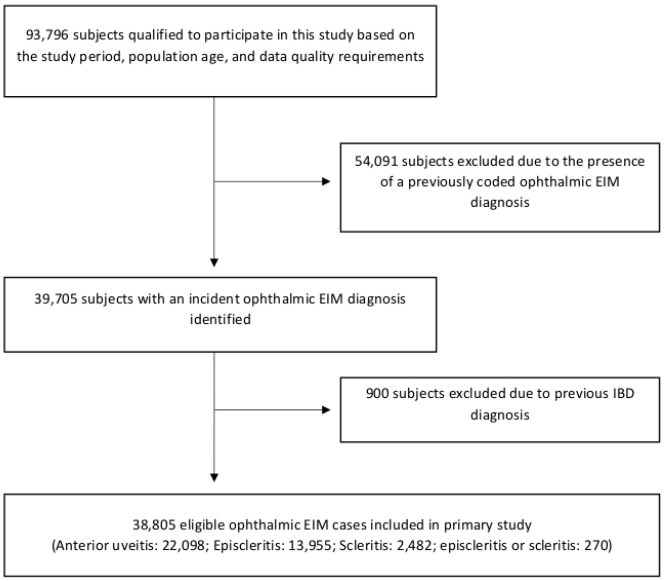
† coded within 6 months of Index date
‡ <11.9g/dL (females); <12.9g/dL (males)
** Coded at baseline*

FIGURE legends

Figure 1 Study flow chart.
Inflammatory bowel disease (IBD).

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

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



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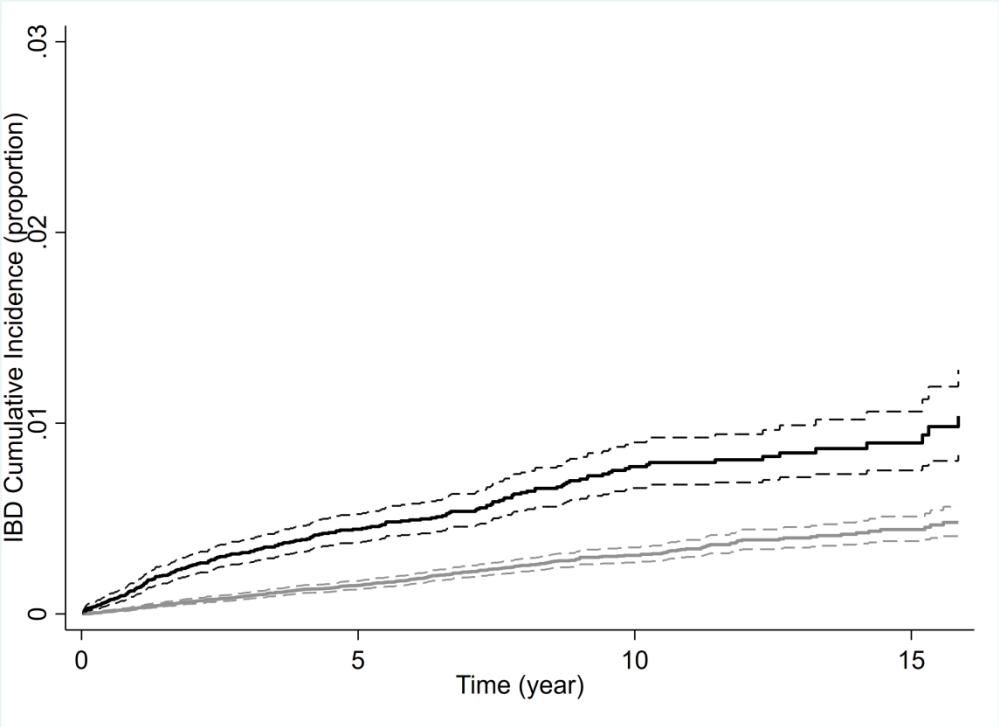
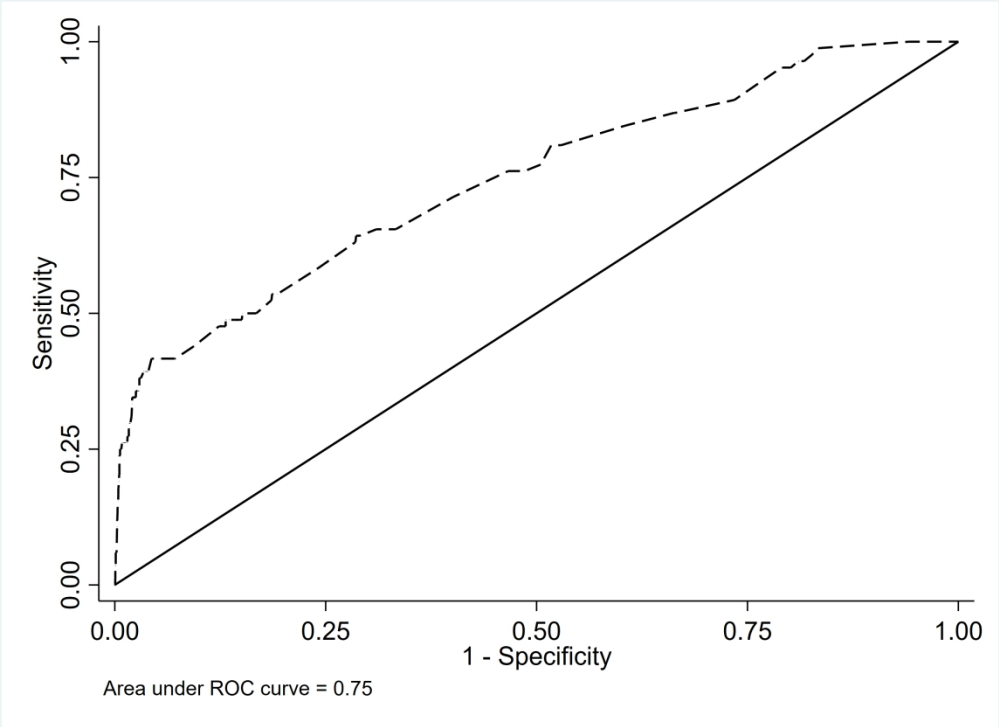


1058x769mm (72 x 72 DPI)



1058x769mm (72 x 72 DPI)

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 IAOIs	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
Lower gastrointestinal bleeding† (reference) no	1.00				1.00				1.00			
yes	6.45	4.48	9.29	<0.001	8.13	5.23	12.64	<0.001	4.25	2.23	8.11	<0.001
Loperamide prescription† (reference) no	1.00				1.00				1.00			
yes	2.09	1.34	3.27	0.001	2.44	1.34	4.44	0.004	1.82	0.94	3.52	0.077
Diarrhoea† (reference) no	1.00				1.00				1.00			
yes	4.46	3.25	6.13	<0.001	3.37	2.12	5.34	<0.001	5.99	3.87	9.27	<0.001
Axial arthropathy* (reference) no	1.00				1.00				1.00			
yes	2.77	1.77	4.36	<0.001	2.49	1.32	4.71	0.005	3.15	1.66	5.99	<0.001

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

EIM: extraintestinal manifestations

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

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

† coded within 6 months of Index date

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

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

	Inflammatory Bowel Disease				Ulcerative colitis				Crohn's Disease			
	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value
Anterior uveitis	3.39	2.70	4.25	<0.001	2.23	1.63	3.04	<0.001	5.77	4.04	8.24	<0.001
Sex (reference) Male	1.00				1.00				1.00			
Female	0.81	0.65	1.02	0.077	0.75	0.56	1.02	0.06	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	0.93	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	0.36	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	0.002	1.46	0.63	3.35	0.376
Diarrhoea† (reference) no	1.00				1.00				1.00			
yes	4.87	3.23	7.36	<0.001	2.72	1.42	5.21	0.003	8.01	4.74	13.55	<0.001
Axial arthropathy* (reference) no	1.00				1.00				1.00			
yes	2.08	0.58	2.64	0.008	1.45	0.59	3.56	0.42	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
>30Kg/m²	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)

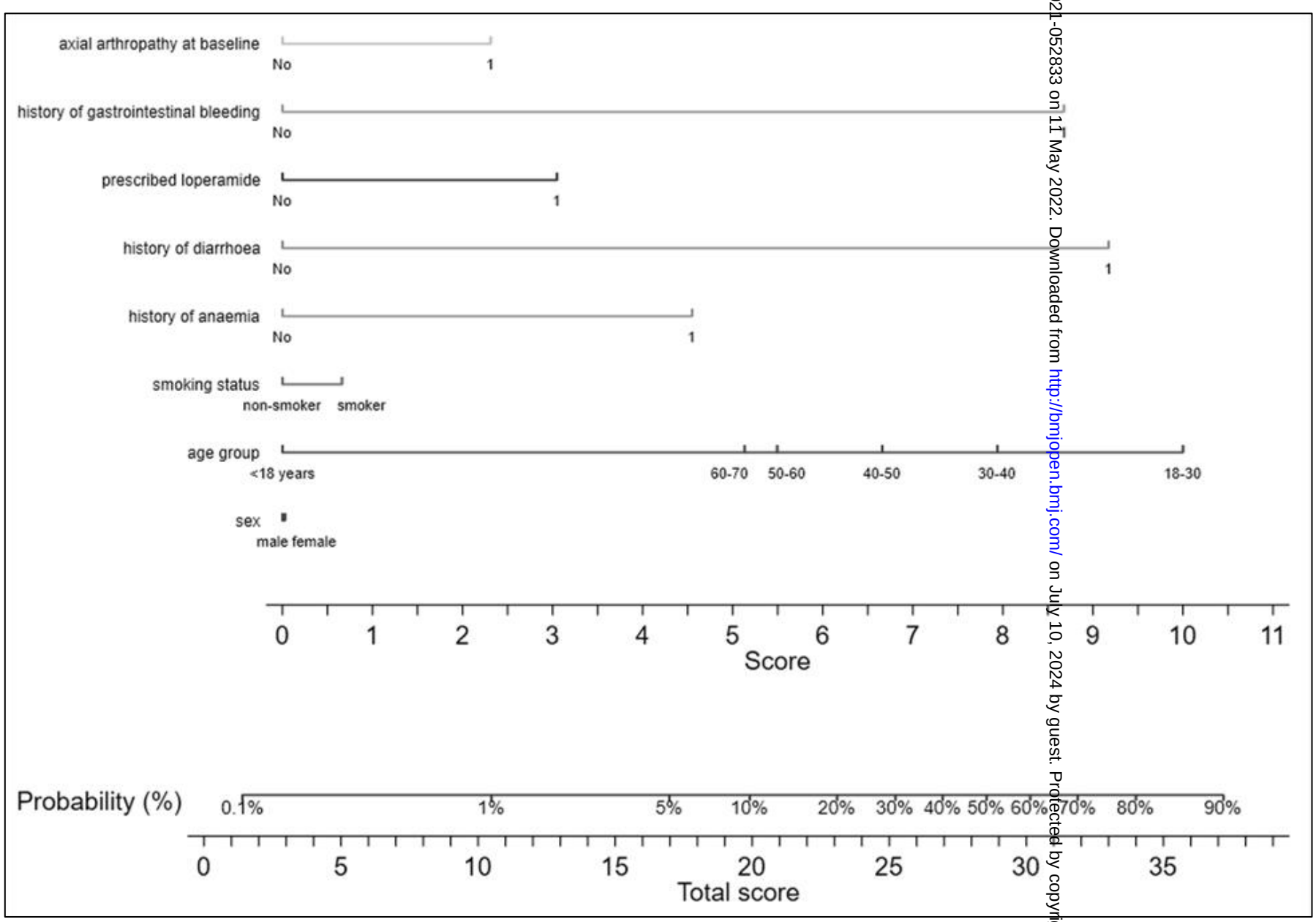
	aHR	[95% Confidence Interval]		p-value
Any IBD associated ocular inflammation				
Inflammatory bowel disease	2.29 (2.25)	1.86	2.80	<0.001
Ulcerative colitis	1.43 (1.65)	1.07	1.90	0.015
Crohn's disease	3.95 (3.37)	2.88	5.41	<0.001
Anterior uveitis				
Inflammatory bowel disease	3.49 (3.39)	2.69	4.51	<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



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	7, 8 & 9
✓	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.