BMJ Open

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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To cite: King D, Chandan JS, Thomas T, *et al*. 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. *BMJ Open* 2022;**12**:e052833. doi:10.1136/bmjopen-2021-052833

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-052833).

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Received 10 May 2021
Accepted 24 April 2022

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ABSTRACT

Objectives Ophthalmic conditions including anterior uveitis (AU), episcleritis and scleritis may occur in association with the inflammatory bowel diseases (IBD) as ophthalmic extraintestinal manifestations. The 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% women) and matched to 153 018 subjects without IAOI.

Measures The risk of a subsequent diagnosis of IBD in subjects with IAOIs compared with age/sex matched subjects without IAOI. HRs were adjusted for age, sex, body mass index, deprivation, comorbidity, smoking, 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 365–2043) days in those with IAOI and 1403 (IQR 623–2516) in those without. The adjusted HR for a subsequent diagnosis of IBD was 2.25 (95% CI 1.89 to 2.68), p<0.001; for UC 1.65 (95% CI 1.30 to 2.09), p<0.001; and for CD 3.37 (95% CI 2.59 to 4.40), p<0.001 in subjects with IAOI compared with 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 (95% CI 0.69 to 0.80).

Conclusions Subjects with IAOI have a twofold 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.

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* (eg, metastatic CD); *drug-related*

(eg, anti-tumour necrosis factor (TNF) associated skin lesions or steroid-induced cataract development); *associated*—signalling a predisposition to autoimmunity (eg, ankylosing spondylitis); or *reactive*—implying common pathophysiological pathways without histopathological similarity (eg, 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 patients with IBD, 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 with 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 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 1 year since the installation of the computerised medical record system and achievement of an acceptable mortality recording 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 1 January 1995 to 25 September 2019 was undertaken to investigate the association between IBD outcome and all studied IAOI exposures (AU, scleritis and episcleritis), with secondary studies of AU alone and combined episcleritis and scleritis. Individuals were eligible for inclusion from either the date of eligibility of their primary care practice or 1 year after they were registered, whichever was later. Those subjects with an incident IAOI diagnosis of interest (recorded through Read codes—online supplemental appendix 1)[22] and without an established IBD diagnosis (exposed) were compared with 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 (25 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 AU.

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 (eg, infective), were selected for inclusion along with episcleritis and scleritis. Clinical codes used to identify UC, CD and IAOI are listed in online supplemental 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 IQRs. 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 HR (aHR) of IBD diagnoses in participants with an IAOI compared with 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

HRs 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 (<11.9 g/dL for women and <12.9 g/dL for men), 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 AU. 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 comorbidity 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 data set (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 V.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% women). IAOI cases included those coded as AU: 22 098 (57%); episcleritis: 13 955 (36%); scleritis: 2482 (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)

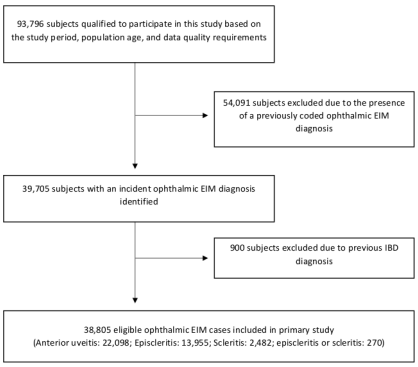

Figure 1 Study flow chart. EIM, extraintestinal manifestation; IBD, inflammatory bowel disease.

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 5 years with a total of 244 503 person years (py) of follow-up time in subjects with IAOI and 934 847 py in those without IAOIs.

In those with an IAOI, 2.9% (1116) had another, non-ophthalmic EIM at index date compared with 0.9% (1433) in subjects without IAOIs. Subject characteristics are shown in table 1.

Risk of IBD 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 with 329 (0.2%) (215 UC and 114 CD) in the matched control group. A total of 893 (2.3%) subjects with IAOIs had an axial arthropathy recorded at baseline and 35 (0.1%) had the HLA-B27 genotype coded, compared with 1013 (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 365–2043) days in subjects with IAOIs versus 1403 (623–2516) days in those without IAOIs. For a UC diagnosis 922 (410–1910) versus 1360 (547–2406) days and for a CD diagnosis 738 (269–2011) versus 1625 (641–2779) 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 subjects with IAOI compared with those without IAOIs was 2.25 (95% CI 1.89 to 2.68), with an aHR of 1.65 (95% CI 1.30 to 2.09) for UC and 3.37 (95% 2.59 to 4.40) for CD, p values<0.001 (table 2; full models are shown in online supplemental appendix 2). Figure 2 shows the cumulative incidence plot for IBD diagnoses in subjects with IAOIs compared with those without.

Risk of IBD diagnosis in AU, 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 online supplemental 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% women) 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. A total of 152 (0.7%) IBD diagnoses (67 UC and 85 CD) were observed in subjects with AU 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 (373–2027) days in subjects with AU compared with 1457 (539–2700) in those without AU (log-rank test p<0.001). The median time to a UC diagnosis was 1117 (489–2008) days in subjects with AU and 1490 (553–2553) days in subjects without AU. For a CD diagnosis, the median time to diagnosis was 687 (286–2006) days in subjects with AU and 1160 (516–2892) 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 with matched subjects without AU was 3.39 (95% CI 2.70 to 4.25); for UC aHR was 2.23 (95% CI 1.63 to 3.04) and for CD 5.77 (95% CI 4.04 to 8.24), all p values<0.001 (table 2 (full models are shown in online supplemental appendix 4)).

In the analysis of episcleritis and scleritis combined, 17 439 subjects (14 752 (85%) episcleritis and 2976 scleritis; median age 48 (36–61) and 62% women) 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. A total of 104 (0.6%) IBD cases (23 UC and 81 CD) were observed among subjects with episcleritis and scleritis and 53 (0.1%) (30 UC and 23 CD) among those without these IAOIs. The median time to an IBD diagnosis in subjects with episcleritis and scleritis was 848 (348–2239) days compared with 1522 (577–2838) 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 with matched subjects without these IAOIs was 1.73 for IBD (95% CI 1.31 to 2.28), p<0.001 (table 2 (full models are shown in online supplemental 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 online supplemental appendix 6.

Prediction model

In total 22 547 subjects with AU 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. Eighty-four (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 (IQR 39–68) years, respectively, p<0.001) but there was no difference in sex, smoking status or BMI 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

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	2142 (5.5)	9086 (5.9)
18–30	3264 (8.4)	13 924 (9.1)
30–40	5620 (14.5)	23 644 (15.5)
40–50	7589 (19.5)	30 586 (20.0)
50–60	7221 (18.6)	28 622 (18.7)
60–70	5989 (15.4)	22 990 (15.0)
>70	6980 (18.0)	24 166 (15.8)
Female sex	22 249 (57.3)	87 694 (57.3)
Townsend quintile		
1—least deprived	8880 (22.9)	34 368 (22.4)
2	7520 (19.4)	29 210 (19.1)
3	6989 (18.0)	27 726 (18.1)
4	5873 (15.1)	23 272 (15.2)
5	3814 (9.8)	15 312 (10.0)
Missing	5729 (14.8)	23 130 (15.1)
Charlson comorbidity score		
0	24 457 (63.0)	106 735 (69.8)
1	8414 (21.7)	28 888 (18.9)
≥2	5934 (15.3)	17 395 (11.4)
Smoking status		
Current smoker	6632 (17.1)	28 586 (18.7)
Non-smoker	32 173 (82.9)	124 432 (81.3)
Body mass index		
<25 kg/m^2	12 799 (33.0)	51 136 (33.4)
25–30 kg/m^2	11 200 (28.8)	40 782 (26.6)
>30 kg/m^2	7683 (19.8)	26 849 (17.6)
Missing	7123 (18.4)	34 251 (22.4)
Anaemia*†	2102 (5.4)	5469 (3.4)
Abdominal pain*	837 (2.2)	2574 (1.7)
Lower gastrointestinal bleeding*	363 (0.9)	1042 (0.7)
Loperamide prescription*	558 (1.4)	1506 (1.0)
Diarrhoea*	974 (2.5)	2424 (1.6)
HLA-B27 positive at baseline	35 (0.1)	7 (0.0)
Axial arthropathy at baseline	893 (2.3)	1013 (0.7)
IAC at baseline (other than ophthalmic)‡	1116 (2.9)	1433 (0.9)

*Coded within 6 months of index date.
†<11.9 g/dL (women); <12.9 g/dL (men).
‡IAC: IBD associated condition: axial arthropathies, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, aphthous stomatitis.
HLA-B27, human leucocyte antigen B27; IBD, inflammatory bowel disease.

Table 2 Adjusted HRs for risk of inflammatory bowel disease

	aHR	(95% CI)	P value
Any inflammatory bowel disease associated ocular inflammation			
Inflammatory bowel disease	2.25	1.89 to 2.68	<0.001
Ulcerative colitis	1.65	1.30 to 2.09	<0.001
Crohn's disease	3.37	2.59 to 4.40	<0.001
Anterior uveitis			
Inflammatory bowel disease	3.39	2.7 to 4.25	<0.001
Ulcerative colitis	2.23	1.63 to 3.04	<0.001
Crohn's disease	5.77	4.04 to 8.24	<0.001
Episcleritis or scleritis			
Inflammatory bowel disease	1.73	1.31 to 2.28	<0.001

Adjusted HR (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.

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 χ^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 ROC curve, shown in figure 3, produced an area under the curve (AUC) C-statistic of 0.75 (95% CI 0.69 to 0.80). Following internal validation by bootstrapping, resampling the data set 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 (95% CI 0.67 to 0.77).

A probability calculator was produced to determine the likelihood of an IBD diagnosis within the AU cohort using the following examples: (1) a woman, 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 AU diagnosis; (2) a man, 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 woman, 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 online supplemental appendix 7.

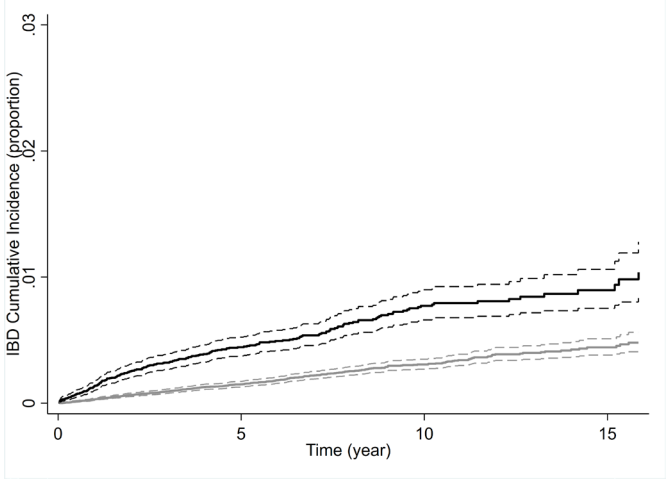

Figure 2 Cumulative incidence of IBD in subjects with ophthalmic conditions (black line) and those without (grey line) with 95% CIs (dashed lines). IBD, inflammatory bowel disease.

DISCUSSION

In this study, we have shown that subjects with an IAOI, but without a recorded diagnosis of IBD, are at a twofold 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 2 years. When AU was examined alone, subjects had a threefold greater risk of a later IBD diagnosis compared with matched subjects without AU and again the risk was highest for a subsequent CD diagnosis at almost sixfold.

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 (AU or episcleritis and scleritis), were at increased risk of developing a subsequent diagnosis of IBD over time (combined IAOI aHR 2.25 (95% CI 1.89 to 2.68), p<0.001). The time to a diagnosis of IBD was shorter in those with ophthalmic conditions compared with matched controls (median time 2.4 years vs 3.8 years, respectively). However, the time from IAOI diagnosis to IBD was often greater than 2 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,

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)	1173 (8)
30–40	18 (21)	2092 (14)
40–50	18 (21)	2912 (19)
50–60	14 (17)	2861 (19)
60–70	12 (14)	2531 (16)
>70	5 (6)	3285 (21)
Female sex (%)	45 (54)	8365 (54)
Smoking status (%)		
Current smoker	21 (25)	2893 (19)
Non-smoker	63 (75)	12 565 (81)
Body mass index (%)		
<25 kg/m^2	37 (44)	4999 (33)
25–30 kg/m^2	23 (27)	4588 (30)
>30 kg/m^2	14 (17)	3111(20)
Missing	10 (12)	2760 (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.
†<11.9 g/dL (women); <12.9 g/dL (men).
HLA-B27, human leucocyte antigen B27; IBD, inflammatory bowel disease.

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 subjects with IBD, with subjects with CD and UC 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 with less than 1% of matched controls. Other investigators have examined IBD and arthritis in UK primary care databases. However, type 1 and type 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

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	OR	(95% CI)	P value
Sex				
Male (reference)		1.00		
Female	0.001	1.00	0.64 to 1.56	0.995
Age category				
<18 years (reference)		1.00		
18–30	2.56	12.88	4.57 to 36.30	<0.001
30–40	2.05	7.75	2.79 to 21.59	<0.001
40–50	1.69	5.41	1.94 to 15.05	0.001
50–60	1.40	4.04	1.41 to 11.52	0.009
60–70	1.30	3.65	1.26 to 10.54	0.017
>70	0.00	1.00		
Smoking status				
Current smoker (reference)		1.00		
Non-smoker	–0.17	0.85	0.51 to 1.42	0.528
Anaemia*‡				
No (reference)		1.00		
Yes	1.13	3.11	1.61 to 6.00	0.001
Diarrhoea*				
No (reference)		1.00		
Yes	2.38	10.76	5.99 to 19.33	<0.001
Loperamide				
No (reference)		1.00		
Yes	0.74	2.10	0.86 to 5.12	0.102
Lower gastrointestinal bleed				
No (reference)		1.00		
Yes	2.27	9.69	4.54 to 20.70	<0.001
Axial arthropathy†				
No (reference)		1.00		
Yes	0.67	1.95	0.83 to 4.60	0.128
Intercept	–7.08	0.0008	0.0003 to 0.0024	<0.001

*Coded within 6 months of index date.
†Coded at baseline.
‡<11.9 g/dL (women); <12.9 g/dL (men).

axial arthropathy increased the risk of IBD more than twofold and was found to be associated with later IBD in AU. 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 with 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 AU 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 of 18–30 had the highest risk compared with under 18 year-olds, however

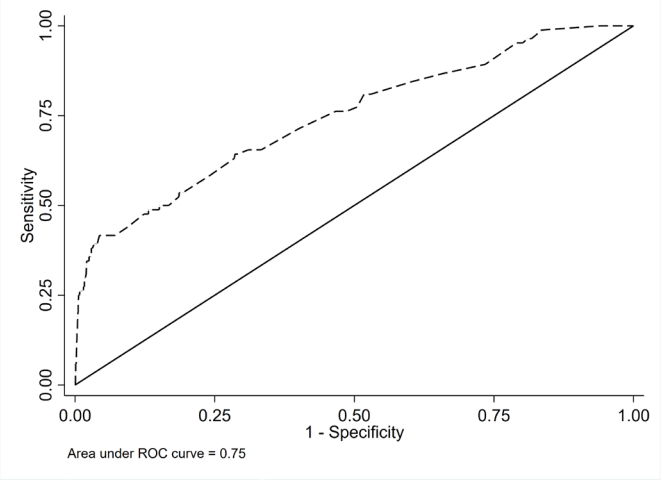

Figure 3 Receiver operating characteristic (ROC) curve of ability of prediction model to detect an inflammatory bowel disease diagnosis within 3 years of an anterior uveitis diagnosis.

all ages up to 70 had an increased IBD risk compared with 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 with 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 AU, 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 with 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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Contributors All authors contributed to the conception and design of the work. DK, NJT, TT, JSC, KN, NA and RR contributed to the acquisition of the data. DK, NJT, TT, JSC and NA contributed to the analysis of the data and all authors including AKD and TB contributed to the interpretation of data. DK drafted the manuscript and all authors contributed to the revision and critical review of the manuscript. All authors gave final approval of the version published and agree to be accountable for all aspects of the work. NJT and NA as co-joint authors act as guarantor for this work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests KN reports grant from AstraZeneca, Sanofi and Boehringer Ingelheim, outside the submitted work. NJT reports grants from Dr Falk, MSD, AstraZeneca and Pfizer, outside the submitted work.

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.

Patient consent for publication Not applicable.

Ethics approval 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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The data underlying this article were provided by IQVIA Medical Research Data under licence and are not available for open access.

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