The risk of later diagnosis of inflammatory bowel disease in patients with dermatological disorders associated with inflammatory bowel disease

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Title Page

The risk of later diagnosis of inflammatory bowel disease in subjects with dermatological disorders associated with inflammatory bowel disease

Short title:

Inflammatory Bowel Disease risk in associated skin disorders

Summary:

Dermatological extraintestinal manifestations (D-EIM) of inflammatory bowel disease (IBD) may precede IBD. D-EIMs are associated with a 6-fold risk of later IBD compared with matched subjects without D-EIMs. Prediction model for later IBD diagnosis in new erythema nodosum performed well.

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Author Contributions

Study concept and design was jointly conceived by DK, NT, KN, NA, RR and JC. Data extraction was performed by DK and analysis was performed by DK, NA, RR and NT. Manuscript was drafted by DK. The data and manuscript were critically reviewed, revised and approved by all authors.

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.

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Data Availability statement:

The data underlying this article were provided by IQVIA Medical Research Data under licence and is not available for open access.

Abbreviations:

Extra-Intestinal Manifestation (EIM); Erythema Nodosum (EN); Inflammatory bowel disease (IBD); Crohn's disease (CD); Ulcerative colitis (UC); Incidence rate (IR); Incidence rate ratio (IRR); Hazard ratio (HR); The Health Improvement Network (THIN).

Abstract

Introduction

Dermatological conditions such as erythema nodosum (EN), pyoderma gangrenosum (PG), Sweet's syndrome and aphthous stomatitis can occur with inflammatory bowel disease (IBD) and are considered dermatological extraintestinal manifestations (D-EIMs). Rarely they may precede IBD. Other common conditions such as psoriasis have also been associated with IBD.

This study examined the risk of a subsequent IBD diagnosis in subjects presenting with a D-EIM.

Methods

A retrospective cohort study compared subjects with D-EIMs and age/sex-matched subjects without D-EIMs. Hazard ratios (HR) were adjusted for age, sex, body mass index, deprivation, comorbidity, smoking, loperamide use, anaemia and lower gastrointestinal symptoms.

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

Results

7,447 subjects with D-EIMs (74% female, median age 38 (IQR 24-65) years) were matched to 29,297 subjects without D-EIMs. 131 (1.8%) subsequent IBD diagnoses were observed in those with D-EIMS compared to 65 (0.2%) in those without. Median time to IBD diagnosis was 205 (IQR 44-661) days in those with D-EIMs and 1,594 (693-2,841) in those without. The adjusted HR for later diagnosis of IBD was 6.16 (95%CI 4.53-8.37),p<0.001; for ulcerative colitis 3.30 (1.98-5.53),p<0.001 and for Crohn's disease 8.54 (5.74-12.70),p<0.001. Subjects with psoriasis had a 34% increased risk of a subsequent IBD diagnosis compared to matched controls (1.34 (1.20-1.51), p<0.001).

4,043 subjects with an incident EN diagnosis were included in the prediction model cohort with 87 (2.2%) diagnosed with IBD within 3-years. The model had a bias-corrected c-statistic of 0.82 (95% CI 0.78-0.86).

Conclusions

Subjects with D-EIMs have a six-fold increased risk of later diagnosis of IBD. Younger age, smoking, low BMI, anaemia and lower gastrointestinal symptoms were associated with increased risk of diagnosis of IBD within 3-years in subjects with EN.

Introduction

The inflammatory bowel diseases (IBD), consisting of Crohn's disease (CD) and ulcerative colitis (UC), can be complicated by the presence of extraintestinal manifestations (EIM). The classical EIMs that may complicate IBD include dermatological, ophthalmic, musculoskeletal and hepatobiliary disorders [1]. EIMs may be diagnosed at the same time, later in the course or more rarely prior to diagnosis of IBD [2–4]. Although well recognised, EIMs are not seen in all patients with IBD and may be seen in isolation. The reported prevalence of these conditions varies widely, largely due to the varying definitions of an EIM [5,6].

Dermatological conditions associated with IBD are among the most common EIMs reported [7]. The classical dermatological EIMs (D-EIMs) include Erythema nodosum (EN), pyoderma gangrenosum (PG), Sweet's syndrome (SS) and aphthous stomatitis (ApS). These conditions are associated with IBD or are reactive cutaneous manifestations rather than those directly related to medications used in the treatment of IBD or disease specific conditions such as perianal or metastatic CD [8]. While they tend to have a mainly benign course and some are straightforward to manage, such as EN, this is not always the case, and they may be debilitating and have major consequences for quality of life [9,10]. Although not a "classic" EIM, psoriasis is also associated with IBD and in particular those with CD appear to be at increased risk of this skin condition. Both conditions appear to have overlapping inflammatory regulator pathways and previous studies have demonstrated an increased risk of IBD in those with an established psoriasis diagnosis [11,12]. Although for many EIMs, treatment relies on controlling the underlying bowel condition given their parallel nature [13], this does rely upon the recognition of the underlying IBD. There is currently little evidence to guide clinicians on the incidence of IBD in those presenting with a D-EIM, or the potential lag time from D-EIM to IBD diagnosis [4]. Healthcare professionals who diagnose D-EIMs may not consider IBD, the symptoms of which can be non-specific, leading to extended periods of untreated symptoms [14].

The principal aims of the study were to investigate the risk of a later diagnosis of IBD in subjects presenting with skin conditions compared to those without skin conditions, the risk factors for IBD in these groups and the time from diagnosis of these skin conditions to a subsequent IBD diagnosis.

Materials and methods

Data source

This study was conducted using IQVIA Medical Research Data (IMDR-UK) primary care database. IMDR-UK is derived from over 700 general practices across the United Kingdom (UK) and contains data on approximately 15 million subjects. It is representative of the UK population.[15] Patient-level data is captured longitudinally and includes prescriptions, primary and secondary care investigations, diagnoses and subject demographics. Data is uploaded electronically using a hierarchy of clinical (Read) codes [16]. IMDR-UK practices were required to have achieved an acceptable mortality recording (AMR) threshold and have at least one year since the installation of the electronic medical record system to be included in this study[17]. These inclusion criteria aim to ensure improved data reliability and reduce the risk of under-recording.

Study Design

Cohort study

A retrospective matched cohort study was conducted of classical D-EIMs (erythema nodosum (EN), pyoderma gangrenosum (PG), Sweet's syndrome (SS) and aphthous stomatitis (ApS)), with secondary studies of two individual D-EIMs (EN and PG) and of psoriasis. Subjects of any age with an incident (first recorded during the study period and after registration with the practice) coded diagnosis of the D-EIM of interest (recorded through Read codes – Appendices 1 and 2) were compared to subjects without D-EIMs matched by age at cohort entry (±2 years), sex, and GP practice registration on index date in a ratio of 1:4. Index date was the date of D-EIM diagnosis for the D-EIM group. Only subjects without an IBD diagnosis at index date were included in the study. Subjects with an EN code were excluded from the study if they had a record of tuberculosis, sarcoidosis or sulfasalazine prescription within a 6-month period prior to EN diagnosis. These factors

are strongly associated with the development of EN and may therefore confound interpretation of results [18]. Individual subjects were eligible for inclusion from the later of the date their practice became eligible or one year after they were registered, in order to ensure adequate baseline characteristics were captured.

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 CD or UC. Subjects with a code for both UC and CD were allocated to one based on the frequency of coding. For those with equal coding frequency, the earliest diagnosis date and the latest IBD subtype was used.

Prediction model

Subjects with an incident diagnosis of EN were investigated to predict the risk of having a diagnosis of IBD within the following 3- years. Case examples were used to demonstrate the probability of diagnosis of IBD in subjects presenting with EN.

Validation

Clinical codes used to identify UC, CD, D-EIMs and psoriasis are listed in Appendix 1. Individual D-EIMs and contributions are detailed in Appendix 2. Coding in primary care to identify patients with IBD has been previously validated [19,20]. EIM codes were reviewed for validity by two gastroenterology clinicians, having been first sourced from other published primary care database studies [21,22].

Statistical analysis

Cohort study

The time from index date to a later diagnosis of IBD in those with and without a baseline D-EIM were presented as median time to combined IBD, UC and CD diagnoses with accompanying interquartile range (IQR). Log-rank tests were used to compare time to IBD diagnosis between those with (exposed) and without (unexposed) D-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 D-EIM compared to matched unexposed subjects. Adjusted HRs were produced for IBD (combined), UC and CD outcomes. For EN and PG, aHRs were produced only for combined IBD diagnoses due to relatively few IBD diagnoses in these secondary analyses. For psoriasis, aHRs were produced for IBD (combined), UC and CD outcomes. Hazard ratios were adjusted for age at index; sex; smoking status; body mass index (BMI); Townsend level of deprivation (quintiles); Charlson comorbidity score; within 6-month of 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 [23]. Missing data for Townsend deprivation were considered a separate category. The proportional hazards assumption was assessed using log-log plots and the Schoenfeld residuals test. Cumulative incidence plots were produced to demonstrate the cumulative risk of IBD diagnosis over time.

Prediction model

Multivariable logistic regression was used to establish a prediction model for IBD diagnosis within 3-years in subjects presenting with a new diagnosis of EN. 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 select 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. Candidate predictors recorded within 6 months of EN diagnosis included the following: anaemia, abdominal pain, weight loss, lower gastrointestinal bleeding, loperamide prescription and diarrhoea (prior to an IBD diagnosis). A receiver operating characteristic (ROC) curve with accompanying c-statistic was used to assess model discrimination; calibration was assessed using the Hosmer-Lemeshow test for goodness of fit. A complete case analysis was performed where subjects with missing values were excluded. Of explored predictors, only BMI had missing values. Subjects without BMI values were therefore excluded for the complete case analysis. To further assess

missingness, multiple imputation of missing BMI values was performed, producing 10 imputed datasets. The models were well calibrated in both the complete case analysis and when subjects with missing BMI values were also included. Multiple imputation had minimal impact upon the discrimination of the model as assessed by the AUROC c-statistic. All subjects were therefore included in the prediction model development with a missing category for BMI included. 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 [24].

Results

Study subjects

Following exclusions (Figure 1), 7,447 subjects with D-EIMs were identified: 74% female and a median age of 38 (IQR 24-65) years. D-EIM subjects were age, sex and general practice-matched to 29,297 subjects without D-EIMs. The median follow-up time for subjects was five and half years, with a total of 47,377 person-years (py) of follow-up in D-EIM subjects and 185,889 py in those without D-EIMs. Cohort characteristics are shown in Table 1.

Risk of inflammatory bowel disease in subjects with dermatological conditions

Among D-EIM subjects, 131 (1.8%) diagnoses of IBD (33 UC and 98 CD) were observed compared to 65 (0.2%) (30 UC and 35 CD) in matched subjects without D-EIMs. The median time to subsequent diagnosis of IBD from D-EIM diagnosis (index date) was 205 (IQR 44-661) days compared to 1,594 (693-2,841) days for subjects without D-EIMs. For UC the median time to diagnosis was 231 (43-1,230) days and 1,544 (551-2359) days respectively, and for CD 159 (47-598) days and 1,690 (915-2,962) days respectively. For IBD, UC and CD, the log-rank test p was <0.001. Following adjustment, the hazard ratio for an IBD diagnosis in D-EIM subjects compared to matched subjects without D-EIMs was 6.16 (95%CI 4.53-8.37), p<0.001. For UC the aHR was 3.30 (1.98-5.53), p<0.001 and for CD 8.54 (5.74-12.70), p<0.001 (Table 2; full models are shown in Appendix 3). Figure 2 shows the cumulative incidence plot for IBD diagnoses in subjects with D-EIMs compared to those without.

Risk of inflammatory bowel disease in erythema nodosum and pyoderma gangrenosum

The characteristics of D-EIM and matched subjects without D-EIM in these subgroup analyses together with full Cox models are shown in Appendices 4 and 5 respectively. 6,329 subjects with incident EN were identified with 5,917 remaining once tuberculosis, sarcoidosis and sulfasalazine use had been removed. 327 individuals with pre-existing IBD were then excluded (Figure 1). Following exclusions, 5,590 EN subjects (79% female, median age 38 (23-52)) were matched to 22,039 subjects without EN, contributing 36,324 and 139,304 py of follow-up, respectively. 104 (1.9%) IBD diagnoses (23 UC and 81 CD) were observed in subjects with EN and 53 (0.2%) (23 UC and 32 CD) in those

without EN. Median time to IBD diagnosis was 151 (42-615) days for EN subjects compared to 1,618 (728-2,895) days for those without EN (log-rank test p<0.001). For UC the median time to diagnosis was 224 (28-1,230) days for EN subjects and 1,620 (1079-2,841) days for those without, and for CD, the median time to a diagnosis was 133 (44-552) days for subjects with EN and 1,549 (460-3,315) days for those without EN (log-rank test p<0.001 for both CD and UC). The adjusted hazard ratio for an IBD diagnosis in subjects with EN compared to matched subjects without EN was 6.49 (4.62-9.11), p<0.001 (Table 2).

In the PG study, 1,143 subjects with incident PG were identified prior to exclusions, with 166 having a pre-existing IBD diagnosis (Figure 1). In the PG subgroup analysis, 977 subjects with PG (60% female and median age 57 (39-73) years) were matched to 3,852 subjects without PG, contributing 5,301 and 23,963 py of follow-up time, respectively. 21 (2.1%) IBD diagnoses (10 UC and 11 CD) were observed in subjects with PG compared to 11 (0.3%) (6 UC and 5 CD) in those without PG. Median time to IBD diagnosis was 392 (127-1,323) days for subjects with PG compared to 1,890 (1,111-4,626) days for those without PG (log-rank test p<0.001). For UC the median time to diagnosis was 405 (77-3,327) days for PG subjects and 2,816 (1,426-4,146) days for those without PG, and for CD the median time to a diagnosis was 282 (101-946) days for subjects with PG and 2,529 (1,890-5,948) days for those without PG (log-rank test p<0.001 for both CD and UC). The adjusted hazard ratio for an IBD diagnosis in PG was 6.27 (2.84-13.86), p<0.001 (Table 2).

Risk of inflammatory bowel disease in psoriasis

In the psoriasis study, 121,195 subjects with incident psoriasis and without a pre-existing IBD diagnosis were identified (53% female and median age 45 (29-61) years). Psoriasis subjects were matched to 476,281 controls by age and sex; subjects with psoriasis and matched controls contributed 759,831 and 2,895,686 py of follow-up time, respectively. Characteristics of subjects with and matched subjects without psoriasis are shown in Appendix 6. 407 (0.3%) IBD diagnoses (398 UC and 178 CD) were observed in subjects with psoriasis compared to 1090 (0.2%) (692 UC and 398 CD) in those without psoriasis. Median time to IBD diagnosis was 1,502 (604-2,646) days for

subjects with psoriasis compared to 1,366 (623-4,536) days for those without psoriasis. For UC the median time to diagnosis was 1,378 (558-2,410) days for psoriasis subjects and 1,315 (588-2,462) days for those without psoriasis, and for CD the median time to a diagnosis was 1,743 (626-2,905) days for subjects with psoriasis and 1,481 (721-2,583) days for those without psoriasis (log-rank tests for IBD and CD were p<0.001, and for UC p=0.002). The aHR for an IBD diagnosis in psoriasis was 1.34 (1.20-1.51), p<0.001. For UC the aHR was 1.20 (1.03-1.39), p=0.020, and for CD 1.60 (1.34-1.92), p<0.001) (Table 2).

Prediction model

5,590 EN subjects were identified with 4,043 eligible for inclusion in the prediction model development cohort based on sufficient follow up time or an IBD diagnosis within 3-years of EN diagnosis. 87 (2.2%) had the outcome of an IBD diagnoses within 3-years (79% CD). Characteristics of EN subjects with and without an IBD diagnosis by 3-years after EN diagnosis are shown in Table 3. Those with an IBD diagnosis were younger (median age 25 (IQR 19-35) and 37 (24-52) years respectively, p<0.001) but no significant difference was seen by sex between the groups, p=0.384. Smoking was more common in IBD subjects though not significant at the 5% level (23% compared to 16%, p=0.067) and there was a higher proportion within the lowest body mass index category (<25 kg/m^2) – 48% compared to 31% in those not diagnosed with IBD, p=0.003. When those diagnosed with IBD within 6-months of an EN diagnosis (64%) were compared to those diagnosed with IBD later than 6-months there was no statistical difference between the two groups for coding of anaemia, abdominal pain and diarrhoea.

Following backwards stepwise regression, sex, lower gastrointestinal bleeding and loperamide prescription exceeded the alpha-to-remove threshold set at 0.20, however sex was retained in the model. The results of a multivariable logistic regression model to assess the risk of being diagnosed with IBD within a 3-year period following EN diagnosis, including beta-coefficients and odds ratios with their 95% confidence intervals, are presented in table 4. The Hosmer-Lemeshow chi^2 test for goodness of fit was applied to the entire data set and was not significant at 0.539, suggesting good

model fit. The receiver operating characteristic (ROC) curve, shown in Figure 3, produced an area under the curve (AUC) c-statistic of 0.83 (0.78-0.87). Following internal validation by bootstrapping, resampling the dataset 200 times, the mean difference between the original AUC and AUC in each bootstrap sample was 0.01. This produces a bias-corrected c-statistic value of 0.82 (95%CI 0.78-0.86).

A probability calculator was produced to determine the likelihood of an IBD diagnosis within the EN cohort using the following examples: 1) A female, 34-year-old, non-smoker with a body mass index (BMI) of 21 kg/m^2 and a within 6-month history of anaemia and abdominal pain would have a 7% risk of IBD being diagnosed within 3 years of her EN diagnosis. 2) A male, 17-year-old, current smoker with a BMI of 24 kg/m^2 and a history of abdominal pain and diarrhoea would have a 43% 3-year IBD diagnosis risk. 3) A female, 49-year-old, current smoker with a BMI of 30 kg/m^2 and a history of diarrhoea and abdominal pain would have an 11% risk of 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 a D-EIM but without a recorded diagnosis of IBD, are at greater risk of later being diagnosed with IBD than matched subjects without a D-EIM. A subsequent diagnosis of IBD in those with a new dermatological EIM diagnosis was recorded at a median of 205 days after D-EIM diagnosis with 50% of cases recorded between 44 and 661 days. A substantial number of new IBD diagnoses were therefore not made until more than a year following an EIM diagnosis. Considering dermatological EIMs usually present when bowel disease is active, our findings might suggest a missed diagnostic opportunity. Although these skin manifestations may accompany bowel activity, they do not always relate to disease extent or severity [25–27] and as such it is plausible that symptoms of IBD may not have manifested themselves clinically. That being said, in the prediction model presented, 55% of participants with EN who were later diagnosed with IBD had a record of either anaemia, abdominal pain, loperamide prescription, diarrhoea or lower gastrointestinal bleeding at the time of dermatological EIM diagnosis, compared to only 18% of non-IBD diagnosed subjects. We found a predominance of CD diagnoses in exposed subjects with EIM, which is in keeping with previous observations that EIMs are more common in those with CD. This was also observed, though the numbers were small, in the PG cohort, whereas others have shown an predominant association with UC in this condition [8,28,29].

Extraintestinal manifestations of IBD are numerous, however certain “classical” EIMs have been accepted. The classical dermatological types include EN, PG, ApS and SS: conditions which were examined in this study. Attempts have been made to categorise EIMs based on their presumed biological cause. Other, non-classical EIMs, not included in this study, include mucocutaneous CD, which represents intestinal pathophysiology located outside the gut, and anti-tumour necrosis factor (anti-TNF) associated skin conditions, which relate to specific medications [30]. Classical D-EIMs usually run alongside bowel disease activity, with the exception of PG, which may or may not run in parallel [13]. Dermatological EIMs may occur in isolation or in association with medical conditions other than IBD.

We did not consider psoriasis among the "classical" D-EIMs in this study; however, it is a common skin condition and an association with IBD has previously been shown. As such, psoriasis was included as a separate analysis in this study. We have shown that the risk of an IBD diagnosis is greater in psoriasis and that the association appears to be greatest in CD, which is in keeping with existing evidence [7,31,32].

Erythema nodosum is the most common dermatological EIM and is thought to be a type IV delayed hypersensitivity reaction leading to panniculitis. Mainly affecting the pretibial area, resulting in raised, tender, red/brown nodules, it is predominantly an idiopathic condition that runs a benign course [18]. EN has been reported to affect between 3-15% of those with IBD, with most cases presenting after an established IBD diagnosis [4,8,28] In the current study, 6,329 subjects with incident EN were identified with 5,917 remaining once tuberculosis, sarcoidosis and sulfasalazine use had been removed. 327 individuals with pre-existing IBD were then excluded, but taken together with the 104 subsequent IBD diagnoses, 7% of exposed subjects with incident EN had an IBD diagnosis. In our study, of those subjects with EN subsequently diagnosed with IBD, 2% were diagnosed shortly after EN diagnosis and half more than 5 months later.

Pyoderma gangrenosum is a neutrophilic dermatosis. It is an immune reactive condition resulting in painful ulceration predominantly on the lower limbs, which can be challenging to treat, exhibits pathergy and is prone to a relapsing course [8,33]. PG is rare with a female predominance and prevalence of 5.8 per 100,000 population [34]. Around 34% of those presenting with PG may have underlying IBD[35–37]. With the excluded 166 pre-existing IBD diagnoses and 21 IBD diagnoses subsequently observed among incident PG subjects, 16% of exposed subjects were associated with IBD. As with EN, we found that 2% of IBD cases were diagnosed following a PG diagnosis. In the case of PG, however, more than 50% of IBD diagnoses were made greater than 12 months after the PG diagnosis.

Aphthous stomatitis (ApS) and Sweet's syndrome (SS) were not studied individually but made up a significant minority (9% and 3% respectively) of the individuals with dermatological EIMs. ApS is common, with a fifth of people suffering from these lesions, although diagnostic criteria and populations studied have resulted in a wide variation in prevalence [38]. ApS is seen in 7-10% of patients with IBD in observational studies, with CD subjects predominating [8,28]. It is likely that ApS, especially milder forms, are under-reported. When reviewed separately, only 4 (0.6%) participants with ApS were later diagnosed with IBD, three quarters of which were CD. Sweet's syndrome (otherwise known as febrile neutrophilic dermatosis) is a rare condition characterised by fever, neutrophilia and skin lesions. It may be drug induced, present as a paraneoplastic phenomenon or be termed "classical" and associated with IBD, streptococcal pharyngitis, pregnancy or may appear in isolation [32]. Little is known about its prevalence, with the published literature dominated by case reports, however, it predominantly affects females which was also the case in the present study (62% female) [39]. Only two (1%) individuals with SS were later diagnosed with IBD. Although their Charlson comorbidity scores were both 0, making malignant causes less likely, it remains challenging to comment further on this rare syndrome, other than to say that vigilance for IBD should be exercised if SS is encountered in the absence of an alternative cause.

The use of a large primary care database such as IMDR-UK has both strengths and limitations. French and Swiss studies of IBD subjects found that a younger age and female sex were significantly associated with dermatological EIMs, that they were associated with familial IBD and in the French study, PG was associated with black African ethnicity [27,40]. A limitation of the IMDR-UK database is the limited ethnicity and family history data that has been recorded. Unfortunately, these limitations mean that assessing the impact these variables have in the diagnosis of IBD in D-EIM subjects was not possible. There is also a lack of nuance in the coding of IBD in primary care with regards to the severity and site of IBD within the bowel. Although this did not affect the study outcome, that of an IBD diagnosis, it is noteworthy that colonic and ileocolonic disease seems to be more strongly associated with EIMs than isolated small bowel disease and unfortunately this could not be further

explored in this study [4,7]. Attempts were made to reduce bias due to other potential confounders that may be causative in terms of EIMs (exclusion of subjects with EN with a recent coding of tuberculosis, sarcoidosis and sulfasalazine prescription), however, many EIMs have a multitude of associations, making comprehensive exclusions both impractical, and, given the unknown aetiology and causal pathways for these conditions, inappropriate.

Misclassification bias is a potential concern in all primary care database studies and the gold standard of external validation is often prohibitive [41]. Conditions diagnosed in secondary care are relayed to general practices who then upload these to their computerised systems. This would be the case for IBD; IBD coding in primary care has previously been validated, [19] and, furthermore, in our study more than 60% of subjects with IBD had at least two IBD codes in their patient record. PG has been previously validated in UK primary care, with the code for "pyoderma gangrenosum" generating a positive predictive value (PPV) of 76% and coding of "pyoderma" producing a 50% PPV [22], however numbers were small and the methodology relied upon general practitioners responding to a questionnaire. Given that PG is a diagnosis of exclusion and dermatology specialty referral will be involved, it is likely that coded cases record true PG. Given our controlled studies, if there were an impact of under-classification, it is likely to reduce the hazard associated with IBD compared to controls, and so our findings may in fact be an underestimate of the risk. A primary care database validation study for EN has not been done, and this too warrants further consideration. EN is a relatively benign condition and although causes maybe sought, a diagnosis may be made in primary care without further specialty intervention. There is also a risk that EN may be under-reported as well as misclassified, which again may lead to an underestimate of the risk presented.

The presence of multiple EIMs in a single patient may affect the risk of IBD, and having one EIM appears to increase the risk of developing further ones [8,26]. In the present study a first recorded dermatological EIM allowed for study inclusion, however, subsequent EIMs were not examined, meaning a subject may have several EIMs either previously diagnosed, in the case of non-dermatological EIMs, or subsequently for all types. This interaction may be important and should be

considered in future research. It is clear that delays in the diagnosis of IBD can lead to unfavourable outcomes with increased hospitalisation, potential exposure to an avoidable surgical risk and significant costs [14,42,43].

Few studies have examined the time lag from an EIM diagnosis to a subsequent IBD diagnosis. In the vast majority of cases an EIM is diagnosed in concert with or following the IBD diagnosis [4]. Furthermore, a longer duration of IBD is associated with a greater risk of EIMs [44]. Consequently, the focus of this study is unique. Given that most dermatological EIMs present in concert with bowel activity, it is reasonable to presume that those who went on to be diagnosed with IBD, following a diagnosis of a dermatological EIM, may have had active bowel disease which was only mildly symptomatic or uncharacteristic of IBD at the time. The prediction time period was limited to 3-years in order to capture the maximum subsequent diagnoses in the database and also be practical for a clinician and patient, however, IBD diagnoses made many years after an EN diagnosis are not accounted for with this model. The prediction model presented here has been internally validated and performs well, however, a limitation was the relatively few IBD outcomes available and external validation is required. Nevertheless, it is noteworthy that the features that increase the likelihood of a subsequent diagnosis of IBD, in particular anaemia and lower gastrointestinal symptoms, should be considered by all clinicians who make a diagnosis of an associated dermatological condition.

In conclusion, we have demonstrated that those who present with a D-EIM are at increased risk of a subsequent IBD diagnosis. Clinicians who see patients with dermatological conditions should be aware of this risk association, and symptoms of IBD should be sought in such patients and, if found, investigated and gastroenterology referral considered in order to reduce diagnostic delays and avoid harm.

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549 **Table 1. Demographic characteristics of exposed subjects and controls**

	Exposed subjects with any associated dermatological condition	Controls
Number of subjects	7,447	29,297
Median py of follow-up (IQR)	5.5 (2.3-9.6)	5.4 (2.3-9.5)
Median age (IQR)	38 (24-56)	38 (23-54)
Age category, n (%)		
<18 years	1149 (15)	5031 (17)
18-30 years	1356 (18)	5208 (18)
30-40 years	1360 (18)	5350 (18)
40-50 years	1113 (15)	4468 (15)
50-60 years	968 (13)	3746 (13)
60-70 years	724 (10)	2793 (10)
>70 years	777 (10)	2701 (9)
Female sex, n (%)	5,533 (74)	21,785 (74)
Townsend deprivation quintile, n (%)		
1 - least deprived	1532 (21)	6349 (22)
2	1386 (19)	5277 (18)
3	1386 (19)	5402 (18)
4	1239 (17)	4540 (15)
5 - most deprived	805 (11)	3282 (11)
missing	1100 (15)	4447 (15)
Charlson comorbidity score, n (%)		
0	4888 (66)	21804 (74)
1	1706 (23)	5361 (18)
>/=2	853 (12)	2132 (7)
Smoking status, n (%)		
current smoker	1152 (15)	5128 (18)
non- smoker	6295 (85)	24169 (82)
Body mass index, n (%)		
<25 kg/m2	2340 (31)	9539 (33)
25-30 kg/m2	1656 (22)	5991 (20)
>30 kg/m2	1498 (20)	4251 (15)
missing	1953 (26)	9516 (32)
Anaemia†‡, n (%)	941 (13)	947 (3)
Abdominal pain†, n (%)	190 (3)	600 (2)
Lower gastrointestinal bleeding†, n (%)	83 (1)	164 (1)
Loperamide prescription†, n (%)	139 (2)	212 (1)
Diarrhoea†, n (%)	240 (3)	503 (2)

py: person years
IQR: Interquartile range
† coded within 6 months of Index date
‡ <11.9g/dL (females); <12.9g/dL (males)

Table 2. Adjusted hazard ratios for risk of inflammatory bowel diseases

	aHR	[95% Conf. Interval]		p-value
Any associated dermatological condition				
Inflammatory bowel disease	6.16	4.53	8.37	<0.001
Ulcerative colitis	3.30	1.98	5.53	<0.001
Crohn's disease	8.54	5.74	12.70	<0.001
Erythema Nodosum				
Inflammatory bowel disease	6.49	4.62	9.11	<0.001
Pyoderma Gangrenosum				
Inflammatory bowel disease	6.27	2.84	13.86	<0.001
Psoriasis				
Inflammatory bowel disease	1.34	1.20	1.51	<0.001
Ulcerative colitis	1.20	1.03	1.39	0.020
Crohn’s disease	1.60	1.34	1.92	<0.001

aHR: Adjusted hazard ratio.

551 **Table 3. Characteristics of Erythema Nodosum subjects with and without an IBD diagnosis by 3 years**

	IBD diagnosis (87)	No IBD diagnosis (5,486)
Median age (IQR)	25 (19-35)	37 (24-52)
Age category, n (%)		
<18 years	14 (16)	604 (15)
18-30 years	45 (52)	721 (18)
30-40 years	13 (15)	851 (22)
40-50 years	5 (6)	662 (17)
50-60 years	5 (6)	540 (14)
60-70 years	4 (5)	357 (9)
>70 years	1 (1)	221 (6)
Female sex, n (%)	72 (79)	3,122 (79)
Smoking status, n (%)		
current smoker	20 (23)	622 (16)
non- smoker	67 (77)	3334 (84)
Body mass index, n (%)		
<25 kg/m2	42 (48)	1217 (31)
25-30 kg/m2	14 (16)	908 (23)
>30 kg/m2	9 (10)	795 (20)
Missing	22 (25)	1036 (26)
Anaemia†‡, n (%)	28 (32)	44 (11)
Abdominal pain†, n (%)	9 (10)	104 (3)
Lower gastrointestinal bleeding†, n (%)	3 (3)	42 (1)
Loperamide prescription†, n (%)	7 (8)	55 (1)
Diarrhoea†, n (%)	24 (27)	113 (3)

† coded within 6 months of Index date
‡ <11.9g/dL (females); <12.9g/dL (males)
IBD: Inflammatory bowel disease
IQR: Interquartile range

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Table 4. Multivariable logistic regression prediction model

Factors associated with diagnosis of inflammatory bowel disease within 3 years of an erythema nodosum diagnosis

	β-Coefficient	Odds Ratio	[95% Conf. Interval]		P value
Sex					
Male (reference)		1.00			
Female	**0.04**	**1.04**	**0.56**	**1.93**	**0.90**
Age Category					
<18 years (reference)		1.00			
18-30 years	**0.75**	**2.12**	**0.97**	**4.65**	**0.06**
30-40 years	**-0.78**	**0.46**	**0.18**	**1.17**	**0.10**
40-50 years	**-1.22**	**0.29**	**0.09**	**0.94**	**0.04**
50-60 years	**-1.04**	**0.35**	**0.11**	**1.16**	**0.09**
60-70 years	**-0.94**	**0.39**	**0.11**	**1.40**	**0.15**
>70 years	**-2.45**	**0.09**	**0.01**	**0.75**	**0.03**
Smoking Status					
current smoker (reference)		1.00			
non smoker	**-0.40**	**0.67**	**0.38**	**1.17**	**0.16**
Body mass index					
<25 kg/m^2 (reference)		1.00			
25-30 kg/m^2	**-0.59**	**0.55**	**0.29**	**1.06**	**0.07**
>30 kg/m^2	**-0.92**	**0.40**	**0.19**	**0.85**	**0.02**
Missing	**-0.74**	**0.48**	**0.24**	**0.94**	**0.03**
Anaemia†‡					
no (reference)		1.00			
yes	**1.41**	**4.11**	**2.48**	**6.79**	**0.00**
Abdominal pain†					
no (reference)		1.00			
yes	**0.92**	**2.51**	**1.06**	**5.96**	**0.04**
Diarrhoea†					
no (reference)		1.00			
yes	**2.60**	**13.42**	**7.59**	**23.74**	**0.00**
Intercept	**-3.44**	**0.03**	**0.01**	**0.09**	**0.00**

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

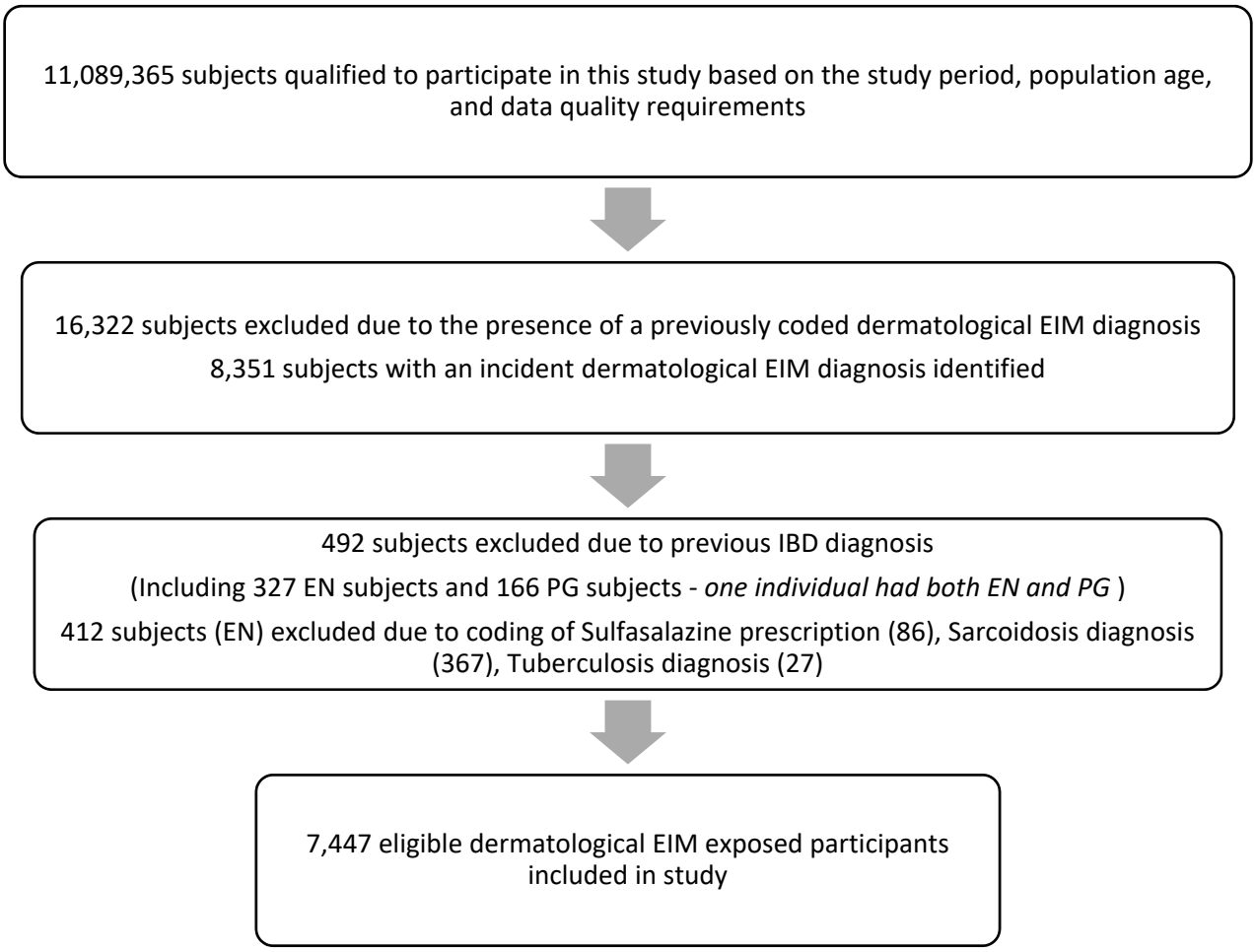

Figure 1. Consort flow chart.

EIM: extraintestinal manifestation; IBD: inflammatory bowel disease; EN: erythema nodosum; PG: pyoderma gangrenosum.

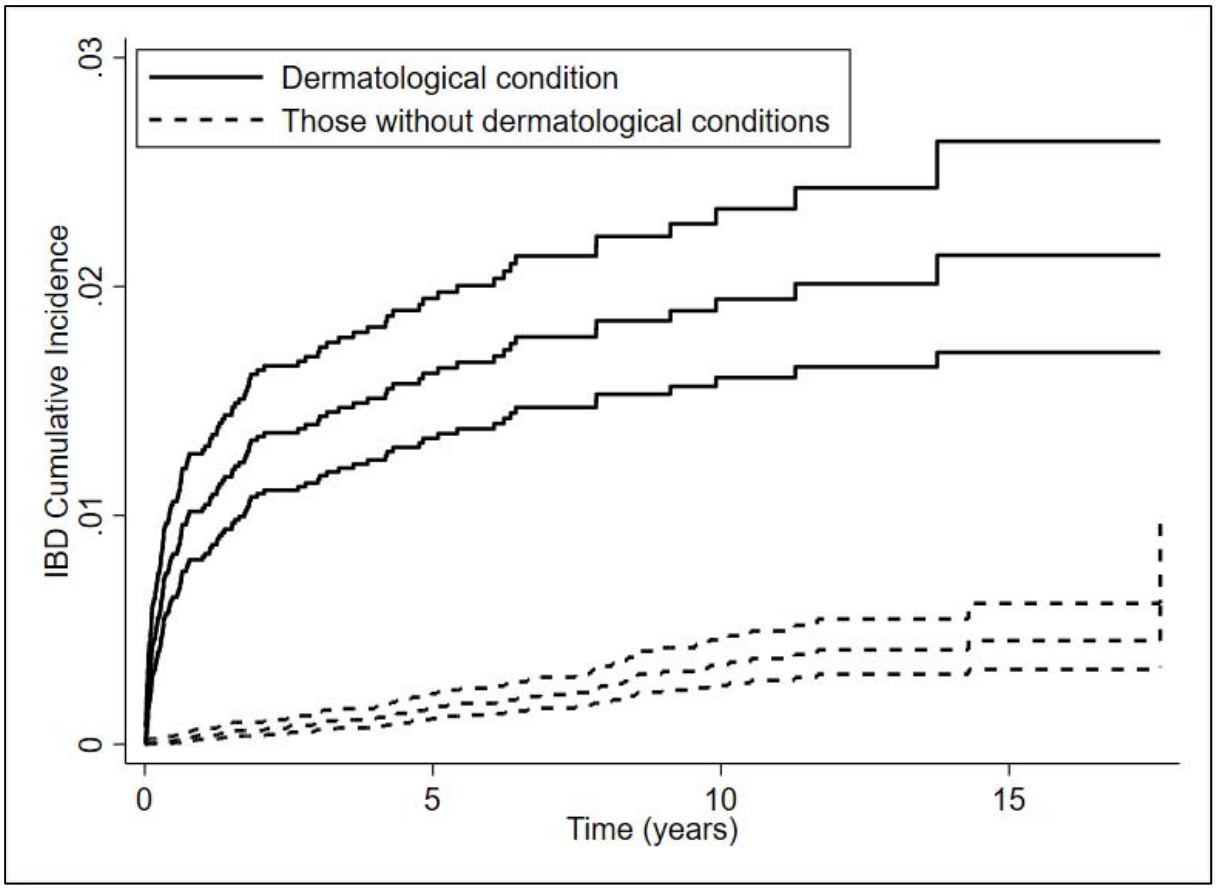

Figure 2. Cumulative incidence (with 95% confidence intervals) of IBD (inflammatory bowel diseases) in subjects with dermatological conditions and those without.

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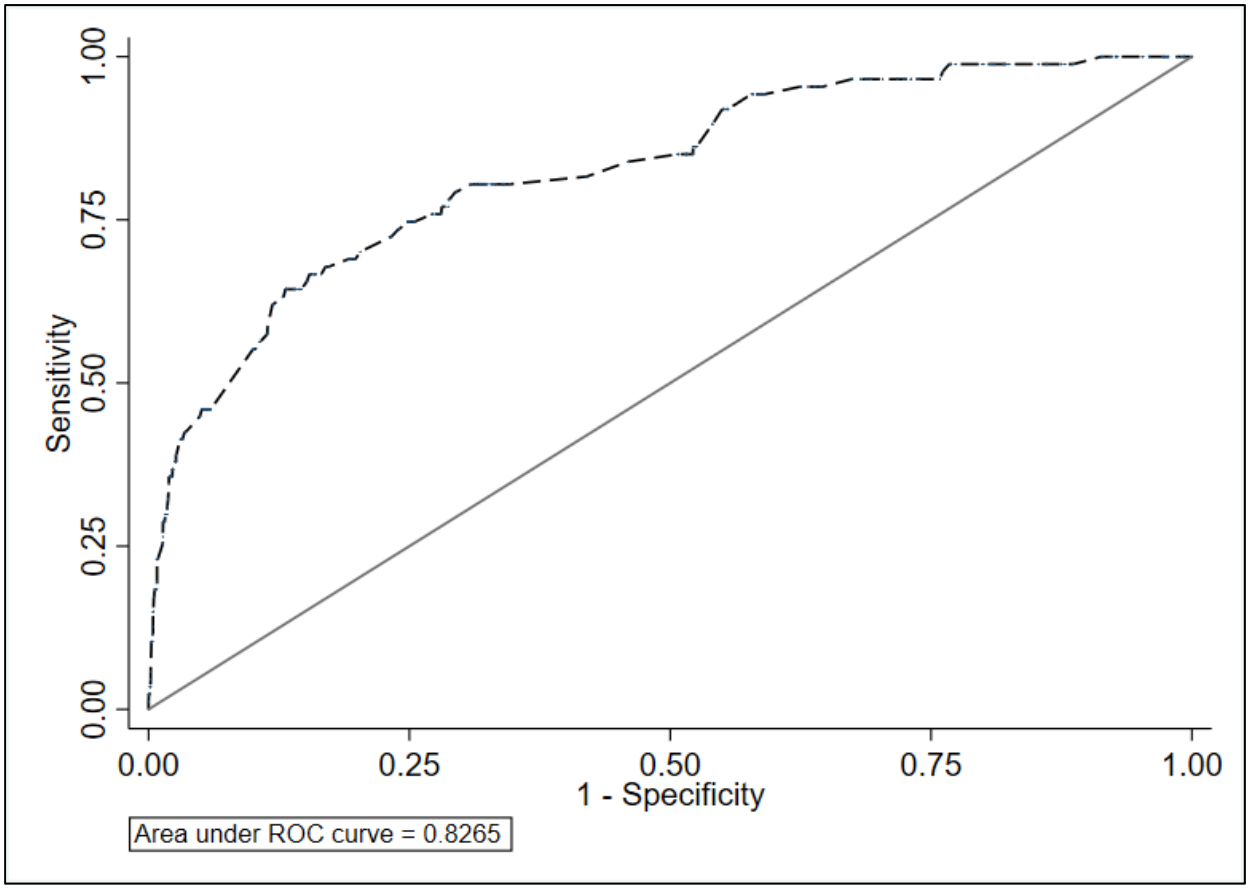

Figure 3. Receiver operating characteristic (ROC) curve of diagnostic ability of prediction model to detect an inflammatory bowel disease diagnosis within 3-years of an erythema nodosum diagnosis.

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